Haemophilia

Haemophilia (2012), **18** (Suppl. 3), 1–208

01-ACQUIRED HEMOPHILIA

FP-MO-01.1-1
Efficacy and safety of B-domain deleted recombinant porcine factor VIII (OBI-1) in the treatment of acquired hemophilia A: interim results

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OBI-1 is an investigational B-domain deleted recombinant porcine factor VIII (FVIII) with low cross-reactivity to anti-human FVIII antibodies. Acquired hemophilia A (AHA) is caused by autoantibodies (inhibitors) against FVIII. Patients are usually elderly and have co-morbidities. Current management of bleeds is guided by clinical assessment alone, as there is no laboratory surrogate for efficacy. Importantly, OBI-1 efficacy can be monitored by FVIII levels in addition to clinical assessment. Accur8 Auto-antibody trial (NCT01178294) is a prospective, open-label, Phase 2/3 study. The primary objective is to evaluate efficacy of OBI-1 treatment for serious (life- or limb-threatening) bleeds in patients ≥18 years with AHA. FVIII levels are obtained before and within 10–20 min following the initial OBI-1 dose (200 U kg^{-1}) and at 2–3 h. Additional OBI-1 doses (≤ 400 U kg^{-1} every 2–3 h) are administered to achieve target FVIII levels. The primary efficacy outcome is the control of bleeding 24 h after starting OBI-1. As of December 2011, 7 patients with severe bleeds were entered into the trial and all had successful control of hemorrhage at 24 h and subsequent resolution of the bleed. Therapeutic FVIII activity levels were achieved and maintained with intermittent OBI-1 administration based on FVIII levels. Five serious adverse events were reported, all being not related to OBI-1. Additional confirming data would establish OBI-1 as a useful treatment option for AHA.

Table.

Sex (Age, y)	Primary bleed site	Anti-human FVIII titer (BU)	Anti-OBI-1 titer (BU)	FVIII activity (%) Pre-first infusion	20 min post-first infusion	2–3 h post-first infusion	24 h clinical outcome
Male[a] (72)	Surgical incision (thigh & buttock)	23[d]	<1	9	361	186	Positive
Male[b] (69)	Soft tissue (arm) & femoral line	80	<0.6[d]	<1	119	42	Positive
Male[b] (86)	Surgical incision (arm)	28	<1	9	417	198[e]	Positive
Female[b] (79)	Retroperi-toneal	860	1	<1	77	20	Positive
Female[b] (64)	Hematoma (arm)	11	<0.5	3	288	197	Positive
Female[c] (82)	Hematoma (leg)	21	Not available	<1	258	230	Positive
Male[b] (69)	Hematoma (arm)	27	Not available	22[f]	270	233	Positive

Disclosure statement: The research was supported by Inspiration Biopharmaceuticals, Inc., Laguna Niguel, CA, U.S.A., and the investigative sites received funding for study activities.

PO-MO-001
The efficacy of corticosteroid monotherapy in acquired factor VIII inhibitor

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Background: Acquired factor VIII inhibitor is a rare bleeding disorder caused by auto-antibody directed against factor VIII and typically presented later in life. Patients with acquired factor VIII inhibitors are at high risk of developing catastrophic bleeding.
Objective and methods: The aim of this retrospective study was to evaluate clinical characteristics and outcomes of the patients with acquired factor VIII inhibitor diagnosed at Chiang Mai University hospital from 1999–2011.
Results: The total number of patients was 25 (10 men, 15 women), with a median age of 59 (range 17–89). Most of the patients (80%) presented with soft-tissue and intramuscular bleeding. A minority of the patients had hemathrosis (8%), post-operative bleeding (8%), and only 1 patient had no clinical bleeding. Fifteen patients (60%) had idiopathic disease, while 40% had underlying diseases of autoimmune illness (20%) and malignanacy (20%). Twenty patients (80%) received hemostatic agents (FVIII concentrate, cryoprecipiate, FFP, or rFVIIa). For controlling bleeding, corticosteroid monotherapy was the most commonly used immunomodulatory agent (92%), with an overall response rate of 96% (complete response rate of 76%). The median time of response was 55 days (range 21–210) with a median duration of response of 19 months (range 0–142). Associated diseases did not affect the response to treatment. Two patients died from uncontrolled bleeding. After tapering off corticosteroid, only 9% of evaluable patients (n = 23) released with a relapse rate of 9%. All of them responded to the reinstitution of corticosteroid monotherapy.
Conclusion: Corticosteroid monotherapy is the effective treatment for antibody eradication in acquired factor VIII inhibitor with a durable response.

PO-MO-002
Patterns of bleeding, comorbidities, and clinical courses in acquired hemophilia A (AHA) and in acquired von Willebrand disease (AVWD): Experience from a single hemophilia centre in Pavia

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Background and patients: AHA and AVWD are rare acquired coagulopathies generally associated with solid or hematologic malignacies, or immunologic or cardiovascular disorders; in the elderly they are often idiopathic. Diagnosis is made by prolongation of aPTT not corrected by mixtures with normal plasma and by detection of low plasma levels of FVIIIC alone (AHA) or in association with vWFRicof (AVWD). Bleeding episodes are generally mucocutaneous and muscular hematomas and, according to the severity, they could require management by an experienced team. This study reports the circumstances of diagnosis, patterns of bleeding, and treatment in patients with AHA and AVWD observed in our hemophilia centre during the last 5 years: 6 patients with AVWD, 14 with AHA, with an age range of 27–94 years (mean 72 years, median 70 years). These coagulopathies were associated in 7 patients with hematologic malignancies, in 3 patients with cardiovascular disease (arterial hypertension, atrial fibrillation, dilatative cardiomiopathy), in 2 patients with diabetes mellitus, in 2 patients with chronic bronchitis, in 2 patients (AHA) in the post-partum phase, in 2 patients with chronic inflammatory bowel disease, in 1 patient with rheumatoid arthritis, and in 1 patient with a viral infection. Monoclonal gammopathies were present in 3 patients with AVWD and in 2 patients with AHA (3 lymphoproliferative disorders, 2 MGUS). The mean delay of diagnosis from bleeding manifestations was 4 months (24 h to 8 months). Sixteen patients had complete remission after treatment of the underlying disease (in 10 patients) or after immunosuppresive therapy (in 6 patients). At diagnosis, 18/20 patients presented hemorragic manifestations: 4 epistaxis, 9 muscular hematomas, 1 hematuria, 2 blood in stools, 1 post-partum hemorragia, and 1 hemarthrosis. In 2 patients, only prolonged PTT prompted us to perform diagnostic procedures. The presence of severe bleeding requiring hospitalization and treatment in emergency occurred in 10 patients with AHA (70%) and in 3 patients with AVWD (50%). No patient died because of hemorrhages.
Conclusion: AHA and AVWD are rare but severe bleeding disorders associated with similar underlying diseases and patterns of presentation. AVWD seems to be more frequently related to monoclonal gammopathies. The cure of underlying diseases is often effective in also resolving the acquired coagulopathies.

PO-MO-003
Acquired hemophilia: Clinical course and treatment outcomes in 25 patients

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Acquired hemophilia is a rare disorder caused by autoantibodies against FVIII with a typical occurrence in elderly patients and serious bleeding manifestation. We report on the clinical course and outcomes in a group of 25 patients with acquired hemophilia (11M/14F, aged 23–96 years) treated in our centre between 1996 and 2011. At diagnosis, the median level of FVIII was <1 IU dL^{-1} (range 0.2–8 IU dL^{-1}) and inhibitor titer 32 BU mL^{-1} (6-1260 BU mL^{-1}). The disorder was associated with lymfoproliferative and immunologic diseases, neoplasia, and pregnancy in 6,10,3, and 2 patients, respectively. The most prevalent symptoms were large skin hematomas (44%), mucosal (28%), and joint bleeds (20%); 4 patients presented with life-threatening post-traumatic bleeding. A total of 57 bleeding episodes were treated with bypassing agents (FEIBA in 25 and r-FVIIa in 32 episodes); in 2 patients, sequentional therapy was used. Overall success of inhibitor eradication was 84%, 19/76% patients achieved complete remission (CR) with prednisone and/or cyclophosphamide (time to remission 1–13 weeks, median 3 weeks), 1 patient with CsA and 1 with rituximab. Inhibitor relapsed in 3–7 months in 6 patients, 5 of them achieved a second, sustained CR. Median follow-up in successfully treated patients was 6 (1–11) years. Four patients with refractory inhibitor died because of underlying disease, only 1 (96-year-old) patient had post-traumatic bleeding in the terminal phase of disease.
Conclusion: Early diagnosis of acquired hemophilia and effective bypassing agents substantially improved previously poor prognosis of disease. Immunosuppressive therapy provides a chance for inhibitor eradication in more than 80% of patients.

PO-MO-004

Acquired hemophilia at Chris Hani Baragwanath Academic Hospital

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Acquired hemophilia is a rare bleeding diathesis caused by inhibitors/autoantibodies to factor VIII, and is associated with significant morbidity and mortality. It typically presents in older patients with spontaneous soft tissue/muscle bleeds, associated with a prolonged partial thromboplastin time. More than half the patients have no underlying cause (idiopathic). Therapy is aimed at arresting the bleeding (usually with the use of bypassing agents), treating the underlying cause (where detectable) and eradicating the autoantibody with immunosuppressive therapy. During the period from January 1, 1996 to December 31, 2011, only 5 patients with acquired hemophilia were seen at the adult Clinical Haematology Unit, Chris Hani Baragwanath Academic Hospital. The clinical characteristics of the patients are detailed in the table below:
There were 3 females and 2 males with a F:M ratio of 1.5:1. The mean age was 58 years, with a range of 32 to 82 years. A secondary cause was evident in 60% of the patients, while 1 of the 2 patients with an idiopathic aetiology developed a malignancy 10 years after her initial presentation, bringing into question the possible association of malignancy, manifesting years after the initial diagnosis. The uncommon association of HIV with acquired hemophilia is noteworthy in the context of an area of high endemicity for the virus. The patients were supported with blood products, given appropriate factor replacement (initially with lyophilized factor concentrates and now with either FEIBA or Novo 7) and immunosuppressive therapy. Three of the 5 patients have died (one with a survival of 128 months) and 2 are alive and well at present.

Table. XXXXX

NO.	F8 LEVEL %	GENDER	AGE	MAJOR SITES OF BLEEDING	UNDERLYING CONDITIONS	OUTCOME
1.	2	F	73	Soft tissue/muscle, hemarthrosis, mucosal	Idiopathic Developed Ca Breast 10 years after initial presentation	Died. Survival 128 months
2.	0	M	32	Hematuria, post-surgical wound site, abdominal	HIV	Died. Survival <1 month
3.	0	F	57	Hemetemesis, soft tissue/muscle, hemarthrosis	SLE	Died. Survival 2 months
4.	1	M	49	Soft tissue/muscle	Rheumatoid arthritis	Alive
5	2	F	82	Soft tissue/muscle, hemarthrosis, hematuria	Idiopathic	Alive

PO-MO-005

Sequential combined bypassing therapy in the treatment of unresponsive bleeding in patients with acquired hemophilia

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An appropriate management of the acute bleeding episodes in patients with acquired hemophilia A (HA) and high titer inhibitors require the use of bypassing agents. Two bypassing agents (APCC, FEIBA® and rFVIIa, NovoSeven®) are currently available and have been shown to be safe and efficacious in the treatment of bleeding episodes in patients with AH. However, whichever treatment is used initially, 10–20% of bleeding episodes cannot be controlled by the use of a single bypassing agent. Sequential combined bypassing therapy (SCBT) has been reported to be successful in the treatment of unresponsive bleeding in patients with hemophilia and high responding inhibitors to FVIII. We report our experience in two females with pregnancy-related AH, who experienced severe bleedings and were successfully treated with SCBT. Patient 1 (age 28) suffered from a large spontaneous hematoma. She was first treated with high doses of rFVIIa (270 μg kg^{-1} every 4 hours) without any clinical improvement and was shifted to the use of FEIBA (85 U kg^{-1} every 8 h) with no further success. SCBT with FEIBA (85 U Kg^{-1} every 6 h) alternated to rFVIIa (180 mg Kg^{-1} every 6 h) but resulted in a stable hemostatic response with improvement of clinical conditions and no further requirement of red cell transfusions. Patient 2 (age 31) needed emergency surgery of ovariectomy. She was initially treated with rFVII (270 μg kg^{-1}) without effective hemostasis. FEIBA treatment was, therefore, introduced (85 U kg^{-1}) without hemostatic efficacy. Sufficient hemostasis was achieved only after introduction of SBCT with alternated injections of FEIBA (80 U Kg^{-1}) and rFVIIa (250 μg kg^{-1}) every 4–6 h. SCBT was discontinued after 7–14 days. No clinical adverse events were observed. We conclude that SCBT is an effective modality of treatment in patients with AH and unresponsive bleeding to a single bypassing agent, even if it represents a salvage treatment due to potential thrombotic risks. Further prospective clinical trials are needed in order to optimize the treatment.

PO-MO-006

Recurrence of thrombotic complications after termination of oral anticoagulation coinciding with immunosuppression due to acquired factor VIII autoantibodies

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Objectives: Acquired hemophilia is a rare bleeding disorder requiring rapid diagnosis and effective treatment. Rebound rise in factor VIII activity levels related with the administration of rituximab might also be associable with an increased risk of thromboembolism.
Methods: In a 70-year-old female patient suffering from recurrent deep venous thrombosis in the lower extremity, no oral anticoagulation was performed, taking multimorbidity (transient global amnesia, polymyalgia rheumatica) into account. Elevated and reproducible factor VIII levels (>300%) were found, whereas no link for thrombophilia (including factor V Leiden and prothrombin G20210A mutation) existed by laboratory screening. Continuously given daily oral doses of steroids (8 mg prednisolone per day) were needed, also representing a potential thrombophilic trigger mechanism.
Results: Our patient spontaneously developed extensive skin and retroperitoneal hematomas besides muscle bleedings (M. psoas) during hospitalization and prophylactic anticoagulation using low molecular weight heparin. Global coagulation assays, platelet count, and function were found to be normal, while FVIII ranged about 26%. Plasma exchange in vitro as well as factor VIII inhibitor testing revealed low responder state of factor VIII (2 BU). Medical thromboprophylaxis had been discontinued and therapy according to the GTH-AH 01/2010 protocol (phase 3) with prednisolone, 3 intravenous doses of rituximab, and activated recombinant factor VII (total amount 166 mg) had been initiated. Complete remission was achieved after 5 weeks of treatment. In the follow-up, factor VIII activity continuously increased up to 265%. One year later, anticoagulation was still interrupted, while immunosuppression was continuously administered using oral doses of 8 mg prednisolone. Deep vein thrombosis was then suspected in the patient. One further thrombotic complication in the femoral vein could be verified by ultrasound. FVIII activity ranged at about 420%. No bleeding was encountered under consistent initiation of dose-adjusted, intravenously given unfractionated heparin.
Conclusion: The patient, highly at risk for recurrent venous thrombotic complications related to the clinical course, history, and immunosuppression, developed one further thrombotic complication associable with extremely high factor VIII. This phenomenon can be interpreted as a rebound phenomenon. According to international recommendations on the diagnosis and treatment of patients with acquired hemophilia A, an adequate therapy is necessary, particularly in patients predisposed for thrombosis. Practitioners should, therefore, also be aware the complexity of such clinical rarities and control aPTT and factor VIII besides PT and INR in the long-time follow-up of oral anticoagulation.

PO-MO-007

High dose of FVIII concentrate as first-line therapy in 4 patients affected by acquired hemophilia A and cardiovascular disease

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Bleeding control is the first priority in acquired hemophilia A (AHA). International guidelines recommend bypassing agents (BA) as first-line therapy. However, literature shows that BA use may be associated with thromboembolic complications, more likely in patients with underlying cardiovascular diseases. We describe 4 cases of bleeding in AHA patients with high cardiovascular risk successfully treated with FVIII concentrate. **Case 1.** A 69-year-old man, with a recent history of myocardial infarction treated with angioplasty and stenting, presented with anemia (Hb 79 g L^{-1}) due to rectus abdominis hematoma, FVIII:C 0.3%, inhibitor 6 BU mL^{-1}. **Case 2.** A 65-year-old man, with carotid artery disease and previous mesenteric stenting, was admitted with severe anemia (Hb 46 g L^{-1}) due to bilateral hematoma of the upper limbs, FVIII:C 10.4%, inhibitor 1 BU mL^{-1}. **Case 3.** A 75-year-old man was admitted for a large calf hematoma; he had a history of severe coronary heart disease and carotid stenting. Hemoglobin levels were normal, FVIII:C was 15.3% and inhibitor 3.48 BU mL^{-1}. **Case 4.** A 78-year-old male, affected by severe coronary heart disease and previous right carotid endoarterectomy, presented for a syncope and anemia (Hb 90 g L^{-1}) due to a retroperitoneal hematoma. FVIII:C was 2.4% and inhibitor 10.5 BU mL^{-1}. All patients were treated with 100–360 IU kg^{-1} day^{-1} of FVIII concentrate (FANHDI, Grifols, and in Case 4 also HAEMOCTIN, Biotest) (bolus followed by continuous infusion), over 11.25 ± 3.1 days average therapy time. In all cases, hemorrhaging stopped at once; therapy with prednisone and cyclophosphamide was started, obtaining inhibitor disappearance in approximately 3 weeks. No thrombotic complications occurred. Our clinical experience shows that FVIII concentrates are effective in controlling hemorrhages in AHA patients, particularly if inhibitor titer is low, and could be considered as first-line therapy in AHA patients with cardiovascular comorbidity.

02-AGEING

S-WE-03.2-2
Pain management in the older person with hemophilia
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Chronic pain in the older person has become an important area of research and clinical practice in recent years. Persistent pain in older adults has a prevalence of between 50 to 80%. It is commonly believed by both patients and healthcare professionals that pain is a by-product of ageing, but this is a myth and presents as a barrier to appropriate pain management. Throughout the ageing process, pain appears to decrease in some areas of the body, for example chest pain, and increases in other areas, such as joint pain. With the advent of blood products and improved medical management, the life expectancy of the person with hemophilia is comparable to the non-hemophilic population. As a result, the incidence of chronic or persistent pain in the older adult is high and is set to rise over the coming years. The impact of chronic pain in the older adult can be far reaching and is linked to increased levels of depression, anxiety, cognitive impairment, reduced physical activity, increased functional impairment, sleep disturbance, social isolation, and reduced quality of life. The management of chronic pain in the adult patient with hemophilia will be reviewed during the presentation in terms of physical activity, education, cognitive behavioural therapies, and other modalities such as heat and cold. It is strongly recommended that individuals should stay active and participate in individually tailored exercise programs. Self-help and education strategies are also advocated combined with cognitive behavioural therapies to promote coping strategies and well-being.

S-WE-03.2-4
Ageing and oral health
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Oral diseases are the most common of the chronic diseases worldwide and are an important public health problem because of their prevalence, their impact, and the expense of providing treatment. Oral health affects people both physically and psychologically and influences their quality of life. Many people with hemophilia have suffered intractable toothaches and chronic infection and consequently many end up with few teeth in later life. However, demographics are changing with a new generation of dentate older adults with higher expectations regarding their oral status. The value of good oral health into older age cannot be underestimated for people with hemophilia as it affects speech, food choices, self-esteem, and relationships, in addition to a feeling of well-being and peace of mind. Oral health also affects general health and has a marked effect on other chronic diseases commonly seen in older people, such as heart disease and diabetes. Good oral health is especially important for those older individuals for whom infection of an oral origin can cause higher morbidity; for example, those who are immune suppressed, have joint replacements, or for individuals taking drugs that impact the mouth, such as the bisphosphonate drugs commonly used to treat osteopenia. Oral diseases are expensive to treat, especially in people with hemophilia; however, planners continue to overlook the need for prevention of oral diseases. This continued oversight in older individuals, who often have multiple acquired risk factors for oral disease, will lead to more rapid decay, loss of teeth, and expensive, ineffective clinical interventions. Yet there are a number of effective and cost-effective methods available to prevent oral disease. Health policies for older people with hemophilia should be reoriented to ensure the continued maintenance of good oral health into older age using preventive socio-dental approaches to assess individual risk for oral disease and by facilitating access to preventive dental care.

S-WE-03.2-3
The ageing MwH and sexuality
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Ageing men with hemophilia have to deal with several factors that can interfere with smooth sexual functioning. In their younger years, various joints have been damaged by bleeding. As a result, they lack the flexibility for normal sexual movements and their lovemaking can be disturbed by joint pains. At a later stage, many men have been infected with the hepatitis C virus. Both carrying the virus and treatment with interferon can increase the prevalence of sexual dysfunction. In addition, depression and antidepressant medication can negatively influence sexual function. The next disadvantage is HIV. Not only being seropositive but also getting HAART treatment can cause sexual impairment. On top of these disturbances, the ageing body can take its toll. Although age in itself is not a reason not to have sex, lifestyle can diminish sexual flexibility and performance, with an ageing partner and decreasing arousability being additional factors. Although some men accept this sexual loss easily, for many others it will mean a substantial loss of quality of life. Since patients tend to be too shy to bring up the subject of sexuality, hemophilia care professionals should proactively explore existing sexual dysfunctions. The most important recommendation for professionals is to open up the lines of communication. Next to quality of life, there are good arguments to keep sexuality at an optimal level, because various aspects of sexual expression are accompanied by health benefits. This presentation will highlight how hemophilia care professionals can integrate the topic of sexuality in their approach.

S-WE-03.2-5
Impact of ageing from the patient's perspective
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In the early sixties, the average life expectancy of people with hemophilia (PWH) was 20 years. Today, thanks to the treatment with factor concentrates, and despite the catastrophe of HIV and Hepatitis C, we have a first generation of elderly PWH not only in Sweden, and fortunately the number of senior PWH is increasing. The tremendous change of average life expectancy of PWH changes our life perspectives as well. The meaning of rather common phrases or words like "old age," "home for aged people," "retirement," and other similar ones whose relevancy we understood but couldn't relate to ourselves, now starts to be real and concrete even for us. Despite all troubles with our joints and often chronic pain, we do not consider ourselves to be ill or our bleeding disorder to be an illness. To be a person with hemophilia is, as my friend expressed it, rather a way of living. It is not a desirable way of living, but one accepts the limitations and gets used to it. We are used to managing ourselves; for example, most of us having home treatment administer the injections by ourselves. Therefore, the question "What will happen to me when I can't administer the factor concentrate by myself or am unable to tell if I have a bleeding?" evokes much angst. When those of us with hemophilia talk about aging among ourselves, we are like any other elderly people. We know that age-related diseases not directly related to hemophilia may and probably will hit us, but like other people, we do not think about it, and we push such thoughts away. We believe that Hemophilia Care Centres (HCC) can and will coordinate the treatment with a specialist in the particular disease. However, we often revile our fears about what will happen when we will are no longer able to manage our treatment by ourselves. This is one of the first observations in a recently started project with elderly PWH in Sweden and Norway. This issue should be considered by staff of the HCC.

S-WE-03.2-1
The physical and psychological issues in ageing
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In countries with access to a safe, adequate supply of factor concentrate, the life expectancy of a person with hemophilia is almost equivalent to that of the non-hemophilia population. A person's ageing will be influenced by their lifetime experiences and their health, education, and employment. People with hemophilia (PWH) are now living well into old age. This being the case, education of the hemophilia population needs to target such issues as maintaining vein health for long-term prophylaxis, maintaining joint function, good educational and vocational guidance, and men's health issues. Along with the emergence of age-related medical conditions in the hemophilia population, including heart disease, renal disease, diabetes, malignancy, and osteoarthritis, there also may be health issues related to transfusion acquired viral infections. Falls and balance issues as well as osteoporosis and obesity need to be addressed in the older patient with hemophilia, who may encounter musculoskeletal (MSK) problems at an earlier age than their non-hemophilia affected peers. PWH need to maintain good communication with their treating centre as many screening/diagnostic procedures for age-related diseases such as colonoscopy, prostate biopsy, and cardiovascular procedures require specialist hemophilia management. Hemophilia treatment staff now have new challenges in planning for patients requiring assisted accommodation. Along with the physical effects of ageing are the psychological ones. Changes in relationships, wherein partners may need to take on more of a care-giver role, or a change in job or a reduction in working hours due to deterioration in physical health may cause financial stress/anxiety or a change in the dynamics of the relationship. Although aging issues are experienced by the general population, having hemophilia can sometimes add a level of complexity. Good hemophilia care can aid the ageing patient with hemophilia to live well into old age and help in the management of the ageing issues they may encounter.

FP-MO-01.2-2
Acute coronary syndromes in persons with hemophilia: comments on ESC guidelines by the Advance Working Group
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Aims/Background: As life expectancy in persons with hemophilia (PWH) increases, cardiovascular disease management becomes more important. Currently, evidence-based guidelines for antithrombotic management in PWH are lacking. ADVANCE is an expert panel of European hemophilia centres supported by an educational grant from Bayer Healthcare.
Methods: Using structured communication techniques and a 35-point questionnaire to establish consensus, 15 ADVANCE members reviewed recent ESC guidelines for STEMI, NSTEMI, and myocardial revascularization with regard to hemophilia.
Results: Questions are shown with percentage of agreement in parenthesis. A hemophilia expert should be consulted as soon as PWH present with an acute coronary syndrome (ACS) (100%). PWH should be managed according to the ESC "high bleeding risk" patient category (100%). Treatment of an ACS should be started immediately (33%) or delayed until replacement therapy is available based on known factor levels (66%). Fibrinolysis is justified in replaced PWH when early PCI is not available (100%). Target factor level should be ≥30 (100%), ≥50 (78%), ≥80 (53%). Target peak level for early PCI should be ≥30 (100%), ≥50 (93%), ≥80 (80%). Bare metal stents are preferred

over drug eluting (93%). All patients should receive dual antiplatelet therapy (87%). Anticoagulants are not advisable in non-replaced PWH (80%), but are acceptable in replaced PWH (100%) with a preference for unfractionated heparin and enoxaparin. The trough level for PWH undergoing long-term dual antiplatelet therapy should be ≥1% (100%); ≥5% (87%); ≥10% (40%); ≥30% (33%).
Conclusions: In ACS and myocardial revascularization, hemophilia treaters have to deal with controversial therapeutic aims such as clotting factor replacement and therapeutic standards, including anticoagulation and antiplatelet therapy, which is normally contraindicated in PWH. Complete consensus was not achieved, especially concerning dosage of clotting factors. Risks and benefits have to be assessed for every situation. The results of our process could aid decision making when tailoring therapy for each PWH and setting.

FP-MO-01.2-2
The prevalence of hypertension in hemophilia: a single center experience

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Introduction: Mortality rates from cardiovascular disease (CVD) for patients with hemophilia (PWH) in the US are higher than for age-matched males, but little is known about prevalence of cardiovascular risk factors or optimal CVD prevention strategies in PWH. Hypertension is a major risk factor for CVD and predisposes to intracranial hemorrhage. Since intracranial hemorrhage is a major cause of death in hemophilia, we investigated prevalence and treatment of HTN in adult PWH at a single center compared to the US general population.
Methods: PWH (age 18–67 $n = 75$; 18–39 years, $n = 44$; 40–59 years, $n = 22$; ≥age 60, $n = 9$) were evaluated retrospectively (≥2 years) for hypertension (defined as SBP ≥140 mmHg or DBP ≥90 mmHg on ≥3 visits, or recorded antihypertensives). Results were compared to the prevalence of hypertension HTN in the nationally representative sample provided by the National Health and Nutrition Examination Survey (NHANES).
Results: Prevalence of hypertension was higher in PWH compared with age-matched males in NHANES for all age groups. The difference was highly significant among males 18–39 years old, among whom the prevalence of hypertension was 27% (±7%) in PWH compared with 7% in age-matched males in NHANES ($P < 0.001$). Trends were similar in the older age groups, with 45% (±10%) of PWH 40–59 years old and 89% (±11%) of PWH ≥60 years old having hypertension, compared with 31% and 66% of age-matched males of NHANES, respectively ($P = 0.2$ for both comparisons). Hypertension was treated in only 10% (3/30) of hypertensive PWH compared with 70% of subjects with hypertension in NHANES. In all 3 PWH on antihypertensive medication, hypertension remained uncontrolled.
Conclusion: This pilot study revealed a significantly higher prevalence of hypertension for PWH compared to the US norm. Larger, prospective studies are urgently required for confirmation and development of cardiovascular care models in hemophilia.

PO-WE-001
Prevalence of cardiovascular disease or its equivalents in patients with inherited coagulopathies

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Background: Cardiovascular disease (CVD) is one of the age-related problems with which patients with inherited coagulopathies (PWIC) will be confronted with increasing life expectancy. Current data is conflicting about the protective effect of the hypocoagulable states on the occurrence of ischemic heart disease (IHD). Our aim was to assess the prevalence of CVD and/or its equivalents in adult PWIC.
Materials and Methods: The study cohort comprised 37 PWIC, born before 1982, from a single hemophilia centre in Turkey. Demographic information, type and severity of bleeding disorder, data on CVD risk factors (hypertension, dyslipidaemia, diabetes, obesity, and smoking) were collected.
Results: A total of 37 PWIC (4 females, 33 males) were included. Median age was 45 years (31–80). Five patients had von Willebrand disease (VWD: 2 females, 3 males), 1 female patient had acquired FII, VII, IX, X deficiency, 1 female patient was diagnosed with FXI deficiency, 4 patients had hemophilia B (HB), and 26 patients had hemophilia A (HA). Seventeen patients (45%) had severe hemophilia. None of the patients had inhibitor. Hypertension was identified in 9/37 (24%), dyslipidemia in 11/37 (29%), diabetes in 1/37 (2%), and obesity in 5/37 (13%) patients. Twenty-seven patients (78%) were smokers. Four patients had overt IHD (2 VWD, 2 HA). One patient underwent percutaneous coronary intervention, the other 3 had coronary bypass grafting. All the study patients were negative for HIV, which could be an additional risk factor for CVD.
Conclusion: A growing number of PWIC suffer from age-related comorbidities. IHD risk factors should be checked in PWIC, and CVD risk should be determined. Patients at risk should be treated as their non-haemophiliac counterparts.

PO-WE-002
Carotid endarterectomy in 2 patients with hemophilia

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Controversy exists as to whether persons with hemophilia (PWH) are protected against arterial disease. With increased life expectancy, hemophilia teams are now facing the challenges of treating arterial disease in this group. Here we describe 2 cases of embolic stroke and subsequent carotid endarterectomy in PWH. **Case 1:** A 64-year-old male with moderate hemophilia B (factor IX 7 IU dL^{-1}), hypertension, type 2 diabetes and a heavy smoker, presented with a 1-day history of slurred speech, left-arm numbness, and weakness. CT head showed cerebral infarcts in left basal ganglia and subcortical white matter of the right frontal lobe. An arterial duplex scan showed >90% stenosis of the right carotid artery. He had a right carotid endarterectomy, initially with cover of a continuous infusion of Benefix, thereafter followed by boluses for 7 days. He re-presented 21 days later with neck swelling around the surgical site. A right carotid pseudotumour was diagnosed, which was excised with Benefix cover. **Case 2:** A 73-year-old man with mild hemophilia A (factor VIII 8 IU dL^{-1}), previous coronary artery bypass graft and hypertension, presented with left-sided facial weakness. CT head revealed no bleed or thrombosis. CT angiogram of the carotids showed 70–90% stenosis of the right coronary artery. He underwent a right carotid endarterectomy under local anaesthesia with the cover of Refacto AF boluses. Post- operatively he received 10 days of factor VIII cover with good healing and has no residual neurological deficits. He was discharged on clopidogrel and has no increase in bleeding symptoms.
Discussion: These cases illustrate the challenges of managing PWH and embolic stroke secondary to carotid artery stenosis. Carotid endarterectomy should be considered if appropriate and can be performed safely with appropriate factor concentrate cover. Challenges remain regarding ongoing antiplatelet use and post-surgery prophylaxis, especially in those not able to self-administer treatment.

PO-WE-003
Describing occurrence of coronary events and treatment in person with hemophilia (Doceth Registry): report of 27 patients

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Introduction: The prolonged life expectancy of and growing impact of cardiovascular risk factors (CVRF) on persons with hemophilia raise concerns about the management of cardiovascular events in these patients. Little literature with data on this type of case is available.
Methods: A retrospective-prospective registry of coronary artery disease (CAD) in persons with hemophilia was established in Italy in September 2009.
Results: Twenty-seven patients (hemophilia A/B: 25/2; 2 high-responding inhibitors) were reported from 16 centres. Thirteen (48%) were severe, 3 moderate, and 12 mild (FVIII/FIX 6-36%). CAD was occasionally diagnosed in 2 patients, whereas symptoms occurred at a median age of 63 years (range: 22–81) in 6 cases with stable angina and in 19 (70%) with acute coronary syndromes (ACS: unstable angina 7, ST elevation myocardial infarction [STEMI] 7, non-STEMI 5). Factor concentrate infusion was temporally related in only 4 cases (16%). Most patients showed >2 (89%) or >3 (63%) established CVRF (hypertension 89%; obesity/overweight 63%; dyslipidemia 52%; active smoking 44%). Twenty patients (16/19 ACS) underwent coronary angiography, receiving heparin and antiplatelet agents together with replacement treatment (bolus, 30–70 IU Kg^{-1}; continuous infusion in one case), with bleeding complications in 3 (15%). Severe three-vessel disease was shown in 10 patients (50%), leading to coronary artery bypass grafting in 6. Angioplasty was carried out in 10 patients (3 severe), with stenting in 9, followed by antiplatelet treatment (double in 6 implanted with drug eluting stents). Of 17 patients (6 severe) on prolonged antiplatelet therapy, 8 (47%, 5 mild) showed bleeding complications, severe in 5. No bleeds were reported in 5 patients receiving concomitant concentrate prophylaxis. Such regimens enabled the continuation of antiplatelet treatment in a further 3 mild patients. Five fatal cases were reported, 4 of them not having received antiplatelet agent at all.
Conclusions: Persons with hemophilia may experience severe CAD. Our data highlight the need for reducing the impact of CVRF and of an aggressive treatment in symptomatic patients, balancing thrombotic and bleeding risk.

PO-WE-004
Cardiovascular disease history and risk factors in hemophilia patients

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Background and Aim: Cardiovascular disease (CVD) mortality is reported to be lower in hemophilia patients than in the general population, but reports on the occurrence of non-fatal CVD and CVD risk factors are conflicting. The aim of our study was to assess this occurrence in a large cohort of hemophilia patients.
Methods: Baseline data on CVD history and risk factors of 709 Dutch and UK hemophilia patients aged ≥30 years who are enrolled in a prospective CVD study were analysed and compared with the general age-matched male population. QRISK®2-2011 CVD risk scores were used to assess risk profiles.

Results: Mean age at inclusion in the study was 49.8 years (range: 30–94). Most patients (84%) had hemophilia A, and 48% had severe hemophilia. 388 patients (55%) were from the Netherlands and 321 from the UK. The cumulative incidence of myocardial infarction was lower in patients with severe hemophilia than in the general population (1.7% vs. 4.0%), while the occurrence of angina pectoris was similar (4.2% vs. 3.7%). Hypertension occurred more often in hemophilia patients (in 49%, vs. 40% in the general population), while the prevalences of obesity and hypercholesterolemia were lower, especially in patients with severe hemophilia, and those of diabetes and smoking were similar. 10-year QRISK®2 risks were higher in our patients than in the general population (8.9% vs. 6.7%), indicating more unfavourable cardiovascular disease risk profiles overall. This increased risk became apparent after the age of 40 years.
Conclusion: Our results suggest a protective effect of severe hemophilia against acute ischemic CVD, despite more unfavourable risk profiles.

PO-WE-005
Cataract surgery in hemophilia

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Introduction: Cataract is frequently seen in elderly hemophilia patients. Surgery for cataract is a minimally invasive procedure for which bleeding risk is considered to be low. In the present study we retrospectively assessed the bleeding risk of cataract surgery in patients with hemophilia.
Methods: Data on clotting factor correction, type of anesthesia, and bleeding complications were collected from all hemophilia patients who were treated at the Van Creveldkliniek, University Medical Center Utrecht, at any time between 1985 and 2012 and who had cataract surgery.
Results: Fourteen patients underwent a total of 19 surgical procedures for cataract. The median age was 65 years (range: 30–85 years). Eight patients had mild, 4 moderate and 7 severe hemophilia; 16 could be evaluated. To prevent bleeding from retrobulbar anesthesia, clotting factor concentrates were given between 1–2 h before the procedure, aiming at levels between 80% and 100%. As cataract surgery does not enhance bleeding, no second dose was given. Three patients with mild hemophilia did not receive any clotting factor correction; in these patients topical anesthesia was given. Post-operative subconjunctival bleeding occurred in 1 patient with severe hemophilia A and a high titer inhibitor against FVIII.
Discussion: Cataract surgery has evolved over the last decades to a minimally invasive procedure using phaco-emulsification and micro-incisions with topical or sub-Tenon's anesthesia. The bleeding rate with modern cataract surgery is low, but is increased in patients with increased bleeding tendency. Most bleeding, such as subconjunctival hemorrhage or dot hyphema, is clinically insignificant. However, retrobulbar bleeds with serious vision loss do occur, although rarely. As blindness is a serious complication, we would recommend the correction of clotting in these patients, aiming at clotting factor levels between 80–100%.

PO-WE-006
Ageing and quality of life in persons with hemophilia

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Currently, persons with hemophilia are living longer and their life expectancy is reaching almost that of general male population. However, bearing in mind that their health condition will dramatically deteriorate with age, we investigated how these changes affect their everyday life, particularly the level of personal well-being and happiness. We conducted an empirical survey among adults with hemophilia in Croatia (N = 135). The sample was divided into 4 age groups: ≤ 30 years; 31–40 years, 41–50 years, and ≥51 years. Subjective well-being was measured by using the Personal Wellbeing Index – Adult (PWI-A), which measures satisfaction within life domains. The affective component of subjective well-being was examined by using the Happiness Measure from the Fordyce scale. The level of happiness and all domains of subjective well-being in relation to age showed a statistically significant negative correlation. However, the significance was reversed if the influence of disability level and/or movement impairment was excluded. The most significant decrease in well-being and personal happiness level (lowest score in all analyzed domains) was observed among persons with hemophilia in the third age group (41–50 years). The average educational and employment levels in that group were significantly lower than in the previous group (31–40 years), but the degree of disability was significantly higher. These results suggest that aging per se is not a direct predictor of lower levels of personal well-being and happiness, unless it is accompanied by increased movement impairment and a higher degree of disability, which in persons with hemophilia often correlates with age. Moreover, our results show that the third age group is the most vulnerable among persons with hemophilia and requires special attention. In the subsequent analysis, we revealed an objective cause for such finding, and our results clearly emphasize the importance of a prompt and adequate treatment to prevent excessive bleeding that can result in musculoskeletal disorder and an increased level of disability. At the same time, this is a clear indication of the strong need to encourage education among young persons with hemophilia and to orientate them towards professions in which a reduction of the body's motor functions would not significantly limit performance that can lead to loss of employment.

PO-WE-007
Nursing the ageing person with hemophilia: Cardiovascular challenges

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The UK has a higher proportion of older people in its population than ever before. That older population is more likely to experience complex health needs, especially those with chronic disease, placing demands on a health service already under pressure. A literature review showed that with improved factor concentrates and comprehensive care centres coordinating patients' care, people with hemophilia are also living longer with an improved quality of life. With increased life expectancy of hemophilia patients, cardiovascular disease and its management is becoming more frequent in daily practice. Although the reviewed research suggests some protection in atherosclerosis, atheroma has been present. As in the general population, the classic risk factors also apply to those with hemophilia: age, smoking, hypertension, hyperlipidemia, diabetes, and obesity are all of significance. A major role for hemophilia nurses is to include health education strategies, not just for the management of hemophilia but for the prevention of developing cardiovascular disease. When cardiovascular disease develops and interventions are required, management should involve a close liaison between cardiology, hematology, primary care, and the patient; the specialist nurse is usually the consistent person throughout.

PO-WE-008
Newly emerging problems among ageing patients with hemophilia in Japan

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Objective: In Japan almost 40% of patients with hemophilia were infected with HIV through contaminated plasma-derived coagulation factor products. More than 90% of HIV-positive patients with hemophilia have HCV. HAART has been available in Japan since 1996, and the AIDS mortality rate has dropped to a low level as a consequence. Currently, liver disease is the main cause of death in Japan. Advances in both hemophilia and HIV/HCV treatment have led to longer life expectancy and enhancement of the activities of daily living. As the number of elderly patients with hemophilia is increasing, the amount of clinical data is inadequate. We conducted a cohort study of hemophilia patients at our hospital.
Methods: 690 patients with hemophilia are registered in Ogikubo Hospital. Patients born before 1985 were followed up, and the mortality rate and the number of intracranial hemorrhages (ICH) were enumerated. Among patients aged over 20 years, blood pressure measurement and blood tests, including lipids, uric acid, glucose, and renal function, were conducted between January 2009 and January 2013.
Results: The mortality rate of patients with HIV infection was 47/133 (35.3%) from 1985 to 2013. The mortality rate is significantly lower than the rate reported from other developed countries. The mortality rate from liver disease and the incidence of ICH were significantly higher in the HIV- positive group than in the HIV-negative group. Hypertension, hyperlipidemia, decreased renal function, and hyperuricemia were significantly higher in the HIV-positive group than in the HIV-negative group.
Conclusion: Because there are many survivors in the HIV-infected hemophilia population, they face new problems such as ICH or hypertension. As it is not clear what supports are required for elderly patients with hemophilia, it is important to share experiences in caring for these patients.

PO-WE-009
The elderly hemophilia population: A Nordic patient organization prospective

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Background: The number of senior persons with severe and moderate hemophilia is increasing in the Nordic countries, due to better care and treatment. During the last decade this fact has had a big impact on the hemophilia societies, and the situation for the ageing hemophilia population has frequently been discussed whenever the Nordic societies get together. From several perspectives there is a lack of knowledge on how to handle ageing problems that also affect elderly PWH—among the PWH themselves and their relatives, as well as within the medical health care system and social authorities and institutions. In order to address these issues, a 3-year project was begun last year by the Swedish and Norwegian Hemophilia Societies with support from Bayer AB.
Aim of the Project: The aim of the project is to identify new needs of elderly PWH in two Nordic hemophilia societies, in Sweden and Norway, and to further communicate these needs to members, the medical profession, and social authorities in the countries.
Methods: A steering group from each country takes the project forward and communicates results. Yearly gatherings of elderly members in both countries are used as reference groups. The medical needs of elderly PWH are also the subject of cooperation between the Nordic Hemophilia Care within an advisory board. The advisory board will, when needed, serve as medical backup and have access to results from the project.
Results: During the first project year, identified ageing problems of elderly PWH will be communicated through information material and checklists on the needs of elderly PWH—produced in close contact with the medical profession and the local care and social authorities—and a produced Patient Diary to be used in contact with the local care providers. The work of the Nordic hemophilia societies during the years to come will hopefully contribute to a better life for the ageing hemophilia population.

03-CAPACITY BUILDING

S-TH-03.2-2
Working together: Lessons learnt from the Dominican Republic
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The Fundación Apoyo al Hemofílico (FAHEM) is the non-profit association that works toward improving hemophilia care in the Dominican Republic. During its 15 years of helping others, its members have acquired vast knowledge, but the most important has come through sharing experiences with different institutions, some related to hemophilia and others linked with other diseases. This presentation will focus on the major alliances in which FAHEM has participated, will show how to work with other groups, the lessons learned, and the benefits obtained, serving as an example for other associations. One of the first organizations that lent their support was Kelley Communications; it provided the guidelines that helped FAHEM organize as a group. Their support allowed FAHEM to prepare itself to enter to the World Federation of Hemophilia (WFH). As part of the WFH, and through the Twinning Program with the Venezuelan Association of Hemophilia, FAHEM learned how other organizations work and how to lobby with government health departments, as well as how to share information with associations of patients with hemophilia from other countries. WFH has also provided development opportunities through workshops, congresses, and courses. Through an alliance with the HIV patients' group from Robert Reid Cabral Hospital, FAHEM obtained a space in the hospital to build a care center for patients. We are also part of Alianza Latina, an organization of several Latin American institutions working to benefit patients with hematologic diseases. Our most recent experience has been with the association Fundación Solidaria Divino Niño Jesús, which is linked with international organizations such as AmeriCares and the National Cancer Coalition. From them, FAHEM has received large donations of medicines. These alliances have been very helpful because FAHEM has learned and taught others.

S-TH-03.2-1
Working together: Lessons learnt - Example from Italy
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In the last 3 years, as the Board of the Italian Society of Haemophilia Association (FedEmo), we identified the following as the main challenges for the Italian patients' community: to safeguard the same standards of hemophilia care across Italian regions; to guarantee the safety of patients with hemophilia (PWH), especially during acute bleeding and in emergency care; to make young people's and families' needs a top priority in the patient society agenda. We identified as key stakeholders the local chapters, the Italian Association of HTCs Directors (AICE), companies, national and regional institutions, foundations, and we adopted specific policies to govern each relationship. In particular, the adoption of a transparent policy with companies, in accordance with the EFPIA code of conduct, allowed us to launch a successful funding campaign for FedEmo projects. An "accreditation" program for HTCs, "Safe Factor," and "DNA" were the projects promoted by FedEmo in order to address the main priorities in term of needs.The slogan adopted in our vision was building a network between professionals, companies, patient organizations, institutions in order to bring the best value to each individual patient. According to our experience, our success in working together is made possible by a clear definition of roles and commitments, by the capacity of companies to provide financial support together with professional and unconditional expertise, by public recognition, and, finally, by well-defined time management of the projects. In addition, we realized that public-private initiatives and wide partnerships could be advantageous in times of economic recession, allowing the public to provide patient services that otherwise might be cut. On other hand, we were not surprised to find project management in the areas of improvement, since FedEmo is more a volunteer-based than a staff-based organization, and the relationship with medical bodies has suffered by the increase of visibility and pro-active approach of the patient organizations.

S-TU-01.3-3
Youth programs and concepts from an emerging country
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In the work of re-engage and motivate to the youth of our communities of hemophilia, the most important is to identify their needs and find a sustainable way of satisfy them, or give them tools that help in this. It is essential to understand the best as possible the collective for then proceed with efficiency. Additionally it is important to work in create a positive environment, motivating and with the facility of generate activities that exceed the patients association. As first step, is effective establish a base group, the word "team" fits better with the concept of this group. This team should learn all they can about hemophilia so they are well-informed and can even educate others. Is necessary encourage a genuine leadership, committed with the common goals and with the capacity of appreciate the virtues of each one. It is also important for this group of leaders to work as a group. Is useful provide them skills in planning and organization of activities, this is going to make easy do a call or implement a schedule for their activities. When the base group stay in the same tune and they have shared the enough to know the talents and skills of each of their members, will be the moment of develop an activity plan based in the needs of the collective of young people with hemophilia in our communities. When this plan has been developed, will be the moment of prepare the launch and presentation for it. As you know, one of the most attractive elements of a book is his cover. The first impression could be the beginning of a dynamic circle of participation between the potential members.

S-TH-03.2-3
Working together: Lessons learnt from Poland
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The Polish Hemophilia Society (PHS) was founded in 1988. Before 1990, factor VIII use in Poland was never larger than 0.3 IU/capita per year. All patients, unless in an emergency, were treated with cryoprecipitate and fresh frozen plasma. In larger cities plasma-derived factor VIII concentrates started to be used to treat regular bleeds on demand in children around 1993, but home therapy was unavailable. The organization faced a number of challenges at the beginning of its activity, for example, isolation and lack of communication between patients over the country and insufficient recognition as partners in development of care among medical experts. The first successful efforts towards improvement of care reinforced its position and laid a foundation for close cooperation with doctors, as reflected in the establishment of the medical council as an integral body of PHS, comprising experts in bleeding disorders from different Polish treatment centres. This contributed to a sustained, gradual increase in the use of factor concentrates. Later it proved invaluable in efforts for implementation of the National Hemophilia Treatment Program 2005–2011, as well as its continuation for the period of 2012–2018. Major breakthroughs that took place in the meantime—for example, exceeding the factor VIII use of 2.0 IU/capita in 2007 and the introduction of primary prophylaxis for children in 2008—were the result of close collaboration between doctors and patients supported by umbrella organizations. The activity of the national patients' organization is essential to efficiently and accurately voice the needs of patients and thus make a difference in hemophilia care, while its credibility is almost entirely dependent on the support of medical experts.

S-TH-03.2-4
EURORDIS–The European Organisation for Rare Diseases
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EURORDIS, Paris, France

EURORDIS was founded in 1997; today, it brings together over 500 rare diseases patients' organisations across Europe and beyond, including 29 National Alliances of rare disease patients' organisations in Europe and 35 European federations or networks of specific rare diseases such as Haemophilia. EURORDIS' mission is to build a strong pan-european community of patients living with rare diseases and to be their voice at the EU level. EURORDIS' legitimacy stems from its strong membership base to raise awareness of rare diseases, promote basic and clinical research on rare diseases, promote better healthcare organisation for improving access to adequate diagnosis, care and treatment, advocate for adapted social services and integration of people living with rare diseases in the society. It is recognised by European institutions and other stakeholders as the major patient advocacy group in the field of rare disease policies and one of the major health NGO. The presentation will focus on the vision, the strategy, the achievements to make the cause of rare diseases emerge as a public health priority and the people living with rare diseases as a civil society movement while shaping public policy and taking an active part in their implementation.

S-TH-03.2-5
Models from the European Union: DG Sanco
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Health and Consumers General-Directorate (SANCO), Luxembourg

Rare diseases, including those of genetic origin, are defined by the European Union as life-threatening or chronically debilitating diseases which are of such low prevalence (less than 5 people per 10 000) that special combined efforts are needed to address them so as to prevent significant morbidity or perinatal or early mortality or a considerable reduction in an individual's quality of life or socio-economic potential. This definition appeared first in European Union legislation in Regulation (EC) No 141/2000 of 16 December 1999 on orphan medicinal products[1] and extended to the public health field by Commission Communication on Rare Diseases: Europe's challenges[3] of 11 November 2008 and Council Recommendation on an action in the field of rare diseases[4], of 9 June 2009. Thousands of distinct rare diseases exist today (currently 8461 diseases or groups of diseases are described in the Orphanet database), affecting between 6% and 8% of the population in total. In other words, between 27 and 36 million people in the European Union are affected by a rare disease. The specificities of rare diseases - limited number of patients and scarcity of relevant knowledge and expertise - single them out as a unique domain of very high European added-value. There is probably no other area in health where collaboration between 27 different national approaches can be as efficient and effective. This coordination at EU level involves the following steps: 1) making rare diseases more visible by developing proper identification and coding of rare diseases, many of which currently go unrecognised, leading to inappropriate treatment for individuals and lack of appropriate resources overall; 2) encouraging member states to develop national rare diseases plans in their health policies to ensure equal access to prevention, diagnosis, treatment and rehabilitation; 3) providing European support and cooperation, such as ensuring that common policy guidelines are developed and shared everywhere in Europe in specific areas as research, centres of expertise, access to information, orphan medicines and screening. Rare diseases patients have a significantly lower life expectancy. Many are complex, degenerative and chronically debilitating, whilst others are compatible with a normal life - if diagnosed in time and managed and/or treated properly.

S-TU-01.3-2
Keeping youth involved
D. POULIOT
Volunteer from the Canadian Hemophilia Society (CHS)

Objective: Recruiting and retaining youth is critical to ensuring the long-term stability of national member organizations (NMOs), and succession planning should be a top priority. Unfortunately, too often organizations limit their time and energy to reaching out to young people and do not invest the time and effort required to keep them involved.
Implementation strategy: This session will mainly share the Canadian experience. The Canadian Hemophilia Society (CHS) has utilized a variety of strategies to keep youth involved at all levels of the organization, including delegating responsibilities, maintaining regular communication, and offering training opportunities. Several provincial chapters have their own youth groups. In addition to the CHS, which has created a youth ex-officio position on the national Board of Directors, youth are represented on 8 out of 10 CHS provincial Boards of Directors. Ongoing communication to young people with bleeding disorders takes place through regular committee teleconferences, email exchanges, blogs, a youth column in the CHS newsletter, and the youth section of the CHS website. Youth from across Canada are invited to participate in an annual youth conference where they gain leadership skills. They are also encouraged to become actively involved in initiating youth activities in their local chapters. Of course, a key element in all of the youth activities is to have fun! The above strategies have been successful in motivating and developing a new generation of Canadian youth with bleeding disorders that will be prepared to lead the organization in the future.

S-TU-01.3-4
Youth program and concepts from an established country
D. PRADINES
French Hemophilia Society, Paris, France

The objective of the Youth Committee of the French Hemophilia Society is to gather young adults to share experiences, build relationships, and encourage interest for the French Hemophilia Society's activities. The first initiative for youth occurred in 1995, but in the 2000s, the Youth Committee encountered several dormant years. It still existed, but was not lead by young people and only gathered a couple of people once a year, without a long-term strategy. Since 2009, the Youth Committee has seen a renewal, but it has developed quite slowly. I then became responsible for the Youth Committee and have shared this position with my twin sister since 2010. We tried various means of raising the interest of youth for the Committee and the NMO: Social networks, a website, and articles in the NMO journal, summer camps, and a short story contest. We were keen, thinking that this would give a new boost to the Committee. However, our efforts resulted in a situation that was not as successful as expected. Maybe the plan was too ambitious for so short a term, but the strategy to reach youth within the NMO, as well as those who are not associated with the NMO, definitely needs further improvements. Yet it cannot be generalized, and the French example highlights a few concepts on youth from established countries. First of all, it seems that youth who have encountered more difficulties related to the disease are more prone to join the youth programs. In general, however, youth do not feel the need of meeting other people concerned by a bleeding disorder because their everyday life has become almost normal with the new treatments. The youth program should, therefore, emphasize the role of the NMO. It is indeed crucial that youth realize how much the NMO achieves in terms of advocacy, and that it needs "fresh blood" to cope with the coming challenges.

S-TU-01.3-1
Health Quality & Safety Commission New Zealand
D. YORK
Haemophilia Foundation of New Zealand, Christchurch, New Zealand

It is well acknowledged that succession planning is a challenge facing many national member organizations (NMO) of the global bleeding disorders community. Succession planning ensures continuity of the mission and vision of your organization and the opportunity to introduce new ideas to successfully maintain and enhance systems. A key element of succession planning is including, and preparing, the next generation. This session discusses a number of case studies from around the world where hemophilia and related bleeding disorder support organizations are preparing the next generation of leaders to move forward in their organizations and assume responsibility for the future of their NMO.

PO-TU-001
First international Pakistani disabled player with hemophilia
F. AHMED
Pakistan Hemophilia Patient Welfare Society, Lahore, Punjab, Pakistan

In a developing country, it is too hard to live with hemophilia as a healthy person, especially when you are living in a rural area. God bestowed twins upon my parents: my brother and me. We were the youngest among our siblings. My parents were illiterate. Both of us suffered from occasional bleeding episodes. Many old, traditional practices were performed on us, which had a negative impact on our physical condition. At an early age, my parents came to know that their twins had the bleeding disorder called *hemophilia*. No one in the family knew about the severity of the disease, so no emergency action was taken whenever we were injured. But we were restricted in that we could not play as normal children did. This isolated us from the society and was a major cause of discrimination. We were keen on sports and used to play together. Unfortunately, I received a severe injury to my left knee, which led to my disability (shortening of leg). But disability could not defeat my passion. I participated in many provincial and national badminton and cricket championships and won often. Because of my interest, I was provided with opportunity, and I was selected for trials. I qualified and was selected as a badminton player in 9th FESPIC Games in 2006 Malaysia, where I beat India. As I was also a cricketer, I had a chance to try out for cricket and was selected as the first hemophilic player on the Pakistan national disabled team. I have played in many international series (Singapore, Malaysia, Sri Lanka, and UAE) for disabled cricket players and performed well. Now, I am acting as Punjab coordinator of the Pakistan national disabled team as well as the opening batsman of team. As a person with hemophilia and national player, it is my great achievement and I am proud to be a Pakistani person with hemophilia acknowledged in print and electronic media.

PO-TU-002
I, in my elements
M. ANSER
Government of Pakistan, Multan, Pakistan

I am Muhammad Khalid Anser, son of a farmer, born in an economically disintegrated village in Pakistan on August 19, 1984. I have been suffering from severe hemophilia since childhood, when facilities for hemophilia treatment were rare even in Multan, the city nearest to my village. Broken roads, no conveyance, and economic crisis could never defeat the poor farmer's child, and with a low socioeconomic status and inadequate hemophilia treatment facilities, I struggled a lot to get education and treatment. Living below the poverty line, looking my disease in the face, I earned my B.Sc degree with first class and was admitted to Bahauddin Zakaria University, Multan, for an M.Sc in economics. After that I did my M.Phil. in economics from The Islamia University of Bahawalpur with first division. During my whole educational career, I devoted myself to the mission of arranging donors for transfusing the FFP. I qualified in the lectureship competition exams from the Punjab Public Service Commission and am now working as a lecturer in economics, teaching multitudes of poor village boys. Because of my ailment, I feel it is my mission to arrange blood camps for the purpose of transfusing FFP to hemophiliac patients. The patients with hemophilia and their parents are mostly uneducated, and print and electronic media are foreign to them. Generally, patients with hemophilia are overprotected and subjected to seclusion, which makes them socially and educationally disabled. I try to educate them orally about their eclipsed abilities, hemophilia, and its modern treatment. Using my own example, I encourage the hemophiliac families to become productive assets to society and to live healthy lives. Mostly, I am successful in educating hemophiliac patients, who eventually lead normal lives. I have planned to make my socioeconomic research mature for the first time in Pakistan about hemophiliac patients.

PO-TU-003
Multidisciplinary team for treatment of hemophilia, Istanbul experience
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Hemophilia A and B are caused by inherited deficiency in factor VIII and factor IX, respectively. Replacement therapy with deficient factor concentration is required to control bleedings. Despite the available factor concentrates, there are still patients who have severe arthropathies. In this study we want to share and summarize our experience of hemophilia, working as a multidisciplinary council from five different centres in Istanbul consisting of pediatric hematologists, orthopedic surgeons, and specialists in physiotherapy and nuclear medicine. Between June 2003 and December 2011, the council evaluated 150 cases 380 times by means of anamnesis, physical examination, joint X-rays, and MRI. 122 patients were diagnosed with hemophilia A (7 with inhibitors), 19 patients were diagnosed with hemophilia B, and 9 with von Willebrand disease. The council decided to perform arthroscopic synovectomy in 8 cases (1 total) and radiosynovectomy in 45 cases. For 50 patients, physiotherapy, and for 51 cases, secondary prophylaxis was recommended. Psoas hematoma (2 patients), fracture (1 patient), and aseptic necrosis (1 patient) were the other problems diagnosed by the council during evaluations of the patients for their complaints. The comprehensive, multidisciplinary team approach brings hematology, orthopedic, nuclear medicine, and physiotherapy specialists together for the treatment of patients. The main goal of hemophilia treatment is to prevent bleedings and to allow normal integration in social life. Our experience shows that the multidisciplinary team approach and effective coordination are important for optimal treatment of hemophilia patients.

PO-TU-004
Integrating ageing with a bleeding disorder into Canadian Hemophilia Society (CHS) strategies
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Canadian Hemophilia Society, Montreal, QC, Canada

Today, a person with a severe bleeding disorder who has access to advanced care has almost the same life expectancy as someone unaffected. This positive news, however, is accompanied by the increased incidence of ageing illnesses complicated by the underlying bleeding disorder. Since 2010, the Canadian Hemophilia Society (CHS) has undertaken a variety of strategies to identify needs and to develop programs to optimize quality of life of people with bleeding disorders as they age. A survey of Canadian hemophilia treatment centre (HTC) healthcare providers was conducted to determine the information and support needs of health care providers within and outside the HTC setting in dealing with the age-related health complications of people with bleeding disorders. In 2011, the topic "hemophilia and ageing" became a centrepiece of the biennial CHS Medical and Scientific Symposium. Focus group methodologies were used to enable patients to share personal experiences of ageing with a bleeding disorder; identify needs and challenges; and make recommendations for CHS program initiatives to optimize quality of life amid

ageing processes. Educating patients, family members, and HTC healthcare providers was identified as a priority and a new column on ageing, The Sage Page, is now featured in the CHS newsmagazine, *Hemophilia Today*. A first appointment wallet card, Partners in Care, was developed, encouraging specialists and other medical professionals to contact HTCs before undertaking invasive procedures. In 2012, the model for a regional workshop on ageing is being piloted in Ontario and will eventually be implemented across Canada. HTC initiatives include the development of a clinic checklist for use during appointments with older patients and a model for specialized multidisciplinary clinics for 40-plus patients. It is hoped that these and future strategies will optimize the quality of life of people with bleeding disorders in Canada as they age.

PO-TU-005
Development of a model of quality evaluation and improvement within a hemophilia service: Moving from patient involvement through patient participation to patient partnership
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Introduction: It has long been advocated that patient input in service quality development is essential. We have developed a model of quality evaluation and improvement within a comprehensive hemophilia service, and we describe the issues and improvements that resulted from the process.
Methods: The project utilized an action-research methodology. Seven patients were recruited from the hemophilia service for the initial focus groups. The main themes explored were patients' experience of the outpatient, inpatient, and weekend services, and provision of information. The focus group data was analyzed using basic content analysis.
Results: The main themes the initial focus group identified were the need to optimize the annual review, emergency care, and inpatient facilities. Following this, the hemophilia care team worked on improving these issues. At the second focus group, the patients contributed at a higher level—that of patient participation. Patients assisted in addressing outstanding issues such as ID alert-card content and the algorithm of care for emergency services. Finally, a patient panel was developed, and the relationship became one of direct negotiation and partnership with the hemophilia team to address issues within the service.
Conclusion: The expectations and needs of patients attending the hemophilia comprehensive-care service are complex. The process of including patients as partners at the highest level of patient involvement evolved and proved an effective method of service evaluation and development, facilitating lateral decision making, not only improving care directly, but also improving the user experience.

PO-TU-006
The Importance of Multidisciplinary Approach to Patients with Hemophilia
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The modern management understanding foresees team work, as the multidisciplinary approach in the hemophilia. During the formation of the team, it is important to determine the priorities, to take decisions in solving problems and to arrange the relationships between the employees. Team work requires a specifically defined common goal, well established duties and responsibilities, participation of all in decision making, environment of trust, and communication for understanding and support. The team can achieve its goals only by the team members working in harmony, with a common view, courage and compromising. Team work is required to work in harmony, to apply the team strategy and techniques, to learn how to share the roles and the responsibilities, to discover the new ways of thinking and communication and to understand the importance of the individual differences. The obstacles in team work arise from institutional, administrative and employees' individual aspects. A multidisciplinary team work is a work system which establishes a secure atmosphere by improving independency and communication between the individuals in the institution and which ensures persistence of this environment. The team members in the hemophilia unit succeed by deciding the goals, collecting data and defining the problems, as well as by taking decisions together to solve the problems and sharing the responsibilities. Multidisciplinary approach to patients with hemophilia makes it easier for the team members to understand the problems by building their awareness of themselves and others. It is important to motivate the hemophilia team, to seek solutions to the problems without exaggerating them, to learn how to control the feelings, to improve the self-confidence and the respect, and to give credit to the technological communication media, socio-cultural activities, and oral and written communication tools, for the multidisciplinary team work.

PO-TU-007
A recruitment plan for volunteers
N. MCAULEY, F. BRENNAN and B. O MAHONY
Irish Haemophilia Society, Dublin, Ireland

The Irish Haemophilia Society organizes three conferences annually with five separate streams: an adult program and four children's groups. Over the past number of years, attendance has increased, and this increase is projected to continue. Volunteers lead the children's programs at conferences and assist in educating the children on bleeding disorders. Given the increasing attendance and the requirement for a high volunteer-to-attendee ratio for children's activities, the need to expand the volunteer base was apparent. In 2011, the society implemented an ambitious volunteer recruitment plan. Previously, the majority of volunteers were people with hemophilia or siblings. A decision was made to broaden this base. The society took part in a volunteer fair and also targeted recruitment efforts at students studying psychology, childcare, or healthcare. Specific staff members were designated as responsible for volunteer recruitment and training. Presentations were made at the relevant colleges. Once an expression of interest has been made by an individual, they are requested to submit an application form and invited to attend an induction day where they receive information on hemophilia and training in child protection. During this induction, the candidate will also have a one-on-one interview with the child protection officer. In just 6 months, the society has seen an increase of 60% in the number of registered volunteers. The society will continue to recruit new volunteers, but acknowledges the fact that the biggest challenge will be volunteer retention.

PO-TU-008
Canadian Hemophilia Society involvement in Canada's blood system
D. PAGE
Canadian Hemophilia Society, Montreal, Canada

The Canadian Hemophilia Society (CHS) has a long history of involvement in Canada's blood system, a role that expanded greatly following the tainted blood tragedy of the 1980s. The CHS lobbied for creation of the *Commission of Inquiry into the Blood System in Canada* (the Krever Commission) in 1993 and had legal standing throughout the 4 years of the inquiry. Following the publication of the Krever Commission findings, the CHS played an integral role in the creation of the reformed blood system in 1998, operated by Canadian Blood Services (CBS) and Héma-Québec. During the 2000s, the CHS obtained representation on both the CBS and Héma-Québec boards of directors and on many national and provincial blood safety committees. This helped the CHS to develop greater expertise in broader blood policy, raise concerns of the bleeding disorder community at the highest level of decision making, and communicate with recipients during a period in which faith in the blood system was being restored. The CHS served on the national *Selection Advisory Committee* in 1996, 2001, 2008, and 2012 to advise on toll fractionation and selection of factor concentrates for the Canadian marketplace. To report to recipients and the public on progress in reforming the blood system and providing quality service to Canadians, the CHS published *A Report Card on Canada's Blood System* in 1999, 2002, 2004, 2007, and 2010. The CHS provided expertise throughout the 2000s to the WFH Blood Safety, Supply and Availability Committee and participated in all WFH Global Forums. The CHS has sustained this involvement through its own Blood Safety and Supply Committee with over 300 years combined experience in blood system issues. In recent years, however, as the tainted blood tragedy fades in the public mind, the CHS and recipients have lost several key roles in the blood system.

PO-TU-009
Hemophilia as Source of Inspiration
S. RIAZ
Pakistan Hemophilia Patient Welfare Society, Lahore Chapter, Pakistan

Working as volunteer in hemophilia world is great exposure for me. I am hemophilic and suffer bundles of dilemma in my childhood as well as in my youth phase. In developing countries like Pakistan it's too hard to deal with hemophilia. Many subjects regarding treatment, socially and psychologically have to face, which has realistic impacts on practical life. But in terms of mine evaluation, it is tremendous, I was blank and has no education about hemophilia when I was in matriculation; only know that it is just a thinness of my blood and nothing else. But after joining the Pakistan Hemophilia Patients Welfare Society [PHPWS] for better quality treatment, my awareness regarding treatment raised. I was fully guided and sensitized about my bleeding disorder that I have factor IX deficiency "Hemophilia B", and was fully counseled about the disease and the ways to cope with hemophilia. Gradually, I started to take interest in society matters and soon adopted the society as my grooming institute. In fact, it was the real time to prepare myself to become an activist/advocate for hemophilia. Seeing, my interest I was honored as Joint secretary in the Executive Board. As joint secretary, I worked for two years where I learnt a lot from my seniors. Leading from joint secretary to general secretary was golden era for me. During my tenure as general secretary I have organized the Hemophilia Volunteer Youth Group (HVYG). Mainly this group is formulated for peer counseling, delivery of correct information about hemophilia and fund raising activities. Work for hemophilia is my interior satisfaction and innovate new ideas for the betterment of hemophilia community and this is my real capacity building.

PO-TU-010
The establishment of western Kenya's first hemophilia treatment centre
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**Moi Teaching & Referral Hospital, Eldoret, Kenya; †Indiana University School of Medicine, Indianapolis, USA; and ‡Indiana Hemophilia & Thrombosis Center, Inc., Indianapolis, USA*

Background: Kenya, a country of 41 million people, has an estimated 4000 individuals with hemophilia. To date, only 450 have been identified by 2 medical facilities in Nairobi, the capital city. Since 2009, the Indiana Hemophilia & Thrombosis Center, Inc. in the USA has partnered with Indiana University (IU) and Moi Teaching and Referral Hospital (MTRH) in Eldoret, Kenya, to begin a new and western Kenya's first, comprehensive Hemophilia Treatment Centre (HTC). The program is being centered on the following four core services: (1) diagnostic laboratory, (2) treatment modalities, (3) education, and (4) a national hemophilia registry.
Discussion: In 2010, a diagnostic coagulation laboratory was established at MTRH. The laboratory is initially running prothrombin times (PTs), activated partial thromboplastin times (aPTTs), and factor VIII and IX assays utilizing a Diagnostica Stago Start4 machine and reagents. All laboratory equipment was validated, and a 3-day training curriculum and wet workshop was developed and taught by senior laboratory technicians from the University of Colorado at Denver HTC. Local reference ranges for PT and aPTTs were established utilizing 40 normal controls. Modest donations of recombinant and plasma-derived clotting factor concentrates have been procured, and collaboration was forged with the Eldoret Regional Blood Center to improve capacity to manufacture quality-

assured cryoprecipitate and fresh frozen plasma. A three-day hematology symposium was conducted in 2011, with support from the World Federation of Hemophilia; over 200 attendees representing various healthcare professions were in attendance. Content presented included diagnosis, treatment, and pathophysiology of bleeding disorders, as well as training on the comprehensive model of care promoted by the international hemophilia community. Culturally appropriate educational brochures and materials are being developed and translated into Kiswahili. Finally, in collaboration with medical providers and patient advocacy groups in Nairobi, a national hemophilia registry is being developed.

PO-TU-011
Ageing and hemophilia: whose problem is it?
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**The Haemophilia Society, London, UK; and †North Hants Haemophilia Comprehensive Care Centre, Basingstoke, UK*

Reason for Study: The pilot study's aim is to investigate attitudes, beliefs, and self-perceptions on ageing, health and social care needs, and health promotion. This is undertaken with a view to assist health and social care providers and policy developers in the development of a consistent and high-quality health and social care framework for both health and social care systems involved in caring for persons with hemophilia and related bleeding disorders in the UK.
Methods: A focus group session was conducted to explore self-perceptions of ageing and health and social care needs from a group of 18 individuals affected by hemophilia. The 4 main areas discussed included: health promotion, current health care and social needs, changes in health care and social needs in later life, and end-of-life health care and social needs. Qualitative research methods were applied to the analysis of the data collected from the focus group meeting.
Results: Uncertainties were identified regarding solutions to the increasing difficulty of venous access; reduced access to hemophilia centres, due to increasing disability and poor mobility; a decrease in quality of life; and a reluctance to accept dependency on others. These issues were the main concerns of the group. In addition to this, scepticism and fear of a poor knowledge base regarding hemophilia among general health care providers, the community/social care system, and care homes was evident.
Conclusions: The results of this pilot study indicate the need for further research into two main aspects of ageing and hemophilia. Firstly, an in-depth investigation into the beliefs and attitudes concerning health and social needs of the senior hemophilia community across gender, ethnicity, marital status, and geographical location should be undertaken. Secondly, an investigation into different role profiles within hemophilia care should be undertaken, to see which combination of roles would be best suited to provide specialised knowledge and support to non-specialised accredited bodies, care agencies, and informal carers operating in the area of providing care and support to the senior hemophilia community.

PO-TU-012
Prospective and challenges of pediatric hematology at KFSH&RC
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King faisal Hospital & Research Center, Riyadh, Saudi Arabia

Benign and pre-malignant hematologic disorders constitute a major portion of the patient population seen and/or treated at the department of Pediatric Hematology / Oncology. According to the compiled data of the last six years, on the average we are seeing 160 newly diagnosed cases per year. Among these, hemophilia, thalassemia, sickle cell anemia, bone marrow failures, von Willebrand disease (VWD), and nutritional anemia along with thrombosis are quite common. We are presenting our experience of these patients at KFSH&RC for the last six years from 2005 to 2010. We saw a total of 43 cases of hemophilia. Most of these patients were coming from Riyadh region with 53.5% having a positive family history and 35.3% parental consanguinity; 90.7% were hemophila A type having 66.7% severe disease. One-third of the cases presented with post-circumcision bleeding. Major target joints involved were knees (12.8%) followed by elbows (5.8%). We will be presenting our data on the bleeding disorders cases in terms of demographics, signs and symptoms at presentation, treatment offered, complications, and the treatment outcome for the last 6 years from 2005 to 2010.
Conclusion: Benign and pre-malignant hematologic disorders constitute one-third of our newly diagnosed patient population at the department of Pediatric Hematology/Oncology. These patients present from all over the KSA and with their typical complaints. Our data supports the distribution and dynamics of these disorders as quoted in the medical literature from the other countries.

PO-TU-013
Impact of training the trainers in hemophilia care in Pakistan
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**Pak International Medical College, Peshawar, Pakistan; †Hemophilia Treatment Center, Rawalpindi, Pakistan; ‡Rawalpindi Medical College, Rawalpindi, Pakistan; and §PAEC Hospital, Rawalpindi, Pakistan*

Objective: To train a team of master trainers, doctors, nurses, and other paramedical staff to conduct workshops in their areas for self-care among the hemophilia patients and their families.
Methods: Educational workshops were organized in all 4 provincial capitals (Peshawar, Lahore, Karachi, and Quetta), keeping in view the core objective of sustainability of educational and management activities by the transfer of knowledge and skills from the resource team to the local master trainers. Educational booklets were developed in local language and translated into English. Master trainers used the 6 booklets to share knowledge about joint problems and resulting disabilities. The need for specific exercises and physiotherapy to overcome the joint disabilities was also highlighted. The participants were informed about dental complications, which they are prone to suffer. The need for prevention of dental disease was also emphasized. The importance of educating the family, patient, friends, and other persons interacting with the patient was highlighted. The psychosocial pressures and their remedies were also discussed. The details of bleeding disorders affecting women were also passed on to the participants. The participants were given a practical demonstration on factor preparation, ice treatment, suitable exercises for common joints, dental care, the use of transamin capsules, tea bags, the selection of a correct toothbrush, flossing, and correct brushing technique. The baseline knowledge of participants was assessed by a pre- and post-workshop knowledge, attitude and practice (KAP) survey through questionnaire.
Results: 198 care givers were trained. The KAP survey showed improved post-workshop ratings. These workshops were a good learning experience and were accepted as extremely important for continuing awareness and education of hemophilia patients throughout the country.

04-CARE DELIVERY

S-MO-01.2-2
Clinical advancements in the care of patients with inherited bleeding disorders co-infected with HIV and HCV: Promoting health and minimizing side effects
J. KUHN
Virginia Commonwealth University

Primary objective: The aim of this presentation is to highlight the advancements in HIV and HCV care in patients with inherited bleeding disorders and present strategies to assist patients in promoting optimum health in the setting of comprehensive care.
Background: Significant progress has been made in the 30 years of treating people with hemophilia who are co-infected with HCV and HIV. A broad overview of advancements in clinical care will be presented. These profound changes in medical management of co-infected patients have evolved concurrently with the ageing of this population and advancements in hemophilia care.
Summary: Co-infection with HCV and HIV in the population with hemophilia provides challenges to decisions regarding when to start treatment, how to modify clinical care to address side effects and bleeding risks, and what adaptations are needed to promote wellness in an ageing population. Additionally, the dramatic evolution of medical treatment of HCV and HIV has unfolded during the lifespan of these patients, significantly influencing their decisions regarding medical care. Factors influencing these clinical decisions will be discussed. Strategies for monitoring progression of disease, specifically cirrhosis and hepatocellular cancer will be considered.
Author recommendations: The author will provide general recommendations in the light of the comprehensive clinic model to address collaboration with patients and their families in managing treatment of these chronic illnesses.

S-WE-03.3-3
Enhanced communication skills
B. O MAHONY
Irish Haemophilia Society, Dublin, Ireland

National Hemophilia patient organizations have a duty to effectively represent the interests of their members. Effective representation is always predicated on good communication skills and presentation based on knowledge of the data and facts and a command of your brief on behalf of your members. Societies need representatives who are capable of drafting briefing papers setting out their case in both detailed and summary or key-message formats. They need to prepare well for meetings and understand how to deal effectively with health officials, politicians, and the media. These require separate skills and may not all be found in one individual in the organization. Communication and advocacy can vary from education, to advocating with health workers on behalf of individuals, co-ordinating with doctors to positively achieve shared objectives, representing the community on focus groups, committees, and other bodies, or representation on formal or statutory bodies or agencies such as Tender Commissions, National Councils or Blood Authorities. Good communication is essential in all these scenarios, and the core elements are identical. Understand the rationale for the case you are making and support it with compelling data. Be aware of the counter arguments and be prepared to rebut these. Communicate in a non-aggressive or non-adversarial way, but speak with authority and conviction. Be proactive in proposing solutions in addition to highlighting problems. Focus on achieving your organization's objectives, and do not get lost in bureaucratic processes or unnecessary jargon. Prepare well for all meetings, and ensure your representatives have the opportunity to acquire the knowledge, information, and training they require to be effective. Learn from people who communicate well. The case for optimal hemophilia care is compelling. Ensure that your communication reflects this and is equally compelling, well thought out, and effective.

S-MO-01.2-1
Integrating healthcare professionals and patients with hemophilia A/B and HCV/HIV infections
MV. PULIGA, F. SKRLY, A. TERRULI, P. COPPINI, D. CASAROSA and A. ANDRACKA
Clinical Nurses of Haemophilia Care Unit, Careggi Hospital, Florence, Italy

"Our goal is not to transform one into another, but to know one another and learn to see and respect in what he is: the opposite and our completion" (Antoine Marie Roger de Saint-Exupéry). The care of the patient with hemophilia suffering from HIV and HCV is very important for monitoring therapy and for the verification of compliance in order to improve the quality of life of the patient.
Aim of the study: The purpose of this study is to evaluate how the research and best clinical practice have improved the quality of life of the patient.
Methods: In our centre, we have treated about 700 patients with hemophilia A and B, 130 of them have contracted the hepatitis C virus, 50 of these 130 patients have contracted both viruses thus developing a co-infection. The control method consists of having patients return to perform periodic follow-up (every 3 months) of blood tests, ultrasound abdomen, Fibroscan, bone and musculoskeletal evaluation (Pettersson score), and visits to our consultants (infectious disease specialist, orthopedist, rheumatologist, and others). There are many ongoing clinical trials and testing of new drugs (long active factors) that help in the choice of which may be the best antiretroviral drug to be associated in the course of infection. During this phase of the study, patients are given questionnaires assessing the quality of life.
Results: We have obtained very important results, and patients, so far, have been more involved and experienced a greater compliance to therapy, thus improving the quality of life.
Conclusions: We evaluated how this experience may have been positive in all aspects: teamwork has made it possible to improve the health of many patients and has enabled us to form a multidisciplinary team that is able to follow patients with hemophilia to 360°.

S-WE-04.2-5
Emerging country case study: Physiotherapist
A. SABBOUR
Faculty of physical therapy, Cairo University, Egypt

Without replacement therapy, patients with severe hemophilia (PWH) will have 5 damaged joints by the age of 20, which will limit activities and prevent normal participation in society. As described in this presentation, a conservative, non-operative physiotherapeutic regime for the management of patients suffering from hemophilia limited a comprehensive care team in an emerging country with limited or no factor. Three cases describe the rapid development and progression of the complications affecting the musculoskeletal system (acute hemarthrosis, chronic synovitis, and arthropathy) and the role of physical therapy in dealing with such problems. The aims of hemophilia physical therapy are to relieve pain and sensory disturbances, help the reabsorption hemorrhagic and inflammatory process, improve physical condition and quality of life, and prevent and treat injuries. The techniques used are also diverse and range from exercise sports for patients without lesions, kinesitherapy techniques, thermotherapy, electrotherapy, magnetic therapy, laser therapy, hydrotherapy, ultrasound, and orthotics and shoe adaptations. But lacking a comprehensive care team, the physiotherapist has to work not only as a therapist but also as a teacher and trainer for patients, families, and society in dealing with and solving these problems.

S-WE-03.3-4
Toolbox: Rules of thumb
C. SAFADI MÁRQUEZ
Fundación de da Hemofilia, Buenos Aires, Argentina

The aim of this presentation is to understand how a national hemophilia organization meets one of its main duties: To represent the interests of patients. This requires an analysis of internal and external behaviour of the organization as it defends the interests of the community. Therefore, the organization developed each of these points: The organization in its "outside" behaviour must 1) create a stable presence at the government in all the branches; 2) keep a high profile in society; 3) maintain daily contact with physicians; and 4) maintain a proper relationship with the pharmaceutical industry. In the organization's internal work, it should: 1) create adequate channels of patient involvement in the organization; and 2) convey the sense of "being heard" to the patient community. Probably the most important point is the effectiveness in the exercise of lobbying on behalf of patients. The lobby is not influence-peddling but requires specific techniques to be successful. As Napoleon said, ten people talking make more noise than ten thousand in silence, so the presence of patient organizations in places of decision making is the best way to protect the interests of people with hemophilia.

S-WE-03.3-1
Patients: Members of the Care Team
D. SILVA
Spanish Federation of Hemophilia, Madrid, Spain

Being a member of any kind of team primarily involves PARTICIPATION. And participation involves the process of decision making and thus responsibility. It is an awareness that contributes to peoples' empowerment which leads to action. Patient participation is a vital partnership for the team involved in medical and psychosocial care. Patients are aware of their problems and they have to participate in finding its solution. This gives them motivation and it involves them in an essential way as part of the comprehensive care scheduled by health professionals. This is the point in the hemophilia field. This participation should be developed in two ways: within the care team and also within the patients' associations. At the same time, these associations should be involved at other levels: in the health field (with care teams and health authorities, e.g., doctors, hospitals) as well as in the political field (advocating with health policy makers). This is a lifetime learning process: getting to know how to participate gradually in order to create a culture of participation. If patients are empowered, involved, and committed to their own treatment, they will become agents capable of transforming their reality to improve it. Learning this at an early age will be of great benefit to other aspects of their lives. We should, therefore, encourage such practices among the bleeding disorders community, as it will be beneficial for these patients and their families as well as the patients' organizations and society in general. Just as modern and advanced societies require responsible and involved citizens to maintain or increase the common welfare, the care teams need responsible and involved patients for success in comprehensive care.

FP-MO-01.4-4
Pregnancy and successful delivery of patients with FXIII deficiency on prophylaxis in Iran: A report of 17 cases
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Background: For prevention of abortion and pregnancy loss in severely FXIII-deficient women, replacement and prophylaxis with a source of FXIII throughout pregnancy is essential. The aim of this study was to evaluate the bleeding score and rate of successful delivery in Iranian FXIII- deficient pregnant women on regular prophylaxis.
Materials and Methods: A total of 17 FXIII- deficient Iranian women with an age range of 18–35 years old (mean 24 years old) were enrolled in this study. All patients had a history of previous abortion, except 1 patient. All of the patients were on regular prophylaxis for a period of 24–62 months (10 IU kg^{-1}, every 4 weeks before pregnancy and every 2 weeks during pregnancy). The patients were followed up for any bleeding episodes and also evaluated for bleeding score before and after prophylaxis according to standard form.
Results: The monochloroacetic acid test and 5M urea test was normal in all patients after starting prophylaxis. The bleeding score was significantly decreased from 11–16 (12 ± 1.5) to 2–3 (mean 2.2 ± 0.4) after starting prophylaxis. ($P < 0.001$) 13 minor bleeding episodes were recorded in patients during prophylaxis. All of the patients had successful delivery at 36 weeks gestation without any significant coagulation complications during or after delivery.
Discussion: In this study we experienced a successful pregnancy maintenance and delivery in Iranian women with FXIII deficiency. It is recommended to precise detection and diagnosis of FXIII deficiency in women with coagulation disorders for appropriate prophylaxis and prevention of pregnancy loss.
Key Words: FXIII deficiency, abortion, delivery, bleeding score, Iran

PO-MO-009
Patients' opinion surveys are necessary to assess the quality of the organization of a health facility
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The French national plan on rare diseases identified reference centres on several rare diseases (including von Willebrand disease) to improve the overall clinical management of patients. Five years after their certification, these centres were evaluated by a national health authority according to various criteria. One of them was the assessment of the opinions of the patients about the organization of the centres. Thus the VWD reference centre implemented in 2011 a survey on the patients' opinion about the conditions of their visit in the centre. The survey focused on the admission conditions, communication with the staff, good understanding of the information, confidentiality, waiting time, and hospital facilities. A questionnaire was posted to 1032 patients with VWD who had come in the last 5 years to 3 of the reference centre sites (Lille, Nantes, Paris-Clamart) for routine clinics. Responses were anonymous. The response rate was 48%, and 495 questionnaires were analysed by the Quality Unit of the Hospital of Lille. Of those who completed the questionnaire, 70% were the patients themselves and 30% were the parents of children (mean age: 10 years). Half of the patients lived at a distance of 31–100 kms from to the centre. Regarding the overall satisfaction, about 43% were very satisfied, 51% satisfied, 3% somewhat dissatisfied, and 2% very dissatisfied. The main reason for dissatisfaction was related to the waiting time before being seen by the physician or by the nurse before blood sampling or to the delay in receiving the clinic's written record. Interestingly, 15% of patients who were seen in the company of an accompanying person would have preferred to be seen individually.This type of survey allows the entire centre staff (physicians, nurses, secretaries) to identify areas for improving the quality of visits of patients.

PO-MO-010
Getting the most from hemophilia patient home infusion records . . . is there an app for that?
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Background: A major focus of the hemophilia treatment centre (HTC) is supporting hemophilia patients' autonomy in preventing and quickly managing bleeding episodes. In partnership with patients and their families, HTCs negotiate individualized home infusion protocols. A significant challenge is how to evaluate the effectiveness of the home infusion program for each patient. One tool that provides data for this purpose is the home infusion record. Records take many forms, paper or electronic, and some patients choose not to record their infusions. While having no infusion data is challenging, the authors assert that having detailed home infusion data also presents significant challenges in the evaluation of home infusion effectiveness.
Objective: To address the challenge of managing and analyzing home infusion records, the authors are developing a software solution that translates data into accessible, manageable, and understandable graphic displays.
Method: HTC team members identified several data points that were not readily accessible with the current infusion data format. Excel software was employed to create graphic displays to present individual and aggregate clinic infusion data in relation to these data points.
Results: Patient infusion records are transformed into a single-page summary of several data points that are easily stratified into specific time frames (week, month, year). Hemophilia care providers and patients quickly recognize patterns, which promotes increased collaboration on effective bleed prevention and management.
Conclusion: This approach to the analysis and display of home infusion data promotes communication between patients and the care team, and provides a fuller picture of treatment adherence and effectiveness. The authors plan to develop a full application compatible with common operating systems and devices.

PO-MO-011
New treatment tender: change management challenges in rural and remote communities
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In June 2011, the National Blood Authority in Australia announced the result of its tender for the supply of recombinant factor VIII (rFVIII) products, resulting in a change from one major supplier to another. In Australia, this is the first time a widely-used product has been withdrawn from the market. In the state of Queensland, it has been necessary for around 80% of patients with hemophilia A to switch to a new FVIII product within a 12-month deadline. Staff at the Queensland Haemophilia Centre faced some unique challenges with rural and remote communities. The state of Queensland covers 1.7 million square kilometres, around 3 times the size of France. Based in Brisbane city, the Queensland Haemophilia Centre staff (Royal Brisbane and Women's Hospital) in conjunction with the Royal Children's Hospital, have assisted the transition of product for patients located in far reaches of the state through means of outreach clinics, education days, telehealth clinics, email, phone, and mailouts. This poster outlines the activities of the staff during this time, adopting the popular ADKAR model for change management (Awareness, Desire, Knowledge, Ability, and Reinforcement). This model has helped staff to identify goals for patient education and awareness of new products. It has provided a focus for the treating team to support and engage with rural and remote families, therefore reducing barriers to change. It has helped identify and assist other key parties such as outlying hospital pharmacies, general practitioners, emergency departments, and outpatient treatment centres. Nurses and the data manager have also been able to stocktake and coordinate the usage of all residual FVIII stock in regional centres, ensuring no wastage of this precious resource during the transition period.

PO-MO-012
A current assessment of severe hemophilia A patient care in Latin America
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Introduction: While the quality of hemophilia care in Latin America (LA) has improved in recent years, there may still be opportunities to further improve treatment in this region. The purpose of this analysis was to evaluate current trends in severe hemophilia A care and patient outcomes for 4 countries in LA.
Methods: A cross-sectional survey of severe hemophilia A patients ≥18 or older, or the parent/caregiver of patients aged 2–17 was administered in collaboration with hemophilia associations in Argentina, Chile, Colombia, and Mexico. Patients meeting inclusion criteria who consented to participate completed the questionnaire in two phases: from October to November 2009 (Argentina) and June to August 2011 (Chile, Colombia, Mexico). Patients were asked about their hemophilia treatment and outcomes, including treatment regimen, annual bleeds rates (ABR), target joints, and quality of life (QOL).
Results: 460 severe hemophilia A patients participated in this study, of whom 58% were adults. The median age for adults was 31 years, and 9 years for children. Overall, 207 (45%) patients were either on primary (10%, PP), or secondary (35%, SP) prophylaxis. Of those on prophylaxis, only 33% were dosing at the MASAC-recommended amount and frequency (25–40 IU kg^{-1}, 3 times weekly). The majority of patients were on plasma-derived FVIII therapy (67%), while 31% were on recombinant, and 7% on cryoprecipitate. Only patients in Mexico and Argentina reported being on cryoprecipitate. The median ABR (total bleeds) differed significantly between primary prophylaxis, secondary prophylaxis, and on-demand (5, 12, and 25 bleeds, respectively [$P < .0001$]) demonstrating the benefits of prophylaxis overall for these patients. Similar trends for joint bleed rates and target joints were also observed.
Conclusions: Based on these results, hemophilia care in this region appears to differ from MASAC-recommended care. Further assessment of how to improve care for severe hemophilia A in the LA region appears warranted.

PO-MO-013
Patients with hemophilia and emergency department care
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Although therapeutic education has improved the daily life of patients with hemophilia, some situations might require patients with severe or with moderate hemophilia and severe phenotype to go to the local emergency department. This procedure normally is a source of stress for the child and the family. To facilitate the communication between the patient's family and the emergency department health professionals who may have little experience in the domain of coagulation, we have produced the following 4 documents: (1) a brochure for the patient's family, with a summary of the main information to give

to the emergency department health professionals; (2) a brochure for the emergency department physicians concerning the priority procedures and things to be avoided when caring for a patient with hemophilia; (3) a brochure for the emergency department nurses; and (4) a passport to be filled in by the nurse with the information on what has been done at the emergency department and to be put in the health record of the patient with hemophilia. The objective of these documents is to improve the quality of the admission procedure and treatment of patients with hemophilia as well as the traceability of the clotting factor replacement products that were injected.

PO-MO-014
The European Haemophilia Network (EUHANET) Project
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The European Haemophilia Network (EUHANET) is a new project funded in 2012 by the European Union. It is a collaborative project between the Universities of Sheffield, Utrecht, and Milan, together with the European Haemophilia Consortium (EHC), European Haemophilia and Allied Disorders organisation (EAHAD), and MDSAS (UK IT centre). The aim is to bring different hemophilia activities together and will cover the following main areas: Will develop the standardized criteria for quality of care for designation of expert and standard hemophilia centres. Centres will be able to apply for certification into European level 1 (expert) and level 2 (non-expert) centres. A hemophilia central website will provide, in one location, all the relevant information sites. Among activities to be found here will be a list of all hemophilia centres in Europe, a mobile phone application that will locate the nearest centre, information about all inherited bleeding disorders, cumulative results from the EUHASS project, a news service and a question-and-answer service. Centres will also be invited to try HAEMTRACK, an information system whereby patients record their home treatments online and this is visible to their hemophilia centre. The European Haemophilia Safety Surveillance project (EUHASS) will be expanded to cover serious platelet disorders and acquired hemophilia. It will also record data on unexpected poor efficacy of concentrate treatment. The rare diseases database will start collecting prospective data in patients with fibrinogen and FXIII deficiency. All European centres (whatever the size) caring for persons with hemophilia are invited to participate in this project.

PO-MO-015
Smart Medication - a new telemetric smartphone application for monitoring and evaluation of hemophilia home treatment
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Background: Hemophilia A and B are rare diseases and require medical care in specialized treatment centers. Because of long distances between patients and hemophilia center, telemedicine may be helpful to bring the right patient to the right doctor. Bleeding or treatment problems, usually reported during consultation at the hemophilia center, may be identified earlier and close to when they occur. Automated documentation and online analysis of the data is less time consuming and helps to avoid documentation errors.
Method: A new telemetric system for documentation of home treatment, based on Google's Android and Apple's iOS, called "smart medication" was developed in collaboration with IT-experts of Philipps-University, Marburg, Germany. The application was built for real-time surveillance of treatment and bleeding episodes and online analysis of the transmitted data. It consists of three components: 1. A patient based smartphone for simple and rapid entry of relevant treatment and bleeding data. It can also be used as an emergency phone, for sending written messages and photographs or to inform about hospitalization. Unusual and frequent bleeding or treatment patterns generate immediate alerts to the hemophilia center. 2. A smartphone at the hemophilia center front desk for easy medication management. Concentrates given to the patient are assigned to the patient's electronic file allowing early identification of out-of-stock, non-documentation problems, and a complete backtracking. 3. A web based monitoring tool at the hemophilia center for online surveillance and analysis of treatment and bleeding patterns and control of medication management. So far, 30 Patients with severe hemophilia A or B from two German Hemophilia centers were allocated. Practical experiences and results from statistical tools will be presented.
Summary: Smart medication is a new smart phone based tool for monitoring and evaluation of treatment and bleeding in hemophilia home care. First real time experiences and results from analysis tools will be presented.

PO-MO-016
Patient organisation involvement in management of hepatitis C
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In Ireland, there are 145 persons with hemophilia who have hepatitis C. A further 104 have died of HIV or hepatitis C, of whom 67 were co-infected. An increased incidence of cirrhosis, hepatocellular carcinoma and requirement for liver transplant have now become apparent. The Irish Haemophilia Society has prioritized the provision of information, education, and assistance to members who require or are contemplating treatment. An individual phone survey was carried out on the hepatitis C genotype of members. Provision of tests for the genetic markers IL28B and KIR-2DS3 were coordinated with the treatment centres. Meetings were organized in 2 cities to provide information on the new treatments available for genotype 1. The first in a planned series of specific newsletters on hepatitis C was produced. The society has worked with the health authorities to arrange for assessments of each individual's requirements and the provision of assistance required during treatment, including counselling, assistance with domestic work, and transport. The society provides financial assistance and accommodation for members with hepatitis C with mobility difficulties or severe side effects from treatment who have to travel to the treatment centres frequently for treatment monitoring. Our objective is to ensure that all those with genotype 1 who could avail themselves of treatment are aware of the new therapies, actively consider treatment, and receive all the support necessary to enable them to comply with the treatment regime and hopefully achieve a sustained virological response.

PO-MO-017
MUOVIAMOCI (Italian Musculoskeletal Global Project)
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We present the Italian Musculoskeletal Global Project, an initiative sustained by Paracelso Foundation and conducted by Angelo Bianchi Bonomi Hemophilia and Thrombosis Center of Milan. The main aim of this 3-year project is to provide medical assistance to those patients who have not routinely had global musculoskeletal evaluation (as foreseen in the frame of a regular follow-up schedule). An orthopedic surgeon and a physiotherapist will arrange a time to visit patients at involved hemophilia centres across Italy. The project will address general and specific aspects. General aspects will concern information on musculoskeletal status, need for rehabilitation, and indication for major orthopedic surgery. Specific aspects will focus on the results of surgery and rehabilitation programs. All this information will be included in an Italian Registry of Major Orthopedic Surgery (IREMOS).

PO-MO-018
Fostering collaboration in hemophilia care
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The effectiveness of a multidisciplinary approach to hemophilia care has been well established in hemophilia treatment centres around the world. Patients with bleeding disorders have unique and complex needs which are best addressed by a team of experts working in cooperation. For treatment centres in the developing world, creation of a collaborative multidisciplinary team has been shown to be an important factor in improving outcomes for patients with hemophilia. Health care in India is divided among various centers, including autonomous institutions such as academic healthcare facilities, private hospitals, government-funded centres, and non-governmental organizations (NGOs). Patients with hemophilia may need to visit several facilities to access the medical and support services that they require. Hemophilia Society [Delhi] (HSD) started providing comprehensive care as an NGO in 1987, when such treatment was not otherwise available in Delhi. For the past 3 years, government centres have provided factor replacement therapy, free of cost, under specific conditions. Financially, HSD is unable to provide this, but continues to offer consultation, counselling, laboratory support, and physiotherapy. The situation seems complementary, but this complicated provision of care can be confusing for patients and families, and may lead to critical gaps in the effective management of the acute and chronic issues these patients face. Through the World Federation of Hemophilia Twinning partnership between Delhi, India and Winnipeg, Canada, we are attempting to address and streamline this complex process. With the input from key representatives of the different institutions, we can identify the unique services that are available from each centre. In cooperation with local government to address the infrastructural issues, we hope to be able to encourage the development of a collaborative network within Delhi for hemophilia care. Ultimately, this will enhance care available to persons with hemophilia throughout Delhi, and can become a model for other developing programs.

05-CARRIERS AND PRENATAL ISSUES

FP-MO-01.1-4
Tosetto bleeding score and factor VIII or IX levels in hemophilia carriers
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Background: Hemophilia carriers may have reduced FVIII/IX levels. It is important to establish the type and severity of bleeding symptoms that they experience in order to provide adequate care for this group. The aim of this study was to investigate the association between FVIII/FIX plasma concentration and the severity of bleeding in carriers of hemophilia.
Objective and Methods: In this observational cross-sectional study, we sent the standardized version of the Tosetto Bleeding Score to 179 carriers with documented FVIII/FIX plasma levels at the Hemophilia Treatment Center-Academic Medical Center (HTC-AMC). We report on the first 98 questionnaires that were returned. For the Tosetto Bleeding Score (range -3 to 45), a bleeding score (BS) of ≥4 was considered a clinically relevant bleeding tendency.
Results: The respondents proved representative of the total group (FVIII/FIX range 0.01–2.00 IU ml^{-1}), as their FVIII/FIX plasma concentrations and the proportion with FVIII/FIX plasma concentrations <0.40 IU mL^{-1} were similar (respectively median=0.74 IU ml^{-1} and 14% <0.40 IU mL^{-1} vs. median=0.74 IU mL^{-1} and 15% <0.40 IU mL^{-1}). The study group had a median BS of 1 (range -3 to 14) and a mean age of 40 years. Fourteen of 98 (14%) carriers had a factor VIII/IX level <0.40 IU mL^{-1} with a median of 0.34 IU mL^{-1} (range 0.27-0.38). The median BS in this group with FVIII/IX <0.40 U mL^{-1} was 3.5 (range -2 to 12) vs. 1.0 (range -3 to 14) in the group with FVIII/IX >0.40 IU mL^{-1}. A BS ≥4 was present in half of the group with clotting levels <0.40 IU mL^{-1} and in 31% of the group with FVIII/IX ≥40 IU mL^{-1}.
Conclusion: Fifteen percent of the carriers can be considered as mild hemophilia patients. Although the median BS in carriers with low FVIII/IX level is higher compared to the group with normal plasma concentrations, the reported high BS (31%) in carriers with normal plasma concentrations remains unexplained.

PO-MO-19
Mild hemophilia may hide severe hemophilia
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Hemophilia B is an X-linked coagulation disorder caused by a wide range of mutations in the factor IX (F9) gene. Identification of the causative mutation is not necessary for the diagnosis of the disease but is essential for genetic counselling. We report on the case of a male mild hemophilia B patient (FIX:C=7%) who has no family history of the disorder and where the gene mutation studies have modified the characteristics of the disease from mild to severe. We identified in this patient a new mutation on exon 8 g.30925-30926delTGinsA. This mutation must be considered as associated with severe hemophilia and cannot explain the mild phenotype of the patient. This mutation was identified at a heterozygous state, while the hemizygous state is expected in a male, suggesting various hypotheses: (1) Klinefelter syndrome, (2) chromosome X isodisomy, or (3) F9 gene duplication. All these hypotheses being eliminated, we conclude an exceptional mosaicism in this patient. This is of particular significance for genetic counselling, since this patient has 2 daughters who were first reassured because of the mild form of their father's disease but now have to be considered as carriers of severe hemophilia and at risk of having affected male children with the severe form. About one third of hemophilia cases are due to a de novo mutation. The majority are thought to occur in a single germ cell but some, occurring during early embryogenesis, produce a germline and/or somatic mosaic. In hemophilia, somatic mosaicism has been generally observed in women and seems to represent a fairly common event, while it is exceptional in men. Assessment of mosaicism in mothers of apparently isolated cases is now part of genetic counselling. It is important now to take this risk into account in men, and it underlines the importance of identifying the mutation in patients.

PO-MO-20
Pregnancy outcome in hemophilia A carriers over a 5-year period in a U.K. hemophilia comprehensive care centre (CCC)
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Pregnancy outcomes in known carriers of hemophilia A (HemA) managed by our multidisciplinary team were retrospectively reviewed. Over a 5-year period, 28 pregnancies occurred in 21 carriers (5 moderate and 16 severe HemA). All the women had a normal factor VIII level confirmed and fetal sexing prior to delivery. Two women had postpartum hemorrhage: 600 ml and 800 ml. In the 16 severe HemA carriers, there were 21 pregnancies and 11 male fetuses, 10 confirmed on USS and one unaffected male identified by chorionic villus biopsy. Normal vaginal delivery occurred in 8 of the 10, 1 forceps delivery and 1 caesarean section. Six of the 10 boys were affected with severe hemophilia A. Nine out of 10 deliveries occurred in the CCC hospital; one women refused and delivered in her local hospital. Following a forceps delivery, the baby and mother were transferred to the CCC. The mother had no complications, but the baby developed a cephalohematoma and was confirmed to be affected with severe HemA. He received a single treatment of recombinant FVIII (rFVIII) treatment; USS imaging found no evidence of intracranial hemorrhage. All affected boys received vitamin K (5 orally and 3 IV). Of the12 female babies, 1 girl is a compound heterozygote with moderate HemA (father mild HemA, mother carrier severe HemA). No routine USSs of the head were undertaken and no ICH developed in the series during the neonatal period. During the 5-year period, 3 children were born and subsequently diagnosed with severe HemA with no family history (1 girl [with factor VIII<1% due to 100% lyonization) and 2 boys). The 2011 UKHCDO guidelines on management of hemophilia in the fetus and neonate were followed, with the exception of routine cranial USS. No significant complications were seen.

PO-MO-21
Experience in prenatal diagnosis for hemophilia at Castelfranco Veneto, Italy
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Families with hemophilia A (HemA) and B (HemB) require genetic counselling to determine the carrier status in females at risk of transmitting the disease, and prenatal diagnosis (PND) in case of pregnancy. In our centre, 271 out of 496 and 180 out of 258 females were found to be carriers for HemA and HemB respectively, by molecular F8 and F9 gene analysis. As stated by the Italian Association of Haemophilia Centres (AICE), PND is offered only in severe cases. To date, 93 instances of prenatal counselling were required. The conventional prenatal diagnosis of hemophilia involves sampling cells of fetal origin by amniocentesis or chorionic villus sampling (CVS). Genomic DNA was used for sex determination, using specific primers for single-copy amelogenin-encoding gene (AMD), mapping both on the X and the Y chromosomes. In male fetuses, the mutation detection was performed by long-distance PCR for F8 gene inversion involving intron 22 and 1, or PCR followed by CSGE screening, or direct sequencing of the previously identified mutated F8 or F9 gene fragment. In 12 cases, DNA was not analyzed because of miscarriage, and 81 PND were performed: 54 for HemA and 27 for HemB, on 64 severe hemophilia carrier women. In 12 cases, female fetal gender determination was obtained from caryotypic or maternal peripheral blood analysis and no further investigation was needed. Gender sex determination was done for 81 fetal samples and we found 38 female fetuses (47%) and 43 male fetuses (53%). Among the male fetuses for which we carried on with molecular analysis, 22 were affected and 21 were not affected (27% and 26% respectively). Molecular investigation in hemophilia has made PND in carrier females possible, making feasible a reproductive choice for parents. If the familial mutation and the carrier testing information are already at hand before pregnancy, the subsequent PND is generally complete in 2 to 4 days starting from the CVS, in order to give the pregnant women the genetic analysis results as soon as possible.

PO-MO-22
Awareness of carrier status as a result of genetic counselling improves hemophilia patient care
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Background: Morbidity and mortality in children with hemophilia can be prevented by early diagnosis. As up to 70% of patients with hemophilia have a positive family history, identification of hemophilia carriers is important. In order to create awareness of carrier status, active genetic counselling has been available at the Academic Medical Center-Hemophilia Treatment Center (AMC-HTC) since 2005. Active genetic counselling includes (1) identification of potential carriers by pedigree analysis, (2) a letter of invitation for genetic counselling by a genetic specialist, and (3) DNA analysis and clotting factor analysis.
Objective and Methods: To evaluate the effect of active genetic counselling, the time of diagnosis and patient treatment history were retrieved for all new pediatric hemophilia patients at the AMC-HTC between 2005 and 2012 (actual cohort). The collected data were compared with the results of a similar study undertaken at the AMC-HTC in 2002 with hemophilia patients born between 1990 and 2002 (historic cohort).
Results: In the historic cohort of the AMC-HTC, 16 of 52 mothers (31%) were not aware of their carrier status during pregnancy. In 4 hemophilia patients (25%), a life-threatening iatrogenic bleeding was observed. In the actual cohort, 26 children with hemophilia were diagnosed, 8 sporadic cases and 18 with a positive family history (69%). Almost 90% of the mothers with a positive family history received genetic counselling before pregnancy. Due to perinatal preventive measures no (iatrogenic) bleeding was observed in the neonatal period of the patients. The 2 remaining children with mild hemophilia were diagnosed at the ages of 2 and 4 years, after major bleeding complications (post-operative and traumatic gum bleeding). Retrospectively, both family histories proved positive for hemophilia in the third grade.
Conclusion: Active genetic counselling increases awareness of carrier status. Awareness of carrier status reduces perinatal and life-threatening hemophilia bleeding complications.

06-CLINICAL ASPECTS

S-TH-01.1-3
Observational studies and health-technology assessment (HTA)
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In an ongoing HTA of hemophilia treatment in Sweden, performed by the governmental agency Dental and Pharmaceutical Benefits Agency (TLV), the Swedish Council on Health Technology Assessment (SBU) was called upon to evaluate the treatment of hemophilia A and B and von Willebrand disease (VWD) with clotting factor concentrates. A full systematic review was performed. The aim was to perform an assessment of treatment with factor replacement therapy, including long-term prophylaxis and surgery, as well as inhibitor treatment with immune tolerance induction and bypass therapy. The overriding questions were (1) What are the short-term and long-term effects of different treatment strategies?, and (2) What methods are available to treat patients with hemophilia who have developed inhibitors against factor concentrates? The review showed that the scientific evidence is insufficient to determine whether there are differences in effects between different dosing strategies in replacement therapy with coagulation factor concentrates. Results from one randomized trial, supported by results from several non-randomized studies, suggest fewer joint bleeds and fewer major bleeds in prophylactic replacement therapy compared to on-demand treatment. Furthermore, in patients with severe hemophilia, regular administration of factor VIII starting from early childhood, before the onset of joint bleeds, has protective effects against joint damage. We conclude that treatment of congenital bleeding disorders with factor replacement is costly, and studies comparing different regimens are difficult to perform with high scientific precision, as the disorders are rare and outcomes need to be assessed longitudinally over many years. Therefore, long-term observational studies rather than randomized clinical trials should guide the development of treatment regimens.

S-TH-01.1-2
Definitions in hemophilia – Project Group of the Factor VIII/IX Subcommittee of the International Society on Thrombosis and Haemostasis (ISTH)
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Assessment and care of persons with hemophilia varies widely between countries, ranging from limited facilities for accurate diagnosis and access to care to the ability to accurately determine the gene mutations causing hemophilia and unlimited access to safe virus-inactivated plasma-derived or recombinant factor VIII and IX concentrates. The greatest barrier to optimal hemophilia care is cost. Safe factor concentrates are extremely expensive, reflecting, at least in part, the high cost of developing such products. In addition, the necessary, but onerous, requirements for prelicensure testing of such products required by regulatory authorities impose challenges to the hemophilia community. These challenges are currently at an all-time high, since a number of manufacturers of factor VIII and IX concentrates are initiating prelicensure clinical trials of novel factor concentrates, including long-acting factor VIII and IX products. Against this background, the ISTH factor VIII/IX Subcommittee commissioned a project group to address the complex issue of standardized definitions for use in assessment and care of persons with hemophilia. Items considered by the Definitions in Hemophilia Project Group included severity of hemophilia (mild, moderate, and severe); cut-off for presence of an inhibitor; joint/muscle bleeds; target joint; primary and secondary prophylaxis and response to treatment. Although their task is difficult because of lack of evidence for many items, the project group has established consensus definitions that will be presented. These definitions will facilitate the comparison of results for different factor concentrates obtained as part of pre–clinical licensure trials of new products, and post marketing surveillance or investigator-led prospective clinical studies.

S-TH-01.1-1
Optimizing clinical trial design for product development in hemophilia
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The Design of Clinical Trials in Hemophilia Project Group (PG) is a project group of the SSC Factor VIII/IX Subcommittee of the International Society of Thrombosis and Hemostasis (ISTH). The concept for this PG, which began its deliberations in February 2011, was proposed by Professors Flora Peyvandi and Alok Srivastava to initiate a focused discussion of the recruitment difficulties anticipated from the simultaneous conduct of relatively large new product trials in hemophilia A and B, both rare diseases. The mission of this PG is to evaluate the current requirements for preregistration clinical trial design, and to make evidenced-based recommendations to the FVII/IX Subcommittee and to the wide hemophilia constituency for the optimal design of prospective prelicensure and observational postlicensure new product trials in hemophilia on the basis of (1) the harmonized safety and efficacy data required by regulators for registration, (2) the availability of clinical trial subjects, and (3) innovative clinical trial design strategies. This is being accomplished by using consensus definitions (provided to the group by the Definitions Project), as well as guidance from regulators in the US and Europe; industry, scientific, and methodological experts; as well as clinical investigators. This PG's efforts will be further harmonized as appropriate with those being initiated through the WFH. It is anticipated that this work will be ongoing for a period of at least 2 years, after which its conclusions and recommendations will be submitted to the SSC as a communication. An update of the Project Group's activities will be presented by its Chair on behalf of the entire membership: Flora Peyvandi, Alok Srivastava, Nisha Jain (FDA); Anneliese Hilger (EMA); Sebastien Lacroix- Desmazes; Frits Rosendaal and John Scott (FDA).

FP-MO-04.4-1
Clinical presentation and management of adult patients responding to the Hemophilia Experiences Results Opportunities (HERO) study
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Objectives: To describe treatment characteristics of patients with hemophilia A, B, or inhibitors (HwI).
Methods: The HERO web survey was conducted in 10 countries, targeting 600 patients ≥age 18.
Results: The 592 patients reported on average 2.4/18.3 bleeds in the past month/year. Most were hemarthroses (ankle/knee/elbow). Patients visited hemophilia treatment centres (HTCs) on average 4.3 times per year (HwI 6.5 vs. 4, $P < 0.05$), with 66% reporting very/quite easy access. Seventy-six percent declared themselves self-responsible for hemophilia management, with 15% relying on their family; HwI patients were more likely to rely on healthcare professionals (24% vs. 6%). Overall, 45% were treated on demand (OD), 31% on "regular prophylaxis", and the remainder on a combination of OD with prophylaxis around events/activities. Patients reported treating exactly as instructed (34%), more than instructed (13%), less than instructed (30%), and sometimes more/less (17%). Compared to patients with hemophilia A, HwI patients were more likely to treat exactly as (44% vs. 32%) or less than instructed (44% vs. 26%, $P < 0.05$). Treatment was always/mostly in the home setting (51%/25%) with variation by country (France, 82%/17%; Algeria, 7%/13%). Overall, 2/3 self infuse, and 23% have nurse/physician assistance (greater in Algeria/China, 56%/33%). Patients decided the need for treatment independently (66%) vs. consulting the HTC (24%). Prophylaxis patients were more independent (prophylaxis 72% vs. OD 57%, $P < 0.05$); HwI patients were more likely to consult the HTC (34% vs. 23%, $P < 0.05$). Forty percent had had difficulty obtaining replacement factor in the last 5 years or had concerns about availability or affordability; common reasons cited were hospital supply (50%), insurance (48%), affordability (47%). Patients perceived their disease as generally controlled (mean 7.3/10).
Conclusion: Self-managing patients reported a mix of OD and prophylaxis treatment. The correlation of bleed frequencies, treatment regimens, and country-specific issues warrant additional analysis; as well, their impact on the psychosocial well-being of patients warrants a mulitvariable analysis.

FP-MO-04.4-2
Age at the first bleeding could be a predictor of hemorrhagic phenotype in patients with severe hemophilia
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Ten to 15% of patients with severe hemophilia A or B are known to have a low bleeding frequency. The reason is poorly understood and literature remains controversial concerning the role of prothrombotic factors (mainly due to the low prevalence of the most important ones and the low number of patients included in the studies). A prospective multicentric study was conducted in France in persons with severe hemophilia treated on demand. The main endpoint was the number of bleedings per patient-year (b/p-y). The studied markers were prothrombotic factors (FV Leiden, FII mutation, TAFI polymorphisms), type of hemophilia (HemA or HemB), hemophilia gene mutation, and age at the first bleeding. Only two hundred twenty-six patients could be included between 2003 and 2008 (instead of the 400 expected) because of widespread use of the prophylactic regimen. The median age at inclusion was 24 years (range 4–80]. The hemorrhagic phenotype was not influenced by the presence of prothrombotic factors nor by the gene mutation type nor by the mutation spot (heavy or light chain or B domain of the FVIII protein) in HemA. A significant difference ($P = 0.04$) in the number of b/p-y was observed between patients with HemB (median 10.4 [6.7–18.8]) and those with HemA (median 19.6 [6.7–27.5]). Thus, the most critical marker was age at the first bleeding ($P = 0.005$): the median number of b/p-y was 26 (range 15–37) for a baby receiving the clotting factor infusion during the first month of life, 18 (range 10–27) for a child first treated between 1 month and 2 years of age, and 10 (range 7–13.5) for those treated later. These results suggest that first bleeding during the neonatal period, for whatever the reason, and other, as yet unidentified risk factors, are predictors of frequent bleeding. This finding reinforces the need for early prophylactic treatment that might be particularly targeted at a subgroup identified with a "bleeder profile."

PO-WE-010
Patterns of gastrointestinal hemorrhage in hemophilia
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Peptic ulcer has been reported to be the cause of bleeding in 53–85% of hemophilia patients with gastrointestinal hemorrhage (GIH). The management of GIH in persons with hemophilia during the past decade has been affected by the availability of plasma or recombinant concentrates, an increasing occurrence of chronic liver disease, and wide-

spread use of endoscopic procedures. To determine the present patterns of GIH, we reviewed our experience at the Hedi Chaker Hospital, Sfax, Tunisia, over the last 10 years. Ten (10%) of 100 persons with hemophilia experienced 10 episodes of GIH (7 with hemophilia A and 3 with hemophilia B, 7 severe and 3 mild). Duodenal ulcer (2 cases), unknown site (6 cases), and gastritis (1 case), and angiodysplasia (1 case) were the most common diagnoses. The use of fiberoptic endoscopy resulted in the recognition of diagnoses such as gastritis, esophagitis, Mallory-Weiss syndrome, and esophageal varices. Red cell transfusion was required in 2 cases. The amount of factor VIII replacement used by hemophilia patients with GIH correlated with the severity of gastrointestinal bleeding but not with the cause of gastrointestinal bleeding. In conclusion, persons with hemophilia develop GIH secondary to a variety of causes as do persons without hemophilia. Fiberoptic endoscopy, after correction of factor VIII level to 0.40 U ml^{-1}, is a safe and valuable diagnostic procedure in persons with hemophilia. The specific etiology of GIH in hemophilia patients should be aggressively sought and appropriate specific therapy provided.

PO-WE-011

The medical and economic burden of mild hemophilia in comparison to the severe type: Long-term data from a single German centre

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Background: Mild hemophilia A (HemA) is generally rated a milder bleeding disorder. However, delayed diagnosis and under treatment may lead to severe morbidity.
Methods: The data of 35 mild and 7 moderate patients with hemophilia (PWH) diagnosed and continuously treated at our centre between 1985 and 2008 were retrospectively compared to 46 birth year– matched severe PWH (age 1–24 years, median age 13). Since no patients with mild HemA suffered from an inhibitor, inhibitor patients were excluded.
Results: Mild HemA was diagnosed later (mean 46.3 months, with known positive family history 14.1 months) than moderate (16.9/8.7) or severe HemA (11.7/3.7, $P < 0.001$). The reason for diagnosis was bleeding in 43% (mild), 57% (moderate), and 54% (severe) vs. family history in 31%, 43%, and 39% respectively. Despite a family history, 18% of mild PWH were diagnosed only after bleeding (moderate 14%, severe 9%). Genetic mutations were found in 33% (mild), 86% (moderate), and 96% (severe). The first bleed occurred in mild HemA at a median age of 46.3 months (1–181 months), moderate 16.9 (3–29) and severe 11.7 (1–54, $P < 0.001$). Treatment of bleeds was delayed in mild PWH (2.6 days) compared to severe PWH (1.4 days). Forty percent (mild) vs. 71% (moderate) vs. 91% (severe) experienced joint bleeds, 6% vs. 43% vs. 50% suffered from arthropathy. Factor usage per kg body weight (BW) and year increased with school age. In median, mild PWH used 296.8 U kg^{-1} BW/year (30–892.9, all treated on demand), moderate 1659.8 (77.3–4009.2) and severe 4053.6 (121.7–9219.2, 93% on prophylaxis).
Discussion: Mild HemA was diagnosed late, even with a family history. This, together with a delay in treatment might be responsible for the encountered bleeds.
Conclusion: Better teaching of affected families and pediatricians could help to identify patients earlier. Further studies are needed to evaluate whether the treatment of mild HemA should be intensified.

PO-WE-012

Technical issues in implementing prophylaxis in children with hemophilia: An international survey

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Background: While the benefits of prophylaxis in pediatric patients with hemophilia (PPWH) are indisputable, there is some debate about when to start prophylaxis. Furthermore, there are technical issues in implementing prophylaxis, such as venous access, the use of central-venous-access-devices (CVAD), and potential CVAD-related complications (e.g. infections, inhibitor development, thrombosis, etc.).
Aim: To collect data on the initiation of prophylaxis in PPWH, including the use of CVAD and the protocols to use such devices.
Methods: A survey among the members of the Global Emerging Hemophilia Expert Panel (GEHEP). GEHEP is a forum funded by Bayer HealthCare, including hemophilia treaters from Canada, France, Germany, Great Britain, Italy, Japan, Norway, South Africa, Spain, Taiwan, and the United States. Eight members of this panel treat pediatric patients, representing small to large hemophilia centres around the world.
Results: GEHEP members care for 425 PPWH; among those 245 have severe hemophilia A. Diagnosis was established within the first year of life in 80% of cases. Prophylaxis was started in 4 centres prior to, and in 4 following, the first joint bleed, with a dose of factor concentrate ranging between 20 IU kg^{-1} body weight (BW) 1 time per week to 50 IU kg^{-1} BW 3 times per week. A dose escalation protocol was used by 6/8 centres. While peripheral venous access was preferred, in some centres more than 50% of the patients required a CVAD. Measures to avoid complications such as infections differed (e.g., antiseptics used). An analysis of the complications encountered is currently ongoing.
Conclusion: When and how to start prophylaxis depends on individual decisions for each patient. Therefore, non-standardized registries and cohort studies must document these circumstances exactly to allow comparison of possible treatment-related complications. This also applies to the use of CVAD, since every centre uses its own protocols due to the lack of uniform guidelines.

PO-WE-013

Twenty-two years of modern hemophilia care in the Czech Republic

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The Czech Republic, with its 79 000 km^2 and over 10 million inhabitants, is home to about 800 people with hemophilia. Before 1989, factor concentrates were not available in the former Czechoslovakia, and hemophilia care was almost solely based on treatment with FFP and cryoprecipitate. The Iron Curtain precluded proper hemophilia care for Czech persons with hemophilia. The only "benefit" of the country's isolation at that time was the low incidence of HIV-infected people, including persons with hemophilia. Since 1990, the concentrates are available for Czech PWH (persons with hemophilia). In accord with WFH recommendations and the European principles of hemophilia care, the network of hemophilia centres (CCC, HTC) was built up and anchored firmly within the Czech National Haemophilia Program (CNHP). The authors present data from the CNHP registry showing demographic and therapy-related data about the Czech hemophilia population as reported in 2010. Currently all Czech children with a severe phenotype of hemophilia are offered prophylactic treatment. Home treatment is offered to all persons with hemophilia. The treatment of choice for newly diagnosed persons with severe hemophilia is primary prophylaxis. 11.9% of Czech PWH registered within CNHP are HCV positive and only 0.6% of them are positive for HIV. Czech persons with hemophilia bleed in median 3 times per year (hemophilia A: Adults—severe 10/year, moderate 7/year, mild 0/year; children—severe 4.5/year, moderate 2/year, mild 0/year). Joint bleeds account for 59.3% of all episodes. No bleeding per year was recorded in 23.7% of PWH. Consumption of FVIII was 3.6 IU $capita^{-1}$ in 2010. In median we used about 83 000 IU per treated patient per year in our hemophilia centres in 2010. Around 10% of this consumption was in recombinants, the rest in highly purified plasma-derived concentrates. The use of rFVIII has been increasing constantly since 2006. Today about 20% of children are begun on rFVIII. Young adults are encouraged to continue on prophylaxis started during their childhood. Inhibitor rate is low in HA, with prevalence below 5% and incidence (excluding transient inhibitors) of 6% in age group 0–18 years. Total hip replacement and other surgeries are available for all who need it, including patients with inhibitors. The authors believe that during the past 22 years, the Czech hemophilia care has been built from "ground zero" to a level comparable with other European countries where this care already has a long tradition.

PO-WE-014

Causes of death in patients with hemophilia attended at the National Hemophilia Center of Venezuela (1989–2011)

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Since 2001, Venezuela has been providing treatment for all persons with hemophilia (PWH) with safe clotting factor concentrates (CFC), developing a network of basic HTCs, and improving the home treatment program. To evaluate how these advances have influenced the mortality of PWH, we performed a retrospective analysis of medical records and compared data from 2001–2011 with those from 1989–2000. We reviewed age and cause of death, hemophilia type/severity, presence of inhibitor, liver disease (LD), and AIDS. Death was categorized according to the International Classification of Diseases (ICD-10).
Results: We have 1878 PWH registered between 2001–2011; 60 deaths at a mean age of 37.2 ± 19.2 (range 1–77 years); severity: 35% severe, 38% moderate, and 27% mild. The causes of death were hemorrhages (33.3%, 80% of them intracranial (ICH); violent death (homicide/car and motorcycle accidents/drug abuse) (33.3%); LD (11.7%); AIDS (8.3%); malignancies (5%); cardiovascular diseases (CV) (5%); sepsis (1.7%); and unknown causes (1.7%). Eight out of 60 (13%) had inhibitors, and the main causes of death were ICH or violence. Most of mild hemophilia subjects were age >60. Between 1989–2000 79 PWH died at a mean age of 27.4 ± 12.8 (range 2-66 years); severity: 47% severe, 47% moderate and 6% mild. The main causes of death were AIDS (50.6%); hemorrhages (21.5%), 47% of them intracranial (ICH); LD (10.1%); violent death (10.1%); cardiovascular diseases (CV) (2.5%); sepsis (2.5%); and unknown causes (2.5%). Five percent had inhibitors.
Conclusions: From 2001 to 2011, as expected, we observed a decline in AIDS deaths, while liver disease–related deaths remained constant. The occurrence of ICH and especially violent deaths was higher than in the previous decade. It is necessary to consolidate campaigns to avoid dangerous behaviour in PWH. The numbers of deaths in mild hemophilia patients could reflect an increment in registered cases.

PO-WE-015

Cardiac surgery in persons with hemophilia: Report of 14 consecutive cases

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With increased life expectancy in hemophilia, cardiac surgery becomes more frequent. However, the experience remains limited and no guidelines are available yet. Here, we present a retrospective cohort study (1982–2011) of 13 patients undergoing 14 cardiac surgical procedures in three French university hospitals. Different types of surgeries were performed: 7 coronary artery bypass grafting (CABG), including 3 off-pump revascularizations; 4 aortic (biological) valve replacements (AVR); 1 CABG + AVR, 1 CABG + ascending aortic replacement; and 1 ventrical septal defect repair. The population included 1 infant (3 months old) and 12 adults (aged 45–78 years): 9 patients with hemophilia A (1 severe, undergoing 2 different surgeries; 1 moderate; and 7 mild), and 4 patients with moderate hemophilia B. All were inhibitor-free. All patients, except the infant, had at least 1 cardiovascular risk factor; the logistic euroscore ranged from 0.88 to 20. Patients received a pre-operative bolus of plasma-derived or recombinant factor VIII/IX followed by repeated infusions in order to maintain factor VIII/IX level >80% over 4 days, then >50% during 2–3 weeks. Conventional anesthesic and surgical protocols were performed (heparinization, protamine, aprotinine, tranexamic acid). Thromboprophylaxis (aspirin, heparin) was individually adapted. One single patient experienced post-operative pericardic bleeding, not related to hemophilia, requiring re-operation. Other complications were: infections (1 pneumopathy, 1 cutaneous infection), and heparin-induced thrombocytopenia (1). Mean total factor VIII consumption was 290 IU kg^{-1} (68–787 IU kg^{-1}) in mild hemophilia. The patient with severe hemophilia A received 1031 IU kg^{-1} (bolus) for the first surgery and 846 IU kg^{-1} (continuous infusion) for the second surgery (12 years later). The infant (moderate hemophilia A) required 1660 IU kg^{-1}. Mean total factor IX consumption was 1600 IU kg^{-1} (1420–1949 IU kg^{-1}) in hemophilia B (moderate) patients. No inhibitor occurred. No post-operative mortality was observed. Cardiac surgery can safely be performed in persons with hemophilia and requires multidisciplinary management.

PO-WE-016

The history and evolution of clinical treatment for hemophilia type A: A systematic review over the past 40 years

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Hemophilia is a disease with a long history. It is estimated that 1 in 5000–10 000 males are born with hemophilia A. The clinical spectrum of severe hemophilia has evolved throughout history from being a catastrophic and fatal disorder in the early 20th century to a chronic but manageable condition in recent decades. A systematic search was conducted in September, 2011, using the following databases: Journals@Ovid, ACP Journal Club (ACP), CCTR (formerly Cochrane Controlled Trials Register), The Cochrane Database of Systematic Reviews (COCH), The Health Technology Assessment database, The National Health Service (NHS), Economic Evaluation Database, Ovid Medline, CAB abstracts, Econlit, and Embase. A total of 1755 articles were retrieved from the search as potentially relevant references; 1749 publications were recognized after controlling for duplicates; after abstract scanning, we obtained 142 relevant references; 50 full-text articles were screened for eligibility criteria, and 12 full-text were excluded; a total of 38 publications were included in this qualitative analysis. This systematic review depicted important aspects of the evolving treatment options and of the body of knowledge regarding hemophilia A. Notwithstanding the ups and downs in the history of hemophilia care, sustained success has emerged from the larger availability of safer plasma-derived and recombinant replacement products from the late 1980s onwards, especially in the developed world. Improvement in administration techniques and dosing regimens; the introduction of home treatment; a progressive shift from on-demand treatment to prophylaxis; the onset of antibodies inactivating the infused clotting factor (inhibitors), but the further development of options to treat and possibly eradicate them, account for this recent success story. Further research is needed regarding the long-term financial sustainability of health systems facing lifetime care; additional robust cost-effectiveness studies comparing the current on-demand practice in developing countries with alternative prophylaxis regimes are also needed.

PO-WE-017

The association between the coagulation factor VII gene polymorphisms and cardiovascular diseases in the Iranian population

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Background: The association between coagulation factor VII (FVII) gene polymorphisms and FVII level and activity and also cardiovascular diseases (CVD) has been reported in several studies. The aim of this study was to determine whether 2 FVII gene polymorphisms including -401 G>T and HVR4 influence the risk of CVD in the Iranian population.

Material and Methods: A total of 79 patients with cardiovascular disease confirmed by angiography (45 male and 34 female, mean age 55.4 ± 10.8 years) and 51 age- and sex-match controls (29 male and 22 female, mean age 53.8 ± 9.7 years) without cardiovascular disease (confirmed by angiography) were genotyped for these polymorphisms.

Results: Although TT genotype of -401G>T polymorphism was at a higher frequency among the control group as compared to patients (17.6% vs. 16.4%), the difference was not statistically significant ($P > 0.05$). Also, carriers of the H7-allele (H7H7) were at a higher frequency among the control group in comparison with the group of patients (25.5% vs. 22.7%), but it was not statistically significant ($P > 0.05$).

Discussion: Although some studies found that TT and H7H7 genotypes had protective effects against CVD in some populations, we could not find any association between these polymorphisms and CVD in the Iranian population; however, future studies with larger study groups are recommended for more evaluation of these associations.

Key words: factor VII, polymorphism, cardiovascular diseases, Iran.

PO-WE-018

The laboratory diagnosis situation of hemophilia in Latin America: RED LAPI analysis (Red Latino Americana de Profilaxis e Inmunotolerancia)

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Introduction: RED LAPI (Red Latino Americana de Profilaxis e Inmunotolerancia) started in 2010 as a group of specialized doctors in the treatment of hemophilia in Latin America. The main objective is to optimize diagnosis and treatment, and to improve the quality of life of people with hemophilia in our region. The countries comprising Red Lapi are Argentina, Uruguay, Chile, Perú, Colombia, Paraguay, Venezuela, Bolivia, República Dominicana, Ecuador Honduras, Guatemala, and Panamá. This abstract shows the work of the Diagnosis Committee. The estimated population of these 13 countries is of 225 500 000 inhabitants and the number of persons with hemophilia is around 11 826.

Objective: To show the diagnosis situation of countries in Latin America allowing to plan actions to improve critical points, through projects and collaborations.

Material and Methods: Information was collected using questionnaires for participants of Red Lapi. Each participant was asked whether his/her country could perform FVIII, IX and inhibitors dosage; what method was used; whether reference laboratories were present in the country; and whether there was ability to perform genetic analysis. Each participant solicited additional information from colleagues in other centres or hospitals, to obtain representative information of the country.

Results: The Reference Laboratory definition was used as provided by Levine et al[1]. Most of the countries use the coagulometric method for factor dosage and the Bethesda technique for inhibitor dosage.

Country	FVIII and FIX dosage	Anti-FVIII inhibitor's dosage	Reference Laboratory	Genetic analysis
Argentina	•	•	•	•
Colombia	•	•	•	•
Uruguay	•	•	•	•
Venezuela	•	•	•	•
Panamá	•	•	•	•
Peru	•	•	•	-
Chile	•	•	•	-
Dominican Republic	•	•	-	-
Honduras	•	•	-	-
Guatemala	•	•	-	-
Ecuador	•	-	-	-
Paraguay	•	-	-	-
Bolivia	-	-	-	-
Total n=13 (100%)	12 (92%)	10 (77%)	7 (54%)	5 (38%)

Conclusion: A precise diagnosis is the first step for adequate treatment. There is a huge heterogeneity of diagnosis in Latin America. Results from Red Lapi will allow for bettering characterizing of the real situation in our region and allow collaboration and unified diagnosis and treatment criteria.

Reference:

1 Levine et al, "A Proposed System of Classification of Hemophilia Centers for the World Federation of Hemophilia (WFH)" Scand J Haematol- Suppl 40, Vol 33, 1984,459–460.

PO-WE-019

Evaluation of the utilization of factor concentrate and frequency of bleeds among patients with severe and moderate factor VIII and factor IX deficiency

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Objectives: Hemophilia A and B are X-linked bleeding disorders which result in decreased blood levels of coagulants, causing recurrent bleeding into joints and soft tissues.

According to some studies, the Hemophilia Severity Score (HSS) is higher in severe Hemophilia A (HemA) than in severe Hemophilia B (HemB).
Methods: This is a single-institution retrospective study, and we gathered information from the records of our hemophilia clinic over the period of 1 year, from October 2010 to September 2011. Our samples consisted of 176 hemophilia A and 35 hemophilia B severe and moderate deficient patients. All of our patients used on-demand treatment with plasma-derived factor concentrates. All the calculations were performed with MedCalc Statistical Software 11.5.0 version.
Results: Overall admission rates for patients with hemophilia A were 3.125/patient/year and for hemophilia B 0.77/patient/year ($P < 0.05$). The amount of factor concentrates used by our patients with hemophilia A was 3 731 500 IU of FVIII (21 201.704 IU/patient/year); the amount used by our hemophilia B patients was 611 000 IU of Factor IX (17 457.142 IU/patient/year).The difference in the usage of factor concentrate was not statistically significant ($P = 0.57$).
Conclusion: The data suggest that the 2 inherited coagulation disorders (hemophilia A and hemophilia B) have a different severity of clinical phenotype. In our study, overall admission rates and bleeding episodes with HemA were about threefold higher than for HemB, at all levels of severity. But there is not any statistically significant difference in the usage of factor concentrates between the 2 groups, which is related to the lower in vivo recovery of infused FIX compared with FVIII. Our findings correlate with the findings of some other, similar studies that have been published recently.
Keywords: hemophilia, bleed frequency, overall admission rate.

PO-WE-020
Review of the prophylaxis in patients with hemophilia in 13 Latin American countries

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Introduction: In 2010, 13 representatives of Latin American countries began to meet with the purpose of evaluating the big differences existing in the care of hemophilia in the region. This is how Red Lapi was created (Red Latino Americana de Profilaxis e Inmunotolerancia). Once this reality was known, the second step taken was to design programs to treat and diagnose with the best standards all the hemophilia patients in each country.
Objective: To know, in each country that is already applying prophylaxis programs, which product is used; in which way it is done (taking into account that prophylaxis is the gold standard of the treatment of hemophilia, especially in children); to diminish bleeding episodes along with impairment; to improve quality of life and lower the possibility of inhibitor generation.
Material and Methods: A questionnaire was completed by each active member of Red Lapi. In many of the countries there are no national programs available, which is why, with some exceptions, the presented reports pertain to specific groups in each country.

Results	
Primary Prophylaxis	7 out of 13 countries can offer prophylaxis, 4 of them have National Programs, reaching all the population, 6 have few or none access to lyophilized FVIII or IX and still offer cryoprecipitate of fresh frozen plasma.
First prophylaxis dose	2 out of the 7 countries that can offer prophylaxis before 2 year of age can start it before 2 year of age and 5 countries do so after the first hemarthrose of severe bleeding episode. 100% do prophylaxis in scalonated manner, starting once a week and increasing up to 3 times per week.
Time of primary Prophylaxis	3 out of 7 countries can maintain prophylaxis lifetime. One country maintains it until 10 years of age, 2 until 15 years of age (one of them intends to continue until 18 years old). In this case patients with primary prophylaxis still have not reached 12 years old.
Product Used	Only 3 countries use recombinant lyophilized products. All countries however use plasmatic factors.
Secondary prophylaxis	8 out of 13 countries provide secondary prophylaxis. The other 5 only can do on demand treatment. Some of them do not have access to lyophilized products and still have to use cryoprecipitate or fresh frozen plasma.
About Bypass agents	6 countries can do prophylaxis in patients with inhibitors.

Results: Results are summarized in the table below:
Conclusions: We believe that prophylaxis is essential to the proper care of severe hemophilia; it is already proven that it avoids complications, improves quality of life, and significantly reduces inhibitor production, compared to on-demand treatment. To diminish costs in our countries, one approach could be to start with lower doses than recommended in the literature. Prophylaxis should start after the first severe episode, not in the neonatal period. Prophylaxis should be offered at least to the age of 20, but ideally should continue during the entire patient's life. The use of coagulation factors near vaccinations should be avoided. It is desirable that the conclusions about Latin America should become well known among doctors dedicated to hemophilia, health authorities, and public opinion. Education about self-infusing prophylaxis at home (by the patient or a relative) is also important. An urgent need is that all Latin America countries have access to lyophilized commercial products, to ensure patient well-being and safety.

PO-WE-021
The usefulness of multidetector computed tomography angiography (MDCTA) in hemophilic patients previous to embolization of the middle geniculate artery (MGA)

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Objective: To evaluate the efficiency of the popliteal artery (PA) MDCTA for the visualization of the MGA in hemophilic patients.
Method: From March 2009 to June 2011, 9 patients with hemophilia with recurrent bleeding in the knee were referred from the Centro de Enseñanza de Hemofilia to the Unidad Médica Especializada (UNEME) de Imagenologia de Villahermosa in order to perform bilateral PA MDCTA. These studies were done in a 64-row CT scanner. The images obtained were processed with maximum intensity projection (MIP) and volume rendering (VR) techniques. Visualization, calibre, and length of each MGA were evaluated. The degree of knee articular damage was graded according to the Arnold-Hilgartner classification. The radiation dose received was also documented.
Results: In 16 of the 18 knees, the MGA was visualized (88.8%). One MGA arose directly from the PA. Anatomical variants found were as follows: 13 MGA arose directly from the superior geniculate artery (SGA) branch; in one patient 1 of his MGA arose directly from SGA and the other arose from the PA. Calibre and length of the MGA were directly related to the degree of articular damage. MGA anatomy was better depicted with the MIP technique. The mean radiation dose per study was 454 mGy cm^{-1}.
Conclusions: PA MDCTA proved its efficacy in the visualization of the MGA. There were a high percentage of anatomical variants. Calibre and length of the MGA may increase with a higher degree of articular inflammation present in more advanced states. The radiation dose received is not significant.
Contribution to Medical Practice: Knowledge of the MGA anatomy is useful to the interventional physician as a road map previous to embolization; this procedure is used to avoid recurrent bleeding in the knee and further articular damage.

PO-WE-022
Clinical presentation and management of pediatric hemophilia patients as reported by parents surveyed in the Haemophilia Experiences Results Opportunities (HERO) survey

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Objectives: To describe parent-reported treatment of children with hemophilia A, B, or with inhibitors (HwI).
Methods: A web survey was conducted in 10 countries targeting 600 parents of hemophilia patients <age 18, reporting on their oldest affected son.
Results: Parents of 503 hemophilia patients reported on average 8.94 bleeds in the past year (HwI 15.7 vs. 8.5, $P < 0.05$). Most were hemarthroses (ankle/knee/elbow). Parents visited hemophilia treatment centres (HTCs) on average 6.3 times per year (HwI 8.4 vs. 6.2, $P < 0.05$), with 72% reporting very/quite easy access. Most parents (72%) reported responsibility for managing their son's hemophilia (83% of mothers vs. 41% of fathers, $P < 0.05$), with few relying on healthcare professionals (6%). Overall, 65% of the children were on prophylaxis, 26% on demand (OD), and the remainder OD with prophylaxis around events/activities. Parents treated exactly as (58%), more than (15%), or less than instructed (13%), and sometimes more/less (11%). Parents administering prophylaxis were more likely to treat exactly as instructed (prophylaxis 67% vs. OD 46%, $P < 0.05$) or administer more factor (14% vs. 6%, $P < 0.05$) compared with those treating OD. Treatment was always/mostly in the home setting (50%/22%) with variation by country (France 72%/19%; Algeria 2%/13%). Infusions were normally administered by parents (71%), or with healthcare professional assistance (23%; 43% for children <5 years). The decision to initiate treatment transitioned from parent/HTC (at diagnosis) to parent (childhood) to parent/patient (adolescence). Parents administering OD were more likely to consult the HTC (13% vs. prophylaxis 4%, $P < 0.05$). Parents perceived their child's disease to be generally well controlled (mean 8/10). Thirty percent of parents had had trouble obtaining treatment in the past 5 years, with lack of supply reported (48%).
Conclusion: Parents reported a different picture of hemophilia and its treatment than adult respondents, with home therapy and self- or parent-administered infusions representing the usual care in most countries.

PO-WE-023
Comprehensive spectrum of inherited bleeding disorders from south-west Iran

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Objective: The purpose of the present study is to assess the frequency, magnitude, and diversity of different bleeding disorders in south-west Iran.

Materials and Methods: A total of 415 cases of inherited bleeding disorders were assessed from April 2010 to July 2011. A comprehensive evaluation such as diversity presentations, clinical manifestations, and demographic data were recorded.
Results: A total of 415 (320 male, 95 female) patients in the range of 1 to 85 years old were diagnosed at Shafa hospital. One hundred and sixty-six patients (40%) were Arab and 249 patients (60%) were attributed to non-Arab ethnicity. Amongst these, 361 (87%) patients had coagulation disorder, while only 54 (13%) patients had platelet dysfunction disorders. Amongst the coagulation disorders, hemophilia A (195 patients, or 54%) was the most common disorder, followed by VWD type (58 patients, or 16%), hemophilia B (39 patients, or 10.8%), factor VII deficiency (16 patients, or 4.4%), factor V deficiency (12 patients, or 3.3%), VWD type 1 (11 patients, or 3%), factor V+VIII deficiency (8 patients, or 2.2%), factor XIII deficiency (5 patients, or 1.4%), factor XI deficiency (4 patients, or 1.1%), VWD type 2 (4 patients, or 1.1%), afibrinogenemia (4 patients, or 1.1%). Glanzman's thrombasthenia, with 53 patients (98.1%) was the most common platelet function disorder, followed by Bernard-Soulier syndrome (1 patient, or 1.9%).
Conclusion: In spite of the apparent rarity of inherited bleeding disorders, Iran and Khuzestan province have a considerable number of patients with these disorders. A large number of these patients have hemophilia.
Acknowledgement: The authors and patients gratefully thank Novo Nordisk Company for providing the budget for screening and patient registration.

PO-WE-024
The role of angiogram and embolization in patients with hemophilia
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Objective: To review our experience with the use of angiography in managing the complications of hemophilia.
Materials and Methods: Data of all patients with hemophilia-related complications who required angiography between 2000 and 2011 was reviewed using the computerized hospital information on patients. Clinical details, indication for the procedure, patient preparation for the procedure, findings on imaging, details of angiography with intervention, if any, and outcome as well as follow-up data was collected and analyzed.
Results: Six patients, aged between 16 and 59 years, underwent angiographic procedures during this period. All had severe hemophilia. The indications included expanding massive spontaneous hematoma of the anterior abdominal wall - 1, persistent postoperative bleeding from an amputated stump - 1, chronic osteomyelitis with bleeding - 1, pre-operative evaluation of an expanding / compressing pseudotumor (paravertebral region, right thigh, ileopsoas) - 3. All patients underwent angiogram through a femoral arterial access and embolization, if needed, after adequate factor replacement to cover the procedure and 48 hours after that. Bleeding vessels were identified were embolized. Polyvinyl alcohol particles were used for embolization. Peripheral hypervascularity was noted in pseudotumors. Embolization of the major vessels on the surface was done to ease the dissection and excision of pseudotumors. There were no complications during the procedure nor were there any post-procedure bleeding or hematoma at the site of arterial access.
Conclusion: Angiogram and embolization, if needed, is a useful procedure in carefully selected patients with hemophilia to either stop persistent bleeding, which may be from a vessel, or to ease excision and reduce the chances of bleeding at the time of surgery in patients with large pseudotumors.

PO-WE-025
Hypovitaminosis D and osteopenia/osteoporosis and a hemophilia population: A study in HCV- and HCV/HIV-infected patients
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Recent reports show a correlation between hemophilia and bone mineral density reduction. HIV, HCV, and their treatments are independently associated with an increased risk of osteoporosis. A pivotal role in bone mineralization is played by Vitamin D. This study compares Vitamin D level, bone metabolism markers, and bone mineral density (BMD) in persons with hemophilia, with or without co-infections. Seventy-eight adult patients with severe or moderate hemophilia A or B were subdivided into 3 groups of 26 patients each (HIV-HCV co-infected, HCV mono-infected, and uninfected). BMD was measured by dual-energy X-ray absorptiometry (DXA) at the femoral area (F) and the lumbar spine (L) and was correlated to laboratory values and hemophilic arthropathy assessed using the World Federation of Hemophilia orthopedic joint scale (WFH score) and the radiological Pettersson score. DXA showed a homogeneous F-BMD reduction apart from the belonging group, while L-BMD was significantly lower in co-infected patients ($P < 0.05$). The WFH score was higher in co-infected ($P < 0.002$) and in mono-infected ($P < 0.006$) groups. The radiological score was higher in mono-infected than in the other two groups ($P < 0.001$). Overall 25-hydroxyvitamin D was reduced in 87% of patients, in particular in 100% of co-infected, 73% of mono-infected, and 88% of uninfected subjects. Bone-specific alkaline phosphatase (b-ALP) and telopeptide were increased in co-infected ($P < 0.001$ and $P < 0.01$) and in mono-infected ($P < 0.001$ and $P < 0.02$) patients. The worse clinical and radiological scores in patients with infections are most likely related to the number of patients with more severe coagulopathy in those groups. A high prevalence of hypovitaminosis D has been found in persons with hemophilia, a part from the belonging group. The homogeneous F-BMD reduction could be explained by the pivotal role of arthropathy; the lower L-BMD in co-infected and the increase of b-ALP and telopeptide in co-infected and mono-infected groups suggest faster bone metabolism in the case of infections.

PO-WE-026
Obesity and hemophilia: The problem of weight and the ability to change; Review of an MDT weight management clinic
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Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health (WHO, 2006). Obesity is a worldwide epidemic and is of growing concern among treaters of individuals with hemophilia. Obesity increases the risk of CV disease, diabetes, some cancers, and musculoskeletal disorders. There is a theoretical risk that obese persons with hemophilia may suffer from more bleeds and worsening arthropathic joints. As a consequence of a regional care quality initiative (CQUIN) designed to monitor the body mass index (BMI) of hemophilia patients, a pilot MDT weight management program was developed. Following training from the dietician, the hemophilia nurse specialist and physiotherapist led in providing first-line advice for all identified overweight patients (BMI>25), educating on activity modification and eating habits. Those with BMI>28 were referred to dietician-led clinics with motivational interviewing and behaviour-changing techniques. Measures of weight, BMI, waist circumference, and the HAL were used to evaluate input. Of the 178 patients on active treatment (severe and moderate), 59 (33%) were overweight/obese. All patients received first-line advice; 23 (obese) were referred to the dietician, but only 12 (52%) followed up on the referral. Twenty-seven were excluded for other medical/psychosocial reasons. Eleven (17%) patients overall achieved weight loss (range 0.4–11.9 kg; mean 4.7 kg). Those patients who lost weight reported improvement in overall well-being. In this cohort, only 12.9% were classified as obese compared to the UK national figure of 22%. Weight loss requires concerted effort from the individual involved and support from the medical and wider social circle. Hemophilia care support should focus on long-term general health and well-being, not solely on cost of treatment. Patients have to be at the contemplative stage of change to enable health providers to facilitate them further. The low clinic attendance highlights the need for long-term education for patients who need help in weight loss.

PO-WE-028
Is there an increase in the number and type of surgical procedures performed in patients with hemophilia over the last 20 years?
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Introduction: Nowadays in the Netherlands, patients with severe hemophilia start with primary prophylaxis after their first joint bleeding to reduce the risk of arthropathy. In contrast, most eldery patients suffer from arthropathy due to the fact that they did not receive proper treatment in the past. The aim of this study was to evaluate the impact of this change of treatment regime on the incidence of hemophilia-related surgery over the last 20 years.
Method: We conducted a single-centre cohort study on patients with moderate and severe hemophilia A and B ($n = 101$). We documented data of patients who underwent surgical procedures in period A (1988–2001) or B (2002–2011).
Results: Sixty-six patients (65% of total cohort) underwent 141 surgeries. The majority of the surgical procedures (87, or 62%) were "hemophilia related," i.e., orthopedic interventions (42) or insertion or removal of a port-a-cath (PAC) (38). Sixty-nine percent of the procedures were performed in period B. The table summarizes the number and different types of procedures during childhood or adulthood in the 2 different time periods. The peri-operative management of 16 surgical procedures was complicated by the presence of inhibitors. Post-operative bleeding complications occurred in 11 patients, after 13 surgeries (12 hemophilia related). Three of the 4 bleeding complications at childhood were inhibitor related. Surgery-related mortality was 0%.

	Total number of surgeries	Hemophilia-related surgeries	Insertion or removal PAC	Surgeries to control bleeding	Orthopedic surgeries
Period A					
Child	24	9	8	1	0
Adult	20	13	0	1	12
Period B					
Child	49	34	30	3	1
Adult	48	31	0	2	29

Conclusion: The availability of clotting products enables an increased number of hemophilia-related surgeries, i.e., insertion of PACs in the young and orthopedic surgery in elderly persons with hemophilia, with an acceptable risk (8%) of bleeding complications.

PO-WE-029
Correcting dilutional coagulopathy in hemophilia
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Patients with severe hemophilia A are undergoing surgery more frequently, increasing the risk of intraoperative bleeds and dilutional coagulopathy. Standard management is with FVIII replacement. Once hemodiluted, it is unclear if this treatment will normalize clot formation and stability compared to non-haemophiliac patients undergoing a similar degree of hemodilution. The aims of this study were to examine the impact of 50%

dilution on clot stability in hemophilia plasma (HP) vs. normal plasma and examine the effect of adding FVIII to diluted HP.
Hypotheses: Hemodilution causes impairment in clot stability in control plasma and to a greater extent in HP. Addition of FVIII to HP fails to normalize clot stability.
Method: HP, HP spiked with FVIII and normal control (Technoclone) were undiluted or diluted 50:50 with Gelofusin or 0.9% NaCl. Clotting was triggered with tissue factor 1:40 000 plus calcium and turbidity measured (FLUOstar Omega). Tissue plasminogen activator (*0.75nM)* was added simultaneously and the area under the turbidity curve was recorded as a measure of clot stability.
Results: Dilution with both Gelofusin and NaCl caused a significant decrease in clot stability in control and HP from baseline (Mann-Whitney $P < 0.05$). The effect of Gelofusin on clot stability did not differ between the control and hemophilia group. However, diluting with NaCl caused a greater impairment in clot stability in the HP (mean AUC HP:55, C:69, $P < 0.001$). Addition of FVIII to HP failed to normalize clot stability compared to undiluted control plasma and plasma diluted 50:50 with NaCl.(p-value).
Conclusion: In this pilot study, FVIII failed to correct clot stability in diluted HP compared to the normal control, suggesting that when hemophilia patients undergo major surgery, FVIII alone is insufficient and hemodilution itself should be additionally monitored for and treated.

PO-WE-030
Prevalence of sporadic and familial severe hemophilia: Has anything changed?

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Forty years ago, the prevalence of sporadic hemophilia was estimated by Biggs and Macfarlane (1966) to be about one-third of all cases. More recently, an analysis of 804 hemophilia pedigrees (*Haemophilia*, 2007) estimated that in 569 patients with severe hemophilia B and A, 43% and 56% respectively were sporadic, i.e., either isolated cases or brothers in the first affected sibship. The causative mutation was detected in 88% of these cases' mothers and 19% of their maternal grandmothers. Since the activation of the Emilia-Romagna Network for inherited bleeding disorders in 2001, the evaluation of pedigrees allowed us to notice that in 10 years there had been a significant increase of new sporadic cases of severe hemophilia. In this study we evaluated all severe patients born from late 1990s until now in Emilia-Romagna Region. Among 45 analyzed pedigrees, 37 were sporadic cases (82%) and 8 (18%) were familial. All severe cases of hemophilia B and 80% of hemophilia A cases were sporadic. We further distinguished the "isolated cases": only 1 affected patient in the family, from the "sporadic sibship"; in our cohort we had only 1 family with 2 affected sibships. The characterization of the causative mutation in all these sporadic patients gave us the possibility of screening the DNA of their mothers and maternal grandmothers. We found out that 87.5% of mothers and 31% of maternal grandmothers were carriers. This study also considered the influence of prenatal diagnosis and the termination of pregnancy in obligated carriers (daughters of persons with hemophilia). In Emilia-Romagna, 7 prenatal diagnoses were performed, finding 1 affected male (termination of pregnancy), 1 healthy male and 5 female. Many reasons, which need further investigation, could explain the increase in sporadic cases; for example, family sizes are smaller than in the past, and there is more awareness in affected families.

PO-WE-031
Clinical and epidemiological profile of congenital coagulopathy patients attending at general emergency department

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Background and Purpose: The clinical and epidemiological profile of patients with congenital coagulopathies attended to at the emergency department (ED) is not yet defined.
Methods: We selected all patients from April 1, 2011 to November 30, 2011 with congenital coagulopathy (hemophilia A, hemophilia B and von Willebrand disease) attended at ED.
Results: 68 patients with congenital coagulopathy were attended to in this period: 47% HemA, 42.6% HemB and 10.3% VWD patients; mean age 36.3 ± 13.3 (15–72 years). 59.4% were severe HemA patients vs. 28.6% of HemB patients (P 0.185). The most frequent ED presentation was bleeding complication.
Major and minor bleeding showed with similar frequency (13.2%, $P = 0.20$) with no difference in severity of diseases. Major bleeding required more frequent replacement of deficient clotting factors (77.8% vs. 22%, $P = 0.001$), had a higher admission rate (66.7% vs. 13.6%, $P = 0.000$), more often are infected with HBV (22.2% vs. 3.4%, $P = 0.025$).

Table 1. ED presentations.

	n	%
Bleeding manifestations	17	25
Abdominal symptoms	11	16.2
Fever	8	11.8
Non-traumatic neurological deficit	7	10.3
Mechanical pain	5	7.4
Trauma without head trauma	4	5.9
Traumatic brain injury	2	2.9
Urinary symptoms	2	2.9
Respiratory symtoms	1	1.5
Others	6	8.8

Table 2. Bleeding causes.

	% (n)
Minor bleeding	13,2% (9)
Subcutaneous hematoma	4,4% (3)
Gingival bleeding	4,4% (3)
Epistaxis	2,9% (2)
Mouth bleeding	1,5% (1)
Major bleeding	13,2% (9)
Lower gastrointestinal bleeding	5,9% (4)
Upper gastrointestinal bleeding	1,5% (1)
Pharyngeal hematoma	1,5% (1)
Hemoptysis	1,5% (1)
Retroperitoneal hematoma	1,5% (1)
Intramuscular hematoma	1,5% (1)

Conclusion: Most of the patients consulted for bleeding complications. Most frequently, high-risk bleeding required clotting factor replacement and showed a high admission rate without difference in type and severity of diseases. This determines that the assessment as a life-threatening condition of all bleeding patients with congenital coagulopathy should be independent of disease severity.

PO-WE-032
Indications and barriers to prophylaxis adoption in Italian hemophilia Patients of <18 years of age: Outcomes of the Italian Working Group on Prophylaxis (Gruppo Italiano Di Lavoro Sulla Profilassi - GILP*)

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Continuous long-term prophylaxis started during the first years of life is the only proven strategy to prevent chronic arthropathy and other invalidating complications in patients with severe hemophilia. In addition, prophylaxis significantly improves the quality of life (QoL) and the social integration of patients and their families. The therapy is, however, associated with difficulties that may limit its adoption and continued use. Between 2009 and 2010, GILP (the Italian working group for prophylaxis) conducted a survey to identify parameters that influence doctors' decisions on whether to adopt a prophylactic regimen in hemophilia patients under 18 years of age. Twenty clinical and environmental parameters were identified (14 concerning the paediatric age and a further 6 regarding the adolescent age). The 16 clinicians of the GILP assigned a score (from 0 to 5) to the importance and influence of each parameter on their decision. For any age group, the most influential parameters appeared to be the severity and frequency of bleeding (with a median score of 5; ranges 4–5 and 3–5 respectively). Moreover, in patients aged between 0 and 2, an additional parameter was the presence of a genetic mutation with a high risk of inhibitor development (median score 4; range 2–5). A difficult venous access represented a severe obstacle to the adoption of prophylaxis in children under the age of 2 for only 1/3 of the doctors. In patients aged 3 to 6 and 7 to 12, the major additional parameters for the adoption of prophylaxis were the presence of target joints (median score 5; ranges 0–5 and 4–5), a reduction of QoL (median score 5, range 3–5), and the evidence of joint damage (median scores 4 and 5; ranges 0–5 and 3–5). These parameters also appear to have an influence on doctors' decision in patients >12 years (median score 5, 4.5, 4; range 2–5). On the other hand, doctors' opinions varied as to the influence of conditions such as the perception of less-than-optimal adherence to prescriptions, low socio-cultural status of the family, sports and recreational activities, and type of hobbies in patients over 6 years of age. Overall, the results of the survey made it possible to identify intervention strategies aimed at overcoming the difficulties involved in extensive use of prophylaxis in Italian hemophiliac children and adolescents under age 18.
Acknowledgement: Independent working group supported by Baxter through an unrestricted grant.

PO-WE-033

Hemophilia and cancer in Latin America: A first approach to the issue

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Introduction: Adequate treatment of hemophiliac patients has diminished the rate of mortality and increased life expectancy; we now face new conditions, such as cancer, that tend to appear frequently at an older age. Questions have arisen about the treatment of cancer in these patients; we wonder if standard protocols apply; what the predominant type of cancer is; what cancer's relationship to HIV and HC is; if bleeding episodes increase during cancer treatment; and what its mortality rate is. Through literature review, we found that trials are scarce; this is why the group RED LAPI (Red Latino Americano de Inmunoprofilaxis e Inmunotolerancia) wants to diagnose and characterize the situation in our region and provide data on handling cancer in hemophilia. Red LAPI consists of representatives from 13 Latin American countries and was created with the purpose of increasing knowledge and providing better care of hemophiliac patients within the region.
Objective: Describe the situation of persons with hemophilia suffering from cancer in Latin America, in order to be of future use in optimizing care.
Material and Methods: Research of available databases on the Internet was done, using the following key words: hemophilia, malignancies, cancer, HIV, and hepatitis. We propose a descriptive trial to the members of RED LAPI, collecting information from the last 10 years through questionnaires, identifying incidence of cancer, its type, frequency, complications, treatment in case of inhibitors, its relationship with HIV and hepatitis, and prognosis. The countries involved will be Argentina, Uruguay, Chile, Peru, Colombia, Paraguay, Venezuela, Bolivia, Dominican Republic, Ecuador Honduras, Guatemala, and Panamá.
Discussion: Cancer studies in hemophilia are of upmost interest, but are scarcely performed. When the available literature was evaluated, case reports were found, but few reviews. It is important to define the relationship between cancer development, HIV and hepatitis, since the development of cancer is higher in infected patients. By demonstrating the situation in Latin America from this viewpoint, we can provide useful knowledge to the world.
Conclusions: Cancer with hemophilia is a recent clinical condition and not enough data is yet available in order to elaborate a consensus for its management. With the participation of 13 Latin American countries, this study will supply interesting data which can provide useful information, permitting the elaboration of strategies directed at optimizing the situation.

PO-WE-034

A prospective study on the side effects of desmopressin in patients with bleeding disorders

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Introduction: Desmopressin can be used to treat patients with bleeding disorders to increase von Willebrand Factor and factor VIII. Although side effects are mostly mild, several cases of severe side effects such as hyponatremia, seizures, and acute myocardial infarction have been reported. We performed a prospective study to establish the prevalence and severity of side effects of desmopressin.
Methods: Patients with bleeding disorders who received desmopressin were included. Patients received 0.3 μg kg^{-1} infused during 30 min. Blood samples were obtained before, 1, 3, 6 and 24 h after administration. Serum sodium, osmolality and hematocrit were determined. Patients were asked each time about potential side effects, and vital functions were measured.
Results: Seventy-one patients were included (34% males). The median age was 32 years (range 15–86). Patients were diagnosed with VWD (n = 58), mild hemophilia A (n = 9), platelet disorder (n = 1), and unexplained bleeding tendency (n = 3). None of the infusions was prematurely stopped because of side effects. Blood pressure significantly decreased from 122/73 mmHg to 114/65 mmHg after infusion. Fifty-two patients (79%) reported side effects 1 h after desmopressin, 34 patients (48%) after 6 h. Headache occurred in 16/66 patients (24%) 1 h after desmopressin and persisted in all these patients at 6 hours. In 15/66 patients (23%), fatigue was reported after 1 h and 6 h. In 24/66 patients (36%) flushing and in 43/66 patients (65%) bloodshot eyes were present after 1 h; this did not sustain at 6 h. Eight patients (12%) reported dizziness only after infusion. After desmopressin, no significant decrease of sodium and serum osmolality was found. Urine osmolality significantly increased with 237 mOsm kg^{-1} and weight with 200 g after 1 h. Hematocrit significantly decreased 0.03 L/L.
Conclusions: Seventy-nine percent of patients receiving desmopressin reported side effects. However, these side effects were mild, transient, and without clinical consequence.

PO-WE-035

Hemophilia in developing countries: A clinical profile of Cameroonian patients

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Background and Objectives: There is generally scarcity of data on hemophilia in Africa, and more so in Cameroon, where little is known on its clinical characteristics. Thus, a study was carried out on a group people with hemophilia (PWH), seen in the Haemophilia Treatment Centre of the Yaoundé University Teaching Hospital (YUTH), in order to describe the clinical profile of PLWH in Cameroon.
Methodology: Sociodemographic information and clinical data were obtained from each participant after informed consent through a complete medical interview and physical examination. Furthermore, and where appropriate, laboratory analyses including prothrombin times (PT), activated partial thromboplastin times (APTT) and factor VIII and FIX activities were measured using standard techniques. The type and severity of disease was established for each case.
Results: Among 88 PWH, the mean age was 16.2 ± 12.4 years (range 2–57 years). Hemophilia A represented 88.6% of cases (n = 78) with 11.4% hemophilia B. Severe hemophilia was noted in 67.9% (n = 53), all hemophilia A. Late diagnosis of the disease seemed a common feature. Joint bleeds were predominant (62.5% cases). The mean number of bleeds per person and annum was 14 (range: 1–48]. A high frequency of joint complications was also observed (72.3%).
Conclusion: Early screening for hemophilia in suspected cases and effective strategies to reduce the frequency of bleeding adapted to local settings may positively contribute significantly to the clinical status of PLWH in Cameroon.
Key Words: hemophilia; clinical characteristics; Cameroon.

PO-WE-036

Safe concurrent use of intravenous or oral tranexamic acid and aPCC in patients with hemophilia complicated by high-titer inhibitors

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Concomitant use of recombinant activated factor VII (rFVIIa) and antifibrinolytic agents such as tranexamic acid (TA) is recommended for bleeding control in patients with hemophilia complicated by high-titer inhibitors in various clinical settings. In contrast, the use of antibrinolytics is not recommended in patients receiving activated prothrombin complex concentrate (aPCC). In the first scenario, there is evidence that TA may enhance the effect of rFVIIa and improve hemostasis, while in the second; there is apprehension (but not evidence) of thromboembolic complications. We report here on 9 patients, aged 20–71 with hemophilia A complicated by high-titer inhibitor toward factor VIII, in whom on 16 occasions aPCC was administered concurrently with oral or intravenous tranexamic acid. The reasons for treatment were dental extraction (n = 11), gastrointestinal bleeding (n = 1), oral cavity bleeding (n = 3), and epistxis (n = 1). The duration of concurrent aPCC and TA administration ranged from 1 to 16 days (median 5.5) and the median aPCC daily dose while on TA treatment was 155 U kg^{-1} (range 70–160 U kg^{-1}). The universal daily TA dose was 3.0 g. Three patients on 6 occasions received concurrent treatment of aPCC and rFVIIa (''sequential therapy'') together with TA. In those patients the median daily rFVIIa dose was 180 μg kg^{-1}. The treatment proved safe and effective in all 16 cases. No symptomatic thromboembolic complications were observed in any of the cases, including patients with elevated markers for systemic activation of coagulation (D-dimer). Based on the results of our study observations we conclude that in selected hemophilic patients treated with aPCC, the concurrent administration of tranexamic acid may be warranted; this particularly applies to a subset of patients at high risk of mucous membrane hemorrhage who failed monotherapy with aPCC or rFVIIa as well as sequential aPCC/rFVIIa therapy.

PO-WE-037

Large individual differences in the in vivo recovery of factor VIII concentrations in Japanese hemophilia A patients

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Background: We have reported large individual variations in the in vivo recovery (IVR) of factor IX concentrations in Japanese hemophilia B patients (ISTH, 2011), while the FVIII IVR in Japanese hemophilia A patients has not been reported recently.
Method: Thirty-five hemophilia A (27 severe, 5 moderate, 3 mild) patients without inhibitors were eligible for the study. We measured the FVIII IVR 30 min post-infusion and compared it in two age groups (C: <18 years, A: ≥18 years). Furthermore, we studied the IVR for 2 recombinant factor VIII (rFVIII) products (R1, R2) and 1 plasma-derived factor VIII (pdFVIII) product (P1). We also investigated the influence of the body weight (BW), hematocrit (Hct) and body mass index (BMI) on the variability of the IVR. We calculated the FVIII dosage as the actual titer of each product.
Results: Subjects ranged in age from 2 to 65 years (median 12 years). The mean IVR values were 1.75 ± 0.35 IU dL^{-1} (IU kg^{-1}) $^{-1}$ in group C (n = 25) and 1.69 ± 0.38 IU dL^{-1} (IU kg^{-1}) $^{-1}$ in group A (n = 10); thus, there were no significant differences in the IVR

values between the 2 age groups. However, large individual differences in IVR were seen within each age group; there were no correlations of the IVR with the BW, Hct or BMI. The mean IVR values were 1.70 ± 0.34 IU dL^{-1} (IU kg^{-1}) $^{-1}$ for R1 (n = 21), 1.73 ± 0.31 IU dL^{-1} (IU kg^{-1}) $^{-1}$ for R2 (n = 9), and 1.69 ± 0.49 IU dL^{-1} (IU kg^{-1}) $^{-1}$ for P1 (n = 5). There were no evident differences in the IVR values among the FVIII products.

Discussion: We showed that FVIII IVR was not dependent on the patient's age or the kind of FVIII product used, unlike in the case of FIX IVR. However, large individual differences in FVIII IVR were observed within each age group.

PO-WE-038

Increased risk of cancer in patients with hemophilia A: A population-based case-controlled study

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Introduction: Cancer is the major cause of mortality and morbidity in the general population. The hepatitis virus and human immunodeficiency virus (HIV) have a high prevalence in hemophilic patients, which might lead to a higher cancer incidence. However, studies investigating the risk of cancer in hemophilia patients have been scant, and with a limited number of patients.

Patients and Methods: Hemophilia A patients more than 20 years of age and without prior diagnosis of cancer were identified from the National Health Insurance Research Database in Taiwan from 1997. Age- and sex-matched controls without hemophilia were randomly extracted from the database in a 1:4 ratio. Cumulative incidence of cancer was estimated using the Kaplan-Meier method, and logistic regression analysis was used to investigate the risk of cancer between the 2 groups.

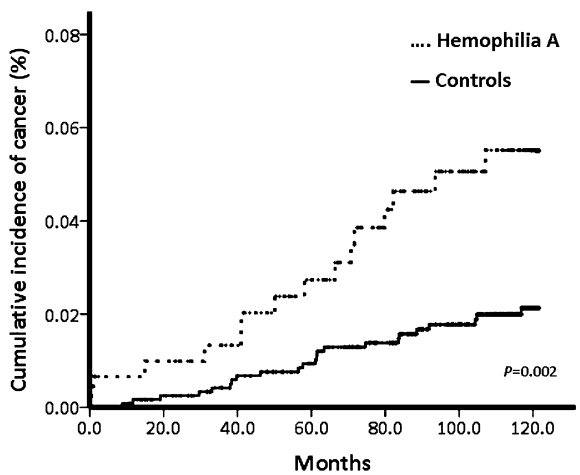

Fig. 1. Cumulative incidence of cancer in patients with hemophilia and age- and sex-matched controls.

Results: The data of 305 patients with hemophilia were retrieved from the database, with a median age of 32 years (range 20–81). After a median follow-up of 120.8 months (range 0.2–121.7), a total of 15 patients developed cancers: hepatocellular carcinoma (HCC) for 3, colorectal cancer for 3, lung cancer for 2, leukemia for 2, and other types of cancer for the remaining 5 patients. When compared with 1220 controls, the cumulative incidence of cancer was higher in hemophilia patients (10-year 2.1% vs. 5.5%, hazard ratio [HR] 2.69, 95% confidence interval [CI] 1.39–5.22, P = .003). For non-HCC cancers, the incidence rate remained higher in the hemophilia population (10-year 1.5% vs. 4.4%, HR 2.91, 95% CI 1.38–6.17, P = .005).

Conclusion: Patients with hemophilia A encounter a higher risk of cancer, which might be independent of the effects of the hepatitis virus and HIV.

PO-WE-039

Intracranial bleeds in bleeding disorders: A northern Pakistan experience

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Introduction: Intracranial bleeds are a serious problem in bleeding disorders, resulting in increased morbidity and mortality. They are the most common cause of death in hemophilia. In Pakistan, where consanguineous marriages are common, intracranial bleeds are also seen with severe rare bleeding disorders. The objective of this study was to document all patients presenting with intracranial bleeds to the hemophilia treatment centre (HTC).

Patients: 659 patients are registered with the hemophilia treatment centre, 547 males and 112 females. 366 males (66.9%) have factor VIII deficiency and 56 (10.2%) have factor IX deficiency. Von Willebrands disease (VWD) is seen in 53 (9.7%) males and 54 (48.2%) females. Rare bleeding disorders (RBDs) are present in 49 (8.9%) males and 45 (40.2%) females.

Methodology: Data of all patients presenting to the HTC from January 2007 to December 2011 were recorded on performa with details of age, sex, type and severity of bleeding disorder, sign and symptoms. A record of investigations and treatment was also kept.

Results: 13 male patients presented with 15 episodes of intracranial bleeds. The age range was 4 months to 11 years; 9 patients had hemophilia A, 1 had hemophilia B, 1 had VWD, and 2 had factor XIII deficiency. A history of trauma was present in 12 episodes. The presenting symptoms in 10 patients were headache and vomiting. One patient was irritable, while 2 patients were in coma on arrival. All cases had a CT scan except 1 patient who arrived in coma and died before any investigations or treatment. The bleeds were subdural in 6 and intracerebral in 9. Appropriate treatment was given to all patients prior to investigations. There was complete resolution in 10 patients, while 3 died.

Conclusion: Intracranial bleeds are not uncommon in this part of the world. Early and appropriate treatment is essential for full recovery.

07-CLINICAL ISSUES AND TRIALS

FP-MO-03.2-3

An open-label phase I study to evaluate the pharmacokinetics and safety profile of Bay 94-9027, a PEGylated B-domain-deleted recombinant factor VIII, in previously treated patients with severe hemophilia A

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Objectives: BAY 94-9027 is a B-domain–deleted recombinant factor VIII (BDD-rFVIII) designed as a longer-acting rFVIII therapy via site-specific attachment of polyethylene glycol (PEG) at an introduced cysteine mutation (K1804C). We assessed pharmacokinetics (PK) and safety of BAY 94-9027 after single and repeated administration.
Methods: This 8-week, prospective, multicentre, open-label, non-randomized, phase I trial was conducted in subjects (aged 21–58 years) with FVIII <1% and ≥150 exposure days to FVIII who were immunocompetent and had no history of FVIII inhibitors. After a ≥3-day washout period, subjects received a single dose of currently available sucrose-formulated rFVIII (rFVIII-FS; cohort 1 [n = 7], 25 IU kg^{-1}; cohort 2 [n = 7], 50 IU kg^{-1}) for a 48-h PK study. After another ≥3-day washout, cohort 1 received BAY 94-9027 25 IU kg^{-1} 2x/wk (16 doses); cohort 2 received BAY 94-9027 60 IU kg^{-1} 1x/wk (9 doses). A 168-hour PK study was performed after the first and last BAY 94-9027 dose.
Results: All subjects completed the study. No treatment-related serious adverse events were reported. No FVIII inhibitors or antibodies against PEG or BAY 94-9027 were detected. PK data are shown in the table below.

Regimen	Dose, IU kg^{-1}	C_{max}/dose, kg dL^{-1}	$T_{½}$, h	AUC/dose, kg h dL^{-1}
rFVIII-FS (n = 7)	25	2.8	13.1	43.2
BAY 94-9027 single dose (n = 7)	25	2.6	18.2	63.4
BAY 94-9027 twice weekly, 16 doses (n = 7)	25	3.2	18.4	81.2
rFVIII-FS (n = 7)	50	4.6	14.6	54.3
BAY 94-9027 single dose (n = 7)	60	2.9	18.7	71.0
BAY 94-9027 once weekly, 9 doses (n = 7)	60	3.1	20.0	81.0

Conclusions/Contribution to the Practice/Evidence Base of Hemophilia and Bleeding Disorders: BAY 94-9027 25 IU kg^{-1} (2x/wk) and 60 IU kg^{-1} (1x/wk) demonstrated improved PK, with a 19-h half-life (extended by approximately 30% vs the already relatively long half-life of rFVIII-FS), and was well tolerated with no immunogenicity. Further studies are indicated to determine if this prolonged half-life will permit less frequent prophylaxis dosing with continued protection from spontaneous bleeding episodes.
Conflicts of Interest: T. Coyle and M. Reding are advisory board participants for Bayer. L. Michaels and A. Shah are employees of Bayer HealthCare Pharmaceuticals. J. Powell receives clinical trial support from Bayer, Octapharma, and Biogen Idec.

FP-MO-03.2-6

Results of a phase I international clinical trial of recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP) in patients with hemophilia B (PROLONG-9FP)

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Factor IX (FIX) replacement therapy is the standard of care for patients with hemophilia B. FIX products currently available have a relatively short half-life, requiring intravenous prophylactic treatment 2–3 times a week to achieve a significant bleeding reduction. An rFIX albumin fusion protein (rIX-FP) was generated by genetic fusion of human recombinant albumin to rFIX to extend the half-life of FIX. A first-in-human, international, prospective, dose-escalation safety and pharmacokinetic (PK) study was performed in previously treated patients with severe hemophilia B (FIX ≤ 2%). The objectives of the study were to determine the PK property and to evaluate safety of rIX-FP up to 28 days following intravenous injection of 25, 50, or 75 IU kg^{-1} of rIX-FP. Sixteen hemophilia treatment centres in 6 countries participated in the study. Twenty-five study subjects received at least 1 dose of rIX-FP; 7 received two doses of rIX-FP. rIX-FP was well tolerated in all subjects. Four AEs in 3 subjects, all mild in severity, were considered possibly related to rIX-FP. No allergic reactions, no SAEs, no inhibitors to FIX, or antibodies to rIX-FP were reported. The mean values post 50 IU kg^{-1} of rIX-FP (n = 13) for incremental recovery; half-life; $AUC_{0\text{-inf}}$ and clearance were 1.38 IU dL^{-1} per IU kg^{-1}; 92 h; 7089 h*IU dL^{-1}; and 0.75 mL hr^{-1} kg^{-1}, respectively. As compared to post 50 IU kg^{-1} of rFIX (n = 8), incremental recovery was 46% higher, the half-life was over 5 times longer, the AUC was sevenfold higher, and the clearance was at least sevenfold slower. In addition, rIX-FP maintained a baseline-corrected mean trough level of 7.4% and 13.4% at Day 7, 2.5% and 5.5% at Day 14 after 25 or 50 IU kg^{-1} rIX-FP administration, respectively. This phase I study has demonstrated excellent clinical safety and improved PK parameters of rIX-FP, which may permit routine prophylaxis with longer treatment intervals between dosing.

FP-MO-03.2-2

Enhancing the pharmacokinetic properties of recombinant factor VIII: A first human dose trial with GlycoPEGylated recombinant factor VIII in patients with hemophilia A

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N8-GP is a recombinant FVIII (rFVIII) molecule with a prolonged half-life. It is produced by site-directed glycoPEGylation where a 40-kilodalton polyethylene glycol molecule is attached to the B-domain *O*-glycan of turoctocog alfa (rFVIII product, Novo Nordisk A/S). This first human dose trial in patients with severe hemophilia A investigated the safety and pharmacokinetic properties of a single intravenous dose of N8-GP. Twenty-six previously treated patients received 1 dose of their previous FVIII product, followed—after a washout period of at least 4 days—by 1 dose of N8-GP at the same dose level (25, 50, or 75 U kg^{-1}). A single dose of N8-GP was well tolerated with a low frequency of adverse events. The type and rate of related adverse events were as expected. None of the patients developed inhibitors. The pharmacokinetic profile of N8-GP appeared to be dose-linear in the range 25–75 U kg^{-1}. The mean incremental recovery of N8-GP was 0.025 ((U mL^{-1}) (U kg^{-1})$^{-1}$), and the mean clearance was 1.79 mL h^{-1} kg^{-1}. The AUC was 14.74 U*h mL^{-1}, 38.85 U*h mL^{-1} and 46.76 U*h mL^{-1}, for the 25, 50 and 75 U kg^{-1} dose groups respectively. The estimated mean time from dosing of N8-GP to a plasma activity of 1% was 3.8 days (25 U kg^{-1}), 6.4 days (50 U kg^{-1}), and 5.3 days (75 U kg^{-1}). The mean terminal half-life of N8-GP was 18.4 h, which was 1.6 times higher than the mean half-life of patients' previous FVIII product. These results indicate that N8-GP will to reduce dosing frequency during prophylaxis.

PO-WE-045

ITI with a VWF/ FVIII concentrate in hemophilia A patients with inhibitors and a poor prognosis for ITI success: Progress report on octanate® in the ObsITI Study

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Background: FVIII inhibitors that neutralize FVIII efficacy are the most serious complication of FVIII replacement therapy in patients with hemophilia A (HemA) and can be overcome with high-dose FVIII (Bonn protocol) during immune tolerance induction (ITI) therapy.
Objectives: To analyse prospective interim ITI success data for octanate®, a human plasma–derived, von Willebrand factor-stabilized FVIII, from the ongoing investigator-initiated Observational Immune Tolerance Induction (ObsITI) study in HemA patients with inhibitors, including those with a poor prognosis for ITI success.
Methods: Data were analysed for a subgroup of 47 consecutively recruited patients who received octanate® as the sole FVIII replacement therapy for a treatment/follow-up period of 36 months. ITI success was determined by fulfilment of three stringent criteria: (1) inhibitor titer <0.6 Bethesda Units, (2) incremental in vivo recovery ≥80% of 1.5% per IU kg^{-1} body weight reference, and (3) FVIII half-life ≥7 h. According to the criteria fulfilled, patients achieved the following: partial response (1), partial success (1, 2), complete success (1, 2, 3), or failure. Following complete success, patients received prophylaxis with VWF-containing FVIII product every second day. Forty-seven patients, all with at least 1 risk factor for a poor ITI outcome, have completed the 36-month observation period.
Results: Inhibitor was eradicated in 35 patients (74.5%). Complete and partial success was achieved in 32 patients (68.1%); 3 patients (6.4%) had a partial response and ITI failed in 12 patients (25.5%). Treatment with octanate® administered according mainly to the Bonn protocol is safe and effective for ITI, even in patients with a poor prognosis for ITI success.

PO-WE-046

Low inhibitor incidence in previously untreated patients with hemophilia A treated with octanate®'s latest interim results from a PUP-GCP clinical trial

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Octanate® is a human, highly purified, double virus-inactivated plasma-derived factor VIII (FVIII) concentrate with all coagulation FVIII bound to its natural stabilizer VWF in a VWF:RCo/FVIII:C ratio of approximately 0.4. Five prospective GCP studies with octanate® were conducted in 77 previously treated patients with severe hemophilia A for an observational period of at least 6 months. None of the PTPs treated exclusively with octanate® developed an inhibitor and no spontaneous report of inhibitor formation in a PTP has been notified to the Drug Safety Unit of Octapharma. To assess the immunogenicity in previously untreated patients (PUPs), a prospective clinical trial was initiated in 2000. Patients with severe hemophilia A without previous exposure to FVIII may be enrolled. Efficacy and tolerability are assessed by a 4-point verbal rating scale. Inhibitor assay according to modified Bethesda method is applied pre-treatment, every 3-4 exposure days (ED 1–20) and every 10 EDs (ED 21–100) but at least every 3 months. Two of 46 (4.3%) subjects receiving treatment developed clinically relevant inhibitor titers over the course of the study. Another 2 displayed inhibitors that disappeared spontaneously without change of dose or dosing interval. All inhibitors developed under on-demand treatment and before ED 50. Of the 46 subjects, 42 had exceeded 50 EDs at the time of this analysis. Octanate® was well tolerated and the adverse event profile was consistent with the population studied. The hemostatic efficacy of octanate in prophylaxis and treatment of bleeding were generally rated as "excellent" and no complications were reported for surgery. Despite frequent inhibitor testing and predominant on-demand treatment, octanate® showed a minimal rate of inhibitor formation (4.3%).

PO-WE-047

Nutritional intake and bone mineral density in boys with severe hemophilia

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Background: Individuals with hemophilia may have lower bone mineral density (BMD) than their healthy peers. Whether suboptimal intake of nutrients essential for bone health is a causative factor remains unknown.
Objectives: The aim was to estimate average daily intakes of calcium (Ca), vitamin D (D), vitamin K (K), and protein in children and youth with severe hemophilia A or B to examine the relationship between nutrition and BMD.
Methods: In this cross-sectional, observational study at McMaster Children's Hospital (Hamilton), nutrient intakes of males ages 4–18 years were estimated from a Food Frequency Questionnaire and compared to the recommended Estimated Average Requirement (EAR) or Adequate Intake (AI). Whole-body BMD was measured by dual-energy x-ray absorptiometry and expressed as Z-score for age.
Results: Sixteen subjects were recruited (13 FVIII, 3 FIX), age (mean [SD]) was 9.6 (4.6). Mean daily nutrient intakes by age compared to EAR or AI are summarized:
Intakes were <EAR/AI for the 14- to18-year-old group: 75% of subjects for Ca, 100% for D, and 25% for K and protein. Mean whole-body BMD Z-score was–1.12 (0.93), significantly lower than 0 ($P < 0.001$).

	Calcium, mg	Vitamin D, IU	Vitamin K, μg	Protein, g
Intake/day	1544 (544)	N = 16	96 (33)	97 (39)
4-8 year, *n* = 12	736 (307)	335(166)	110 (75)	67 (23)
14-18 year, *n* = 4				
4-8 year	EAR for age	EAR for age	AI for age	EAR for age
14-18 year	800	400	55	15
	1100	400	75	44

Conclusions: Inadequate intakes of all bone nutrients occurred only in the adolescent group. BMD Z-score was significantly lower than reference values. The relationship between nutrient status and BMD will be explored with a larger sample group and after adjusting for confounders of physical activity, drug therapy, and joint health.

PO-WE-048

Low bone mineral density and increased fat mass in boys with severe hemophilia

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Background: A growing body of evidence suggests that children with hemophilia are at risk for low bone mineral density (BMD). The majority of studies evaluating the BMD of children with hemophilia have been performed in settings where prophylactic factor replacement is not the standard of care. In addition, these studies have not adjusted for height, age, and weight, thus resulting in possible over- or underestimation of BMD.
Objectives: This study aimed to determine if BMD in Canadian children and youth with severe hemophilia A or B was different from height, age, and weight-adjusted controls.
Methods: In this cross-sectional observational study, subjects 3–18 years, with severe hemophilia A or B and on prophylactic factor replacement, were recruited from the Hamilton-Niagara Regional Hemophilia Centre. Subjects underwent DXA scans of the lumbar spine (LS), bilateral hips and whole body (WB). Results were expressed both as Z scores and as height, age, and weight (HAW) scores.
Results: Seventeen subjects were recruited (3 FIX, 14 FVIII). Mean age (± sd) was 9.0 ± 4.0. LS BMD was increased in subjects with hemophilia compared to controls ($P < 0.01$), while there was no difference in hip BMD. WB BMD was significantly reduced ($P < 0.001$). These differences were maintained whether BMD was expressed as a Z score or as a HAW score. DXA scans identified an increased fat mass ($P < 0.05$) with no statistically significant differences in WB bone mineral content or lean body mass between subjects and controls.
Conclusions: In our cohort of 17 subjects aged 3–18 with severe hemophilia A or B, WB BMD was lower than controls, LS BMD was increased, while hip BMD was the same as controls. The increased fat mass may represent a response to reduced physical activity that, in turn, results in a decrease of cortical bone with a reduced WB BMD.

PO-WE-049

Reduced dose and frequency of NONACOG BETA PEGOL compared to recombinant factor IX and plasma-derived FIX in treatment of bleeding episodes and surgery in hemophilia B patients using population pharmacokinetic modelling and simulations

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Objectives: N9-GP is a recombinant, PEGylated derivative of human coagulation factor IX (FIX) intended for prophylaxis, on-demand treatment of bleeding episodes, and prevention of bleeding during and after surgery. The first human dose (FHD) trial indicated fivefold prolonged half-life of N9-GP and increased recovery compared to both plasma-derived FIX (pdFIX) and recombinant FIX (rFIX). In this context, the use of N9-GP is explored by modelling and simulation.
Methods: A population pharmacokinetic (PK) model was developed, based on FIX activity data derived from the FHD trial (testing 3 dose levels: 25, 50, and 100 U N9-GP kg^{-1} and pdFIX/rFIX). This model was used to simulate the PK profiles of N9-GP compared to rFIX and pdFIX, following the treatment recommendations of WFH Guidelines for the Management of Hemophilia (2006) in 3 clinical pictures: joint bleed, intracranial hemorrhage (ICH), and medium intensive surgery.
Results: The PK of N9-GP, rFIX and pdFIX were all appropriately described by linear 2-compartment models. Recommended factor IX plasma activity levels in case of joint bleed, ICH, as well as during and after surgery is achieved by both a reduced amount of factor concentrate and a significant reduction in dosing frequency, when simulating the PK profile of N9-GP as compared to rFIX and pdFIX.

	Knee bleed		ICH		Surgery	
	No. doses	Total FIX (U kg^{-1})	No. doses	Total FIX (U kg^{-1})	No. doses	Total FIX (U kg^{-1})
N9-GP	1	55	7	200	3	120
pdFIX	4	190	29	1220	17	750
rFIX	4	250	29	1540	17	790

Conclusions: Based on the WFH Guidelines for the Management of Hemophilia and a population PK model, the prolonged half-life and higher recovery of N9-GP is expected to allow significant reduction in both dose level and frequency when treating bleeding episodes and preventing bleeding during and after surgery as compared to the current marketed factor concentrates rFIX and pdFIX.
Conflicts of Interest: P. Collins is a paid consultant to Novo Nordisk, is participating in clinical trials with Novo Nordisk, and has been supported to attend educational events by Novo Nordisk. T. Colberg is a Novo Nordisk employee. E. Watson and J. Møss are Novo Nordisk employees and shareholders.

PO-WE-050

Interim results (2-year) of a French non-interventional study to assess the long-term safety and efficacy of BeneFIX

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Introduction: Clinical studies have demonstrated the efficacy and safety of BeneFIX for on-demand treatment and prophylaxis. However, these studies can present limitations concerning extrapolation of their results to routine clinical practice, and a non-interventional study with high quality standards is an appropriate mean to assess the long-term safety and efficacy in an unselected population of patients.
Objective: To evaluate the safety and efficacy of long-term BeneFIX therapy in the usual care settings in French patients with hemophilia B.
Methods: All patients receiving BeneFIX can be included in this non-interventional study. Data are collected on standardized case-report forms, and monitoring visits are performed regularly to ensure high data quality.
Results: The study started in 2009. As of December 2011, 55 patients from 17 sites were enrolled and evaluable for safety (median age 17.9 years; range 0.2–66.9). Among the 27 patients contributing to the efficacy analysis (FIX:C ≤ 1%, no inhibitor, ≥1 follow-up visit, sufficient diary information), 19 had at least a period of prophylactic treatment (median duration 355 days) and 13 had at least a period of on-demand treatment (median duration 351 days). The mean dose per infusion for prophylactic treatment was 45.2 ± 11.1 IU kg^{-1} (median 42.6; range 25–69). The annualized mean number of

bleeding episodes was respectively 4.2 ± 4.6 (median 4.1) and 17.7 ± 13.2 (median 19.5) during prophylaxis and on-demand treatment. A total of 323 bleeding episodes occurred, mostly in a joint (59.4%). Overall, 85.1% of bleeding episodes were resolved with 1–2 injections. The mean dose per infusion for all bleeding episodes was 46.4 ± 14.4 IU kg^{-1} (median 45.1; range 25–73). All patients had a negative inhibitor test at baseline and have not developed an inhibitor or shown any allergic reaction until now.
Conclusions: This ongoing non-interventional study evaluating treatment with BeneFIX in the usual care settings confirms the safety and efficacy results from clinical trials.

PO-WE-051
Vitamin D improves bone health in patients with hemophilia
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Background: Studies have shown that children with severe hemophilia have reduced bone density compared with gender- and age-matched control subjects. Patients with severe hemophilic joint disease exhibited the lowest bone mineral density. The question that arises is whether the low bone density is due to increased resorption of the bone or to decreased mineralization. In this study we would like to look at markers of bone resorption/formation as well as the incidence of vitamin D deficiency and the impact of Vitamin D supplementation on bone mineral markers and density once the deficiency is corrected.
Objective: Our hypothesis is that (1) vitamin D deficiency is prevalent in patients with hemophilia and (2) correcting the vitamin D deficiency with vitamin D and calcium will improve the bone health.
Methods: Seventeen pediatric hemophilia patients were screened for their vitamin D and calcium intake, extent of physical activity, vitamin D levels, bone density, bone age, and markers of bone resorption (N-telopeptide) and formation (osteocalcin). Patients who were deficient in vitamin D (<32ng ml^{-1}) were supplemented with vitamin D and calcium for 1 year before the same parameters were remeasured.
Results: Seventeen patients have been enrolled, and here we present preliminary data of our study. 14/17(82%) were vitamin-D deficient, and nutritional assessment showed 11/17 (65%) had low vitamin-D intake. 6/17 (35%) had low bone density (z <-2). Of the 6 patients for whom osteocalcin levels pre- and post-vitamin D are available, 4 (67%) showed improvement. Urine N-telopeptide/Cr levels decreased in 5/5 patients for whom results are available.
Conclusions: Vitamin D deficiency is highly prevalent in pediatric patients with hemophilia. Preliminary data show that vitamin D treatment resulted in increased bone mineralization and reduced bone resorption.

PO-WE-052
Managing major surgical operations in a large hemophilia centre in northern India
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Our hemophilia centre in MAMC and LN Hospital, with 1026 hemophilia patients, was involved in managing 17 major surgical operations in 15 patients. With a view to drawing up guidelines for the use of antihemophilic factor (AHF) during a proposed surgery to achieve sufficient hemostasis for the desired duration, thus avoiding bleeding complications, chart reviews were done for the 15 patients who underwent 17 major surgical operations in our hospital during past 3 years. Twelve were hemophilia-A and the other 3 were hemophilia-B. All the patients were negative for inhibitor screening. Fourteen patients had a prior detailed work-up in hemophilia centre, whereas the remaining 1 was diagnosed post-operatively. After reassessment, patients were given AHF replacements pre- and post-operatively, as per our protocol. Out of 15 patients, 5 had abdominal surgery, 6 orthopedic surgery, 2 ophthalmologic surgery, 1 reconstructive urosurgery, and 1 otological surgery. One child had 3 separate eye operations, thus totalling 17 surgeries in 15 patients. All these operations required general anesthesia. Total AHF requirements varied across the type of operations, ranging from 118 IU Kg^{-1} (for ruptured appendix) to 13 IU Kg^{-1} for ophthalmological, averaging 57 IU Kg^{-1}. The mean duration of hospitalization was 7 days, range 15 days (orthopedic surgery) to 1 day (eye surgery). The AHF requirement was directly proportional to the extensiveness of surgery. There were no hemostatic inadequacies during the period, nor were there any post-operative surgical complications. Successful hemostasis was achieved in all instances. Details of AHF used and monitoring are discussed. A good pre-operative evaluation, followed by appropriate AHF replacement during the different phases of surgery, results in successful hemostasis and outcome. A diagnosis of hemophilia should be kept in mind in cases with excessive and unexplained bleeding during/following a surgical treatment.

PO-WE-053
Safety and efficacy of B-domain-deleted recombinant factor VIII (ReFacto AF®) in usual healthcare settings
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Aim: The aim of the study is to continuously monitor safety and efficacy of ReFacto AF® in usual health care settings.
Method: Patient data are collected via a non-interventional trial, open to all patients in Germany and Austria treated with ReFacto AF®.
Result: Within the last 2½ years, 59 patients were recruited of whom 44 were eligible for analysis with at least 1 documented injection. Three patients were <6 years upon entry. All 44 patients were previously treated (PTPs), and almost all (43) had more than 100 exposure days upon entry into the study. One patient had a pre-existing inhibitor to FVIII. Twenty-six patients had moderate to severe hemophilia A. Mean duration of study participation was 511 days overall and 319 days in children, with a median age of 22.63 years. At baseline, 33 patients received prophylactic, 7 on-demand and 3 a mixed treatment regime; 1 was unclassified. Efficacy was evaluated by the number of FVIII injections needed to control a bleeding episode and by the reduction of bleeding episodes due to prophylaxis. Only 1–2 injections per bleed were needed. The mean number of annual bleeds (mean ± SD) was reduced from 28.2 ± 20.0 in the on-demand regime to 7.2 ± 3.4 in the mixed regime and to 5.6 ± 4.8 by prophylaxis. Overall, 16 of all 44 patients reported any adverse events (AEs) and/or serious adverse events (SAEs); 5 of these patients reported both AEs and SAEs. No AEs or SAEs were related to ReFacto AF®. In particular, there was no inhibitor with ReFacto AF®. No apparent relationship was seen between the individual total ReFacto AF® administration and the occurrence of SAEs over 28 months.
Conclusion: The data presented here underlines that ReFacto AF® is efficacious and well tolerated and reflects safety and efficacy from conducted clinical trials.

PO-WE-054
Four-year interim results of a non-interventional trial to assess the safety and efficacy of treatment with recombinant factor IX, BeneFIX®
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Introduction and Objective: Non-interventional trials with high quality standards, such as approval by an ethics committee and monitoring, are appropriate means to assess long-term safety and efficacy in rare indications such as hemophilia B. Here, we report on the results of a 48-month study evaluating the safety and efficacy of treatment with recombinant factor IX (rFIX).
Methods: This study is a non-interventional study (NIT). All patients receiving rFIX can be included. Data on safety and efficacy are collected on standardized case-report forms, and monitoring visits are performed regularly to ensure high data quality. The focus is on the collection of adverse events, including inhibitor development and allergic reactions.
Results: After 48 months of the study, 36 of 54 registered patients were evaluable for safety and efficacy, 3 of them previously untreated (PTPs). The median age of patients was 16.5 years (range 0.2–64.9). The median annual dose was 120 747 IU/year for prophylactic, 70 134 IU/year for on-demand treatment, and 128 158 IU/year with a mixed regimen. In a median of 930 observation days, patients experienced an overall median of 6.5 bleeding episodes. Annually, 1.9 bleeding episodes (median) occurred, 0.90 with prophylaxis, 3.71 with on-demand, and 6.21 with a mixed regimen. All patients had negative inhibitor tests at baseline and did not develop an inhibitor or show any allergic reaction. Ten patients have reported a total of 56 AEs, none related to BeneFIX®. Nine patients have reported 24 SAEs, 1 considered by the investigator to be related to BeneFIX®.
Conclusions: This NIT evaluating treatment with BeneFIX® in the usual healthcare setting underlines the safety and efficacy results from clinical trials, and highlights the acceptance of patients and physicians to collect data in the case of rare indications such as hemophilia B.

PO-WE-055
Safety and pharmacokinetic results of a phase I/II clinical trial of recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP) in previously treated patients with hemophilia B (PROLONG-9FP)
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The goal of hemophilia therapy is to treat and prevent hemorrhage. Currently available FIX products have a short half-life, requiring intravenous prophylactic treatment 2–3 times a week to achieve a significant reduction of spontaneous bleeding episodes. A phase I/II, open-label, multicentre, safety, pharmacokinetic (PK) and efficacy study of recombinant fusion protein linking coagulation factor IX with recombinant albumin (rIX-FP) is being performed in previously treated patients with severe hemophilia B (FIX ≤ 2%) as part of the PROLONG-9FP clinical program. The objectives of the study are to determine long term safety of rIX-FP and to evaluate PK of rIX-FP. The study consists of screening, a 1to14-day rIX-FP PK evaluation, and an approximately 5-month safety and efficacy evaluation period of both prophylaxis and on-demand treatment of bleeding episodes with rIX-FP. Plasma FIX activity levels are measured prior to rIX-FP infusion, and 30 min, 3, 24, 72, 120, 168, and 240 h after 25 IU kg^{-1} rIX-FP infusion. Following PK evaluation, subjects begin either weekly prophylaxis treatment or on-demand treatment with rIX-FP for the remaining study period. Safety is assessed on the basis of the type and incidence of adverse events, development of antibodies against rIX-FP and inhibitors against FIX, laboratory parameters (hematology, biochemistry), vital signs, and physical examination. Seventeen subjects from hemophilia treatment centres in Israel and Bulgaria have participated in the study. rIX-FP has been well tolerated in all subjects. No allergic reactions, SAEs,or inhibitors to FIX have been reported as of January 10, 2012. All PK parameters were significantly improved over currently marketed FIX products. Thus far, the phase I/II study has demonstrated clinical safety and improved PK parameters of rIX-FP. Due to its prolonged half-life, rIX-FP has the potential to permit routine prophylaxis with longer treatment intervals between dosing. Detailed PK analysis and the safety data will be presented.

PO-WE-057

Study design of 2 randomized, crossover, open-label trials to evaluate the pharmacokinetics, efficacy, and safety of plasma protein-free recombinant factor VIII formulated with sucrose (BAY 81-8973) in previously treated patients with severe hemophilia A

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Objectives: BAY 81-8973 is a new, full-length recombinant factor VIII (rFVIII) product. We describe the Leopold I and II studies, which will assess pharmacokinetics (PK), safety, and efficacy of BAY 81-8973 for prophylaxis and treatment of bleeds in patients with severe hemophilia A (HemA). Pooled results will assess bleeding frequency and in vivo recovery in both trials.
Methods: Leopold I and II are 1-year, open-label, randomized, crossover studies. Patients receive BAY 81-8973 with potency assigned using a chromogenic substrate assay (CS/EP) or mimicking a classical 1-stage assay (CS/ADJ) for 6 months. Leopold I has 2 parts: assessing (a) PK and (b) safety, tolerability, and efficacy of prophylaxis (2–3x/wk) with BAY 81-8973. In Leopold II, high- and low-dose prophylaxis regimens are compared with on-demand treatment. Males aged 12–65 years with ≥150 prior exposure days to FVIII and no inhibitor history were eligible. Patients currently received on-demand or prophylaxis FVIII treatment (Leo Ib) or on-demand FVIII treatment (no prophylaxis for >6 consecutive months in 5 years) (Leo II). Primary outcomes assess safety/efficacy of BAY 81-8973 for prophylaxis and bleed treatment (Leo Ib) and superiority of prophylaxis over on-demand therapy, assessed by number of bleeds per year (Leo II). Pooled data from both trials will be analyzed to show non-inferiority of CS/EP- vs. CS/ADJ-based dosing.
Results: With recruitment complete, 62 and 80 patients have enrolled in Leopold I and II, respectively; 26 patients completed Leopold Ia (PK). No safety concerns have arisen.
Conclusions: The Leopold studies will assess BAY 81-8973 PK, safety, tolerability, and efficacy, and noninferiority of the CS/EP assay and superiority of prophylaxis vs. on-demand treatment for bleeding frequency in patients with severe HemA.
Contribution to the Practice/Evidence Base of Hemophilia and Bleeding Disorders: The Leopold studies will determine the clinical utility of BAY 81-8973 and evaluate switching from 1-stage to chromogenic rFVIII potency assignment.
Conflicts of interest: K. Kavakli has received research funding, honoraria, and scientific congress travel expenses from Bayer. M. Maas Enriquez is an employee of Bayer Pharma AG.

PO-WE-058

Regional differences in baseline patient-reported outcomes in a randomized, controlled, prospective trial of secondary prophylaxis VS on-demand treatment in patients with severe hemophilia A

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Objectives: In patients with severe hemophilia A, prophylaxis reduces joint bleeding. When started early in life, prophylaxis significantly reduces the development of arthropathy; when started later, the effects on arthropathy are unclear. We present baseline, patient-reported outcomes (PRO) data from a trial (SPINART) evaluating bleeding frequency in patients receiving secondary prophylaxis vs. on-demand treatment with sucrose-formulated recombinant factor VIII (rFVIII-FS).
Methods: This 3-year, randomized, controlled, prospective trial in Argentina, Bulgaria, Romania, and the USA enrolled previously treated patients aged 12–50 years with severe hemophilia A who had not received prophylaxis for ≥12 consecutive months in the past 5 years. Patients were randomized to rFVIII-FS prophylaxis (25 IU kg^{-1} 3x/wk) or on-demand treatment. PRO assessments included health status (EQ-5D utility and visual analog scale [VAS] scores), hemophilia-related quality of life (Hemo-QoL-A), and physical activities questionnaires. Baseline data were analyzed by country (US vs. non-US) with *t* tests and Fisher's exact tests.
Results: Baseline PROs were balanced across treatments (N = 84 patients). Mean baseline EQ-5D utility (US, 0.84; non-US, 0.78; $P = 0.04$) and VAS scores (US, 81; non-US, 68; $P < 0.001$) were higher in US vs. non-US patients. All domain scores on the Hemo-QoL A were higher for US vs. non-US patients, with a marked difference in physical functioning (US, 71; non-US, 53; $P < 0.001$). US patients reported higher physical activity vs. non-US patients ($P = 0.01$); 47% of US vs. 29% of non-US patients had unrestricted activity, and 12% vs 41% had limited school, work, or recreation activity.
Conclusions/Contribution to the Practice/Evidence Base of Hemophilia and Bleeding Disorders: Better baseline QoL scores and less physical activity limitation observed in US vesus non-US patients may result from more severe hemarthropathy in non-US patients.
Conflicts of Interest: S. Valluri and W. Hong are employees of Bayer HealthCare Pharmaceuticals. M. Reding has been an advisory board participant for Bayer. T. Lissitchkov, L. Rusen, and V. Uscatescu have no conflicts of interest to declare.

PO-WE-059

Safety of continuous rFVIII-FS infusions via 8-hour 250cc 0.9 IV bag

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Statement of the Problem: The safety and efficacy of continuous rFVIII-FS infusions has been documented. A variety of methods of continuous infusions have been used by hemophilia treatment centres (HTCs), most often with a mini-pump not widely available in some areas. rFVIII-FS is known to adhere to the polyethol-gylcol tubing of IV tubing, potentially affecting accurate dosing of factor.
Aim: This study identified the safety and efficacy of continuous infusion using a 250cc 0.9 NS IV bag via standard pump every 8 h without additional infection risk.
Method: Ten hemophilia A subjects participated. Subjects received bolus rFVIII (Kogenate FS ™) infusion with a pre and 1-h post rFVIII-FS levels determining recovery levels. On the day of the 8-h continuous infusion, subjects received bolus rFVIII-FS for correction to 100%, followed by individually calculated continuous infusion rFVIII in 250 cc 0.9 NS. rFVIII levels were drawn from the IV bag and peripherally at the following time points: pre-infusion, 1-h, 2-h, 3-h, 4-h, 5-h, 6-h, and 8-h. Blood cultures were drawn from the IV-bag and IV tubing pre-infusion, 4-h, and 8-h.
Results: Fourteen subjects agreed to participate; 4 failed to follow up, so 10 subjects were included in analysis (7 severe, 2 moderate, and 1 mild). The age range was 26–62 years; the ethnicities were 5 African- American, 4 Caucasian, and 1 Hispanic. The ranges of rFVIII-FS were 65–135% (blood) and 62–200% (bag). Serum rFVIII-FS levels remained stable throughout the 8-h time period despite decrease in rFVIII-FS levels in the IV bag consistent with previous rFVIII-FS continuous infusion studies. After the start of infusion, there were no significant differences noted between the hourly rFVIII-FS levels in subjects and IV bag values (p-value range 0.36 to 0.9). A total of 60 time points of cultures during the study were negative. All subjects tolerated the 8-h infusion without reported adverse events or inhibitor development.
Conclusions: The alternative delivery method and safety of 8-h continuous infusions of rFVIII-FS has been confirmed and well tolerated by all subjects. This method can be helpful where mini-pumps are not available, allowing a standard safe delivery of rFVIII-FS continuous infusion by available means.

PO-WE-061

Pharmacokinetic results and correlations with intrinsic von Willebrand factor levels from a randomized, double-blind study of prophylaxis with once-weekly BAY 79-4980 vs. 3-times-weekly sucrose-formulated recombinant factor VIII

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Objectives: We present pharmacokinetic (PK) data and correlations with intrinsic von Willebrand factor (VWF) levels in patients with severe hemophilia A in a phase II trial of BAY 79-4980 (liposome-reconstituted sucrose-formulated recombinant factor VIII [rFVIII-FS]) or rFVIII-FS prophylaxis.
Methods: Previously treated, non-inhibitor patients in a multinational, randomized, double-blind study received prophylaxis with once-weekly BAY 79-4980 (35 IU kg^{-1}) or thrice-weekly rFVIII-FS (25 IU kg^{-1}). PK parameters (area under the curve and maximum concentration normalized for body weight [AUC_{norm}, $C_{max,norm}$], half-life [$T_{1/2}$], mean residence time [MRT], and clearance) were evaluated at weeks 1 and 26. Spearman rank correlations assessed relationships of vWF levels with patient age and PK.
Results: Of 131 per-protocol (PP) patients (age range 13-64 years; BAY 79-4980, $n = 63$; rFVIII-FS, $n = 68$), 27 ($n = 15$; $n = 12$, respectively) were evaluable for PK assessment. Baseline VWF levels (means 75–177%, depending on age group) correlated with PP patient age ($r = 0.53$; $P < 0.0001$). There was no significant difference in PK results between treatments; thus, all patients were analysed together. At weeks 1 and 26, AUC_{norm}, MRT, and $T_{1/2}$ significantly increased with increased VWF levels (all $P \leq 0.001$); clearance significantly decreased with increased VWF levels (week 1, $P = 0.003$; week 26, $P = 0.002$). $C_{max,norm}$ was not correlated with VWF levels (week 1, $P = 0.8$; week 26, $P = 0.4$).
Conclusions: In these patients, VWF levels increased with age. The AUC_{norm}, MRT, and $T_{1/2}$ of both BAY 79-4980 and rFVIII-FS were significantly increased and clearance was significantly decreased with increasing VWF levels, with no influence on $C_{max,norm}$.
Contribution to the Practice/Evidence Base of Hemophilia and Bleeding Disorders: VWF levels were significantly positively correlated with patient age as well as AUC_{norm}, MRT, and $T_{1/2}$ of BAY 79-4980 and rFVIII-FS.
Conflicts of Interest: J. Powell receives clinical trial support from Bayer, Octapharma, and Biogen Idec. M. Maas Enriquez is an employee of Bayer Pharma AG. I. Scharrer has received research funding from Bayer HealthCare.

PO-WE-062

Experience with electronic patient diaries in a randomized, double-blind study of prophylaxis with once-weekly BAY 79-4980 vs. 3-times-weekly sucrose-formulated recombinant factor VIII

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Objectives: Electronic patient diaries (EPDs) can be used to transmit clinical data. We describe EPD use in a randomized, double-blind phase II trial in patients with severe hemophilia A receiving prophylaxis with BAY 79-4980 (liposome-reconstituted sucrose-formulated recombinant factor VIII [rFVIII-FS]) or rFVIII-FS.
Methods: Patients used EPDs (smartphones) to record data including information on bleeds (e.g., date, time, type, location) and FVIII injections (e.g., date, time, reason). Lot numbers were entered by barcode scanning. Data were automatically transmitted to a centralized server. Reports generated by the database were sent to the site to monitor patient adherence, dosing, and bleeding outcome. A non-validated EPD satisfaction survey based on patient experience was completed by investigators and study coordinators to assess data including overall satisfaction and frequent problems.

Results: In total, 139 patients (median study duration 351 days) documented 19 500 injections for prophylaxis and bleeding treatment in the EPDs. Date, time, dose, and lot numbers were available for >99% of injections. The median interval between infusion administration and reporting in the EPD was 1.7 h; 2/3 of patients completed the EPD ≤ 1 day after injection (data entry time for most patients ≤ 30 min). Investigators from 29 sites in 9 countries completed 64 satisfaction questionnaires. Most considered the EPD to be user friendly (87%) and easy to understand (94%). Common issues included sporadic scanner failure (n = 31/64), data transmission issues (n = 31/64), and duplicated data entry (n = 14/64).
Conclusions/Contribution to the Practice/Evidence Base of Hemophilia and Bleeding Disorders: EPDs successfully communicated clinical data from patients to investigators in this trial. Infusions were documented in the EPD within a median of 1.7 h of FVIII injection, indicating good patient compliance with documentation.
Conflicts of Interest: K. Schafer is a member of the Bayer HealthCare Pharmaceuticals Speaker Bureau. D. Tseneklidou-Stoeter and M. Maas Enriquez are employees of Bayer Pharma AG. L. Nelson is a contractor for Bayer HealthCare Pharmaceuticals.

PO-WE-063

Efficacy, safety, and pharmacokinetics results of a phase II, double-blinded, randomized, cross-over study with Biostate® in subjects with hemophilia A (the SWIFT-HA Study)

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The SWIFT ("Studies with von Willbrand factor/Factor VIII") program is evaluating the pharmacokinetics (PK), efficacy, and safety of Biostate® in hemophilia A and VWD patients for global availability. All SWIFT studies are designed in accordance with the European clinical and pediatric guidelines. Biostate® (CSL Biotherapies) is a low-volume, highly active, plasma-derived von Willebrand Factor (VWF)/factor VIII (FVIII) concentrate that contains a large proportion of high-molecular-weight VWF multimers and a VWF:FVIII ratio of greater than 2:1.
Objective: The SWIFT-HA study aimed to investigate the efficacy and safety of Biostate® in subjects with hemophilia A (>12 year of age). The study also assessed whether the PK of Biostate®SP (Study Product) and Biostate®RP (Reference Product) are comparable. Biostate®RP is the predecessor of Biostate® SP. The new product is currently manufactured using an additional filtration step to enhance prion removal.
Method: PK Part 1 consisted of a single dose 50 IU kg^{-1} of either Biostate®RP or Biostate®SP in a double-blind, cross-over design on Day 1 and 8 (n = 16). In PK Part 2 the PK of Biostate®SP was repeated on Day 180 (n = 15). The Efficacy/Safety Part consisted of treatment for up to 6 months of Biostate®SP (min. 50 exposure days, n = 81).
Result: The mean FVIII plasma PK results were comparable between Biostate®SP and RP. The PK results of SP over time (Part 1 and 2) were similar. Hemostatic efficacy was judged by investigators as either excellent/good for at least 97.5% of treatments in any monthly period, in 96.4% of bleeding events, and in 80% and 100% of major and minor surgical events. The subjects assessed the hemostatic efficacy of Biostate® as excellent or good in 87.9% of the cases. Biostate was well tolerated without any findings of concern.
Conclusion: Biostate®SP is shown to be bioequivalent to Biostate®RP and its PK profile is similar over time. Biostate®SP is efficacious and safe for hemostatic efficacy treatment in hemophilia A patients.

PO-WE-064

Pharmacokinetics, efficacy and safety interim results of an open-label, multi-centre study with Biostate® in subjects with von Willebrand disease (the SWIFT-VWD Study)

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The SWIFT (Studies with von Willebrand factor/factor VIII) program is evaluating the pharmacokinetics (PK), efficacy and safety of Biostate® in hemophilia A and VWD patients for global availability. All SWIFT studies are designed in accordance with European clinical and pediatric guidelines. Biostate® (CSL Biotherapies) is a low-volume, highly active, plasma-derived von Willebrand factor (VWF)/factor VIII (FVIII) concentrate that contains a large proportion of high-molecular-weight VWF multimers and a VWF:FVIII ratio of greater than 2:1. The VWF profile of Biostate® resembles that of normal human plasma and is strongly correlated with high collagen binding activity, effective platelet adhesion, and efficient platelet aggregation.
Objective: The SWIFT-VWD study aimed to investigate the hemostatic efficacy and safety of Biostate® in subjects with severe VWD (≥12 years of age) who require treatment of non-surgical bleed (NSB) events. In addition, the initial and repeat PK profile of Biostate® was determined. The study of a prophylaxis regimen is ongoing.
Method: PK consisted of a single dose 80 IU kg^{-1} of Biostate® on Day 1 (n = 15) and Day 180 (n = 8, Type 3 VWD subjects only). In the efficacy/safety part of the study, subjects received Biostate® as on-demand therapy for 12 months (n = 22 including 3 adolescents; 13 subjects have Type 3 VWD).
Result: After an initial Biostate® infusion, the mean VWF:RCo, VWF:Ag, and VWF:CB plasma concentrations developed similarly over time, and were similar in the repeat PK evaluation. In the efficacy part of the study, 21 subjects required treatment for a total of 405 NSBs. Seven of these were classified as major mucosal bleeds. Hemostatic efficacy was judged by both subjects and investigators as excellent or good in more than 96% of the treatments; Biostate® was well tolerated without any findings of concern.
Conclusion: Biostate® PK profile is similar over time. Biostate® is efficacious and safe for the treatment of bleeding in VWD patients.

PO-WE-065

A prospective post-authorization safety surveillance (J-PASS) evaluating clinical experience in Japanese PTPs with antihemophilic factor (recombinant) plasma/albumin free method (rAHF-PFM)

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Introduction: In 2007, Japanese Post-Authorization Safety Surveillance (J-PASS) programs were initiated along with J-PUPs (previously untreated patients) to evaluate the safety and efficacy of ADVATE (rAHF-PFM) in routine clinical practice settings for re-examination of product under Japanese ordinance Good Post-Marketing Study Practice (GPSP).
Method: Prospective, multicentre, open-label observational surveillance was designed to capture data of hemophilia A subjects with any regimen of rAHF-PFM by physicians, any age, with more than 3 exposure dates (EDs), with or without inhibitors at time of enrollment. Data including inhibitor development were collected and evaluated at 6-month intervals up to 2 years using the electronic data-capture system (EDC).
Result: As of November 22, 2011, data for 383 subjects from 96 sites had been collected, and 192 subjects (50%) had completed the 2-year study period. The majority (86.2%) had severe or moderately severe hemophilia (FVIII ≤ 2%). The mean age was 25.5 ± 17.6 years (range 1–81 years). At study entry, EDs ranged from ≤ 50EDs (n = 42), 51-150EDs (n = 16), to ≥151EDs (n = 325). Thirty-six subjects had inhibitor history at the time of enrollment, 4 of which had a positive titer at study start. Of the 32 subjects with a prior history of an inhibitor at study start, none developed recurrent inhibitors. Three of 39 subjects with ≤ 50EDs at entry and no inhibitor history developed an inhibitor (7.7%, 95%CI:1.62, 20.87), all were low titer. No de novo inhibitor developed in 308 subjects with ≥51ED (0%, 95%CI:0, 1.19). No inhibitor was detected in subjects who switched from pd-FVIII or 2nd generation rFVIII to rAHF-PFM. This study will be completed by June 2012.
Conclusions: This interim result further supports the safety profile of rAHF-PFM in a large Japanese hemophilia A population.

PO-WE-066

Clinical experience of previously untreated patients (PUPs) with antihemophilic factor (recombinant), plasma/albumin-free method from post-authorization safety surveillance in Japan: 5-year update

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Introduction: PUP studies are important to understand the natural history of hemophilia treatment. Clinical real-life practice during the early treatment phase of Japanese persons with hemophilia has been documented by the ADVATE (rAHF-PFM (ADVATE) PASS program since 2007 as a re-examination of product under the Japanese ordinance Good Post-Marketing Study Practice (GPSP).
Method: This prospective, multicentre, open-label,observational surveillance cohort study was conducted to assess data of PUPs with ≤ 3 exposure days (EDs) at study entry. Data was collected every 6 months using the electronic data-capture system (EDC).
Result: As of November 30, 2011, data for 98 PUPs (0 ED: 80, 1-3 EDs: 18) out of 119 enrolled patients from 62 sites was available. 80% of subjects had FVIII ≤ 2%, 5% had FVIII >2–5%, 12% had FVIII >5%, and 3% had missing data. The mean age at entry was 4.1 ± 10.5 years (median 1 year, range 0–81 years). 52% of 98 patients had over 50 infusions (mean 87 ± 116, median 42, 1–502 infusions) on study. Most patients were diagnosed and started treatment before the age of 1 year. At time of last report, 15 subjects (15.3%, 95% CI: 8.83, 23.99) had developed an inhibitor (6 high- and 9 low-titer). Of the 15 inhibitor cases, 8 had 1 or more of the following risk factors: intracranial hemorrhage (ICH) and intensive FVIII treatment before 1 year of age (n = 6); family history of inhibitors (n = 5).
Conclusions: The safety profile of ADVATE in Japanese rAHF-PFM PUPs appears consistent with previous reports with 15.3% (95% CI: 8.83, 23.99) of subjects developing an inhibitor as of this report. Strategies to prevent ICH and avoid intensive treatment during the early FVIII exposure period should be explored as a means to reduce the incidence of inhibitor development.

PO-WE-067

Safety and Efficacy of Anti Inhibitor Coagulation Complex (AICC) In Routine Clinical Management: A Post-Authorization Safety Study (PASS)

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Introduction: Hemophilia patients with inhibitors present a treatment challenge due to an increased risk of bleeds that may be hard to control. Activated prothrombin complex concentrate AICC [FEIBA NF], has been used prophylacticly or on demand for the prevention and management of bleeding events for over three decades. FEIBA NF PASS is a prospective open-label, observational surveillance program that documents the adverse events (AEs) and hemostatic efficacy associated with FEIBA NF use in routine practice. Data collection includes FEIBA infusion details as well as bleeding information and efficacy assessment.

Methods: An electronic data collection system is utilized to monitor the safety and efficacy of FEIBA NF in subjects for 12 ± 2 months. Standard quality of life assessment tools (SF-36, Peds-QL and EQ-5D) are used at time of enrollment and at the end of the observation period.

Results: As of December 2011, forty study sites in nine countries have been initiated and over 70 patients have been enrolled. Fifty patients have completed a 1 year study period. Enrollment has closed in the UK, France Germany and Spain, but is still ongoing in Belgium, Sweden, Poland, Italy, Canada, Brazil and the United States. 84% of enrolled patients have been diagnosed with congenital hemophilia A, 15% with acquired hemophilia A and one patient with congenital hemophilia B. Forty-one patients were identified as receiving prophylaxis therapy at time of enrollment, and 12 patients were receiving AICC while on ITI. Three related serious adverse events have been reported, all associated with on demand treatment.

Conclusion: FEIBA NF PASS provides an opportunity to collect data on hemophilic patients with inhibitors during routine care, and serves as an invaluable tool for documenting the safety and efficacy of FEIBA NF in a variety of clinical settings including prophylaxis and bleed management during ITI.

08-CLOTTING FACTOR CONCENTRATES

FP-TU-01.1-2
Recombinant FVIIa-XTEN as a long-lasting form of rFVIIa with an enhanced PK profile

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Objectives: For hemophilia A and B patients with inhibitors, bypass agents, such as rFVIIa, demonstrate efficacy in stopping bleeding. However, rFVIIa has a circulating half-life of 2–3 hours, so patients are primarily limited to on-demand regimens and often require multiple doses to control bleeding. Development of a long-lasting form of rFVIIa may reduce injection frequency and enable prophylaxis. Thus, recombinant linkage of rFVIIa to XTEN (unstructured polypeptide repeats lacking hydrophobic residues) of 288 and 864 amino acids was investigated as an approach for increasing the half-life of rFVIIa.
Methods: The pharmacokinetics in hemophilia A mice of rFVIIa-XTEN288 and rFVIIa-XTEN864, rFVIIa (NovoSeven®), and rFVIIaFc were determined using the soluble tissue factor-dependent prothrombin time (sTF-PT) assay.
Results: rFVIIa-XTEN288 and rFVIIa-XTEN864 had improved PK profiles compared to rFVIIa and rFVIIaFc. All 4 molecules undergo 2-compartment decay with comparable distribution half-life except for that of rFVIIa-XTEN864, which was ~2.5–3.1-fold longer. The terminal half-lives of rFVIIa-XTEN288 and rFVIIaXTEN864 were 7.6–7.8-fold increased vs. rFVIIa, respectively, and 2.2-fold increased vs. rFVIIaFc. The AUC/dose of rFVIIa-XTEN288 and rFVIIaXTEN864 were 5.0–6.4-fold increased vs. rFVIIa, respectively, and 3.7–4.7-fold increased vs. rFVIIaFc, respectively. Further, the activity of rFVIIa-XTEN288 and rFVIIa-XTEN864 were compared to rFVIIa and rFVIIaFc by thrombin generation assay (TGA) and rotation thromboelastometry (ROTEM).
Conclusion: XTEN fusion is a novel strategy to improve the circulating half-life of rFVIIa beyond that which has been achieved by Fc fusion. Approaches to significantly improve the activity potency of rFVIIa-XTEN are under development, so that rFVIIa-XTEN may provide on-demand and prophylactic benefits for hemophilia A and B patients with inhibitors and patients with FVII deficiency.

FP-TU-01.1-3
One-year clinical experience with solvent/detergent-filtered (S/D-F) cryoprecipitate

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Background: A new medical device was developed for solvent/detergent inactivation and filtration (S/D-F) of small pools of cryoprecipitate. S/D-F cryoprecipitate is dose-labeled for FVIII, VWF RCo activity units, as well as clottable fibrinogen, which allows for proper dose calculation.
Aim of Study: Follow-up on clinical efficiency and safety of S/D-F cryoprecipitate.
Patients: S/D-F cryoprecipitate was used by 20 severe hemophilia A patients for treatment of bleeding episodes according to national guidelines. This group of patients had a mean of 25 exposure days during the last 15 months. Five adult patients are on a low-dose prophylaxis protocol (20 IU FVIII kg^{-1} once weekly) as well as a 3-year-old child (20 IU FVIII kg^{-1} twice weekly). Five patients used S/D-F cryoprecipitate for surgical prophylaxis during circumcision, 1 patient for ankle arthroscopic arthrodesis, and 3 patients for knee arthroscopic synovial cautery. It was also used for surgical prophylaxis for a type 3 VWD patient for large umbilical hernia repair operation as well as for a type 1 VWD patient for excision of a pilonidal sinus. S/D-F cryoprecipitate was also given to correct fibrinogen deficiency in a patient with hereditary afibrinogenemia at a dose of 60 mg fibrinogen kg^{-1}.
Results: S/D-F cryoprecipitate was effective in controlling bleeding episodes and in reducing or preventing bleeding episodes in patients following FVIII low-dose prophylaxis protocol. Intraoperative as well as post-operative hemostasis was successful in hemophilia A patients as well as the two VWD patients. In the patient with hereditary afibrinogenemia, transfusion of S/D-F cryoprecipitate at a dose of 60 mg fibrinogen kg^{-1} body weight was able to correct prothrombin time and activated partial thromboplastin time (aPTT) to normal and to increase the blood level of fibrinogen from <5 mg to 50 mg dL^{-1}. None of the patients treated by S/D-F cryoprecipitate has so far developed anti-FVIII inhibitors. No adverse events were reported.
Conclusion: Accumulating clinical experience using the S/D-F cryoprecipitate strongly suggests that it is both safe and efficient.

FP-TU-01.1-4
Enhanced phosphorylation and sulfation of human recombinant factor IX for production by the hepatoma cell line HuH-7

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Due to the increasing demand for recombinant proteins, the interest in mammalian cell culture, especially of Chinese hamster ovary (CHO) cells, is growing rapidly. This is accompanied by the desire to improve cell lines in order to achieve higher titers and a better product quality. Until recently, human cell lines for coagulation factor production were unavoidable. Indeed, a human cell–based expression system can provide recombinant coagulation factors whose post-translational modifications could be as close as to those of plasma-derived proteins. Recombinant human factor IX (rhFIX) molecules are usually prescribed for the treatment of patients with hemophilia B. CHO cells are commonly used for the production of rhFIX, but their weak capacity for introducing efficient phosphorylation may explain at least partly the lower in vivo recovery observed in patients compared to plasma-derived FIX molecule. In the present study, the human hepatoma cell line HuH-7 was used for the production of an rhFIX as FIX is primarily expressed in the liver. The human rhFIX secreted by a HuH-7 clone stably transfected clone with the corresponding expression vector was biologically active. The molecule was then purified for a detailed evaluation of post-translational modifications in comparison to FIX molecules available on the market (Benefix® and Mononine®). Glycosylation and sialylation profiles were similar to plasma-derived and rhFIX, and mass spectrometry analysis demonstrated the presence of phosphorylated and sulfated forms of rhFIX secreted by the HuH-7 cell clone. These qualitative studies did not allow us to precisely quantify each form and the ratio of phosphorylated form, but our data strongly suggest that HuH-7 cells are more efficient than CHO cells for rhFIX phosphorylation. In conclusion, HuH-7 cells may represent an effective cellular system for the production of rhFIX with improved phosphorylation. Next steps, including large-scale expression, phosphorylation/sulfation quantitation, and pharmacokinetic parameter establishment, are currently being carried out in our laboratory.

FP-TH-01.1-2
Measurement of Adamts13 in a factor VIII concentrate, 8Y®

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Objectives: Case reports have been published showing that levels of the VWF cleavage protein, ADAMTS-13, in the factor VIII concentrate 8Y® are sufficient for it to be used successfully in the treatment of congenital thrombotic thrombocytopenic purpura (TTP). In this study, the concentration and potency of ADAMTS-13 in 13 lots of 8Y were determined and compared to those measured in a number of comparator FVIII concentrate products.
Methods: ADAMTS-13 was measured in 13 final product lots of 8Y, using two commercial kits. The first was an enzyme-linked immunosorbent assay (ELISA)-based method and measured activity and antigen levels (Technozym® ADAMTS-13, Technoclone). The second method measured activity using FRET technology (Actifluor™ ADAMTS-13 Activity Assay, American Diagnostica Inc). In addition, ADAMTS-13 was measured in 8Y and a number of comparator factor VIII products (Fanhdi®, Haemate® P, Haemoctin®SDH, and Octanate®) using an in-house ELISA against a plasma standard.
Results: ADAMTS-13 Content of 8Y (n = 13)
ADAMTS-13 activity levels in 8Y final product ranged between 3 and 4 times normal plasma levels, and the results for the 2 activity methods used in the study showed good correlation. The level of ADAMTS-13 measured in 8Y was at least 5 times that found in any of the comparator factor VIII products tested; 8Y levels measured at 354% normal plasma; comparator products ranged from 3 to 70%.

	Technozym® ADAMTS-13 Activity (%)	Technozym® ADAMTS-13 Antigen (mg ml^{-1})	Actifluor™ ADAMTS-13 Act. (mg ml^{-1})
Mean	350	7.5	3.5
Range	294 – 425	5.5. – 9.9	3.1 – 4.0
% Coefficient of Variation	12.6	15.6	7.8

Conclusions: This study shows that batches of 8Y contained a consistent level of ADAMTS-13, at approximately 300–400% normal plasma levels. 8Y contained more ADAMTS13 than the 4 other factor VIII products tested. These results may help to explain the reports of positive clinical outcome using 8Y for treatment of TTP.

FP-MO-03.2-5
Does PEGylated factor VIII induce antibodies against PEG?

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Conjugation of therapeutic proteins with polyethylene glycol (PEG) has been successfully used to increase the half-life of proteins in the circulation. Whereas PEG has long been considered to be non-immunogenic, recent reports indicated that treatment with PEGylated proteins can lead to the development of anti-PEG antibodies in animal models and in patients (Armstrong et al. 2007). Based on these reports, we asked if there was a risk that PEGylated human factor VIII (FVIII) could induce anti-PEG antibodies. We hypothesized that PEGylated human FVIII would induce antibodies against PEG only when FVIII was recognized as a foreign protein. In this case, FVIII would provide immunogenic peptide epitopes to $CD4^+$ T cells, thus allowing T-cells to help B-cells generate antibodies against PEG. We used 2 different mouse models to test our hypothesis. The first model was the conventional hemophilic E17 mouse model, which recognizes human FVIII as a foreign protein. The second model was the recently described human FVIII transgenic hemophilic mouse model that expresses human FVIII as a transgen and recognizes human FVIII as a self protein. We treated mice of both models with up to 8 weekly intravenous doses of 2 different PEGylated FVIII preparations (PEGFVIII1 and PEGFVIII2) and analyzed the development of antibodies against human FVIII and against PEG. When treating mice of the conventional hemophilic mouse

model, both PEGFVIII1 and PEGFVIII2 induced antibodies against FVIII and against PEG. PEGFVIII2 was more immunogenic and induced higher titers of antibodies against both FVIII and PEG. When treating human FVIII transgenic mice, only PEGFVIII2 induced antibodies against FVIII, not PEGFVIII1, indicating that PEGFVIII1 maintains, whereas PEGFVIII2 breaks, immune tolerance. Interestingly, only PEGFVIII2 induced antibodies against PEG, not PEGFVIII1, which supports our hypothesis that the induction of anti-PEG antibodies by PEGylated FVIII requires presentation of immunogenic FVIII epitopes by $CD4^+$ T cells.

Disclosures: The authors are full-time employees of Baxter Innovations GmbH.

FP-TH-01.1-3
Normalization of blood coagulation with Bay 86-6150

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Activated FVII (FVIIa) is known as an important tool in patients with bleeding disorders, but there are many problems, such as a short half-life and the lack of lab methods measuring the efficacy of FVIIa. BAY 86-6150 is a new recombinant FVIIa preparation with increased half-life and improved potency to bind to activated platelets. Our project is to find out which lab parameter is suitable to underline this hypothesis and which kind of blood samples should be used in coagulation labs. The focus of our investigations is to find practical guidelines for measuring under normal lab conditions in a clinical laboratory.

Patients/Methods: All patients were from the centre of blood coagulation and had a history of bleeding disorders. As controls, we used healthy subjects from our lab. The measurements were done in whole blood, in platelet-rich (PRP) and platelet-poor (PPP) plasma with different methods ranging from fully automated systems (ACL TOP IL) with wave function analysis to whole blood methods such as ROTEM (Matel GmbH Munich) and fluorimetric measurements with different methods of thrombin generation (CAT and TGA).

Results: ROTEM methods were successful for measuring the contribution of platelets in patients with hemophilia and patients with disturbed platelet function by ASS or P2Y12 antagonists by comparing the results with PPP and PRP. Measuring the catalytic function of platelets as function of platelet number was done with thrombin generation as CAT or TGA. The action of BAY7 in PPP can be detected with fully automated systems in all patients ranging from patients with DIC to patients with oral anticoagulants, unfractionated heparins, new anticoagulants, and hemophilia patients with and without inhibitors and disseminated intravascular coagulation calculating the first derivative of the activated partial thromboplastin time (aPTT) curve. The wave function analysis is also suitable for comparing patients with different kinds of factor deficiency.

Conclusions: We have different methods to show the hemostatic effect of BAY 86-6150. Depending on the problem (extended half-time, action of platelets, or action as hemostatic agent) we have to select the best available method to demonstrate the effect of BAY 86-6150 on the coagulation system. The differences between patients and controls are very clear and there were no signs of excessive coagulation activation.

FP-MO-03.2-4
Safety of polyethylene glycol (PEG) in biopharmaceuticals: Focus on PEG-rFVIII

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Ethylene glycol polymers have a long-lasting history of human use with food, cosmetics, and pharmaceutical products. Parenteral drugs contain PEG of different molecular size as excipients, and PEG has been used for more than 20 years for chemical modification of proteins with the goals of improving the safety and pharmacokinetics of protein drugs. Clinically used PEG polymers are generally considered to be non-toxic and safe for human oral, injectable, and topical administration. The polymers range in molecular size from 5 to 60 kDa. While the monomer ethylene glycol of which PEG is formed can be actively metabolized through several enzymatic pathways to metabolites which can be quantitatively eliminated, larger PEGs cannot be degraded because mammals do not have enzymes that would cleave and degrade ether bonds. PEGs with a molecular size of ≤ 20 kDa are still cleared largely via the kidneys and excreted into the urine. PEG clearance also involves the uptake by macrophages like any other non-degradable entity as part of the physiological clearance mechanisms. This results in vacuolization, which is seen upon PEG exposure of mammals to large PEG polymers and high doses, e.g. with an antibody fragment conjugated with a 40 kDa PEG at dose levels around 22 000 μg kg^{-1} per week. In animal toxicity studies, vacuolization always resolved over time and exhibited no cell damage or functional deficits and therefore was mostly considered non-adverse. In humans, toxicity of PEG was seen only at high doses of ~200 000 mg/week where PEG was used as an excipient. PEGylated FVIII candidates currently under development represent PEG-protein conjugates where the amount of PEG attached to the protein is minimal and, due to the high molar activity of FVIII, the absolute amount of conjugated PEG applied with PEG-FVIII is comparably small. Typical PEG exposure for PEG-rFVIII is ~3 μg kg^{-1} per week. Baxter currently develops BAX 855, which is a PEGylated full-length rFVIII based on the parent FVIII molecule also used for the licensed ADVATE™ product. The PEGylation approach for BAX 855 has the advantage of performing minimal PEGylation, so that the amount of PEG per dose is small compared to other PEGylated drugs. Furthermore, conjugation uses a branched PEG consisting of 2 10 kDa PEG arm, which offer the possibility for rapid elimination through excretion via urine and feces.

FP-TU-01.1-1
An engineered "super" factor Va mutant as a potential bypassing agent in hemophilia

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Because a significant number of persons with hemophilia with inhibitors fail treatment with FVIIa-based bypassing agents, new intervention strategies are urgently needed. Activated FV (FVa) enhances thrombin formation by the prothrombinase complex and is a target for activated protein C (APC) anticoagulant activity. Mutation of the APC cleavage site, R506Q (FV_{Leiden}), conveys increased thrombotic risk and improves hemostasis in humans and mice with severe hemophilia. We therefore evaluated the potential of recombinant engineered FVa-derivatives as novel bypassing agents in hemophilia. Introduction of a disulfide bond (Cys609-Cys1691) connecting the FVa A2 and A3 domains (Fva[A2-SS-A3]) prevents the dissociation of the APC-cleaved A2 domain fragment (residues 507–709) which is a key for APC inactivation of FVa. Additional mutations of the APC cleavage sites (Arg506/306/679) yielded "^{super}FVa" that had ~fourfold higher specific activity compared to wt-FVa. When added to FV-deficient plasma, ^{super}FVa corrected the aPTT at 20–40-fold lower concentrations compared to wt-FVa. In endogenous thrombin potential (ETP) assays, a 5–10-fold lower concentration of ^{super}FVa compared to wt-FVa was required to normalize thrombin generation in FV-deficient plasma. In hemophilia A plasma, when tested at 30 nM ^{super}FVa but not wt-FVa, FVa(A2-SS-A3) or FV_{Leiden}(A2-SS-A3) markedly improved thrombin generation. Furthermore, ^{super}FVa was resistant to inactivation by APC. In purified prothrombinase assays, ^{super}FVa retained 100% activity in the presence of APC, whereas FVa(A2-SS-A3) lost >70% of its activity. In FV-deficient plasma reconstituted with wt-FVa or FVa(A2-SS-A3), APC severely compromised thrombin generation, but APC did not affect thrombin generation upon reconstitution with ^{super}FVa. These results indicate that molecular engineering of FV, which combined two alterations for improving thrombin generation (increased specific activity and APC resistance), provided a FVa-mutant with unique procoagulant properties. Either alone or in combination with FVIIa-based bypassing agents, the ^{super}FVa mutant may provide therapeutic benefits as a novel bypassing strategy in hemophilia patients with inhibitors.

PO-000
Registry of Clotting Factor Concentrates

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The Registry of Clotting Factor Concentrates was created in 1997 to help medical personnel identify available concentrates and stay abreast of pharmaceutical company changes. It provides an overview of products available for export and clarifies differences among them. There are products manufactured for use in single countries that are not included in the registry. It is updated every couple of years as needed.

The Registry describes measures that help ensure the safe use of plasma. Nucleic acid tests that directly detect viruses are now commonplace. Plasma obtained from donations of whole blood is called recovered plasma and plasma obtained by apheresis is called source plasma. Donors of whole blood are not paid any substantial amount in the countries listed in the registry. Donors of apheresis plasma generally donate more frequently and are paid a small compensation.

Within the Registry, concentrates are grouped first according to method of fractionation, then according to method of viral inactivation or degree of purification from lowest to highest. Fractionators cite the purification level of clotting factors as specific activity, or the amount of the desired clotting factor per milligram of total protein, minus any added albumin.

The Registry lists FVIII concentrates made by techniques generally associated with a lesser level of purification as well as concentrates made by techniques allowing higher level of purification, including recombinant FVIII concentrates. Also listed are products that are specifically licensed for the treatment of VWD. Prothrombin complex concentrates, which are not highly purified, are also described. The Registry includes concentrates intended for use in patients with inhibitors. Concentrates of factor IX and for rare clotting factor deficiencies (FVII, FX, FXI and FXIII) are described. Rare factors are not widely available, and there are some deficiencies for which no concentrate is made. Finally, concentrates for deficiencies of anti-thrombotic factors are described.

PO-TU-014
Cellular stress in endothelial cells, platelets, leukocytes, and osteoblasts induced by plasma-derived factor VIII products in vitro

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Aim: In a previous study, proteins of blood cell and complement activation have been identified in several plasma-derived factorVIII (pdFVIII) products of different purities. Whether these impurities induce cellular stress that might be of clinical relevance was examined by investigating their impact on cellular stress sensors.

Method: The effect of 3 different batches of FVIII concentrates (0.5 and 1 U ml^{-1}) was examined. Recombinant FVIII (rFVIII) products and pdFVIII products of different purity were investigated. The mitochondrial transmembrane potential, $\Delta\psi m$, of endothelial cells (HMECs), platelets and osteoblasts, as well as the microparticle formation of platelets, monocytes, and granulocytes were investigated by flow cytometry.

Results: While rFVIII had no negative influence on the mitochondrial membrane potential of human endothelial cells, platelets, and osteoblasts, the pdFVIII products showed a depolarization of the membranes. As depolarization of the inner mitochondrial transmembrane is an early marker of apoptosis and microparticle formation, it was investigated in further experiments. Some pdFVIII products induced a strong, significant

formation of platelet microparticles and induced strong and significant microparticle formation of monocytes and granulocytes, compared to negative and positive controls. rFVIII did not show any negative effect.
Conclusion: Mitochondrial dysfunction contributes to the severity or progression of cardiovascular disease, and microparticles are regarded as an important marker of cardiovascular risk. Considering the frequency of drug applications and the high concentration of applied proteins, chronic activation of the stress defence system and chronic cell irritation could be important for patients with hemophilia. Cellular stress may also contribute to inflammation and chronic hemarthrosis.
Acknowledgement: This work was supported by a grant of Bayer Vital GmbH, 51368 Leverkusen.

PO-TU-015
Experience in the treatment of Cuban patients with severe bleeding using recombinant FVIIA
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The development of recombinant factor VIIa concentrate strongly improves the management of hemophilia A and B with inhibitors. Due to its unique effects on the hemostasis system it will be useful for other indications as well, including patients with congenital factor VII deficiency, with bleeding and liver function impairment, with quantitative and qualitative platelet defects, and individuals who have sustained multiple traumas. The efficacy of recombinant activated factor VII (rFVIIa, NovoSeven) in five patients is reported: four with hemophilia A with high-response inhibitors and one with severe hemorrhagic event and anticoagulant therapy. Four individuals with hemophilia had complicated hematoma of the psoas muscle and the other one was a patient under therapy with warfarine who presented a severe gastrointestinal bleeding not controlled with the standard treatment. In every patient the outcome was favorable. These results demonstrate the efficacy of rFVIIa.

PO-TU-016
Focus on the evolution of clotting factor concentrate consumption in seven French hospitals
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The aim of this study was to analyze the consumption of clotting factor concentrates (CFC) in different types of French hospitals (5 university hospitals and 2 local hospitals) during 2 years (2009/2010). CFC were used for both hospitalized and ambulatory patients. We obtained data from pharmaceutical files with the support of network pharmacists and compared these data with national information. Total consumption of FVIII was equal to 46 MIU (12% of total French consumption) in 2009 and 51 MIU (14%) in 2010. Total consumption of FIX was equal to 7.8 MIU (15% of total French consumption) in 2009 and 9.6 MIU (14%) in 2010. In 2009, human plasma–derived FVIII represented 34% (18% of national data) and recombinant FVIII 66% (82% of national data). In 2010, recombinant data consumption increased to 75% (86% for national data) and human VIII decreased to 25% of total consumption (14% for national data). In contrast, ratio recombinant/human IX was almost the same in 2009 and 2010. The distribution of ambulatory and hospital use was different between the types of hospital. In local hospitals CFC are used mainly in an ambulatory context (97%). However, the proportion of hospital consumption is less important in university hospitals (86%) because major surgery, e.g., total knee replacement is managed within these structures. We observed the use of prophylaxis in a majority of patients with 2 types of structures, depending on the physician's recommendation. However, it is very important to know the activities of CFC dispensation at the local hospital near the patient's home, because we can contribute to optimizing their quality of life and compliance of treatment. To conclude, our pharmaceutical network contributes to the understanding of the evolution of medical practices and allowed us to compare our results with national data.

PO-TU-017
Evaluation of glycan sialylation on the clearance of B-domain-deleted factor VIII-Fc fusion protein (rFVIIIFc) in hemophilia A mice
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Factor VIII is a heavily glycosylated protein containing 20 N-linked and at least 7 O-linked glycans, most of which reside in the B-domain. For full-length FVIII, the removal of sialic acid from the glycans resulted in rapid clearance of FVIII through interaction with hepatic asialoglycoprotein receptor (ASGPR). To evaluate the impact of the sialic acid content of N-linked and O-linked glycans on the function and clearance of recombinant B-domain-deleted (BDD) FVIII-Fc fusion protein (rFVIIIFc), we determined the activity and pharmacokinetics (PK) of rFVIIIFc in hemophilia A (HemA) mice, before and after removal of sialic acid. Desialylated rFVIIIFc was prepared via enzymatic desialylation, and a control was also treated in the same manner without the addition of enzyme. Both the desialylated and the control materials were further purified by liquid chromatography and buffer-exchanged into formulation buffer. The articles were administered to HemA male mice by tail vein injection, and plasma samples were collected to determine PK parameters. The activity and antigen levels of rFVIIIFc in plasma were monitored by the chromogenic activity and enzyme-linked immunosorbent assay (ELISA) assays, respectively. The removal of sialic acid from rFVIIIFc glycans did not affect the specific activity of rFVIIIFc. However, the half-life of desialylated rFVIIIFc in HemA mice was shortened to 9–10 h from 18–19 h for the sialylated rFVIIIFc control, despite the comparable initial recovery (C_{max}), as shown by both the chromogenic and ELISA assays. The results suggest that, similar to full-length FVIII, the desialylated BDD FVIIIFc is also cleared more rapidly, possibly mediated by the ASGPR, which is often implicated in clearance of glycoproteins containing undersialylated higher-order complex glycans. This observation is also in agreement with many previously reported findings about selective clearance of asialylated receptor-Fc fusion proteins through the ASGPR pathway. These results underscore the importance of sialylation in maintaining the normal catabolism of rFVIIIFc in vivo.

PO-TU-018
One-year assessment of coagulation markers and monitoring for thrombotic events in patients with hemophilia B treated with nonacog alfa
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Objective: Thrombotic risk with factor IX (FIX) remains a concern for regulatory agencies, based on experience with initial FIX complex concentrates. This analysis aimed to assess the incidence of thrombotic events and the changes in blood coagulation markers in patients with hemophilia B treated with a recombinant FIX (nonacog alfa; BeneFIX®). Methods:
This retrospective pooled analysis evaluated thrombotic events and coagulation markers from 5 prospective clinical studies that utilized on-demand, prophylaxis, and preventive nonacog alfa regimens in subjects with mild, moderate, or severe hemophilia B (N = 141).
Results: Mean age was 24.4 y (range 0–69), with 35 (25%) subjects aged <12 y and 10 (11%) <2 y. Mean number of exposure days was 45.7 (range 1–125). Overall, 6,521 infusions were administered. Doses were determined by investigators except for 1 study where subjects received 2 prophylaxis regimens (50 IU kg^{-1} biweekly and 100 IU kg^{-1} once weekly). Ten subjects underwent surgical procedures, with investigator-determined preoperative doses of nonacog alfa. In total, 69 (49%) subjects received 1,033 infusions of nonacog alfa that were ≥100 IU kg^{-1}. Four of the 5 studies measured blood coagulation markers, including thrombin-antithrombin III complexes, prothrombin fragment 1 + 2, and fibrin split products (D-dimer). No thrombotic events were reported in 141 subjects. No differences between baseline and final levels of thrombotic markers were observed (Table).

Table xx. Summary of selected data (coagulation markers) at baseline and final visit

Parameters	Visit	n	Mean	SD
Thrombin antithrombin III complex, μ/L	baseline	79	2.9	5.4
	final	79	7.8	21.4
D-dimer, ng/mL	baseline	81	168	270.0
	final	80	278	887.5
Prothrombin fragment 1+2, Nmol/L	baseline	79	1.8	12.8
	final	88	2.2	13.6

Conclusions: No clinical thrombotic events were observed in all 5 studies. Coagulation markers did not indicate clinically significant variations between baseline and final levels. Nonacog alfa did not demonstrate thrombotic risk in pediatric, adult, or surgical subjects with hemophilia B receiving different treatment regimens or doses, including nonacog alfa ≥100 IU kg^{-1}.

PO-TU-019
Real-time, label-free surface plasmon resonance (Biacore™) analysis of rIX-FP, a recombinant fusion protein linking coagulation factor IX with albumin, shows binding to FcRn comparable to plasma-derived human albumin - correlating with extended half-life in vivo
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Patients with severe hemophilia B are at risk of recurrent bleeding episodes. Due to the half life of FIX (17–34 h), prophylatic treatment usually involves 2–3 injections of FIX concentrates per week. In contrast, immunoglobulins and albumin have half-lives in the range of 10–21 days and 20 days, respectively, due to their capacity to bind to the intracellular salvage receptor FcRn at endosomal pH (5.5–6.0) following macropinocytosis, subsequent recycling to the extracellular milieu, and rapid release at neutral pH. rIX-FP, a recombinant fusion protein of coagulation factor IX with albumin, has been shown to have improved pharmacokinetics in vivo when compared to BeneFIX ™, with a terminal half-life increased at least threefold. To analyze the mechanism underlying this prolongation of in vivo half-life, we have used surface plasmon resonance (SPR) analysis using the Biacore™ system to compare the binding of rIX-FP, BeneFIX ™ and plasma-derived albumin to the recombinant FcRn ectodomain, both at pH 6.0 and pH 7.4. The results show comparable binding of rIX-FP and albumin at pH 6.0 and no detectable binding of either at neutral pH (7.4), whereas BeneFIX ™, demonstrated only negligible binding under either condition, as expected. Thus, binding of the albumin moiety of rIX-FP is largely unaffected by fusion to FIX, suggesting that almost maximal half-life extension has been achieved for rIX-FP. Ongoing clinical studies will show whether these properties translate into improved kinetics in hemophilia B patients.

PO-TU-020
Variable activation kinetics of different recombinant full-length and B-domain deleted factor VIII concentrates

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Background: Recombinant factor VIII (rFVIII) concentrates differ in B-domain length, the cell lines used for expression, and included polymorphisms. This study compares the activation kinetics of 4 different rFVIII concentrates. Material/Methods:
FVIII activity (FVIII:C) and FVIII antigen (FVIII:Ag) of the full-length rFVIII concentrates ADVATE, Helixate, Kogenate, and the B-domain-deleted rFVIII Refacto AF were measured. For analysis of the activation profile, concentrates were subjected to thrombin. Time course of activation was visualized by Western blot. Different amounts of applied FVIII protein were analysed. A FXa-generation assay was performed.
Results: Kogenate and Helixate showed significantly higher FVIII:C and FVIII:Ag values compared to ADVATE and Refacto AF. Additionally, they showed the fastest equal rate of A2-domain-formation for all thrombin concentrations. With 1 nM thrombin, Refacto AF presents the lowest rate of A2-formation, and ADVATE showed an activation profile in between. The difference between ADVATE and Refacto AF disappears with 10 nM thrombin. Changing the amount of applied FVIII protein did not influence the obtained differences. The fastest FXa-generation was obtained for Kogenate and Helixate. ADVATE and Refacto showed statistically significant lower values for FXa-generation. No variation of the FXa-generation was seen when the concentrates were adjusted to the antigen.
Conclusion: The 4 rFVIII concentrates showed differences in the FVIII:C levels as well as in the activation kinetics. The discrepancies in the FVIII:C levels are caused by the different ways of standardization. The activation profiles of the 2 identical FVIII proteins (Kogenate and Helixate) showed no significant difference. ADVATE showed a slightly slower activation and Refacto AF a significant slower A2-domain-generation. Different cell lines used for expression might contribute to the observed data. Furthermore, the slower activation kinetics of the BDD-rFVIII might be due in part to the absence of the B-domain, which may contribute to the structured integrity.

PO-TU-021
One-year clinical experience with mini-pool solvent/detergent-filtered (SD-F) plasma

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Background: A medical device for virus inactivation of mini-pools of plasma by solvent and detergent (S/D-F) is now available for use by blood establishments or national service centres. We report here our clinical experience using mini-pool SD-F plasma for various clinical indications.
Patients: Mini-pool SD plasma was transfused to 10 patients with end-stage liver disease with coagulopathy, 2 with FV deficiency, 1 with FX deficiency, and 1 with FVII deficiency for treatment of their bleeding episodes. Therapeutic plasma exchanges were performed for a patient with TTP and another for cytotoxic renal antibodies removal. S/D-F plasma was also used to correct INR due to overdose of oral anticoagulants in 3 patients.
Mini-pool S/D Plasma Infusion: For correction of coagulopathies the dose of S/D-plasma was 10 ml kg^{-1} body weight. Plasma exchange was based on replacement of defective plasma by an equal volume of S/D-F plasma in TTP patient and by 50% of the volume as 5% saline albumin and 50% of S/D plasma in the patient with renal cytotoxic antibodies. Evaluation of outcome of S/D plasma transfusion was based on correction of global hemostasis tests (prothrombin time and activated partial thromboplastin time [aPTT]), control of specific coagulation factors, control of bleeding episodes, and report of any adverse events.
Results: There was good correction of global hemostasis tests in patients with hereditary FV and FX deficiency and of the level of these factors. The correction of prothrombin time and aPTT was poor in patients with end-stage liver coagulopathy but was not significantly different from that obtained with standard FFP in the same patients. The TTP patient was corrected by the S/D-F plasma exchange sessions. The patient with renal cytotoxic antibody has completed 6 sessions of therapeutic plasma exchange and the degree of reduction of cytotoxic antibodies is still to be evaluated. Correction of INR in patients with anticoagulant overdose was efficient. In all patients transfused with S/D-F plasma with volumes from 200–2000 ml, there was no report of adverse events, except in 1 with high INR who reported moderate allergic reaction at her second S/D-F plasma transfusion day.
Conclusion: Accumulating clinical experience with mini-pool SD-F plasma strongly suggests that it is both efficient and safe.

PO-TU-022
High margin of pathogen safety of a plasma-derived FXIII concentrate

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Congenital factor XIII (FXIII) deficiency is an extremely rare, serious, and life-threatening condition, especially due to intracranial hemorrhage, which can be treated by a plasma-derived FXIII concentrate (Fibrogammin/Corifact). The pathogen safety of this plasma-derived protein is achieved by the complementary measures of (1) selecting and testing the starting material, human plasma, (2) releasing the plasma pool for fractionation when non-reactive for viral markers and genomic material of blood-borne viruses, and (3) ensuring adequate capacity of the production process to reduce a wide range of viruses as well as prions. Product intermediates from selected steps of the manufacturing process for the FXIII concentrate, derived from different production lots, were spiked with enveloped and non-enveloped viruses of diverse physico-chemical characteristics and processed according to a scaled-down, validated manufacturing process. Both prion spike preparations were removed equally by the manufacturing step $Al(OH)_3$ adsorption/defibrination and the virus filtration step. The manufacturing process, studying the dedicated virus reduction steps "pasteurisation" and "virus filtration" (two filters in series with a mean pore size of approx. 19 nm [Planova 20N]), and an ion exchange chromatography, achieves overall virus reduction factors of $\geq$18.8 $\log_{10}$ for HIV; $\geq$16.4 $\log_{10}$ for BVDV; $\geq$18.2 $\log_{10}$ for PRV; $\geq$13.3 $\log_{10}$ for HAV; and 10.8 $\log_{10}$ for CPV (canine parvovirus). WNV (West Nile virus) was reduced by the 2 dedicated virus reduction steps by $\geq$14.8 $\log_{10}$. Therefore, it can be concluded that the measures taken result in a FXIII concentrate [Fibrogammin/Corifact] with a very high margin of safety for a wide range of viruses. The prion reduction factors demonstrated for the manufacturing steps studied resulted in reduction factors of $\geq$6.2 $\log_{10}$ for microsomes and >7.2 $\log_{10}$ for purified PrP^{Sc} providing also for prions, e.g., the agent causing variant Creutzfeldt-Jakob disease, a high margin of safety.

PO-TU-023
Binding and uptake of rFVIII and GlycoPEGylated rFVIII (N8-GP) by human monocyte-derived dendritic cells

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Background: N8-GP is a selectively O-glyco-PEGylated recombinant FVIII with approximately twofold prolonged half-life in animal models, and is currently in clinical development. Cellular uptake of FVIII by dendritic cells is believed to be the initial step in presenting FVIII to the immune system. The aim of the current study was to assess binding and uptake of N8-GP in human monocyte-derived dendritic cells (MDDCs).
Methods: Human peripheral blood mononuclear cells (PBMC)-derived monocytes were differentiated into MDDC by 6 days of culturing with IL-4 and GM-CSF. Expression of CD14, CD86, CD209, and CD83 were controlled by flow cytometry. Binding of ^{125}I-labeled N8-GP and rFVIII starting material (turoctocog alfa, i.e., B-domain-truncated rFVIII) were analyzed at 4°C at time points up to 48 h, and the binding and uptake analyzed at 37°C up to 3 h. Excess unlabelled N8-GP and rFVIII (turoctocog alfa) was used to assess non-specific binding.
Results: Binding of rFVIII and N8-GP was maximal after 24 h at 4°C. The K_d was 73 ± 28 nM for rFVIII and 104 ± 52 nM for N8-GP. However, the maximal binding capacity was 2187 ± 441 fmol/10^6 cells for rFVIII and 302 ± 91 fmol/10^6 cells for N8-GP. Also at low concentrations (0.3–20 nM) were a 2–3-fold lower specific binding of N8-GP than of rFVIII observed. When binding and uptake were analyzed at 37°C, the internalization was lower for N8-GP than for rFVIII. At 3 h, the internalization was 22.7 ± 1.8 fmol/10^6 cells for N8-GP and 423 ± 158 fmol/10^6 cells for rFVIII.
Conclusions: The binding affinity of N8-GP to the MDDCs was similar to that of rFVIII. However, the maximal binding capacity was 7-fold lower for N8-GP compared to rFVIII. Furthermore, the internalization was reduced for N8-GP. This may indicate that the presentation of N8-GP to the immune system is decreased. The clinical relevance of this finding remains to be established.

PO-TU-024
Target-mediated clearance and bio-distribution of a monoclonal antibody against the Kunitz-type protease inhibitor 2 domain of tissue factor pathway inhibitor

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Introduction: A monoclonal antibody (mAb 2021) that neutralizes the function of human tissue factor pathway inhibitor (TFPI) has been developed as a potential therapeutic agent for prevention of bleeds in hemophilia patients. The antibody binds to the Kunitz-type protease inhibitor (KPI) 2 domain of human TFPI with high affinity and displays species cross-reactivity to rabbit and monkey TFPI, but not to rat TFPI. The aim of this study is to explore bio-distribution and clearance of mAb 2021.
Methods: Binding of mAb 2021 to endothelium was explored using HUVEC cells, the endothelium-like human cell line EA.hy926 (positive for TFPI) and aerolysin-treated EA.hy926 AR cells (negative for TFPI). To evaluate the bio-distribution of the antibody, rabbits were dosed with 10 mg kg^{-1} of either mAb 2021 or an isotype control. Tissues were excised and subjected to histochemical analysis by double immunofluorescence. Pharmacokinetic analysis was performed in rats, rabbits, and cynomolgus monkeys dosed with a single dose of 2 mg kg^{-1} or 20 mg kg^{-1} of mAb 2021. Plasma samples were collected and analyzed by ELISA. Results were subjected to non-compartmental analysis.
Results: The specificity of mAb 2021 towards KPI2 allowed interaction with cell surface bound TFPI as shown by abrogation of the inhibition of tissue factor/factor VIIa-mediated factor X activation on HUVEC cells; and in binding to the endothelium-like human cells EA.hy926 but not to aerolysin-treated EA.hy926 AR cells. Using immunofluorescence, we found an accumulation of the antibody on the rabbit endothelium of the microvasculature in several organs with marked co-localization with endogenous rabbit TFPI but with negligible sub-endothelial accumulation. The pharmacokinetics of mAb 2021 in rabbits and monkeys was consistent with a target-mediated clearance, whereas rats showed log-linear pharmacokinetics.
Conclusion: We found that the TFPI KPI2 antibody mAb 2021 binds to endothelium both in vitro and in vivo, and is cleared from circulation by a target-specific mechanism.

PO-TU-025
FVIIa-CTP and FIX-CTP are novel long-acting coagulation factors with prolonged hemostatic activity in hemophilic animal models

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Background: Prolor Biotech Inc. is a clinical stage public company developing biobetter long acting versions of existing therapeutic proteins utilizing a technology called CTP. The technology involves fusion of the C terminus peptide of hCG to one or both ends of the target protein. The technology was clinically validated and proven as a safe and efficient way for increasing the half-lives of several therapeutic proteins while maintaining their biological activity. Aims:
To determine the pharmacokinetic, pharmacodynamic, and hemostatic effect of FVIIa-CTP and FIX-CTP in a murine FVIII-/- and FIX -/- mice.
Methods: FVIIa-CTP and FIX-CTP were expressed in CHO cells transfected with the proper genes and purified utilizing a purification process including a CTP specific step. FVIIa-CTP and FIX-CTP were administered to murine FVIII-/- and FIX-/- mice, PK and PD profiles were determined and the long acting homeostasis effect was evaluated following bleeding challenge and compared to commercial products.
Results: FVIIa-CTP pharmacokinetic parameters, as assessed by a clotting assay, were superior to those of rFVIIa. Its half-life and AUC were 5 and 3.5 fold higher, respectively, and significantly improved recovery was observed. In a TVT study, FVIIa-CTP had a profound survival effect, which was maintained for a significantly longer period. Following CTP fusion, FVIIa specific activity was slightly reduced. FIX-CTP half-life (by aPTT) was 4 times longer than rFIX and a significant reduction in bleeding duration and intensity following a tail vein bleeding challenge in FIX -/-mice was observed. Fusion of CTP significantly improved FIX recovery while its specific activity was slightly reduced.
Conclusion:
Fusion of CTP to FVIIa and FIX has markedly enhanced pharmacokinetics, increased exposure, increased recovery and prolonged hemostatic effect in hemophilic mice. Our data suggest that CTP fused coagulation factors have the potential to significantly improve the prophylactic and on demand treatment in patients with hemophilia.

PO-TU-026
Clotting factor consumption in hemophilia A and B according to patients' characteristics: Results from the FranceCoag Network

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Clotting factor consumption in hemophilia is highly variable. Our objectives were to assess the annual mean consumption of clotting factor concentrates according to various parameters and to identify the consumption's associated factors. Indeed, the associations with some factors are well known: severity of hemophilia, treatment modality (on-demand/prophylaxis), surgical procedures, and presence of an inhibitor. However, some parameters are less studied: type of hemophilia, age, treatment period, type of administered clotting factor (recombinant/plasmatic), and desmopressin administration. The analysis was based on the prospective cohort of hemophilia patients, which was implemented in 1994 and includes today almost all patients followed up in French treatment centres. This first analysis focused on periods with on-demand therapy without surgical procedures or inhibitors. By November 2011, 5846 persons with hemophilia were included in FranceCoag Network. Among them, 4669 (representing 17 280 person-years) follow the selection criteria: 3799 HemA (81%) and 870 HemB (19%). The annual mean consumption was 423 IU kg^{-1} $year^{-1}$ representing 12 exposure days per year and a total of 24 753 IU $year^{-1}$. The mean consumptions of factors VIII and IX, were respectively, 1037 and 841 IU kg^{-1} $year^{-1}$ in severe cases, 264 and 175 IU kg^{-1} $year^{-1}$ in moderate cases, and 45 and 42 IU kg^{-1} $year^{-1}$ in mild cases. For moderate hemophilia, the mean consumption varies widely according to the lowest basal level of coagulation factors, falling from 513 IU kg^{-1} $year^{-1}$ for patients presenting a basal level of 1% to 219 IU kg^{-1} $year^{-1}$ for those with a level of 2%. Regarding the age, the annual mean consumption rises up to 16–18 and decreases after 30 years of age. The mean consumption per exposure day is higher for patients with a body weight below 5 kg compared with those above 5 kg (103 vs. 38 IU kg^{-1} per exposure day). This may be related to a lower factor recovery and/or to the drug packaging which is inadequate for the lowest body weight. This study provides an accurate assessment of the national consumptions of clotting factors in hemophilia.

PO-TU-027
Functional characterization and comparison of rIX-FP lots manufactured in pilot scale and full scale

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Improvement of the pharmacokinetic properties of factor IX (FIX) is a desired goal and has the potential to improve the convenience and compliance of treatment for severe hemophilia B patients by reducing the dosing frequency. A concept for half-life increase of FIX was developed based on a recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP) via a cleavable linker (Metzner H.J. et al., Thromb Haemost 2009; 102: 634–644). The aim of this study was the functional characterization and comparison of rIX-FP lots manufactured in pilot scale and full scale. rIX-FP was produced in Chinese hamster ovary cells (CHO) and purified by a series of chromatographic steps. Proteolytic activation of rIX-FP resulting in the formation of activated FIX (FIXa) and albumin was achieved by incubation of rIX-FP with activated factor XI. Enzymatic and structural functionality were assessed by investigating the ability of FIXa to activate factor X (FX) and by inhibition of FIXa by antithrombin (AT) using chromogenic substrate assays. In a concentration-dependent manner, AT was able to inhibit FIXa activity completely. The half-maximal inhibition was comparable for different rIX-FP lots, demonstrating consistency of manufacture of these lots. In a time- dependent manner, FXa was formed in presence of activated factor VIII (FVIIIa) by activated rIX-FP. Analysis of different rIX-FP lots resulted in similar initial curve slopes in measured absorbance increase and final absorbance values. Taken together, the investigations performed using different rIX-FP lots confirm an excellent lot-to-lot consistency of rIX-FP in terms of enzymatic properties and interaction with AT.

PO-TU-028
Pharmacokinetics, organ distribution, and light microscopic autoradiography of rFVIIa

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Objective: The aim of the present study was to evaluate the pharmacokinetics, the distribution into preselected organs, and the cellular distribution inside kidney, liver, and vascular tissue using a degradation-resistant human rFVIIa after IV administration to rats. We have used glyco-iodination technology to synthesize an iodinated FVIIa with greatly improved in vivo stability, which allows for accurate analyses at late time points.
Methods: The rats were dosed IV 100 μg kg^{-1} of ^{125}I-rFVIIa. Blood and plasma were sampled in the interval of 0–24 h post administration. Blood and citrate-stabilized plasma underwent 3 forms of drug quantification: gamma counting, antigen, and activity analysis. At time points of 1.5 hours, 3 hours, and 24 hours, animals were euthanized and flushed with saline via the heart. Hereafter, 21 preselected organs were sampled for quantification of drug content by gamma counting. Samples of kidney, liver, and a muscle block containing the saphenous vein were collected for light microscopic autoradiography (LMA).
Results: The glyco-iodination of rFVIIa was stable in the studied interval, as observed by comparison of gamma counting and antigen analysis of rFVII in plasma, and minimal accumulation in the thyroid gland. The estimated half-life of rFVIIa was in the range of 0.78–2.5 hours, depending of the assay employed. The 4 organs that contained the most radioactivity/g organ were the kidney, liver, spleen, and jejunum. Using LMA, ^{125}I-rFVIIa was found primarily in the kidney associated with proximal tubules and in the renal papilla. A widespread weak staining was found in the liver parenchyma, more localized staining in the endothelium of the portal and central veins, and diffuse staining of the stroma surrounding these vessels. Furthermore, diffuse staining was observed in the vascular stroma surrounding the saphenous vein.
Conclusion: Using an in vivo stable labelling technique, the kidneys and the liver were found to be the main clearance organs of FVIIa. The autoradiographic stain for ^{125}I-rFVIIa in the kidney was primarily associated with proximal tubules consistent with absorption of rFVIIa from the ultrafiltrate. A weak stain in the liver was distributed throughout the parenchyma, consistent with hepatic clearance. The diffuse accumulation around the saphenonous and portal veins was consistent with passive distribution into the extravascular space.

PO-TU-029
Allometric scaling used to predict human pharmacokinetics (PK) of GlycoPEGylated rFVIII (N8-GP)

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Introduction: GlycoPEGylated recombinant factor VIII (N8-GP) has shown a prolonged half-life in several animal species. Allometric scaling can be a useful method to assist design of clinical studies. The allometric model approach has been evaluated on known data for rFVIII.
Methods: The PK of N8-GP and rFVIII was explored after intravenous administration to mice, rats, rabbits, monkeys, and hemophilia A dogs. Dose levels ranged from 50–280 U kg^{-1}, and blood was sampled and analyzed by enzyme-linked immunosorbent assay (ELISA) and/or FVIII chromogenic activity assay. The PK was assessed by non-compartmental analysis. Allometric scaling of clearance (CL) and volume of distribution at steady state (V_{ss}) was applied using the empirical power function of the species body weight.
Results: The clearance of rFVIII and N8-GP was estimated to be in the range of 2.3–10.5 and 1.5–10 ml h^{-1} kg^{-1}, respectively, and the volume of distribution was estimated to be in the range of 35–100 ml kg^{-1}. In all species, the terminal half-life ($T_{½}$) of N8-GP was approximately twofold longer than for rFVIII. Using allometric scaling, good correlation was found for both CL (R^2 = 0.93 and R^2 = 0.99) and V_{ss} (both R^2 = 0.99). The estimated values for rFVIII in a 75 kg human being were Cl=3.7 ml h^{-1} kg^{-1}, V_{ss} of 38 ml kg^{-1} and therefore a $T_{½}$ of 7.5 h (CL=ln2/$T_{½}$*Vss). The mean FVIII $T_{½}$ reported in a clinical trial was 10 h, which gives a deviation of 25% between predicted and actual $T_{½}$. Similarly, the predicted values for N8-GP in a 75 kg human being were Cl=1.7 ml h^{-1} kg^{-1}, V_{ss} of 36 ml kg^{-1} and therefore a $T_{½}$ of 15.6 h.
Conclusions: This study demonstrated an approximately twofold prolonged half-life and reduced clearance of GlycoPEGylated rFVIII (N8-GP) across species as compared to rFVIII.

Based on allometric scaling, the estimated terminal half-life of N8-GP was estimated to be approximately twofold prolonged compared to the similarly predicted value for rFVIII.

PO-TU-030
Analysis of the composition of a factor VIII concentrate, Optivate®
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Objectives: Optivate® is a factor VIII concentrate containing von Willebrand Factor (VWF). This study analysed the composition and activity of Optivate alongside those of a number of comparator FVIII products.
Methods: This study assessed the composition of 6 FVIII concentrate products: Optivate®, 8Y®, Fanhdi®, Haemate® P, Haemoctin®SDH, and Octanate®. Two batches of each product were tested. The following tests were included in this study: total protein; FVIII (chromogenic); VWF antigen, ristocetin cofactor, and multimer analysis; fibrinogen; fibronectin; FXIII; IgM; albumin; IgG; and IgA.
Results: Data for comparator products A–D shown in no particular order. ND=none detectable.

Product:	8Y	A	B	C	D	Optivate
Protein (mg mL^{-1})	6.3	6.1	8.9	0.5	1.3	2.3
FVIII (IU mL^{-1})	22.7	90.5	48.0	38.0	92.6	95.9
FVIII SpAc (IU mg^{-1})	3.6	15.0	5.4	75.0	71.0	41.4
vWF:Ag (IU mL^{-1})	70.9	153	128	18.0	41.2	244
vWF:RCo (IU mL^{-1})	32.1	77.0	99.4	11.1	33.1	133.5
vWFRCo:FVIII (IU/ IU FVIII)	1.4	0.9	2.1	0.3	0.4	1.4
Fibronectin:FVIII (μg / IU FVIII)	31	0.70	0.68	0.27	0.25	0.55
Fibrinogen:FVIII (μg / IU FVIII)	195	0.08	1.3	2.1	2.6	0.74
Factor XIII:FVIII (μg / IU FVIII)	0.02	ND	4.8×10^{-5}	ND	ND	2.1×10^{-5}
IgA:FVIII (μg / IU FVIII)	1.8	ND	ND	ND	0.21	ND
IgG:FVIII (μg / IU FVIII)	ND	ND	ND	ND	ND	ND
IgM:FVIII (μg / IU FVIII)	2.1	0.12	0.31	0.24	0.19	0.12
Albumin:FVIII (μg / IU FVIII)	1.8	62	174	0.021	0.020	0.018

Conclusions: Optivate® had the highest VWF:Ag concentration, its ratio of VWF:RCo to FVIII was the same as 8Y® and only exceeded by 1 of the other products tested. The protein profile was similar in all the concentrates tested, except 8Y® which showed higher levels of fibrinogen, fibronectin, FXIII, IgM and IgA.

PO-TU-031
Real-time evaluation of thrombin-mediated release of factor VIII variants from von Willebrand factor
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Objectives: A novel single-chain (SC) isoform of factor VIII (FVIII), resulting from incomplete proteolysis at residue R1648 during biosynthesis, may provide superior manufacturability and stability relative to native FVIII. We have previously demonstrated that a single recombinant B domain deleted factor VIII molecule fused to an immunoglobulin Fc domain (rFVIIIFc) and its purified SC counterpart (SC-rFVIIIFc) exhibited similar specific activity in one-stage clotting assays using plasma depleted of von Willebrand factor (VWF), but SC-rFVIIIFc exhibited lower specific activity in the presence of VWF. This study was undertaken to determine if VWF-bound rFVIIIFc, SC-rFVIIIFc, and rBDD-FVIII (Xyntha®, ReFacto, AF®) differ with respect to thrombin-mediated proteolytic release from VWF.
Methods: Equimolar amounts of rFVIIIFc, SC-rFVIIIFc, and rBDD-FVIII were captured on an optical biosensor chip on which human VWF had been immobilized by amine coupling. Human α-thrombin at a range of concentrations was infused over the chip surface, and the rates of FVIII release from immobilized VWF were monitored in real time. The half maximal effective concentration (EC_{50}) of α-thrombin was determined for each FVIII species.
Results and Conclusions: α-thrombin EC_{50} values for rFVIIIFc and rBDD-FVIII were comparable (3.7 ± 0.2 U mL^{-1} and 3.2 ± 0.3 U mL^{-1}, respectively), whereas the EC_{50} value for SC-rFVIIIFc was greater than 3-fold higher (11.7 ± 0.9 U mL^{-1}). This finding that SC-rFVIIIFc is released more slowly from VWF than are either rFVIIIFc or rBDD-FVIII is consistent with a previously observed discrepancy between the activities of rFVIIIFc and SC-rFVIIIFc in a one-stage clotting assay (aPTT) in which SC-FVIIIFc had a lower apparent activity only when VWF was present in the assay plasma sample. However, all samples possessed equivalent activities in a mouse bleeding model, indicating that responsiveness of FVIII preparations to thrombin in the release of FVIII from VWF does not correlate with efficacy *in vivo*.

PO-TU-032
Effects of GlycoPEGylated rFVIII (N8-GP) in a new sensitive venous bleeding model in hemophilia A mice
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Introduction: Prophylaxis with rFVIII is an efficacious treatment of hemophilia A; due to the half-life of FVIII, a dosing frequency of 2–3 times weekly is current treatment standard. To develop a less frequent dosing regime, a 40K GlycoPEGylated rFVIII-derivative (N8-GP) with a longer circulating half-life is under clinical development. In the current study, the dose–response relationship for N8-GP and rFVIII is compared in a new sensitive vena saphena bleeding model in hemophilia A mice.
Method: A 23-G needle was used to make an entry hole in the vena saphena, 5 min after IV dosing with increasing doses of N8-GP or rFVIII (ADVATE®). At initial hemostasis, a longitudinal distal cut was made in the vein, followed by 30 min of observation. At each subsequent hemostasis incident, the formed clot was gently disrupted with a blunted needle, whereby bleeding was reinitiated. End points were (1) total number of clot formations, (2) maximum bleeding time (bleeding episode of longest duration), and (3) average blood loss.
Results: N8-GP and ADVATE® dose-dependently increased the number of clot formations and dose-dependently reduced maximum bleeding time and average blood loss, reaching statistical significance at 5 or 10 U kg^{-1} and with comparable ED50 for the two compounds. Doses of 5 U kg^{-1} N8-GP and 10 U kg^{-1} ADVATE® reduced the maximum bleeding time to a level not significantly different from the normal level. For the number of clot formations and the average blood loss, normalization was reached at 10 U kg^{-1} and 25 U kg^{-1} for N8-GP and ADVATE®, respectively. In addition, preliminary data indicate a significantly prolonged duration of the effect of N8-GP compared to conventional rFVIII.
Conclusions: N8-GP and rFVIII improved coagulation dose-dependently in the vena saphena model with similar potency and efficacy. In this sensitive bleeding model, normalization was obtained with N8-GP and rFVIII at doses as low as 5–10 U kg^{-1}.

PO-TU-033
In vitro reversal of the direct Xa inhibitor rivaroxaban using high-purity factor X concentrate (factor X)
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Objective: Rivaroxaban (Xarelto®) is one of a number of new specific factor Xa inhibitors. It reversibly inhibits free, prothrombinase-bound and clot-associated FXa. Reversal of the anticoagulant effect may be necessary in the event of a major bleed or emergency surgery. A recent study has shown that prothrombin complex concentrate (PCC) can correct the prothrombin time (PT) of Rivaraxaban in healthy volunteers (Eerenberg, 2011). FACTOR X is a high purity factor X concentrate developed for the treatment of hereditary factor X deficiency. The high factor X potency and low thrombogenic potential of FACTOR X hypothetically make it a possible candidate for use in reversal of direct Xa inhibitors. The PT assay has been used to investigate this possibility in vitro.
Methods: Commercially available Rivaroxaban calibration plasmas (Hyphen Biomed) were spiked with FACTOR X or PCC and the PT measured (Neoplastin Plus, Diagnostica Stago).
Results: Rivaroxaban showed a concentration dependent increase in the PT times. Addition of FACTOR X reduced the PT times of the Rivaroxaban plasma (Figure 1).

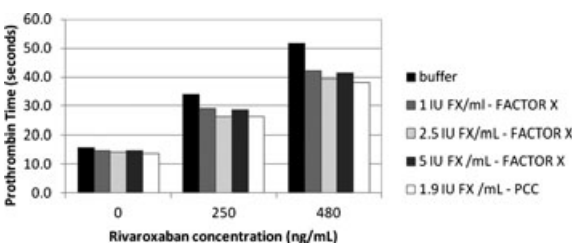

Fig. 1. PT results

Conclusion: FACTOR X reduced the PT of the Rivaroxaban plasma. Correction back to the normal range was not achieved using these FACTOR X doses. The absence of a dose response provides further evidence that routine PT tests may not accurately report hemostatic potential in these anticoagulated patients. This study suggests FACTOR X may be an effective option for reversal of direct Xa inhibitors. Clinical research is needed.

PO-TU-034
In vitro characterization of factor X in global hemostasis tests
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Objective: FACTOR X is a high purity factor X concentrate developed for the treatment of hereditary factor X deficiency. Global hemostasis tests (thrombin generation assays, thromboelastography) have been used alongside the traditional activated partial thromboplastin (aPTT) and prothrombin time (PT) to demonstrate the in vitro efficacy of FACTOR X in immune-depleted and congenital deficient plasmas.
Methods: FACTOR X was spiked to a final concentration of 1 IU mL^{-1}, into factor X immune-depleted plasma (HaematologicTechnologies Inc) or congenital deficient plasma (Helena Biosciences). Four batches of FACTOR X were tested. Samples were assayed using aPTT (Synthasil, IL), PT (Recombiplastin, IL), thrombin generation (Technoclone), and thromboelastography with kaolin activation (TEG, Haemonetics).
Results: Two immune-depleted plasmas (IDP1 and IDP2) and 1 congenital deficient plasma (CDP) were tested. In the absence of FACTOR X, all had prolonged aPTT (143, 76.8, and 84.9 s respectively) and PT (>100, 59.3, and 69 s respectively). There was no evidence of coagulation in the TGA or TEG. There were no significant differences between the batches of FACTOR X; however, there were some differences between plasmas in the thrombin generation and TEG tests (Table1).

Table 1: Mean (±standard deviation) results from four batches FACTOR X for each plasma.

plasma	PT (seconds)	aPTT (seconds)	Thrombin Generation			TEG	
			Lag Time (mins)	Peak Thrombin (nM)	AUC (nM)	R (min)	Angle (deg)
IDP1	12.3±0.3	33.7±0.9	14.4±2.4	235±74	3174±545	12.5±0.5	54.0±4.7
IDP2	11.8±0.2	34.0±0.7	12.7±2.4	299±59	3483±248	13.3±0.8	26.9±2.2
CDP	13.5±0.2	33.3±0.5	13.3±3.4	357±105	4259±589	13.8±1.0	57.1±5.4

Conclusion: BPL FACTOR X corrects the clotting times and thrombin generation in both immune-depleted and congenital factor X–deficient plasma. These parameters are within the published ranges for normal plasma in each test. The differences seen between plasmas are due to the sensitivity of the TGA and TEG assay to the levels of the other clotting factors, platelet and fibrinogen content.

PO-TU-035
Identification of sites of glutamic acid gamma-carboxylation in recombinant factor IX (rFIX) and FIX-Fc fusion protein (rFIXFc) by Lys-C Peptide mapping using LC-MS/MS with electron transfer dissociation

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Factor IX is a vitamin K–dependent (VKD) coagulation factor that contains 12 potential γ-carboxyglutamic acid (Gla) residues, many of which are critical for FIX function by mediating binding to the phospholipid surface. Recombinant FIX (BeneFIX®, rFIX) possesses incomplete γ-carboxylation at E36 and E40, which doesn't have an effect on FIX function. Recombinant FIX-Fc (rFIXFc) also has similar overall levels of γ-carboxylation. We sought a simple method to assess all the individual γ-carboxylation sites simultaneously to characterize the Gla occupancy. We report herein a novel Lys-C peptide mapping method, using LC-UV-MS/MS with electron-transfer dissociation (ETD) to localize the Gla sites of FIX and therefore identify the incomplete γ-carboxylation site(s). The results obtained for rFIXFc and rFIX were similar, and showed that E36 and E40 are not fully γ-carboxylated, which is consistent with literature reports. In addition, this methodology was applied to 2 less active fractions, A and B, which were removed during the final purification step of rFIXFc production. Fraction A possessed reduced activity as compared to the purified rFIXFc, whereas fraction B was essentially inactive. ETD data demonstrated reduced γ-carboxylation at E17 for both fractions, but with greater prevalence for fraction B as compared to purified rFIXFc. Published structural data for the Gla domain suggest that Gla17 interacts with 3 calcium ions to form a well-defined tertiary structure which may be critical for binding to the phospholipid surface. Incomplete γ-carboxylation at E17 could contribute to reduced or almost no specific activity of these fractions. Trace levels of under-γ-carboxylation at other sites were also detected. In summary, the developed method efficiently identified the major sites of incomplete γ-carboxylation in rFIX and rFIXFc as E36 and E40, consistent with literature reports on rFIX. This new method provides a valuable tool to characterize the γ-carboxylation sites for FIX and other VKD proteins.

PO-TU-036
Repeated application of a new recombinant factor IX in rats and macaques

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Baxter has developed a new rFIX product that is produced by a genetically engineered Chinese hamster ovary (CHO) cell line in a cell culture medium free from any animal or human proteins. In rats and macaques, the systemic toxic potential of rFIX was tested. The already-licensed rFIX served as a control. After intravenous administration of Baxter's rFIX every other day for 28 days at 200 or 750 IU kg^{-1} and licensed rFIX at 200 IU kg^{-1}, various safety endpoints, toxicokinetics, and the formation of anti-product antibodies were assessed. There were no mortalities, no clinical signs attributable to treatment, and no effect on body weight, food consumption, ophthalmology, urine variables, or clinical pathology variables. Macroscopic, microscopic examination and organ weights revealed no test-item related adverse effects. After the recovery phase of the treatment with Baxter's rFIX, low titers of binding anti-human FIX antibodies were detected in single rats. None of the antibodies had neutralizing activity. In macaques, binding antibodies were detectable in single animals treated with Baxter's rFIX or licensed rFIX. None of the antibodies had neutralizing activity except for in one animal treated with licensed rFIX. The exposure within the whole study period could be confirmed by the toxicokinetic analysis. Systemic exposure of rFIX activity increased in an approximately dose-proportional manner across the dose range. No apparent sex-related difference was observed. Toxicokinetics revealed similar results for Baxter's rFIX and licensed rFIX. In conclusion, intravenous administration every other day of rFIX at 200 or 750 IU kg^{-1} day^{-1} for 28 days did not result in any evidence of systemic effect. Therefore, 750 IU kg^{-1} rFIX was considered the no-observed-adverse-effect level (NOAEL) in these studies. The good safety profile of Baxter's rFIX during the preclinical program was the basis for proceeding with human trials, which have been initiated.

PO-TU-037
Preclinical safety of a new recombinant factor VIIa

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To serve the needs of hemophilia A or hemophilia B patients who have inhibitors, Baxter has developed a recombinant FVIIa (rFVIIa) product. Baxter's new rFVIIa is produced by a genetically engineered Chinese hamster ovary (CHO) cell line in an animal or human protein-free cell-culture medium. In a preclinical program that included pharmacology safety studies in telemetered macaques, rabbits, normal and spontaneously hypertensive rats and guinea pigs, the anaphylactoid and thrombogenic potential of rFVIIa and its effects on blood pressure, cardiac and respiratory function, and the coagulation system were assessed. In addition, studies in hemophilia A mice, rats, and macaques were performed to investigate the single and repeated dose toxicity. Local tolerance was tested in rabbits and comparative immunogenicity in mice. Licensed rFVIIa served as the active reference item. rFVIIa treatment did not cause any anaphylactoid reaction and also had no adverse effect on the hematology variables or on respiratory or cardiac function. Studies on thrombogenicity showed that Baxter's rFVIIa does not have a greater thrombogenic potential than the licensed rFVIIa. Single and repeated dose toxicity studies, at a dose of 2.7 mg kg^{-1}, showed the safety of Baxter's new rFVIIa. Due to the pharmacological action of rFVIIa, high doses of both recombinant FVIIa products resulted in exaggerated pharmacological effects such as thrombus formation in some organs, as was expected for this class of compounds. The intravenous administration of the rFVIIa was well tolerated at the injection site. Comparative immunogenicity studies showed that Baxter's new rFVIIa and the licensed rFVIIa product have a similar immunogenicity profile. In summary, the results lead to a safety profile of Baxter's rFVIIa that supports the evidence necessary for proceeding with human trials.

PO-TU-038
Safety of a PEGylated variant of recombinant factor VIII after repeated application in rats and macaques

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Baxter and Nektar have developed BAX 855, a PEGylated form of Baxter's recombinant FVIII (rFVIII) product based on the Advate manufacturing process. The product is derived from a Chinese hamster ovary (CHO) cell line using a plasma-protein-free method and a virus inactivation step. The objective of this preclinical program was to evaluate the safety of BAX 855 in different species. The systemic toxic potential of BAX 855 was tested in rats and macaques. The product was given intravenously at 350 or 700 U kg^{-1} to rats every other day for 28 days. Macaques were treated at doses of 150, 350 or 700 U kg^{-1} every 5 days for 1 month. In addition to various safety endpoints, toxicokinetics and the formation of anti-product antibodies were assessed. In rats, no drug-related changes were noted on any endpoint investigated. At the study end, lower levels of FVIII activity and FVIII-bound PEG in plasma correlated with the presence of neutralizing antibodies. In macaques, there were no signs of toxicity at any dose level. Minor findings, including a prolonged APTT in all animals treated with BAX 855, were noted during the last week of dosing. These observations were likely caused by the development of cross-reactive neutralizing anti-FVIII antibodies against endogenous FVIII. The formation of binding and neutralizing antibodies was also reflected in a statistically significant decrease in exposure observed during toxicokinetic analysis at the study end. The formation of antibodies against BAX 855 is an expected immune reaction after repeated application of heterologous human proteins to animals, which is also well known for non-PEGylated FVIII products. In conclusion, intravenous administration of BAX 855 for 28 days did not result in any evidence of an adverse systemic effect. Therefore, 700 U kg^{-1} was considered the no-observed-adverse-effect level (NOAEL) in these studies. The good safety profile of BAX 855 during the preclinical program provides the basis for proceeding with human trials.

PO-TU-039
Absorption, metabolism, distribution, and excretion of a PEGylated variant of recombinant factor FVIII following intravenous administration to rats

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Baxter and Nektar have developed BAX 855, a PEGylated variant of Baxter's rFVIII product based on the ADVATE™ manufacturing process using Nektar's polymer technology. Radiolabeled BAX 855 was synthesized by conjugation of rFVIII with tritiated [3H] PEG polymer. The absorption, metabolism, distribution, and excretion (ADME) of radiolabeled BAX 855 was investigated after single dose IV injection to male and female rats. Animals received a single intravenous 1 mg kg^{-1} dose of [3H] PEG-rFVIII when designated for the collection of excreta and blood or 2 mg kg^{-1} for whole body autoradiography (WBA), corresponding to a radioactivity//FVIII chromogenic activity dose of 122 μCi kg^{-1}//2088 U kg^{-1} or 251 μCi kg^{-1}//4176 U kg^{-1}, respectively. Urine and feces were collected for 1008 h post-dose. Blood was collected at specified times during 1008 h post-dose. Blood, plasma, urine, and feces were analyzed for total radioactivity. Rats designated for WBA were killed at specified times during 168 h post-dose and rats designated for tissue excision were killed at specified times during 1008 h post-dose. Radioactivity was eliminated from blood and plasma with half-lives ($t_{1/2}$) of 827 and 655 h, respectively, in males, and 306 and 276 h, respectively, in females. The distribution of drug-derived radioactivity was extensive in both males and females, with radioactivity quantifiable in blood and plasma and all matrices analyzed. The maximum concentrations (C_{max}) of radioactivity for tissues were observed at the 1, 8, 24, and 168 h collections. The highest maximum concentrations of radioactivity were observed in the plasma, blood, mesenteric lymph nodes, spleen, liver, adrenal glands, and kidneys in both males and females. Elimination of radioactivity occurred primarily via urine. At 1008 h post-dose, urine, feces, and daily cage rinse corresponded to 51.9, 38.4 and 4.01% of the dose administered to males, and 55.7, 45.0, and 3.53% of the dose administered to females. The mean overall recoveries in males and females were 97 and 107%, respectively. In conclusion, the results of this study show that radio-labeled PEG-rFVIII was

distributed to tissues without binding to cellular blood components and radioactivity was excreted quantitatively within 6 weeks via urine and feces.

PO-TU-040
Pharmacokinetics (PK) of recombinant and plasma-derived factor VIII (FVIII) products in pediatric patients with severe hemophilia A

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A review of current literature and FVIII product inserts was conducted to determine if the half-lives of available recombinant and plasma-derived FVIII products are comparable in pediatric patients. There is widespread PK data for FVIII use in adults, but this data cannot be applied to pediatric patients due to several significant physiologic differences. Specifically, ADVATE, Kogenate FS, and Xyntha demonstrate 3 variable PK trends, which include a lower area-under-the-curve, a higher clearance rate, and a lower half-life.

Table 1. Pharmacokinetic parameters of recombinant FVIII products in various age groups.

Product	Age	Mean Half-life (h)	Mean AUC (IU*h dL^{-1})	Mean Clearance (dL hr^{-1} kg^{-1})
ADVATE	1 month to <2 years	8.86 ± 1.78	1385 ± 476	0.039 ± 0.015
	2 to <5 years	10.27 ± 1.94	1545 ± 616	0.038 ± 0.016
	5 to <12 years	10.89 ± 1.60	1282 ± 509	0.044 ± 0.012
	12 to <16 years	11.70 ± 3.72	1447 ± 528	0.038 ± 0.012
Kogenate FS	4.4 to 18.1 years	10.7 (7.8–15.3)	1320.0	0.041
	12 to 33 years	14.60 ± 4.38	1487.08 ± 381.73	NA
Xyntha™ NA=not available	12 to 16 years	8.03 ± 2.44	1150 ± 520	0.052 ± 0.024

Pediatric PK studies are available for ADVATE, Kogenate FS, and Xyntha . However, each FVIII product defines their age groups differently when reporting PK data (Table 1), thereby making it difficult to compare their half-lives. Moreover, there is no pediatric PK data for any of the plasma-derived products, thus excluding possible comparisons with recombinant-derived products. Currently there is strong evidence that reducing the number of bleeds in young children is vital in the prevention of hemophilic arthropathy. Also, clinical trials with pediatric patients demonstrate that tailoring dosing frequency to an individual's half-life can have clinically significant outcomes in terms of bleeding prevention. We recommend that future research involve defining uniform age groups that every FVIII product will adhere to when reporting PK data. This will allow healthcare providers to compare the products and make evidence-based decisions regarding patient care.

PO-TU-041
Biophysical characterization of recombinant human factor VIII with and without GlycoPEGylation

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PEGylation has become widely used as a modification methodology for improving the biomedical efficacy and physicochemical properties of therapeutic proteins. N8-GP is a GlycoPEGylated recombinant factor VIII in clinical development for treatment of hemophilia A. N8-GP is PEGylated using selective enzyme-based GlycoPEGylation technology. The recombinant factor VIII (turoctocog alfa) used for GlycoPEGylation is a B-domain-truncated factor VIII. In this study, various biophysical techniques were used to compare structural properties and stability of N8-GP and turoctocog alfa. Spectroscopic techniques, such as far and near UV Circular Dichroism (CD) have shown that the secondary and tertiary structure of the protein in N8-GP is similar to that of turoctocog alfa. Thermal stability has been investigated using Differential Scanning Calorimetry (DSC) and Light Scattering (LS). The apparent denaturation temperature of N8-GP is increased compared to that of turoctocog alfa. More importantly, the reversibility is significantly improved upon GlycoPEGylation. Denaturation of turoctocog alfa is irreversible, and it is not possible to separate thermally induced unfolding and aggregation processes. In contrast, the unfolding of N8-GP is characterized by being partly reversible and less prone to thermally induced protein aggregation. In conclusion, the secondary and tertiary structure of turoctocog alfa is maintained upon GlycoPEGylation. However, GlycoPEGylation delays the thermally induced denaturation and aggregation processes.

PO-TU-042
rIX-FP, a recombinant fusion protein linking coagulation factor IX with albumin, demonstrates superior kinetics in cynomolgus monkeys and hemophilia B dogs

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Objectives: Patients with severe hemophilia B are at risk of recurrent bleeding episodes. Due to the half-life of coagulation factor IX (FIX) of 17–34 h, prophylactic treatment usually involves 2–3 injections of FIX preparations weekly. To increase treatment convenience, a reduced infusion frequency is desirable. The aim of the present studies was to demonstrate that rIX-FP, a recombinant fusion protein linking coagulation factor IX with albumin, confers an improved pharmacokinetic profile.
Methods: Single intravenous doses of 50–500 IU kg^{-1} of rIX-FP were administered to cynomolgus monkeys and hemophilia B dogs. Plasma concentrations were determined using activity (dogs only) and antigen-based assays. Additionally, activated partial thromboplastin time (aPTT) values were determined in hemophilia B dogs. Results were either compared to published recombinant (r) FIX data or to BeneFIX® as a direct study comparator.
Results: In both species, terminal half-life of rIX-FP was increased compared to rFIX reference data. In cynomolgus monkeys, terminal half-life was prolonged at least threefold (i.e., 39.8–55.9 vs. 12.7 h). In hemophilia B dogs, a minimum human FIX antigen level of 0.05 IU mL^{-1} was kept more than 3 times longer in the presence of rIXFP (7.3 days) in comparison with BeneFIX® (2.3 days), while clearance was decreased more than fourfold. Respective calculations based on FIX activity levels confirmed observed superior pharmacokinetics. Furthermore, aPTT values of these dogs remained below 60 s around 4 times longer following rIXFP treatment (5.9 days) as compared to BeneFIX® (1.5 days), demonstrating sustained efficacy.
Conclusion: The recombinant albumin fusion technology was successfully applied to human FIX for improvement of pharmacokinetic parameters and sustained efficacy. While these results add to the promising data in rodents and rabbits, ongoing clinical studies will show whether the observed improved kinetics translate into a significant half-life extension in hemophilia B patients.

PO-TU-043
Roman numerals to denote clotting factors: A potential source of medical errors

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Based on anecdotal reports, the use of Roman numerals to denote clotting factors is a potential source of medical error. In one case, a carrier of hemophilia B was scheduled for elective surgery. Her surgeon, knowing her carrier status and tendency to bleed, ordered a factor IX assay in advance of the surgery. When the woman went to hospital for the results, the surgeon reported that her factor IX level was close to C per C. The woman, who was past LXXX, looked across the desk at the chart in front of the physician and said, ''It may well be, but you've tested my factor XI level.'' Indeed, this was the case. The test had to be repeated. In another report, a person with factor XIII deficiency needed treatment at the Emergency Department in the middle of the night. The hematologist on call ordered factor XIII concentrate. The patient was dismayed to see the ED staff preparing factor VIII concentrate. The medical error was barely averted. Whether because of dyslexia or unfamiliarity with Roman numerals, IX and XI, VIII and XIII, and VII and VIII are frequently written or read in error. A letter by the author to the JTH (Page DA. *Change designation of clotting factors to Arabic numerals*. J Thromb Haemost 2009; DOI: 10.1111/j.1538-7836.2009.03524.x.) elicited from physicians many other examples of errors or near misses. Discussion with manufacturers and regulators revealed that a universal change to Arabic numerals was simply not realistic. To reduce the potential for medical errors, some precautionary measures include prescribing brand names of clotting factor concentrates and writing the number of the coagulation factor in brackets in Roman numerals as in ''factor IX (factor 9)''. Submitted for review January XV, MMXII.

PO-TU-044
Cryoprecipitate transfusion in on-pump cardiac surgery

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Background: Cardiopulmonary bypass (CPB) during cardiac surgery is associated with platelet and coagulation defects including hypofibrinogenemia. In Canada, cardiac surgery is the most common indication for cryoprecipitate (CRYO) transfusion; yet there are no clinical studies to support its use in this setting. Scores to predict probability of allogeneic blood transfusion in cardiac surgery have been published (eg. Transfusion Risk Understanding Scoring Tool, or TRUST). However, no literature exists on predictors of requirement for fibrinogen replacement post-CPB.
Methods: We evaluated the prevalence of CRYO transfusion post cardiac surgery on CPB at St. Michael's Hospital. Charts of all adults undergoing CPB from January 1 to May 31, 2010 and who consented to blood transfusion were retrospectively reviewed.
Results: Five hundred seventy-nine charts were reviewed. Baseline characteristics were as follows: females 27.5%, mean age 66 years, non-isolated CABG 30.9%, non-elective OR 42.7%, previous cardiac surgery 4.5%, pre-existent liver disease 0.7%. 278/579 (48%) patients required allogeneic blood transfusion. 28/579 (4.8%) patients received CRYO transfusions within 24 h post-operatively. Patients who received CRYO were 21.4% female, mean age 61 years, mean TRUST score 3.07, non-isolated CABG 78.6%, non-elective OR 35.7%, previous cardiac surgery 17.9%, pre-existent liver disease 17.9%. Patients who did not receive CRYO were 27.8% female, mean age 66.6 years, mean TRUST score 2.68, non-isolated CABG 25.9%, non-elective OR 43.0%, previous cardiac surgery 3.8%, pre-existent liver disease 0.9%. Pre-operative hemoglobin, BSA, and prevalence of renal disease were similar in both groups. All patients who received CRYO also received RBC. 17/28 (61%) of patients had fibrinogen measured prior to CRYO transfusion; average pre-transfusion level was 1.21 g L^{-1}. The reason for CRYO transfusion was ''coagulopathy and bleeding'' in all cases.
Conclusion: About 5% of patients received CRYO post-CPB. Patients who received CRYO tended to be younger, with higher TRUST scores, pre-existent liver disease, previous cardiac surgery, and were undergoing non-isolated CABG and non-elective surgery.

PO-TU-045
Characterization of the binding properties of recombinant FVIII concentrates with von Willebrand factor
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The FVIII concentrates ADVATE, Kogenate and ReFacto are produced using diverse manufacturing processes, raising the question if the various products show differing VWF-binding properties. The aim of the investigation was the characterization of the binding properties concerning recombinant FVIII concentrates to von Willebrand factor (VWF). The investigation of the complex formation of FVIII and VWF was performed by using an in vitro system. Concerning this matter, a polyclonal VWF-binding antibody was immobilized to the surface of a micro well plate. VWF was added to each well and later incubated with the various FVIII concentrates. Bound FVIII was detected by activity and antigen level. Analysis of bound FVIII to VWF was accomplished by endpoint determination, using multiple FVIII concentrations and steady incubation time as well as by kinetic measurement, consistent concentration and various incubation times. Results obtained by the measurement of bound rFVIII activity, after incubation with steady activity levels, were used to determine the dissociation constant and the velocity constant of complex formation by applying the Langmuir model for independent binding sites and the equation of complex-concentrations of the balance reaction. In summary, it could be observed that ADVATE and Kogenate show similar binding properties. Furthermore, the steady rising curves of the kinetic measurements elucidated that along with the active rFVIII, inactive proteins slowly bind to VWF as well. ReFacto differs in its binding behaviour. Kinetic measurements always led to saturation curves, and the activity determination showed a significantly increased amount of bound FVIII, implying elevated binding possibilities of the much smaller protein, due to the deleted B-domain, to the steric hindered VWF concerning the binding assay. Despite significantly higher amounts of bound rFVIII concerning ReFacto there are no significant differences in binding velocity, as proven by kinetic calculation.

PO-TU-046
Factor XIII levels a in hemophilia: Treatment implications
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Hemophilia is characterized by abnormal thrombin generation resulting in the formation of unstable clots and characteristic bleeding symptoms associated with hemophilia. Recent laboratory studies indicate that adding standard factor concentrates combined with FXIII maximally enhances clot stability in whole blood and plasma from individuals with hemophilia[1,2]. It is unclear whether the clot-promoting effect of adding FXIII results from a correction in unexpectedly low FXIII levels in patients or due to the effect of enhancing FXIII to supra-physiological levels. The aim of this study was to perform a retrospective survey of FXIII measurements made in patients with hemophilia over 3 years to establish whether levels were within a normal range. It was hypothesized that FXIII levels would not differ from the reference range.
Methods: FXIII antigen was evaluated using the HemosIL FXIII antigen assay (ACL Top, Intrumentation Laboratory, Bedford, MA). A database search (following approval) extracted FXIII measurements from patients with hemophilia. The results were compared to a reference established on in-house samples from 50 healthy adults (0.61–1.77 Arbitrary Units (AU) x 10^3 L^{-1}).
Results: Twenty-two FXIII results were collected from 22 patients (6 severe A; 7 moderate A; 8 mild A; 1 mild hemophilia B), (mean age 19 years, range 0–67). FXIII levels lay within the normal reference range for all patients, and there was no difference difference in mean values comparing individuals with mild, moderate, and severe hemophilia (Mann-Whitney $P > 0.3$). Of note, FXIII levels show correlation with age (Spearman rank $P < 0.016$), reflecting reports in the general population[3].
Conclusions: In this retrospective survey, FXIII levels in individuals with hemophilia do not differ from the normal range. This indicates that adding FXIII to factor-deficient whole blood or plasma in laboratory studies improves clot stability by raising FXIII levels to a supra-physiological level, rather than by correcting an underlying FXIII deficiency.
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PO-TU-047
rFVIIFc zymogens with enhanced activation kinetics
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Antithrombin III (ATIII) inhibition constitutes a major pathway in the clearance of therapeutic recombinant FVIIa. This process is dependent on the activity of FVIIa and, consequently, FVIIa analogs with increased specific activity are cleared by ATIII at a faster rate. Modifications to the FVII protein that make it resistant to ATIII inhibition should decrease the rate of clearance and may allow for the generation of high specific activity variants with better pharmacokinetic properties. Therapeutic administration of the non-activated form of FVII is not a viable option due to poor activation kinetics in vivo. Alternatively, we have generated novel rFVIIFc enhanced zymogens comprising a thrombin cleavage site for activation in vivo in the presence of thrombin. We reasoned that this zymogen would remain in the non-active form and resistant to ATIII inhibition until thrombin is generated at the site of coagulation. Furthermore, the enhanced zymogen was generated as an Fc fusion to further improve its pharmacokinetic properties. An enhanced zymogen with an optimized thrombin cleavage site revealed activity in thrombin generation assays following activation by trace amounts of thrombin. Enhanced zymogen variants with mutations that confer high specific activity displayed similar in vitro activation kinetics by thrombin as the wild type version, but significantly higher activity in thrombin generation assays. Furthermore, both wild type and high specific activity variants displayed amidolytic and FXa generation activity following thrombin activation, with the high specific activity variants showing significantly enhanced activity. As anticipated, both wild type and high specific activity enhanced zymogen variants displayed resistance to ATIII inhibition in the absence of thrombin activation. In summary, we have generated rFVIIFc thrombin-activatable variants that are resistant to ATIII inhibition and display FVIIa activity following activation by thrombin. In addition, this approach may allow for the generation of high activity FVIIa therapeutics with enhanced pharmacokinetic properties.

PO-TU-048
Efficacy of a recombinant factor IX in mouse models of hemophilia B
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Baxter is developing a recombinant factor IX (rFIX) product for the treatment of patients with hemophilia B. Hemophilia B (FIX ko; B6.129P2–*F9*^{tm1Dws}) mice were used to assess the efficacy of Baxter's rFIX in three different models: a tail-tip bleeding model (TTBM), a carotid occlusion model (COM), and using thrombelastography (TEG). Animals included in the COM and TEG studies received intravenous prophylactic treatment with 75 IU kg^{-1} of either Baxter's rFIX or a commercially available rFIX product, which served as the active control item. To obtain dose-effect curves, Baxter's rFIX was additionally tested in the TTBM at different doses of 10–100 IU kg^{-1}. Buffer served as the negative control item in all studies. Animals were anesthetized using ketamine and xylazine. In the COM study ($n = 10$) the left carotid artery was exposed and the endothelium was denuded by topical application of $FeCl_3$. Time to occlusion [min] was assessed. In the TEG study ($n = 10$), citrated whole blood was sampled by venipuncture of the caudal vena cava. R-time (time to clot formation [min]) was assessed as the primary endpoint. In the TTBM ($n = 16$), the tip of the tail was cut off and total blood loss [mg] was assessed over 60 min. Median results of buffer-treated animals were COM: ≥30 min (no occlusion), TEG: 98.7 min and TTBM: 1036 mg. Median results of groups treated with 75 IU kg^{-1} of Baxter's rFIX were COM: 3.3 min and TEG: 54.5 min vs. COM: 4.6 min and TEG: 56.2 min after treatment with the active control item. Median results after treatment with different doses of Baxter's rFIX in the TTBM were 32 mg with 100 IU kg^{-1}, 145 mg with 75 IU kg^{-1}, 204 mg with 25 IU kg^{-1} and 927 mg with 10 IU kg^{-1}. In summary, a similar efficacy of Baxter's rFIX and the active control item was demonstrated at 75 IU kg^{-1}. Furthermore, the dose-dependency of the hemostatic effect of Baxter's rFIX was shown.

PO-TU-049
Efficacy of a new recombinant factor VIIa in animal models of hemophilia
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Baxter is developing a new recombinant FVIIa (rFVIIa) product for the treatment of patients with hemophilia A or B with inhibitors. The efficacy of Baxter's rFVIIa was evaluated in different animal models of hemophilia: Hemophilia A (FVIII ko) and B (FIX ko) mice, factor VIII (FVIII)-inhibited rabbits, and warfarin-pretreated rats. In all studies, Baxter's rFVIIa was tested at different doses to obtain dose-effect curves. A commercially available rFVIIa served as the active control item, buffer as the negative control item. Mice were used in a prophylactic setting. Twenty FVIII ko mice and 20 FIX ko mice per group were included in a tail-tip bleeding model. Baxter's rFVIIa was tested at 3 doses up to 2.7 mg kg^{-1}, the active control item at 2.7 mg kg^{-1}. Ten FVIII ko mice per group were used to assess the influence of rFVIIa on the thrombelastogram of hemophilic mice. Both items were tested at 3 doses up to 1.2 mg kg^{-1}. Rabbits and rats received therapeutic treatment after infliction of a bleeding injury. Six NZW rabbits per group were used in a nail-cut model. The animals were pretreated with a goat polyclonal FVIII-antibody to deplete endogenous FVIII. Baxter's rFVIIa was tested at 5 doses up to 3.0 mg kg^{-1}, the control item at 2.0 mg kg^{-1}. Six CD rats per group were used in a tail-tip bleeding model. The animals were pretreated with warfarin to deplete vitamin K-dependent coagulation factors. Baxter's rFVIIa was tested at 3 doses up to 2.0 mg kg^{-1}, the control item at 2.0 mg kg^{-1}. A dose-dependent hemostatic effect of Baxter's rFVIIa could be shown in all primary pharmacodynamic studies performed. Statistical analysis of the results showed no statistically significant differences between the efficacy of Baxter's rFVIIa and the licensed rFVIIa product after treatment with the same doses. In summary, the results of our studies show that Baxter's rFVIIa is prophylactically and therapeutically effective in animal models closely reflecting the conditions in patients with hemophilia and inhibitors.

PO-TU-050
Efficacy of a PEGylated variant of recombinant factor VIII in mouse models of hemophilia A
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Factor VIII (FVIII) is a critical component of the intrinsic coagulation pathway. FVIII concentrates are used in patients with hemophilia A to provide a hemostatic FVIII level. Multiple administrations are necessary per week to maintain a FVIII level of at least 1% of normal to prevent or reduce spontaneous bleeding episodes. A longer-acting FVIII concentrate would reduce the frequency of infusions. Baxter is developing a recombinant (r) FVIII modified with polyethylene glycol (PEGylation) to achieve longer circulation (BAX 855). The aim of the presented studies was to evaluate the efficacy of BAX 855 in hemophilia A mice using a tail-tip bleeding model (TTBM) and a carotid occlusion model (COM). BAX 855 was tested at a dose of 200 IU kg^{-1} rFVIII. Advate, a commercially available rFVIII, served as the active reference item. Mice received i.v. treatment with either BAX 855 or Advate 12–40 h before the start of the experiment. Buffer was used as a negative control item and administered 5–15 min before the experiment. In the TTBM (n = 16), the tip of the tail was cut off and total blood loss [mg] was assessed over 60 min. In the COM study (n = 10), the left carotid artery was exposed and the endothelium was denuded by topical application of $FeCl_3$. Time to occlusion [min] was assessed. Buffer-treated animals had a median blood loss of 951 mg in the TTBM and did not show vessel occlusion within 30 min in the COM. In the TTBM, a prophylactic effect of Advate could be observed for up to 18 h (121 mg). Prophylactic efficacy of BAX 855 could be observed for up to 40 h (73 mg after 30 h, 436 mg after 40 h). In the COM, treatment with Advate 12 h before the experiment shortened the time to occlusion to 3.8 min. With BAX 855, a similar efficacy could be observed for up to 24 h after administration (5.2 min). In summary, the results of our studies show that BAX 855 is efficacious in these two mouse models of hemophilia A and that the efficacy of BAX 855 is prolonged compared with an unmodified rFVIII.

PO-TU-051
Characterization of recombinant single chain FVIII, rVIII-singlechain (CSL627)
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Factor VIII (FVIII) is a heterogeneous, two-chain glycoprotein with an approximate molecular weight of up to 280 kDa. During blood coagulation, FVIII is cleaved by traces of thrombin at specific sites. All currently available plasma-derived and recombinant FVIII products are essentially two-chain proteins. This increases the possibility that dissociation of the heavy and light chains during manufacture or storage may affect stability. An alternative concept is investigated with CSL627, a single-chain recombinant FVIII molecule, rVIII-SingleChain. It was expected that rVIII-SingleChain would generate the same active complex upon reaction with thrombin and, therefore, would exhibit a physiological effect comparable to that of other FVIII products, while improving molecular stability and integrity. Aim of the presented study was the characterization of this new molecule and the comparison with commercially available rFVIII products. rVIII-SingleChain was expressed in CHO cells and purified by a multistep chromatographic process. Different methods were applied for analyzing the purified drug substance. Size-exclusion chromatography was performed under isocratic conditions by means of a silica-based column. Reversed-phase chromatography using a C-4 solid phase was performed in a water/TFA/acetonitrile gradient. Finally, capillary electrophoresis in the presence of SDS (CE-SDS) was carried out, using a Beckman PA 800 system. Size-exclusion chromatography demonstrated that rVIII-SingleChain is a highly homogeneous molecule of high purity. This result was supported by reversed phase chromatography. One main peak was detected representing the predominant portion of the total area. CE-SDS also revealed a main peak corresponding to the expected molecular weight. Analysis of thrombin-activated single-chain FVIII by RP-HPLC indicated the formation of fragments identical to those of other activated licensed rFVIII products. In summary, it could be demonstrated that rVIII-SingleChain is a highly purified and homogeneous recombinant single-chain FVIII product indistinguishable from other FVIII products after activation.

PO-TU-052
Collaborative study for the establishment of Korean standard for blood coagulation factor IX concentrate
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Objectives: A collaborative study among 4 laboratories including 3 manufacturers and 1 national control laboratory was carried out to evaluate the suitability of a candidate to serve as the 1st Korean Standard for blood coagulation factor IX.
Materials and Methods: The candidate material for national standard was manufactured according to the WHO guideline for biological standards and the Minimum Requirements for Biological Products in Korea, issued by KFDA. It was distributed to 4 laboratories and assayed using a one-stage clotting assay with 2 kinds of equipment against the 4th International Standard for FIX Concentrate (07/182) to determine the potency of this candidate. Accelerated thermal degradation at -20, 4, 20, 37, 45°C and the real-time stability. Long-term storage for up to 18 months for was examined. The 3rd IS for Blood Coagulation Factors II, VII, IC and X, Plasma, Human (99/826), and Standard Human Plasma was also included to evaluate the relationship between the factor IX plasma and concentrate unitage.
Results: One hundred thirty-one sets of clotting assay results were analysed. Based on the data collected from all participants, intra-laboratory variability was found to range from 2–5.55% and good inter-laboratory agreement with the majority of GCV around 5% was obtained. Stability studies indicated that the candidate was very stable. The measurement of the clotting time, which depends on the equipment used, showed little difference on the potency value. The estimated mean value obtained from the one-stage clotting assay was 12 international units (IU)/vial.
Conclusions: As the result of this collaborative study, the candidate standard is adopted as the 1st Korean National Standard for blood coagulation factor IX, concentrate.
Contribution: It is expected that this will contribute to the globalization of quality control in factor IX products by establishing the national standard.

PO-TU-053
The stability of FVIII in cold condition
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Indonesia is a large country and consists of more than 1000 islands. Diagnosis of hemophilia is suspected if there is a bleeding history and specific clinical symptoms such as hemarthrosis and delayed bleeding. Laboratory tests such as APTT and assay of F VIII or F IX are required to confirm the diagnosis of hemophilia. Unfortunately only very few laboratories in Indonesia can perform the assay of F VIII or F IX, so patients who lived in remote area cannot be diagnosed properly. Therefore the purpose of this study is to know the stability of F VIII in cold condition.
Material and methods: Using blue cap vacuum tube containing sodium citrate 0.105 M, blood was collected from 12 hemophiliacs in Dr.Cipto Mangunkusumo Hospital, Jakarta. After centrifugation at 2000 g for 10 min, plasma from each subject was separated in five Eppendorff tubes. The first tube was kept in room temperature, the second and third tubes were kept in styrofoam box containing 20 ice packs, and the fourth and fifth tubes were kept in styrofoam box containing 5 kg, and 10 kg dry ice, respectively. Assay of F VIII in the first tube from each subject was done within 2 h after blood collection. The assay of F VIII in the second, third, fourth, and five tube were done after 6 h, 10 h, 24 h, and 48 h, respectively. Coagulation factor VIII deficient plasma (cat. 546527A), Pathromtin SL (cat. 536440), Calcium chloride solution (cat. 539447), Dade's Owren Veronal Buffer pH 7.35 (cat. 527697), Standard Human Plasma (cat. 503215B), and Normal Control Plasma (cat 509927B) were all made by Siemens. The assay of F VIII was performed on coagulometer Sysmex CA-500 at Clinical Pathology Department, Dr. Cipto Mangunkusumo Hospital, Jakarta.
The results of F VIII assay from second, third, fourth, and fifth tubes were compared to the first tube. Statistical analysis was done using paired t-test if data showed normal distribution, and Wilcoxon test was chosen if data indicated abnormal distribution even after logarithmic transformation.
Results: Comparison of F VIII activity in the plasma kept in cold condition with fresh plasma showed that there was no significant difference between F VIII activity in plasma kept in ice pack for 6 h (mean temperature 4°C) with fresh plasma, and no significant difference between F VIII activity in plasma kept in dry ice for 24 h (mean temperature -31°C) with fresh plasma.
Conclusion: The stability of F VIII is 6 h in plasma kept in 4°C and 24 h in plasma kept in -31°C.
Conflict of interest: All reagents used in the study were donated by Indonesian Sysmex Company, the distributor of Siemens.

PO-TU-054
A case of inhibitor to factor IX in a two-year-old boy with severe congenital hemophilia B
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The inhibitor incidence in hemophilia B is estimated to be less than 3%. Indeed, the development of inhibitor antibodies to factor IX is a serious complication and its management is delicate, especially when discovered at an early age. A Caucasian boy in whom severe congenital hemophilia B was diagnosed at the age of 8 months in front of diffuse bruising on his body. Both of his parents had no hematological antecedents. An underlying mutation with a high risk of inhibitor development was found (from the 5' main proximal promoter to 3' polyadenylation site) resulting in a complete deletion of the gene of factor IX. At the age of 2 years, the occurrence of left ankle hemarthrosis required a substitution of deficient Factor IX with Benefix® intravenous at 1000 IU for 2 days a week. A biological survey was done once a week before the next dose. At the twelfth dose, an inhibitor to factor IX was detected (1BU). The treatment was stopped and a prophylactic treatment with a recombinated activated factor VIIa (Novoseven®) was initiated (250 μg kg^{-1}). Novoseven® is a bypassing agent that enhanced thrombin formation and promotes hemostasis it's a well-established with congenital hemophilia complicated by antibody inhibitors. The inhibitor continues to rise up to 2 BU at the seventh dose of Novoseven®, then decreased to 0.57 BU. The eventual immune tolerance treatment was discussed in order to manage any hemorrhagic events due to Novoseven®. Despite the severity of the mutation of factor IX, no allergic reaction or nephrotic syndrome was noticed, and the boy had a good clinical tolerance to treatment with Novoseven®.

PO-TU-055
Comparative field study evaluating the activity of recombinant factor VIII-Fc fusion protein (rFVIIIFc) in plasma samples at clinical hemostasis laboratories
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Objectives: A recombinant monomeric factor VIII-Fc fusion protein (rFVIIIFc) comprised of a single FVIII molecule fused to the dimeric Fc region of immunoglobulin G1 demonstrated a significant increase in plasma half-life in hemophilia A patients in a Phase I/IIa clinical trial when compared to ADVATE®. To verify that the plasma levels of rFVIIIFc can be accurately quantified using common 1-stage or chromogenic assay reagents and current FVIII laboratory standards, we tested a set of spiked plasma samples at clinical hemostasis laboratories throughout the US, Canada and the E.U.
Methods: Human hemophilic donor plasma was spiked with rFVIIIFc or ADVATE at 5, 20 or 80 IU dL^{-1}. Laboratories were blinded with respect to the drug product or concentration in each vial and were asked to test 3 sets of samples on different occasions. The results were evaluated for intra- and inter-laboratory variation, accuracy, and possible rFVIIIFc-specific assay discrepancies.
Results: The inter-laboratory CV ranged from about 12% to 30% for the 1-stage assay and up to 50% for the chromogenic assay. In both assays, the variability observed for rFVIIIFc and ADVATE was comparable. There were no outlier results for rFVIIIFc, which suggests that both products could be assayed equally well in this representative set of FVIII activity assays using a variety of reagent and instrument combinations.
Conclusion and Contribution to the Practice/Evidence Base of Hemophilia and Bleeding Disorders: Our results demonstrate that plasma rFVIIIFc levels can be monitored in patients by either the 1-stage or the chromogenic assay routinely performed in clinical coagulation laboratories with an accuracy that is comparable to current FVIII products and without the need for a product-specific rFVIIIFc laboratory standard.

PO-TU-057
2D-DIGE as a tool to analyze lot-to-lot consistency of complex therapeutic products such as BAX 855, a PEGylated recombinant FVIII
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Two-dimensional difference gel electrophoresis (2-D DIGE) is a method that circumvents the gel-to-gel variability inherent in conventional 2-dimensional gel electrophoresis (2-DE). We developed a 2-D DIGE protocol for recombinant factor VIII (rFVIII), a therapeutic protein used for the treatment of hemophilia A. The FVIII heterodimer is composed of heterogeneous, strongly glycosylated heavy and light chains that are held together by a divalent cation. 2-DE of rFVIII led to a separation of the various fragments and their identity could be determined by Western blot. A comparison of two rFVIII batches by 2-D DIGE revealed their identical composition, whereas an rFVIII variant lacking its central B domain was congruent with the smallest heavy and light chain fragments of rFVIII only. A simpler pattern was obtained upon removal of the terminal sialic acids of rFVIII's glycans due to a better focusing in the first dimension. 2-D DIGE was also well suited to structurally evaluate BAX 855, a PEGylated longer-acting variant of recombinant FVIII. 2-D DIGE thus proved an excellent and straightforward method for structural analysis of rFVIII. Our data suggest that the method could serve as a tool to characterize and control quality of very complex pharmaceutically active ingredients such as PEGylated proteins.

PO-TU-058
Influence of expression of recombinant human ADAMTS13 in cell lines from different species on its glycosylation pattern and pharmacokinetics
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A severe functional deficiency of the von Willebrand factor (VWF) cleaving protease ADAMTS13 is associated with thrombotic thrombocytopenic purpura (TTP), a rare disease in which the accumulation of uncleaved VWF multimers in the patient plasma results in platelet aggregation and systemic thrombus formation in the microcirculation. Standard care of treatment of TTP patients involves frequent plasma exchange with fresh frozen plasma, however, substitution therapy with a recombinant (r) ADAMTS13 would be more desirable. We have developed genetically engineered human embryonic kidney 293 (HEK293) and Chinese hamster ovary (CHO) cell clones to produce rADAMTS13 under serum-free conditions. Highly purified rADAMTS13 from both cell species was analyzed for post-translational modifications, especially regarding N-glycosylation, in comparison to ADAMTS13 purified from normal human plasma (pdADAMTS13). In addition, the pharmacokinetic (PK) parameters of the different preparations were investigated in ADAMTS13 knock-out mice. Glycosylation analysis revealed differences between the N-glycans and the degree of sialylation made by HEK293 cells compared to ADAMTS13 from CHO cells and pdADAMTS13. Comparative studies in mice showed similar PK profile for rADAMTS13 from CHO cells and pdADAMTS13, and demonstrated a significantly faster clearance for rADAMTS13 from HEK293 cells. In conclusion, these data showed that HEK293 cells were not suitable for rADAMTS13 production due to inadequate N-glycosylation, reflected also in different half-lives in mice compared with ADAMTS13 from CHO cells or human plasma.

PO-TU-059
Establishment of a manufacturing process for recombinant human ADAMTS13 retaining high specific activity
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Thrombotic thrombocytopenic purpura is an acquired or hereditary rare disease that is linked to a reduced or missing activity of the metalloprotease ADAMTS13 in plasma. Currently patients are treated by frequent exchange of plasma with fresh frozen plasma, but a substitution therapy with a rADAMTS13 would be more convenient. The development of a manufacturing process for recombinant human ADAMTS13 based on a CHO expression cell line will be presented. The upstream process applies a continuous culture system in a protein-free chemically defined media. The downstream process consists of a series of chromatographic purification steps, including 2 dedicated virus inactivation and reduction steps. A successful scale-up was performed and data from preclinical production campaigns as well as a partial characterization of the rADAMTS13 bulk drug substance will be shown.

PO-TU-060
Susceptibility of von Willebrand factor from different mammalian species to cleavage by human recombinant ADAMTS13
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The hemostatic activity of von Willebrand factor (VWF) is physiologically regulated by the plasma metalloprotease ADAMTS13, which limits the size of the VWF multimers by cleaving the Tyr_{1605}-Met_{1606} bond in the A2 domain. A severe functional deficiency of ADAMTS13, as is characteristic for thrombotic thrombocytopenic purpura (TTP) patients, results in the accumulation of uncleaved VWF multimers that can lead to increased platelet aggregation and thrombus formation in the microcirculation. Human recombinant ADAMTS13 (rADAMTS13) holds great promise as a potential new therapeutic protein for TTP patients. Preclinical studies designed to evaluate the efficacy of rADAMTS13 in different animal models need to ensure that the VWF of these species can serve as substrate for the human enzyme. This is particularly important because of the species-dependent variability of ADAMTS13-mediated proteolysis of human rVWF. We tested mouse, rat, rabbit, guinea pig, mini-pig, dog, and cynomolgus monkey as sources of the plasma-derived VWF substrate. Cleavage of orthologous VWF was assessed by using equal volumes of citrated plasma in the presence of urea with different concentrations of rADAMTS13. Specificity of VWF cleavage was shown by blocking ADAMTS13 activity with neutralizing anti-ADAMTS13 antibody and EDTA. The efficiency in proteolyzing VWF was evaluated by agarose multimer separation and immunoblot analysis. Although differences in the extent of multimer cleavage of the orthologous VWF substrates were observed, VWF from all species tested has proven susceptible to human rADAMTS13 cleavage in vitro and thus appropriate for preclinical evaluation in vivo.

PO-TU-062
Development of a large-scale production process for BAX 855, a PEGylated rFVIII product
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Baxter and Nektar have developed BAX 855, a PEGylated form of Baxter's recombinant FVIII (rFVIII) product based on the ADVATE™ manufacturing process. The conjugation process for preparing BAX 855 uses proprietary stable PEGylation from Nektar Therapeutics. Similar technology has been successfully employed for marketed and licensed PEGylated drug products including proteins and peptides in clinical use. The manufacturing process for BAX 855 comprises several steps, including chromatographic purification on a strong cation exchanger, which allows the fractionation of species with different PEGylation degrees and concentration of the conjugate collected by an ultra- / diafiltration step leading to the pre-formulated bulk drug substance (BDS). Final formulation of the BDS includes a filling and lyophilization step to obtain the final drug product. The process described is suited to manufacturing BAX 855 in gram scale and showed a good batch-to-batch consistency, ensuring an equivalent product quality for each batch. BAX 855 manufactured by this process has a specific activity similar to that of rFVIII in ADVATE™ and PEGylation degrees in the narrow range of 2 to 3 mols PEG / mol rFVIII. SDS-PAGE and Western blot analysis of BAX 855 confirm the stable PEGylation and demonstrate an increase in the molecular weight of the various FVIII domains. PK studies in different species displayed longer survival of BAX 855 compared to ADVATE™. In summary, BAX 855, a PEGylated rFVIII derivative, can be manufactured reproducibly without changes to the protein structure characteristic for a functional FVIII molecule, and consequently the functional properties of BAX 855 were retained, indicating that PEGylation did not have an impact on the hemostatic function of rFVIII in vitro and in vivo.

PO-TU-063
Functional characterization of BAX 855, a PEGylated recombinant FVIII
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Baxter and Nektar have developed BAX 855, a longer-acting PEGylated form of Baxter's recombinant FVIII (ADVATE™ process) using stable PEG technology from Nektar.

BAX 855 was functionally characterized in vitro and its features were compared with those of the unmodified parent rFVIII. The overall hemostatic potency of BAX 855 was assessed using a thrombin generation assay. Similar to unmodified rFVIII, BAX 855 corrected the impaired thrombin generation of the FVIII deficient plasma in a concentration-dependent manner. The role of FVIII within the tenase complex was determined by measuring the kinetics of FXa generation with a FIXa-cofactor activity assay, using either untreated or thrombin activated BAX 855. Comparison of the kinetic parameters and the maximum FXa generated revealed similar characteristics between BAX 855 and unmodified rFVIII. A similar approach revealed that BAX 855 fully retained its ability to be activated and inactivated by thrombin. The susceptibility of BAX 855 to activated protein C (APC) inactivation was also similar for BAX 855 and unmodified rFVIII. The binding affinities for VWF were similar for unmodified rFVIII and BAX 855, and the binding capacity of BAX 855 was also only slightly reduced. In contrast, the binding capacity of BAX 855 to the low-density lipoprotein receptor–related protein (LRP) clearance receptor was 55% less than that of the unmodified rFVIII. PK and hemostatic efficacy studies in different species display longer survival and longer action of BAX 855 compared to ADVATE™. In summary, the functional properties of BAX 855 were fully retained, indicating that PEGylation did not have an impact on the functional properties of rFVIII.

PO-TU-064
Assessment of preclinical safety for BAX 326, Baxter's recombinant human factor IX

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Baxter has developed a recombinant FIX product (BAX 326) which is produced by a genetically engineered Chinese hamster ovary (CHO) cell line in a cell culture medium free from any animal or human proteins. The objective of this preclinical study program was to evaluate the safety of BAX 326 in different species. The preclinical program included studies on established models of general safety pharmacology (conscious, telemetered cynomolgus monkey), thrombogenicity (rabbit, Wessler test), single and repeated dose toxicity (mouse, rat, cynomolgus monkey), local tolerance (rabbit), and comparative immunogenicity (mouse, rat, cynomolgus monkey). Commercially available licensed rFIX and pdFIX served as active reference items. Thrombogenicity studies showed no thrombogenic potential of BAX 326. General safety pharmacology revealed no adverse effects on clinical signs, or cardiovascular or respiratory variables. Single dose toxicity studies in mice, administered at doses of up to 7500 IU kg^{-1} BW, and repeated administration of BAX 326 in rats and cynomolgus monkeys, administered doses of up to 750 IU kg^{-1}, confirmed the safety of the new product. Furthermore, BAX 326 was well tolerated at the injection site after intravenous injection. No differences in immunogenicity between BAX 326 and the reference items were revealed by comparative immunology studies. This good safety profile of BAX 326 was the basis for a comprehensive clinical program, which will lead to a market application in 2012.

PO-TU-065
Structural characterization of BAX 855, a PEGylated recombinant FVIII

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Baxter and Nektar developed a longer-acting recombinant FVIII (BAX 855), which is manufactured by coupling stable PEG, using Nektar technology, to Baxter's full-length rFVIII bulk drug substance from the protein-free ADVATE™ manufacturing process. BAX 855 was characterized by a number of analytical methods, focusing on the elucidation of the primary structure, post-translational modifications, PEGylation site distribution, and 3-dimensional structure. Tryptic peptide mapping revealed a sequence coverage of 94%, with good consistency demonstrated between different BAX 855 batches. The composition of the N-linked oligosaccharides showed a similar pattern of BAX 855 and unmodified rFVIII, confirming that the N-glycosylation pattern remained intact during the PEGylation process. PEGylation site distribution and detailed analysis of the consistency of PEGylation was investigated by activating BAX 855 with thrombin. The resulting PEGylated and non-PEGylated fragments were separated using a RP-HPLC approach, and the bound PEG was measured for each thrombin fragment. The distribution of PEG among the different thrombin fragments of rFVIII was shown to be consistent between several BAX 855 batches. The random PEGylation of rFVIII was shown, using antibodies with different epitope specificities. Dynamic light scattering and Fourier-transformed infrared spectroscopy (FTIR) were used to monitor the consistency of 3-dimensional structures. The mean hydrodynamic diameter of BAX 855 was between 30 and 40 nm, which is a characteristic size for a ~300-kDa protein. Several BAX 855 batches produced in sequence showed almost overlapping FTIR absorbance spectra, indicative for good consistency of the manufacturing process. In summary, BAX 855, a PEGylated rFVIII derivative, can be manufactured reproducibly without changes to the protein structure characteristic for a fully functional FVIII molecule.

PO-TU-066
Characterization of BAX 817, a recombinant FVIIa drug candidate

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Human coagulation factor VII (FVII) is a vitamin K–dependent protein with a molecular weight of 50 kDa. Activation of FVII occurs by a single cleavage resulting in 2 disulfide-linked peptide chains. The therapeutic utility of rFVIIa is based on its capacity to trigger hemostasis independently from factor VIII and factor IX, even in the presence of inhibitors against these proteins. Baxter has developed BAX 817, a recombinant FVIIa (rFVIIa) that is synthesized by a genetically engineered Chinese hamster ovary (CHO) cell line. No materials of human or animal origin are employed in the manufacture, purification, or formulation of the final product, thus reducing the risk of transmission of adventitious agents. The growth medium is a chemically defined medium, and the downstream process does not use monoclonal antibodies for the purification of rFVIIa. The rFVIIa drug candidate was functionally characterized in vitro, and its features were compared with those of a commercially available rFVIIa. Preclinical and clinical lots of rFVIIa were characterized with respect to their sialic acid content, degree of gamma-carboxylation, sulfation, and phosphorylation. The overall hemostatic potency of rFVIIa was assessed by its FVIII-bypassing activity in a human FVIII-deficient plasma with high-titer inhibitor, using a thrombin generation assay and thrombelastography. Both tests showed dose-dependent normalization of all impaired parameters similar to that of the commercial rFVIIa. Similar FXa-generating potency was found for rFVIIa and commercial rFVIIa measured on the surface of TF-expressing fibroblasts, suggesting a full capability to bind to TF-bearing cells and trigger hemostasis on their surfaces. rFVIIa could be inactivated by antithrombin III-heparin in solution with no relevant difference to the comparator product. Tissue factor pathway inhibitor (TFPI) effectively inhibited FXa generation in a cell-based activity assay, with a similar IC50 for rFVIIa and the comparator. Similarity could be shown between the preclinical and clinical lots of BAX 817 in all these assays. The functional and biochemical characterization of Baxter's recombinant BAX 817 also showed similarity to the comparator product. Based on the results of the comprehensive preclinical development program, a CTA was granted and the product was brought into Phase 1 clinical development.

PO-TU-067
Characterization of BAX 326 a recombinant human factor IX drug candidate

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Human coagulation factor IX (FIX) is a vitamin K–dependent coagulation factor whose absence or dysfunction causes hemophilia B. Treatment of hemophilia B is based on replacement therapy using highly purified FIX concentrates. Baxter has developed BAX 326, a recombinant factor IX for treatment of hemophilia B patients that is produced in a CHO cell line using a serum and protein-free fermentation technology. The purification process avoids the use of immune-affinity chromatography and includes two viral reduction steps. The final drug product is formulated in the absence of proteins of animal or human origin. Baxter's recombinant FIX resembles commercially available rFIX in most characteristics, with the exception of a significantly lower FIXa content, which might improve standardization compared with commercial rFIX products. Preclinical and clinical lots of rFIX were characterized with respect to their sialic acid content, degree of gamma-carboxylation, sulfation, and phosphorylation. The same lots were also examined for their hemostatic potency, efficiency of activation by FIXa and FVIIa in the presence of tissue factor, and capacity to bind to phospholipid vesicles. Three lots of commercial rFIX with different potencies and one lot of a plasma-derived FIX product were included in the study. Similarity could be shown between the preclinical and clinical lots of rFIX in all these assays. Furthermore, the functional and biochemical characterization of Baxter's recombinant FIX showed that it resembles the recombinant comparator product except for a lower content of activated FIXa. Based on the results of a comprehensive preclinical development program, a CTA was granted and the product was brought into Phase 1 clinical development.

PO-TU-068
Safety of BAX 855, a polyethylene glycol (PEG) conjugated full-length recombinant factor VIII product

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BAX 855 is a recombinant human full-length Factor VIII (rFVIII) covalently conjugated with polyethylene glycol, resulting in a PEGylated rFVIII product indicated for the treatment of hemophilia A. It is derived from the parent licensed rFVIII product ADVATE™, which is PEGylated with a branched PEG monomer consisting of 2 10 kDa end-capped PEG chains. The PEGylation procedure results in a minimally PEGylated FVIII conjugate which retains all functionalities of ADVATE™, including clotting and chromogenic FVIII activity, thrombin activation and inactivation, APC cleavage, and binding to VWF. The product was tested in several pharmacological and toxicological studies to assess its safety for use in humans. BAX 855 has a prolonged half-life in mammals, including animals with hemophilia A. In addition to studies which investigated the systemic toxic potential upon single-dose treatment, BAX 855 was also repeatedly applied to different species. Macaques generally tolerated BAX 855 well, with no adverse test item–related findings. In repeated dose-toxicity studies in rats and macaques, animals were treated every other day for 28 days (rats) and every 5 days for 1 month (macaques) at doses up to 700 U kg^{-1} body weight. Despite the expected development of cross-reacting, neutralizing anti-FVIII antibodies, because human FVIII is a xenogenic protein for other species, no results indicating toxicity or adverse systemic effects were observed. A unique study was performed in which the PEG reagent was labeled by ^{3}H and the labeled PEG reagent was conjugated to FVIII. In this study, in which distribution, metabolism, and excretion of radiolabeled PEG-rFVIII were determined in rats, it was found that the ^{3}H-PEG-rFVIII was completely eliminated via urine and feces over time with no signs of accumulation in isolated organs. Based on the favourable results of the preclinical studies, a clinical trial application was granted and BAX 855 was tested in a Phase 1 human clinical trial.

PO-TU-069

Preclinical efficacy of rVIII-singlechain (CSL627), a novel recombinant FVIII

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A novel recombinant coagulation factor VIII, rVIII-SingleChain (CSL627), produced and formulated free of animal- or human-derived materials, is under development at CSL Behring. The present non-clinical studies were conducted to gather knowledge about the pharmacodynamic characteristics in a mouse model mimicking clinical conditions of severe hemophilia A. Furthermore, different animal species were employed to assess the safety and toxicity profile and to enable a more precise prediction of the tolerance and efficacy of CSL627 for the future use in hemophilia A patients. During the safety program, the allergic or thrombogenic potential of CSL627, its impact on safety pharmacology variables, and systemic toxicity parameters as well as local tolerance were assessed in different rodent and non-rodent species. For investigating the pharmacodynamic characteristics, relevant intravenous doses of CSL627 or marketed comparators comprising BDD or full-length FVIII were administered to hemophilia A mice. Blood loss was determined for a 30-min period starting 15 min after application of the study drugs. FVIII plasma concentrations were determined measuring FVIII activity or antigen. Treatment with CSLB's rVIII-SingleChain did not result in any allergic reaction, had no adverse effect on the safety pharmacology variables measured, and was devoid of clinically relevant prothrombotic potential. In acute and subchronic toxicity studies, when dosed up to 1500 IU kg^{-1}, CSL627 revealed an excellent safety profile with no local intolerance or relevant procoagulant activity associated with thrombus formation. In the tail-bleeding model, CSL627 exhibited a pharmacodynamic efficacy comparable to the licensed rFVIII products when measuring clinically relevant endpoints. The pre-clinical toxicology and safety program conducted points to an excellent tolerance and high safety profile of CSLB's rVIII-SingleChain. The presented investigations did not reveal any safety concerns and support the evidence necessary for proceeding into human trials.

PO-TU-070

Preclinical pharmacokinetic characteristics of rVIII-singlechain (CSL627), a novel recombinant single-chain FVIII

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A novel recombinant coagulation factor VIII, rVIII-SingleChain (CSL627), produced and formulated without added animal- or human-derived materials, is under development at CSL Behring. The present non-clinical studies were conducted to gather knowledge about the pharmacokinetic characteristics of CSL627 in different rodent and non-rodent species, to enable a more precise prediction of the pharmacokinetic properties of CSL627 for future clinical use in hemophilia A patients. The pharmacokinetic behaviour of CSL627 was assessed in hemophilia A mice, rats, rabbits, and monkeys. Intravenous doses encompassing a relevant dose range of 50 to 250 IU kg^{-1} for CSL627 or marketed comparators comprising B-domain-deleted or full-length FVIII concentrates were administered to animals. Plasma samples were drawn after treatment, and FVIII plasma concentrations were determined measuring FVIII activity or antigen using a chromogenic assay or an enzyme-linked immunosorbent assay (ELISA), respectively. Overall, treatment with CSLB's rVIII-SingleChain resulted in slightly, but consistently, superior pharmacokinetic properties compared to licensed rFVIII products serving as active reference items when measuring systemic FVIII activity—a clinically relevant and representative parameter—in plasma. Notably, in all species distinct increases in the area under the curve and mean residence time with concomitantly decreased clearance rates were observed, which in turn translated into an observably improved half-life of rVIII-SingleChain compared to marketed reference items, whereas variables such as in vivo recovery and volume of distribution of CSL627 were consistently nearly comparable to competitor molecules. The current pre-clinical investigations conducted point to excellent pharmacokinetic characteristics of CSLB's rVIII-SingleChain in several species. The presented results support the evidence necessary for proceeding into human trials to also confirm their predictive value and to explore whether such improved preclinical PK properties can translate into clinical benefit.

09-COAGULATION

FP-TU-01.1-5
Patients with hemophilia A and B have increased platelet tissue factor pathway inhibitor (TFPI)
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Background: Inhibition of TFPI allows the extrinsic blood coagulation pathway to proceed in the absence of factor VIII or IX and reduces bleeding severity in animal models of hemophilia. Therefore, TFPI blocking agents are being developed to treat hemophilia. Total TFPI and TFPIα were measured in plasma and platelets from blood donors and hemophilia A/B patients.
Methods: Plasma and detergent-lysed platelets (10^9 mL^{-1}) were measured by enzyme-linked immunosorbent assay (ELISA). TFPI was captured via high-affinity (25 pM) anti-K2 antibody. Total TFPI was detected using polyclonal anti-TFPI antibody, while TFPIα was detected using a high-affinity anti-K3 antibody.
Results: Compared to blood donors, there was a trend for increased total plasma TFPI and decreased TFPIα in patients with hemophilia. The ratio of TFPIα to total TFPI was decreased in hemophilia B patients when compared to severe hemophilia A patients ($P < 0.05$). Total platelet TFPI was significantly greater in all patients with hemophilia compared to blood donors ($P < 0.01$ for mild/moderate hemophilia A, $P < 0.001$ for severe hemophilia A, $P < 0.05$ for hemophilia B, vs. blood donors).

			Plasma TFPI			
	Number	Age Range (years)	Total (ng mL^{-1})	TFPIα (ng mL^{-1})	TFPIα/Total (%)	Platelet Total TFPI (ng mL^{-1})
Blood Donors	80	18–82	132.8 ± 27.2	51.6 ± 12.8	39.1 ± 7.1	27.7 ± 8.5
Mild/Moderate Hemophilia A	22	4–73	141.7 ± 27.3	44.8 ± 11.3	31.8 ± 6.8	47.1 ± 18.8
Severe Hemophilia A	34	2–53	141.8 ± 29.9	45.9 ± 12.3	32.6 ± 7.2	55.1 ± 23.2
Hemophilia B	8	4–31	151.8 ± 35.0	37.9 ± 10.8	24.6 ± 5.2	51.4 ± 25.4

Conclusions: The lower plasma TFPIα to total TFPI ratio in hemophilia B than hemophilia A is consistent with results of Tardy-Poncet (*Hemophilia* [2010] 17:312). Although slightly lower plasma TFPIα may decrease bleeding severity, platelet TFPI is elevated 75–100% in hemophilia patients. The cause of this is unknown but may result from selective absorption of plasma TFPI by platelets in hemophilia patients. We have shown that platelet TFPI regulates thrombus formation in vivo (ATVB (2011) 31:821). Therefore, the elevated platelet TFPI may exacerbate hemophilia bleeding. Development of pharmaceutical agents that block platelet TFPI as well as plasma and/or endothelial TFPI may be important for their therapeutic efficacy in treatment of hemophilia.
Results are presented as the mean ± standard deviation

FP-WE-04.2-5
Evaluation of antibody responses to rFVIIIFc compared to Xyntha® and Advate® in hemophilia A mice
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rFVIIIFc is a recombinant fusion of a B-domain-deleted (BDD) FVIII with the dimeric constant region (Fc) of human IgG1. rFVIIIFc exhibits comparable in vivo recovery, but an approximately twofold longer half-life in HemA mice compared to the currently available BDD-rFVIII (Xyntha) or full-length rFVIII (Advate), and is currently in Phase 3 trial for treatment of hemophilia A. Here we evaluated the antigenicity of rFVIIIFc relative to Xyntha, Advate, and a chimeric human FVIII-murine Fc fusion protein (rFVIII-mFc) in HemA mice. Male HemA mice received 4 weekly intravenous injections of 50, 100, or 250 IU kg^{-1} (n = 10/dose/treatment) of respective rFVIII. Retro-orbital blood was sampled 14, 21, and 28 days after the first dose for anti-FVIII antibody analysis. We observed a good correlation between the total and neutralizing antibodies to FVIII ($R^2 = 0.7452$), and the titers of both increased over time. Within the therapeutic dose range (50 and 100 IU kg^{-1}), the number of mice that developed FVIII-specific antibodies as well as the antibody titers in rFVIIIFc and rFVIII-mFc treatment groups were significantly lower compared to Advate ($P < 0.05$), and marginally lower vs. Xyntha ($P = 0.05$). Specifically, no anti-FVIII antibodies were detected in 70–90% of animals treated with rFVIIIFc, or 50–80% treated with rFVIII-mFc, but only 10–30% following Xyntha or Advate treatment. However, a supraphysiological dose (250 IU kg^{-1}) of rFVIIIFc or rFVIII-mFc resulted in significantly higher antibody titers compared with Xyntha and Advate. In summary, the human Fc moiety did not exacerbate antibody development in comparison to murine Fc in HemA mice. On the contrary, HemA mice were largely tolerant to therapeutic doses of rFVIIIFc and rFVIII-mFc with no or little development of anti-FVIII antibody following repeated dosing. The cellular mechanism for the tolerance is under investigation. The results suggest a potentially low immunogenicity of rFVIIIFc, which requires validation in clinical trials and postmarketing surveillance.

FP-TH-01.1-1
Gene expression of coagulation factors in hepatocytes under structurally and functionally mimicked 3-dimensional hepatic tissues in vitro
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Objectives: Because many coagulation factors are produced by hepatocytes, it is essential to establish an efficient hepatocyte culture system for studying the mechanism of coagulation factor production. However, hepatocytes are known to lose their functions within several days under conventional monolayer culture conditions. In this study, we created a layered structure mimicking hepatic cord (a structural unit of the liver) by stratifying monolayer endothelial cell (EC) sheet on cultured hepatocyte using a cell-sheet technology. Morphological assessments and functional assays, including gene expression profiling of coagulation-related factors, were performed.
Methods: Hepatocytes were isolated from adult rat livers and were cultured on type-I collagen coated culture dishes. Bovine arterial ECs were cultured on temperature responsive culture dishes and a uniform layer of ECs (EC sheet) was created by lowering the culture temperature. The EC sheet was then stratified on primary cultured hepatocytes. After stratification, cultured cells were periodically harvested for assessing the hepatocyte-specific functions, such as albumin production and urea synthesis, for 30 days. In addition, the gene expressions of coagulation factors in hepatocytes were comprehensively analyzed by real-time PCR, using rat-specific primers.
Results: Hepatocyte-specific functions of EC-stratified hepatocytes were found to be maintained throughout the experimental period, while conventionally cultured monolayer hepatocytes showed marked decreases in functions. Electron microscopic examination revealed that EC-stratified hepatocytes created active bile canaliculi, an important structure as a hepatic tissue. Regarding coagulation factors, monolayer hepatocytes showed significant down-regulation of factor V and VIII, while EC-stratified hepatocytes maintained these expression levels. Other factors showed no significant differences among these 2 groups.
Conclusion: In this study, we developed a novel culture system for creating functionally active EC-stratified hepatocytes, which significantly resembled hepatic cord structure. This new culture system could be a valuable technology for clarifying the mechanism of coagulation factor production, as well as establishing liver tissue engineering approaches toward the coagulation disorders.

PO-TU-076
A steroid pulse therapy increases thrombin generation and clot intensity
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Background and Objectives: Steroid pulse therapy is applied to treat various diseases, such as encephalitis and Kawasaki disease. Heparin is used together with the steroid, in order to prevent thrombosis during the therapy. However, the influence of the therapy on the blood coagulability has yet to be clarified. In order to clarify the thrombogenicity of steroid pulse therapy, we measured the coagulation profiles before and after the therapy in an animal experiment.
Methods: Methyl-prednisolone (m-PSL; 30 mg kg^{-1} day^{-1}) was administered to rabbits via the ear vein for 3 days, and physiologic saline was administered in a similar way to control animals. The results of the thrombin generation test (TGT), thromboelastography (TEG), and blood coagulation tests (PT, APTT, AT, fibrinogen, D-dimer) conducted before and after the therapy were examined.
Results: In regard to the blood coagulation profile, while the PT was shortened after the therapy, other coagulation parameters remained unchanged. In the TGT, both the ETP and peak were significantly increased, while the lagtime was significantly shortened. A tendency towards shortening of both TT-peak and start-tail was observed, however, these changes were not significant. Furthermore, in the TEG, the CT was significantly shortened, while both the α-angle and MCF were significantly increased.
Conclusion: These results, indicating an increase of the thrombin generation ability and increase of the clot intensity following steroid pulse therapy in the animal experiment, suggest that steroid therapy may induce a hypercoagulable state, indicating the validity of anticoagulation during the therapy.

PO-TU-077
Adaptation in hemophilia A patients during long-term prophylactic treatment
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Objectives: Therapy using pdFVIII concentrates is one of the most effective and commonly used treatments for hemophilia A patients. Yet there are no data on whether long-term prophylactic treatment can cause any adaptation in patients. We monitored a group of patients with severe hemophilia A to answer this question.

Methods: Five patients with FVIII:C<1% were switched from a therapy of 25 IU kg^{-1} of FVIII to 50 IU kg^{-1} every 3 days due to low clinical response. We used APTT, FVIII:C and the thrombodynamics assay (a new method based on a spatial fibrin clot growth registration) to evaluate the efficacy of the new treatment. The standard test of pharmacokinetics included a 3-day washing period and blood sampling at 0.5, 1, 3, 6, 24, and 48 h after infusion. We analyzed pharmacokinetic parameters after administration of pdFVIII concentrate right after the first infusion and after 6 months of continuous prophylactic therapy. Also we analyzed the number of bleedings per month.
Results: Our findings show that after 6 months of continuous prophylactic therapy of 50 IU kg^{-1} of FVIII, the time period of hemostasis normalization increased from 24 to more than 48 h, and number of bleedings decreased from 1–2 to 0 per month. Yet the peak level of FVIII after administration decreased from 108% to 84%, and APTT did not change.
Conclusions: Long-term prophylactic treatment using 50 IU kg^{-1} of pdFVIII concentrate in severe hemophilia A patients did not have any negative side effects, but increased the time period of hemostasis normalization.
Contribution to the Practice: Mechanisms of treatment adaptation are still poorly understood, but perhaps they should be included in clinical practice.
Support: RFBR grants 10-01-91055, 11-04-00303, 11-04-12080.

PO-TU-078
The use of the new ReFacto AF laboratory standard (RLS AF) confirms reliable measurement of FVIII:C level by a one-stage clotting assay in ReFacto AF–treated patients

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Introduction: We previously demonstrated in an in vitro study in ReFacto AF mock plasma samples that the use of RLS AF for FVIII:C measurement using the one-stage clotting assay (OSA) led to a decrease by a factor 3 of the discrepancy between OSA and chromogenic substrate assay (CSA). The aim of this multicentric study was to evaluate whether the use of RLS AF could lead to the same results in plasma samples from ReFacto AF–treated patients, and whether some differences could also be observed between the 2 methods with other recombinant or plasma-derived FVIII concentrates.
Methods: A post-infusion sample was collected in 78 persona with hemophilia (FVIII ≤ 5%) without FVIII inhibitor treated with ReFacto AF® (n = 21), Advate® (n = 26), Kogenate® (n = 16), or Factane® (n = 15), in 6 centres. FVIII:C level was measured using 2 or 3 procedures; for all samples, OSA (APTT reagent and analyzer currently used by each laboratory) and CSA (Hyphen Biomed, France) were performed with calibration curves obtained by diluting plasma standard (PS) FVIII (NIBSC, UK) in buffer, and for ReFacto AF plasma samples, OSA was also performed with calibration curves obtained by diluting RLS AF in buffer.
Results: In ReFacto AF®–treated patients, the difference between FVIII:C measured with OSA and CSA was reduced when RLS-AF was used as a standard in OSA (mean ratio OSA-PS/CSA=0.73 ± 0.02 vs. mean ratio OSA-RLS AF/CSA=0.90 ± 0.03); the latter ratio was close to mean OSA-PS/CSA ratios observed for plasma of patients treated with other FVIII concentrates: 0.88 ± 0.02 (Advate®), 0.81 ± 0.03 (Kogenate®), 0.89 ± 0.02 (Factane®).
Conclusions: This study demonstrates that OSA with RLS-AF offers a valuable alternative to CSA in ReFacto AF®–treated patients, as the discrepancy observed between OSA and CSA is similar or lower than those observed with other FVIII concentrates.

PO-TU-079
Bypassing therapy in patients with hemophilia and inhibitors: In vivo studies of thrombin generation capacity

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Background: Clinical response to bypassing therapies is often unpredictable, and the lack of a laboratory test aimed at monitoring their efficacy renders their management still empirical. The thrombin generation (TG) test is a global coagulation assay that may serve in this setting. Recently, dose tailoring of bypassing agents was performed using in vitro spiking experiments in order to establish the most adequate drug to cover elective surgery in inhibitor patients.
Methods: In this study, TG capacity was evaluated in vivo in inhibitor patients treated with aPCC or rFVIIa in a non-bleeding state. TG test was performed in platelet-rich (PRP) and platelet-poor (PPP) plasma with the addition of corn trypsin inhibitor (18.3 mcg ml^{-1}). Blood was drawn at baseline, 30 min, 3, 6, and 24 h after drug administration. Four parameters of the TG curve were evaluated: lagtime, endogenous thrombin potential (ETP), peak, and time to peak. Patients were defined as responders to bypassing agents when able to control mild/moderate bleeds by home treatment.
Results: Eight patients with hemophilia A and high-responding inhibitors aged 20–38 years (median: 33) received rFVIIa at a dose of 90–120 mcg kg^{-1} and aPCC at a dose of 80 IU kg^{-1}. In 6 patients, the test was also performed after the administration of 270 mcg kg^{-1} of rFVIIa. Four patients were responders to aPCC, 1 to rFVIIa and 2 to both. Median values of the TG curve observed at baseline and after 30 minutes are shown in the table below. Similar variations were observed after administration of either rFVIIa or aPCC and after the administration of different rFVIIa doses.

	Lagtime (min)		ETP (nM x min)		Peak (nM)		Time to peak (min)	
	PPP	PRP	PPP	PRP	PPP	PRP	PPP	PRP
Baseline	9.9	13.2	231.0	235.0	10.9	7.9	22.9	27.6
aPCC	10.0	12.6	179.0	104.2	8.8	4.7	21.7	22.5
rFVIIa 90-120 mcg kg^{-1}	12.4	24.5	79.7	62.0	2.6	2.6	22.5	26.9
rFVIIa 270 mcg kg^{-1}								
30 min post-infusion	5.9	11.3	897.0	921.2	39.0	34.0	16.4	47.4
aPCC	4.4	5.8	913.0	949.0	67.8	26.4	12.6	21.5
rFVIIa 90-120 mcg kg^{-1}	5.8	10.4	719.0	867.0	42.6	26.2	14.9	34.2
rFVIIa 270 mcg kg^{-1}								

Conclusions: Our results show that the in vivo administration of bypassing agents causes an increase of TG capacity in inhibitor patients; however, the extent of such increase does not seem to be related with either the type or the dose of the drugs.

PO-TU-080
Can in vitro neutralization kinetic of FVIII (human or porcine) in patients with FVIII inhibitors be applied to tailor treatment?

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Background: Therapy for hemophilia patients with inhibitors is challenging. Low titer inhibitors may respond to high doses of FVIII, but titer alone does not predict the response, which is influenced also by the inhibitor affinity, rate of neutralization, and other factors. In vivo PK is useful to plan treatment in PWH without inhibitors, but fails to do so in inhibitor patients, since there is continuing in vitro inhibition during the time from venopuncture to lab assessment. The observation of normalization of point-of-care PTT despite non-measurable FVIII plasma levels suggest the presence of some circulating FVIII. In vitro neutralization testing may identify patients with "slow" inhibitors that may respond to continuous FVIII infusion at a rate corresponding to its inhibition.
Methods: Neutralization kinetics was performed on the plasma of 7 inhibitor patients by measurement of residual FVIII over 120–160 min after spiking with 2 U ml^{-1} of human FVIII or recombinant porcine FVIII (obtained from Inspiration Biopharm Inc). TG was measured at 4–5 time points over the 2 h. Inhibitor cross-reactivity against FVIII was measured by Bethesda Units.
Results: In 4/7 patients, the anti-human FVIII inhibitory effect was 2–10-fold higher than the anti-porcine. The inhibitor titer did not reflect the relatively slow rate of inhibition seen in the neutralization kinetic test allowing to use continuous infusion with human or recombinant porcine FVIII. One patient who underwent major orthopedic surgery was treated with FVIII according to his neutralization curve, and the measured levels corresponded to the expected one. TG results correlated with FVIII neutralization curves.
Conclusions: Our findings suggest that neutralization kinetic analysis is a potentially effective tool in tailoring treatment of continuous infusion with FVIII. In more than half of our patients, the use of porcine seems to be more effective than human VIII, due to lower cross-reactivity.

PO-TU-081
Platelet procoagulant activity and thrombin generation in patients with severe hemophilia

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Objective: The clinical phenotype of patients with severe hemophilia varies widely despite similarly low factor levels (≤1% of normal activity). The biological determinants that drive these different bleeding patterns in patients with severe hemophilia are largely unknown. Differences in thrombin generation have been identified as a potential mediator of this difference. We hypothesized that differences in platelet activation potential may account for the variability in thrombin generation and clinical bleeding severity.
Methods: Patients with severe hemophilia A or B (HA,HB) were recruited from our hemophilia treatment centre. Thrombin generation in platelet-rich plasma (PRP) was assessed after initiation by tissue factor (1 pM). Washed platelets were stimulated with (1) threshold concentrations of agonist, followed by assessment of surface P-selectin or (2) thrombin and the GPVI agonist convulxin, followed by assessment of procoagulant platelet potential. Statistical analyses were performed using correlation and linear regression functions.
Results: Thirty patients with severe hemophilia (28 with HemA and 2 with HemB) were assessed. Marked variability was noted in procoagulant platelet potential (48 ± 17%) and thrombin generation in PRP (Time to peak [35 ± 16 min [; endogenous thrombin potential [1185 ± 627 nm*min]). An inverse correlation was noted between procoagulant platelet potential and time to peak in the thrombin generation assay (P = 0.047). No correlation was found between thrombin generation and activation potential by threshold concentrations of agonists.
Conclusions/Contribution: Here we demonstrate for the first time an association between the rapidity of thrombin generation in PRP and platelet procoagulant potential. Since thrombin generation was determined without convulxin present, this result suggests that procoagulant platelet potential to thrombin and convulxin may reflect the platelet's procoagulant potential in multiple settings. Studies are ongoing to determine whether platelet procoagulant activity or thrombin generation is predictive of bleeding severity in patients with severe hemophilia.

10-DATABASE AND REGISTRIES

FP-MO-04.4-6

Web-based HTC databases on a national scale: An integrated, effective and data-secure, nurse-led system for providing data for studies, information and low-cost treatment

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Introduction: As WFH President Mark Skinner detailed in his inaugural address at the Vancouver WFH Congress in 2008, an integrated database on a national scale has to be the standard to cover the medical and financial issues and problems of hemophilia treatment in the upcoming decennia. Our system combines the advantages of the function of a nurse specialist in each country's HTCs with the possibilities of ICT and the Internet.
Methods: The patient at each HTC has an account at the Internet portal with a single sevenfold menu. For this purpose, each HTC has a stand-alone, interactive application, which is easy to use, SSL secure, web based, fully data integrated, and independent from software monopolies. Only authorized staff can change or create files. From Internet access points, patients provide all treatment data. These data are augmented by HTC data to create a complete dataset for each case. A hand-scanner is available and integrated to identify the vials before use. Patients can come in contact with the staff at an Internet conference room. Anonymous and non-traceable data, e.g. treatment schedules, bleeding events, volume of used units, occurring inhibitors, are available to the National Ministry of Health, the National Society of Haemophilia Treaters, the National Patients' Foundation, the National Foundation of Haemophilia Nurses, and other non-profit organizations.
First Results: The Maastricht Model of this system, published by the author (former RBDO-nurse at the HTC-MUMC) at the WFH 2008 Congress, has been used since 2006 without any technical problems. It is one of the central tasks of the nurse specialist. Compliance is in twofold higher by the patients than by other healthcare professionals. No life-time differences have resulted from patients using the system. Processing healthcare has become more direct, fast, and effective. Time waste has disappeared. Adherence to medical regimes has improved. Misunderstandings in medical communication have decreased. Only the digital version is valid. By direct contact with the HTC, stress, anxiety, and wrong dosages disappear from the patient's home treatment situation. The first national database is planned in Europe by using this system.
Conclusions and Future Directions: Web-based HTC databases on a national scale are the step to create valuable data for decisions at the Ministry of Health, improve treatment schedules, and minimize the "white areas" of treatment possibilities when great distances separate the members of the treatment circle. By using the national database for non-profit research and study purposes, the overview of bleeding disorders becomes more specified and complete. This can lead to more valuable, secure, and cost-effective decisions at the political and healthcare levels. Data security should never be underestimated.

FP-MO-04.4-5

Complications of hemophilia in children in the first two years of life: A report from the Centers for Disease Control (CDC) Universal Data Collection (UDC) system

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Objective: To describe the complications experienced by infants and toddlers (hitherto referred to as children) with hemophilia in the US during the first 2 years of life.
Methods: We used a standardized collection tool to obtain consented data on eligible children with hemophilia enrolled in the CDC-sponsored UDC surveillance project at the hemophilia treatment centres (HTCs) across the USA.
Results: There were 488 children with complete data in the first 2 years of life. Racial distribution was similar to the general US population. Eighty-three percent had hemophilia A, 59% had severe disease, and 71% were diagnosed at <1 month of age. The mother was a known carrier in 39%, 24% had some other family history, and 35% had a bleeding symptom that prompted diagnosis. Eighty-five percent of infants had a bleed during the first 2 years. The most common site of bleeding during the newborn period was circumcision; thereafter, soft tissue bleeding was most common. Only 4% received no factor treatment for a bleed. Ninety-one percent received recombinant factor, 8% plasma-derived factor, 8% recombinant VIIa, 4% activated prothrombin complex concentrates, 37% non-plasma products, and 3% blood products. There were 44 intracranial hemorrhages (ICH) in 35 infants; 16 were spontaneous, 15 with delivery, 10 traumatic, 2 associated with a procedure, and 1 unknown cause. A total of 158 central venous access devices (CVADs) were placed in 131 infants. Among the 120 ports, 20 surgically inserted central catheters, and 18 peripherally inserted central catheters placed, complications developed in 37%, 60%, and 61%, respectively. Complications included infection in 32%, bleeding in 13%, mechanical in 6%, and thrombosis in 2% of CVADs. Inhibitors occurred in 98 (20.1%) of the infants. Infants with inhibitors were more likely to have had an ICH (15% vs. 5%), a CVAD (62% vs. 18%), and a CVAD complication (31% vs. 5%).
Conclusion: Children with hemophilia are likely to experience bleeding events that require treatment with factor in the first 2 years of life. CVADs, which are frequently placed for factor infusion, have a high rate of complications. Complications are worse among infants with an inhibitor.
Implications: Children with hemophilia experience bleeding complications beginning at birth and continuing through the toddler years. This may provide justification for initiation of early prophylaxis. Awareness, recognition, and prevention of bleeding episodes are crucial to preventing long-term sequelae.

PO-MO-023

FranceCoag Network: A Multidisciplinary Partnership between Patients and Health Professionals

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FranceCoag Network (FCN) is a national multicentre cohort of patients suffering from hereditary hemorrhagic disease. Its main objectives are to obtain exhaustive information about this population and provide a public health surveillance tool in the event that a new agent transmitted by treatments is suspected. Set up in 2003, FCN is a multidisciplinary partnership between patients, health professionals, institutions, and research scientists. Two representatives of the French Hemophilia Society (AFH) are members of the steering committee and take part in all the reunions, publications, decisions, and votes. Patients are included in the FCN during a routine medical visit: after reading the information note presented by the doctor, the patient, or the patient's legal representative, consents to their being included in the project. The doctor then submits the anonymous medical information on the patient on the FCN's highly secure website. This project is authorized by the Commission on Information Technology and Liberties. Patients may at any time demand to be informed of, rectify, or request that they no longer be monitored in the database. Only 3 patients have asked to be removed. A total of 7341 patients are included. Since 2005, some 530 new patients have agreed to join the project every year, for a median follow-up of 4.2 years (range 0–17.7 years). Patients get feedback on the FCN data, thanks to regular publication of articles in the AFH journal and on its website; a twice-yearly update of the national statistics in the public section of the FCN website; and reports from national and international congresses. In 2011, it published a brochure informing patients of the progress of the project. This feedback is aimed at encouraging patients to participate actively and durably, something that is vital if this kind of register is to be effective.

PO-MO-024

Update data of the FranceCoag Network, the French National Registry for Congenital Bleeding Disorders

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FranceCoag Network (FCN), the national registry of patients with hereditary hemorrhagic diseases, except platelet disorders, was implemented in 2003 (in 1994 for hemophilia) and relies on data proceeding from 40 treatment centres. The main objectives are dedicated to epidemiology and pharmacosurveillance, including a biobank. Inclusion criteria are: Factor II, FV, FVII, FX or FXIII<10%, FXI<20%, FVIII, FIX or FV+FVIII<30% and von Willebrand disease (VWD) type 3, type 2 (VWF:RCo or VWF:CB/VWF:Ag<0.7 or FVIII:C/VWF:Ag<0.5 or RIPA positive at low ristocetin concentration) or type 1 (VWF:Ag<30%). As of November 2011, 7534 patients had been included, with a median follow-up of 4.2 years (range 0–17.7). Among the 7341 patients alive at last visit, the distribution of the diseases is hemophilia A (n = 4654; 63.4%), hemophilia B (n = 1004; 13.7%), VWD (n = 1301; 17.7%), deficiencies in FXI (n = 125), FVII (n = 113), FI (n = 38), FV (n = 37), FXIII (n = 25), FX (n = 18), FIX Leiden (n = 17), FV+FVIII (n = 8), and FII (n = 1). The distribution of severity of hemophilia A and B shows respectively 1,671 (35.9%) and 324 (32.3%) severe; 861 (18.5%) and 330 (32.9%) moderate; and 2,119 (45.6%) and 350 (34.9%) mild cases. Patients are seropositive for HIV in 6.8%, HCV in 27.1%, and coinfected in 6.6% of the cases. Data about treatments that are carefully recorded will be reported elsewhere. Death occurred in 193 cases, at a median age of 52.8 years (range 0.01–93.3) and was mainly related to C hepatitis (n = 42), AIDS (n = 16), cancer not linked to HIV/HCV (n = 35), and hemorrhage not linked to HIV/HCV (n = 36), including 13 post-traumatic. Exhaustiveness is a crucial point for estimating prevalence of a disease and providing non-biased results. It requires strong involvement of patients and clinicians. In accor-

dance with ISTH criteria, the raising of the threshold to 40% for the inclusion of hemophiliac patients is planned and should lead to a larger proportion of mild forms, towards complete exhaustiveness of the national registry FranceCoag.

PO-MO-025
Hemophilia in Taiwan: A population-based study on epidemiology, age at diagnosis, mortality, and 13-year trend by National Health Insurance Research Database 1997–2009

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Objectives: To investigate the population-based epidemiology of hemophilia in Taiwan, which is a distinctly Chinese society with 23 million people.
Methods: We analyzed the data of male patients between 1997 and 2009, retrieved from the National Health Insurance Research Database and Ministry of Interior in Taiwan, using the International Classification of Disease, Ninth Revision (ICD-9) code 286.0 and 286.1.
Results: During the 13-year period, annual prevalence rates of hemophilia A (HA) and hemophilia B (HB) in the male population (MP) increased from 4.95/100 000 to 7.30/100 000 and from 0.95/100 000 to 1.34/100 000, respectively. Annual incidence rates of HA and HB varied from 5.63/100 000 to 12.83/100 000 male births and 0.73/100 000 to 4.83/100 000 male births, respectively. In the age distribution of persons with hemophilia, it appeared there were more young patients and fewer elderly ones than in the general MP, but it tended towards age distribution of the general MP year by year. The proportion of pediatric (<age 18) patients with hemophilia decreased from 41.5% to 28.2%, with 1.85-time reducing velocity of the general pediatric MP. The proportion of elder (>age 60) persons with hemophilia increased from 2.5% to 5.7%, with 1.39-time increasing velocity of general elderly MP. In total 493 newly-diagnosed cases, with mean diagnosed age was 21.5; peak age of diagnosis was before age 3 and age 10–40. To compare data of the calendar periods of 1997–2000 and 2006–2009, age at diagnosis was earlier in 2006–2009 ($P = 0.035$). In total, there were 76 cases of mortality, with a mean mortality age of 44.4; the peak age of mortality was between age 18 and age 60. Compared with mortality age before 2005, mortality age after 2005 became more delayed ($P = 0.033$). Before age 80, average age-specific crude death rates of persons with hemophilia were higher than that of the general MP. The overall standardized crude death rate of persons with hemophilia was 10.2/1000 population. The standard mortality ratio was 1.98.
Conclusions: This is the first population-based epidemiologic study of hemophilia in Taiwan. It was valuable for estimating epidemiology of Chinese persons with hemophilia.

PO-MO-026
Clotting factor concentrate use by hemophilia patients at home

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Outline: Comprehensive patient recording of clotting factor usage is important. Finding an effective tool to record home use of clotting factor concentrate (CFC), however, has been difficult. Recording tools have, in the past, been created without widespread stakeholder engagement; uptake of recording tools has therefore been suboptimal. To the best of our knowledge, hemophilia patients and parents have not been approached to design a recording tool that meets the needs of patients and families and that will lead to broader uptake of recording programs.
Method: Patient/parent questionnaires were sent to all families who participate in the home therapy program. Data was collected on the following to guide in the development of a new recording tool: (a) How often do you record home therapy CFC? (b) What methods are used to record home therapy CFC? (c) Who records it? (d) How important do you think recording home therapy CFC is? (e) What things make it hard to record home therapy CFC? (f) If we were to design a new recording tool, what things would be important to you?
Results: Sixty families were identified, with 30 replies received. Of these, 22 recorded CFC use for all treatments, and they did not find the recording process difficult. Families felt they benefited from recording, as it was a way of keeping track of their child's treatment regimen. There were many comments on the routines and nuances of recording CFC usage which will be useful information for designing a new recording tool. As part of the questionnaire, we also asked families if they would be happy to participate in a follow-up interview to explore themes raised in the questionnaire more thoroughly. These interviews will form the second part of the project and will further investigate the practices of home recording and explore what families feel about recording and sending data into their HTC.
Conclusion: Engaging families and patients is critical to secure information on recording clotting factor concentrate. The information from questionnaires and interviews will inform the design of a new tool for recording clotting factor usage and lead to broader uptake of clotting factor recording.

PO-MO-027
Epidemiological data of Aziza Othmana Hemophilia Treatment Center from Tunisia

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Background: The Haemophilia Treatment Center of Aziza Othmana Hospital (HTCAOH), Tunis, provides care for 60% of Tunisian patients with inherited bleeding disorders. Inherited bleeding disorders registries can be useful to estimate the prevalence of the disorder, to document their natural history, and to improve health care of these disorders.
Objectives: The purpose was to assess, based on retrospective analysis of the HTCAOH registry, the epidemiological data of bleeding disorders.
Results: Our regional hemophilia centre currently follows 319 patients with coagulation disorders: hemophilia A was found in 143, hemophilia B in 33, von Willebrand disease in 60, and rare coagulation disorders in 83.
Conclusion: On the one hand, we concluded that, consistent with most reported data, hemophilia remains the most common bleeding disorder in our HTC. On the other hand, rare bleeding disorders reach a higher prevalence (26%) because of the frequency of consanguineous marriage.

PO-MO-028
Hemophiline: A modern online information and surveillance system

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Background and Aim: Hemophiline is an information and surveillance system in inherited bleeding disorders aimed at the continuous systematic collection, analysis, and interpretation of health data. We aimed to introduce the Hemophiline system in Turkey.
Presentation: The Hemophilia Society of Turkey (HST) has coordinated national data collection on chronic, rare, and inherited bleeding disorders since 1997. In 2001, the hemophilia health report card system program was started by the Turkish ministry of health. In 2007, within a regional framework, hemophilia patient tracking software was introduced by the Aegean University to collect orthopedic and other medical data about persons with hemophilia. In 2010, the HST introduced Hemophiline in all regions of Turkey. Some features of Hemophiline, such as surveillance capability and hosting standard interfaces for integration with other systems, are similar. Hemophiline offers such advantages as patient risk scoring opportunities, follow-up of patients with drug use information, the possibility of continuing education, and the statistics displayed on the map, making it more useful than Universal Data Collection in the US and the National Hemophilia Database in the UK. Based on the data collected since the initiation of Hemophiline, the most common inherited bleeding disorders in Turkey were found to be hemophilia A, hemophilia B, von Willebrand disease, factor VII deficiency, factor X deficiency, factor XIII deficiency, factor V deficiency, and platelet disorders, in order of decreasing prevalence. In Turkey, the areas where hemophilia A is most common are found to be the regions of Marmara, Central Anatolia, and Aegean.
Conclusion: We hope that these efforts will lead to further opportunities to develop and evaluate prevention strategies and to further the mission of preventing or reducing complications in people with bleeding disorders.

PO-MO-029
Updating the national registry of persons with clotting deficiencies in Mexico

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Since 2001, the NMO Mexican Federation of Hemophilia organized, through its affiliated regional organizations of hemophilia, the development of the only record of its kind in Mexico. This database fulfills the criteria of confidentiality of medical information under Mexican law; the elements it contains are reviewed by volunteer health professionals; and records can be done by patients themselves or their families. It is updated every day and includes basic information about location, treatment centres, basic diagnosis of deficiency, serology, and inhibitors. As of December 31, 2011, 5093 people with clotting deficiencies had been recorded. The most common (with 76.693%) is FVIII, followed by FIX (with 11.723%), VWD (with 4.182%), and rare coagulation deficiencies or platelet clotting disorders (only 0.002%). In 7.40% of cases, the type of deficiency is unknown. 24.17% have a severe form, 25.7% moderate, 19.44% mild, and 30.69% unknown clotting activity. The presence of inhibitors is known in 3.84% of patients. Age distribution is 15.04% (0–9 years); 28.45% (10–19 years); 26.29% (20–29 years), and 30.22% (30–99 years). The National Registry is one of the most important tools for lobbying nationally to increase the supply of clotting factors and improve the quality of comprehensive care that public health institutions provide. It has also been used to contact patients and increase their participation in the activities of the organization.
Proposal: In collaboration with the CLATH group and Mexican Society of Hematology, new elements will be implemented to increase the accuracy and precision in information sources. We hope that the National Registry will be administered by the Ministry of Health for the epidemiological control of coagulation deficiencies.

PO-MO-030

Epidemiology of hereditary bleeding disorders in Greece: First report of the Greek national registry

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Objectives: The national registries of hereditary bleeding disorders are useful instruments for the collection of epidemiological information, necessary for documenting the prevalence of these rare diseases, planning care, and evaluating effectiveness of recourses.
Aim: We present the epidemiological and therapeutic aspects of the patients with hemophilia and allied disorders included in the Greek national registry.
Patients and Methods: The Greek registry was established in 2007 and all the hemophilia centres of the country are participating. An electronic database is installed in all 5 centres, and the data are centralized and analyzed in the administrative centre. The recorded information includes demographic data, the severity and phenotype of the disease, the treatment and its adverse events (inhibitors, viral infections), and it is routinely updated.
Results: A total of 1866 live patients are registered. Among them, 890 (47.7%) have hemophilia A (738, or 39.5%) or B (146, or 7.8%). The severity of disease is as follows: severe 258 (20.5%); moderate 212 (31.4%); and mild 408 (45.9%). Age distribution is: 24% aged <18 years; 42% aged 19–40; 27% aged 40–60; and 16% aged >60. Replacement therapy with factor concentrates is given as primary prophylaxis in all children with severe disease and as primary or secondary prophylaxis in about 20% of young adults with severe disease. 90% of FVIII/FIX concentrates used are recombinant, and annual consumption reaches 3.3 IU/per capita for FVIII. Forty-nine hemophilia A and 3 hemophilia B patients have inhibitors (28.5% PUPs and 2.8% PTPs). Twenty-three of them are HR (13 or them on ITI), 9 LR, and 16 have transient inhibitors. The registry also includes 791 subjects with VWD (42.2%), 156 with other factor deficiencies (FVII:57, FXI:60, FXIII:13, FV:10, FX: 5, FIB:11), and 21 with PLT disorders. The prevalence of viral infections is hepatitis B (27, or 1.8%), hepatitis C (335, or 28.5%), and HIV (64, or 3.59%).
Conclusions: The collaboration of the Greek hemophilia centres in achieving the establishment of a national registry resulted in reliable data concerning the prevalence of hereditary bleeding disorders and their treatment. These data can be easily compared with international data, and are a useful tool for continuously improving the quality of care for these patients.

PO-MO-031

The Austrian hemophilia registry: Update 2012

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The Austrian Haemophilia Registry is a web-based database for collecting data of patients suffering from hereditary bleeding disorders. Currently, 644 patients from 8 hemophilia centres in Austria are included in the registry. There are 544 (84%) with hemophilia A and 100 (16%) with hemophilia B. Median age of the patients is 33 years (range 1–87 years). Overall, 23% (n = 147) are children (< 18 years) and 77% (n = 497) are adults. Of these, 259 patients (40%) have a severe form: 90% (234) hemophilia A and 10% (25) hemophilia B. Among patients with severe hemophilia, 18.9% (49) had an inhibitor in their medical history, compared with only 3.1% (12) in the non-severe hemophilia group. Currently, 4.3% (28) of the patients with hemophilia in Austria have an inhibitor. With regard to type of therapy, among patients with severe hemophilia, 32% (84) receive on-demand therapy, 55% (142) secondary prophylaxis, and 13% (33) primary prophylaxis. The age group of 6–18 years has the highest percentage of primary prophylaxis with 34% (24) and of secondary prophylaxis 59% (41). Among patients with severe hemophilia aged between 18 and 40 years, 63.9% (69) are on secondary prophylaxis. In the age group 41–60 years, 43.1% (25) receive secondary prophylaxis and 56.9% (33) on- demand. Patients aged >60 years have the highest percentage of on-demand therapy, with 76.9% (10). With regard to the type of product, 69% (180) of patients with severe hemophilia are treated with a recombinant factor concentrate, whereas 31% (79) receive plasma-derived factor concentrates. In conclusion, the Austrian hemophilia registry is an essential instrument to monitor the epidemiology of hemophilia and its treatment. Thereby, the registry will also allow us to optimize the treatment of our patients in the future.

PO-MO-032

The current status of hemophilia in Korea: Results from a nationwide survey

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The patient group of persons with hemophilia is one of the biggest groups within the medical expenses support program for "rare and incurable diseases support system" in Korea. With the pharmaceutical expenditure scale increasing, healthcare costs have been rising continuously, which may limit the preservation of the National Health Insurance's current reimbursement system. There are no accurate prevalence or epidemiologic data and full registry data base system. To analyze the status and realities of hemophilia and promote comprehensive care, we evaluated a questionnaire from doctors who treat patients, with the review of medical records. A total of 780 cases were analyzed. There are 683 cases of hemophilia A (Factor VIII deficiency), 135 cases of hemophilia B (Factor IX deficiency), 14 cases of hemophlia C (Factor XI deficiency), and 99 cases of von Willebrand disease. For the severity, there are 72% of severe, 14% of moderate, 14% of mild type in hemophilia A, and 50% of severe, 31% of moderate, 19% of mild type in hemophilia B. Joints were the major sites of hemorrhage: ankle (32.9%), knee (30.2%), elbow (21.8%), and shoulder (9.2%). There are 30 cases of patients with HBs Ag positive, 11 cases for HIV positive. There are 49 cases of hemophilia patients with inhibitor (44 cases for hemophilia A, 5 cases for hemophilia B). However there are still some barriers and limitations based on the unique issues in rare disease, imperfect data of national health insurance system and biased aspects of medical expenses subsidy on "Rare and incurable disease support system". From this study, we found the current status of hemophilia. Coping with the problems, long-term planning and progressive ongoing study system should be established.

PO-MO-033

Long-term outcome of patients with severe hemophilia A or B in Sweden: Results from a cohort registry study

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Aim: To evaluate long-term incidence, prevalence, and survival in Swedish patients with severe hemophilia.
Background: The cohort consists of patients enrolled in a large national registry, including 1431 with hemophilia A or B, born between 1883 and 2008. Registry data were linked to the In- and Out-patient, Cause of Death, Cancer, Medical Birth, Prescription, Migration and Multi-Generation registries. Severity of hemophilia was known for 934 out of the 1431 patients.
Methods: The 384 patients with severe hemophilia were compared to 1918 age- and sex-matched controls. Kaplan-Meier analysis was used to estimate survival and median life expectancy. Cox proportional hazard regression models were used to estimate hazard ratio.
Results: The mean follow-up was 30.1 years. Seventy-eight of the 384 patients were diagnosed with HIV and 167 with viral hepatitis. The median life expectancy for all-cause mortality was 59.6 years, 95% CI: (51.5-67.6). The median life expectancy was increased to 72.2, 95% CI (64.8-79.5) when subjects with an HIV-related cause of death were excluded. The corresponding median life expectancies for the controls were 81.5, 95% CI: (80.0-83.0), and 81.5 95% CI: (79.2-83.7). The relative risk for all causes of death was 5.2, 95% CI: (3.72-7.23), $P < 0.001$ for those with hemophilia compared to controls. When HIV-related deaths were excluded, the relative risk decreased to 2.48, 95% CI: (1.57-3.93), $P < 0.001$ and when both HIV and/or viral hepatitis were excluded, the relative risk was 3.16, 95% CI: (1.49-6.68) $P < 0.001$ compared to controls. The most common causes of death were HIV/AIDS (28%) and hemostatic disorders (21%).
Conclusion: This study shows that patients with severe hemophilia have a higher risk of death both with and without HIV and/or viral hepatitis compared to controls. This unique cohort will provide further valuable insight into comorbidities and allow evaluation of first degree relatives.

PO-MO-034

The reality of hemophilia in Panama

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As a hemophilia centre, we have carried out the collection of data to detect our reality with regard to the number of people with hemophilia A, B, and other rare types, severity according to the percentage of factor in each of the groups and their distribution in the country. Data were obtained through tours of uptake of new cases and reassessment of the known previous contact with the staff of health of different areas of the interior and Panama City, with two trips to areas of greatest concentration of people with hemophilia. We assessed patients in 9 provinces, in the main health centres known to have the greatest concentration of patients, and the convening of patients from nearby areas to go to the area of the tour for medical, orthopedic evaluation and sampling blood for detection of new cases and re-evaluation of the known. Epidemiological data that were and who needed a reassessment in the light of modern technology and top teams have been confirmed. This has shed a total of 242 people with hemophilia A, 28 with type B and 23 of the rare types. Mild types have 116 and are the most frequent, and the serious 98 patients. The province with the highest concentration of people with hemophilia is a Panama City with 138 cases. The largest number of cases age group is over the age of 18 years with 198 and it is followed in frequency from 0 to 13 years with 56 patients.

PO-MO-035

Australian Bleeding Disorders Registry (ABDR): An update

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The Australian Bleeding Disorders Registry (ABDR) is a collaboration between clinicians - the Australian Haemophilia Centre Directors' Organisation (AHCDO), government - the National Blood Authority of Australia (NBA), and the national patient organization (Haemophilia Foundation Australia (HFA). The redeveloped ABDR is a web-based information system, used in the clinical environment to aid the capture of data critical to hemophilia treatment centre (HTC) management. The system is used to assist in daily patient management, clinical review, and government management obligations. The ABDR has been further developed on an industry standard technology enabling improvements in performance, reporting, and adoption of international collaborations. Demographics for individual centres are produced with total usage of product in each state (comprising multiple centres). Median usage of FVIII in severe, moderate, and mild hemophilia A is 180 000, 50 000 and 10 000 units per year respectively. Numbers of those with inhibitors in HemA are severe 20.4%, moderate 5.7%, and mild 3.4%. The ABDR in revised form can present valid Australia-wide statistics on hemophilia and other inherited bleeding disorders. There is increasing uptake by HTCs with improved data entry. Improvement in reporting to individual HTCs is scheduled for June 2012, enhancing the ability to adopt data entry fields to meet international collaborations, e.g., EUHASS, and the development of specific areas for physiotherapy and psychosocial assessment.

	No. in register June 2009	No. who received product in 08/09	No. in register June 2010	No. who received product in 09/10	No. in register June 2010	No. who received product in 10/11
Hem A	1918	693	2015	833	2111	858
Hem B	466	153	490	186	517	185
vWD	1714	101	1856	183	1966	153
Other factor deficiency	235	21	261	18	284	22
Platelet disorder	161	1	170	4	191	8

PO-MO-036

Incidence of factor VIII inhibitor in hemophilia A in Ceara-Brazil

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Introduction: A dangerous complication of concentrate therapy is the developement of inhibitor alloantibodies, which are directed against the respective coagulation factor. The developement of inhibitors may have also genetic causes. Factor inhibitor is a complication of hemophilia A treatment in 10–30% of patients. The variability of inhibitor prevalence is influenced by several factors, such as frequency of determinations, patients' age, exposure days, preparation of factor, and the severity of hemophilia. The Bethesda method has been frequently applied to the inhibitor's identification and it is primary in the determination of FVIII residual activity. Some factor inhibitors disappear spontaneously, while others require treatment with immune-suppressive drugs and/or high concentrations of coagulation factors, which are associated with high costs. In addition, factor VIII inhibitor bypassing activity (FEIBA) and recombinant activated factor VII also are used.

Objective: To assess the incidence of factor VIII inhibitors in hemophilia A, Brazilian patients registered with the Center of Hematology and Hemoterapy of Ceara (HEMOCE), Brazil.

Patients and Methods: Survey patients registered with retrospective databases going back 15 years (1996–2011).

Results: The results showed that determinations of FVIII were made in 444 patients; 16 (3.8%) patients presented with inhibitor; of these, 15 (93.75%) individuals had severe and 1 (6.25%) individual had moderate hemophilia A.

Conclusion: The factor VIII inhibitor is mainly a complication of severe hemophilia A and, in the minority of the cases, temporary.

PO-MO-037

Update of Italian hemophilia B (HB) mutation database: Suggestions for genetic counselling in patients and related females

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Molecular investigation led to the identification of causative mutations for hemophilia B (HemB) which shows wide allelic heterogeneity. About 2% of cases are caused by gene deletions. Therefore, the HemB mutations database created for the Italian Association of Haemophilia Centres (AICE) should be a powerful tool for the management of the bulk of recorded data. Mutation detection is based on standard polymerase chain reaction (PCR) and Conformation Sensitive Gel Electrophoresis (CSGE) screening, followed by DNA sequencing. Recently, a method to detect gene copy variations (Multiplex Ligation-dependent Probe Amplification, MLPA) has been introduced for large deletions or duplications investigation on the F9 gene. The database includes 432 diverse mutations; 354 were unrelated. In 3 unrelated patients (1 severe and 2 mild) the mutation was not found. Detailed analysis of the mutations revealed 183 unique mutations (10 large deletions, 11 small deletions, 1 combined deletion/insertion, 2 insertions, 118 missense, 21 nonsense, 15 mutations in splicing site, 4 in the promoter, and 1 silent variant). Most patients (70%) have missense mutations, showing different distribution in severe (57%) and in non-severe (91%) patients. Deletions and nonsense mutations are more frequent in the severe patients, the first accounting for 34 cases in severe and 1 in moderate/mild class, the second accounting for 41 cases in severe and 2 in moderate/mild patients. Among severe patients, 9 (3%) developed inhibitors; 4 showed complete gene deletion, confirmed by MLPA, 5 have nonsense mutations. The Italian HemB database has provided opportunities to perform carrier testing by specific mutation analysis in 233 at-risk females. In this cohort, 23 out of 180 carriers asked for PND in 32 instances. Carrier status determination and PND are easily performed with the HemB mutation database genetic information. It is therefore recommended that HemB patients have their F9 genotype established early, to obtain both useful information regarding the risk of inhibitor/anaphylaxis and counselling for other family members.

PO-MO-038

An Iranian registry for hemophilia and other inherited bleeding disorders

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In the year 2000, the first Iranian comprehensive hemophilia care centre (ICHCC) was inaugurated as an affiliate of the Iranian Haemophilia Society (IHS). Efforts to establish a program for recording patient information led to the creation of a database prototype in Microsoft Access. A year later, the prototype was transformed into a client server database by employing the Standard SQL Engine. The information collected concerns patients affected by hemophilia A and B and their carriers; von Willebrand's Disease; inherited platelet dysfunctions and rare bleeding diatheses; as well as thrombotic disorders. In order to permit access of provincial IHS chapters and other hemophilia treatment centres in the country, data collection forms were put into a web-based format. The database is entirely password protected. Comprehensive patient-related information is collected, such as: sociodemographic data; results from the phenotypic; routine; genotypic and molecular virology laboratories; clinical information from outpatients; hepatitis; orthopaedic and dentistry clinics, as well as the physiotherapy, pharmacy, and social workers' departments. In addition, the ICHCC database is also responsible for managing the pharmacy inventory, patient reception, and the production of laboratory reports. Data entry points are currently provincial chapters of the IHS, but all treatment centres throughout the country and specialized pharmacies licensed to distribute therapeutic fractions may also be included. Every patient is identified through a unique coded number, which is attributed at the ICHCC point of diagnosis. Data from 70% of patients from the entire country has been confirmed and recorded on the ICHCC database so far. At present, 4187 hemophilia A, 882 hemophilia B, 877 von Willebrand, 758 platelet dysfunction, 1219 rare bleeding disorder patients are registered on the database, and over 500 deceased cases are also documented.

11-DENTAL ISSUES

S-TU-03.4 –1
Challenges of the ageing population
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Data from the global survey carried out by the World Federation of Hemophilia (WFH) has shown an increasing number of patients live into old age. The paper will look at the rate at which the older population within the hemophilia and associated bleeding disorders community is increasing and then consider the risks of oral disease and management of dental problems in older adults. The global survey divides the population into different age groups, and from this data, the rate of increase of the older population will be calculated. The different geographic areas used by the WFH will be studied, namely the Middle East and Africa, North America, South America, Europe, Asia, and Western Pacific. The relevance of the changes in each area will be discussed. The common problems in elderly populations are the retention of teeth into older age, with higher risks of periodontal disease, root caries, and tooth wear, as well as the need for provision of prosthodontic replacement of missing teeth. Patients with bleeding disorders expect to receive similar treatment to all other patients. The aim of dental care is the maintenance of a high level of oral hygiene and the maintenance of a functional dentition sufficient to maintain nutrition. A number of barriers exist that prevent a patient from maintaining their oral health and these will be studied. The use of modern materials and techniques will be considered as well as the use of implant-retained dentures.

S-TU-03.4-2
Challenges of Dental Care in Ageing Patients with Hemophilia
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The advances in healthcare programs for patients with hemophilia in developed countries have resulted in an increase of life expectancy. The recent WFH Global Survey shows that the largest cohort of patients with hemophilia is now 45+ years. This category of patients demonstrates several health challenges that may have a hemostatic impact as a result of ageing. Many of these patients suffer from transfusion-transmitted infections such as HIV and HCV. Advanced infections may result in certain hematological parameters such as thrombocytopenia and coagulopathies, due to a deficiency of vitamin K dependent coagulation proteins, as well as coagulation inhibitors (due in particular to HCV infection with advanced liver disease). Hepatocellular carcinoma has a high incidence rate in patients with HCV, and other malignancies are common in patients who suffer from HIV. Anti-viral treatment of both HCV and HIV is another challenge as these drugs may induce thrombocytopenia or anemia. The ageing population of patients with hemophilia is also prone to advanced age diseases such as coronary heart disease. These patients are managed by either medical treatment, mainly anti-platelet drugs, or by invasive procedures such as stinting or coronary artery bypassing grafts. Such patients will also require antiplatelet or anti-coagulant therapy, which may pose a greater challenge to the proper hemostatic control of these patients. An ageing hemophilia population is also more prone to dental problems due to the complexity of their medical conditions. Invasive procedures are of particular challenge, where a balance between infusion of factor concentrates and their other hemostatic therapies such as anti-platelet drugs or anticoagulants should be taken into consideration. Local hemostatic agents may have a primary role in oral surgery in such complex situations as fibrin sealants, local antifibrinolytic drugs, as well as agents containing tissue repair agents (such as platelet gel and platelet glue). These agents have the advantages of promoting local oral hemostasis and healing and avoiding the systemic effects of these drugs in patients that need critical balance of their hemostatic conditions.

S-TU-03.4-3
The role of the specialist nurse in the facilitation of optimal dental care in the ageing population with inherited bleeding disorders
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Achieving optimal dental care for people with inherited bleeding disorders should be fundamental in prioritizing services for this population. This helps maintain good nutrition, quality of life, and avoids dangers and complications that are associated with poor dental care and complications. This session will describe the role of the specialist nurse within the wider multi-disciplinary team in providing optimal dental care to the increasing ageing population with inherited bleeding disorders. Education plays a primary role in the maintenance of good oral care and the specialist coagulation nurse is a prime member of the multi-disciplinary team to assist in this. Input early in a in a person's life can be very influential in how that person will grow up and care for their oral hygiene into adulthood and, eventually, their latter years. However, education should to be provided throughout the person's entire life and should be adaptive and responsive to their varying life/developmental stages. This may also need to involve other family members and/or care takers. An understanding of the barriers to good dental care is paramount, as is a holistic nursing model of care. The specific dental issues that are more likely to affect this patient population need to be understood along with how other co-morbidities will impact their management course. Good working relationships within the team as well as collaborative working on protocols between the comprehensive hemophilia care team and dental team are essential for the goal of 'optimal dental care' in this cohort to be achieved.

S-TH-03.4-1
Trauma
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Management of oral trauma differs significantly between patients with and without bleeding disorders. If a patient with hemophilia is taken to a general emergency ward following an accident, the treating emergency physician should immediately contact the patient's hematologist. Stopping any bleeding is the first and most important step, and this is done with both systemic and local treatment. When the bleeding has stopped, the next step is to determine whether to act on the trauma or to wait until the edema subsides. Edema may prevent proper visualization of the wound, in which case a local cold pack should be applied to reduce swelling. If there is major facial trauma, it is advisable to hospitalize the patient and carry out a thorough radiologic and clinical evaluation. The patient's inhibitor status will also play a major role in the subsequent management of the trauma. Surgery should be planned accordingly, if necessary, with the hematologist and performed if possible within 1 month of the trauma in the case of bone fracture. Various cases of soft tissue and bone trauma will be presented. In all cases it is very important to control the patient closely after surgical or other treatment has been undertaken. Close collaboration between the surgeon and the hematologist is of vital importance in the treatment of facial or oral trauma in patients with hemophilia and other bleeding disorders.

S-WE-01.5-1
Periodontist issues
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Periodontal care is a major component of oral health care for all patients, but unfortunately this has not been stressed enough with reference to the population with bleeding disorders. Healthy gums are required before surgery or other dental procedures, and this is particularly true for patients with bleeding disorders. The 2 major pathologies of soft tissues in the oral cavity are gingivitis, swelling of the gums that leads to bleeding, and periodontitis, in which the swelling causes decreased attachment between teeth and bone, with potential dental mobility or dental loss. Timely treatment is essential. Periodontal treatment reverses gingivitis and results in healthy gums. In periodontitis, though treatment may lead to gingival health, the attachment is not recovered and there is radicular exposure. Bleeding of the gums is the consequence of periodontal tissue pathology. Hemophilia and other clotting disorders exacerbate the bleeding and can potentially pose a major health threat. The aim of periodontal treatment is to restore health to the gingiva, which will also reduce the need for factor concentrates. Gingival bleeding in various clinical situations decreases. Periodontal treatment for patients with bleeding disorders requires certain modifications to standard treatment. Patient education becomes a major tool in preventing periodontal disease. The protocol used for patients of all ages at the Hemophilia Foundation of Argentina, along with 2 local hemostatic agents commonly used, will be described. After restoring gingival health, maintenance becomes the key factor. Ideally, patients should be seen every 3–4 months for periodontal control.

FP-WE-01.5-2
An investigation into the value and importance of oral health for people with hemophilia
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Background: International studies have shown that people with hemophilia (PWH) have a lower oral health–related quality of life and poorer oral status than the general population. There are currently no published qualitative studies which explore the value and importance of the oral health status for this group relative to their other health and personal issues.
Aims and Objectives: To explore and be able to understand the meaning and value of good and poor oral health for adults living with hemophilia. To explore the personal experience of oral health and oral health care for PWH.
Methods: Qualitative data were collected though semi-structured, in-depth, face-to-face interviews with a purposive sample of 25 PWH geographically located throughout the country. Data were analyzed using constant comparison methodology.
Results: Good oral health is important for PWH. It ensures peace of mind for this group, who worry about the possibility of dental problems causing infection, pain, and bleeding. Delay in accessing appropriate oral care for PWH means that they are likely to have experienced considerable dental pain and distress for lengthy periods and consequently sometimes choose not to disclose their bleeding disorder to dentists for fear of being refused care. PWH report a history of problems in accessing appropriate dental care due to a number of consistent barriers, regardless of the severity of their disease. Common themes include a longstanding fear of dental care, due to a history of hemorrhage or hospitalization following treatment; reports of family dentists being scared to provide simple non-invasive or preventive dental treatment, for fear of doing harm; and PWH not being sure whether or not they were allowed to visit a dentist, leading to oral disease progressing unchecked. Significant bleeding from the mouth due to untreated or uncontrolled gum disease can be severe enough to cause anxiety and distress, with associated halitosis and bleeding preventing PWH from eating certain foods in public, and interfering with their personal and sexual relationships.
Conclusion: Oral health is important for PWH, and the personal cost of poor oral health can be high. Oral status impacts on domains such as comfort, function, nutrition, and general health. However, it can also impact on many important psycho-social domains so

person-centred oral health risk assessment and management strategies, and prevention of oral disease for PWH, should be considered an important part of comprehensive multidisciplinary care planning.

FP-WE-01.5-3
Regular primary dental care access for patients with inherited bleeding disorders: The barriers and solutions
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Patients with inherited bleeding disorders (IBD) often face difficulties in accessing primary dental care. This can lead to dental neglect, unnecessary dental pain, potential life-threatening infections, and eventual invasive dental treatment, most likely dental extractions. One hundred and five patient surveys from the Royal London Hospital and 53 dentist surveys from local dentists in the East London area were collected to investigate (1) the barriers that IBD patients faced when accessing primary dental care and (2) local dentists' experiences in treating IBD patients. Responses indicated IBD patients were likely to encounter patient-related barriers rather than disease-specific barriers when attempting to access primary dental care: only 20% had been refused dental treatment by their local dentist, while 45% did not have confidence in their local dentist to look after their oral health because of their bleeding disorder. The dentist surveys showed that 40% of local dentists were not confident in treating IBD patients, and 92% were interested in attending a continued professional development course on the dental management of IBD patients. Regular preventative advice given by the hemophilia centres and dentists will prevent future dental neglect. IBD patients can have some dental procedures safely carried out by their local dentists; other procedures, such as dental extractions, need to be referred to the hospital dental services. We have developed a "shared care" approach to the dental management of IBD patients, with hematologists and dentists working together to provide safe, efficient dental treatment and identifying educational opportunities that address bleeding disorder issues. Our "dental liaison" letter to local dentists, coauthored by hematology and dental consultants, serves both these purposes, clearly stating what is safe to be done in the community and how to directly refer to named dental consultants at our university dental institute for more specialist invasive work, in partnership with the hemophilia clinicians.

FP-TH-03.4-5
Dental implants in severe hemophilia: Case report
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Implantology is a treatment that is speeding its way through the dental treatments every day. Although there are some contraindications, it is still one of the most successful treatments in dentistry. The aim of this case report is to suggest that if the condition of surgery and post surgery sustains, then the treatment will succeed. Case is a male aged 57 with hemophilia A (factor VIII <1%). With hepatitis C and the mandibular ridge was knife age. Before preparation patient received three 500 cc of human factor VIII (Koate-DVI). Patient was treated with block anesthesia .An insigne was made from 4 to 8 lower right teeth. At the region of lower right 5 mandibelar reduction was done. Due to the short space the first implant was placed at an angle of 100° compeer to lower right canine. The second implant was placed at the position of lower light7.At this surgery two Nobel Bio care implant were used. One 3.5 × 13 at the position of lower light 5, and one 3.5 × 10 at the position of lower light 7. Both implants were submerged. The bleeding was normal due to prescription of factor VIII before the surgery. Sutures were placed and pressure was applied by the patient for one hour to sustain the bleeding. Amoxicillin 500 mg and Metronidazol l 250 mg was subscribed and cold dressing was applied after the surgery. Anti hemophilic human factor VIII after 6 h of the original dose was also injected. The patient had no complains of pain after the surgery. There was no edema seen after the surgery. The patient was visited at the second, third and fifth day after the surgery and the sutures were removed after 10 days. A three months using panoramic radiography osteo integration was checked. By applying the same dose of human factor VIII the implants were exposed and gingival formers were placed at both implants. After 2 weeks abutments were placed and a three unit bridge was prepared for the patient. Fallow ups were done every 2 months. Now after 23 months the implants are functioning perfectly, and the patient is a candidate for another three unit implant.

FP-WE-01.5-4
Successful outcome following periodontal therapy for a patient with type 2B VWD and an atypical bleeding history
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Case Report: Management of periodontal disease in patients with bleeding disorders remains a significant challenge for the dental team. A 57-year-old woman with type 2B von Willebrand disease (VWD) presented with repeated incidences of spontaneous, bleeding from the mouth sufficient to impact on her quality of life. As a consequence, she had developed a profound fear of dental treatment and had avoided attending for routine dental care for several years. At least 7 instances of severe, prolonged bleeding following surgical interventions, including dental extractions, were reported despite appropriate systemic factor replacement. Clinical examination revealed bleeding from chronic gingival inflammation associated with a 5 mm periodontal pocket in the upper molar quadrant and full-mouth root debridement, and maintenance care was prescribed. VWF concentrate (Wilate®, Octapharma), 1 pool of platelets, and oral tranexamic acid (Cyclokapron®, 1 g) were administered prior to the dental procedure. However, following root debridement of posterior molars, significant bleeding continued from the base of 2 pockets for more than 1 1/2 h despite use of the standard protocol of local pressure +/– ice and irrigation with cyclokapron solution (4.8%). This clinical picture was consistent with problems experienced previously, whereby bleeding had continued for several days following "deep cleaning." Local deposition of fibrin glue at the base of the pocket and local application of gauze drenched in cyclokapron resolved the bleeding after 5 min. Twenty-four hours later, no further bleeding problems remained. Cyclokapron-drenched gauze packs were applied following inter-dental care for 2 weeks until local inflammation ceased. The patient returned for ongoing preventive dental care 1 week and 1 month later with no reports of bleeding of note. Quality of life questionnaires were completed prior to treatment and 1 month post-treatment.
Conclusions: Oral health–related quality of life improvement was shown following provision of necessary periodontal treatment. Management of hemostasis in the dental environment can build patient confidence and change patterns of behaviour and attendance. Conventional systemic and local hemostatic measures may require further targeted topical measures to arrest bleeding from the base of periodontal pockets following root planing in patients with bleeding disorders. Patients may require additional topical hemostatic measures at home in order to reduce the barriers associated with provision of effective interdental cleaning.

FP-TH-03.4-3
The dental wand: Is it cost effective for patients with bleeding disorders?
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Quality, innovation, productivity, and prevention (QIPP) is a Department of Health strategy which aims to improve the quality and delivery of care while saving costs. Collaborative work with the Dental Hospital provides safe dental treatment for patients with bleeding disorders. Significant volumes of coagulation factor are used prior to local anesthetic inferior dental blocks, and it seemed that considerable financial savings could be obtained by the introduction of The Wand STA (Single Tooth Anaesthesia) System (Dental Wand). The Wand enables pressure-regulated computerized local anesthetic delivery via the periodontal ligament to a single tooth. It removes the need for factor replacement in patients with bleeding disorders who need restorative procedures, and it avoids a painful dental block. Research has shown that The Wand's appearance induces less anxiety than the conventional anesthetic syringe. A retrospective audit was undertaken to assess the number of patients with bleeding disorders requiring hemostatic treatment prior to inferior dental block delivery for restorative procedures. Financial analysis assessed whether purchasing a Dental Wand would be a cost improvement in line with the QIPP agenda. In the 12 month period audited, 14 patients with bleeding disorders would have been candidates for treatment using The Wand, based on bleeding risk. The total cost of all hemostatic treatment was £7,625 in the assessed period (excluding staffing-related financial and time costs). A Dental Wand costs £2,653 and, with minimal spend on consumables; can result in long-term financial savings while making significant improvement to a patient's dental experience. The conclusion was that The Wand would be a service innovation, allowing significant cost improvements while reducing patient discomfort for dental procedures. We have now purchased a Dental Wand and will (1) collect prospective data related to adverse bleeding events or factor replacement required and; (2) obtain patient feedback on their dental anesthetic experience with The Wand.

FP-TH-03.4-4
Last development in dental surgery in patients with hemophilia and inhibitors
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The development of surgery for Hemophilia patients with Inhibitors has always constituted a great challenge; one of the most serious problems is the postoperative bleeding. The patients with Hemophilia and a high – responding inhibitor has in most bleeding episodes to rely on alternative treatment (By pass Therapy). This treatment is decided on and dosed according with a protocol which is designed in the laboratory after the evaluation of the levels of factor. This protocol is accompanied by local hemostatic therapy, but in the case of patients with high responding inhibitors, it sometimes became very difficult to achieve the best hemostatic technique; in fact, we have had a high number of cases in which the bleeding episodes persisted. The aim of this paper is to show our management of dental surgery on inhibitor patients with the preventive use of prophylactic strategies together with a protocol composed of factor replacement therapy and local hemostatic agents to reduce the risk of bleeding.

FP-WE-01.5-5
Proper prophylaxis promotes good dental health in boys with hemophilia
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Objectives: Boys with hemophilia are at risk of poor oral health. The primary goal of modern dental care is prevention. At our centre, the boys with severe hemophilia start early prophylactic clotting factor therapy. Children visit a dentist at least once a year for check-up and preventive care. The aim of the study was to describe their dental condition and need of intervention in 2009–2010.
Methods: This study comprised 28 of the 30 boys with hemophilia (2 mild, 7 moderate, 19 severe) followed at Children's Hospital, Helsinki, Finland. Of them, 21 had hemophilia A and 7 hemophilia B. Six had a history of inhibitors, all had been successfully immunotolerized. The median age at the latest dental check-up was 11.3 (mean 11.4, range 5.3 – 17.4) years. The following parameters were gathered: decayed, missing, and filled teeth in both the deciduous (dmft) and the permanent dentition (DMFT), community periodontal index (CPI), and signs of dental enamel defects. The data was then compared with those of healthy boys from the Helsinki area.

Results: The median number of dental visits per patient during the two-year period was 3 (mean 3.8, range 1–11). Twenty-two of the 28 patients (79%) had dmft+DMFT scores within the reference range for their age. All the 6 patients under the age of 9 years had normal scores. Only 1 tooth (deciduous) had been extracted. However, 61% patients had at least 1 decayed, missing, or filled tooth (dmft+DMFT>0). The dmft+DMFT scores did not correlate with the severity of hemophilia. The CPI score registered in 19 patients was ≤ 2 in all, but only 2 had the score 0. Almost half (12/28, 43%) had developmental enamel defects. During the appointments, preventive care was given to 21/28 patients (75%).
Conclusion: The majority of the patients had good dental health. Preventive dental care during hospital visits in childhood may contribute to good oral health and encourage patients to receive regular check-ups later in life.

FP-TH-03.4.2
Assessment of minimal clotting factor concentrate requirements for teeth extractions in patients with hemophilia

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In patients with hemophilia, teeth extractions are associated with a high bleeding risk. Even in countries with wide access to clotting factor concentrates (CFC), they may account for significant morbidity and major health costs, due to high CFC consumption and frequent hospitalization. We have developed a protocol based on the realization of an effective local hemostasis by expert oral surgeons in association with no or limited replacement therapy, determined according to the severity of the hemophilia and the possible existence of inhibitors. We report the evaluation of all procedures performed in accordance with this protocol from 2001 to 2009. During this period, 111 procedures were performed in 67 adult patients with hemophilia. Fifty-one procedures (46%) concerned patients with severe hemophilia; among them, 5 concerned inhibitor patients. All extractions were performed on an outpatient basis. The mean number of exposure days to CFC per procedure was 2, 1, and 0.3 respectively in cases of severe, moderate, and mild hemophilia. The mean CFC consumption was 67, 9, and 10 U kg^{-1} for factor VIII; and 63, 17, and 14 for factor IX in the 3 groups of severity. In the 5 procedures performed in inhibitor patients, administration of bypassing agents was limited to 1 to 3 exposure days with a total of 1–3 CFC infusions. No severe adverse event occurred (no blood transfusion, no hospitalization). The highest CFC consumptions were recorded in patients aged more than 70 and in those with psychological problems impairing compliance to the hygienic and dietetic advice. In conclusion, our experience provides detailed assessment of the minimum amount of CFC required for teeth extractions in patients with hemophilia, according to the severity of the disease, the age of the patients, and their capacity to follow recommendation. These data could help medical teams evaluate the efficacy of their management.

PO-WE-069
A comparison of dental diseases between hemophilia patients and normal patients, an analysis of treatment protocols at the children's hospital

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Objectives: Compare the incidence of dental complaints between hemophilic and non-hemophilic patients. Compare the types of dental diseases between these two groups of patients. Analyze the differences in treatment protocols.
Research Design: A hospital-based study (at the Dental Department of the Children's Hospital, Pakistan Institute of Medical Sciences, Islamabad) in which regular records was kept between January and December 2011 (1 year). The subjects were children between the ages of 1 and 12 years.
Selected Results and Conclusion: In this case study, 50 persons with hemophilia with dental diseases were compared with 50 normal control subjects over a period of 1 year. It was found that persons with hemophilia had less tooth decay than the control group by a ratio of 1:5.6, which resulted in a lower number of filled teeth at a ratio of 1:10 compared with the control group. Gum diseases, on the other hand, were more prevalent among the persons with hemophilia as compared to the control group, by a ratio of 4:3. A higher percentage of persons with hemophilia were given oral hygiene instructions in comparison to the control group. The major dental complaint of persons with hemophilia was that of bleeding gums during the tooth-shedding stage, while the control group complained more of cavities. Fear of brushing was found to be the main cause that could be causing trauma to the gums of persons with hemophilia.

PO-WE-070
Restorative dentistry and third-molar surgery in a patient with an inhibitor to FVIII: A case report

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Introduction: Since hemophilic patients with an inhibitor to FVIII may be particularly at risk during oral surgical procedures, the aim of this report was to present the treatment of mentioned patient for restorative dentistry and surgical third-molar extractions.
Case Report: A 23-year-old male patient with inhibitor to FVIII required preventive, periodontal, and restorative dental treatments and third-molar extractions. Injection of tranexamic acid and antibacterial mouthwash course were given for the restorative dental procedures, while a recombinant activated factor VII (rVIIa) and antifibrinolytic agent, with the usual antibiotic and antibacterial mouthwash course, were used for the periodontal treatment and surgical extractions of third molars. Several teeth were successfully restored by composite with well-controlled gingival bleeding. Surgical extractions were done with careful mucoperiosteal flap elevation and bone drilling with crown and root separation. Surgical wounds were treated with the oxidized cellulose, which completely filled bone defects. Superficial parts of bone defects were filled with fibrin glue and covered with sutured mucoperiosteal flaps. Post-operatively, the patient had mild intraoral bleeding on the third and fifth days, which was successfully controlled with rVIIa and tranexamic acid. No re-pack of sockets was done, since hemostasis was achieved.
Discussion and Conclusion: Decision for third-molar surgery could be discussed as a preventive treatment, especially in the case of partially erupted teeth with a susceptibility to dental infections. Since third-molar extractions are related to local trauma, greater importance was given to the reduction of surgical trauma in soft and hard tissue. Possible uncontrolled late bleeds after extractions in patients with inhibitor FVIII must be controlled with intraoperative surgical wound management. It can be concluded that the verification of dental procedures, restorative and surgical, which could be performed as preventive treatments in hemophilic patients, are necessary to avoid further possible severe and life-threatening complications, especially in patients with inhibitors to FVIII.

PO-WE-071
Caries study: Oral hygiene and changes on dental surfaces associated with fructose consumption in patients with hemophilia and von Willebrand disease

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Introduction: Caries is traditionally evaluated based on WHO criteria using the most common indicators, such as the decayed/missing/filled teeth (DMFT) for adults and children with mixed dentition and decayed/extracted/filled teeth (DEFT) for children with deciduous dentition. There are other indicators which observe the state of the enamel surfaces: the international caries assessment and detection system (ICDAS); the O'Leary method for good oral hygiene; and Löe- Silness for non-visible plaque.
Aim of the study: Observe the oral hygiene conditions and caries presence in 15 patients with hemophilia and von Willebrand disease. Watch the suface conditions of the deciduous molars in 4 children from the sample and observe the surfaces a year after the change of consumption from saccharose-glucose to fructose, in Barinas State, Venezuela.
Materials and Methods: From December 2010 to December 2011, 86 patients of hemophilia and von Willebrand disease were motivated toward dental care; 15 patients attended at least 1 time. Common sugar consumption was changed to fructose in a 3-year-old child showing no damaged or altered surfaces in any of his teeth. The other children maintained the same common sugar consumption habits; stains in the occlusal surface of some of their teeth were found.
Results: The study obtained a DEFT of 3.5 (moderated) and a DMFT of 6 (high) in children with mixed dentition; a DMFT in adults of 5.7 (high) and a ICDAS of 4.3 for 55 molar; 0.00 for 54 and 0.00 for 64, 65, 74, 75, 84, and 85 molars.
Conclusions: Patients with hemophilia and von Willebrand disease have special needs when it comes to dental care, and attention must be paid in order to avoid unnecessary risks to their living conditions. A change in alimentary habits is highly recommended in order to lower the risks to dental health. The final goal is to motivate the other 71 patients to improve their living conditions with hemophilia to lower the risk of dental emergencies.

PO-WE-072
A review of dental surgical operations in 64 patients from a large hemophilia centre in northern India

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Dental problems are common in hemophilia, the management of which may have logistic issues in the developing world. A review of patients from our hemophilia centre who underwent dental surgical procedures in the allied on-campus dental institute is presented. All 64 hemophilia patients with dental problems requiring surgical intervention since May 2008 were analyzed. The centre had prior detailed workup records on all those who were negative for factor inhibitors. Fifty-eight were hemophilia A and the other 6 were hemophilia B. The age range was 3–65 years, mean 16.3, with 78% under 20 years.
Patients' diagnostic groups are tabulated below:
Two patients had interventions twice, making a total of 66 surgeries in 64 patients. All surgeries were performed under local anesthesia. Patients were infused single dose of anti-hemophilic factor (AHF) 50–60 min pre-operatively. Mean AHF dose was 20.8 IU kg^{-1}, 80% receiving under 30 IU kg^{-1}. All but 1 received less than 42 IU kg^{-1}. Antifibrinolytic tranexamic acid was administered locally to all, pre- and post-operatively. Post-operatively, patients were re-evaluated and observed for 2 h in our hemophilia centre. Successful hemostasis was achieved in all the patients; only 3 patients had post-operative bleeding, which was considered attributable to the primary pathology/procedure. No patient required additional AHF or other circulatory support. Frequent dental pathologies in young persons with hemophilia were carious/ broken/ exposed/decayed teeth and mobile deciduous teeth. A single dose of AHF, coupled with local antifibrinolytics, produces sufficient hemostasis for most dental surgical interventions.

S. No.	Diagnostic group	Number	Hemophilia A	Hemophilia B
1	Caries tooth	25	24	1
2	Mobile deciduous tooth	24	21	3
3	Retained deciduous tooth	3	2	1
4	Periapical abscess	3	2	1
5	Impacted third molar	2	2	0
6	Fractured tooth	2	2	0
7	Adult permanent mobile tooth	1	1	0
8	Foreign body	1	1	0
9	Scaling	2	2	0
10	Curettage	1	1	0

PO-WE-073
Dental surgery with minimal factor support an update assessment of 120 patients
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Background: Patients with inherited bleeding disorders have historically had factor cover, where available, for oral surgery. Factor support is expensive, time consuming to administer, and places the patient at a potential risk of complications in therapy.
Methods: A protocol employing rigorous local measures and minimal factor replacement are used to obtain hemostasis following simple and complex oral surgery on one hundred and twenty consecutive patients with inherited bleeding disorders, referred to the Alfred Health Dental Unit from the Ronald Sawers Haemophilia Centre, Alfred Health, Melbourne. A review of the patients' oral hygiene, smoking habits, and the use of Cox-2 inhibitors was carried out on the last 40 patients to assess if any of these factors had any effect on adequate hemostasis.
Results: Excellent hemostasis continued to be achieved, using our standardized local measures of 5% tranexamic acid solution, Surgicel, careful surgical procedures, and placement of monocryl or vicryl sutures.
Conclusions: Oral surgery and the use of inferior dental nerve blocks may be considered safe to perform on patients with inherited bleeding disorders, using minimal factor support and meticulous local hemostatic measures.

PO-WE-074
Specialized dental care programme for people with congenital coagulopathies offered in the hemophilia unit of the Hospital Vall D'Hebron (HVH)
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Introduction: Dental problems in people with coagulopathies are common, some due to a lack of health education, others to a fear of blood loss after brushing. Certain injuries and minor manipulations or interventions – that for normal people would be trivial – may necessitate treatment in the case of persons with hemophilia. Besides, an important part of this community is infected with HIV or hepatitis C, and their dental pathology might constitute an important focal point of infection. Regarding this situation, in 1997 the Private Catalan Hemophilia Foundation drew up a collaboration agreement with private and public organizations to create a specialized dental service for attending to the needs of patients in the hemophilia unit of Hospital Vall d'Hebron (HVH). Since 2008, the Blood and Tissue Bank has also participated in this programme.
Objectives: Creation of a specialized dental care program for people with congenital coagulapathies in the HVH hemophilia unit.
Description: Dental care is offered twice a week in the HVH hemophilia unit installations, attending to patients with appointments or emergencies. In the last year, 580 treatments were carried out on 296 patients, half of whom have hemophilia A or B. Before each treatment, a dental medical record is done, as well as a clinical oral check-up, a radiology exploration, and a coagulation study, if necessary. After this, the hematologist and the dentist coordinate a therapeutic plan to guarantee an adequate level of hemostasis. We also develop preventive plans for periodontal disease and tooth decay through individualized programs, and we encourage patients' early introduction to dental care.
Conclusion: The implementation of the program, with its own dental care service in the hemophilia unit, has been instrumental in improving the oral health of patients with congenital coagulopathies.

PO-WE-075
Periodontal management of Malagasy hemophilia patients
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The objective of this study was to establish a periodontal therapeutic strategy adapted to Malagasy persons with hemophilia. A cross-sectional descriptive study was conducted on 11 subjects suffering from hemophilia, aged 4 to 35, members of the "Association pour le Bien-Être des Hémophiles à Madagascar" in Antananarivo, Madagascar. All subjects were presented a plaque-induced gingivitis with a periodontitis for 3 adults. All the patients had poor oral hygiene. Gingival bleeding was a common manifestation in all patients, and it had required hospitalization in 5 cases. No patient had had previous periodontal treatment. Improved oral hygiene in persons with hemophilia reduces gingival inflammation and prevents periodontal disease, sources of gingival bleeding, while maintaining periodontal health. The mechanical treatment by ultrasonic supragingival scaling does not require substitute treatment if it is conducted carefully on a slightly inflamed gingival. Otherwise, interventions must be performed in a hospital centre with addition of the missing factor and hematologic monitoring. Our study highlights a close collaboration between hematologists, periodontists, and dentists for better management of hemophilia in Madagascar.

PO-WE-076
Oral health status and oral health–related quality of life in Iranian hemophilic pediatric patients
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Objective: The aim of this study was to determine the oral health status and oral health–related quality of life (OHR-QL) in pediatric patients with severe hemophilia who were referred to Mofid educational hospital, Tehran, Iran.
Methods: Dental caries scores in permanent and primary teeth (DMFT-DMFS, dmft-dmfs), Oral Hygiene Index, temporomandibular joint status, occlusion, and enamel hypoplasia, and jaw pseudotumours were evaluated in 47 patients with hemophilia aged between 2 and 15 years, and their healthy controls. Oral health–related quality of life (OHR-QL) was also evaluated by questionnaires. Independent t-test and Mann-Whitney were used for data analysis.
Results: The group of patients with hemophilia included cases with several types of factor deficiency, including factors VIII, IX, XI, XIII, and VWF. Hemophilia A and B were recorded in 72.4% and 8.5% of subjects, respectively, and the presence of inhibitors was reported in 21.3% of all patients. A history of oral bleeding was present in 57.4% of cases, mostly related to tongue or gingival bleeding (during primary tooth eruption). Oral hygiene instructions were given to patients in 34.8% of cases. Significantly better results were recorded for patients with hemophilia in terms of decay level by independent t-test ($P = 0.04$, $t = -2.02$), dmfs ($P = 0.03$, $t = -2.1$), and the OHR-QL of patients 2–5 years of age by Mann-Whitney (mean rank 16.97, $P = 0.04$). All patients with hemophilia received professional dental services during their referrals, mostly in 1 session and with general anesthesia.
Conclusion: Young patients with severe hemophilia had significantly better scores of decay in primary teeth as well as better oral health–related quality of life in comparison to healthy controls.
Contribution to Practice: The results of this study may reflect the importance of an organized team-work approach that per se involves early dental visits.

PO-WE-077
Dental invasive procedures in hemophilia A/B (HA/HB) and von Willebrand disease (VWD) patients: Experience of a single centre
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Background: Dental procedures in patients with hereditary bleeding disorders (HBD) can be complicated by excessive bleeding. Replacement prophylactic therapy and local measures dramatically reduce the risk of complications in these surgeries. Moreover, self-infusion and home treatment reduce therapy cost.
Aim: To describe the dental procedures performed in a group of HA/B and VWD outpatients utilizing systemic prophylactic therapy and local measures.
Patients and methods: In 5 years, in our dental department, we performed 97 surgeries on 30 patients (28M, 2F, median age 47 years, range 11–78) affected by HBD: 13 severe, 2 moderate, 7 mild HA; 1 mild HB; 2 type 1, 1 type 2a, 2 type 2b, 2 type 3 VWD. The hemophilia centre provided personalized therapeutic schemes on the basis of coagulopathy type/severity and type of surgery. Factor VIII concentrates were administered in severe, moderate, and a few cases of mild HA; FIX concentrates in HB; desmopressin in mild HA, VWD type 1 and type 2a; FVIII/vWF concentrates in VWD type 2b and type 3. Seventy-five dental and roots extractions, 9 third molar surgical extractions, 1 excisional biopsy, 1 cyst enucleation, 10 scaling and roots planing, and 1 gingival graft were performed under local and loco-regional anesthesia. Local hemostasis was ensured by applying gelatine packing, fibrin glue, absorbable suture, and 15-minute compression with tranexamic acid–saturated gauze. In the post-operative period, patients were treated with antibiotics and continued the self-infusion of concentratesdesmopressin for an average period of 5 days (3–7). Tranexamic acid mouthwashes (3 times a day for 3 days) were prescribed; acetaminophen was used as the only pain-relief treatment.
Results: We didn't observe any hemorrhagic or infectious complications. All patients completed the post-surgery home treatment.
Conclusions: A tailored prophylactic treatment ensures a good hemostasis in HBD patients undergoing dental procedures. A multidisciplinary approach allows the management of coagulopathic patients without bleeding complications; home treatment reduces management cost.

PO-WE-078

A minimally invasive method for the diagnosis of lesions affecting the jaws

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Introduction: All surgical interventions in patients with bleeding disorders should be as minimally invasive as possible, to minimize risk of hemorrhage. Bone lesions can be studied by open biopsy or bone puncture biopsy (BPB).The latter poses the advantage of being a less traumatic and less invasive methodology with high effectiveness rates, according to the medical literature. Bone puncture biopsy is rarely used in the dental setting and little has been reported on its effectiveness.
Objectives: The aim of this study was to evaluate the effectiveness and convenience of using BPB as a methodology to obtain samples of lesions affecting the jaws, and with a mixed radiographic appearance.
Materials and Methods: Bone marrow biopsy needles, 11 gauge/10 cm long, were used in patients with intramaxillary lesions requiring biopsy for diagnosis. Forty (40) lesions with a mixed radiographic appearance were biopsied. The obtained material was fixed with 10% formalin and demineralized in 7% nitric acid. Paraffin-embedded sections were stained with HE.
Results: Material for the histopathological study was successfully obtained in all cases. No intraoperative or post-operative complications occurred. Accurate diagnosis was established in 100% of lesions, which allowed performance of the corresponding treatment.

PO-WE-079

Dental management of children with bleeding disorders: The Kuala Lumpur Hospital experience

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Introduction: Children with bleeding disorders merit special consideration because, if poorly managed, the affliction can be disabling with sometimes devastating consequences. These children may be at risk of infection either due to their condition or resulting from poor management, with the attendant risk of prolonged bleeding and the development of antibodies to the factors used to manage their condition. This paper will present the interdisciplinary management of children with bleeding disorders referred to the dental clinic of the Pediatric Institute, Kuala Lumpur Hospital.
Methods: Cases seen were patients referred by various health practitioners. Since the formation in 1998 of a multidisciplinary team comprising dentists, hematologists, physiotherapists, and orthopedic surgeons to manage patients with bleeding problems, particularly hemophilia and von Willebrand disease, the department has rendered comprehensive dental treatment to patients registered with the National Blood Centre. This included promotive, preventive, curative, and rehabilitative aspects of oral healthcare. Initially, the patients seen attended with poor oral hygiene and untreated diseases. Apart from the 2 common dental diseases, namely caries and gingivitis, other oral lesions managed were pseudotumours of the orofacial region and dentigerous cysts. Besides providing treatment to the patients as and when necessary, other activities carried out were oral health education and toothbrush drill, as well as seminars and workshops for minders and healthcare providers. Guidelines on the comprehensive management of patients with bleeding disorders were also developed and distributed to all public healthcare facilities in the country.
Conclusion: Multidisciplinary management of patients with bleeding disorders is important so that appropriate treatment resulting in good function and esthetics is achieved, boosting the patients' morale and self-esteem that subsequently improve their quality of life.

12-EDUCATIONAL MODELS

S-TH-01.3-5
Twelve years of active work on improvement of quality of life in persons with hemophilia in Russia: Developing education models
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In 2000 the Russian Hemophilia Society (RHS) was established. At the time it consisted of 58 regional chapters. Since 2005, the RHS has made efforts so that Russian PWH (children and adults), in accordance with order #122 by the Ministry of Health, receive home treatment with factors concentrates by prescriptions, free of charge under standards of treatment approved in 2008. Since 2000, the RHS has held (once every three years) a national conference for hematologists, the Congress for regional chapter leaders and visitors from CIS countries, as well as representatives from the WFH. The Conference has demonstrated modern methods of treatment for hemophilia and von Willebrand disease. Annually, 250–350 people have taken part in these conferences. November 2012, will mark the the 5th National conference. During the last 11 years, we have conducted regional conferences in 30 of the biggest Russian cities. We invite hematologists, lab doctors, nurses, orthopedists, gynecologists, dentists, PWH, and adults and parents of children with hemophilia to these regional conferences. Speakers at these conferences are professors from leading clinics of Moscow, Saint-Petersburg, and Barnaul. The RHS considers publishing educational materials one of the most important goals. In 2006, we published a manual on home treatment (5000 copies); in 2007 we republished it (5000 copies) and published guidelines for von Willebrand disease treatment and hemophilia treatment (2 reissues in 2007 and 2009), for rehabilitation of PWH we published "Therapeutic exercises" by Raissa Osipova (5000 copies), passport of PWH was reissued multiple times and shared free of charge among regional chapters, and two newsletters were also published: "Heminform" (for adults with hemophilia and parents, 1990 till now), and "TiM" (for children, 2000–2006). We created the RHS "Hemophilia in Russia" website, which includes not only contemporary events, but also translations of publications on hemophilia treatment, legal documents, containing interpretations on obtaining status of disabled persons, and the benefits on secondary education and higher education. In the Twinning Program frameworks, we used the experience of hematologists and lab doctors (MD, S. Kitchen, MD, P. Bolton-Maggs) in order to train doctors. There were five lab workshops conducted in Moscow and Saint-Petersburg with participation of P. Bolton-Maggs and physiotherapists and a dentist. I thank the WFH for organizing this Twinning Program.

S-TU-04.3-1
Models around the world: Psychological approach in a hemophilia center in Brazil
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Brazil has 27 states divided into 5 regions, and its estimated population is 196,000,000. The amount of factor units per capita recorded in 2010 was still low; 1.1. Great efforts are made by the local Hemophilia Federation and Ministry of Health to have primary prophylaxis and immune tolerance treatment projects approved for 2012. Management of care and treatment are done according to each hemocentre, which coordinates other smaller ones called hemonucleos. Access to medical and psychosocial support is free of charge. An overall view would show that to date, only 2 states have neither a psychologist nor social worker on their team. Nineteen teams have both, and 6 only a social worker. A social worker in Brazil is not allowed to provide counselling or psychotherapy. Nevertheless, psychologists and social workers are seen as being of major importance. The psychological interventions I started in 1994 are embedded in the context of supporting people with hemophilia (PWH) and their families who receive on-demand treatment. This situation can be compared to patients with moderate and mild hemophilia who are treated in other countries on-demand as well. These interventions focus mainly on primary prevention and psycho-education using different expressive techniques that also assist literacy issues within our population. Flashcards like hemoaction-playing and learning about hemophilia is one of them. Patients' caregivers are also given information and psychological support to cope with different phases of living with hemophilia. Short-term psychotherapy is necessary at times when the patients has to face situations regarding their studies, employment, relationships, family dynamics, and in both minor or major orthopedic procedures. Outcomes like early awareness, better self-management of hemophilia, and coping with life events are reported by patients who are followed through the years.

S-TH-01.3-3
The U.K. Haemophilia Society's "Young Bloods" website
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This presentation will rehearse the development of the "Young Bloods" website designed to be used by children and teenagers to educate themselves about their condition. When the U.K. Haemophilia Society consolidated its websites, it realized that children and teenagers used websites very differently than other members of the Society and need very different information. The Society decided to develop a website specifically for these groups. The website was development by the Haemophilia Society based on feedback from our younger members. The name "Young Bloods" was suggested by a young member as part of a competition. Careful attention was paid both to what subjects should be included and how the information should be presented. As part of this project, the Haemophilia Society has developed web-based games. An attempt has been made to create games that are enjoyable and help bring children and teenagers to the site, while at the same time containing an educational message. In particular, the presentation will suggest NMO learning points in the following areas: a) the principles for developing a website for children and teenagers; b) the resource implications of website development; c) challenges associated with running forums for younger members; d) the development of education games; and e) opportunities for other NMOs to become involved with this website.

S-TH-01.3-5
Developing education models: A Malaysian perspective
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Education is not preparation for life; education is life itself (quote from John Dewey). As hemophilia is a life-long disease, educating the society in general is of utmost importance. Based on the principle "prevention is better than cure," the Hemophilia Society of Malaysia (HSM) embarked on a three-pronged strategy of educating patients and parents, medical providers, and the general public throughout the 32 years since its establishment. Each individual, each different culture, has its own approaches to educating their young ones. Similarly, in its earlier years, HSM used a trial-and-error method to developing and educating the local communities about hemophilia. Thus, what you can expect from this talk is a genuine sharing of the ways and methods that HSM has been developing and implementing education of its members and the general public about hemophilia care. For example, how effective or different is the camp that HSM has been organizing compared to the summer camps held by other hemophilia societies from the developed countries? In addition, you may expect to learn more about the challenges that HSM endured in organizing their educational activities and the ways it tried to counter these challenges. Lastly, there will also be a glimpse into what HSM hopes to do in their future educational plans to make sure that a continuous learning and awareness about hemophilia care is always embedded within the communities.

S-TH-01.3-1
Developing education models: Background and approach
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Sharing knowledge through education and training is a key component of the World Federation of Hemophilia's (WFH) mission to improve and sustain care for people with inherited bleeding disorders around the world. In order to be most effective, education must be provided at multiple levels: patients must be educated about their disease in order to manage it appropriately, healthcare professionals must be knowledgeable in order to provide adequate care, patient organizations must learn how to advocate effectively for the collective, and governments must be informed in order to make sound decisions for the provision of treatment. Along with its programs and activities, the WFH aims to provide educational and resource materials for each of these target audiences. Using concrete examples, this session will provide guidance on how to identify and assess the need for education and/or training and on how to plan, develop, implement, and evaluate a successful education program.

S-TH-01.3-2
Models from NMOs: France
L. ROBIN
French Hemophilia Society, Paris, France

The French NMO has a new initiative called a "patient resource" (PR). A PR is someone directly concerned with hemophilia that can provide help and support for their peers. This initiative comes out of an assessment by healthcare professionals and the French Hemophilia Society showing that patients have good knowledge of the disease and treatment, *but* knowing that, they don't follow those principles all the time. The goal of this new initiative is, for example, to work complementarily with healthcare professionals, to go further than teaching injections, to improve disease management over a lifetime, and to increase patient autonomy. The PR is chosen either by a healthcare professional or by the French NMO. He or she is someone with moderate or severe hemophilia, over 18 years old, and someone who treats themselves frequently. The PR can also be a "parent resource"—someone with a child who has hemophilia. To become a PR, the candidate will have to be recruited first, then be trained and evaluated, and then be involved in therapeutic education sessions. I will discuss these things in my presentation. It is a great thing that patients can be involved in therapeutic education sessions with other patients. PRs can bring help and support that is complementary to that of healthcare professionals. PRs will not teach how to self-infuse, but would preferably work on behaviours: they will listen to their peers and will try to support them to improve disease management. PRs can be a live example of what to do and what not to do. Since they have experience, they may be powerful way to incite others to imitate them or to follow their advice.

S-TU-04.3-2
Model from the Philippines
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In recent years, Haplos has adopted a holistic approach to addressing the psychosocial health of people with Hemophilia (PWH) and their families. This involves PWH

becoming physically active, mentally alert, emotionally healthy, spiritually strong, and socially involved. In the Philippine context, amid the financial and geographic limitations imposed on the organization, Haplos believes this is relevant because it will promote the growth of PWH to become more productive and self-sufficient individuals, not simply dependent on the organization. It has aligned its programs according to these five aspects, with the belief that addressing the holistic development of individuals will enable them to adequately cope with the psychosocial situation and needs that confront them and their families daily. This approach is facilitated through the forming of small interest groups, the development of a familial and community environment, and close personal relationships. This system is undergoing continuous study to evaluate and validate the effectiveness of the current psychosocial model through surveys, interviews, and observation of workshops. The current results show that the psychosocial model of intervention in Haplos is facilitated through informal and close personal connections in small groups. The system mainly relies on informal supportive relationships between members, which enhance the positive experience of community and group activities. In Haplos, members support one another through bonding activities aligned to aspects of the holistic approach, along with various forms of media communication outside of formal meetings. In conclusion, we suggest that the organization increase the frequency of group meetings, with more activities to strengthen camaraderie and form friendships, with the end goal of developing a community identity and feelings of belonging. We encourage members in each sector to meet regularly outside of general assemblies and to establish yearly evaluation systems and goal setting.

S-TU-04.3-3
Psychosocial models of care in Australia: Risky business?

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Australia is a diverse country located in the Southern Hemisphere. It lays between Indonesia, East Timor, and Papua New Guinea to the north and New Zealand to the southwest. Australia is a diverse and highly developed country ranking well in measures such as quality of life, health, and education. The Commonwealth of Australia is made up of 6 states and 2 territories. Each of these states has established hemophilia centres and staff who provide clinical management and support for people with inherited bleeding disorders. The state of Queensland occupies the northeast of the mainland; is the country's second largest state by area and is often referred to as the *Sunshine State*. The Queensland Haemophilia Centre (QHC) is based across from the Royal Brisbane and Women's Hospital and the Royal Children's Hospital in the capital city of Brisbane. The Queensland Haemophilia Centre has recently celebrated the 10 year anniversary of formal funding. This funding ensures employment of a dedicated multidisciplinary team consisting of a hematologist, nursing and physiotherapy staff, and a fulltime social worker or psychologist. Comprehensive care is offered to all patients who are registered at the Qld Haemophilia Centre. The benefits of psychosocial input into models of care for people who have hemophilia and other chronic health conditions are recognized worldwide. Australian hemophilia centres provide varying levels of psychosocial support, and this presentation will explore the current situation. In addition, the presenter will report on a small survey of 9 Australian centres conducted in 2009 to provide a snapshot of psychosocial services. The Queensland Haemophilia Centre is in a unique position with two full-time psychosocial workers employed to provide a service across the pediatric and adult hemophilia communities. The presentation will look in-depth at the psychosocial work that is being currently conducted at the Queensland Haemophilia Centre. It will also explore whether the high standard of service is at risk of demise as burgeoning health issues in Australia compete for limited funding dollars.

PD-SU-NUR-2
Are nurse education programs effective? Evaluation of a program offered in South Africa

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Education for health carers, patients, and their families was a principle recommendation of the World Federation of Hemophilia (WFH) (2004) to enable the provision of the basic components of care and appropriate treatment. To this end, in 2002 the National Health Department of South Africa (SA) supported the first Haemophilia Nurses' Education Program (HNEP). Although offered annually, the program has not undergone a rigourous evaluation process—an essential component of any education program. The purpose of this PhD study, therefore, is to determine if, over the 10 years that the HNEP has been available, (1) the program has contributed to the management and care of people with hemophilia (PWH) in SA and (2) the nurses who have attended the program report being more confident and competent to manage the care of PWH and their families. The study involved a qualitative approach involving registered nurses from SA. A purposive sample of 20 respondents agreed to participate. Four participants were involved in one-to-one interviews and 16 in 4 focus groups in 3 cities. All data were managed by NVIVO (Richards, 2009) and analyzed using the Kirkpatrick Four Levels of Evaluation (2006) model. Preliminary findings show that these nurses expressed an increase in competence and confidence in caring for PWH, especially in crisis situations. Within these critical situations, the nurses acted as advocates for the PWH and the family. The knowledge gained via the HNEP had empowered these nurses to intervene and provide care in the best interests of their patients. Indeed, parents requested their assistance in crisis situations if they believed the care provided was detrimental to their child's welfare. These findings therefore demonstrate how the HNEP has influenced the practice of these nurses, which, one may propose, could reduce the morbidity and mortality of PWH in SA.

PO-TU-082
Hemophilia educational project in Pakistan: Analyzing behaviours of patients with hemophilic—a dental perspective (2007–2011)

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Overview and Objectives: The Hemophilia Educational Project (HEP) was the first awareness program on hemophilia in Pakistan. It was introduced in 3 phases and aimed at improving the overall awareness levels of hemophilia among patients, doctors, and the Pakistani society in general. While the first phase consisted of program development and several stakeholder sessions, in the second phase, the project carried out several awareness campaigns and training sessions in Rawalpindi and Islamabad. Short booklets were published in Urdu language, as a part of the project, by a team of national experts in hematology, dentistry, and physiotherapy. After the success of the second phase, the project was extended to all 4 provincial capitals in Pakistan, and master trainers were developed by the experts from Islamabad. In the final part of the project, follow-up sessions were conducted so that the experts could audit the performance of the newly established hemophilia centres across Pakistan.
Methods: Before the launch of the national Hemophilia Education Project, a Knowledge, Attitude, and Practice (KAP) survey was conducted in the first hemophilia awareness meeting, held at the Dental Department of the Children's Hospital in the Pakistan Institute of Medical Sciences. Several key informant interviews (KII) and various focus group discussions (FGDs) were held throughout Pakistan among the stakeholders before the launch of the project, during its phases, and after the end of the last phase of the project. Separate record registers for blood disorder patients, which were maintained at the Pakistan Hemophilia Patients Welfare Society (PHPWS) in Rawalpindi and at the Dental Department at the Children's Hospital of Pakistan Institute of Medical Sciences, have been studied to produce an extensive pre- and post-evaluation of the impact of the Hemophilia Education Project on the dental behaviour of people with hemophilia (PWH) across Pakistan using descriptive statistics. Change in the behaviour of dentists and paramedical staff with regards to treating PWH was also analyzed before and after the HEP.
Conclusion and Results: The Hemophilia Education Project was tremendously successful in achieving its initial objectives. Statistics demonstrate a very high rate of satisfaction with regards to parents of patients with hemophilia being able to treat their children at home in case of minor bleeds. The establishment of 4 provincial hemophilia centres and the training of their medical staff have also led to a stark reduction in the number of patients travelling to Islamabad/Rawalpindi for medical advice or checkups. The sustainability of efforts to increase awareness on hemophilia and consistency in developing master trainers for patients with hemophilia in cities besides Islamabad and the provincial capitals have been identified as the major challenges for the continuation of efforts that ease medical and social problems of patients with hemophilia in Pakistan.

PO-TU-083
Dedicated day: A platform for the interdisciplinary team

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Context: Clinic observation shows that (1) young adults with severe hemophilia who have had access to factor concentrate since diagnosis have a high rate of hemophilic arthropathic joints; (2) participation in high-risk sports and low adherence to the treatment plans are associated with an increased risk of developing hemophilic arthropathic joints; (3) early diagnosis influences parents' view of the child, resulting in identity construction difficulties, such as lower self-esteem and altered body image; and (4) protection from distress may result in maladaptive denial.
Hypothesis: Interdisciplinary intervention is facilitated by dedicated days aimed at (1) primary prevention, whereby intervention is started from the onset of diagnosis; (2) better understanding of bleeding disorders, the importance of prophylaxis, and the long-term consequences of bleeding; (3) sharing with peers and professionals successes and hardships in applying the treatment plan and adapting to it; and (4) dealing with emotions towards loss and the reality of disease.
Methods: Dedicated days are the first step in studying the effects of interdisciplinary intervention during biannual medical appointments. Forty patients attend dedicated days focused on groups of: educational nursing; social work counselling with parents; psychotherapeutic intervention with children 5 to 18 years old; child–parent bonding activity for children under 5, with psychologists.
Outcome: Increased (1) coherence of teaching starting from earliest age; (2) comprehension of disorder; (3) ability in accessing and expressing difficult emotions; (4) motivation to make good use of groups with psychosocial professionals.
Conclusion: Interdisciplinary intervention through dedicated days is well underway. It is already proving to be an effective way for patients and parents to learn about the disorder, to engage with psychosocial professionals, and to access difficult emotions in a secure environment. It also helps patients and parents to reflect on limits and to change behaviours with regard to hemophilia. This innovative global care mode of treatment is the foundation for a future evaluative study.

PO-TU-084
Training and Education Programme for Haemophilia Assistants

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The German haemophilia care guidelines (''Leitlinien zur Qualitätssicherung der Hämophilie-behandlung'') demand nurses and assistants with special qualifications and some of them even with further education as study-nurse. Also the EAHAD (European Association for Haemophilia and Associated Disorders) demands in the European

principles of haemophilia care "designated nursing staff to co-ordinate treatment supplies, the home treatment programme and patient and family education". In order to guarantee these haemophilia-specific qualifications the nurses and assistants need "ongoing specialist education and development for practice in this field". The working group of the German haemophilia assistants organizes educational sessions, enables exchange of experiences and tries to optimize haemophilia care, especially the nurses' part of it. One of these projects has the goal to develop an educational catalogue for haemophilia assistants in order to reach and to guarantee a standard of specific qualifications. In the following we want to present the result of our work, a draft version of such a catalogue. We want to discuss this catalogue with haemophilia treaters in order to optimize the programme and to look for ways of implementation. In order to achieve this special competence, education and training in the following fields is necessary: basics of coagulation, coagulation disorders (e.g. haemophilia A/B, von Willebrand disease), thrombotic disorders (e.g. FV-Leiden, protein C/S-deficiency, prothrombin-mutation), genetics and diagnosis of congenital coagulation disorders, therapy of coagulation disorders, home-treatment and self-infusion, complications of treatment (e.g. inhibitors), special problems (e.g. dental problems, surgical interventions, gynecological problems), basics of psychology, education and sociology, communication, organization. The education and training for nursing staff as well as proof and certification of acquired qualifications could be organized similar to the programme for physicians to attain the additional qualification as specialist for haemostaseology.

PO-TU-085
Concept maps: An educational tool for teenagers with hemophilia?

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Hemophilia education is essential to improve the well-being of adolescents and to enhance their quality of life. It allows them to acquire autonomy from their parents or from the medical environment, and to attain better socio-professional integration. For this purpose, personal experiences must be taken into account, since they result from interactions, not only with one's own pathology, personal history and beliefs, but also with one's family's view of disease. Using concept maps allows a better understanding of these different dimensions and thus better adaptation of educational sessions to the teenager's needs. The idea is that caregivers can use these concept maps to bring the patient to think about a specific word that represents the central concept. Then, he or she will say or write some key words related to this concept, while explaining why these words come to his or her mind. We use the term "maps" because at least two concepts are connected by a linking word to form a proposition (which could describe cause, consequence, or specific behaviour) reflecting on the knowledge, the experience, and the resources of the patient. To show the direction of the relationship, each arrow connects two concepts. Concept maps are visual representations used to organize and to spatially represent: what they know what they understand, and what they believe on. They depict relationships among concepts too. When used for educational diagnosis, these concept maps identify teenagers' pre-existing knowledge or misconceptions, and they can also be used as an evaluation tool during the educational program. This project of concept maps for teenagers' education should be developed further in Nancy and Dijon hemophilia treatment centres. We think that it is important to introduce other health professionals involved in education to concept maps.

PO-TU-086
Acquired hemophilia A and the knowledge/awareness level of Turkish hematology fellows: On behalf of the Turkish Hematology Association, Acquired Hemophilia Working Group

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Background: Acquired hemophilia A is a rare disorder with high morbidity and mortality. Its onset, clinical presentation, and treatment are different from those of congenital hemophilia A. Objective: To determine the knowledge/awareness level about acquired hemophilia A and to develop training programs for the diagnosis and treatment of acquired hemophilia accordingly. Methods: A survey consisting of 14 questions aimed at measuring the knowledge and awareness level was prepared by the Acquired Hemophilia Working Group. In a session which all the Turkish Hematology School students were attending, they were asked to fill out the survey. The first part of the survey consisted of 5 questions and measured the competency of hematology fellows in the diagnosis and treatment of acquired hemophilia A. In the second part, which was consisted of 9 questions, the level of knowledge about the disease was measured. Ninety-four hematology fellows answered the survey. Statistical analysis of the results was performed.
Results: Ninety-eight percent of the fellows were aware of the disease, and 69.4% of them stated that they would consider acquired hemophilia in the differential diagnosis of the patient while evaluating the clinical and laboratory results. Only 26.5% of the fellows reported their knowledge level as sufficient for diagnosis. Similarly, only 22.4% rated their knowledge level as sufficient for differential diagnosis. The percentage of fellows who reported that they were competent for the treatment and follow-up of acquired hemophilia patients was only 18.4%. The ratios were similar for pediatric and adult hematology fellows.
Conclusion: The results of the survey show that the knowledge level about acquired hemophilia is not sufficient, even among hematology fellows. The awareness of the early diagnosis and treatment of acquired hemophilia should be raised, and national training programs should be developed. Increasing the knowledge/awareness level of acquired hemophilia will contribute to increase the quality of care and management of acquired hemophilia to international standards.

PO-TU-087
Tailor-made therapeutic education program for hemophilia patients

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Experience has demonstrated the need to structure and implement educational programs for patients with hemophilia; however such a standardized approach has not yet been formalized. We propose a tailor-made educational program for hemophilia patients focused on 3 main topics—knowing, dealing with, and living with hemophilia in daily life—which has been approved by health authorities. We implemented a systematic, innovative, interactive, and collaborative program including a hematologist and a pluridisciplinary team (biologists, pharmacists, nurses, rheumatologists, physiotherapists, rehabilitation specialists, psychologists, social assistants, a Qigong practitioner, and hemophilia patients taken as trainers). Our program contains 8 sessions (6–8 patients) and uses interactive slide kits, educational movies, Metaplan®, patient testimonials, and opens panel discussions. Each session is based on a dynamic, interactive, enjoyable, 1-hour dialogue focused on a specific issue: diagnosis, biology, complications, bleeding, pain management, treatment and drug administration, and daily life with hemophilia. Before and after each session, patients fill out evaluation forms, which are kept for follow-up. Psychological evaluation interviews, adapted sophrology and/or Qigong courses complete the theoretical sessions. In addition, intensive training weekends, which are more specifically addressed toward young patients and their families, are organized 3 times a year. Each patient benefits from a tailor-made, individualized program adapted to his or her physical condition (age, disease, severity, joint health, and so on), knowledge of the disease and its management, and personal needs. The complete programs, specifically recommended to severe patients with poor knowledge about the disease, takes up to 2 months. Evaluation and follow-up of the program and its benefits are organized in parallel. This individual assessment includes the evaluation forms filled out at each theoretical session, which are of particular importance for monitoring and following the level of understanding of the disease and its impact on its daily management, and a satisfaction survey completed at the end of the educational program.

PO-TU-088
Hemophilia knowledge and frequently used and valued information sources: Patient/parent perceptions from the Hero study

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Objectives: To determine patient and parent perceptions of their hemophilia knowledge and identify the information sources they use frequently and value most.
Methods: A web survey was conducted in 10 countries, targeting 600 patients ≥ age 18 and 600 parents of patients <age 18, mostly recruited through patient organizations.
Results: Ninety-three percent of hemophilia patients (552/592) and 96% of parents (482/503) felt very/quite knowledgeable about hemophilia. Compared to hemophilia A/B patients or parents, significantly fewer inhibitor patients (73% versus 96%) and parents (85% versus 97%) felt very/quite knowledgeable. Most patients (76%) and parents (78%) were members of a hemophilia association (including 46% and 57% who attended meetings) or an online support group (41% and 43%). Patients/parents reported their main source of information as the hematologist (76%/85%), hemophilia association (63%/73%), hemophilia websites (49%/52%), hemophilia nurse (44%/56%); these were also the most frequently used by patients/parents (31%/31%; 16%/15%; 12%/12%; 8%/17%). Additional sources of information for patients/parents include other hemophilia patients (42%/52%), meetings (29%/39%), hemophilia treatment centre (HTC)-provided literature (26%/42%), scientific journals (24%/20%), pharmaceutical websites (18%/20%), and literature by pharmaceutical companies (14%/23%). Patients/parents referred to the most used sources less than once every 3 months (22%/23%) or on a monthly basis (17%/20%). The single source patients/parents considered most useful was the hematologist (33%/33%), association (15%/14%), nurse (8%/16%), or websites for hemophilia patients (11%, 9%).
Conclusion: Adult hemophilia patients and parents of pediatric patients are confident in their hemophilia knowledge, seeking information from HTC staff, societies, websites, and scientific journals. Patients and parents coping with the added challenge of inhibitors were less certain of their knowledge.

PO-TU-089
Evaluation of the therapeutic education of 35 patients with hemophilia

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Introduction: Therapeutic education aims to help patients achieve or maintain the skills they need to better manage their lives with hemophilia. As a result, it was one of the

priorities of the multidisciplinary team treatment of hemophilia and bleeding disorders. This national program is structured around 6 monthly workshops for each group session.
Objective: Reduction of bleeding and consumption of anti-hemophilic factor.
Methods: In this study we report the results from therapeutic education of 35 persons with hemophilia and their parents (167 hemophilia patients) formed between May 2009 and June 2011, using: evaluation questionnaires completed by hemophiliacs and their parents before and after training as well as record books of hemophilia care.
Results: Thirty-five persons (22 children and their parents, 13 adults) with hemophilia A; 88.6% exhibiting: severe hemophilia (age range 8 months–36 years). Eighty-three percent followed the training. Knowledge acquisition was considered good in all participants but was better for young children and their parents, as assessed by participants' knowledge on understanding the disease and its complications, mode of transmission, nature and indications of treatment. Seventy-seven percent of adults and 50% of parents (especially parents of very young children who preferred medical assistance) acquired the capacity of self-infusion. This training reduced the consumption of clotting factor concentrate and the frequency of bleeding (10 persons with hemophilia achieved a reduction of 39,500 IU per year and 19.66% of bleedings per year). In addition, the program has strengthened the relationship between caregivers and patients. The direct testimony by patients about the improvement in managing their disease has been recognized as beneficial by the participants and extremely motivating.
Conclusion: The therapeutic education program allowed us to achieve our two goals by reducing the consumption of antihemophilic factor and bleedings for patients who completed the training.

PO-TU-090
Developing the design of an educational game for children with hemophilia

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Introducing the disease and its context to children and teenagers with hemophilia is challenging for parents and health professionals. It is therefore necessary to develop an efficient means of communication that supports them to understand, participate in, and accept questions related to the disease. The purpose of this project is the development of a children's educational game to help them learn more about hemophilia. This development is an integration of information technology and hemophilia care. This work describes the process of the game's design. Children and teenagers, who are the end users of the game will participate in the design development process. This methodology is called "participatory design," and the technique used in this project is the BrainDraw. BrainDraw is a participatory prototyping session where the participants are enrolled in the design process. The first session took place in a hemophilic centre, and 10 children were part of it. All participants were male with severe hemophilia, 90% with hemophilia A and 10% with hemophilia B. They were split into 2 groups: a group of 5 children between 5 and 8 years old (an average age of 6.4 years), and another group of 5 children between 9 and 13 years old (an average age of 10.8 years). The session had 4 rounds and each one had a main topic: hemophilic character, a coagulation factor, the inhibitor, and the setting of the game. In each round, participants were told to draw anything related to the topic. Each one received a blank sheet and switched their papers every 5 minutes. All the sessions were assisted and accompanied by 6 adult observers. This game approach is interesting, because the player can draw what is in his mind without being criticized. The goal is to use the drawings to produce a game closer to what hemophilic children idealize. The most recurrent subjects of the drawings were syringes, ambulances, medals, swimming, swimming pools, and injured knees. All of them will be included at some point in the game.

PO-TU-091
Optimize hemophilia awareness in the emergency room Panama

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The project lies in assessing the knowledge of hemophilia by health personnel, doctors and nurses, who should receive the patient with hemophilia in the Emergency Room and impart knowledge through an Educational Program in hemophilia, which is to achieve greater understanding for better management of Hemophilia and to avoid that they do not receive the treatment they need. An educational program in hemophilia is a necessity in Panama, there is none and offers an excellent tool to the doctor and nurse and the patient achieve and maintain quality of life. The hemophilic moves inland several days a week to specialized centres because the provinces emergency room does not accept apply the factor, because you do not know the disease properly or strategies of therapy and are frightened of order and apply it, even if the patient takes the factor. Doctors and nurses of primary health care centres, are people with hemophilia and to ignorance of the subject, are frightened of not able to solve the problem they decide to move to the capital, to carry their vials of treatment and a recipe for the specialist for the implementation of the deficient factor, the nurse refuses to apply itarea doctor refuses to endorse it and is the patient and his family that they end up losing time, money and health, this chain of doubts and fears. This leads to the need to solve the problem through an educational program and with a well-crafted final product achieve a goal and improve the living conditions of the person with hemophilia

PO-TU-092
Severe bleeding disorder alert cards

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In a country with a recognized network of comprehensive hemophilia treatment centres, expertise can be concentrated in these centres, and management of bleeding disorders can be effectively carried out by these centres in conjunction with home treatment programs. A problem can arise when a patient, in an emergency, has to present to a hospital without a treatment centre. Emergency department staff may not appreciate the importance of infusing with factor concentrates rapidly, and significant delay may result from an insistence on diagnostic imaging or other assessment before treatment is provided. This can lead to a danger of morbidity or mortality, particularly in the case of head injury or trauma. In Ireland, each hospital stocks a limited supply of factor concentrates for emergencies, but delays have been documented in the provision of treatment in emergencies despite the patient being well informed and requesting rapid treatment. The Irish Haemophilia Society has produced a series of Severe Bleeding Disorder Alert Cards for the comprehensive centres. These cards are designed to be carried in the patient's wallet and presented to the doctor, nurse, or triage nurse on arrival at the emergency department in non-treatment-centre hospitals in their catchment area. They instruct the medical staff to immediately contact the relevant comprehensive centre for advice on treatment. Contact details are provided on a 24-hour-a-day basis. The Health Authorities will also be officially informing all hospitals of the cards and instructing them to comply with the instructions.

PO-TU-093
Multidisciplinary formation and treatment in hemophilia: A Mexican pilot project contribution from the health psychology

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The theoretical approach underlying the present work is the psychology of health, which uses the biopsychosocial model consisting of treating the physical, psychological, and emotional interaction of the patient with his family and their environment; in which it is privileged the multidisciplinary work for the integral treating of the patient. One of the lines of research examines chronic diseases, because having a disease of this type requires special care, treatment, information, and support. This line of research includes the study of hemophilia, because of the great impact that it has on people diagnosed with it and the impact that it has on the patient's family. As we have an agreement of collaboration between the Mexican Federation of Hemophilia and UNAM-FES Iztacala, the general objective of this project is to consolidate a multidisciplinary team to address systematically and holistically the biopsychosocial issues faced by hemophilia patients, their families, and health personnel. The project targets 3 populations: (1) university professors (FES Iztacala), (2) university students (students of all professions), and (3) patients with hemophilia and their families. The specific objective is to provide teachers and students with systematic and updated training in the integral management of patients with hemophilia. The knowledge gained will be applied in brigades and workshops and used in the production of scientific texts (manuals, articles, etc.). The objective with the patients and their environment (families, schools, hemophilia associations, etc.) will be to train and support the biopsychosocial management of issues arising from their disease, and improving and/or maintaining their quality of life. The instruments that will be used for data collection are the A36 Hemophilia QoL and clinical reports of each specialty, which will allow the statistical comparison of the levels of quality of life perceived by patients, families, and professionals, before and after interventions.

PO-TU-094
"Don't Push Your Luck!" Board game for children's decision making in their hemophilia care

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The purpose of this board game is to help children strengthen their role as partners in hemophilia care by exploring typical life scenarios and requisite decision-making skills. This game is for children with hemophilia (ages 8 and up), families, friends, and caregivers. The game is based on study recommendations on how children understand their role in family-centred care of their bleeding disorder (Pritchard, 2008). The game design is evidence-based, developmentally appropriate, and uses active learning principles, while reflecting children's vision to create a resource that is colourful and fun. Key features of the board game include qualities required for child and family-centred teamwork; critical thinking steps, including reflecting on actions and consequences; and scenarios representing typical life experiences based on quality-of-life indicators. Players explore their everyday life choices, while trying to meet their best interest to be healthy and balanced in 4 key areas: physical (my body); emotional (my feelings); social (my friends and family); and mental (my smarts). This game is developed in collaboration with designers from the Game Artisans of Canada who specialize in "Euro games." Euro games are different from traditional roll-and-move games; instead, this type of game play emphasizes working through challenges, making decisions, and exploring consequences in a fun manner. This encourages open-ended inquiry to consider options, while engaging all players until the end of the game. Prototype testing results with targeted focus groups indicate that this board game is enjoyable and effective in creating meaningful conversations. The first edition of the board game has a targeted availability for Canadian hemophilia treatment centres by fall 2012. This project is funded through an unrestricted grant from Bayer.

PO-TU-095
Hemophilia: Teaching program at the University of Valencia (Spain)

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The concept of hemophilia, the severity of clinical manifestations and disease problems, health problems, social problems, and economic problems—all of these represent the universe of ignorance inhabited by many people, including some government officials. This lack of training and information also affects the medical community. Since 1983, the University of Valencia has devoted resources to training in this pathology. Specifi-

cally, the department of physiotherapy annually offers a subject (diagnosis and treatment of the coagulopathies), 2 credits (20 hours) of free choice. Training has been conducted continuously each academic year until 2011. From the academic year 2011–12, at the Faculty of Physiotherapy at the University of Valencia, the new curriculum (Bologna Process) for a degree in physiotherapy includes the study of hemophilia in third year: Clinical Physical Therapy Specialties. The aim of this paper is the description of the teaching guide. In summary, the course guides students in learning how to evaluate and treat coagulation disorders (with special attention to hemophilia). No prior knowledge of the disease is required and there are no restrictions to admittance to the course. The resulting competencies are knowledge of clinical practice guidelines, evaluation of injuries, treatment planning objectives, and evaluating and reporting results. The course contents include an overview of the coagulopathies, with a focus on common musculoskeletal injuries in the hemophilic patient; diagnosis; evaluation; and treatment. The classroom activities include theory and practice in the laboratory (biomechanics, gym, pool, ultrasound, orthopedic clinics, and so on). The course also includes practice in the hospital, in the hemostasis and thrombosis unit, and the development of individual activities, in which qualification is assessed by a tutor, is mandatory. The final evaluation includes a theoretical exam and a practical test to ensure that the student possesses the ability to diagnose and aid in the functional recovery of common musculoskeletal injuries in the hemophilic patient.

PO-TU-096
The development of a tool to assist patients in identifying health care coverage: Personal health insurance toolkit

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Objective: Choosing a source of healthcare coverage is one of the most difficult, yet important decisions, an individual with a bleeding disorder must make. The process is often time-consuming and confusing. Historically, coverage options for those with bleeding disorders in the U.S. have been limited to state or federal programs or commercial group plans offered through an employer. Approximately 61% of individuals with bleeding disorders in the U.S. receive their healthcare coverage through an employer-sponsored plan. Through individual conversations with patients at chapter educational events, it was discovered that patients did not have a full understanding of the complexities of healthcare coverage.
Methods: An online survey of people with bleeding disorders and of caregivers was designed to assess knowledge of their current healthcare coverage. Questions included their perceptions of access to hemophilia specialists, treatment therapies, out-of-pocket costs, and delivery of factor products.
Results: A total of 147 surveys were completed; 49% were affected individuals 18 and older, and 51% were caregivers. Of these respondents, 80% were receiving treatment at a hemophilia treatment centre and 50% were treated prophylactically. Results indicated that while most respondents were aware of coverage related to treatment of their disorder, they were less aware of the plan's full range of benefits and the out-of-pocket costs associated with their plan. Several patients indicated a thorough review of each plan had not been completed prior to their making a decision on coverage and cited difficulty in the navigation of plan documents as a reason. Therefore, there is a need to educate patients with bleeding disorders about healthcare coverage options and how to evaluate which plan design best covers their needs.
Conclusion: A toolkit was designed containing a glossary of healthcare terms, a plan-comparison guide, a cost-comparison worksheet, and a personal experience fact sheet. The toolkit was shared with local advocacy organizations and their members as well as hemophilia treatment centre social workers. The toolkit was recently approved and adopted by several national chronic disease patient advocacy organizations for use within their patient communities.

PO-TU-097
Pedagogical practices with the use of informatics resources for people with hemophilia

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This work presents the implementation of a pioneer educational project - the use of informatics as a resource and learning tool for social insert, which was established in 2008. Centro dos Hemofilicos do Estado de Sao Paulo – CHESP is a non-governmental organization – NGO, on behalf of the health of people who have Hemophilia and Von Willebrand Disease. It is located in São Paulo – Brazil. This service seeks to reduce the difficulties faced by people who live with hemophilia associated with problems resulting from the low social and economical levels, which is characteristic to developing countries. Aiming at the well being and improvement of the quality of life, CHESP offers a differentiated care in the educational area, using informatics as a tool and introducing a pedagogue in the multiprofessional team. The work proposal is divided in two areas: Pedagogical follow-up for children in basic education period; Professional education for youngsters and adults, also including family/companions; In order to participate in the course, the student is submitted to an evaluation of the knowledge about informatics, which will determine the appropriate level for him. The objective of the course on technical Informatics and pedagogical Informatics is to provide hemophilic participants an opportunity of professional, educational and personal growth, because the knowledge obtained will be as much valid for their participation in society as for their family life, using computers in a conscious and safe way at home, school or work. At each step or level attained, students become capable of developing quality and creativity in their work, stirring up not only their cognitive but also their affective capacity as for the effort and dedication invested in learning will be valuable for the various aspects of their lives. The work with pedagogical informatics at Chesp is still in development and improvement process, always looking for new sources, researches and methodologies in order to enable these students to use new technologies.

PO-TU-098
Learning about hemophilia at school

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Introduction: At 1most schools there is no information about hemophilia, as schools rarely have pupils suffering from this disease. When hemophilic children go to school for the first time, their parents face a big challenge, as sending their child to school presents more risk. There, the children are without the surveillance and care of the adult family members. Our work is intended to help children with hemophilia enter and remain at school, just the same as any other children their age. There is a need to inform and train their schoolmates and the school staff about what hemophilia is and to address the most important aspects of caring, the risks, and how to act in case a child suffers any knocks or blows, etc.
Objective: To contribute to the psychosocial development of children with hemophilia at school, by means of raising awareness in schoolmates and other educational figures about hemophilia.
Material and Method: Awareness workshops were carried out at schools in the province of Salta, in the capital city and surrounding areas of the province where hemophilic children attend. These workshops were intended for principals, teachers, and pupils. Brochures and PowerPoint presentations were produced. The proposed methodology was flexible, in order to adjust it to each school and each age group. To attend these workshops, the consent of every child and his or her parents (if they were under age 12) was required.
Results: The foundation is caring for 30 school-aged pupils, who are distributed over 25 schools within the capital city of the province of Salta and surrounding areas. A total of 14 schools were trained. Only 1 adolescent did not accept the workshop at his / her school.

SCHOOL	DATE	TEACHERS	PUPILS	Patients with hemophilia
Fray Honorato Pistoia	08/25/2011	2	18	1
Niño Jesús de Praga	08/31/2011	4	70	2
P. de MElo. El Carril	09/27/2011	3	25	1
Campaña del Desierto	09/29/2011	2	16	1
S. Catalina. Tartagal	10/06/2011	8	68	2
Ed. Técnica. Tartagal	10/06/2011	3	15	1
L. M. Pretti. Tartagal	10/06/2011	2	27	1
M. A. Castro	10/11/2011	3	49	1
M. A. Castro. T. Noche	10/12/2011	9	79	1
E. Hogar. C. Puch	11/03/2011	4	36	2
Jesús Miguel Reyes	11/14/2011	6	49	1
Gendarmería Nacional	11/23/2011	2	28	1
C. F. Perdiguero	12/05/2011	1	19	1
C. Santísima Trinidad	12/13/2011	23	-	1
Total	**14**	**72**	**499**	**17**

Conclusions: By means of the workshops, an interesting exchange and greater rapport was gained between school staff, pupils, and the foundation. The teachers were able to have their questions answered with respect to hemophilia, and this knowledge could then replace the fears that appear when a pupil with this disease attends the school. Pupils became more familiar with hemophilia and could tell people at home what they had learned during the workshops; this is also helpful in alerting other people about this disease who might later learn that they are suffering from it.

PO-TU-099
Continuing education program in hemophilia: Touching base by getting all professionals together

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Brazil is the largest South American country, and there are approximately 12,000 patients with inherited bleeding disorders registered. Due to the sociocultural diversity of the country, continuing education programs are fundamental in improving patients' quality of life by increasing the number of professionals involved in the patients' care. In 2009 a multidisciplinary program in continuing education was organized to promote the unique experience of professionals involved in hemophilia care getting together and discussing it, facing the characteristics of each region of the country. A joint committee of hematologists, orthopedics, physiotherapists, psychologists, social workers, nurses, laboratory technicians, and dentists was organized. The Brazilian Federation of Haemophilia and Novo Nordisk Brazil supported the project. Professionals from each region of the country were selected to attend the meeting. They were divided by area of speciality for particular discussions of related topics. After that, all the professionals got together

for discussion of a prepared clinical case, simulating the day-by-day clinical multiprofessional approach. Since 2009, 300 professionals of all correlated areas have participated in the project. From this group, 25 dentists attended the meeting and contributed to the development of 2 educational materials, one designed for professionals and one for patients. For the professionals, the material was made according to Brazilian Manual of Dental Care for Patients with Hereditary Coagulopathies. For the patients, it focused on simple every-day questions, and it was addressed to parents of children under 2 years old, to teenagers, and to other to adults. This material was distributed in all hemophilia treatment centres in the country. The objective of this work was to demonstrate the feasibility of organizing a multidisciplinary educational program in hemophilia care and to present its results. Supported by Novo Nordisk Brazil.

PO-TU-100
Helping boys to learn hemophilia self-management
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Introduction: In the Netherlands, most patients with severe hemophilia treat themselves at home. At the van Creveldkliniek, most boys learn to self-infuse from the age of 10 years. The learning process has a practical and a theoretical component followed by an exam. Most boys do not need a lot of time to learn to self-infuse, which limits the time to discuss the theory. Evaluation among our boys showed that they know everything about preparing and administration of the clotting factor, but their knowledge of hemophilia is limited to their own experience only, and they lack self-management skills. However this is the only formal test of their knowledge. So how can we be sure that our boys are able to manage their hemophilia?
Methods: A literature search for reviews January 15, 2012, using the keywords ''chronic disease,'' ''patient education,'' and ''self-management'' yielded 88 articles in PubMed and 10 in Cochrane library.
Results & Conclusion: unknown yet
If no leads are found, the education will have to be developed based on the facts a few of our boys expressed in interviews: developing a new learning protocol with 3 different education parts: self-infusion, knowledge of hemophilia, and self-management skill training; spreading the learning process over a longer time period; incorporating the self-efficacy theory of Bandura into the protocol; making possible more peer or slightly older contact.

PO-TU-101
New teaching strategy: ''Educational Manual of Hemophilia and von Willebrand for Parents and Patients'' in Panama
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The accumulated personal experience of more than 10 years in the daily care of parents and children with hemophilia and von Willebrand disease, in the clinic of congenital coagulopathies in the Hospital del Niño (Children's Hospital), has made it possible to offer a practical tool for the education of parents, as a reference about the disease and all the basics. It has been a very interesting experience, because for its realization the educational needs of parents were identified; as well as, the manual is very useful as new teaching strategy within the care clinic. It is the first comprehensive manual for parents, based on their learning requirements that contribute to improving knowledge maintaining continuous learning, and ensuring that children can achieve greater physical, emotional, and social adaptation to the disease. The manual on hemophilia and von Willebrand promotes the self-care of children and their parents integral to the management of congenital hemorrhagic disease. It consists of 7 chapters with accurate and adequate information to contribute to the knowledge of patients and their parents. It contains practical objectives for each chapter and ends with relevant conclusions and questions to assess the acquired learning. The educational manual contributes to the formation of independent reasoning and necessary skills to cope with critical situations through the life of the person with hemophilia and their parents.

PO-TU-102
Development of an educational tool for hemophiliacs: Advice of the pharmacist
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Hemophiliacs need a good level of knowledge of their disease and related medication to optimize and secure self-management. For this purpose, we created a brochure aimed at giving a comprehensive approach of the mechanisms of the disease and the mode of action of therapeutics. This brochure was elaborated by a multidisciplinary team including pharmacists, hematologists, nurses, patients, and relatives, in accordance with the French Health Authority's guidelines (HAS). The brochure contains (1) a brief presentation of the disease: definitions, physiopathology, inheritability, symptoms, severity, complications; (2) treatment goals and therapeutic strategies: prophylactic and on-demand regimens; (3) characteristics of plasmatic and recombinant products; (4) practical advice: how to store, prepare, and infuse antihemophilic factors; (5) a focus on tracing medication: update of the consumption; (6) recommendations on vaccinations; (7) information on the importance of the ''hemophiliac leaflet'' and the ''hemophilic health record''; (8) first aid kit information; (9) travel advice for persons with hemophilia; (10) a list of prohibited drugs; (11) precautionary measures for medical, contra-indicated measures, and caution; (12) information on the collection of waste products; (13) a list of hospital pharmacies that dispense blood clotting factors for home use and hemophilia treatment centres. The brochure will be given by the pharmacist during a dedicated talk. This approach is part of the educational program of the Centre de Competence Multisite Grand Est comprised of 4 university hospitals: Dijon, Reims, Nancy, and Besançon.

13-ELECTRONIC COMMUNICATIONS IN HEMOPHILIA

S-TU-03.3-1
E-communications to patients, for patients
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With an ease of availability of tablets and smartphones, the whole world is now living in the revolutionary era of social networks. Facebook alone has more than one billion active accounts. Facebook is one of the various types of electronic communications that ensures that you can break through the clutter and get your message across cost effectively. It can allow patients to plug into an existing audience of organizations that have opted into similar interest groups. It can also help patients' organizations collaborate, connect easily, and increase their network of volunteers and supporters via televised pictures, conversations, graphics, circuits, and interactive software. In addition, the event-posting capabilities allow organizations to advertise upcoming events easily and efficiently. Facebook can be a critical tool for patients to communicate with other patients or medical supporters, because it is a great way to connect with others who might not have known about your background. Almost all technologies in this world have their pros and cons. Similarly, there exist advantages and disadvantages of electronic communication as well. The main issue with electronic communication is security and privacy. We cannot deny that social media will continue to grow and eventually become a source where a growing majority can research their health. It underscores the responsibility of health professionals to educate patients to critically question what they read online. In-spite of its disadvantages, most of us depend on electronic communication for our everyday work, as it has become an integral part of our lives.

S-TU-03.3-2
Patient and family blogs
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It is an empowering experience to publish your writing as a blog to a global audience. Receiving comments on your blog can reaffirm that you aren't alone in your life's journey. A compelling story can be posted on a personal blog site, which may promote better understanding of a topic, and even motivate others toward support for change. Writing, like talking, has been found to be a healing experience according to a 2002 UCLA study by Dr. Shelley E. Taylor et al. entitled "A Female Response to Stress: Tend and Befriend, Not Fight or Flight." Understanding how you can combine personal blogs and group blogs together can help to build a community. MyGirlsBlood, an international social network of women with bleeding disorders manages a website that includes the links to the personal blogsites of their community members. They also host a MyGirlsBlood group blogsite, which is a collection of writings contributed from various members of their community. There are easy to use, online tools to develop personal blogsites. Some are free of charge. Proficiency is gained as a blogger embellishes their writings with graphics and photos. A blogger gains a sense of accomplishment by sharing their blogsite with others and increasing their reader base. A blogger must remember that anyone can read their blog. This means that others (including your employer, relatives, strangers, or governmental officials) may read your blog. Be careful to respect the copyright of others. Speak from your personal experience and opinions only, and maintain the privacy of others (such as family members or healthcare providers), unless you have their permission to use their names. Before setting up your site, take time to search the Internet for helpful rules to blog safely.

S-TU-03.3-4
E-communications for lobbying
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The use of websites and online media actively engage members of the NMO and go beyond simply providing information. Can online tools be used to help more members participate in the work of the NMO? Over the last few years the U.K. Haemophilia Society has consolidated its websites and expanded the use of Facebook and Twitter. Despite the organizational risks involved, NMOs must take the opportunity to reconnect with socially or geographically isolated members and give them the opportunity to become actively involved. As increasing numbers of people with bleeding disorders have access to treatment delivered to their home, the chances of meeting other people in a similar situation at the hemophilia centre are reduced. The challenge facing NMOs is how to use the Internet to replace this traditional way of providing mutual support. Website, social media, and email can also allow an NMO to react extremely fast to political or media developments without spending large amounts of money. In particular, we must focus on the follow learning points for NMOs: involving members in website design and layout; achieving the necessary cultural change in the NMO; using a website to campaign, advocate, and lobby; providing online meeting places including Facebook; determining whether it is better to monitor one large online meeting place or lots of smaller sites; using the internet to take media opportunities.

S-TU-03.3-3
Internet social network: Our new communication breakthrough
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The Indonesian Hemophilia Society (IHS) was founded in 2004 and has a total of 14 chapters throughout Indonesia. The IHS's commitment is to build good communication between patients and healthcare staff and to ensure that the government of the Republic of Indonesia builds sustainable hemophilia treatment in Indonesia. For these reasons, the IHS aims for good communication between chapters and patients. When it comes to advocating with the government and others, all information is useful. Unfortunately, within the Society, communication has sometimes been a problem because, at times, we only communicate within certain chapters and among staff, thereby getting less information from members. For some reason, getting detailed and updated information has been viewed as an obstacle. The solution appeared in 2009 when social networking boomed in Indonesia. Many Indonesians now have the Internet. We see this as an opportunity both to spread information widely and also to get information through websites, email, and social networking. Because our main goal is to give and get detailed information, we see that social networking sites, especially Facebook, could become a useful tool. Recently, in Indonesia, almost every cellular phone and computer comes equipped with social network applications, making it easier to communicate with members and to get information directly. Social networks have other advantages as well: They can be updated in real time and patients can use them as a discussion room with other members, doctors, board members, and even with foreign patients. Moreover, new patients can be provided with information and others can be encouraged to share their stories or display photos. For the organization, our efforts can be displayed online and can be used as motivational tools to convince members to participate in all of our programs, which will help to establish the kind of comprehensive treatment plan that we are all dreaming of.

PO-TU-106
Use of Short Message Service (SMS) to document bleeding episodes in children with hemophilia
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Introduction: The increasing emphasis on home-based treatment for the management of children with hemophilia has meant that it is difficult to report the incidence of bleeding episodes and efficacy of treatment, as these children no longer regularly report to a medical facility. The aim of this study was to assess the feasibility of using a short message service (SMS) to record bleeding episodes in children with hemophilia.
Methods: One hundred four children with moderate and severe hemophilia A or B were recruited from the 3 eastern states of Australia to take part in a 1-year prospective study between 2008 and 2010. Children or their parents received a weekly SMS, via their mobile telephone, asking if they had had a bleeding episode in the preceding week. Response rates were calculated. Back-up reporting methods in the form of a toll-free telephone number and bleeding diaries were used. Positive responses were followed up with a telephone call to gain more information about the bleeding episode.
Results: Children were followed for a total of 4,839 person-weeks with SMS replies received for 4,201 weeks (86.8% follow-up). Median responses rates were 94.2% (IQR 86.1%–100%). Telephone interviews were conducted for 327 of the 336 study bleeding episodes (97.3%).
Conclusion: Weekly SMS is a feasible reporting tool for documenting bleeding episodes in children with hemophilia, at least when used in a research context. It is associated with high response rates and minimal expense and intrusion. The use of SMS could also be extended to encourage compliance to prophylactic treatment, particularly in adolescents with hemophilia.

PO-TU-107
Blood 4: A blog to cope with hemophilia with the use of images
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In 2008, I decided to create Blood4, a blog from the perspective of a psychologist working with people with hemophilia. To blog is to share information by posting articles appearing in reverse chronological order and requires interaction with your visitors, who leave messages, comments, or questions. In the past 4 years, Blood4 contributed to making hemophilia more well-known and provided people with hemophilia easy access to information and an exchange of experiences in coping with a chronic bleeding disorder.
Method: Short texts about topics related to hemophilia are written by the author in 2 languages, English and Portuguese, and sometimes in French or Spanish as well. The focus of the topics is hemophilia: from the simple definition to several medical and psychosocial aspects of living with the chronic condition. The use of images along with the text is a must. That way, children are also interested in looking at flashcards, photographs of other kids and of animals, and paintings and drawings that show experiences of coping with hemophilia and living life normally and also show symbolic aspects of bleeding and blood. Tags and categories can orient the visitor to choose topics of his interest. The blog is a space for reflections of different aspects of living with hemophilia and also an opportunity to work as a psychologist who believes in different ways of communication, education, and well-being.
Results: Blood4's first objective was to share a project I did called Hemoaction: playing and learning about hemophilia. The Hemoaction flashcards were quickly accessed on the web. In 2009, the WFH adopted it as an official educational tool, and it has been translated into 5 languages and distributed around the world. Mixing images with short texts is a way to communicate, in a joyful way, serious and important topics for the community involved in hemophilia care.

PO-TU-108
Remote control: Is it enough?
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The Children's Queensland Haemophilia Centre (QHC) is based at the Royal Children's Hospital (RCH) in Brisbane, Australia. The centre provides a state-wide service which includes the provision of treatment, care, and support by a multidisciplinary team comprised of doctors, a nurse, a physiotherapist, and a psychologist. All children with inherited bleeding disorders who live in Queensland or Northern NSW are registered at the QHC. Because of the geographical diversity of families accessing the services of the centre, regular outreach clinics have been developed to provide face-to-face contact for families in their local hospital settings at various regions in Queensland. In a new initiative, the QHC also provides regular telehealth services to families living in the regions of Rockhampton, Townsville, Mackay, Cairns, and Hervey Bay. Telehealth clinics function in a similar fashion to face-to-face clinical consultations. When there is a need for a physical review, modern technology allows the camera to zoom as required, to closer view any region of the body, providing clear images for the medical team. Six to 8 telehealth clinics are conducted yearly. This service has been utilized by at least 20 families, with an increasing demand of this service observed. The partnership between the RCH and regional hospitals reaps benefits in many ways. Patients benefit from having access to regular clinic reviews at their local hospitals at a lower financial cost and greater time efficiency compared to overall costs and implications of regular visits to the RCH in Brisbane. Medical teams across both the RCH and regional hospitals are able to discuss each case as required, thus augmenting communication between both teams. To enhance clinical practice and ascertain patient satisfaction, a survey was conducted with families who use the service. Results of the survey would be presented and further recommendations and implications for practice discussed.

PO-TU-109
Using a Smartphone app and medication bar-coding for treatment recording to improve patient safety and reduce treatment costs
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Self-treatment in hemophilia with coagulation factor concentrate (CFC) is central to the management of the condition. However, there have been ongoing issues with this form of treatment, including reconciliation and traceability. These issues arise because completing and returning a manual treatment sheet (diary) is cumbersome, time consuming, and retrospective, which has led to poor compliance. St James's Hospital, Dublin, Ireland has implemented an electronic diary, based on medication bar-coding and a Smartphone app. Patients on home treatment are offered a free smartphone with a specially designed app that is used to capture their usage data and reason for treatment, by simply scanning a 2D (datamatrix) barcode on the CFC box. The app was designed in conjunction with a patient focus group and after being piloted by 18 patients initially; 75 patients now use the app to record their CFC usage in the home. Before the patient self-infuses, he launches the app, which then takes him through a number of intuitive screens. Once the patient scans the barcode on the medication box, 3 safety checks take place. Firstly, the name of the CFC is compared with their prescribed treatment, secondly the expiry date is checked, and finally the product is checked against a recall list. If any of these checks fail the patient gets an audible and visual alert, and the treatment centre is also alerted via email. Results show that the app is user friendly, and compliance for patients using the app is almost 100%. This project demonstrates that technology already exists that can improve patient safety, increase compliance, and provide higher-quality data Real-time visibility of patient usage data has also allowed the treatment centres to control costs by alerting patients to incidents of potential overtreatment and to offer clinical reviews to patients who have recorded unexpected or high risk bleeds.

PO-TU-110
The world of hemophilia: "Everybody Intercommunicated"
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Fundación de la Hemofilia de Salta, Argentina

Introduction: The Foundation for Hemophilia in Salta has a group of teenagers that meets periodically to relate and share experiences. In July 2011, together with management and the professionals of the foundation, they started a project named "everybody communicated." Those patients with from hemophilia are aware of their pathology to a greater or lesser extent. Therefore it is necessary to foster contact among individuals with this disease, their relatives, institutions, and the like, to learn about the reality of each of them and to promote mutual help. Objectives: To create a social network so that people with hemophilia, their families, foundations, organizations, and health professionals specializing in hemophilia get to know, communicate with, and help each other.
Material and Method: A Facebook account named "Hemophilia Argentina" was created to spread the knowledge about the existence of the Foundation of Hemophilia in Salta, and begin communication among the patients with this disease throughout the world. Each contact was sent a file (English/Spanish) requesting full name, email, address, and country, inquiring if they had within their reach any foundation or organization and if they wished to have a network of communication. All links established were supervised and supported by the Foundation of Hemophilia of Salta.
Results: Communication was established with 17 countries: Brazil, Nicaragua, Jamaica, Colombia, Venezuela, Chile, Uruguay, México, Perú, Dominican Republic, U.S.A., India, Japan, Spain, France, Vietnam, and Argentina. A total of 894 patients with hemophilia A, B, and von Willebrand disease were contacted as well as 98 organizations. Most of them knew of the existence of the institution in their own countries and all of them were interested in intercommunication and contact through this means. By December 2011, 570 friendships had been made on Facebook.
Conclusion: The response has been positive, showing a great interest from all those concerned. The main difficulty lies in language and Internet resources, which must be taken into account to optimize the scheduled activities. Lack of or faulty communication leads to a state of ignorance and shortage of resources. We strongly believe that this new kind of communication could reverse the former situation.

PO-TU-111
Social network for girls and women with bleeding disorders
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Women with bleeding disorders (WWBD) are underserved and geographically dispersed within our global bleeding disorder community. They deserve a support system to become better educated and empowered. Women themselves may not realize that they have a bleeding disorder because of the pervasive stereotype that only men can have hemophilia, and that hemophilia is the only type of bleeding disorder. WWBD often feel alone and helpless. Many have never met another woman with a bleeding disorder and may be unaware that they have shared experiences with women around the world. MyGirlsBlood (www.mygirlsblood.org), a nonprofit social network, was established in 2009. As of October 2011, there were 327 unique visitors to the website from 9 countries—Austria, Canada, Germany, India, Iran, Israel, Philippines, the U.K. and the U.S.A.—and growing each month. Personal stories written by WWBD are published on the website. There is also free assistance to WWBD from a writing coach and editor. The MyGirlsBlood Facebook site has attracted over 175 WWBD from nearly 20 countries. A Twitter feed announces new stories and information of interest to our community of WWBD. The MyGirlsBlood group blogsite, as of the end of 2011, had 26 blogs from 10 different women. The MyGirlsBlood website provides links to WWBD personal blogsites. Women are empowered when they share ideas with other women who also have bleeding disorders. Women become affirmed through this forum by sharing personal life stories. They dialogue and provide mutual support and mentoring with other WWBD. They encourage each other to participate in maximum health and wellness through online conversations. A WWBD no longer has to feel alone. She can become an active participant in her own medical decisions. She can become better informed by connecting with other WWBD using the MyGirlsBlood online social network.

PO-TU-112
Implementation of an online home treatment record-keeping system (Haemtrack) in a large London comprehensive care centre
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The Royal London Haemophilia Comprehensive Care Centre has 1,248 registered patients with inherited bleeding disorders of all severities. Eighty patients have their concentrate delivered to their home, enabling self-administered prophylaxis. Traditional record keeping of home-infused concentrate dose, timing, batch number, and indication (prophylaxis versus bleed or trauma) was all previously paper based. Haemtrack is a bespoke, online self-reporting software package developed by MDSAS for the U.K. Haemophilia Centres Doctors Organisation. Haemtrack is interfaced with the U.K. HCIS database used by many U.K. hemophilia centres, which in turn is interfaced with the U.K. National Haemophilia Database. Patient use of Haemtrack to return infusion data removes a time-consuming manual step of staff transposing data from paper copy to the HCIS computer system, avoiding the inherent risks of transcription errors. We made the decision to implement Haemtrack at our centre in January 2011, aiming for 50 of the 80 home treatment patients to be registered and utilizing the software within one year. Patients were informed of the opportunity to use Haemtrack by letter and at review clinic appointments. Those who already communicated with the centre by email were approached as first-wave candidates. By end of December 2011, 60 patients had successfully registered and started using Haemtrack. Twenty patients have declined to use it. For those who return electronically with Haemtrack, there is now an opportunity at every clinic appointment to review all infusions, colour-coded for indication of infusion in a more meaningful way. Calendar view and visible timings, with contemporaneous patient comment about circumstances, enable a constructive review, particularly identifying habits that might require addressing (eg., evening dosing) and analysing bleeds relative to time since last infusions. National use of this software has important implications for more accurate and unified data capture.

PO-TU-113
Haemnet: Building on shared experience in hemophilia nursing
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Background: Haemnet (www.haemnet.com) is a secure, social network–based, education and communication tool for health care professionals caring for people with hemophilia and bleeding disorders. The site allows professionals to share knowledge, discuss complex cases, keep up to date with news, form research-based collaborations, and conduct online surveys. The site is supported by the U.K. Haemophilia Nurses' Association (HNA), which seeks to raise professional standards in clinical practice and has previously developed a core competency framework for nursing professionals in hemophilia. Haemnet contains an online version of this framework, which allows nurses to assess their own level of professional development and identify the areas in which they need to develop skills. Haemnet has been developed by an independent agency and has secured multi-company funding from companies working in the pharmaceutical sector.
Findings: Registration to the site is open to all healthcare professionals who manage people with hemophilia and other bleeding disorders. By January 2012, 130 healthcare professionals were registered as members of Haemnet. Most are hemophilia nurses, nurse

specialists, and nurse consultants covering a wide geographical spread mainly across the U.K., Europe, and Australia. A wide range of conversation topics relevant to patient care and professional development have been initiated, including management of patients' inhibitors to coagulation factors; transition of children to adult services; use of joint scores by physiotherapists; the need for hepatitis vaccination; anaphylaxis policies in newly diagnosed children with hemophilia B; use of antidepressants and their impact on bleeding patterns.

Discussion: Haemnet offers a valuable learning and communication opportunity for healthcare professionals. Peer support is being established through online forums, and ideas and experiences are being shared. The distribution of site members suggests that Haemnet has the potential to support healthcare professionals in smaller hospitals away from the major cities where hemophilia treatment centres tend to be located.

PO-TU-114

Role of Telemedicine in managing bleeding disorders in rural Pakistan

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Bleeding disorders are poorly understood and managed. This is due to not only the low number of clinical hematologists in the country but also lack of awareness among healthcare professionals working in rural areas. Pakistan's ministry of information technology launched its Health Net Project in November 2007. This project was funded by the Federal Ministry of Information Technology for 3 years, with commitments from the provincial governments of Punjab and Sindh to continue and bear the cost of recurring expenditures. The project demonstrated the use of technology as a solution for overcoming the lack of quality healthcare infrastructure in rural or remote areas of Pakistan. The objective was achieved through setting up telemedicine hubs in tertiary care centres connected via PAKSAT-1 to 4 telemedicine centres in rural hospitals, and by utilizing and complementing available national resources and infrastructure. A total of 15 satellite-based telemedicine centres were established in Punjab and Sindh provinces. The three hubs are the tertiary care centres at Holy Family Hospital, Rawalpindi; Mayo Hospital, Lahore, Punjab Province; and Jinnah Postgraduate Medical Centre, Karachi, Sindh. All these centres are equipped with telemedicine peripherals to facilitate teleconsultations in various specialties. These have been providing teleconsultations to their remote catchment areas. Hematology has now been added to otolaryngology, dermatology, and surgical specialties such as orthopedics. The initiative includes continued medical education programs for health care professionals working in district and tehsil hospitals, and provides teleconsultations for new patients and follow-up for registered patients of hemophilia treatment centres.

14-FAMILY DYNAMICS

S-TH-01.2-3
Psychosocial issues in sexuality
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Background: As our youth are maturing and transitioning into adults, so are the challenges that go with it. For these young adults, there is an interest in sexual expression, understanding their own sexuality and how it relates to others, especially in the realm of dating and relationships. Navigating through sexuality can be difficult and cause emotional stress. There are pressures to conform and fit in. Having a bleeding disorder only adds to that pressure and presents its own set of issues. Taking into account cultural sensitivities, religious beliefs, and cultural taboos around the topic of sex, this session will provide a platform for viewing these issues on sexuality and hopefully provide some insight and tools for understanding and support. As with any sensitive topic, we each have to look at ourselves in terms of limits, judgments, and how open and available we can be in understanding sexual issues/challenges as they relate to today's world. This session will be presented with the greatest amount of respect as we work with this sensitive topic. Please use your own judgment as to your willingness to attend and hear information with sexual content.
Content: This session will define sexuality. We will identify sexual challenges that are present with young adults today in the bleeding disorders community from a global perspective. We will explore finding a balance between family, culture, beliefs, and growing up in today's world as a young adult. We will discuss the psychosocial challenges from the perspective of how to work with these issues and identify supportive outcomes as our young adults mature into adult men and women.
Conclusion: Looking at sensitive issues like sexuality will provide a better opportunity for success in navigating through these challenges by asking questions and exploring options that fit each person's needs. We can help our young adults navigate through this time of self-awareness, relationships, and transition with the least amount of social trauma and emotional stress by being willing to listen and understand their positions. For those of us who are "mature adults" now, we have faced these same challenges and hold a greater opportunity for providing support by remembering what it was like then, and by recognizing that they are growing up in a different time.

S-WE-01.3-3
Family perspective and support
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The aim for my talk during congress will be the impact of hemophilia on the family, with a particular focus on a sibling's perspective. My starting point will be to inform the audience of the content of my presentation and to give a little background information regarding me and my family. As a mother of a young adult with hemophilia, also a carrier, there is a long history of hemophilia in our family, ranging from uncles, cousins, and brother—all with severe hemophilia A. I will map the early years of growing up in a family that had many affected by the disorder, and how it had very little impact on me personally at a young age. I will discuss things like family holidays and my understanding and perspective at that stage versus the perspective of some of my older siblings. I will then focus on the teenage years, during the late 80s to the mid-90s, and how and why it then began to have a major impact. This was a very turbulent time for my family and me, and it is only now, as an adult, that I fully understand the impact it had. A lot of changes occurred within the family at this point and the ripples and effects have carried forward to this day. I would like to cover some of the physiological impacts and how the need for secrecy/confidentiality caused a great deal of stress and strain. The last part of my presentation will focus on the growth, change, and, in some part, the healing that has taken place within the family. Although a lot of damage has occurred and can never be undone, I feel it has led to excellent treatment and a brighter positive future has emerged.

S-WE-01.3-2
Maximizing the health of boys with hemophilia
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The clinical impact of severely compromised hemostasis in hemophilia is present from an early age, and there is no curative treatment that can avoid it. This condition leads to numerous complications. The first challenge is the delivery of an affected infant. Vaginal delivery is recommended with avoidance of vacuum extraction and forceps. Incidence of intracranial hemorrhage is low and occurs in 2–4% of newborns with hemophilia due to birth trauma, irrespective of the mode of delivery. The majority of people with hemophilia do not bleed in the newborn period. A neonate or infant presenting with bleeding should have laboratory investigation for coagulation disorder. The problem in diagnosis is a combination of limited clinical awareness and inadequate laboratory facilities. The immunization of people with hemophilia carries the risk of hematoma formation at the vaccination site. Most vaccinations can be given subcutaneously, and this should be the preferred route. Routine childhood vaccinations should be given at the appropriate time. All patients with bleeding disorders should be vaccinated against hepatitis A and B. Most patients will experience their first joint bleed during the second year of life. During early childhood, it tends to occur 2 to 3 times per month. Rapid control of the bleeding is the key for reducing bleeding complications. If joint bleeding is not adequately treated, it tends to recur, moving into a vicious circle that may result in severe joint damage, even prior to age 10. Regular infusion of coagulation factors to people with severe hemophilia as a prophylaxis has been an evolving therapeutic tool for preventing joint damage and disabilities. Adolescence, as a transitional stage of physical and mental development, may influence compliance to treatment. Education and learning about hemophilia may convince teenagers of the values and future benefits of preserving the musculoskeletal system. Appropriate sports activities that enhance coordination, strength, and promote a healthy lifestyle should be encouraged.

S-WE-01.3-1
Effect and impact of bleedings disorders on the individual and the family
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Objective: The aim of this study is to assess the impact of hemophilia on the psyche of the individual and the family; to explore the feelings and emotions experienced by the person with hemophilia and their family members; and to assess the availability of the support systems around them.
Methodology: A self-report questionnaire, in-depth psychological interviews, and focus-group discussion (FGD) were conducted separately with children with hemophilia, their siblings, parents, and a few relatives. The study covered persons with hemophilia in the age group of 8 to 17 years, from two cities in north India. In all, 98 PWH were covered, and 5 FGDs were conducted.
Results: The findings suggest that there is a considerable impact of the disorder on the PWH and their family members. The limited availability of resources and accessibility of services adds to the psychosocial burden on children and their families. The issues highlighted among children and adolescents with hemophilia were more related to pain, education, bodily appearance, relationships, physical movements, career, and starting a family. Families were more concerned with the availability of factor concentrates, stigma, social support, and marriage of their daughters with hemophilia. However, there were differences in the perceptions of individuals and families from both the cities in experiencing the effect of the disorder.
Conclusions: The bleeds leave a long-term impact and reduced activities in the individuals suffering with the disorder and their families. They tend to live with the uncertainty, pressures, and fear that unfolds with each episode of bleeding. Better treatment options with psychological interventions and support networks help them to have a better quality of life.

S-TH-03.6-5
Implementation of an educational and psychosocial support program for families with under-five-year-old(s) with an inherited bleeding disorder
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**Oxford Haemophilia Centre and* †*Play Specialist Department, Children's Hospital, Oxford University Hospitals; and* ‡*Oxfordshire Primary Care Trust., Oxford, U.K.*

Introduction: We will present an educational and psychosocial support program for families with children under five years old with an inherited bleeding disorder, in order to provide an increased knowledge base on the specific bleeding disorder and improve the psychological well-being of the child and family.
Method: Over the past eight years we have held a coffee morning every three months for parents and siblings of under-five-year-olds with an inherited bleeding disorder. Advanced nurse specialists along with play specialists facilitated the group, and medical staff were available should their input be required. Various strategies were employed by both the play and nurse specialists, which included role play, distraction, and desensitization techniques to assist both the child and carers in preparing for the invasive procedures they would experience, because of the treatment they would undergo, as a result of the child having been diagnosed with an inherited bleeding disorder. Parents considering whether or not to have a child with an inherited bleeding disorder also attended to see what is involved today in having a child with hemophilia, and to get first-hand experience from the parents/carers of affected children.
Results: Over the past 8 years, 28 families have attended. These families have become more confident and informed about the condition their child has. Parents/carers have become empowered. The children have been able to accept having blood taken and starting prophylaxis more readily; they are far less stressed by these invasive procedures. This environment also created an opportunity for parents to share experiences with each other, as they see practical examples of prophylactic treatment being given and Port-A-Caths being accessed.
Conclusion: This has proved to be a very worthwhile initiative in supporting and educating these children and their families, siblings included. They look forward to these coffee mornings.

S-WE-01.3-4
How to deal with diagnosis
A. SAYYADEH
Jordon Thalessemia and Hemophilia Society, Amman, Jordan

The diagnosis of hemophilia affects the individual's life and the lives of his or her family members. Psychosocial support from the National Hemophilia Organization, medical and nursing services, professionals, and volunteers is, therefore, necessary and has very positive impacts on helping newly diagnosed patients, carriers, and their families to cope with their new condition. This presentation discusses the experience of the Jordan Hemophilia Society in supporting patients with hemophilia, carriers, and their families to deal with the diagnosis and to adjust their lives and behaviours with the new reality through each stage of the child's life. In order to achieve this goal, the Jordan Hemophilia Society created a mothers group with the objective of contacting and meeting with newly diagnosed patients' families. The main role of the mothers group is to initiate different activities based on a national education plan prepared with the help of health professionals and educators, coagulation laboratories' professionals, and the National Hemo-

philia Society. This plan includes organizing meetings for the newly diagnosed families with experienced mothers, volunteers, and health professionals. These meetings provide the newly diagnosed families with general information and training on hemophilia and its treatment; and they encourage families to express their feelings about the illness, to talk about their conditions, and to face their fears.

S-TH-01.2-2
Coping strategies for young adults with severe bleeding disorders in Iran
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Background: Young adulthood, characterized by life-altering decisions, inevitable changes, and new responsibilities can be a traumatic phase in anyone's life; and having to cope with a severe bleeding disorder only adds to the complications.
Aim: We aim to recognize the unique challenges faced by patients with bleeding disorders during young adulthood and re-emphasize the role that patient support organizations can and should play in easing this transition.
Material and methods: A qualitative study was conducted, which included a series of face-to-face open interviews with 25 patients with severe hemostatic defects in Iran. An interviewer began each segment of the interview with an open-ended question about conditions that required coping during young adulthood, the coping mechanism used by the patient, the figures that helped them through the coping process, and how successful they were in coping with these conditions. Also, participants were asked what could have made the process smoother and less traumatic. The interviews were recorded and the information was categorized to yield applicable results.
Results: The participants, who were between 23 and 37 years of age, included both males and females with a variety of severe bleeding conditions including hemophilia A and B, VWD, rare bleeding disorders, and platelet dysfunctions. The patients' concerns were categorized into 4 categories: receiving adequate treatment and its effects on daily life, marriage and love life, employment, and miscellaneous. Different mechanisms were named by patients in their coping process, while parents, siblings, social workers, and others were mentioned as influential figures during this time. Providing adequate treatment was the most frequently mentioned expectation from a support organization, while other social-support options were ranked lower on the list.
Conclusions: Patient support organizations can help ease the transition into adulthood for patients with severe hemostatic conditions by ensuring adequate treatment and providing social support during their late teens through early adulthood.

S-TH-01.2-4
Step-by-step decisions: Career choices and employment challenges
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As individuals with inherited bleeding disorders transition to adulthood they will encounter difficult challenges and choices. Decisions made during this transformative time in life have the potential to increase or limit future opportunities, and will affect quality of life. This presentation will focus specifically on issues including employment, financial stability, and personal relationships. These issues can be difficult enough for any individual transitioning to adulthood, regardless of whether or not they have a bleeding disorder. Peer pressure and inexperience complicate the decision-making process further and can be obstacles to making healthy choices. The presence of a bleeding disorder makes these decisions even more consequential. Family, medical teams, and hemophilia organizations must find effective ways to support the young person with a bleeding disorder in their transition to adulthood. Each patient is different, and patients will face unique circumstances in their lives, but basic principles can assist the individual in navigating these challenges. Individual growth and increased independence can be fostered in young bleeders by helping them identify choices and teaching them where to find the information they need to make healthy decisions. Personal reflections from the perspective of a young adult with hemophilia and von Willebrand disease will be shared to help give concrete examples of how communities can best support patients in their transition to adulthood.

PO-WE-081
Through an ethical lens: Innovative program empowers parents and becomes policy in a hematology department
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Pain management for children with hemophilia undergoing treatment procedures is both clinically important and ethically necessary. Ethically, any treatment or conduct of a procedure, as part of a treatment, should work to maximize a child's best interests and minimize any associated harms. Pain minimization and efficient practices that decrease associated anxiety and pain for the child have both short- and long-term impact—particularly significant for a child who will have an ongoing relationship with the hospital. When the patient is a young child, the parents, the child, and the health practitioners are involved in a series of relationships that evolve over many years, as the child gradually learns to take responsibility for his or her own health. If pain is not managed well in the early years, fear of medical treatment can have an ongoing impact on children and their relationships with practitioners. This paper explores how an innovative, simple intervention to normalize medical treatment worked to minimize harms. The parent/child focused intervention comprised a series of playgroups, facilitated by a pediatrician and music therapist, where parents of children with hemophilia learned how to reduce pain and distress from invasive medical procedures. In this paper, a mother and lecturer in medical ethics describes her experience of having two children with severe hemophilia—one already six, the other a baby, when the first playgroups took place. The comparative knowledge and skills learned had a powerful impact on the family's collective journey. Using an ethical lens, it explores how a family's relationship with treating practitioners was enhanced and anxiety associated with painful and invasive procedures decreased. The program demonstrates that acting in a child's best interests when they are undergoing a potentially painful medical procedure, encompasses the provision of developmentally appropriate creative programs that involve more than clinical technical competence.

PO-WE-082
Mothers of children with hemophilia: An exploration of their experiences
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Aim: There continues to be poor treatment adherence in children and adolescents with hemophilia, despite the obvious benefits of treatment. Parents play a fundamental role in their child(ren)'s treatment adherence, given that they are responsible for administering treatment up until, and often throughout, adolescence. Existing pediatric hemophilia literature is largely quantitative and focuses principally on the quality of life of patients and their parents. The few studies that have investigated parents' experiences of having a child with hemophilia were conducted predominantly in the United Kingdom. We aimed to explore qualitatively the experiences of parents with children who have severe hemophilia A, with the hope of discovering influences on treatment adherence and non-adherence.
Method: Interviews were conducted with 7 biological mothers, of children (ages 2 to 16 years) with severe hemophilia A, on primary prophylaxis. The data were analyzed using interpretative phenomenological analysis (IPA), which involves the meticulous examination of participants' lived experience. Behaviour is, in part, influenced by an individual's beliefs and experience. As such, IPA was undertaken to identify possible influences on parents' behaviour and thus their approach to their child(ren)'s treatment.
Result: Six main themes were extracted: parental responsibility to protect, acceptance, appreciation, self-efficacy, this is dangerous and others don't get it, and treatment importance versus practicality.
Conclusion: Poor adherence in children with hemophilia is a significant and concerning medical issue. Possible interventions for improved adherence include increasing parents' acceptance, appreciation, self-efficacy, and time management; as well as challenging their perceptions of trustworthiness of others and danger. Further research is necessary in order to examine whether improvements in any of these 6 areas can result in improved-adherence behaviours in children with hemophilia.

PO-WE-083
Understanding the challenges of distance and parenting a child with hemophilia
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Parents of children with moderate and severe hemophilia play an essential part in the management of their child's condition. Understanding the experience of parents is paramount to understanding why treatment non-adherence still occurs despite the severe consequences to their child's health. The demands of management have been associated with deteriorating social and family relationships, difficulty maintaining employment, and deterioration in psychological functioning. Parents living some distance from a hemophilia treatment centre face additional challenges around access and availability of specialists and factor concentrate. However, the research involving parents who live some distance from a hemophilia treatment centre is limited. Interpretive phenomenological analysis (IPA) aims to gain detailed understanding of an individual's "personal lived experience" and the processes involved in how that individual makes sense of their experience. Using IPA, this study explored the experiences of 6 parents (5 mothers and 1 father) who lived considerable distances (i.e., between 100 and 1000 km) from a hemophiliac treatment centre. Four main themes emerged from the study encapsulating the emotional struggles, ongoing management challenges, and need for support: "bearing the brunt of diagnosis," which captures the impact of the diagnosis on the parents; "if you can't help me, who can?" which summaries the experience parents had with the health care system; "tackling the challenge of treatment," which encompasses the difficulties faced by parents in adhering to the treatment regime; "I need you to understand," which represents the parents' desire for others understanding. Across each of the themes, there was an emphasis on the desire to have access to hemophilia specialists. The information gained from this study will hopefully provide important insights into the reasons surrounding treatment non-adherence and guide the design of more clinically appropriate measures and interventions to promote treatment adherence in parents of children with hemophilia.

PO-WE-084
Talking about hemophilia inheritance with partners and daughters: What do men with haemophilia a/b think about the issue and how does it impact them?
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Introduction: Consideration of hemophilia inheritance issues has focused on female carriers and their sons frequently omitting the impact on men and their daughters. Anecdotal evidence from medical review clinics suggests that some men struggle to talk about inheritance with significant others.

Objectives: To research the thoughts and experiences of men with hemophilia on the challenge of talking about hemophilia inheritance with both their partners/wives and their carrier daughters.
Methods: The study is on-going and so far 45 men have been contacted and invited to participate in the study. Those who agreed received a research package and had the option of completing the questionnaire either at home or at the Hemophilia Treatment Centre (HTC).
Results: Thirty-four of the 45 men completed a questionnaire, though not all answered every question. Almost all of the men chose to discuss the facts of inheritance with their partners, once their relationship had become serious and thought that daughters should be told they were obligate carriers when they were teenagers. When thinking about daughters being obligate carriers 9/34 (26%) felt worried, 9/34 (26%) felt relaxed, 8/34 (24%) didn't think about it, and 2/34 (6%) felt guilty. 15/26 (58%) believed that the main area of a daughter's life that would be negatively impacted by being a carrier was her marriage prospects.
Conclusion: Some men worry and some don't want to think about how hemophilia inheritance will affect the lives of their daughters, and although concerned about any potential negative implications, they still believe it best to wait until the teenage years to discuss inheritance issues.
Contribution to practice/evidence base: The research highlights a need for HTCs to make an early intervention with new couples/families stressing that feeling uncomfortable about passing on an inherited condition is normal and that staff are experienced and skilled in supporting men and families to talk about these issues.

PO-WE-085
Guidelines for growing: An action plan for parents of children with bleeding disorders

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The National Hemophilia Foundation (NHF) recognizes that youth with bleeding disorders face a number of difficult and ongoing medical challenges as they mature and learn to manage their health. Social workers and other professionals working in Hemophilia Treatment Centres (HTC) have developed a checklist-type tool based on transition guidelines recommended by NHF's Medical and Scientific Advisory Council (MASAC). These guidelines help HTC providers monitor a child's and family's progress, and prompt parents to consider their needs in several areas: social support, health and lifestyle, educational planning, self-advocacy and self-esteem, and ways to understand and make the best use of the healthcare system. In its current format, the transitions document is extremely useful to providers, but less so to consumers. In partnership with the Centers for Disease Control and Prevention (CDC), NHF has revised and translated the document to make it consumer friendly and separated the information into five age-specific brochures titled *Guidelines for Growing*. Each brochure covers transition information for specific age groups beginning with infants (Birth–4), children (5–8), older children (9–12), teens (13–15), and young adults (16–18), and focuses on important milestones of a youth's development as they relate to his or her bleeding disorder. *Guidelines for Growing* has been designed to be used together with the HTC provider team as a guide to help parents judge their child's progress as he or she grows and develops. The brochures have been reviewed by HTC personnel, NHF chapter teams, and the CDC, and are available in both English and Spanish. The brochures have been distributed to 141 HTCs and 49 NHF chapters and are available by contacting NHF's Information and Resource Centre (HANDI) or by downloading from the NHF or CDC website.

PO-WE-086
Impact of hemophilia on relationships with partners, family, and friends: Assessment of adult patient respondents in the hemophilia experiences, results, opportunities (HERO) study

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Objectives: To describe family dynamics and interpersonal relationships of adult patients with hemophilia participating in the hemophilia experiences, results, opportunities (HERO) study.
Methods: A web survey was conducted in 10 countries targeting 600 patients ≥ age 18, mostly recruited through patient organizations.
Results: Of 592 patients, 57% were married (median 11 years), 38% single, and 4% divorced. Fifty-four percent live with their partner, 28% with family, 13% alone, and 6% with others. Overall, 37% felt hemophilia impacted their ability to develop close relationships; significantly higher impact ($P < 0.05$) was reported by patients with inhibitors (56% versus 34%) and those with spontaneous bleeds (43% versus 19%). The most commonly reported reasons were worry over future impact of hemophilia (53%), over continuing to support a family (49%), feeling different (44%), or lack of others' understanding around hemophilia (43%). Overall, patients reported a high level of satisfaction from their partner (94%), with 67% being "very" and 27% "quite" satisfied. Non-inhibitor compared with inhibitor patients scored "very satisfied" in 69% versus 49% ($P < 0.05$) and "quite satisfied" in 25% versus 41% ($P < 0.05$). Top reasons provided included aspects related to love, trust, and emotional support, with less emphasis on financial issues. Support from family was considered satisfactory in 90% of cases, from friend in 85%. Patients reported they were more likely to share their diagnosis with friends than colleagues, neighbors, and social media. Nearly a third of those telling a friend about hemophilia reported this as a negative experience.
Conclusion: Hemophilia's impact on relationships was complicated and varied with disease burden (e.g. inhibitors). Patients were overall satisfied with the support they receive from partners, family, and friends, and emotional and trust aspects were emphasized over financial support. These relationships will be further investigated in a multivariate analysis of the HERO dataset.

PO-WE-087
Impact of hemophilia on interpersonal relationships: Assessment of parent/caregiver respondents in the hemophilia experiences, results, opportunities (hero) study

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Objectives: To evaluate parent/caregiver perceptions of family dynamics and interpersonal relationships.
Methods: A web survey was conducted in 10 countries targeting 600 parents/caregivers of patients <age 18.
Results: Of 503 parents, 422 respondents were married and 297 had more than one child. Of mothers, 81% reported knowing they were carriers; 40% reported knowing before the birth of their first affected son. Mothers told their partner early in the relationship in 70% of cases, while 14% told after becoming pregnant. At variance, 56% of fathers reported they knew their partner was a carrier; 74% found this out after the birth of an affected son. Upon birth of a son with hemophilia, 59%/47% of mothers/fathers were devastated and 13%/17% very disappointed. Ninety-one percent thought it was appropriate for their daughters to be screened for carrier status, but 59% had not been offered screening. Impact on other children was reported as negative (27%), sometimes positive/negative (50%), or no impact (17%). Negative impact was more common in those treated on demand (48%) than with prophylaxis (22%). Parents reported children not getting enough attention (45%) or resenting attention around hemophilia (42%). Positive impact involved "responsibility" (52%) and "maturity" (42%) and family/children being closer (49%/42%). Support from partners/family was generally satisfactory (88%/83%). Most/all of the following were told about hemophilia: friends (63%), classmates (50%), teachers (73%), other adults/coaches (64%) with ≥85% satisfaction with those relationships. Forty-three percent had a negative reaction from telling someone about their son's hemophilia. Dissatisfied parents reported concern with lack of knowledge in classmates (63%), teachers (69%), and other adults/coaches (58%).
Conclusion: Family dynamics are complicated in hemophilia, starting with communicating carrier status and the birth of a son with hemophilia. Parents seem willing to communicate about hemophilia to teachers, coaches, neighbors, and their son's peers, and generally find these relationships supportive.

PO-WE-088
The Afro support group

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The Afro support group was established in June 2011 to meet the needs of African families in the United Kingdom. The goals of the support are: to promote support within the group, for affected individuals, siblings, and parents through shared experiences, the development of friendships, and an understanding of African cultural issues; to raise awareness of hemophilia and bleeding disorders within the African community in the United Kingdom and in the countries that the families originate from; to raise funds to support U.K. activity and, eventually, to be able to offer support in Africa.
Methods: The group was formed by several mothers of children with hemophilia. From informal meetings at hospital hemophilia centres, the mothers established a more formal group through the U.K. Haemophilia Society. Monthly meetings have been held with advertisements for these in the major London hospitals.
Results: Twelve families from Cameroon, Congo, Ivory Coast, Nigeria, Somalia, and the Caribbean, of different religions and cultures, are the core group.
Similarities in cultural issues: The African beliefs that hemophilia is a "women's issue" and that circumcision is essential have been identified. Awareness of hemophilia and related bleeding disorders in the African British community has improved. Awareness of hemophilia in Africa has been heightened. A hemophilia diagnosis has been made in some people who were previously known only to have "bad joints" and "bleeding." Networking has been established with a parent support group in Kenya and through the French Haemophilia Society for French speaking/reading families.
Conclusion: This newly established group has already had an impact on support for Africans in the U.K. There is a network of families who support each other by telephone and face-to-face contact. An increased awareness of hemophiliac in Africa, through affected family members, has been established.

PO-WE-089
Re-PEP program in New Zealand: An opportunity to review, revisit, reflect, and refresh

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The Parents Empowering Parents (PEP) program was designed to educate parents of children with bleeding disorders and improve confidence in parenting skills. Originally developed in the United States, the program is presented by parents of children with bleeding disorders in tandem with a social worker and nurse. The Haemophilia Foundation of New Zealand (HFNZ) has held three PEP programs in 2008, 2009, and 2012. The success of the program with New Zealand (NZ) families created a desire for further training opportunities.
Aims: The two-day Re-PEP program was then created in 2010. It aimed to revisit PEP principles and provide a forum for self-evaluation; to further develop parenting skills in

order to revitalize parenting; and to provide a forum for a PEP parent graduate reunion for renewing mutual, support networks.
Method: Fifteen of the 20 NZ PEP graduate parents attended Re-PEP (75%). Developed by HFNZ using concepts from the original PEP, the program was facilitated by two outreach workers and a hemophilia nurse. Together, parents reviewed the concepts of PEP and discussed the value of the program, revisited their worldview and parenting styles and had the opportunity to reflect on and rewrite their family blueprint.
Results: Participants felt that participation in the PEP and Re-PEP program guided them to empower their children to be honest, independent, and self-reliant people who are able to make sensible and well-thought-out choices for their own safety, well-being, and their role in the wider community. They recommended PEP to all parents with or without bleeding disorders. Several Re-PEP participants have gone on to train to become PEP facilitators. The facilitators of the RE-PEP program will discuss how the program went and their ideas for future RE-PEP programs from the perspectives of both a nurse and a social worker.

PO-WE-090
Family issues faced by women with bleeding disorders and the importance of psychological help in overcoming them
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Family plays an important role in the overall development of an individual. The contribution of family in making women with bleeding disorders more empowered and self-sufficient cannot be overlooked. These women face numerous family issues right from their childhood till adulthood. Such issues range from parental neglect to sibling rivalry to adjustment problems, in addition to others. Persistent unresolved family issues can lead to distorted self-image, low confidence, guilt, and feelings of inadequacy in women suffering from lifelong and chronic bleeding disorders. Most of the time, family issues affect woman's psychological functioning to a large extent. Therefore, seeking help from psychologists/counsellors could be of great value. These professionals not only facilitate the resolution of family issues faced by women with bleeding disorders but also play an important part in improving and enhancing their psychological functioning.
Keywords: Self-image, psychologist, bleeding disorders, psychological functioning.

15-GENE THERAPY

FP-TH-01.1-6
Human FIX-P selectin chimeric protein expression in megacaryocytes derived from human hematopoietic cells
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Background: Gene therapy is a promising strategy for the treatment of severe hemophilia. Sustained expression of factor IX (FIX) has been achieved in preclinical studies, using different gene transfer technologies and a wide range of target tissues. However, clinical trials have resulted in very limited clinical efficacy. We have designed a new ex vivo gene therapy strategy which aims to express FIX in platelets. Our hypothesis is that platelets can deliver the FIX at the site of vascular injury and locally correct the coagulation defect. In addition, this approach may prolong the half-life of the FIX molecule, due to its protection within the platelets. A few trials had been recently conducted in a hemophilia B mice model, resulting in transient FIX expression in platelets. The aim of the present work was to study the expression of the FIX-P selectin (FIX-Psel) molecule in human megakaryocytes. In an attempt to produce an intraplatelet pool of releasable FIX, the cytoplasmic domain of the P-selectin molecule was fused to the carboxy-terminal extremity of the human FIX protein.
Methods: Stem cells from human cord blood were collected and cultured for 2 weeks in a specific megakaryocytic differentiation medium. The megacaryocytes obtained were transfected, using nucleofection with plasmids containing the specific megakaryocytes promoter GPIIb and the sequence encoding for FIX-wild type (FIX-WT) or FIX-Psel. The expression of the molecules was assessed in culture supernatants and cell lysates by enzyme-linked immunosorbent assay (ELISA), Western blot, and electron microscopy coupled with immunogold post-inclusion.
Results: Both FIX-Psel and FIX-WT were detected in culture supernatants and in megakaryocytes with a specific localization of FIX-pselCT within the α-granules.
Conclusion: Our results suggest that FIX-Psel can be expressed in human megakaryocytes, with a specific storage in α-granules, and can be released after cell activation.

FP-TH-01.1-4
Long-term follow-up of liver-directed, adeno-associated, vector-mediated gene therapy in the canine model of hemophilia A
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The results of a recent Phase I/II study utilizing adeno-associated viral (AAV) gene transfer for hemophilia B suggest that this therapeutic approach has significant potential for the long-term delivery of clotting factor protein in hemophilia. With evidence that AAV gene transfer is safe and effective for the first few months following delivery, there is increasing need for information concerning the long-term outcome of this treatment approach. In this study, we have characterized the long-term results of AAV-mediated factor VIII (FVIII) gene transfer in the hemophilic dog model. Eight mixed-breed dogs with severe hemophilia A from the Queen's University colony were treated with liver-directed AAV-mediated gene transfer between 2001 and 2003. The treatment protocol involved a single portal vein infusion of 6×10^{12}/vector particles/kg of an AAV vector containing the B-domain deleted canine FVIII cDNA regulated by a liver-specific promoter. Four dogs received an AAV2 vector, 3 dogs an AAV6 vector, and a single dog was treated with an AAV8 vector. None of the dogs exhibited any acute adverse events at the time of vector infusion. The period of follow-up has been between 8 and >10 years, and no dog has experienced any adverse effects that might be related to the AAV gene transfer. One dog has died of an unrelated condition, but the remaining dogs have remained well, and no dog has developed any malignant disease. In untreated dogs from this colony, bleeding events require transfusion therapy approximately 5 times each year. Over the past decade, bleeding events in the AAV gene transfer dogs have been rare. At 5–7 years post–gene transfer, FVIII levels ranged between 13% and 24% and now, at 8->10 years follow-up, FVIII levels are between 10% and 17%. These values are consistent with whole blood clot times that prior to therapy were between 14 and 18 min and post–gene transfer have remained below 7 min. There has been no evidence of FVIII inhibitor development. In summary, this long-term follow-up of liver-directed AAV FVIII gene transfer indicates that this treatment is effective and safe for at least 10 years in the hemophilic dog model.

FP-TH-01.1-5
In-mouse propagation of hemophilic hepatocytes toward gene correction and cell therapy
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Background: Development of cell and gene therapy using autologous cells has been highly desired as a new-generation therapy for hemophilia. Although hepatocytes are the most functional cell type for the production of coagulation factors, insufficient hepatocyte proliferation under current cell culture conditions has been a major hurdle. The present study describes a novel hemophilic hepatocyte proliferation system in the liver of a living mouse. Experiments based on this system were further conducted for gene transduction, cell recovery, and cell transplantation.
Methods: Hepatocytes were isolated from the liver of FIX knockout (FIX-KO) mice. A total of 5×10^5 viable hepatocytes were transplanted into the liver of uPA/SCID mice, and proliferation status of the hemophilic hepatocyte was assessed by clotting assay and genomic analysis. After the complete repopulation of uPA/SCID liver with hemophilic hepatocytes was achieved, viral vectors expressing human FIX were injected into the mice.
Results: The plasma FIX activity of recipient uPA/SCID mice showed a progressive decrease after FIX-KO hepatocyte transplantation to an undetectable level (<0.5% normal mouse plasma) at week 8. Genomic analyses showed FIX-KO hepatocytes occupied more than 99.5% hepatocytes of the recipient uPA/SCID, indicating that hemophilic hepatocytes actively proliferated to fully reconstitute the uPA/SCID livers. After infusing hFIX-expressing viral vectors, in-mouse repopulated FIX-KO hepatocytes showed efficient gene transduction. These propagated and hFIX-transduced hepatocytes were subsequently recovered and transplanted into FIX-KO mice. Therapeutic level of plasma FIX was achieved by this transplantation procedure.
Conclusions: The present studies demonstrated that hemophilic hepatocytes can be propagated in the living mouse. Since this in-mouse propagation system allows efficient gene transduction and subsequent cell recovery, this system should be useful for generating hepatocytes for cell-based therapy for individuals with hemophilia.

PO-WE-091
Factor IX secretion in human adipose-derived stem cells by non-viral gene transfer
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Background: Hemophilic patients are currently treated with intravenous infusions of either plasma-derived or recombinant factors. This treatment is very efficient, but it is not a cure, and it is very costly. Moreover, the most significant treatment complication in hemophilia is the antifactor immune response that results in the development of antifactor antibodies, called inhibitors because they inhibit the coagulation activity. A long-term expression of coagulation factors, and the absence of adverse effects with an irrelevant immune response, are challenges associated with future treatment of hemophiliac patients. Cell-mediated gene therapy, yielding long-term maintenance of therapeutic levels of coagulation factors, could be an optimal strategy. Due to their intrinsic properties, such as self-renewal, pluripotency, and almost no immunogenicity, the adipose-derived mesenchymal stem cells (ASCs) can be considered promising for cell and gene therapy strategies in vivo.
Objectives: The aim of this study was to establish a non-viral gene therapy protocol to produce human FIX by ASCs obtained from human lipoaspirates.
Methods: Human lipoaspirates were processed to isolate ASCs that were expanded in vitro, characterized and differentiated according to the internationally recognized parameters. ASCs were transfected by nucleofection with a plasmid encoding an enhanced green fluorescent protein (EGFP) and human FIX, linked by an IRES sequence. Human FIX expression and secretion were analyzed by RT-PCR and ELISA, respectively. Transfection efficiency and cell viability were also evaluated.
Results: The cells obtained from lipoaspirates constitute an homogeneous population of ASCs. RT-PCR confirmed that FIX gene was expressed only in transfected cells, and a mean concentration of 44.4 ± 5.6 ng mL^{-1} was detected in culture supernatants. EGFP expression in nucleofected ASCs ranged from 30.7% to 41.9%, whereas the average cell viability was 29.8% ± 4.1%.
Conclusions: In this study, human ASCs were efficiently transfected to produce coagulation factor IX in vitro by nucleofection. Our results suggest that a non-viral ex vivo gene therapy strategy for hemophilia, using ASCs as gene delivery vehicles, is possible. Besides, this approach could be also applied to the treatment of other pathologic conditions where there is a protein deficiency.

16-GENERAL

PO-TU-115
Severe aplastic anemia in a patient with severe hemophilia A

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A seven-year-old patient was diagnosed with severe hemophilia A at 9 months of age when he developed a hematoma after a vaccination. He started to receive FVIII infusions once a month on average, generally for hemarthrosis. He developed inhibitor after receiving 3 doses of plasma-derived FVIII concentrates. In November 2010, his right ankle was treated with radioactive synovectomy. In June 2011, he developed diffuse bruising and extensive oral bleeding secondary to decayed teeth. Two weeks later, he developed progressive pancytopenia and was referred to our hospital. He had diffuse bruising and petechiae on his extremities. He had no organomegaly and lymphadenopathy. Vitamin B12 and folate levels were in the normal range. Bone-marrow aspiration and biopsy findings were consistent with severe aplastic anemia. The DEB test was negative. Platelet and red-blood-cell transfusions were started to treat his bleeding tendency. Tests for human parvovirus B-19, hepatitis B and C, rubella, HIV, EBV and CMV were negative. Bone-marrow aspiration and biopsy were repeated six weeks after, and the findings were consistent with severe aplastic anemia. Immunosuppressive therapy with rabbit ATG, cyclosporin A, methylprednisolone, and G-CSF was started. Three months after the start of the immunosuppressive therapy, he developed a headache. An epidural hematoma was observed in a CT scan. Before and after the drainage of the hematoma, rFVIIa and/or aPCC were given. Five months after the start of the immunosuppressive therapy, an inhibitor test was negative and FVIII level was 88% in the recovery test. Prophylactic FVIII therapy (3 times per week) was started. He doesn't have an HLA matched donor. He is still receiving blood products. The combination of hemophilia and aplastic anemia is very rare. Fanconi aplastic anemia is also reported with hemophilia. However the DEB test was negative in our patient. Although radiation is another cause for aplastic anemia, there are no reports of aplastic anemia following radioactive synovectomy.

PO-TU-116
Elective otorhinolaryngology surgery in hemophilia patients

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Introduction: Adenoidectomy and tonsillectomy are the most common surgical operations performed in children in otolaryngological practice. However elective Otorhinolaryngology Surgery is avoided in Hemophilia patients due to concerns in achieving adequate hemostasis despite replacement therapy and in consequence perioperative or postoperative hemorrhage remains a substantial concern and a potential life threatening problem. Bleeding occurs in an area that may not be easily accessible.
Objectives: Evaluate the incidence of bleeding following tonsilloadenoidectomy and laringectomy surgery in hemophilia patients in a 17-year period.
Method: Retrospective chart review of hemophilia patients that underwent tonsilloadenoidectomy and laringectomy in our centre between August 1994 and November 2011. Six patients (pts) underwent tonsilloadenoidectomy, 4 with conventional surgery and 2 with radiofrecuency ablation, 3 with severe hemophilia A (sHA) 2 mild HA patients, 1 symptomatic HB carrier with FIX 25%, they all share the same indication for surgery that was chronic infection with at least more than 7 episodes in the last year, gross enlargement, and sleep apnea. 2 patients underwent laringectomy both with sHA, one with diagnosis of benign nodes, and one with diagnosis of adenocarcinoma. All procedures received 10 minutes previous bolus ev factor followed by factor infusion, and they were monitored during surgery and on a daily basis in the post op stage with dosage(s) of F VIII and FIX with the aim of maintaining levels above 50%.
Results: Patients that underwent tonsilloadenoidectomy had a median (M) age 13.8 years (3–26 years) required M 6.83 days of hospitalization (3–10 days) M 12.5 days of replacement therapy (7–15 days) M dose of FVIII 51 IU kg^{-1} (37–80 IU kg^{-1}), 1 sHA patient required blood replacement and rehospitalization on day 9 post op due to local hemorrhage, 1 sHA patient developed inhibitors. Patients that underwent laringectomy M 26 days of replacement therapy (7–45 days) M dose of FVIII 62 IU kg^{-1} (60–64 IU kg^{-1}) Media (M) age 51 years (40–63 years) required M 12 days of hospitalization (3–21 days) 2/2 required blood replacement during surgery with no evidence of hemorrhage during postop.
Conclusions: 1/6 patients that underwent tonsilloadenoidectomy had bleeding complications on day 9 post op requiring 72 hours to control bleeding and blood replacement; 1/6 developed inhibitors. 2/2 patient who underwent laringectomy presented with bleeding during surgery that was controlled with factor bolus requiring blood replacement in both cases, neither presented with bleeding during post op in our experience when required tonsilloadenoidectomy and laringectomy proved to be a safe procedure in hemophilia patients.

PO-TU-117
Successful orthotopic liver transplantation in a patient with severe hemophilia A and high titer factor VIII inhibitor

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Objective: Orthotopic liver transplantation (OLT) successfully treats hepatitis-C associated liver cirrhosis. To date, the outcome of OLT in patients with hemophilia A (HA) and high-titer FVIII inhibitors has been poor.
Methods: The hemostatic management of an adult Caucasian with severe HA and high-titer FVIII inhibitors who underwent OLT are described.
Results: OLT was undertaken following administration of 100 $UKg^{-1}$of FEIBA™. Preoperative FVIII levels were less that 1 IU dL^{-1} with a 58 BU FVIII inhibitor. Blood transfusion was in accordance with standard guidelines. During the anhepatic phase 1 g of tranexamic acid was given. NovoSeven® 90 μgKg^{-1} was administered twice during OLT for excessive bleeding. Transfusion requirements were 15 units of packed red cells, 20 units of FFP, 2 units of platelets. Twice daily FEIBA™ 100 UKg^{-1} was administered for 48 hours. The dosage was reduced to 80 UKg^{-1} twice daily with further reduction at 144 hours to 60 UKg^{-1}. From day 12, 60 UKg^{-1} was administered once daily until day 20. On-demand FEIBA™ was used during the patient's rehabilitation. During the postoperative phase the FVIII inhibitor titer fell to a nadir of 0.8 BU secondary to dilutional effects. A concurrent increase in FVIII was observed. An anamnestic response then occurred, FVIII inhibitor levels peaking at 2,355 BU on day 15. At day 90, following an episode of sepsis, computerized tomography demonstrated hepatic artery thrombosis (HAT) with secondary liver abscess formation.
Conclusion: We report a successful OLT in an HA patient with a high-titer FVIII inhibitor present at the time of surgery.
Contribution to the practice: Despite the presence high-titer FVIII inhibitors, successful OLT can be undertaken. Massive transfusion may provide a temporary reprieve from FVIII inhibitor function. Immune-suppression did not prevent an anamnesis. On-demand therapy may have contributed to HAT. This is an important consideration for clinicians managing such patients.

17-HEALTH AND SOCIAL ECONOMICS

S-MO-04.3-3
Pioneering health technology assessments of hemophilia care: Sharing the Swedish experience
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Sweden has pioneered the treatment of Hemophilia and other related bleeding disorders over the last few decades. With adequate prophylactic treatment since the seventies, generations of patients have grown up with little or no joint damage, and most patients can lead normal lives. As the benefits of the treatment are obvious, so are the costs. The first country in the world to do so, the Swedish authority TLV has undertaken a rigorous Health Technology Assessment for treatment of Hemophilia A. The potential conclusions of a negative outcome range from removing high-cost recombinant factors from the reimbursement system, to restrictions of prophylactic treatment. Such conclusions could be interpreted as legitimizing the regression of care in comparable developed countries, while a positive result would be a useful precedent for other hemophilia societies advocating improved care. With a final decision scheduled during the autumn of 2012, key stakeholders currently engaged in the process include the industry, a medical expert team appointed by TLV, and the Swedish Haemophilia Society. The aim of the Society is to underscore the inherent difficulties in applying general Health Economic concepts to a complex treatment regime applied to a small group of patients. We advocate that high uncertainties in the measurements of health benefits, especially in the long term, obfuscate the calculations and that metrics such as QALYs (quality-adjusted life year) inadequately reflect the cost effectiveness of the current treatment. We are grateful for this opportunity to share and learn with the world community.

S-MO-04.3-1
Rationale of registries and data collection
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A prerequisite for the efficient treatment and lifetime care for persons with hemophilia and related disorders in each country is accurate information on the disease prevalence and regional distribution of patients. So far, mostly institutional, regional, and, only in a limited number of countries, national data were employed to estimate hemophilia prevalence and treatment needs. Data other than national data often do not reflect the real situation in a country. In the WFH Survey 2008, only 56% of reports were derived from national registries. This may explain the differences in hemophilia prevalence observed even among the developed countries. Two recent documents encourage the establishment of a national registry in each country, underlying the benefits for persons with bleeding disorders, healthcare providers, and the health ministry/government as well. A registry is a database that collects key information on persons with hemophilia and related disorders, including relevant laboratory and clinical data, treatment patterns, complications, morbidity, mortality, and social status. A national registry permits accurate assessment of disease prevalence and distribution of patients, which creates the basis for the establishment of a national hemophilia program with an efficient network of cooperating hemophilia centers and relevant resource planning. It also serves as an effective surveillance system for monitoring the safety of treatment (inhibitors, infection, other adverse events). A national registry allows objective analysis and inter-regional comparison of standards and outcome of care and may be used as a tool for auditing clinical and laboratory services. The registry helps to ensure equal access to therapy, supports continuous progress towards better quality of care nationwide, and allows integrated international collaboration. Establishment of the registry must not be seen as the end goal of our efforts, but as an effective instrument to achieve the ultimate goal—the appropriate "Treatment for All."

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S-MO-04.3-4
The economics of hemophilia care: An economist's perspective
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Many countries use health technology assessment (HTA) to assess the added value or cost-effectiveness of new pharmaceuticals and technologies in order to aid decisions about their national reimbursement and funding. Organizations such as NICE in the U.K. or the TLV in Sweden perform such HTAs. However, to date in many countries, hemophilia treatment and care has not been subject to formal HTA. This is changing, due to healthcare budget constraints so the cost-effectiveness of hemophilia interventions are starting to be examined. In Sweden there has been an HTA of the use of primary prophylaxis designed to inform clinical practice, and there have been several health economic publications on the cost-effectiveness of primary prophylaxis compared to on-demand treatment. The language of health economics can be daunting, and a barrier to full participation in the HTA process by those not versed in this language. The aim of this presentation is to explain the basics of HTA and provide an overview of the techniques, especially the use of the quality-adjusted life year (QALY), a key outcomes measure used in health economic evaluation. There are many challenges to applying health economics and the QALY to hemophilia care. These include taking account of the lifetime costs and benefits of treatment (in health economics the value of future benefits are reduced by the technique of discounting), overcoming the limits to data on treatment effectiveness, and the rarity of the condition. Of key importance is lobbying HTA organizations to take a broader societal perspective, and combining use of experimental data with experiential evidence as part of the HTA process. Even in those countries that do not have a formal HTA requirement, health economics and HTA can provide a framework to systematically present a case for the societal value of treatments for patients with hemophilia.

PO-MO-039
Determinants of Intensity of Disease in Hemophiliac Patients, Pakistan
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Pakistan is a developing country and its people with hemophilia (PWH) still spend a miserable life due to inadequate hemophilia treatment and poor socioeconomic statuses. In this regard, a basic study was carried out for Pakistani PWH, with the purpose of estimating the determinants of intensity of disease; the secondary objective was to get multidimensional information regarding educational, economical, marital, social, and employment status of PWH. A questionnaire (socioeconomic and medical perspective) has been developed and primary data was collected from a sample size of 257 severe PWH registered at different hemophilia care centres. The latest version of Functional Independence Score in Hemophilia was also used to know functional limitations in PWH. Ordinary Least Square technique was used for econometric analysis of data. "Age of the patient" and "diagnosed age" are the variables positively and significantly affecting the intensity of the disease. But the locality, household size, household per capita income, family history, transport type, type of treatment, home treatment, awareness of RICE (rest, ice, compression, and elevation), and habit of SEP (sports, exercise, and physiotherapy) are negatively and significantly affecting the intensity of disease. On the other hand, individual education, parents' education, father's occupation type, number of PWH in the family, and the distance of the hospital are not significant variables. Among widespread disabilities (only seven are free from it) in PWH, especially age group of 25+. Primary education is highest in younger age group of PWH, but the overall number of graduates and postgraduates are very low. The elder patients don't have white collar jobs; the majority of them are working in their own small shops due to lack of skills and education. Clotting factor concentrates and home treatment encourage minimizing the severe disability in PWH. There is poor awareness about the inheritance of hemophilia.

PO-MO-040
Does Clotting Factor Concentrates Consumption Represent the Evolution of Medical Practices?
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Medical practices have evolved considerably during the last years for the care of patients with hemophilia in France. We have analyzed clotting factor concentrate (CFC) consumption at our centre during the last six years (2006–2011). We have observed an important increase in CFC consumption (+20% FVIII/FIX) for the same cohort of patients (around 450). These evolutions are different depending on the context of use (ambulatory and hospital). We have seen a constant evolution in ambulatory delivery because more and more patients are receiving prophylactic use. On the one hand, all the pediatric patients are treated with long-term prophylaxis. On the other hand, we observed a constant evolution of CFC's quantity that paralleled the weight increase. Immune tolerance induction (ITI) also strongly influences the quantity of CFC use. In the hospital context, CFC consumption is mainly depending on surgical activity. We have observed a moderate decrease in the number of major surgeries per year during the last years, mainly orthopedic procedures, for example, joint replacement in non-inhibitor patients. However, patients with inhibitors represent a new challenge considering the cost of bypassing agents. Although the price per IU is now fixed by the French healthcare system (0.78 €/IU FVIII/FIX), the cost increase can represent a major limitation for the evolution of practices, such as prophylaxis with bypassing agents. We must contribute to obtain a decrease of cost in order to maintain or increase the accessibility to these treatments. This analysis of CFC consumption is a good reflection of the current challenges that will to some extent impact the evolution of medical practices.

PO-MO-041
Bypass Therapy Assay Testing as a Strategy to Reduce Treatment Costs for Hemophilia Patients with Inhibitors
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Objective: Published studies suggest that bypass therapy assay testing can be used to effectively predict treatment response and dosing requirements for an individual hemophilia patient with inhibitors. This study aims to evaluate the costs and treatment outcomes of bypass therapy assay testing vs. no testing strategy on different treatments for mild to moderate bleeding hemophilia patient with inhibitors. This study also investigates the cost implications if testing assays could predict the optimum dose for new types of therapies like concomitant therapy.
Methods: A decision tree simulation model was used to simulate inhibitor treatment costs and outcomes from a US third-party-payer perspective. All estimates of costs were obtained from the literature or expert opinion and were adjusted to 2011 US dollars. Based on a previous published model, the efficacy of APCC and rFVIIa were assumed to be the same in the no testing scenario, while assay testing was assumed to improve the

efficacy of both the products by 10%. Probabilistic sensitivity analysis was used to determine the robustness of the model's results. The model was developed using Microsoft Excel and @Risk.
Results: If bypass therapy assay testing successfully predicts the treatment response and improves treatment efficacy by just 10%, cost savings of $6,939 for APCC and $7,699 for rFVIIa treatment were observed per bleeding episode. Further, if testing successfully predicts the optimum dose for concomitant therapy on the onset of bleeding, significant cost savings were observed when compared to rFVIIa and APCC therapies alone. The results were sensitive to frequency of dosing, efficacy, re-bleed rate and drug price.
Conclusion: Bypass therapy assay testing is recommended for reducing costs while optimizing treatment response and dose before administering treatment in hemophilia patients with inhibitors.

PO-MO-042
Prophylactic versus On-Demand Treatment with rFVIIa in Hemophilia Patients with Inhibitors: An Incremental Cost Analysis

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Introduction: Hemophilia is a rare hereditary bleeding disorder characterized by bleeding episodes. Treatment of this condition relies on replacement of the deficient factor or bypassing agents for patients with inhibitors. In a separate analysis, we determined that if prophylaxis with rFVIIa can achieve a reduction of ≥40% of bleeding episodes, this will translate into a better quality of life as was measured by QALYs.
Objectives: To determine at which percentage of reduction in bleeding episodes with prophylaxis with rFVIIa the cost of therapy would reach a breakeven point relative to those for on-demand treatment.
Methods: We compared the costs of 5 years of treatment for a hemophilia patient in Argentina treated with on demand versus prophylaxis with rFVIIa. For the base case analysis, we considered 15 bleeding episodes per year. Treatment of each episode consisted of 3 doses of 90 μg kg^{-1} of rFVIIa for bleeding control and 5 days of rehabilitation. We considered on-demand treatment as base l case scenario and evaluated the incremental cost of adding a prophylaxis regime of 90 μg kg^{-1} of rFVIIa three times per week at different bleeding reductions ranging from 0% to 100%.
Results: We set the cost of treatment with on-demand rFVIIa as 100%. When we analysed costs related to reduction in bleeding episodes (all 15 to no reduction), the incremental cost of prophylaxis ranged from 67% to 167% of the base case. f i. The breakeven point was 70% reduction in episodes. Assuming that, as reported for non-inhibitor patients, prophylaxis can prevent one major orthopedic surgery, and adding the cost of such a procedure to the base costs, the breakeven point was reached at a prevention of bleeds level of 60%, which is similar to the response to prophylaxis in clinical trials (Konkle et al. J Thromb Haemost. 2007; 5(9):1904–13).
Conclusions: Although prophylaxis is perceived to be more costly than on-demand therapy, a substantial reduction in bleeding episodes is achieved; this strategy can be cost effective and even cost saving.

PO-MO-043
National Plan of Control of Hemophilia: The Moroccan National Plan

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Hemophilia is a genetic disease characterized by spontaneous or prolonged hemorrhages due to a deficiency of factor VIII or IX. The evolution of severe haemophilia, if left untreated,is fatal in childhood and adolescence. In people with inadequately treated hemophilia, the recurrence of hematomas and hemarthrosis is responsible for motor disability involving joint deformities and stiffness, depriving patients of their mobility and independence. In Morocco, the number of patients with hemophilia is estimated at 3,000. According to the registry of the Moroccan Association of Hemophiliacs, more than 1,000 patients have been identified nationally. This observation has prompted the Ministry of Health and several stakeholders in the fight against bleeding disorders to develop a national action plan that aims to reduce mortality, morbidity, and disability associated with hemophilia. This plan is based on three main areas: namely, global and equitable management for patients with hemophilia by training according to national guidelines in terms of appropriate structures; development of reference laboratories to improve diagnosis and proper monitoring of patients, and, finally, epidemiological surveillance with the installation of a national registry. In parallel, the plan accompanying measures is essentially the partnership with national and international research in the field of hemophilia to improve knowledge of hemophilia in Morocco. It is also to create awareness and communication around the benefit of hemophilia, patients, their families, and the general population on the one hand, and policy makers on the other hand, to support national control of hemophilia. The objective of the plan is to provide treatment on demand of the anti-hemophilia factors of 1 IU per capita in 2015.

PO-MO-044
Cost Assessment of Implementation of ITI in Iran

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Background: This study was designed to compare costs attributed to implementation of immune tolerance induction (ITI) for management of Iranian hemophilia patients with high titer and high responding inhibitors and on-demand (OD) use of bypassing agents from the perspective of the national health system.
Method and Materials: The main objective was to find the breakeven point for ITI method in comparison with on-demand (OD) use of bypassing agents in Iranian hemophilia patients with high titer and high responding inhibitors. Good risk patients and complete response were defined according to the consensus of three main study groups on ITI in the world. After a systematic review of articles, we used the results for Pre-assumption for both arms of study about success rate of ITI; mean time to success; dosage of FVIII during ITI and subsequently for controlling minor, moderate, and major bleeding events; dosage of bypassing agents for the same bleeding events during ITI and the years of OD treatment; FVIII and bypassing agents (NovoSeven® in this study) prices; expected number of bleeding events during ITI and OD.
Results: Based on sensitivity analysis breakeven point of ITI and OD usage of NovoSeven® methods varies between 16–34 months post treatment.
Conclusion: This study clearly shows that ITI method is a cost-saving method for management of high responder inhibitor hemophilia patients when compared with on-demand therapy with bypassing agents.
Key Words: Cost, immune tolerance study, inhibitor, bypassing agents

PO-MO-045
Evidence for Mobilizing Policy on Hemophilia in India: I. Utility of Hemophilia Registry Data from Maharashtra, 1989–2009

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Introduction: There is no public health policy for hemophilia and other rare disorders in many developing countries including India, which is paralleled by a paucity of information on the long-term trends of these conditions.
Objective: To determine the 20-year trends of hemophilia in Maharashtra, the second most populous state of India.
Methodology: Data on diagnosed cases reported from seven hemophilia treatment centres were collated. After removal of duplicate entries, the data was analyzed for selected indicators.
Results: Preliminary analysis of the data shows that over the 20 years, average annual-case registrations per year were 203 (median 220, range 8–368). Age structures showed an inverse relationship between increasing age and number of patients with severe hemophilia. There was a shift in the age at diagnosis and registration to younger ages. Family history of hemophilia was present for 23% of patients. The number of cases of other bleeding disorders increased over time, as did the number of female patients.
Conclusion: The data provides evidence on the increasing number of hemophilia patients in Maharashtra, implying increased awareness about the disorder, even as there is no policy on prevention or provision of care to patients.

PO-MO-046
Evidence for Mobilizing Policy on Hemophilia in India: II. An Estimate of Treatment Gap in Maharashtra

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Introduction: The consumption of clotting factor concentrate is an indicator of access to treatment in developing countries like India, which reports one of the lowest levels globally for consumption of treatment product at 0.032 units per capita.
Objective: This study aimed at comparing the amount of clotting factor concentrate that is currently used with the estimated amount required if all bleeding episodes were treated by patients with hemophilia A in the state of Maharashtra.
Methodology: Data from two separate studies was used for the analysis. Data on the annualized bleeding rate for patients in six age groups was calculated from a published study that measured the bleeding episodes and treatment decisions in patients with severe and moderate hemophilia A. The age structure of patients in Maharashtra was determined from the hemophilia registry of Maharashtra. We used national standards to estimate the body weight of patients in order to determine the units of clotting factor concentrate required for infusion. Using these variables, we estimated the annual clotting factor concentrate requirement if all patients treated all hemorrhagic episodes.
Results: Annually, the estimated number of bleeding episodes for 946 severe and 273 patients with moderate hemophilia A was 10,558 and 2,249 respectively. The annual estimated units of clotting factor concentrate required assuming that each bleeding episode was treated with a single infusion of clotting factor concentrate was 11,324,400 units. The reported actual utilization of clotting factor concentrate by the hemophilia treatment centres in Maharashtra was 19% of this amount.
Conclusion: The large treatment gap can be used as an indicator to illustrate lack of access to care and can be used to mobilize policy for addressing human suffering.

PO-MO-047
Indirect Costs among Persons with Hemophilia B: The Hemophilia Utilization Group Study Part Vb (HUGS Vb)

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Objective: Examine indirect costs among adults and children with hemophilia B receiving care at 9 hemophilia treatment centres in the United States (US).
Methods: Data were obtained between June 2009 and December 2011 from the Hemophilia Utilization Group Study Part Vb (HUGS-Vb), a two-year, prospective, multicentre cohort study evaluating the cost of care and burden of illness in persons with factor IX deficiency and their families, in the US. Adult patients or parents of children <18 years with hemophilia B completed a standardized initial questionnaire about so-

ciodemographics, clinical characteristics, and treatment patterns. Participants were followed quarterly for two years through mail, Interne, and telephone surveys. Indirect costs imputed were lost wages from missed work among those employed, lost wages from working part-time or being unemployed due to hemophilia, and unpaid caregiver costs. Average hourly wages were obtained from the US Department of Labor Statistics in December 2011.
Results: Within a one-year time period, 76 of 113 participants completed at least two quarterly follow-up surveys; 47% were adults; 50% had severe hemophilia; and 26% of parents and 20% of adults were unemployed or worked part time due to hemophilia. Average annual work absenteeism for adults was 2.7 days (range = 0–34), with 2.3 days (range = 0–34) due to hemophilia. Parents missed 1.3 days per year from work (range = 0–12) due to their child's hemophilia; 19% of adults and 18% of parents reported utilizing unpaid caregivers. Annual indirect costs per person for mild, moderate, and severe hemophilia respectively are $94 (range = 0–301), $536 (range = 0–1626), and $855 (range = 0–5179) in parents and $1389 (range = 0–8822), $139 (range = 0–843), and $471 (range = 0–2168) in adults.
Conclusion: Time lost from work/school due to hemophilia may incur high indirect costs for patients and families. Accurate measurement of indirect costs will further the development of strategies to increase quality of hemophilia care while decreasing overall costs.

PO-MO-048
Economic Impact of an Efficient Inclusive National Tender System for Factor Concentrates

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A single national tender commission responsible for the purchasing of all factor concentrate requirements for a country is the method recommended in the WFH Guide to National Tenders. In Ireland, an integrated Hemophilia Product Selection and Monitoring Advisory Board was established in 2003. This board includes the directors of the three comprehensive hemophilia treatment centres, the patient organization, health ministry, and the contract holding authority. The board apply a rigorous appraisal process for products based on open competitive tendering and the use of carefully chosen selection criteria including safety, efficacy, quality, and cost. The confidence of consumers and clinicians nationally on the products selected has increased due to the inclusive decision making process and the selection of the safest and most efficacious products. The economic benefits have been very significant especially for the purchase of recombinant FVIII. Prior to the establishment of the board in 2002, prices paid for recombinant FVIII in Ireland were 26% higher than the median prices in European countries. With the new process, significant handling and distribution fees have been eliminated and the purchase cost per international unit also decreased significantly between 2003 and 2011. The major adjustments resulted from procurement processes in 2008 and 2011. Current prices are 57% lower than average prices paid in 2002 and are now significantly lower than the median price in Europe.

PO-MO-049
Characterizing Excessive School and Work Absenteeism in Hemophilia A

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Objective: Identify variables associated with excessive missed school/workdays due to hemophilia A in the United States (US).
Methods: Data were obtained from HUGS Va, an observational study of 329 patients from six hemophilia treatment centres in the US. Patients/parents of patients <18 years old completed an initial questionnaire about sociodemographics, clinical characteristics, and health-related quality of life (SF-12 for adults, PedsQL for children), then were followed for 2 years to collect healthcare utilization and outcome measures, including bleeding episodes and missed school/workdays (total/due to hemophilia). Literature defines excessive school absenteeism for children as missing ≥11 school days per year; excessive work absenteeism as missing ≥8.4 days per year, more than the US average workdays lost. Variables associated with excessive absenteeism were identified by univariate logistic regression. Multivariate analyses are planned.
Results: Complete data were available for 91 children (5–18 years); 117 adults (19–65 years). Due to hemophilia, mean missed schooldays was 4.6 ± 11.0 days per year (Median = 0.97; Range = 0–84); mean missed workdays was 14.4 ± 41.0 days per year (Median = 0; Range = 0–264). Eleven (12.1%) children and 26 (22.2%) adults had excessive missed days. In children, annual number of bleeding episodes (odds ratio, OR = 1.17, $P = 0.0003$), total PedsQL (OR = 0.93, $P = 0.0016$), PedsQL physical (OR = 0.95, $P = 0.0057$) and psychosocial functioning scores (OR = 10.94, $P = 0.0015$) were significantly associated with excessive absenteeism. In adults, annual number of bleeding episodes (OR = 1.06, $P = 0.0002$), SF-12 mental (OR = 0.93, $P = 0.0017$) and physical component scores (OR = 0.96, $P = 0.0408$), having no insurance vs. private insurance (OR = 6.2, $P = 0.0404$), and being HIV positive (OR = 3.3, $P = 0.0095$) were significantly associated with excessive absenteeism. Having severe hemophilia was not significantly associated with excessive missed days in either group.
Conclusion/Contribution to evidence base: Excessive school absenteeism compromises a child's education with future career and economic repercussions. This is also true of excessive missed workdays in adults. Identifying variables associated with missing school/work in hemophilia can guide development of interventions to reduce absenteeism. Severe hemophilia was not associated with excessive absenteeism.

PO-MO-050
A New Methodology to Assess Utility in Hemophilia Using Quality of Life Measures in Parents and Caregivers: The Caregivers' Burden Study

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Background: Utilities of different treatment approaches are commonly measured in patients, either children or adults, who undergo these treatments. Recently, regulatory authorities take into account utilities as perceived by patients' caregivers, particularly when patients are children and/or severely handicapped. No data are available on utilities of caregivers of children with hemophilia. In order to evaluate utility as perceived by patients' caregivers and in particular if primary prophylaxis might have an impact, we designed a prospective study that compares utility in caregivers of children on prophylaxis to those on episodic treatment. The study is also assessing whether patients' quality of life can explain potential differences in caregivers' utilities.
Aim: The aim is to evaluate and to measure caregivers' burden in such a way that it can be included in economic modelling for hemophilia showing the value of the treatment and the benefit not only to the patients but also to the caregivers of prophylaxis and on-demand treatment.
Methods: This is a pilot, non-interventional, multicentre study in at least 100 European patients. Enrolment criteria include patients with severe, moderate, or mild hemophilia A, with or without inhibitor, or history of inhibitor, ages 8–17 years old, and with at least 1 caregiver. Children are given generic (EQ-5D-Y) and specific questionnaires (Haemo-QoL). EQ-5D, SF-36, and Impact of Family Scale (IOF) will be administered to the caregivers.
Results and conclusion: This study will contribute to understanding the value of utility measures in hemophilia patients based on the combination between patients' and caregivers' outcomes.

PO-MO-051
Cost of immune tolerance induction in hemophilia A patients: Results from the ITER study

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Background: Although immune tolerance induction (ITI) is generally accepted as the first choice treatment to eradicate inhibitors (Inh) in hemophilia A patients (pts), little is known about determinants of outcomes and cost consequences.
Aim and Methods: The Immune Tolerance and Economics Retrospective (ITER) study is an observational, retrospective, multicentre, multinational study aiming to estimate cost of treatment in hemophilia A pts undergoing ITI after 1995 with any type of FVIII. Data on hemostatic treatment given in the following time periods were collected: up to 12 months before the diagnosis of Inh, between Inh diagnosis and ITI start, during ITI, and 12 months after the end of ITI. Costs of treatment were calculated in the perspective of the third-party payer and expressed as mean €/patient-month.
Results: 71 valid pts, with median age at ITI start=3.8 (0.4–41) years, were enroled. Before ITI the median Inh peak titer was 18.5 (0.80–704) BU. ITI was applied for a median of 1.22 (0.1–14.0) years and was successful in 84.5% pts. Before Inh diagnosis, pts cost 670€/patient-month for on-demand or prophylaxis treatment. Cost was 3,188€/patient-month between the Inh diagnosis and ITI start (92.1% for bypassing agents), and 60,078€ during ITI (76.8% for ITI, 19.4% for extra FVIII treatment, 3.8% for extra treatment with bypassing agents). The mean cost after ITI was 13,211€/patient-month. No significant relationship was found between cost during and after ITI and the success rate.
Discussion: ITI applied on pts with the characteristics of those involved in the ITER study is successful in 84% of them at a mean cost of 60,000€/patient-month during ITI,

plus 13,000€/patient-month through 1 year later. Further research is encouraged to value long-term benefits and costs attributable to ITI versus non-ITI, in order to identify the most efficient treatment option for the pts and for the healthcare system.

PO-MO-052
Pharmacoeconomic Evaluation with an Activated Prothrombin Complex Concentrate (APCC) in Patients with Hemophilia and Inhibitors (PRO-FEIBA Study)

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Introduction. Prophylaxis with APCC was shown to significantly and safely decrease the frequency of bleeding in patients with severe hemophilia A and inhibitors (Lessinger, Gringeri et al., 2011, NEJM),[1] but its impact on economic resources must be evaluated.
Methods. Patients with hemophilia A with inhibitors, aged >2 and using bypassing therapy to treat bleeding were recruited in a prospective, randomized, crossover study comparing 6 months of APCC. Cost evaluation was based on clotting factors consumption, mainly APCC but also rFVIIa and FVIII, which accounts for 99% of the overall costs and was quantified into monetary terms adopting the perspective of the third-party payer. We calculated the incremental cost per bleeding avoided with the same method used by Gringeri et al. (Gringeri et al., JTH 2011).
Results. As already published (Leissinger et al., 2011) prophylaxis as compared with on-demand therapy was associated with a 62% reduction in all bleeding episodes ($P < 0.001$), a 61% reduction in hemarthroses ($P < 0.001$), and a 72% reduction in target-joint bleeding (≥3 hemarthroses in a single joint during a 6-month treatment period) ($P < 0.001$). The per-patient, six-month cost of prophylaxis in all patients was $499,133 compared with $205,549 of OD. The incremental cost-effectiveness ratio (ICER) in the prophylaxis vs. OD period was 35,566 per bleeding avoided. The cost per bleed was $585 kg^{-1} body weight (mean body weight 60.8 kg). In Subjects with a ≥50% reduction of bleeding events, the per-patient, six-month cost of prophylaxis was $499,453 compared with $202,757 for on-demand treatment. The ICER was $27,282 per bleeding avoided.
Discussion: The magnitude of difference in cost during treatment periods was proportional to the corresponding difference in bleeding rate: in the OD period, costs were 58% lower than in the prophylaxis period, whereas bleeding events during prophylaxis were 62% less frequent as compared to the OD period. The ICER noticeably was more favorable in responders, which is totally attributable to the marked difference in effectiveness. Moreover the ICER during prophylaxis suggests prophylaxis to be more cost effective in children, who could probably derive the greatest benefit in terms of joint disease and long-term disability.

PO-MO-053
Cost of Illness Analysis of Hemophilia A: Resources Use and Direct Costs in Italy

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Background: Hemophilia A is a hereditary bleeding disorder. Its complications (e.g., chronic joint disease, intra-articular and intramuscular bleeds and infections) cause morbidity, impairing patients' quality of life. In 2008, 3,307 boys/men were affected by hemophilia A in Italy. Patients require lifelong infusions of clotting factor, represented by either recombinant or plasma derived factor VIII (FVIII), to prevent bleeding. The objective of this analysis was to estimate the economic impact of hemophilia A in Italy.
Methods: A descriptive cost of illness (COI) analysis was performed from the Italian National Health Service perspective. Only direct medical costs (therapy with coagulation clotting factors, hospitalizations, diagnostic exams, physicians' visits, and physiotherapy) were included. Regarding data input, epidemiological data were taken from the Italian Registry of Hemophilia, economic data from National Tariffs Registries. Medical resource use was measured by utilization of healthcare services at the patient level. All costs were reported in Euro and adjusted for inflation, using the Consumer Price Index (January 2010).
Findings: The COI analysis found that the management of hemophilia depends on different variables. The average cost of management of people with hemophilia is approximately €141.438,64 and €249.546,6 per patient treated with plasma derived and recombinant factor VIII. The analysis shows that the replacement therapy represents the main cost driver, accounting for 98% of total direct medical costs.
Conclusions: The current analysis confirmed that hemophilia A is a rare disease, but a very expensive condition. The high cost of hemophilia management is due especially to the infusion of FVIII, in particular for patients on prophylaxis. Few efforts have been made to quantify the economic burden of the disease in Italy. Otherwise, it would be necessary to estimate the costs of patients developing inhibitors and to calculate indirect costs in terms of work/school days lost to quantify the complete economic burden of disease.

PO-MO-054
Burden of joint disability in hemophilia A and hemophilia B patients

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Objective: To assess differences in healthcare costs and resource utilization among hemophilia patients with and without multiple joint-pain claims.
Methods: InVision™ Data Mart, a product of OptumInsight Life Sciences was used (January 2005-March 2009). Included patients were male, hemophilia A/B diagnosis (ICD-09 286.0 and 286.1), treatment with FVIII/FIX/bypassing agent during the analysis period, and ≥2 years of continuous enrolment from index date of first treatment. Patients were stratified into severe joint pain (SJP), ≥2 joint pain claims (ICD-09 713, 715, 716, 718, 719, 727) 12 months pre- or 6 months post-index, and minimal joint pain, <2 pain claims (MJP). Propensity score matching ensured cohorts were similar on age, factor/bypassing agent treatments, and Charlson comorbidity scores. Random forest analysis identified characteristics differentiating SJP/MJP. Regression models determined drivers of total costs of having hemophilia and hemophilia-related costs. **Results**: 284 patients (142 SJP, 142 MJP); mean age = 30 years. Mean (median) number of FVIII claims = 13.5 (6.5) in SJP, 7.3 (3) in MJP, and FIX claims = 2.4 (0) in SJP and 1.6 (0) in MJP. Over 2 years, average (median) total cost of a hemophilia patient was $630K ($248K). Total costs were significantly higher for SJP ($913K) compared to $354K in MJP ($P < 0.01$). SJP received more joint surgeries (30% SJP vs. 1% MJP) and consumed more healthcare resources, specifically pain medications (34 SJP vs. 17% MJP), joint imaging tests (82% SJP vs. 16% MJP), and hemophilia-related lab tests (average claims: SJP = 3, MJP = 1.7). SJP also consumed more services, more commonly, radiologists (58% SJP vs. 32% MJP), physical/occupational therapy (51% SJP vs. 19% MJP), and orthopedists (40% SJP vs. 3% MJP).
Conclusion: The presence of joint pain impacts costs of having hemophilia through high factor-consumption expenditures and healthcare resources. However, this impact may also be attributed to hemophilia severity, which cannot be identified via ICD-09 codes.

PO-MO-055
Budget Impact of FVIII Concentrates Taking into Account the Incidence of De Novo Inhibitor Formation in PTPs: A Breakeven Analysis Applied to ADVATE in the Italian Context

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Objective. The objective is to identify the number of previously treated patients (PTPs) affected by hemophilia A who, developing anti-FVIII inhibitor using a hypothetical FVIII (*FVIII "x"*), could lead to a breakeven of the cost with respect to the treatment with ADVATE©.
Methods. We perform a breakeven point analysis, developing a model. The breakeven point in the model represents the number of patients who should develop inhibitors using *FVIII "x"* in order to get a budget impact equal to the treatment with ADVATE©, in a population of 348 patients.
Model. Population: we simulate a treatment of 348 PTPs affected by severe/moderate hemophilia (FVIII ≤ 2%), following the characteristics of the population of Oldenburg (*Haemophilia*, 2010). Assumptions: population age≥12y, weight 70 Kg; 5 years time horizon, 3% discount rate; for patients treated with ADVATE© we assume 0.29% probability of developing anti-FVIII inhibitor (Oldenburg 2010). We compare 2 scenarios: all patients treated with ADVATE© and all patients treated with *FVIII "x"*, assuming that in both scenarios 50% of the patients follow an on-demand regime (ADVATE© or *FVIII "x"*: 34.5 IU kg^{-1}; bleeding events: 1.5 per month) and 50% a prophylaxis regime (ADVATE© or *FVIII "x"*: 32.5 IU kg^{-1}, 3 infusions per week). To patients developing inhibitor, a 2-year immune tolerance induction therapy is applied. Adopted cost per IU is: for ADVATE© 0.75 €, for *FVIII "x"* 0.69€. We calculate the following costs: a) treatment with ADVATE©; b) treatment of patients who develop inhibitor with ADVATE©; c) treatment with *FVIII "x"*; d) treatment of patients who develop inhibitor with *FVIII "x"*. The model also estimates a breakeven curve showing the cost gap between the 2 treatments varying the number of patients developing inhibitor with *FVIII "x"*. A sensitivity analysis is performed.
Results. We estimate that in order to reach an equal expense between ADVATE© and another *FVIII "x"* the number of patients who should develop inhibitor using a *FVIII "x"* is 4.44.
Contribution. The results of the paper could have important health economic, budget impact, and health policy implications.

18-HEMOPHILIA PROGRAMS AND ORGANIZATIONS

S-TU-04.2-4
General outreach: The Kenyan experience
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Objective: To highlight the experience of the Kenya Haemophilia Association in designing and conducting outreach campaigns in Kenya.
Introduction: The Kenya Haemophilia Association (KHA) was founded by the late Professor E.G. Kasili, the first hematologist in Kenya, in 1984, in order to offer a comprehensive-care service to people living with bleeding disorders (PLWBD). The KHA is made up of volunteers that include hematologists, nurses, physiotherapists, and laboratory technologists, as well as parents and PLWBD.
Design: The idea of outreach programs was first conceptualized during a general meeting of KHA at which all members, including all cadres of the medical team, were there. Secondly, all parents and PLWBD were invited, and presentations were made by each discipline of the medical team on the different aspects of managing bleeding disorders in an underprivileged society, and in a developing country like Kenya. Thirdly, participants agreed to meet and discuss how to conduct outreach programs. During the subsequent meeting, the main issues discussed were the feasibility and practicability of conducting these campaigns, as well as the prescribed functions of each member. It was agreed that the best way was to conduct educational campaigns for healthcare workers, especially those in the blood and blood banking sector, not just in the capital city of Nairobi, but particularly in the provinces/counties.
Conduct: Several continuous medical educational (CME) talks were conducted in the distant Western, Eastern, Nyanza, Coast, and Central provinces. The participants included physicians, surgeons, obstetricians/gynecologists, dentists, nurses, physiotherapists, and laboratory technologists. The purpose was to refresh their knowledge and to increase their index of suspicion when they come across any patient with bleeding tendencies.
Results: The results were gratifying as all participants were hungry for more knowledge and eager to assist and to contribute towards the comprehensive care of PLWBD.

S-TU-04.2-1
Medical and lay cooperation: A key strategy to implementing a hemophilia care program in Africa
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Hemophilia is a rare and unknown disease among the public, the authorities, and the health staff in developing countries. The big challenge for people dealing with hemophilia care in Africa is to make this disease recognized as part of the health system, where other priorities such as malaria, tuberculosis, and HIV infection are more identified. Medical staff and patients' organizations should have the same vision, and it is imperative for them to work together. The objective of medical and lay cooperation is to reinforce the power of each group to make better arguments in advocacy for hemophilia care, and also to improve the quality of patient follow up. This cooperation needs more understanding from each group, information sharing, and reciprocal consideration. This can be made by permanent exchange between the two groups and good education of lay people on the challenges faced by hemophilia care in the country, in particular regarding diagnosis and access to treatment for people with hemophilia. Inversely, medical staff should be more familiarized on social problems from patients, as this information can be used to improve patient care. A good organization with a precise definition of rules and attributions of each other is necessary to prevent occurrence of potential conflicts between the two groups. Drawing on the Senegalese example, this presentation emphasizes the indispensable need for these two entities to cooperate in order to obtain positive results on hemophilia care in Africa and to escape possible risks of conflicts.

S-TU-04.2-5
VWD outreach
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Background: Von Willebrand disease (VWD) is a hereditary bleeding disorder caused by inherited dominant or recessive defects of von Willebrand factor (VWF). These defects may be quantitative or qualitative. The defect causes increased tendency of bleeding in the affected person. Mucocutaneous bleeding is a particularly prominent feature of the bleeding tendency, although other forms of bleeding may occur. The prevalence of the disease is mentioned to be up to 1% of the population, but most of the affected individuals have mild bleeding symptoms, and in most cases may not be diagnosed. Outreach for patients with VWD requires targeting populations that may be at risk of having the disease. Since the disease affects both males and females, menstruation is of particular importance as many female patients with VWD present mainly by menorrhagia. On the other hand, menorrhagia is a common problem in females during their fertile period. Due to these last two facts, outreach for patients with VWD may best be approached among women with menorrhagia. Other target groups that should be screened include relatives of patients diagnosed with VWD. Increasing awareness among health professionals about VWD is an important way to refer suspect cases, and consequently diagnosis of patients with VWD.
Aim of the study: The study is an epidemiological surveillance to identify prevalence of VWD among women with menorrhagia due to dysfunctional uterine bleeding (DUB), relatives of cases with VWD, and patients referred due to objective bleeding history.
Methods: 1) Bleeding scoring sheet for subjective evaluation of patient bleeding history; 2) menorrhagia scoring sheet; 3) CBC & Ferritin; 4) prothrombin time, aPTT, and TT; 5) FVIII assay, VWF RiCof and antigen; 6) VWF collagen binding and FVIII binding assays for classification of the type of VWD in diagnosed cases; 7) other clotting factor assays, when there is a need, as well as platelet function test.

S-TU-04.2-3
Research and ethical aspects of clinical trials
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With the rapid evolution of new therapies, the hemophilia community is increasingly expected to be involved in many clinical research studies. In developed countries, participation of people with hemophilia in studies is increasing, limited by participant fatigue and possible restriction of treatment regimens in the study setting. Therefore many studies are looking at developing countries to meet their recruitment targets. In developed countries, clinical research policies, practice, and guidelines are well established and are part of the standard of care offered by research facilities. However, many emerging countries may find some of these guidelines not practical or entirely applicable for their prevailing environment. A number of factors including social, economic, cultural, and linguistic barriers may influence the application and implementation of these guidelines. The ethical challenges faced by researchers, study participants, and regulatory authorities in developing countries can further impair successful research participation in the developing countries. The aim of this session is to highlight some of the challenges encountered in doing clinical research in emerging countries and to suggest possible solutions from a developing world perspective.

S-MO-03.2-4
Example from Belarus
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The Republic of Belarus consists of 6 regions and the capital, Minsk, where about 1.5 million people reside. Six years ago the amount of consumed factor 8 was 2 million international units, and no patient registry or up-to-date treatment protocols were available. There was also a shortage of professional doctors having experience and skills in hemophilia treatment. There was no well-organized patients' association, and the existing one covered only the city of Minsk. A substantial reorganization was needed, as the situation was distressful. Some measures have been taken in recent years, namely, the activity of the organization was extended across the country, representatives of all regions are now included on the board of the patients' association, and a door-to-door approach was implemented in the regions. At the same time, the association started its active cooperation with the World Federation of Hemophilia (WFH). The main objectives of this cooperation were training of patients and improvement of clinicians' skills and professional levels. WFH provided aid in many respects, including the provision of medical literature to patients and doctors, participation in negotiations with the Ministry of Health of the Republic of Belarus, financing for training doctors abroad in leading world clinics.
Milestones: 1) The establishment of the hemophilia centre in Minsk; 2) the procurement of 18 million units of factor 8 and 3 million units of factor 9; 3) the implementation of a patient registry in the country; 4) endoprosthesis replacement surgeries started (about 10 done); 5) 2 all-Belarus training workshops for patients conducted, 5 regional hemophilia schools, 4 workshops for doctors with various qualifications; 6) for patients with severe hemophilia, the provision of 10,000 units per quarter for home treatment, or more according to the council of doctors' decision.
Tasks for the near future: 1) Increase factor 8 procurement by up to 40 million; 2) prophylaxis for children under 18 and adults with severe hemophilia; 3) endoprosthesis replacement for everyone who needs it. We still have a lot of problems; however, we hope that by joint efforts and in cooperation with WFH, we will be able to ensure that the lifestyle for patients with hemophilia in our country will not differ in any way from that of healthy people.

S-MO-03.2-3
Example from Egypt: Outreach methodologies
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Background: Since 1971, the Egyptian Hemophilic society (EHS) had been caring for diagnosed patients with hemophilia (PWH). The EHS had 6,200 registered patients in the national registry through the end of 2011, which were differentiated as follows: 3,870 hemophilia A; 967 hemophilia B; 475 von Willebrand disease (VWD); and the rest (888) comprise rare bleeding disorders, including deficiencies of factors I, II, V, VII, X, XI, XII, XIII and platelet dysfunctions. Given that both hemophilia A and B are X-linked recessive disorders, while VWD is caused by inherited dominant or recessive defects of von Willebrand factor (VWF), and that in Egypt, most families prefer marriages among relatives, this positive consanguinity will lead to increasing the number of cases and carriers within the same family.
Aim of the study: 1) Our aim is to increase the number of diagnosed and registered patients with hemophilia, in collaboration with the HTCs, by surveillance of hemophilic families to diagnose carriers and new cases; 2) the diagnosis of VWD among women complaining of menorrhagia and dysfunctional uterine bleeding with collaboration of Al Galaa gynecological outpatient clinic (MOH) and Shabrawishi Hospital hematology clinic and the National Research Centre.
Methods: 1) Patient bleeding history and family history; 2) menorrhagia scoring sheet; 3) CBC; 4) PT, PTT, & TT; 5) factor VIII & IX assay; 6) VWF Ricof., antigen,VWF collagen binding and F VIII binding assays for classification of the type of VWD in diagnosed cases.

S-MO-03.2-2
Example from Mexico: Outreach
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Mexico Hemophilia Federation, Mexico City, Mexico

Aim: Specifically, the aim is to present our experience in outreach and to describe the steps we have followed to create an outreach program in our country, including the resources that were secured and the challenges that were faced.
Summary: In the last 10 years, Mexico has changed the face of hemophilia, going from a registry of 2,098 people with hemophilia (PWH), to a current record of 5,082 PWH; this represents 70% of patients statistically expected. From hospital care mainly with blood component treatments, to a treatment with concentrates, mostly with appropriate home care, even with primary prophylaxis and secondary in some cases. Social security covers 60% of the national population, serves approximately 2,600 PWH, with an index of 1.7 IU factor per capita, within the institution. This has reached an acceptable hematological treatment, allowing patients a better quality of life. Efforts have been focused on orthopedic treatment, rehabilitation, and dental care also to the VWD and inhibitors patients. Approximately 1 000 PWH do not have social security services and are treated in government hospitals. Prior to 2006, patients were treated with cryoprecipitate and plasma; however, all children born after that year have concentrated treatment. Since 2011, this right to health has risen to 10-year-old children, so the number of patients who have modern treatment has enlarged. The national member organization (NMO) has performed constant work in several ways: 1) having a national registry of patients; 2) lobbying national and state health authorities; 3)lobbying the authorities of social-security hospitals and government hospitals; 4) promoting information updating in medical area in the various specialties involved; 5) promoting training on the patients' rights; 6) providing management training skills to the leaders of the 19 regional associations and youth leaders. The NMO keeps working to keep the disease front and centre in the minds of health officials and physicians, in order to keep it on the government's health agenda.

S-MO-03.2-1
Outreach Program: An example from Thailand
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Our main objective was to work with the National Hemophilia Foundation of Thailand (NHFT) and the National Health Security Office (NHSO) on the project ''Early Treatment Program for Hemophilia Patients.'' The ultimate purposes were to improve the standard of care and to improve access to treatment and care. Hemophilia is a high-cost-treatment disease that needs a comprehensive care team with an awareness of patients with Hemophilia (PWH), family members (FM), and the community in order to improve the quality of the life (QOL). Nan is a small province in Thailand with a small economic scale and mostly high plane in the geographical conditions, which leads to transportation difficulties. Despite all the hurdles, we were able to register 16 cases of Hemophilia and engage them, such that they received proper treatment and received factor concentrate on a regular basis from Nan Hospital, which was approved by the NHSO to be the HTC. The establishment of the TPC regional network also helped our patients and the communities understand more about Hemophilia. In 2007, the Nan Hemophilia Patients' Club was formed. In 2008, with the support of NHFT and NHSO, Nan Hospital was appointed to be HTC, which we had explored and motivated the 16 patients to the patient registry. Success resulted from empowering healthcare providers, PWH, FM, and volunteers to set up many programs such as self infusion, self care management, and early treatment, that can be done at home (e.g. RICE). From our starting point in 2007, we found that we had greatly improved the understanding of Hemophilia among PWH, FM, volunteers, and the community, and had also improved the QOL, which is reflected in the ability to go to school, to go to work, and in reduced hospitalization, both in terms of frequency and the length of time in the hospital. We strongly believe, and would like to advocate, that the psycho-social aspect is one of the key success factors. Our next step is to form a self-help group among patients.

PO-MO-059
Disarray to distinction: Fast-track restructuring of hemophilia care in Hong Kong
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Background: Despite being an affluent city offering residents full medical coverage, hemophilia care in Hong Kong (HK) is fragmented. There is a lack of pediatric adult transfer plans, treatment protocols, proper communication between hospitals and with the government, and a complete absence of designated hemophilia nurses and physiotherapists.
Material and methods: A review of the restructuring of citywide hemophilia care was commissioned by the government and helped by the World Federation of Hemophilia (WFH). The 7-million population of HK is divided into 7 administrative districts. In each district hospital, a hemophilia ''local cell'' was formed, consisting of 5 members: an adult and a pediatric hematologist, a physiotherapist, a nurse specialist, and an elected patient representative. Likewise an elected central ''mother cell'' of 5 members deals with the government. Service gaps between the local standard versus the WFH standard (developed countries) were identified. The hemophilia campaign was bundled with a mirror thalassemia campaign to increase voice and clout. The extra resources and manpower needs were calculated and put forward to the government at a patient summit. In a 2-year staged application process, hurdles were overcome by means of hospital-by-hospital lobbying, media pressure, political party involvement, and common-sense talk with the central authorities.
Results: The following objectives were achieved or included in the corporate plan: one designated nursing officer appointed per district for hemophilia plus thalassemia care; endorsement of ''Factor First'' policy at casualty; agreement on treatment protocol and transfer age between adult and pediatric units; agreement on primary factor prophylaxis; appointment of designated trained physiotherapist in each district; recognition of the hemophilia ''cells'' and ''mother cell'' by the health authority, and staging the first WFH-TIF nursing course with local and national endorsement. Genetic testing and inhibitor case management remains unsolved due to system and territorial inertia.
Conclusions: Despite competing needs, through patient empowerment, catch-up efforts in standards of care can be achieved in affluent societies within a reasonable time.
Acknowledgements: Dr. C.K. Li, A. Ling, J. Yau, R. Li, D. Chan, E. Chan, C.Y. Lee, L. Sun, G. Chan (pediatrics), H. Chan, C.W. Lau, R. Wong, S.Y. Lin, V. Mak (adult) A. Chiu, F.C. Pang, L. Lee (head office), A. Leung (physio), C. Ng (nursing) Civic Party, NOW TV, Radio HK.

PO-MO-060
Telemedicine in hemophilia: Virtual consultation for the hematologist at Patient's Home
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Introduction: Domiciliary replacement therapy (DRT) ensures rapid infusion of lacking factors when any bleeding episode occurs and reduces hospital dependency of patients with hemophilia. However, these patients still have to visit the hospital frequently because the hematologist can prescribe general guidelines for home-replacement therapy but cannot adapt them to the bleeding evolution.
Material and method: For reducing hospital dependency, we have designed a domiciliary virtual consultation based on three digital applications that permit a connection between the patient and the hematologist. In the first application, the patient describes the clinical characteristics of the bleeding episode, dose, and length of self-treatment. Consequently, we can contrast the consistency between the medical prescription and patients' compliance at home. These records are downloaded to our database, avoiding manual typing. The second application consists of the electronic monitoring of hemarthrosis in elbows, knees, and ankles and DRT by ultrasounds performed at the patient's home, then sending the images by Internet to the hospital. With this application we combine both the advantages of DRT and the DRT monitoring of hemarthrosis (by fitting dose, frequency, and length of treatment to the ultrasound's results). The last application permits, through a webcam, a virtual intercommunication between the patient and hematologist.
Results: We have included 45 patients, who were recruited by living near the reference hospital, in the first electronic application around 2011. We have performed 41 domiciliary ultrasounds in the same period. We have established 7 virtual consultations by webcam.
Discussion: This virtual consultation will never substitute a hospital medical visit, but it may be a useful tool for both the patient and the hematologist. We can reduce the hospital dependency, implying an improvement in quality of life. *Study funded by Pfizer Inc.*

PO-MO-061
A project to establish clinical and social-assistance infrastructure in Afghanistan
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In a challenging team effort, a network project was carried out by Fondazione Paracelso ONLUS between 2009 and 2011, training a physician and a lab-tech from Esteqlal Hospital in Kabul, Afghanistan, equipping a laboratory with the necessary electromedical devices, and establishing an association of patients, fundamental for purposes of providing social support and information to families, raising awareness, and putting pressure on the health authorities to encourage them to step up their focus on hemophilia. The project was led in strict collaboration with the World Federation of Hemophilia (WFH), the ultimate goal being admission to the only world organization for hemophilia, the hub for international cooperation programs. This will allow Afghanistan to be emancipated from its past dependency on a few (very few to be honest) well-meaning small donors, opening the way to long-distance twinning projects between hemophilia treatment centres (HTCs) and national member organizations (NMOs) from across the world, the training of healthcare professionals (physicians, physiotherapists, orthopedic therapists, nurses, social workers, and psychologists) and donations sustained over time of pharmaceutical products for the treatment of hemophilia, without which, as we all know, life expectancy for patients, both children and adults alike, is alarmingly diminished. At the end of October 2011, a small delegation (one from Fondazione Paracelso, one from Milan HTC) site-visited Kabul to make sure that this embryonic yet vital assistance network had everything it needed to become operational. Back in Italy, Fondazione Paracelso established connections with Italian organizations and authorities, achieving an agreement that will take to Esteqlal Hospital 300,000 IU per year of Clotting Factor Concentrate (CFC) for 2012–2014. A brief video to document our trip and mission in Afghanistan has been shot, reconstructing the evolution of the project, the steps taken to meet the relevant requisites, and its genesis.

PO-MO-062
The first Iranian comprehensive hemophilia care centre: A ten-year experience
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Hemophilia disease has been a very troublesome, expensive, and chronic disorder up to now. A small genetic defect affects the coagulation system and makes a person susceptible to bleeding. If a standard treatment is provided, this is not a life-limiting disorder. In spite of the fact that the number of people with hemophilia is small in comparison to

other chronic disorders, hemophilia presents a deep challenge to governmental health systems. While the cost of treatment is less troublesome for rich countries, it has always been a big concern for medical authorities in developing countries. The history of hemophilia treatment in Iran goes back a few decades when the milestone of treatment was only fresh frozen plasma. Gradually, in the shadow of forerunner physicians' efforts, authorities' attention, and patients' follow up, coagulation factor concentrates became available. After a while, the Iranian Hemophilia society decided to establish a comprehensive hemophilia care centre for these patients. The reasons for this decision were (but are not limited to) overcrowding of governmental centres and the quality and quantity of their services. The first Iranian Comprehensive Hemophilia Care Centre (ICHCC) was established in 2000 and has provided services such as internal and pediatric medicine, dentistry, physiotherapy, routine and coagulation laboratory, genetic laboratory, pharmacy, nursing and vaccination, and psychosocial counselling. During the past 10 years, the centre has had successes and challenges. Providing various and centralized services in one complex is an important distinction for the centre. More than 7000 files have been created for these patients. Genetic studies, chemical synovectomy (rifampicin), immune tolerance induction, low-dose prophylaxis, treatment of von Willebrand disease (VWD) with plasma derived FVIII (instead of cryoprecipitate) all started in ICHCC first and in a positive competitive atmosphere, followed and extended in other centres. Relations between ICHCC and the Ministry of Health or other governmental medical centres and the budget of ICHCC have been our main concerns during these years.

PO-MO-063
How the concept of peer support has been used in Western Australia to improve healthcare outcomes for people with inherited bleeding disorders

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Aim: People affected by inherited bleeding disorders have access to information and education through a variety of sources. However, those affected may feel isolated and may be unaware that many of their fears, anxieties, and experiences are common. The Haemophilia Centre of Western Australia (HCWA) and the Haemophilia Foundation of Western Australia (HFWA) organize and support positive peer-support opportunities, thus increasing awareness, a sense of community, and improvement in accessing health care though the hemophilia treatment centres (HTC).
Methods: There have been a variety of initiatives created to provide peer-support opportunities for all those affected. These include the men's and women's breakfast, morning tea at the HTC, IV access workshops, rural visits and camps, and specific support groups, such as a caregivers' group, which provide an opportunity for people in similar situations to come together. The HTC staff is also able to facilitate one-on-one meetings for people as specific situations arise, such as bringing a women considering pregnancy and a women that has been through uneventful pregnancies together. The HCWA, along with support from the HFWA, created a DVD that allows those requiring frequent IV access to observe a number of men with hemophilia performing IV access, highlighting the notion that everyone finds their own technique that works for them. Future topics include a workshop for young adolescent women who are affected, particularly hemophilia carriers.
Discussion: This collaborative relationship in the provision of education and peer support benefits all parties. The HTC benefits with improved access and attendance by patients and enhanced engagement with patients in decision making. HFWA benefits through the direct access to patients, enabling increased membership and improved sharing of information on current and emerging issues, ensuring HFWA's provision of service is purposeful. Bringing together people affected by inherited bleeding disorders has created a strong and functional community which allows individuals to feel empowered, involved, and active in their health care.

PO-MO-064
Connecting youth: Engaging young people with bleeding disorders in a communication project

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Improvements to treatment and care of young Australians with bleeding disorders have created a new generation with expectations of living a "normal" life. Nevertheless, hemophilia foundations, hemophilia health professionals, and parents have reported that many young people experience significant problems due to isolation and lack of knowledge about bleeding disorders or how to apply this information to themselves. At the same time, they have struggled to engage young people in current and future planning for treatment and care services and in peer education and support. Haemophilia Foundation Australia (HFA) recently commenced a project to better understand the needs of young people with bleeding disorders and to develop a web-based communication tool for them. The tool is intended to enable young people to connect, share experiences, and obtain information about relevant life and lifestyle choices, including work, travel, sport, recreation, relationships, and socializing, while building the youth leadership capacity of HFA. The project has highlighted the importance of a process to establish HFA's credentials with young people as having a credible youth-based approach with activities and resources that are attractive and relevant to them. HFA employed a Youth Project Officer as project leader who is a peer of young people in age and communication style. To involve young people in the consultation and development, a Youth Working Group was set up and young people recruited through regional hemophilia foundations and hemophilia treatment centres. Face-to-face social contact at events such as the national conference and personalized communications between the Youth Project Officer and young people has been key to initial engagement in the project. The project is exploring face-to-face and online-communication approaches to enable young people to feel personally connected and that encourage participation, using popular technologies and styles such as interactive video posting and Q & A blogs.

PO-MO-065
How to manage a hemophilia treatment centre in an emergent country: The Moroccan experience

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Introduction: The hemophilia treatment centre of Rabat (CTHR) launched the challenge in 2009 to become the best hemophilia centre in Morocco and to compete with the best existing treatment centres around the world. This summary contains the most important activities carried out by the CTHR from 2009 to 2011.
Objectives: CTHR's goal during these 3 years was to achieve 3 objectives: 1) a more-available concentrate of factor within the hospital; 2) setting up a national program with the Ministry of Health that had actually started in November 2011; 3) a better quality of life for our patients (home treatment, less absenteeism at school). For this, we have worked on four projects: 1) managing the database: before 2009, the data of the few registered patients was incomplete, inaccurate, and not updated. Today, we have identified more than 400 patients. The database still contains gaps, largely due to the disappearance of some patients; 2) contact with patients: a) define their needs; b) know their socio-economic and cultural status; c) establish a relationship based on trust between them and the medical and paramedical staff; 3) establishment of treatment protocols and publication of articles; and 4) signature of partnerships with pharmaceutical companies and international organizations (GAP) to challenge and raise the level of the centre.
Conclusion: These projects can only be achieved if concentrate of factor are available for all our patients. We went from 0.02 IU per capita in 2007 to 0.08 IU per capita in 2011. Our objective is to reach 0.1 IU per capita in 2012 and 1 IU per capita in 2015.

PO-MO-066
A national infrastructure for rare blood disorders: An evaluation of staffing, training, and services in the US federally-supported hemophilia treatment centres

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Background: The United States Hemophilia Treatment Center Network (USHTCN) was created in 1976 by the US government to develop a national infrastructure for providing coordinated, multidisciplinary care to individuals with rare bleeding disorders. Today this network of 129 centres treats over 30,000 individuals with inherited bleeding and clotting disorders. Despite the longevity of the network no evaluation of the USHTCN has been conducted.
Objectives: The objective of the study was to assess the USHTCN's bleeding disorder staffing patterns and services and examine differences by size of hemophilia treatment centre (HTC) patient base. Methods:
An e-survey was administered to all USHTCN's 129 centres to evaluate HTC characteristics. Demographic data from the 2008 aggregate Hemophilia Data Set were combined with responses from the e-survey to compare HTC characteristics by size of patient base: 1) Small (<115 patients), 2) Midsize (115–289 patients), and 3.) Large (>289 patients).
Results: 93% of all HTCs had all four required core staff (physician, nurse coordinator, social worker, physiotherapist); core staff years of hemophilia experience and educational opportunities to orient new staff were similar across HTC size. Analysis by HTC size showed no difference in the availability of specialty services (e.g., coagulation laboratory testing); 28.7% of HTCs operated outreach clinics to enhance geographic access. Only 12.5% of the smallest HTCs had an outreach clinic, compared to 27.7% of midsize and 46.9% of the largest HTCs.
Conclusion: USHTCN is a model of a national network infrastructure that provides coordinated, multidisciplinary care for persons with rare blood disorders who are geographically dispersed. Regardless of size, the network's 129 centers maintain a highly experienced core staff, provide training for new clinicians, coordinate care with specialists, and expand access to care through outreach clinics.

PO-MO-067
"Governance" in an NMO

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"Governance" is now the new approach to the construction of the public-public, public-private, and private-private process. However, we cannot abuse this concept (recte: of this word), so much so, one of the first theorists of this called this as a "fashionable catchword". And so then, our proposal is to carry out a précis about the diverse meaning of "governance", with special emphasis in "governance" as "relational government" or "network governance"; and then, try to persuade about other meaning of "governance" that we consider "spurious". Only a process to influence to the limited number of stakeholders. Change our structure: A process to auto influence, trying to improve our system and facilitate the relations between the NMO and the stakeholders. Influence the exo-system and the structure of other stakeholders: This process is the "last step" of an organization, having influence in the public or private decision process. Last but not least, NMOs have a very special situation for their relations with industry and policy-makers. Governance can be implemented like "good government", namely, implement measures to warrant independency and impartiality of our organizations respect the exterior; both in the be then in the seam.

PO-MO-068
Unique just like you
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Introduction: The Catalan Association of Hemophilia, whose area of influence is Catalonia, was founded in 1976 and attends to approximately 1,000 members. We could share many stories about these years dedicated to the care and attention of people with hemophilia (PWH) and their families, because our principal aim is to accompany, assess, and attend to the community during each step along the path that starts once hemophilia is diagnosed.
Objective: To film a video that will introduce our organization through the use of new technology. Description:
This video serves as a testimony to the work that we carry out, what we represent now, and the ideas we have about what is involved with living with hemophilia. Art, Alex, Sergi, Isidre, Felipe, and other people from our community explain their own experiences. These different experiences are very valuable because, in fact, with or without hemophilia, each human deals with the task of building a life, giving it sense, and admitting to some limits. For this reason we called the film ''Unique just like you.'' These testimonies highlight the efforts made by the Association to prevent people with hemophilia from focusing their life exclusively towards medical care. Due to this, the Association offers a wide range of different attention programs, because it believes that it is not only about taking care of a body with a chronic disease, but rather about concentrating on a person's general health. All the proposals and services offered by the Association are designed to provide PWH experiences that allow them to build their own experience of hemophilia. The close collaboration between the Association and the Hemophilia Unit of Vall d'Hebron Hospital is fundamental for understanding how it has been possible to offer this integral service to PWH.
Conclusions: We can show in a dynamic, engaging, and participatory video how we want to continue working in collaboration, all together, to guarantee a positive present moment and to build a better future.

PO-MO-069
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The aim of our poster is to highlight important factors for improvement of patient compliance. As a result of the discussion of a recent workshop on this topic, and due to our own long-lasting experiences, current challenges will be presented and potential solutions towards a better patient-compliance management are discussed. **Compliance in hemophilia—requirements for an enduring quality of life**:Patient compliance in medicine means cooperative behaviour by the patient during medical treatment. Due to the chronic nature of their disease, patients with hemophilia have to cope with problems every day that are much different than problems resulting from other chronic diseases. As a matter of fact, hemophilia patients always have to carry their medication with them and need to have the skills that are necessary to administer the respective factor concentrate intravenously. Furthermore, they need to follow the directives of the medical team in order to be able to lead a relatively normal rather than handicapped life. The medical team of the hemophilia comprehensive care centre is always there, following a 24/7 hotline approach. ''Can do'' attitude: patients need to remember the time when they learned the self-administration of factor concentrate. Be a part of the hemophilia patients' network: ''You are not alone''; organization of patient workshops, patient meetings, hemophilia symposia. Cooperation with their general practitioner, cooperation with pre-school, school, and working place. Further information for hemophilia patients on their daily life, sports and travelling

PO-MO-070
A French summer camp for people with hemophilia: An original multidisciplinary program for self-treatment
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For 12 years, the hemophilia treatment centre (HTC) team in Caen organized summer camps related to self-treatment for people with hemophilia (PWH) and patients with von Willebrand disease. In 2010, this self-treatment teaching experience, during a 10-day summer camp, was proposed to 24 patients from Caen and other French HTCs in France: 18 patients with severe hemophilia A (4 of them with FVIII inhibitors and ITI regimen), 1 patient with severe hemophilia B with FIX inhibitor, and 4 patients with mild hemophilia A. One patient had a severe Factor X deficiency. Three of them had a central venous access (portacath). Patients were 7–17 years old, and we organized a sponsorship system where adolescents (7–10 years old) were sponsored by teens (11–17 years). On the first day of camp, each patient had to accept and sign an individual educational program. The training program for self-treatment consisted of educational courses about clinical signs and treatment regimens for the main bleedings, such as hemarthrosis, hematomas … and the high bleeding risk localizations. The steps of self-infusion were also taught. Each afternoon they can evaluate benefits of sports such as swimming, badminton, beach games, canoe, kayak, and physical exercise. This camp was very efficient in teaching children self-treatment and in encouraging independence from parents. The first evaluation of this educational program efficacy was based on the same rules as for the ''French accompanied driving'' at the end of the summer camp and a second evaluation was performed 6 months later. Since this summer camp experience, 12 of the participants have proved able enough for self-treatment, this even includes 2 patients with FVIII inhibitors, and all of them will do this teaching program again.

PO-MO-071
From nothing to comprehensive hemophilia car: An experience of Karnataka Hemophilia Society
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Twenty-three years ago, in the state of Karnataka in South India, hemophilia was almost an unknown disorder even among medical professionals. With no government support, insurance cover, factor concentrates, FFP, cryoprecipitate, or diagnostic facilities, what remained were on-demand whole blood transfusions, pain, severe financial burden, and suffering. With this as background, a few persons with hemophilia (PWH), parents of some children with hemophilia, and their well-wishers formed a support group, the Karnataka hemophilia society (KHS). Funds to run a care centre were raised by a fashion show and accumulated donations. They could also garner resources for a bigger event. A renowned playback singer of the film industry preformed musical concerts, which enabled transforming a 2-bed care centre into a 20-bed hospital. But how to fund the running cost? The answer was the National AIDS Control Organization (NACO), which needed space for spreading its work and KHS, which needed to source funds for the running cost of the hospital; this was a symbiotic win-win situation. The international Twinning Program infused new ideas, instruments, and contacts. Physiotherapists, nurses, and doctors were trained, and a blood bank was started. In 23 years we went from nothing to a 20-bed comprehensive care hospital with diagnostic and treatment facilities—a dream come true for PWH, but also the fruit of unswerving dedication and hard labour on the part of its key persons. With musical evenings, the Twinning Program, partnerships with NACO, along with the activities of lobbying the government, arranging CMEs, youth camps, women's activities, KHS has come a long way indeed, with ideas worth emulating.

PO-MO-072
Strategic advocacy program to involve government in hemophilia care: An experience from India
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Hemophilia, being a ''low volume, high cost disorder'' and having low levels of awareness fails to draw the attention of government, especially in developing countries like India. Hence, it is a challenging task for leaders of the hemophilia community to involve the government in hemophilia care. The objective of this paper is to share the experience of this advocacy effort over the last 20 years. After the formation of self-help groups, the task of creating a public-awareness program was initiated. World Hemophilia Day, health camps, and the involvement of celebrities have attracted the print and electronic media. The Society has not lost any opportunity to get Word Hemophilia Day into the media. The involvement of celebrities has enhanced the visibility of hemophilia within the general and medical communities by garnering support from every section of society. Sensitization of ministers and policy makers at every step of awareness programs resulted in making AHF available at every government district hospital in the state of Karnataka. This example was taken to neighboring states and pressure was mounted on the government to get involved in hemophilia care. Insensitive governments dealt with public interest litigation filed in courts of law, which resulted in forcing the government to step into hemophilia care. Once the government was involved in hemophilia care, the self-help group shifted its focus towards rehabilitation programs for hemophilia, but a vigilant watch-dog role has to be played in follow-up action with the government to continue the support. Involving the government in hemophilia care cannot be achieved overnight. It requires strategic public awareness programs including media the law if necessary. Sensitization of policy makers and bureaucrats with proper data and documents is an important step in advocacy programs including constant and consistent follow-up.

PO-MO-073
Collaborative working: The Newcastle initiative
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A multidisciplinary QIPP workshop was convened in Newcastle under the auspices of the Specialised Healthcare Alliance and North East Specialised Commissioning Group. Participation included clinicians, nurse specialists, commissioners, patient representatives, and industry. The purpose of the day was to explore how hemophilia services could be developed to combine high-quality care with improved efficiency in a cash-constrained National Health Service (NHS). The workshop's recommendations addressed a number of clinical and non-clinical issues affecting hemophilia patients, including the extension of adult prophylaxis on a targeted basis; prioritizing guidance on orthopedic surgery to inform more consistent decision making; and developing hemophilia networks across the country as a means of ensuring equitable access to comprehensive care. The workshop's recommendations were echoed by the Haemophilia Society's ''Fit for the Future'' patient survey and have been incorporated in what is now the Newcastle Initiative, which aims to coordinate multidisciplinary collaboration to achieve the following objectives: widen the focus of hemophilia-related policy communications, while leaving no room for repetition of past mistakes; develop a broader commitment to supporting the highest standards of care; and ensure that patients and their families are at the heart of decision making on services and treatment. The Newcastle Initiative has an annual program of work aimed at achieving these objectives and implementing the workshop recommendations. Regular meetings are supplemented with targeted campaigning on specific issues. Initial success includes the decision of the The United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) to take forward a multidisciplinary review of orthopedic surgery for people with hemophilia. At a political level, the Newcastle Initiative has enlisted the support of parliamentarians to ensure that the highest standards of care are reflected in updated guidance to the NHS, with a view to learning from the past to inform the future.

PO-MO-074
Developing recommendations for the U.K. government on hemophilia services and NHS reform
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Objectives: The project was undertaken to develop recommendations for the U.K. government on the commissioning of specialist hemophilia services during the restructuring of the (National Health Service (NHS) in England.
Methods: Evidence was collected using online quantitative and qualitative surveys of patients, carers, and consultant hematologists specializing in hemophilia and was conducted by the Haemophilia Society and the All-Party Parliamentary Group on Haemophilia.
Results: Three hundred and four responses were received from patients and carers, and 31 responses were received from consultant hematologists specializing in hemophilia. Key themes of patients' and carers' responses included quality of life, access to services, and quality of care. Patients indicated satisfaction with self-management and home treatment, but identified poor mobility and pain management as most significantly impacting on quality of life. The need for further enhanced out-of-hours services and improved dentistry services were also noted. In general, the respondents praised the quality of specialist care they received, but called for improved care from GPs and other non-specialist healthcare professionals. Responses from consultant hematologists identified ensuring access to new and emerging therapies as being most important for specialist services in the next five years. They also noted the importance of clinical research, specialist training, and the development of a national strategy for rare diseases.
Conclusions: Patients, carers, and consultant hematologists specializing in hemophilia identified significant improvements to specialized services during the restructuring of the NHS in England. The Haemophilia Society identified a series of recommendations for the U.K. government on the establishment of the NHS Commissioning Board, service design, and care planning. A report on the recommendations was published by the Haemophilia Society and launched in the U.K. parliament. The Haemophilia Society continues to work with the U.K. government to implement the recommendations.

PO-MO-075
Encouraging positive change for people with bleeding disorders through a national awards scheme
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Reason for the Program: This initiative was undertaken to generate a more favourable political and social climate for hemophilia care in the U.K. by raising awareness of bleeding disorders and understanding of the practical challenges faced by young people who have to cope with them.
Methods Used: Created to recognize the support provided by families, friends, teachers, and carers, the U.K. Haemophilia Society's Buddy Awards were launched at the House of Commons, where MPs and peers, children's TV personalities, and some 150 patients and their families attended. Working with 60 Hemophilia Centres throughout the United Kingdom, nominations were sought, many of which were developed into case studies and have been recruited as media spokespeople and for informal liaison with MPs and opinion leaders. These profiles are a powerful way of bringing the underlying issues to life.
Results: The inaugural awards ceremony has yet to take place (February 2012), but the expensive press coverage so far includes regional, teaching and nursing media, in addition to social media activity and MP websites. The program has provided three separate media opportunities: the launch, case studies, and the award ceremony and has reached 540 families affected by bleeding disorders. Access to a bank of personal insights from a broad range of carers provides a valuable resource for helping to correct public misconceptions about bleeding disorders, and for securing the backing of policymakers at a time when healthcare spending is under unprecedented pressure.
Conclusions: As a long-term instrument for raising awareness and attracting support, the beneficial effect of the Buddy Awards on patients' lives is only measurable in terms of the shift in public and political attitudes over time, but initial feedback suggests that it has already had an overwhelmingly positive effect on the morale and self-esteem of the U.K. bleeding disorders community.

PO-MO-076
"Asha kiran": Summer camps to empower persons with hemophilia and their families
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Summer camps for children, youth, and families with hemophilia and other bleeding disorders provide a constructive means to empowering them. They promote knowledge about the disease, foster team spirit, enhance psychological bonding, and help persons with hemophilia (PWH) and their families to cope with the condition. "Asha Kiran," meaning "ray of hope," is a yearly summer camp for children with hemophilia and their families. Organized by the local hemophilia society located in a university town, the camp was held yearly during the summer vacation in the month of April, from 2007–2011. The setting of the camp was a school that was converted to living quarters. Duration of the camp was 2 days, from Friday to Sunday. The feedback among the participants was evaluated.
The positive impact factors: Bonding between families and youth was strengthened by lasting companionship and regular communications. Daily physiotherapy motivated children and youth for physiotherapy. Fun-filled activities and picnics were opportunities for participants, mostly from rural villages and financially poor backgrounds, to relax their minds and bodies. The camps offered unrestricted (though supervised) and uninhibited opportunities for physical activities like cricket. Improved knowledge about the disease, genetic counselling facilitated lady members to seek counselling, carrier detection, and prenatal testing. Improved knowledge about hemophilia, such as self-infusion, vocational training, and management of bleeds benefitted participants. School-going PWH were also motivated to excel in studies with merit scholarships. Asha Kiran was valued for its activities and the care and interaction it provided with health-professional teams and volunteers.
Feedback for improvements: Problematic areas included 1) communication problems due to the variety (2–3) of local languages of the participants; 2) common activities every year created some sense of monotony; 3) physical facilities were somewhat inadequate. Organizational logistic factors were the medical and volunteer support from students and faculty of the University.

PO-MO-077
"Kite Flying": A Unique idea for public awareness and fundraising: Experience from a rural hemophilia centre in India
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World Hemophilia Day celebrations and summer camps are the times during the year that hemophilia centres focus on public-awareness activities. In an attempt to capture the interest and create a long-lasting impact with respect to knowledge on hemophilia, "kite flying" was used. In 2006 the first kite-flying festival was organized by the local hemophilia society. Kites with the hemophilia logo were sold to the public. The festival had 100's of kites being flown. A kite-flying competition was also held. Awareness about hemophilia was also raised through announcements. The uniqueness of the kites and the success of the event got coverage in the print and electronic media. Subsequently, a kite-flying festival, which had become synonymous with hemophilia in the region, was organized in 2010; and it incorporated lucky-draw coupons for the purchase of kites. Hence, kite flying also became a means of fund raising for hemophilia. Because kite flying is not a regular event in the region, it attracted people of all ages. Persons with hemophilia (PWH) and their families participated in the festival in 2010 as part of the summer camp that was held at the same time. This provided an opportunity for the public to interact with PWH and create awareness about the special needs of these families.
Conclusion: Use of the unique idea of kite flying not commonly prevalent in the region helped the hemophilia society to create awareness about hemophilia and assist in fundraising. The success of the idea was the unique nature of the event which helped to create a lasting impact about hemophilia on the public—the message being, "Fly a kite for hemophilia."

PO-MO-078
Sociocultural challenges of circumcision in patients with hemophilia in Iran
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Objective: Surgical intervention in hemophilia patients is a major concern, especially in developing countries due to a shortage of factor concentrates. Circumcision is considered an important ritual in Jews and Muslims. We aimed to evaluate socio-cultural attitudes of hemophilic patients or their parents toward circumcision.
Methods: This was a cross-sectional study during September-October 2011 in southern Iran. Required data included demographics, past medical history, attitude of the patients or their parents toward circumcision, and frequency of factor consumption.
Results: Participants consisted of 170 patients with hemophilia. Only 18 patients refused to circumcise. Mean age of circumcision was 4.5 ± 4.6 years, median age: 4 years ranging from neonatal period to 28 years. Ninety-one patients had severe hemophilia, 26 moderate, and 35 had mild hemophilia. Cause of circumcision was religious beliefs in all circumcised patients. One hundred and fifteen patients had some degree of bleeding complications after circumcision including mild, moderate, and severe bleeding in 27, 32, and 56 patients respectively. Factor dosage ranged from 15–30 IU kg^{-1} regarding disease severity. The mean number of consumed factor during and after surgery was 8.6 ± 8.6 times, median 6 times and range of 1–50. Among patients who were circumcised at the neonatal period, 1–24 months, and after 2 years, there was not any significant difference regarding bleeding severity ($P = 0.418$) or factor consumption ($P = 0.418$). Conclusions: It seems that circumcision in hemophilia patients is one of the sociocultural challenges that Islamic countries faced due to religious belief. We did not observe any significant differences among different age groups regarding bleeding severity or the number of factor injections. So it seems that 2–5 years of age could be an appropriate age range for circumcision in hemophilia patients who insist on circumcision, due to their having completed toilet training and better control compared to neonatal and infantile period.

PO-MO-079
The Jose Memorial Haemophilia Society Kenya
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The Jose Memorial Haemophilia Society Kenya (JMHS-K) was established as a not-for-profit organization by a group of parents of children with hemophilia, in 2009. The objectives of JMHS-K are to encourage/assist in obtaining medical care and treatment; to promote education of families and affected individuals; to procure the best supplies of blood, plasma, and factor concentrates; to establish hemophilia care across Kenya; to raise funds to support these objectives; to promote hemophilia research and best practices.
Methods: The society was launched in 2009 at hospitals in Nairobi. It gives credibility to the society and creates medical awareness on a nationwide scale via a medical advisory board with hemophilia education provided via overseas hemophilia treaters for both

healthcare professionals and families/patients. Factor has been donated through various sources and its use is coordinated and recorded by the secretary of JMHS-K.
Results: The society has 6 active programs: medical, organizational, family, government lobbying, fundraising, and public awareness and communication. All programs are active with a multidisciplinary healthcare team involved in promoting and lobbying for hemophilia awareness and education alongside a core group of parents and patients throughout Kenya. Over 80 patients with severe hemophilia have been diagnosed and are registered on the JMHS-K database. It is hoped that this will link in to other databases across Kenya establishing a national database in 2012. To date, patients have received education and training, financial support, psychological support, and factor replacement to treat severe bleeds.
Conclusion: Although still in its infancy, the JMHS-K has already had a significant impact on the lives of many with hemophilia in Kenya. The JMHS-K plans to integrate its work with organizations across Kenya in 2012, establishing best medical practice and outcomes for those affected by hemophilia and their families.

PO-MO-080
Australia and New Zealand Inhibitors Workshop: Meeting the challenges
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Inhibitors are considered one of the biggest challenges in current hemophilia care. Families with inhibitors often cannot relate to the experiences of other hemophilia families in developed countries, increasing their sense of isolation. The Australia and New Zealand (ANZ) Inhibitors Workshop was the first educational workshop in the region to focus specifically on the challenges faced by families with inhibitors.
Aims: The ANZ Inhibitors Workshop aimed to: 1) provide information and education about hemophilia and inhibitors; 2) provide a forum for the discussion of issues associated with living with hemophilia and inhibitors; 3) develop a sense of community within the group in order to facilitate networking opportunities and mutual support.
Methods: As numbers of inhibitor patients in Australia and New Zealand are low, a joint 3-day residential workshop was organized, drawing on the clinical expertise from both countries. Participants included parents of children with inhibitors and men with inhibitors of all ages, as well as partners or support people. The program encouraged participation and the message that learning can be fun. The program included information and education from a hematologist, physiotherapist, and hemophilia nurses. Two specific forums for discussion introduced the Te Whare Tapa Wha model of health and wellness and asked the participants to discuss the challenges they face living with inhibitors and their strategies for meeting these. For discussions, participants were split into four groups: adults with inhibitors, young adults with inhibitors, parents of children with inhibitors, and carers/partners.
Results: The top strategies for coping with the challenges of living with inhibitors were identified as: 1) becoming informed or educated: 2) getting connected to others with inhibitors, and: 3) maintaining a good support network. By the end of the workshop all participants reported having gained knowledge, and connected with others with inhibitors, which will hopefully led to ongoing mutual support.

PO-MO-081
National educational program in hemophilia in Ukraine
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Introduction: The cornerstone of effective hemophilia treatment is comprehensive care, delivered by a multidisciplinary team of hemophilia centre. There are not comprehensive care centres for patients with different inherited bleeding disorders in every region of Ukraine. We have no standard programs of diagnostics, treatment, and training. In 2011, a NNHF Grant supported the Haematology Department of the National Medical Academy of Post-Graduate Education for hemophilia care development in Ukraine.
Objective: The goal of this project is to establish a national network to improve hemophilia education, diagnosis, and treatment.
Methods: Development of educational programs and creation of educational materials for hematologists, healthcare professionals, patients, and their families; the establishment of active hemophilia groups in all regions of Ukraine (composed of hematologists, nurses, and physical therapists); improvement of the professional hemophilia skills of doctors-hematologists, healthcare professionals, nurses, patients, and their families.
Results: Manuals on hemophilia, laboratory diagnostic of hemophilia, guidelines of prophylactic and home treatment, Power Point presentations, and educational brochures were developed. Regular workshops for specialists of active hhemophilia groups were arranged for improving their knowledge.
Conclusion: This work is a first giant step and great success in improving hemophilia care in Ukraine.

PO-MO-082
Hemophilia patient outreach: Experience of Vietnam
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Object: Vietnam is a developing country with a population of 86.5 million people; GDP per capita is about US$1,200 per year. The estimated number of people with hemophilia in the country is approximately 6 000 patients, but only very few diagnosed, and the majority of patients are diagnosed late and receive inadequate treatment. In order to actively detect new and undiagnosed patients, since 2006, the hemophilia treatment centre of the National Institute of Hematology and Blood Transfusion has conducted an outreach campaign door to door in North Vietnam.
Method: For the patients who have been diagnosed in the centre, we are creating their pedigree and identifying their family members who have the capability of having the disease, screening bleeding symptoms by questionnaire, conducting a group of medical staff to go to patients' homes and do clinical examinations and blood tests and provide basic training for local medical staff and family members on taking care of hemophilia. In addition, national hemophilia workshops and training on coagulation was held for medical staff nationwide.
Results: From the pedigree of the 54 diagnosed patients, we have discovered 101 new patients including 89 patients with hemophilia A and 12 patients with hemophilia B, and most of them have mild and moderate hemophilia; severe hemophilia accounted for 18.8%. There's one case of a female patient whose father has hemophilia B and whose mother carries the gene for hemophilia B. The average age of diagnosis in patients is 19.96 ± 5.17, ranging from immediately after birth to 65 years old. Most of families can explore the pedigree within 3–5 generations; the average number of patients who are still alive in a family is 3.62 ± 2.3; the largest number of patients who are still alive in a family is 12, with mild hemophilia A. There are 22.77% of newly discovered patients who have arthropathy, 17.8% have muscle atrophy, which leads to a consequence that 39.6% of newly diagnosed patients cannot walk normally. In total, 18 people have died of bleeding at an average age of 16.3, and they all belong to families with severe hemophilia. Furthermore, about 1,000 hematologists, 250 local medical staff, and 872 patients and their family members have been provided with basic knowledge about hemophilia. In addition, cooperation in the field of hemophilia care between hemophilia centres and primary healthcare centers has also been established and improved.
Conclusion: Outreach by analysis of hemophilia patients' pedigree can help to discover those who are undiagnosed within a family that has a known history of hemophilia. This is an effective method of detecting new patients and should be promoted and widely implemented on a national scale.

PO-MO-083
Twinning program between the Panameña Foundation of hemophilia and the Catalan Association of Hemophilia: A hope becomes reality
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Introduction: Members of the Catalan Association of Hemophilia (ACH) and the Panameña Foundation of Hemophilia (FPH) met in a workshop organized by the World Federation of Hemophilia (WFH) in 2002. As a result, a friendship was born, which continued, and thanks to the projects of the WFH it spawned a Twinning Program that lasted for three years (2008 to 2011).
Objectives: The collaboration between the FPH and the ACH was born with great pleasure and the hope that the Panameña Foundation of Hemophilia could operate perfectly once the Twinning Program finished.
Description: Some of the areas of collaborative work were the organization of the FPH office; knowledge of the community; design of attention programs; training and assessment for professionals linked to the FPH; relationships with the health authorities; financial resources uptake.
Conclusions: Our hopes became a reality. We have managed to improve the functioning of the office by opening daily, and for this reason the projects can be followed up and the immediate needs of the community are dealt with. The equipment and the use of new technology have been improved. Certain income has been guaranteed thanks to the use of a photocopying machine. A database has been elaborated to manage the census, and a house to house study is being carried out to detect the community needs, thereby improving relationships with the members. For the first time, in 2009, an annual project was elaborated to support different activities. In 2009, a workshop seminar was organized for families and another one for professionals. The board members were given specific training related to associative tasks. In 2010 we did one for teenagers and young people. Great achievements were reached with the health authorities: Hospital del Niño became officially known as the National Centre of Hemophilia in Panama for Pediatry.

PO-MO-084
The North London Paediatric Haemophilia Network
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Objective: To establish a pediatric hemophilia network in north London to utilize the expertise from a range of hemophilia centres to provide best care for children and ensure smooth transition between pediatric and adult services.
Method: Through the use of meetings, strategy, policy and procedure documents, and information leaflets and posters, combined with pre-existing internal procedures at four London NHS Trusts, we formed the North London Paediatric Haemophilia Network (NLPHN). A hub and spoke system with Great Ormond Street Children's Hospital as the hub and local Trusts as spokes was established to ensure equitable care, joint clinics, and MDT meetings. All children in north London have access to comprehensive pediatric hemophilia care, including initiation of prophylaxis, immune tolerance therapy, and assessment of joint function. Shared education/training/research programs have been initiated. The NLPHN holds monthly MDT meetings to discuss interesting/difficult cases. The hub provides 24-hour on-call services for the entire network.
Results: The network has worked especially well in the treatment of children with inhibitors, with network care led by the hub and delivered by the hub and spokes delivering care geographically close to children. This utilization of network expertise and facilities has led to many positive results for these children.
Conclusion: Specialist commissioned services within the U.K., including for hemophilia, have been moving towards a network model. This is something that is especially true and works very well for hemophilia and inherited bleeding disorders, wherein sharing resources and knowledge available at a number of different centres allows for the best results for patients.

Contribution to Practice/Evidence: Given the appropriate facilities and locations, the network model for hemophilia care could be adopted all over the world. A network's ability to draw the best from all healthcare professionals and allow for transfer of knowledge and best practice means better results for patients and professionals.

PO-MO-085
Management of patients with inherited bleeding disorders in the emergency department
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Background: Treatment of patients with inherited bleeding disorders in the emergency department (ED) is a challenge because hemorrhagic risk can be underestimated and the management is not well known by emergency physicians. At present, there are only guidelines from the National Hemophilia Foundation limited to people with hemophilia (PWH) and rarely applied in our ED. In 2008, the European Association for Haemophilia and Associated Disorders (EHAD) recommended development of a policy to manage these patients.
Methods: The Emilia-Romagna Region (RER) started a project involving all 8 hemophilia centres (HC) and all 44 EDs of the region. The project is based on guidelines for emergency treatment; education for ED nursing, medical staff, and patients; a dedicated web-based software supporting treatment decisions, sharing data with the patients' electronic clinical records.
Results: Regional guidelines for emergency treatment, containing practical instructions for managing patients in the ED, were produced and shared by HC and ED staff. The web-based site, which has a private area for doctors and a simplified public area, enables easy access to descriptions of diseases and instructions for treating bleeds or critical injuries. A specific algorithm suggests the first dose of concentrates for every type and severity of bleed and trauma. Furthermore, all RER patients with bleeding disorders have an electronic USB key by which they can access their own main clinical and therapeutic data, stored in the region's web-based clinical records. The data can be processed immediately by the ED web-based site providing optimal, tailored emergency treatment. The first training-course for ED doctors and nurses started in May 2010. The website www.emofiliarer.it has been active since February 2011, and after site training courses in each ED, the network has been working in the region since June 2011.
Discussion: To our knowledge, this is the first example of a network, involving HC, ED, and patients, for managing bleeding emergencies in these patients with the support of dedicated web-based software.

PO-MO-086
Challenges faced in developing comprehensive hemophilia care and remedies in India
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Background: The hemophilia movement in India is now more than 25 years old; however, during this period, few comprehensive hemophilia care centres (CHC) exist, though there are over 70 chapters. This paper analyzes the reasons for why there are so few comprehensive hemophilia centres (CHC) and remedies.
Methods and Materials: Feedback from 72 chapters under the Hemophilia Federation (India); Interviews with the directors of Hemophilia Care for several CHCs; Evaluation of healthcare facilities and human resources development in health care.
Results: At present there are only 6 CHCs, 350 Medical Colleges, and 200 laboratories that do screening and coagulation tests—but out of these, only 60 laboratories do factor assay whereas inhibitors screening is done in only 15 labs across India. Fifteen to 20 hematologists graduate every year. Eighty per cent of them work in hemotalogy oncology. Physical therapy and other paramedical services are inefficient as the majority of HTCs are in non-governmental institutions and do not have any government aid. Most of the chapters have treatment centres that are private, and other medical & paramedical facilities are not adequate. Or chapter and treatment centres are distantly located, or volunteers do not have adequate training. Also financial burden on societies, volunteers, PWHs add fuel to the fire.
Conclusion: Hemophilia care is still very inadequate in India. The government medical colleges and hospitals should be targeted to develop at least one CHC in every state and 40 HTCs should be developed across India. This will result in taking care of 30 000–40 000 PWH per CHC in each state. This, then, requires a quantum increase in government funding to develop human resources, proper coagulation laboratories, and also to provide AHF to PWH. Lastly, without persistent follow-up from the national member organization, this will be a distant dream.

PO-MO-087
The HEMONLINE Project: Preliminary results
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Introduction: Our regional health service does not offer home care for people with hemophilia (PWH): patients residing far from the hospital and family members involved in treatment have often had difficulties reaching the Hemophilia Centre; the socio-economical costs of workplace absences also created difficulties.
Aims: The aim of the project is to provide therapies, medical and nursing care, and psychological and physiotherapeutic home assistance to patients.
Methods: The HEMONLINE project, winner of a grant promoted by Fondazione Paracelso, allowed the enrolment of 20 persons with severe hemophilia (16 HA, 4 HB, ages 2–73, mean 31.4; 8 children, 12 adults) The staff consists of one doctor, one nurse, one physiotherapist, one psychologist, and one statistician. The study period was from 2011–2014. Three times per year, the staff will go to the patient's home residence, where the doctor will carry out a complete medical check-up, the nurse will bring the replacement therapy, collect blood samples, and perform home therapy; the physiotherapist will suggest suitable hobbies and sports activities for pediatric patients and also implement training programs for adults after a bleeding or orthopedic surgery, as well as continue the rehabilitation exercises; the psychologist will evaluate the patient's mental condition through an interview and by filling out specific questionnaires for patients and parents. Every patient received a notebook, webcam, and Internet connection to contact health professionals easily.
Results: Three months after the start up, 75% of patients have been visited once; nine patients with arthropathy started specific rehabilitation exercises; one continued his program. The psychological evaluation evidenced compromised physical conditions in adults, a difficulty in practising sports or social activities because of hemophilia, as well as difficulties accepting the disease.
Conclusion: The project has just begun; we hope to see a significant reduction of costs for local health services, but mostly an improvement in the quality of life for the patients and their families.

PO-MO-088
What's up in Amirkola Hemophilia Center, Babol, Mazandaran, Iran
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Amirkola Hemophilia Center is located in the northern part of Iran and affiliated with Babol University of Medical Sciences. Fifty-five patients with different hemorrhagic diathesis are registered in this centre with hemophilia A (n = 38) and hemophilia B(n = 7), type III von Willebrand disease (VWD) (n = 6) and Glanzmann's thrombasthenia (n = 3). The age distribution is between 7 and 55 years. In our centre, concentrated factor VIII, factor IX, Humate-p, and concentrated fibrinogen are available. We also have a couple of hemophilia A patients (ages 3 and 7) with inhibitor that receive recombinant factor VII (NovoSeven) and FEIBA. There is not enough coagulation factor at our centre, which is why we ordinarily provide all factors by demand, and we dream about prophylactic treatment of all patients in future. Nevertheless, recently our patients' quality of life is much better than before, and we do our best to provide better conditions for patients.

PO-MO-089
Improved hemophilia care in developing countries through the World Federation of Hemophilia twinning programs: The case of Yaoundé and Geneva
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With paucity of data on bleeding disorders in Cameroon, and with limited resources for appropriate diagnosis and management of these disorders, a twinning program was created by the World Federation of Hemophilia (WFH) between a resource-limited setting (Hematology and Blood Transfusion Service of the University Teaching Hospital of Yaoundé, Cameroon) and an established centre (Haemostasis Service of the University Hospitals of Geneva, Switzerland).
Initiated in 2008, the twinning program officially started in 2009 with the creation of a hemophilia treatment centre (HTC) in the University Teaching Hospital (UTH), Yaoundé. Under the supervision of the WFH, and working in collaboration with the local Association of Hemophilia, the program aims at sensitizing the wider Cameroonian population on issues around hemophilia, screening for bleeding disorders, and managing diagnosed and existing cases, as well as building capacity. By December 2010, there were 4 supervisory visits to Yaoundé by members of the Geneva twin, and various members of the Yaoundé twin had undergone training in hemostasis in Senegal, London, and Geneva; in physiotherapy in Senegal; and in general hematology in Geneva (ongoing). Furthermore, a semi-automatic coagulometer and reagents for diagnoses have been provided for 3 years (gifts from Stago), and clotting factor concentrates (gifts from the WFH and the following industries: Baxter, Bayer, CSL Behring, NovoNordisk) are sometimes made available for the management of patients with hemophilia A and B. In the last 12 months, 20 new cases of hemophilia were diagnosed, 6 suspected cases of von Willebrand disease, and 96 patients were seen and treated. Other activities have included sensitization programs and the extension of the twinning program between the hemophilia association of Cameroon and that of Geneva. As perspectives, we hope to adopt an affordable technique for viral inactivation of cryoprecipitate in the HTC, to eventually develop a suitable physiotherapy service, and to decentralize the HTCs.
Key words: Hemophilia; World Federation of Hemophilia; Cameroon; Geneva; twinning program

PO-MO-090

The ten EHAD (European Association for Haemophilia and Associated Disorders) principles as a tool to evaluate hemophilia management in Algeria

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Objectives: The publication of the 10 European principles of hemophilia treatment offers an objective tool for evaluating progress, quantity, and quality of hemophilia care centres. We propose to analyze the management of hemophilia in Algeria over the past 10 years by applying all these EHAD principles.

Methods and Results: These 10 principles have all been implemented in 18 hemophilia care centers in Algeria, but there are a lot of differences from one centre to another. Four centres (22.2%) were able to apply 5/10 of these principles; four centres (22.2%) realized 9/10, and the remaining 10 centres 10/18 (55.5%) were able to apply all the principles of the EHAD. The National Register of hemorrhagic disease was placed under the supervision of the National Institute of Public Health, official documents granting access totally free for all patients in all treatment of hemophilia and its complications. The structure of national ownership is pyramidal; the base consists of the care unit near the residence of the person with hemophilia for emergency care. These units are attached to their own departmental hospitals attached to teaching hospitals requiring more specific multidisciplinary teams. These centres are involved in diagnosis and screening, patient education, self-treatment, prevention, detection, treatment of inhibitors, functional rehabilitation, dental and surgical specialty acts.

Discussion: there is a very marked improvement in the management of hemophilia during these last ten years in Algeria. The 10 principles of EHAD defining the management of hemophilia are applied at different levels in every hemophilia care centre, sometimes with some shortcomings. Achieving all the objectives of EHAD is an excellent goal, but requires an effort to improve the performance of some existing centers and to create others, especially in remote areas. Real progress is also measured by its sustainability and its longevity.

PO-MO-091

Design and evaluation of pedagogic tools in therapeutic patient education for hemophilic patients: the French experience

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Therapeutic patient education (TPE) is an essential part of chronic disease care, particularly in hemophilia, permitting one to achieve autonomy in health-related decisions, a better quality of life, and better health outcomes. TPE is one of the missions of the French Haemophilia Treatment Center (HTC) and is recognized by the healthcare system. On the occasion of a TPE medical training session, a working group was formed—consisting of 1 physician and 1 nurse from 2 hemophilia treatment centres in Lille and Paris-Necker—in order to elaborate educational tools adapted to teenagers and adults. These tools, illustrated by case-studies that are representative of at-risk situations for hemophilia (selected situations from actual life in hemophilia), were tested on 8 patients with hemophilia (5 adults and 3 teenagers, 12 to 16 years old), 5 parents of children with hemophilia, in Lille, and 6 teenager patients (12–14 years) in Paris-Necker. All patients and mothers actively participated in the discussion. These materials have enabled different groups to formalize their difficulties, allowing for exchanges of experience. They facilitated the useful transmission of information from adults with hemophilia to teenagers with hemophilia, and were of help to the mothers of children with haemophilia, anticipating clinical problems. These tools were evaluated with a specific form filled in by all patient groups, which allowed us to fine-tune the clinical cases and also to validate their relevance. Patient groups also found these educational tools to be useful and appropriate. We concluded that the choice of tools met the goal for which they had been designed: they facilitate communication among patients, mothers, nurses, and doctors and are of good educational value.

PO-MO-092

Hemophilia and other coagulopathies: The current situation in Tabasco Mexico

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Introduction: In Tabasco, Mexico, in the 1980s, there was no record of how many patients with hemophilia there were, and everything about this illness was unknown, so tabasqueña de hemofilia A.C. was founded in April 1989, making a census, outcasting and motivating the general population as well as the medic and paramedic area, sanitation authorities, politicians and top officials being backed by the means of communication.

Objective: To analyze the comorbility of hemophilia and other coagulopaties patients.

Method: Checking of tabasqueña de hemofilia, ''Dr. RNP'' children hospital and social security Mexican institute records between January 2009 and October 2011, evaluation was performed prospectively in each attention centre by the multidisciplinary team.

Results: Tabasqueña de hemofilia: 187 < 15 years of age, 141 from 15 to 59 years, 14 > 60 years; Dr. RNP children hospital: 63 < 15 years; IMSS: 60 from 1 to>65 years; hemophilia A: 348; hemophilia B: 12; von Willebrand disease: 20; factor VII: 3; factor X: 1; factor XI: 1; factor II, VII, IX, X: 1; factor VIII and glannzman trombastenia: 1; inhibitors: 9; VHB: 4; VHC:5; VIH: 1. Mortality: HIV/AIDS 4, HIC 5, inhibitor retroperitoneal bleeding 1, other causes 5.

Conclusion: Nowadays there is a record of patients in the hemophilia teaching centre, which was started in 2007. Multidisciplinary attention is given there and patients get medical assistance in the hospitals where they get sustitutive therapy of plasma derivates and recombinant with the prophilaxis modality for all the surgeries; there has been an advance in primary prophylaxis, there has not been as high mortality of seropositive as in the international literature, the surgical procedures have been performed without any complications, and the innovation of the media genicular artery embolization in boys order than 8 years to prevent the hemophilic arthropaty in patients with grad ii arthropaty has been mentioned.

Practice development: From 1996 to 2011 we have performed more than 38 neurosurgeries, orthopedic and odontologic interventions, as embolization, knee prothesis, exodoncies, all of them with prophilaxis therapy with factors of recombinant and plasma derivates.

19-HOME TREATMENT AND SELF-INFUSION

FP-WE-04.5-5
Cost-effectiveness of telephone counseling for Thai persons with hemophilia receiving home treatment
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Background: The most important aspect of management of hemophilia is to provide adequate replacement to treat or prevent bleeding episodes appropriately.
Materials and Methods: IHTC Bangkok, a comprehensive hemophilia care centre, has provided a 24-hour hotline telephone service to assist patients and parents to cope with effective early treatment. A retrospective analysis of hotline telephone counseling from January to December 2011 was conducted. The persons who responded to the initial call were the hemophilia nurse during office hours and fellows in hematology-oncology outside office hours. Staff and the hemophilia nurse constantly acted as consultants. The number of telephone calls in each shift was recorded, along with the provided advice, and the results were comprehensively evaluated.
Results: In the year 2011, 80 telephone calls (54 at day and 26 at night) from 34 patients (A 30, B 4) were recorded. Eight patients exhibited high-titer inhibitors ranging from 5 to 171 Bethesda units. Their mean age was 13.5 ± 10.15 years. They included bleeding at various sites (n = 72), prevention of bleeding (n = 6), and pregnancy (n = 2). The persons who made the call included patients (n = 9), mothers (n = 60), fathers (n = 6), and physicians (n = 5).The content of consultation involved the necessity of factor concentrate administration (n = 22), repeated factor concentrate administration (n = 14), more serious bleeding requiring hospitalization after the first aid treatment at home (n = 24). The hospitalization included surgery and rehabilitation. The results revealed that the patients were treated appropriately with favourable outcome despite serious bleeding episodes such as high-titer inhibitors with life threatening intra-abdominal bleeding requiring plasma exchange, high dose of factor concentrate and by-passing agents, and emergency exploratory laparotomy.
Conclusions: Telephone counselling was an effective tool for improving the management of home treatment. It is useful for delivering continuing care to patients in economically less-developed countries with limited resources.

PO-WE-093
The impact of home treatment in the management of hemophilia in developing countries
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Introduction: Home treatment is not a luxury. It not only improves the quality of life for patients with hemophilia, but it reduces the cost of care significantly, and especially it prevents the severity of bleeding.
Materials and methods: We started in October 2009. We organized home treatment sessions to 20 patients and their families between 2009 and 2011. Each group does not exceed 5 people, for better communication. Two groups participated in the session more than once, after trying this experience at home.
Discussion: The results of these sessions are very positive: adolescent patients do the injection themselves and can now play sports and participate in trips organized by schools. They are more confident and optimistic about the future. The mothers of these patients are completely satisfied. They are less worried about incidents of bleeding during the night or weekend. They move more frequently with their children when before they were forced to stay near the centre in case of emergency. For the cost of treatment, a single injection of factor concentrates is sufficient to hemarthrosis if injected on the field, while it takes a minimum of 3 injections if the patient waits more than 24 hours with a risk of developing arthropathy. We have the testimony of a young person who was amputated because he had a hematoma of the calf and arrived at the hospital too late (he lives far away), and a mother who saved her child who had an eye injury of blindness by injecting factor concentrate on the field before coming to the hospital.
Conclusion: In emerging countries, distance increases the risk of complications and death from hemorrhage. Home treatment is necessary to reduce the level of motor disabilities, reduce processing costs, and improve quality of life of hemophilia patients.

PO-WE-094
Effect and cost of low dose secondary prophylaxis in patients with severe hemophilia A and advanced hemophilic arthropathy
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Many patients with a severe form of hemophilia in developing countries did not receive primary prophylaxis in the past, and therefore developed hemophilic arthropathy. Recently, it has been shown that secondary prophylaxis (i.e., regular administration of 20 IU kg^{-1} of FVIII concentrate every second day) in patients with hemophilic arthropathy was associated with significant improvement in quality of life. However, such a regimen in adult hemophilia patients is associated with high cost, which often is not acceptable in countries with limited resources. In this study we investigated the effects and cost of a lower-dose regimen of secondary prophylaxis than is used in developed countries in adult hemophilia patients. Regular low dose secondary prophylaxis with FVIII concentrate (mean dose 13.4 IU kg^{-1} BW, two times per week) was administered to 11 adult patients, mean age 26 (20–54) years, with severe hemophilia A and hemophilic arthropathy, during 15.5 (11–20.5) months. The frequency of bleeding was registered and compared to bleeding frequency in 11 patients treated on demand, mean age 25 (19–59) years, with similar grade of hemophilic arthropathy and followed for 18 (9–21) months. In patients treated with low-dose secondary prophylaxis, the mean frequency of bleeding per month was significantly lower than in the patents group treated on demand (0.25, range 0–3.1 vs. 2.5 range 0.3–5.8, respectively). At the same time, the average consumption of factor VIII concentrate per patient in secondary prophylaxis group was 7895 IU per month, while in the on demand group it was 3618 IU per month. The results suggest that secondary prophylaxis even with low-dose FVIII concentrate was associated with significantly lower frequency of bleeding than on demand treatment. Although the cost of treatment in secondary prophylaxis group was higher than in on-demand group, low dose secondary prophylaxis may be an acceptable option for treatment of hemophilic arthropathy in conditions were resources are limited.

PO-WE-095
Determinants of adherence in hemophilia: A systematic review
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Objective: To systematically assess the determinants of adherence to hemophilia therapy.
Methods: Literature search in PUBMED, EMBASE, CINAHL in Oct 2011.
Keywords (used): hemophilia, adherence/compliance and determinants. This search yielded 110 articles; reduced to 21 by further selection on title/abstract. Full paper evaluation yielded 5 relevant articles, which were critically appraised using the STROBE statement.
Results: The articles were based on questionnaires administered to patients (n = 4) or healthcare staff (n = 1). This concerned in total 414 subjects (range 34–147). Results are shown in figure 1. The reported (significant) predictors of adherence were bleeding pattern, beliefs about the necessity of the treatment, mental health, and the severity of hemophilia. Knowledge of the benefits of treatment was the most important (self-rated) facilitator.

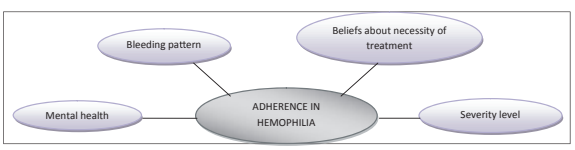

Fig. 1. Determinants of adherence in hemophilia patients, concerning conclusions that are significant, proven in existing literature.

Conclusion: In order to improve outcome of this intensive treatment, it is important to address the issue of adherence. Bleeding pattern, beliefs about the necessity of treatment, mental health, and severity of the hemophilia appeared predictors for treatment adherence in hemophilia. Further prospective research should identify determinants according to subgroups of age and treatment regimen. Contribution to the practice:
These determinants may provide a first step towards design of interventions to promote adherence.
Figure 1: Determinants of adherence in hemophilia patients, concerning conclusions that are significant, proven in existing literature.

PO-WE-096
Home clinical assistance: Italian survey of HCA support for the management of CVC in pediatric hemophilic patients in prophylaxis
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Primary prophylaxis is considered by the World Health Organization (WHO) to be the optimal therapy for treating severe hemophilia A or B (HA, HB); it is the only treatment capable of preventing hemophilic arthropathy. Among pediatric hemophilia patients, peripheral venous access is not capable of supporting proper prophylaxis in the long term. Thus arises the need to make use of central venous catheters (CVC), which may be externally tunnelled (as with the BROVIAC catheter) or completely implantable internally (as with a Port A catheter). The literature reports an infection incidence of 0.66 per 1,000 CVC-years, and some rare cases of thrombosis. An adequate training of the parents is key to the prevention of these complications. Parents need to learn how to handle the CVC correctly and how to follow standard procedures methodically. The Home

Clinical Assistance (HCA) proposed by Baxter is a nursing service available to hemophilia centres, which aims to train parents of children with hemophilia under prophylaxis for home-based management of the CVC. A CVC was positioned in 9 children (8 with HA and 1 with HB) with a mean age of 18.8 months. Five BROVIAC and 4 Port A catheters were used to initiate regimes of prophylaxis in 8 of the cases and of immunotolerance using rFVIII (ADVATE, Baxter) in the remaining case. All of the cases made use of the HCA service. In order to train parents to full independence of use, an average of 10.44 days was required. The mean observation period was 969.9 (98-2400) days. None of the children presented with an infectious complication, nor were there any cases of thrombotic occlusion of the CVC. Even though our casuistic is based on a small number of patients, proper nurse-guided training using standard protocols may well be the key to optimal management of prophylaxis in children with hemophilia in the home setting with minimum discomfort and an improved quality of life for the children and for their parents.

20-INFECTIOUS COMPLICATIONS

PL-MO-02.2
New approaches/horizons to the management of hepatitis C in hemophilia in 2012
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HCV infection acquired from factor concentrates in the 1970s and early 1980s is a major health issue in patients with hereditary bleeding disorders. The main aim of HCV treatment is to eradicate the virus and prevent disease progression. Ideally, cure should be achieved prior to the development of cirrhosis not only to avoid progression to end-stage liver disease but also to reduce the risk of HCC. Major progress has been made recently in the investigation and management of HCV. Non-invasive methods and techniques such as liver transient elastography (fibroscanning) have been developed as an alternative to liver biopsy for assessment of HCV-associated liver fibrosis. Pegylated interferon/ribavirin combination therapy has become the mainstay of eradication therapy in monoinfected as well as in HIV/HCV co-infected patients. Response guided therapy regimen can lead to viral eradication in approximately 40–50% of patients infected with HCV genotype 1 or 4 and in 80–90% of those infected with genotype 2 or 3. Several predictive markers of success to IFN-based therapy have been identified such as the IL28B polymorphism, which may help in treatment choice and decision. The first direct-acting antivirals belonging to the class of protease inhibitors (boceprevir, telaprevir) have been recently approved but are restricted to the treatment of HCV genotype 1 infections. The rates of sustained virologic response (SVR) have increased by 30%, reaching approximately 75% in clinical trials for treatment-naive patients. In treatment-experienced patients, the SVR rates are approximately 80–90% in relapsers, 50% in partial responders, and 30% in null responders. Clinical studies are ongoing for the treatment of HIV co-infected patients. Other classes of direct antivirals are being evaluated in clinical trials with the hope of developing interferon-free regimens with even higher rates of SVR for all main HCV genotypes. These new developments provide hope that in the near future, chronic hepatitis C will become a curable disease in most patients including the currently difficult-to-treat patients.

S-MO-04.1-2
Treatment of chronic hepatitis B virus infections
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Chronic hepatitis B virus (HBV) infections remain a major public health problem worldwide, with approximately 350 million chronic carriers. The goal of antiviral therapy is to prevent liver fibrosis progression and HCC development. To achieve this goal, prolonged viral suppression is required. In patients with HBeAg positive chronic hepatitis B, administration of pegylated interferon for 48 weeks results in viral suppression in approximately 40% of patients and in HBe seroconversion in 30%. Administration of entecavir or tenofovir results in viral suppression in approximately 70% of patients and in HBe seroconversion in 20% after one year, while the rate of viral suppression continues to increase during prolonged treatment beyond 1 year. In patients with HBeAg negative chronic hepatitis B, administration of pegylated interferon for 48 weeks results in viral suppression in approximately 60% of patients. Administration of entecavir or tenofovir results in viral suppression in 90% of patients after 1 year and this rate rises to > 95% during prolonged treatment. Prolonged antiviral therapy with entecavir or tenofovir results in very high rate of viral suppression, which is associated with improvements in serum transaminase levels and in liver histology. In the treatment of naive patients, antiviral drug resistance has not been observed with tenofovir and in only 1% of entecavir-treated patients over periods of >5 years. Since major progress has been made in the last decade allowing the control of viral replication in the majority of patients, clearance of HBsAg has become the next most desirable endpoint. Indeed, HBsAg loss could lead to treatment cessation and is associated with a decreased risk of HCC development. Clinical trials are now ongoing, with new schedules of combination therapy with nucleoside analogs and pegylated interferon as well as with the combination of novel therapeutic vaccines.

PO-MO-095
Clinical outcome in a cohort of HIV/HCV co-infected patients: HCV RNA presence associated to higher GGT levels
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Clinical, immunological, and virological markers were considered to evaluate clinical conditions in a group of 38 HIV/HCV co-infected hemophilic patients. Different parameters like age, HIV and HCV presence and viral loads, hepatic enzymes (AST, ALT, GGT, ALP), CD4, CD8, and platelet counts were evaluated as surrogate clinical progression markers. APRI and FORNS indexes were also calculated. In addition, IL28b polymorphisms were studied to look for an association with their clinical evolution. Student t test or Mann Whitney were used to compare quantitative results while Chi square or Fisher tests were used for qualitative analysis. We observed no statistically significant differences for markers between genotypes CC and CT+TT groups ($P > 0.05$). Ten out of 38 patients (26%) showed values higher than 2X normal GGT values with a median reaching 204 UI l^{-1} (mean: 198 ± 72 UI l^{-1}). Among the group with non-detectable (ND) HCV RNA in plasma (spontaneous or therapy-induced clearance) ($n = 9$), higher platelet counts were observed ($P = 0.04$) in parallel with lower GGT ($P = 0.03$), lower FORNS index ($P = 0.008$), and greater CD4+ cell counts ($P = 0.03$). When considering the group with ND HIV viral load, CD4 were significantly increased ($P = 0.004$) but also higher GGT levels were observed (133 vs. 66 UI l^{-1}; $P = 0.02$). Analysis of the data inside this group showed that patients with detectable HCV viral loads had significantly higher GGT levels (175 vs. 48 UI l^{-1}, $P = 0.01$) and FORNS index was also increased but not statistically significant (5.85 vs. 4.5, $P = 0.06$) than patients with ND HCV loads. In the present report, the GGT increase was significantly associated to the presence of the HCV RNA in plasma samples. The mechanisms for GGT increase are not yet well understood, and the true meaning of the GGT alteration frequently observed in chronic HCV infected patients remains unclear. The pathological changes in the liver due to viral presence could result in an overflow of GGT into the bloodstream. This observation deserves further analysis on the mechanisms involved.

PO-MO-096
Distribution of IL28B gene polymorphisms and presence of 32bp CCR5 deletion in a cohort of HIV/HCV co-infected patients
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IL 28b CC genotype is a strong predictor of viral response to therapy in HIV/HCV co-infected patients, but it was also found to be associated with more rapid progression to HCV related fibrosis. In consequence, in this group, the access to HCV treatment should be of utmost importance. CCR5 is a member of the beta chemokine receptors family of integral membrane proteins and an HIV co-receptor. A 32 base pair deletion (32 bp del) in the CCR5 has been previously demonstrated to be associated to disease progression and has been suggested to influence susceptibility to HCV infection, as well as the natural course and progression of hepatitis C. The distribution of IL28b polymorphisms (locus rs12979860) was analyzed in parallel with clinical, immunological, and viral markers in a group of 38 HIV/HCV co-infected hemophilic patients. CCR5 allele polymorphisms were also characterized. Age, HIV and HCV viral loads, hepatic enzymes (AST, ALT, GGT, ALP), CD4, CD8 and platelet counts, APRI and FORNS indexes were evaluated as surrogate clinical progression markers. To compare groups, the results were analyzed with Student t tests or Mann Whitney depending on their distribution. Chi square or Fisher tests were used for qualitative analysis. In our cohort, IL 28b genotypes were distributed as follows ($n = 38$): 53% CC, 34% CT and 13% TT, similar to our control population ($n = 23$). None of the parameters showed statistically significant differences between groups. Seventy-three per cent of the patients showed wild type allelic variants for CCR5, while only 27% demonstrated the presence of 32bp del in one allele. Among the group with non-detectable HCV viral load, as a result of therapy or spontaneous clearance, 44% showed IL28b CC genotype and 25% showed 32bp del. Also, 44% of the patients with non-detectable HIV loads were CC genotype and 15% of them showed 32bp del in CCR5. Although the number of patients is still small, no combination of polymorphisms in IL28 and CCR5 seemed to be associated to a better or worse progression disease in our cohort.

PO-MO-097
Evaluation of liver fibrosis in hemophilia patients with HCV infection using transient elastography: Fibrotest
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Backround: The use of non-invasive methods for the measurement of liver fibrosis in HCV infected hemophilia persons was prompted by limitations of liver biopsy in these patients (biopsy failure, concerns about the bleeding complications, high cost due to coagulation factors requirements). Fibroscan is based on the measurement of the velocity of propagation of elastic wave induced by the pulse-echo signal transmitted to the liver. Wave velocity measurement provides a measure of liver stiffness. Liver fibrosis is classified as F0-none, F1-minimal, F2-mild, F3-severe and F4-cirhosis.
Methods: We performed the liver fibrosis investigation using fibroscan in 37 anti-HCV-positive hemophilia patients with a median age of 40 (range 21–64) yrs and the duration of HCV infection of ≥20–yrs. The result of liver stiffness measurement (LSM) was expressed as a median of 10 successive measurements at different sites of liver. The ''cut of'' for fibrosis (F ≥ 2) was ≥7.1 kPa.
Results: Twenty-three patients were PCR-HCV-RNA-negative: 6 were never positive and 17 had sustained viral response after antiviral therapy (AVT). Fourteen patients were PCR-HCV-RNA-positive; out of them 3 were AVT-non-responders, 6 relapsed after successful end treatment response and 3 patients have not been treated yet. Twenty-three patients had normal liver function tests and none had clinical cirrhosis. LSM was negative (F0) in 4/11% of patients. LSM was positive in 33/89% patients; out of them, 24/64%, 7/19%, 1/3% and 1/3% had LSM of ≤ F1, F1-F2, F2, F3-4. Surprising has been a high prevalence of minimal fibrosis (≤ F1) in 13/76.5% patients with sustained viral response and even in 6/66.7% PCR-HCV-RNA-positive patients with a failure of antiviral therapy.

Conclusion: The results of evaluation of liver fibrosis with fibroscan in our hemophilia patients suggests that antiviral therapy, even in patients with AVT failure, may have the effect of slowing the progression of fibrosis.

PO-MO-098
Five years on: The uptake and response to hepatitis C treatment in Western Australia

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Aim: The aim of this project was to identify the current HCV status of the inherited bleeding disorder community in Western Australia compared to data collected in 2006.
Method: Patients demonstrating a positive HCV antibody were identified using the Australian Bleeding Disorder Registry. These patients were then further investigated to determine demographics, current HCV infectious status, genotype, treatment attempts and outcomes of treatment.
Results: In 2006 there were 110 HCV antibody positive patients. Forty-one patients were PCR negative, of which 21 had spontaneously cleared the virus. Of the 20 that had achieved a SVR, 50% had cleared the virus with Peg IFN and ribavirin. 3 patients had cleared the virus with single agent IFN and 7 with IFN and ribavirin. Of the 10 successful with Peg IFN and ribavirin, 4 had previously attempted treatment. Of the 20 patients, 45% were genotypes 2 and 3, leaving 40% genotype 1 and the remainder unknown. In 2011 there were 115 patients identified to be HCV antibody positive. Sixty-five patients were PCR negative, of which 30 were spontaneous resolvers. There were 35 sustained responders, with the majority (66%) having eradicated the virus with Peg IFN and ribavirin. Five patients had a SVR with single agent IFN and 7 with IFN and ribavirin. It should be noted that 2 patients that achieved a SVR with IFN and ribavirin hadd already received IFN. Of the 23 patients that achieved a SVR with Peg IFN and ribavirin, 6 had previously had IFN (2) or IFN and ribavirin (4). Forty-five of the patients that achieved a SVR were genotype 1, with 37% being genotypes 2 and 3. The remainder were unknown. Of the 46 patients that remain PCR positive, 21 have attempted eradication therapy, including 13 that were unsuccessful with Peg IFN and ribavirin.
Discussion: The data generated demonstrates both an increase in patients attempting eradication therapy and successful treatment outcomes since 2006. 18 patients underwent single agent IFN with 28% achieving a SVR. 20 patients underwent IFN and ribavirin with 35% achieving a SVR. However the most significant rise was with the introduction of Peg IFN and ribavirin with 36 patients and a SVR of 64%.

PO-MO-099
Complications of HCV infection in patients with hereditary bleeding disorders

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Introduction: Hepatitis C virus (HCV) infection in patients with hereditary bleeding disorders (HBDs), as a consequence of treatment with transfusion of human blood-derived components between the late 1970s and 1980s, represents a major health concern.
Objectives: Assessment and evaluation of the burden of HCV infection, its complications, and treatment in a population of patients with HBDs.
Methods: Analysis of a series of 161 patients with HBDs treated in the Immunohemotherapy Service of the Centro Hospitalar de Lisboa Central (Lisboa, Portugal), consultation and systematic review of the patients' clinical processes, elaboration of a database comprising the information gathered; and statistical study of its variables: age, gender, degree of severity of the bleeding disorder, treatment modality, and major and minor complications of HCV infection.
Results: Sixty-five (40%) of the 161 patients have HCV infection. Among the patients with hemophilia A, 36% are severe and 62% of those have HCV infection; 9% moderate with 57%; 25% mild with 20%. In the hemophilia B group, 8% are severe with 23% infected and 6% moderate or mild with 10%. Concerning the patients with von Willebrand disease, 12% have type 2 with 16% infected and 4% have type 3 with 86%.
Conclusions: HCV infection represents a very significant complication of the treatment employed in the past in the studied population. Considering that most of these patients were infected in the late 1970s and early 1980s, and the natural evolution of HCV infection in patients without bleeding disorders, it is expected that the prevalence of major complications will rise significantly in the coming years. Prophylactic measures should be implemented to enhance the follow-up protocols and prevent further development of liver damage in these patients.

PO-MO-100
Liver stiffness measurements in patients with inherited bleeding disorders and chronic hepatitis C, with and without successful antiviral treatment

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Introduction and aim: Hepatitis C (HCV) is a major co-morbidity in patients with inherited bleeding disorders, leading to progressive liver fibrosis and eventually cirrhosis. Liver stiffness measurement (LSM) is a non-invasive way of assessing the extent of liver fibrosis. This paper describes our experience with serial LSM to prospectively assess changes in fibrosis in patients with inherited bleeding disorders and chronic HCV.
Methods: LSMs were performed in 2005 (LSM 1) and 2009 (LSM 2) in 39 patients who were successfully treated for HCV (SVR+ group) and in 84 patients who did not undergo treatment or in whom treatment was not successful (SVR- group). Changes in liver fibrosis between LSM 1 and 2 were assessed.
Results: Median interval between LSM 1 and 2 was 3.7 years. In the SVR+ group, the median duration of HCV infection was 29 years. Twenty-two patients (56%) underwent successful antiviral treatment before LSM 1 (group 1), and 17 patients between LSM 1 and LSM 2 (group 2). In group 1, the median results of LSM 1 and 2 were similar (6.0 versus 5.6 kPa), so overall, patients remained stable. Group 2 showed a significant improvement in median LSM results (10.3 versus 6.1 kPa, p-value <0.01). In the SVR- group, the median duration of infection was 37 years. The median results of LSM 1 and LSM 2 were similar (7.3 versus 6.6 kPa). On the individual level, deterioration of LSM results of more than 2 kPa was seen in 13 patients (16%), 44 patients (52%) remained stable, and 27 patients (32%) showed improvement of LSM results of more than 2 kPa. These results are comparable to those of paired liver biopsy studies.
Conclusions: LSM appears to be a good alternative for liver biopsies to monitor fibrosis in patients with hepatitis C and inherited bleeding disorders. The extent of liver fibrosis was variable, but limited overall. Even after a long HCV infection duration, successful antiviral treatment led to a significant improvement in LSM results, mainly in the first years after completing treatment.

PO-MO-101
HIV serodiscordant couples with hemophilia: Reproductive care in the hemophilia and thrombosis center of Milan

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Fifteen per cent of people with hemophilia are HIV-positive, and the risk of infecting their female partner has halted their desire to father a child. We report our experience on 17 HIV-discordant couples referred to the Haemophilia Centre of Milan for reproductive assistance, through a specific seminal processing method to remove HIV DNA and RNA from their ejaculate. Couples underwent a preliminary screening to assess their fertility potential in order to select the appropriate method to achieve pregnancy. Semen washing was carried out through gradient centrifugation, spermatozoa rinsing, and swim-up according to the original method. After processing, all final spermatozoa samples tested negative for residual contamination with HIV RNA. In the absence of infertility factors in the female partner and with good seminal quality after sperm washing, couples underwent 3 cycles of intrauterine insemination (IUI) with washed spermatozoa. Extracorporeal fertilization, with standard *in vitro* fertilization (IVF) procedures or by direct intracytoplasmic sperm injection (ICSI) in the oocyte, was selected forthwith when required for poor seminal quality. To date, 29 cycles of reproductive trials have been carried out. Four couples (23.5%) underwent IUI and three singleton pregnancies were achieved and went to term (75%). Thirteen women (76.5%) underwent IVF/ICSI treatment and six clinical pregnancies were achieved: three singletons, one set of twins and one set of triplets, and only one singleton miscarried at week eight(54%). No woman seroconverted for HIV infection after treatment. Women were tested again after delivery and they were all negative. All new-borns delivered were healthy and uninfected. Sperm washing coupled with reproductive assistance gives people with hemophilia infected with HIV the possibility of having children without the risk of transferring HIV infection. Recently an alternative method has been developed to achieve safe conception in HIV-discordant couples based on the potential role of oral pre-exposure prophylaxis with antiretroviral therapy and its application is under investigation.

PO-MO-102
Long-term follow-up of hepatitis C in patients with bleeding disorders

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Many patients with bleeding disorders were infected with HIV and hepatitis C virus by clotting factor concentrates, before these were free from virus at the end of the 1980s. The HIV-infection can now be controlled with HAART, whereas hepatitis C has become an increasingly important comorbidity and cause of death in this group of patients. The aim of the study was to describe the consequences of hepatitis C for patients with hemophilia A, hemophilia B, and von Willebrand disease who were treated with clotting factor concentrates at the coagulation unit of the Karolinska Hospital. Of 249 patients with a positive test for antibodies towards hepatitis C, 228 were included in the study. Data was gathered from patient records regarding bleeding diagnosis, date for diagnosis of hepatitis C, treatment and complications of hepatitis C, and causes of death. Of 228 included patients, 45 (19.7%) had cleared the infection spontaneously and 183 (80.3%) had developed a chronic infection. Of the patients with chronic infection, 124 (67.8%) had been treated for hepatitis C, of whom 71 patients (57.3%) had cleared the infection. In total, 34 patients were co-infected with HIV, of whom 30 had chronic hepatitis C. Mean follow-up time was 30 years, and during this period, in the group that had not cleared the infection after treatment (n = 112), 22 patients developed cirrhosis, 8 patients developed hepatocellular carcinoma, and 13 patients developed liver failure. Of all deaths in the group with chronic infection, liver related mortality accounted for 20.5%.

These results confirm that hepatitis C is an increasingly important comorbidity in the studied group. There is still a considerable part of the patients who remain untreated for hepatitis C, and hepatitis C is a growing cause of death in patients with bleeding disorders.

PO-MO-103
The development of Japanese blood program for assuring safety in supplying domestic coagulation blood products: A case study of the Japanese Red Cross Society

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This presentation examines the process of blood donation program in Japan, which has been designed to assure safety, especially within the Japanese Red Cross Society (JRCS). I will focus on how the JRCS was involved in the incident involving imported HIV-tainted blood coagulation products. This presentation utilizes data from interviews with JRCS staff and other concerned persons, along with related materials. The data has been collected through a joint research project from 2010 to 2012. In Japan, about 1,400 people with hemophilia were infected with HIV by tainted blood coagulation products. People with hemophilia brought lawsuits against the Japanese government and pharmaceutical companies from 1989 to 1996. Compared with other companies, the JRCS had been less involved in the issue of HIV/AIDS because the JRCS did not have the capability to produce enough blood products. The JRCS staff were not even aware of the epidemic of HIV/AIDS in those days. Therefore, the JRCS's closed and bureaucratic system was questioned in the lawsuit, rather than its responsibility. Their system even made the JRCS unable to tackle the epidemic without directions from the Ministry of Welfare. Since 1991, the JRCS has provided blood products that are made from domestically donated blood, then any aspects of screening tests, a mini-pooling NAT testing, virus inactivation, removal and strict management are implemented at the Plasma Fractionation Center. However, the JRCS is decreasing its influence over the Japanese blood program because Blood Products Research Organization reports that the share of the human coagulation factor VIII dropped to 19.4% in 2010. The JRCS is part of a council with the other pharmaceutical companies in order to integrate blood industry and to establish a public corporation. We have to examine how this new corporation will take over the role in assuring safety in supplying domestic coagulation blood products, which the issue of HIV/AIDS has raised.

PO-MO-104
Low levels of adrenal androgens in HIV positive hemophilia patients: Correlation with the presence and degree of lipodystrophy

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Objectives: It is already known that HIV infection affects adrenal function. The aim of this study is to investigate if the presence of HIV infection and lipodystrophy influences the production of adrenal androgens in hemophilia patients.
Methods: Dehydroepiandrosterone sulfate (DHEA-S) and Δ-4 androstenedione (Δ4A) was measured in 61 hemophilia patients, 30 of them HIV positive. The presence and degree of lipodystrophy was assessed with clinical method using a score from 0 to 3, absent (0), mild (1), moderate (2), and severe (3). All HIV positive patients were under antiretroviral therapy.
Results: Mean values of adrenal androgens were found lower in HIV positive hemophilia patients compared to HIV negative patients; DHEA-S 0.9 vs. 1.98 μg mL^{-1} ($P < 0.001$) and Δ4A 1.62 vs. 2.1 ng mL^{-1} ($P < 0.005$) respectively. Among HIV-positive patients, mean values of DHEA-S and Δ4A were lower in those with lipodystrophy, (DHEA-S: 0.82 vs. 1.06 μg mL^{-1}, *P*:0.001 and Δ4A: 1.57 vs. 1.64 ng mL^{-1}, *P*:0.005 respectively). We also observed a significant positive correlation between the drop of DHEA-S and Δ4A levels with the degree of lipodystrophy. Mean DHEA-S values, when lipodystrophy: absent 1.86 μg mL^{-1}, mild 1.16 μg mL^{-1}, moderate 0.70 μg mL^{-1} and severe 0.69 μg mL^{-1} (*P*:0.01) and mean Δ4A values when lipodystrophy: absent 2.0 ng mL^{-1}, mild 1.78 ng mL^{-1}, moderate 1.59 ng mL^{-1} and severe 1.58 ng mL^{-1} (*P*:0.05).
Conclusions: The levels of adrenal androgens (DHEA-S and Δ4A) were found to be lower in HIV positive compared to HIV negative hemophilia patients. The correlation of HIV infection with lower adrenal androgen production was stronger in the presence of lipodystrophy with the lower levels of Δ4A and especially DHEA-S in patients with moderate and severe lipodystrophy. We may conclude that adipose tissue has a role in the regulation of adrenal androgen production which is disturbed in HIV hemophilia patients with lipodystrophy.
Contribution to clinical practice: Oral DEAS treatment in HIV positive hemophilia patients may improve their long term quality of life (QOL).

PO-MO-105
Fibroscan: A non-invasive biomarker of liver fibrosis in hemophilia patients with hepatitis C

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Objective: Chronic hepatitis C is one of the major causes of liver fibrosis and progression to cirrhosis. Liver biopsy, currently considered the "gold standard" for the assessment of liver histology, has limitations and risks. There is reluctance to perform liver biopsy in patients with hereditary hemorrhagic disorders because of concerns about the safety of the procedure in this population. We perform fibroscan, a non-invasive biomarker, to evaluate fibrosis or cirrhosis in people with hemophilia with HCV infection or HCV/HIV co-infection, in combination with clinical and biochemical examination to predict those with a high risk of developing HCC and cirrhosis.
Patients—Methods: Thirty-three patients (hemophilia A: 22, B: 4, VWD: 6, FVII deficiency: 1, GT:1, 18 HCV mono-infected, and 16 HCV/HIV co-infected) underwent fibroscan from July 2010 to December 2011. Fibrosis defined as liver stiffness >7.0 kPa. Ten validated measurements were performed for each patient. The results were expressed in kilopascals. An interquartile range (IQR) of less than 30% of the median value was considered reliable. Patients with liver stiffness values above 13kPa were considered to have cirrhosis. Anti-HCV therapy have received all HCV mono-infected patients and 7 out of 16 HCV/HIV co-infected. All HIV-positive patients were under HAART.
Results: Among HCV mono-infected patients, 12 (67%) were found in group F0–F2 of METAVIR score with mean stiffness 5.3 (range 3.8–6.7) kPa and 6 (33%) in F3–F4 group, with mean stiffness 13.2 (8.8–21.3) kPa, while 50% of the HCV/HIV co-infected patients were found in F3–F4 group with mean stiffness 20.4 (7.8–36.3) kPa. Stiffness values were associated with the success of achieving SVR after anti-HCV treatment in the HCV mono-infected group. Four patients of the low fibrosis score succeeded SVR and 4 were relapsers, while the 6 patients with advanced inflammation were N-R with genotype 1b. The association was not clear in the co-infected group, as the presence of liver steatosis, immunological factors, and the long-term anti-retroviral treatment implicate in the development of liver fibrosis.
Conclusions: Fibroscan, in combination with other biomarkers, is useful for assessing liver fibrosis in HCV+ve hemophilia patients and should be recommended. It is a safe technique and improves the accuracy of diagnosis.

PO-MO-106
"Like a curse": Outcomes of the New Zealand 2011 people with hemophilia and hepatitis C survey

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Over a third of the people with bleeding disorders (PWBD) exposed to hepatitis C (HCV) in blood products in New Zealand continue to live with chronic HCV and the additional toll this has on their health and well-being.
Aims/methods: To understand the impact of HCV in this community, a self-completed survey was circulated to 53 PWBD and chronic HCV in New Zealand. Respondents were asked about demographic information, employment, treatment for hepatitis C, symptoms, liver health, HCV education, and their general health, activities, and psychosocial functioning.
Results: In total, 31 surveys (58%) were completed and returned. Over one third of respondents were aged more than 61 years (39%) and only two were aged less than 30 years. Only half (47%) of those aged less than 61 years were in full-time employment. Interferon therapy had been attempted by half (52%) of the respondents, and 48% had undergone a FibroScan©. Six (19%) of respondents indicated they had fibrosis or cirrhosis and one liver cancer. Fatigue affected 84% of respondents and had the most impact on their lives for 65%. Most respondents (58%) felt they were well-informed about HCV, preferring HFNZ outreach workers and publications and their general practitioner as sources. In general, half of the respondents (51%) reported feeling good or very good, although most reported having physical limitations, especially in relation to vigorous activity (81%). The survey showed that the majority found daily tasks harder to complete, both because of pain (49% at least some of the time), and also loss of energy (67% at least some of the time). Anxiety or worry about the effects of HCV affected 81% of respondents.
Conclusion: Although most reported making positive lifestyles choices to support their liver health, many respondents indicated that living with HCV and especially the associated fatigue encumbers daily living.

PO-MO-107
The role of the rs12979860 polymorphism of the interleukin-28b as predictor of spontaneous clearance of HCV infection in patients with hemophilia

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HCV infection is the most common blood-born infection in adult patients with hemophilia. The vast majority of infections persist, potentially causing chronic liver disease, while up to 10–20% of patients have spontaneous viral clearance (SVC). Some studies in non-hemophilic patients showed that a strong host immune response against HCV favors viral clearance and that the rs12979860 single nucleotide polymorphism (SNP) in the Interleukin-28B (IL28B) gene (interferon-λ3) may play a role. The aim of our study was to evaluate the role of the IL28B SNP as predictor of SVC in patients with hemophilia. The SNP was determined by real-time PCR in 184 people with hemophilia, 59 with SVC (patients with a positive test for anti-HCV antibodies but undetectable HCV-RNA in serum) and 125 with persistent viral infection (PVI). HIV co-infection was present in 19/125 (15.2%) of chronically infected patients and in 6/59 (10.2%) patients with spontaneous clearance. HBsAg positivity was determined in 13/125 (10.4%) of patients with PVI and in 7/59 (11.9%) patients with SVC. The IL28B C allele homozygosis was strongly associated with SVC (69.5% vs. 39.0% in PVI, $P < 0.0005$). HCV infection in the first 2 years of life was also statistically associated with a HCV clearance ($P = 0.008$). By contrast, no association between hemophilia severity and HCV clearance/persistence as well as the presence of HIV or HBV co-infection was shown. In a logistic regression

model, both the IL28B C/C genotype and infection within the first 2 years resulted as independent predictors of SVC, being the IL28B genotype the strongest one ($P < 0.0005$, OR 3.65, 95% CI 1.83–7.25 and $P = 0.010$, OR 2.42 and 95% C.I. 1.23–4.7, respectively). In conclusion, the IL28B SNP is a strong, non-invasive predictor of the ability of the immune system to clear HCV infection in people with hemophilia, independently from the severity of coagulopathy and other blood-borne viral co-infections.

PO-MO-108
The role of the rs12979860 polymorphism of the interleukin-28b as a predictor of sustained virological response after antiviral therapy in patients with hemophilia and chronic hepatitis C

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Background: HCV infection is the main cause of morbidity and mortality in patients with hemophilia. HCV eradication with antiviral therapy is the only approach that can halt disease progression. Rapid virologic response (RVR; undetectable HCV-RNA after 4 weeks of therapy) is the strongest predictor of sustained virologic response (SVR), and recently the CC variant of the single-nucleotide polymorphism rs12979860 (IL28B SNP) was associated with high SVR rates in non-hemophiliacs.
Methods and Results: The SNP was determined by PCR in 207 hemophiliacs treated for HCV infection. HIV and HBV co-infections were present in 48 (23%) and 6 (3%) patients, respectively. HCV genotype was 1 in 127 (61%), and the IL28B SNP was CC in 82 (40%), CT in 106 (51%), and TT in 19 (9%). The median duration of HCV infection was 33 years and the median age at antiviral treatment 39 years. Twenty-four patients (12%) had cirrhosis. Peg-IFN plus ribavirin were used in 156 (75%). The overall SVR rate was 57% (40% if genotype 1 and 84% if genotype 2/3). RVR, EVR, and SVR were more frequent in patients carrying the CC SNP than in those carrying a non-CC SNP (57 vs. 22%, 87 vs. 67% and 77 vs. 45%, respectively; $P < 0.01$). By stratifying patients for HCV genotype, such difference was confirmed only in those with HCV type 1, while no difference was observed in patients with HCV type 2/3. By univariate logistic regression HCV genotype 2/3, CC IL28B-SNP, absence of cirrhosis, RVR and EVR were predictors of SVR (OR 7.9, 4.1, 8.5, 14.5, and 15.7, respectively). By multivariate analysis, only RVR and EVR were independent predictors of SVR (adjOR 6.5 and 17.0, respectively).
Conclusions: The IL28B SNP may serve as pre-treatment predictor of IFN-based therapy outcomes in people with hemophilia with chronic hepatitis C, especially in those with genotype 1.

PO-MO-109
HCV infection of hemophilia and the associated disease patients in St. Marianna University Hospital

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Background: Hepatocellular carcinoma (HCC) and hepatic cirrhosis derived from hepatitis C virus (HCV) are the main causes of death in hemophilia patients. Among the several key HCV genotypes, genotype 1a is the main type resulting from imported human plasma-derived products used in Japanese hemophilia patients.
Method: We investigated HCV-genotype, therapy, treatment outcome, prognosis of 36 patients who acquired HCV infection via transfusion or human plasma-derived products. Among them, 34 had hemophilia and 2 had congenital coagulation disorder.
Results: In Japan, HCV examination was started from 1989. Among 67 patients with hemophilia and associated diseases who were born before 1989, 37 (55%) had HCV infection. Further, among 4 patients with HIV co-infection, 2 died of AIDS. Two patients died of HCC without co-infection with HIV. The average age of surviving patients was 42.6 (28-71) years. The prevalence of serotype I or genotype 1a/1b in HCV patients was 56%. In 30 patients with confirmed infection in medical records, 6 (21%) were only positive for anti-HCV and 21 (70%) progressed to chronic hepatitis C. Among 13 patients who received interferon (IFN) or pegylated (PEG)-IFN therapy, 5 showed sustained virological response (SVR). IFN+ ribavirin (RBV) or PEG-IFN+RBV therapy was administered to 12 patients, including no-effected 5 patients by IFN or PEG-IFN therapy. Seven patients (64%) showed SVR; the therapies of 3 patients were interrupted due to the adverse effects; and 1 patient did not respond to PEG-IFN+RBV therapy. Hence, among 20 chronic hepatitis C patients, 12 achieved SVR.
Conclusion: The frequency of cases with interruption of treatment due to adverse effects and the number of non-responders to HCV therapy was similar. Therefore, it is important to prevent adverse effects when administering new treatments using protease inhibitors.

PO-MO-110
Septic arthritis in patients with hemophilia

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Introduction: Septic arthritis (SA) is a rare complication in patients with hemophilia. An increased incidence has been reported associated with HIV infection. The clinical presentation of SA is similar to usual hemarthrosis, and the diagnosis can be delayed.
Patients and methods: Records of all patients with hemophilia admitted in our centre during the period 2007 to 2011 were reviewed. We report ten cases of SA of native joints.
Results: All patients had severe hemophilia A, with a mean age of 30 (14–51) and previous arthropathy of the involved joint. Eight were HCV-positive and 1 was HIV-co-infected. Swelling, pain, and severe functional impotence of the joint were always present. Eight patients had fever (>38ordm;C). The infected joints were knee, elbow, and ankle. In 3 cases, more than one joint was affected. The mean duration of symptoms before the diagnosis of SA was 8 days. All patients had leukocytosis and increased erythrocyte sedimentation rate. Skin lesions, pneumonia, and use of IV drugs were pointed out as the source of infection in 6 patients. Arthrocentesis was performed in all cases. Staphylococcus aureus was isolated in 6 patients, and blood cultures were positive in only 2. Antibiotic therapy and prompt rehabilitation resulted in good outcomes. The mean hospital stay was 23 days.
Conclusions: The majority of joint infections occurred in HIV-negative patients. Staphylococcus aureus was the most common organism isolated. Diagnosis should be considered when an episode of apparent hemarthrosis fails to respond promptly to replacement therapy or in the presence of fever.

PO-MO-111
Number of patients with coagulation disorders in Japan's 2010 annual report from the research committee for the national surveillance on coagulation disorders in Japan

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Objective: To report the collected number of Japanese patients with coagulation disorders as of 31 May 2010.
Methods: We utilized the database of the Research Committee for the National Surveillance on Coagulation Disorders in Japan, which is the only national registry of Japanese people with hemophilia.
Results: The numbers of patients as of 31 May 2010 were as follows: hemophilia A, 4,394 patients (male 4,368, female 26); hemophilia B, 952 (male 940, female 12); von Willebrand disease (VWD), 944 (male 432, female 512); and hemophilia-related disorders, 502 (male 261, female 241). The prevalence of hemophilia (hemophilia A and hemophilia B) was 8.7 male hemophiliacs per 100,000 Japanese males. Regarding the percentages with HIV or HCV infection in patients with coagulation disorders, 10.2 percent of them had been infected with both HIV and HCV, 0.2 percent HIV only, and 30.5 percent HCV only. The number of newly registered patients in the 2010 surveillance was 177. Their age distribution was as follows: age ≤ 5 years, 65; 6–10 years, 18; 11–15 years, 12; 16–20 years, 4; and 21 years ≤ age, 78. The annual numbers of deaths in the interval from 1998 to 2010 varied between 12 and 22 in HIV-negative patients, and between 8 and 20 in HIV-positive patients. The proportion of deaths with a report of critical liver disease among 402 accumulated deaths was 29% and 55% in HIV-negative or HIV-positive patients, respectively ($P < 0.001$). Among the deaths with critical liver disease, infection with HCV had been identified in 88.2 percent of patients.
Conclusions: There were 177 newly reported patients in 2010. However, they included 116 patients older than 5 years old. Therefore, continuing surveillance is still inevitably necessary to accurately comprehend the prevalence of coagulation disorders in Japan. Death with critical liver disease triggered by HCV has been the most important problem among the present Japanese patients with coagulation disorders.

21-INHIBITORS, PATHOGENESIS, PREVENTION AND TREATMENT

PL-WE-02.2
Prediction and prevention of inhibitor development
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Studies of determinants of the development of inhibitory antibodies in patients with hemophilia indicate that this is a complex process involving several factors. The foundation is characterized by the T- and B-cell repertoire, the antigen presenting cells and type of causative mutation. It is obvious that in order to elicit an immune response to the deficient factor, a predisposing foundation is needed. Hence, in the absence of a certain set of circumstances, there will be no risk for development of inhibitors. Conversely, in patients fundamentally at risk for inhibitors, other genetic or non-genetic factors might add to the risk. These factors may be additive or interactive, and ultimately promote or counteract the immune reaction by modifying immune regulators and the cytokine profile in an individual. In some subjects, only minor inflammatory signals might be needed, whereas in others a more pronounced pro-inflammatory state will be required. In several studies, polymorphisms in the interleukin-10 gene have been associated with inhibitor risk; however, this association is not consistent across patient groups. The same is true for other identified candidate genes. The reason for this is not clear, but could be related to statistical power, family relationships among those studied, and ethnic genomic variation. The Hemophilia Inhibitor Genetics Study (HIGS) has identified additional candidates within the intracellular pathways, all of which require further evaluation to be fully appreciated. The data suggest that it will be possible to calculate a genetic score in order to identify patients at high risk for inhibitor development *before* the start of treatment. By doing so, it may be possible in the future to offer therapeutic options other than the native factor VIII or IX molecule to prevent replacement therapy in an inflammatory setting, thereby avoiding the formation of inhibitors.

S-WE-03.1-3
Models for assessing hemostatic efficacy of bypassing agents
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The first assessment of hemostasis in an animal model of hemophilia was the secondary toenail bleeding time in dogs. Once it became possible to knock out genes in mice, mouse models of hemophilia were created. The initial mouse hemostasis model assessed the amount of blood lost following removal of the tip of the tail. Decreased blood loss following therapy was considered evidence of hemostatic efficacy. Other models have been developed that may have somewhat less variability than the tail-snip models. One type of model involves an injury to a vessel that leaves it intact. An example is a ferric chloride injury in which the endpoint is vessel occlusion. While generally considered a thrombosis model, if properly done this model is sensitive to coagulation factor levels. We have developed a vessel transection model in the saphenous vein; wild type animals have multiple bleeding stops, while hemophilic animals do not stop bleeding. In both the intact vessel model and the vessel transection model, administration of bypassing agent gives a dose-dependent change in the readout, making it possible to generate a dose-response curve. The dose responses of different therapeutic agents can be compared to give an assessment of relative efficacy. In addition to assessing immediate hemostatic effect, there are healing models that assess longer-term effects. We have studied a dermal wound healing model; hemophilic mice have poor wound healing compared to wild type animals. There is also a model in which a penetrating injury to the equivalent of the knee is studied. Numerous histologic features are impaired in hemophilia; therapy decreases the extent of the injury. In both cases, bypassing agents can improve the endpoints, allowing for an assessment of efficacy. These newer models may give us a greater ability to assess different aspects of therapeutic bypassing agents.

S-WE-03.1-2
Assessing the immunogenicity of clotting factor concentrates in humans
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FVIII concentrates' immunogenicity should be appreciated, taking into account immune response host factors, apart from observations that establish associations between risks of inhibitors and mutation, gene polymorphism, or FVIII polymorphism. On a more basic level, 5 facts should be remembered: (1) In the absence of FVIII, there is no sorting out of T cell effectors in the thymus, and there is no active selection of natural regulatory T cells; (2) FVIII is administered by the IV route, which has significant implications for immunogenicity, as the first organs to be hit include the liver and the lung, as well as the spleen; (3) FVIII is by definition administered on a recurrent basis, and each administration is considered as a new challenge for the immune system, irrespective of the results of previous exposures; (4) B cells in a germ-line configuration recognize certain determinants of FVIII; and (5) Overly high immunogenicity kills immunogenicity. Recent findings on FVIII immunogenicity have identified a cascade of events starting with an activation of innate immunity, which acts as a bridge to the development of a highly specific adaptive response. Noticeably, the response to FVIII, as we read it in the clinic—namely the presence of inhibitory antibodies—is the result of a subtle equilibrium between activation and control of both innate and adaptive responses. In light of these observations, we are left with two issues: (1) Can we identify how, when, and where the first activation of the immune system occurs, bearing in mind the development of methods to prevent such activation? and (2) Do we have the possibility of interfering with the immune response at either early or later steps of such response? FIX concentrates' immunogenicity poses less difficulty, insofar as FIX does not, or does only marginally, activate the innate immune system. Interfering with a fully adaptive response under such circumstances is conceptually much simpler.

FP-WE-01.1-2
The change of serum BAFF level in the development of anti-factor VIII antibodies in hemophilia A mice
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Objectives: Hemophilia A is an X-linked bleeding disorder, caused by defects in the factor VIII (FVIII) gene. FVIII antibodies pose a major challenge for replacement therapy. B cell-activating factor (BAFF) is involved in the survival and maturation of B cells and plays a critical role in most immune responses. The purpose of this study was to investigate the relationship between BAFF level and the emergence of anti-FVIII antibodies in an animal model.
Methods: Hemophilia mice (C57BL/6 and 129 mix background, Exon 16 knockout) were intraperitoneally injected with 2 IU (~80 IU kg^{-1}) of human recombinant FVIII (rFVIII) (Baxter) diluted in PBS, with/without anti-CD20 antibody treatment at 4 consecutive weeks. The mice serum and plasma were sampled before injection and after 4 consecutive weekly injections. Total anti-FVIII antibody titers and serum BAFF concentration were determined by ELISA. The difference between those experimental groups was evaluated by one-way ANOVA using PRISM
Results: Four subsequent weekly intraperitoneal injections of 2 IU rFVIII successfully induced high titer of anti-FVIII antibodies (162–306 μg ml^{-1}). For the group which received intraperitoneal injection of 2 IU rFVIII combined with anti-CD20 antibody for 4 continuous weeks, no apparent anti-FVIII antibodies (0.2–2.4 μg ml^{-1}) were detected. Interestingly, BAFF level in the anti-CD20 antibody-treated group increased probably because of compensatory immune responses (>23000 pg ml^{-1}). We also found in the rFVIII-treated group, BAFF level increased before high-titer anti-FVIII antibodies formation.
Conclusions: In the anti-CD20 antibody-treated group (B cells depleted), very low levels of anti-FVIII antibodies were detected. In the rFVIII-treated group, high-titer anti-FVIII antibodies developed after brief BAFF surged. Our preliminary experiment indicated that BAFF may be responsible for the anti-FVIII inhibitor formation and therefore a BAFF targeting strategy might prevent or reduce its occurrence.

FP-WE-04.2-2
Predictors of success of immune tolerance induction in hemophilia A patients with high-responding inhibitors: A score from the Italian registry
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Introduction. Predictors of success in immune tolerance induction (ITI), the only therapeutic approach proven to eradicate inhibitors in patients with hemophilia A, are still debated. Since 2005 a retrospective-prospective ITI Registry is ongoing in Italy.
Methods.ITI outcomes were centrally reviewed according to the current definitions of success (undetectable inhibitor and normal FVIII pharmacokinetics, PK), partial success (titer <5 BU ml^{-1} and/or abnormal PK) and failure. Predictors of success were analyzed in 109 completed ITI courses by logistic regression. Results. Patients underwent ITI at age of [median (range)] 5.6 years (0.3–59.5), with pre-ITI inhibitor titer of 4.1 BU ml^{-1} (<0.5–200) and historical peak of 75 BU ml^{-1} (6–920), 21 mo. (0–332) after inhibitor diagnosis. FVIII/VWF products were used in 27% of courses and recombinant FVIII in the remaining (≥100 IU kg^{-1} day^{-1} in 35% and 75% and daily regimens in 48% and 83%, respectively). Median inhibitor peak titer during ITI was 45 BU ml^{-1} (5–16384). Fifty-six patients achieved success (51%) and partial success was obtained in 15 (14%). Pre-ITI inhibitor titer [<5 BU ml^{-1}, adjusted OR (95% CI) 11.4 (3.3–38.9), $P < 0.001$] and peak titer during ITI [<100 BU ml^{-1}, 14.8 (4.3–51.4), $P < 0.001$] were significant predictors of ITI success, as well the *F8* mutation class. *Non-null* (small insertions/deletions and missense mutations) genotypes showed significantly higher success rate [17/21, 81% vs. 37/82, 45%; $P = 0.03$] than *null* genotypes (large deletions, inversions, nonsense and splice site mutations). When these predictors were used for stratifying risk of ITI failure, the score (1 point in the absence of each favourable predictor) was significantly related ($P < 0.005$) with both rate of success (0, $n = 13$: 85%; 1: $n = 36$, 75%; 2, $n = 40$, 35%; 3, $n = 11$: 0%) and time to achieve success (median, mo, 0: 7; 1: 11; 2: 16).
Conclusions. These data contribute to identify patients' prognostic profiles useful for prediction of outcome and optimizing clinical choices in ITI management.

FP-WE-01.1-1

Polymorphism 131R>H in the FCGR2A gene is associated with inhibitor development in hemophilia A

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Introduction: Inhibitor development is a major complication in the treatment of hemophilia A and the etiology is still poorly understood. The low-affinity Fc gamma receptors (FcγRs), which are expressed on immune cells, provide an important link between cellular and humoral immunity by interacting with IgG subtypes. Genetic variations of the FcγR genes (*FCGR*) have been associated with autoimmune diseases. In this study, we investigated the association between polymorphisms and copy number variation (CNV) of *FCGR* genes and inhibitor development in severe hemophilia A.

Methods: Clinical data and DNA samples of 88 patients with severe hemophilia A (brothers from 46 families) were available for analysis from the previously described MIBS cohort. CNV and polymorphisms of the FCGR2A, FCGR2B, FCGR2C, FCGR3A and FCGR3B gene were studied by the use of an FCGR-specific multiplex ligation dependent probe amplification assay (MLPA). The X^2 test was used to compare differences between CNV and allele frequencies of polymorphisms.

Results: The persons with hemophilia A were mainly Caucasian (94%), and 46 persons (52%) had an intron 22 inversion. Inhibitors developed in 37 patients (42%) of which 20 were high-titer inhibitors. The polymorphism 131R>H in the FCGR2A gene was associated with a twofold increased inhibitor risk (odds) ratio 2.0 (95% CI, 1.1–3.6; $P = 0.03$). The FCGR2A 131HH genotype was present in 46% of the inhibitor patients and 50% of the patients with high titer inhibitors as compared to 29% of the controls. This distribution persisted in the subgroup of patients with inversions ($P = 0.017$). We did not find an association between inhibitor development and CNV of the FCGR2 and FCGR3 genes and the polymorphisms: FCGR2B (232I/T), promoter of FCGR2B and FCGR2C (-386 G/C), FCGR3A (158V/F), and FCGR3B (HNA1a/HNA1b/HNA1c).

Conclusion: Persons with severe hemophilia A and the FCGR2A polymorphism 131R>H have a twofold increased risk for inhibitor development.

FP-WE-04.2-1

Novel MHC-PEPTIDE–T cell receptor interfaces are necessary for inhibitor formation in mild/moderate hemophilia A secondary to missense mutation genotypes

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We are developing an *in silico* risk-stratification strategy using artificial neural networks to identify more accurately a person with hemophilia's inhibitor risk, rather than just a population-based estimate based on the known F8 genotype alone. Missense genotype mild/moderate hemophilia A lends itself particularly well to develop such an analysis, enabling focus on the single, allogeneic amino acid change. We utilize a validated algorithm to model binding of FVIII derived peptides in the groove of multiple HLA DR alleles. Anti-FVIII antibody responses are T cell dependent. Consequently, we also determined whether a novel interface arises between the antigen presenting cell and CD4 T cell receptor (TCR) as a result of a given FVIII mutation. We hypothesised that a missense mutation resulting in a predicted peptide-interface change with a TCR should be capable of stimulating an anti-FVIII response, and conversely, lack of a novel TCR interface is likely to be protective against anti-FVIII antibody formation. Four hundred seventy-nine different missense mutations causing mild/moderate hemophilia A were identified on the HaMSTeRS data base. Each mutation was modelled through all 14 assessable HLA-DR alleles and compared to wild-type FVIII peptide binding. All missense mutations with a reported inhibitor occurrence had a predicted novel interface in at least one of the assessable HLA DR alleles. None of the mutations we predict as having no (or negligible) risk of developing inhibitory antibodies have reported development of such antibodies. More generally, our results show that there is a significant correlation between the inhibitor rate associated with a particular missense mutation and the proportion of HLA DR alleles predicted to bind a T-cell epitope spanning the relevant location. Our results are consistent with the hypothesis that an MHC class II response is necessary, but not sufficient, for a patient with mild/moderate hemophilia A to develop an inhibitor.

FP-WE-04.2-3

Assessment of treatment-related risk factors for inhibitor development in previously untreated hemophilia A patients: Different statistical approaches

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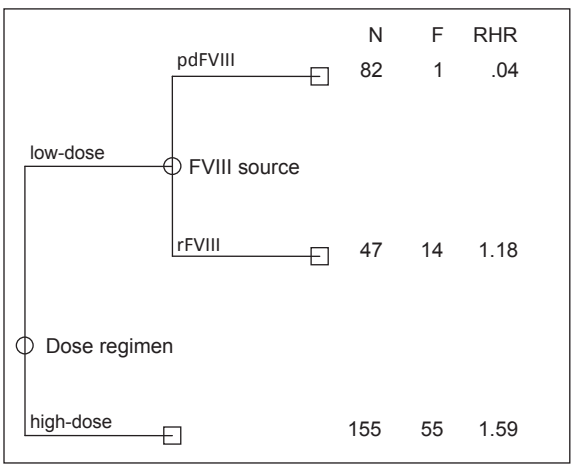
Background/Aim: As an issue of current debate, we aimed to explore the impact of FVIII product (recombinant [rFVIII] *versus* plasma-derived [pdFVIII]) and of the dose regimen on the inhibitor development in hemophilia A patients. Different methodological approaches were applied in order to test the strength of our results.

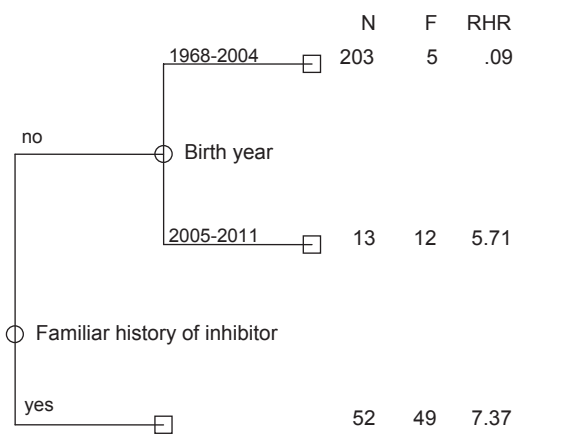
Materials and Methods: Population of study: all previously untreated patients (PUPs) from 6 centres with moderate-severe hemophilia A (baseline FVIII level ≤ 5 IU dl^{-1}) born between 1967 and 2011, studied for a total of 200 exposure days (ED) or until inhibitor formation. Outcome: Inhibitor formation (positive test >0.5 BU; at least two confirmatory tests). Treatment-related risk factors of study: FVIII source (rFVIII *versus* pdFVIII) and dose (high-dose [>30 IU kg^{-1} per dose] *versus* low-dose). Other risk factors included as covariates: birth year, severity of hemophilia, gene mutation, family history of inhibitor, age at the first bleeding, historical period of treatment, centre. Statistical methods: 1) univariate and multivariate Cox regression stratified by-centre; 2) CART analysis; 3) Cox regression with covariate adjustment using propensity scores for concentrate source and dose; 4) Calculation of Average effect of Treatment on Treated (ATT) using propensity score matching with nearest neighbor method.

Results: One hundred and sixty-seven patients out of the 284 PUPs (58.8%) were treated with pdFVIII; 154 patients (54.6%) with a high-dose regimen. A total of 70/284 patients developed inhibitors after a mean of 32 EDs (standard deviation 31.7; median 22, range 5-172). Among patients treated with pdFVIII, 16.7% developed inhibitors, as compared to 35.9% among those treated with rFVIII. Among patients treated with high-dose, 35.5% developed inhibitors, as compared to 11.6% among those treated with low-dose regimens. The table and figures show the results of the different statistical approaches.



Legend: N, number; F, Failures; RHR, Relative Hazard Ratio.

Fig. 1. Multivariate Classification and Regression Tree (CART) analysis. Variables included in the analysis: FVIII source (recombinant [rFVIII] or plasma-derived [pdFVIII]) and dose regimen (high-dose or low-dose).



Legend: N, number; F, Failures; RHR, Relative Hazard Ratio.

Fig. 2. Multivariate Classification and Regression Tree (CART) analysis. Variables included in the analysis: FVIII source (recombinant or plasma-derived), dose regimen (high-dose or low-dose), birth year, severity of hemophilia, kind of gene mutation, familiar history of inhibitor, age at the first bleeding, historical period of treatment, centre.

Table. Cox regression and Propensity Score adjustment.

Cox regression	pdFVIII *vs.* rFVIII HR (95%% CI)	P value	High-dose *vs.* Low-dose HR (95%% CI)	P value
Univariate	0.43 (0.26—-0.71)	0.001	6.20 (3.31—-11.61)	<0.001
Multivariate	0.69 (0.31—-1.51)	0.355	0.66 (0.22—-1.95)	0.454
Multivariate with interaction	If high-dose: 1.02 (0.45—-2.30)	0.966	If pdFVIII: 5.82 (0.95—-35.61)	0.056
	If no-high-dose: 0.04 (0.01—-0.27)	0.001	If rFVIII: 0.25 (0.07—-0.90)	0.034
Multivariate Propensity Score‡‡-adjusted	0.84 (0.41—-1.71)	0.628	1.91 (0.73—-4.99)	0.185
Multivariate Propensity Score‡‡-adjusted with interaction	If high-dose: 1.16 (0.56—-2.40)	0.683	If pdFVIII: 13.48 (1.62—-112.33)	0.016
	If no-high-dose: 0.06 (0.01—-0.55)	0.012	If rFVIII: 0.75 (0.25—-2.29)	0.616
Risk difference	**pdFVIII *vs.* rFVIII ATT (standard error)**	**t**	**High-dose *vs.* Low-dose ATT (standard error)**	**t**
Propensity score‡‡ matching (nearest neighbor method)	0.062 (0.158)	0.392	0.271 (0.250)	1.083

Legend: HR, Hazard Ratio; CI, Confidence Interval; ATT, Average effect of Treatment on Treated. ‡ Variables included in the two propensity scores (for FVIII source and dose) were the same used as covariates in multivariate Cox regressions (birth year, severity of hemophilia, kind of gene mutation, familiar history of inhibitor, age at the first bleeding, historical period of treatment, centre).

Conclusion: Different statistical approaches confirm that apparent risk of inhibitor formation according to treatment strategy was confounded by patient-related risk factors.

Legend: N, number; F, Failures; RHR, Relative Hazard Ratio.

FP-WE-01.1-5
Non-neutralizing antibodies and the impact on thrombin generation in hemophilia A Patients: Results from the MIBS and HIGS Cohorts

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Antibodies directed towards non-neutralizing epitopes on the factor VIII (FVIII) protein may be detected in patients with hemophilia A. We evaluated the prevalence of non-neutralizing antibodies, and the effect on thrombin generation, in 206 inhibitor negative patients with severe hemophilia A, enrolled in the Malmö International Brother Study (MIBS) and the Hemophilia Inhibitor Genetics Study (HIGS). In order to evaluate binding specificity of the antibodies, ELISA plates were coated with two recombinant full-length FVIII products and one recombinant B-domain deleted product. Eighty patients (38.8%) had a history of positive inhibitor titer measured by Bethesda assay and FVIII-antibodies were detected in 20 of them (25.0%). An additional 24 samples from subjects without a history of FVIII-inhibitors were ELISA positive, a frequency of non-neutralizing antibodies of 19.0%. The antibody response towards the different FVIII-products was heterogeneous and was raised not only towards the non-functional B-domain, as earlier suggested, but towards both FL-rFVIII and BDD-rFVIII. The median age in patients with NNA was 26.0 years compared to 14.0 years in patients without NNA, a difference of borderline significance ($P = 0.052$). The number of families with a concordant immune response to treatment was increased when the total antibody response was considered, without any clear association with previously described polymorphisms in the immune response genes. Thrombin generation was reduced in the majority of patients with non-neutralizing antibodies, but no clear relationship to individual products could be observed. Our data show that patients with hemophilia without known inhibitors produce non-neutralizing anti-factor VIII antibodies with different product specificity and encourage further studies to better appreciate their clinical importance.

FP-WE-01.1-6
Inhibitor incidence in PUPs and PTPs: Data from the first three years of the EUHASS Project

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The European Haemophilia Safety Surveillance System (EUHASS) is a prospective adverse-event-reporting system in the field of inherited bleeding disorders in Europe. Participating centres report all adverse events (inhibitors, transfusion transmitted infections, thromboses, acute/allergic reactions, as well as malignancies and deaths) prospectively, and annually they also report the number of patients registered at their centre and the number treated with each concentrate. Sixty-four hemophilia centres from 27 European countries caring for 22,242 patients participated in the first 2 years of the project. Four hundred and ten adverse reactions were reported of which 95 were new inhibitors and 16 were recurrences in patients with previous inhibitors. The inhibitor rate in PUPS with severe hemophilia A was 25% with a similar rate in patients treated with recombinant (25%) and plasma-derived (27%) factor products. Sixteen PTPs with severe hemophilia A developed an inhibitor with a rate of 0.23 per 100 patient years. In hemophilia B, 1 PUP and 2 PTPs developed inhibitors for the first time. In the first 2 years, the number of inhibitors in PUPs was too small to conclude whether there was a difference between the products. The third year data are not available at the time of submission of this abstract. The analysis will be available for 20 Feb 2012. This abstract will be modified to include the year 3 data. A minimum of 50 new inhibitors were so far reported to have occurred in the third year of EUHASS.

FP-WE-01.1-3
Source and purity of factor VIII products as risk factors for inhibitor development in previously untreated patients with severe hemophilia A

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Background: Inhibitor development is influenced by several genetic and environmental factors and the type of factor VIII (FVIII) products may play a role.

Objectives: In order to explore such a role, we designed a cohort study whose novelty resides in the classification of products not only according to the source of FVIII (plasmatic [pd] or recombinant [r]) but also to their degree of purity (expressed as FVIII specific activity per mg of protein). The role of FVIII product as a risk factor for inhibitor development was evaluated in a multivariate model adjusting for potential confounders.

Patients/Methods: Cumulative incidences of all and high-responding inhibitors were calculated for the whole cohort of 721 patients from 3 hemophilia centres. Detailed treatment data up to inhibitor development or 150 exposure days were collected in 377 patients in whom risk factors for inhibitor development including source and purity of FVIII products were analyzed.

Results: Inhibitors developed in 111 (29%; 96 high-responders, 25%). The cumulative incidence was progressively higher from patients treated with low/intermediate-purity pdFVIII to those treated with high-purity pd and rFVIII. The adjusted hazard ratio of inhibitor development was 4.9 with rFVIII and 2.0 with high-purity pdFVIII (95%CI: 2.9–8.3 and 1.1–4.0), taking as a reference low/intermediate-purity pdFVIII. There was no difference in the frequency of inhibitor testing between treatment groups. Sensitivity analysis in patients who never switched product type, previously untreated patients, those treated on demand and those with high-risk *F8* mutations - confirmed an increased inhibitor risk with rFVIII, and high-purity pdFVIII.

Conclusions: This study shows that the degree of purity of FVIII products influences inhibitor development independently from other risk factors, and emphasizes that differences exist within pdFVIII products.

FP-WE-04.2-4
Hemophilia B Mouse Strains Doubly Humanized for Human F9 and MHC Class II Genes for Study of Inhibitors

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Current hemophilia B mouse models are not ideal for investigating the potential immunogenicity of hemophilia B therapies due to differences in mouse and human MHC class II structure and FIX epitope recognition. This recognition depends on CD4+ T cells and their direct interaction with surface-expressed MHC class II molecules complexed with antigen. We have developed a series of mouse lines that do not express mouse FIX or mouse MHC II, but instead express human FIX genes and humanized MHC II- "double humanized" (2H) mouse lines. Our derivation of the 2H mouse lines, all having first been bred through a complete knockout of mouse MHCII (mMHC $II^{-/-}$), resulted in four lines of human HLA-DRB1*1501 mice. These four lines include 1) mouse $FIX^{-/-}$ (complete deletion; cross-reacting material negative (CRM-)); 2) human R29X (expresses human FIX gene with early nonsense mutation; CRM-); 3) human R333Q (expresses human factor IX defective circulating protein with missense mutation; CRM+), and 4) human WT FIX (WT2 expresses hemostatic human FIX; CRM+). Both strains of CRM-2H hu-mice developed inhibitors and anti-hFIX IgG antibodies with similar intensity. CD4+-enriched splenocytes proliferated *in vitro* in response to hFIX challenge and secreted high amount of Th1-derived IFN-γ and moderate Th2 (IL-4 and IL-10) cytokines. However, when compared to the inhibitor-prone strains, conventional (mouse MHC $H2^b$) and hu-DRB1*1501 CRM+ mice (both R333Q and WT2) tolerated hFIX, had larger total Treg populations, increased TGF-β1 cytokine, and demonstrated regulatory apoptosis of CD4+ Teffector cells. The repertoire of human factor IX immunostimulatory peptides identified in 2H mice is different and more complex when compared to immunostimulatory peptides identified in reported epitope mapping studies using $FIX^{-/-}$ mice having mouse MHC $H2^b$, $H2^d$, and $H2^k$ backgrounds. These differences may reflect the fundamental structural and epitope recognition differences between murine and human MHC class II complexes.

FP-WE-04.2-6
A Factor Xa Variant Restores Hemostasis in a Hemophilia A Dog Model

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Effective control of bleeding is needed in many clinical indications. Intrinsic pathway deficiencies, such as hemophilia A (factor VIII) and hemophilia B (factor IX), result in insufficient FXa and thrombin generation. To restore hemostasis, hemophilia patients are treated with protein replacement factors. However, patients who develop inhibitory antibodies against infused factor require alternative bypass therapy (factor eight inhibitor

activity [FEIBA] or recombinant factor VIIa). These products initiate blood clotting through the extrinsic pathway, but in many cases bypass therapy is not adequate. In principle, replacement therapy with direct FXa infusion could also correct bleeding, however the therapeutic potential of FXa is limited due to a very short plasma half-life and a potential for excessive coagulation due to activation of other coagulation factors. A recently described novel FXa variant (FXa^{I16L}) was engineered to overcome these limitations. FXa^{I16L} compared to FXa-wild-type exhibited zymogen-like properties with reduced activity and limited sensitivity towards plasma inhibitors. Yet its biologic activity was restored when bound to factor Va. In vitro and in vivo, the FXa^{I16L} variant normalized thrombin generation in hemophilia plasma and is highly effective in murine hemophilic models. Here, the hemostatic potential of the FXa^{I16L} variant was assessed in FVIII deficient dogs (<1% coagulant activity). Following intravenous dosing of FXa^{I16L}, blood and plasma were collected at various times post dosing. A rapid dose-dependent normalization of hemostasis was observed as measured by thromboelastography (TEG), whole blood clotting time, thrombin generation assay, and activated partial thromboplastin time. Protein infusion was well tolerated with no overt adverse events or changes in clinical chemistries or cellular blood counts. FXa^{I16L} may provide a new and unique way to achieve hemostasis in a number of clinical situations of uncontrolled bleeding.

FP-WE-01.1-4
FVIII Specific CD4+ T Cell Epitopes that Drive Immune Responses to Human FVIII in Humanized HLA-DRB1*1501 Transgenic Hemophilic Mice Bind to Multiple Human HLA-DRB1* Proteins

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The development of neutralizing antibodies against FVIII is the major complication in the treatment of patients with hemophilia A. It remains unclear why some patients develop antibodies while others do not. Experimental and clinical data support the involvement of $CD4^+$ T cells in the generation of antibody responses against FVIII. $CD4^+$ T cells express T-cell receptors that recognize antigen-derived peptides ($CD4^+$ T-cell epitopes) presented by MHC-class II molecules which are expressed on specialized antigen-presenting cells. The conditions under which $CD4^+$ T cells interact with the MHC-class II-peptide complex determine whether the immune system reacts with non-responsiveness, is activated to develop specific antibodies, or is tolerized to suppress antibody responses. Therefore, it is crucial to understand which FVIII peptides are presented by MHC-class II complexes under conditions of FVIII replacement therapy and how $CD4^+$ T cells interact with MHC-class II-FVIII peptide complexes expressed by antigen-presenting cells. We created a humanized hemophilic mouse model to identify FVIII peptides presented by HLA-DRB1*1501 and to study the regulation of antibody responses against FVIII by the interaction of $CD4^+$ T-cell subsets with FVIII peptides presented by HLA-DRB1*1501. Using T-cell hybridoma technology, we identified 8 FVIII peptide regions containing epitopes that were presented by HLA-DRB1*1501 during in vivo immune responses against FVIII. We assessed the binding capacity and binding kinetics of the identified peptide clusters for the 6 most common HLA-DRB1* haplotypes using cell-free in vitro binding assays. Almost all peptides bound to two or more HLA-DRB1* haplotypes. However, the on-rates and off-rates of peptide binding were different for the different HLA-DRB1* haplotypes, which might indicate that the functional outcome of the interaction between $CD4^+$ T cells and MHC-class II-FVIII peptide complexes expressed by antigen-presenting cells might differ between the different HLA-DRB1* haplotypes even if the same FVIII peptides are involved.

PO-WE-097
Effect of immune system polymorphisms on factor VIII inhibitor development in severe hemophilia a patients

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The main problem facing the replacement therapy in severe hemophilia A (HA) patients is the development of factor VIII (FVIII) inhibitors. In addition to environmental agents, genetic factors contribute considerably to the risk of developing inhibitors, FVIII gene mutations and immune system polymorphisms playing a role. The aim of this study was to evaluate whether polymorphisms in different immune system genes may confer susceptibility or resistance to inhibitor development in severe HA patients. A total of 136 severe Brazilian HA patients with (39) and without (97) FVIII inhibitors were genotyped in relation to 15 polymorphisms in eight systems (HLA-G, PTPN22, CTLA-4, IL4, IL4R, IL10, TNFα, and TNFR1). Six of them, HLA-G ins/del 14pb, HLA-G 3142 C>G, IL4R 1902A>G, TNFα -1031 T>C, TNFα -863A>C, and TNFR1 303A>G have never been studied in such series. Genotyping was carried out using standard PCR, PCR-RFLP and real-time PCR. We found an association between IL10 -819C>T and –592C>A polymorphisms and susceptibility to inhibitor development ($P = 0.024$ and $P = 0{,}016$, respectively). The combined IL10 TA haplotype confirms the association ($P = 0.028$). Statistically non-significant differences were observed in all other comparisons, in agreement with some, but not all, previous studies.

PO-WE-098
Effect of in vivo induction of regulatory T cells for immune tolerization and effect on FVIII inhibitor anamnestic response

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Introduction: FVIII inhibitors remain the most significant complication of severe hemophilia A. A minority of patients who undergo immune tolerance induction (ITI) fail to eradicate the inhibitor. Strategies to tolerize these refractory inhibitors include the use of plasma derived FVIII concentrate (pdFVIII) and the addition of immunosuppression (IS). The *in vivo* induction of regulatory T cells (Tregs) may promote tolerization in patients with refractory FVIII inhibitors.
Case description: We report the case of a 17 year-old man who failed ITI after 32 months of a combination of high dose pdFVIII and IS (MabThera and vincristine). After ceasing ITI the patient suffered 2 intra-cranial hemorrhages (ICH) within 4 months; in total he has suffered 5 ICH. A further attempt at ITI with pdFVIII and IS was commenced with the addition of 4 weekly cycles of a combination of intravenous immunoglobulin (IVIg), sirolimus, and a histone deacetylase inhibitors (HDACi) in an attempt to induce Tregs. The FVIII titer was 35.6 BU ml^{-1} prior to commencement of the modified ITI and was 0 BU ml^{-1} 3 weeks after commencing ITI (this compares with figures of 12 BU ml^{-1} and >1600 BU ml^{-1}, respectively, with the prior course of ITI); no anamnestic response was observed. A transient increase in Tregs from 5% to 10% of CD4+ T cells was observed, as determined by immunostaining for CD4/CD25/FoxP3 and exclusion of CD127 positive cells. The increase in Tregs was observed up to a week after completion of the 4 week cycle of sirolimus and HDACi.
Conclusions: The addition of specific IS, HDACi, and IVIg to induce Tregs to an ITI regimen resulted in loss of the immediate anamnestic response and *in vivo* evidence of a transient induction of Tregs. To date this patient has achieved a good partial response with negative FVIII inhibitor titers and measurable plasma FVIII levels.

PO-WE-099
Factor VIII product-dependent recognition of anti-factor VIII antibodies

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The development of anti-factor (F) VIII antibodies in hemophilia A (HA) subjects undergoing replacement therapy has been well-documented. Correlation between antibody development and FVIII product used for replacement therapy remains a subject of discussion, despite numerous studies performed in an attempt to establish such a relationship. In the current study, we evaluated the development of both inhibitory and non-inhibitory anti-FVIII antibodies in 20 HA subjects treated with pharmacologic FVIII product A (contains full-length recombinant (r) FVIII). All 20 subjects developed anti-FVIII antibodies, but with highly variable concentrations (from 50 μm to 570 μm). Eleven of those subjects contained quantifiable inhibitory anti-FVIII antibodies by the Bethesda assay (0.8–3584 BU). There was a strong correlation between the inhibitory antibody titer and the molar concentration of total antibody ($R^2 = 0.60$; $P < 0.0001$). Pronounced differences in antibody recognition by various rFVIII products were observed. For example, the antibody titers determined with product A as a capture protein was 2.4-fold higher than that observed with another full-length rFVIII-containing product and almost 4-fold higher than that measured with a B-domainless rFVIII product. Our data indicate that for this group of HA subjects anti-FVIII antibodies have the highest affinity for the rFVIII product A used for the replacement therapy and that a significant fraction of antibodies bind to the B domain of FVIII.

PO-WE-100
How many patients with high-responding inhibitors do/did not undergo immune tolerance induction in Italy? Why not?

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Introduction. Immune tolerance induction (ITI) is presently the only therapeutic approach able to eradicate inhibitors in hemophilia A patients and represents the first choice in children with recently onset inhibitors. However, ITI is a highly demanding treatment and compliance and cost-utility evaluations may often influence clinical choices, particularly in adults.
Methods. In the frame of the Italian ITI Registry, participating centres were asked to register all patients with severe hemophilia A and high-responding inhibitors followed between 1996 and 2009. For patients who did not undergo ITI, reasons for clinical choices were reported.
Results. Eighteen centres provided data on 149 patients, aged 2–83 years. Eighty-eight patients (59%) underwent ITI over the study period. ITI was attempted in almost all children (<14 years; 65/74, 88%). The lack of parents' consent and/or concerns for poor adherence were reported as reasons hampering ITI in four children (5%). ITI was deferred to achieve inhibitor titers <10 BU ml^{-1} in the remaining 5 children. Twenty-three/88 patients (26%) were aged >14 years at ITI start. In this age group, ITI was not carried out in 52/75 patients (69%). The perception of poor prognosis (long-standing inhibitors, high historical inhibitor peak titer) was the main reason in 21 (40%) patients, whereas inadequate adherence/refusing treatment and mild bleeding tendency were reported in 16 (31%) and 14 (27%) cases, respectively. Venous access was a major problem only in one patient. Among patients not undergoing ITI, 6 adults (12%) died because of bleeding complications.

Conclusions. Data from the Italian ITI registry confirm that ITI is attempted in virtually all compliant children with inhibitors. This choice currently applies to approximately 30% of patients with long-standing inhibitors. Individual cost-utility and long-term prognostic evaluations, including the risk of severe and fatal bleeding, should be carefully considered in these patients.

PO-WE-101
Risk of bleeding and inhibitor development after circumcision of Previously Untreated (PUPs) or Minimally Treated (MTPs) severe hemophilia A patients

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Objective: To evaluate post-circumcision bleeding after low dose FVIII replacement, in addition to time and rate of inhibitor development over a 12 month period in young persons with severe hemophilia A.
Patients and methods: Eighteen previously untreated persons (PUPs) or minimally treated persons (MTPs) with severe hemophilia A, who were less than 36 months of age underwent circumcision from January to December 2009; they were compared with twenty- four matched non-circumcised patients. All 42 patients were treated on demand with a single plasma-derived factor VIII and were inhibitor negative, except 2 had low-titer inhibitor, one in each group. Two doses of factor VIII concentrate (25 U kg^{-1}) were given 1 h before circumcision and 1 h before removal of gauze dressing. Inhibitor was determined every 8 exposure days (EDs).
Results: Only the patient with previous inhibitor bled twice: on day 5, which responded to a single dose of factor VIII (50 U kg^{-1}) and on day 7, post-circumcision, where hemostasis was achieved only after a single dose of recombinant factor VIIa (90 μg kg^{-1}). High-titer inhibitors developed in seven patients: in three patients in the circumcised group (16.6%) after a median of 16EDs (8–40), and four patients (16.6%), who developed high-titer inhibitor in the non-circumcised group after a median of 16 EDs (range 8–64).
Conclusion: There was no bleeding following circumcision in a cohort of severe hemophilia A (PUPs or MTPs) except in a low-titer inhibitor infant. Circumcision was not an additional risk for development of high-titer inhibitor; which was low in all enrolled patients when administered a low FVIII dose protocol.

PO-WE-102
Plasma-exchange and immunosuppressive therapy in a patient with mild hemophilia A and inhibitors complicated by severe muscular bleeding and compartmental syndrome

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The control of bleeding in hemophilic subjects with inhibitors and hemorrhagic shock is still a therapeutic problem to resolve in an emergency. We describe the case of a young mild hemophilia A (MHA) patient, who developed high-titer inhibitors after infusion of rFVIII because of a traumatic spleen rupture and a life-threatening lower limb hemorrhage despite the use of bypassing agent. A 19 year-old man with MHA (FVIII 18 U dl^{-1}, gene mutation Val2251Ala), never infused with FVIII concentrates, and on 10/02/2011, after a car crash, showed a traumatic rupture of the spleen requiring emergency surgery. Full hemostasis was achieved with B-domain deleted rFVIII infusions during the surgery and the consecutive 7 days (total dose 18.000U). On 10/09 he was vaccinated for Str. Pn., H. Infl. and N. Men. Since 10/25 the patient presented progressive prolongation of aPTT not corrected by full-length rFVIII infusion. Inhibitors against FVIII were detected (titer 6 BU). On 10/29 he presented a large hematoma in the lower right limb and anemia; rFVIIa 90 mcg kg^{-1} administered every 3 h was ineffective to stop bleeding. On 11/01 hemoglobin dramatically fell to 6 g dl^{-1}, associated with compartmental syndrome requiring fasciotomy complicated by persistent bleeding and hemorrhagic shock despite full dose coverage with rFVIIa and RBC infusion. Twenty-four hours after the patient started treatment with plasma exchange (3 courses in a week), that was effective to clear the inhibitor. After the first plasma exchange we applied the Malmo protocol with cyclophosphamide plus steroid, plasma-derived (PD) FVIII infusion (5000 U every 8 h), continuing rFVIIa. The bleeding stopped within a few days and detectable FVIII to hemostatic levels was observed. He was discharged on 12/03 on ITI schedule with 100 U kg^{-1} day^{-1} of PD FVIII. Low-titer inhibitors remain after 6 weeks. No recurrences of bleeding or neurovascular damage on his lower right limb occurred.
Conclusion. The patient presented risk factors for appearance of FVIII inhibitors, such as intensive treatment with B-domain deleted rFVIII, splenectomy followed by vaccination. rFVIIa was ineffective to stop life-threatening hemorrhages; plasma exchange, followed by immunosuppression and ITI, was able to reduce inhibitor titer and to stop the severe bleeding, saving the life and the lower limb functions of this young patient.

PO-WE-103
Factor VIII prophylaxis and inhibitor development in previously untreated patients with severe hemophilia A: The RODIN study

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On behalf of the PedNet/Rodin Study Group:
N Clausen, Aarhus; H Platokouki, Athens; M Williams, Birmingham; G Auerswald, Bremen, B Nolan, Dublin; A Thomas, Edinburgh; W Kreuz, Frankfurt; A Molinari, Genova; W Muntean, Graz; A Mäkipernaa, Helsinki; Ch van Geet, Leuven; R Liesner, London; R Ljung, Malmö; H Chambost, Marseille; K Kurnik, Munich; A Rafowicz, Paris; R Pérez Garrido, Seville; P Petrini, Stockholm; S Claeyssens, Toulouse; K Fischer, Utrecht; R Kobelt, Wabern
C Altisent, Barcelona; J Oldenburg, Bonn; E Chalmers, Glasgow; V Jimenez, Madrid; E Santagostino, Milan; G Rivard, Montréal G Kenet, Tel-Hashomer; M Carcao, Toronto; A Cid, Valencia.
Prophylaxis has been associated with a decreased risk of inhibitory antibodies in severe hemophilia A. The objective of this study was to examine the association of dose, frequency, and time of starting factor VIII prophylaxis with inhibitor incidence among previously untreated patients with severe hemophilia A. We performed a cohort study among consecutive patients with factor VIII activity <0.01 IU ml^{-1} born between 2000 and 2010. All patients were followed during their first 75 factor VIII exposure days for the occurrence of inhibitors. Of 606 patients, 32.0% developed inhibitors (22.2% high responder) and 412 patients started prophylaxis. Early during factor VIII treatment the inhibitor incidence was not associated with prophylaxis; after about 20 exposure days, however, prophylaxis was associated with a decreased inhibitor incidence. The relative risk of prophylaxis was 1.01 in the period from 1–10 exposure days, 0.95 in 11–20 exposure days, 0.22 in 21–30 exposure days, 0.27 in 31–40 exposure days, and 0.32 in 41–75 exposure days. Doses and frequencies of prophylaxis that were used in this cohort were not associated with inhibitor incidence. Our findings suggest that prophylaxis does not affect the development of early inhibitors. It may, however, prevent late inhibitors, especially in patients with low risk *F8* mutations.

PO-WE-104
Presence and evolution of anti-factor VIII (FVIII) catalytic activity in severe, mild, or moderate hemophilia patients with FVIII inhibitors

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Several mechanisms of therapeutic FVIII inhibition have been described in patients with hemophilia A (HA). One of them consists in FVIII hydrolysis induced by anti-FVIII catalytic antibodies. These antibodies were identified in plasma of severe HA patients with inhibitor (13/24) (Lacroix-Desmazes et al., 2002). However, these previous studies reported results for severe HA at one time point, exclusively. Thus, we proposed to extend the analysis to patients with mild or moderate HA and follow catalytic and inhibitory activities over the time. We studied plasma samples from 11 HA patients with inhibitor. Six were patients with severe HA and 5 were mild or moderate HA patients. Four were treated on demand or with bypassing agents and 7 were submitted to an immune tolerance induction (ITI) regimen. IgG were purified from plasma by affinity-chromatography followed by a size-exclusion chromatography. Then, catalytic activity was evaluated by the rate of FVIII hydrolysis after incubation with purified IgG (Lacroix-Desmazes et al., 1999). FVIII inhibitors were tested with the modified Bethesda assay. We identified two main profiles, regardless of the treatment regimen: either catalytic and inhibitory activities followed the same trend (''profile 1'': 2 patients), or the evolution of these two parameters was dissociated (''profile 2'': 8 patients). For one patient, no hydrolytic activity towards FVIII was observed despite the variations of inhibitor titer. Six of 7 patients submitted to ITI were found to have a profile 2. For patients treated on demand or with bypassing agents, 1 patient had profile 1, 2 patients had profile 2, and 1 patient did not exhibit FVIII-hydrolyzing activity. These results identified that FVIII catalytic antibodies might not systematically act as neutralizing antibodies, and it is important to follow up patients with FVIII inhibitors or not to determine the relationship between FVIII catalytic antibodies and FVIII inhibitors.

PO-WE-105
Validation of the prediction score for inhibitor development in previously untreated patients (PUPs) with severe hemophilia A

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Background: Treatment of patients with severe hemophilia A is complicated by the formation of inhibitory antibodies in 25–30% of patients. Prediction of risk for antibody formation in PUPs may be a valuable clinical tool for management of these patients.
Objective: To validate the prediction score (ter Avest et al., 2008) for predicting inhibitor development in PUPs with severe hemophilia A.
Methods: The validation population consists of a European multicentre birth cohort (2000–2006), including 371 patients from the RODIN Study. Based on the family history of inhibitors, the presence of high-risk gene mutations, and the presence of intensive treatment at first treatment, the inhibitor risk of each patient was calculated. Calibration was assessed by calculating positive and negative predictive values (PPV and NPV respectively), and discrimination by calculating the AUC of the ROC curve.
Results: In the validation population, the inhibitor incidence was 30% (110 out of 371 patients) compared to 25% (83 out of 332 patients) in the derivation cohort of the original score. The discriminative ability of the score (AUC) was 0.70 and comparable to the derivation cohort (0.74). Comparing the score in the validation with the derivation cohorts, the PPVs and NPVs in the low-risk categories were 6% versus 6% and 63% versus 68%, respectively. However, in the high-risk categories the PPVs and NPVs were 48% versus 57% and 74% versus 83% respectively.
Conclusion: The prediction score did not perform equally well in the validation population, mainly because of the inability to adequately predict inhibitor development in high-risk patients, even though the discriminative abilities of the score were comparable. Additional data on treatment-related risk factors will be used to update and improve the risk score.

PO-WE-106

Successful immune tolerance induction is associated with a shift from FVIII-specific Th17-like pro-inflammatory immune profiles to FVIII-specific anti-inflammatory immune profiles in a patient with hemophilia A and FVIII inhibitors

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The development of high-affinity neutralizing antibodies against FVIII (FVIII inhibitors) represents the major challenge in the treatment of congenital hemophilia A with FVIII products. Immune tolerance induction therapy (ITI) involving regular application of FVIII has evolved as an effective strategy to eradicate antibodies and induce long-lasting immune tolerance. Despite clinical experience, little is known about the immunological mechanisms that cause the down-modulation of FVIII-specific immune responses. To overcome this limitation, we established an analytical approach for immune monitoring that requires as little as 3–4 ml of peripheral blood. This approach includes the analysis of affinity, isotypes, and IgG subclasses of anti-FVIII antibodies; the assessment of FVIII inhibitors and the analysis of FVIII-specific $CD4^+$ T cell signatures based on gene expression profiles analyzed after short-term in vitro re-stimulation of peripheral blood mononuclear cells (PBMC) with FVIII. We will present data derived from the monthly immune monitoring of a patient with congenital hemophilia A and FVIII inhibitors who successfully underwent ITI. The data indicate the presence of high affinity IgG1 and IgG4 anti-FVIII antibodies and a FVIII-specific Th17-like pro-inflammatory gene expression profile in PBMC associated with FVIII inhibitors prior to the start of ITI. In the course of ITI both FVIII-specific antibodies and FVIII inhibitors disappeared. The down-regulation of antibodies was associated with a switch from the Th17-like pro-inflammatory gene expression profile to a FVIII-specific anti-inflammatory gene expression profile of PBMC. These results support the involvement of FVIII-specific $CD4^+$ T-cells in the regulation of FVIII inhibitors. In summary, we established suitable technology to monitor the regulation of FVIII-specific immune responses in small volumes of blood. Importantly, this technology can be applied to multi-centre clinical trials such as the upcoming Hemophilia Inhibitor PUP Study (HIPS) that will monitor the immune regulation associated with the development and prevention of FVIII inhibitors in PUPs.

PO-WE-107

The use of novel models for preclinical immunogenicity assessment of a longer-acting FVIII candidate

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Aim: The aim of this study was to evaluate the immunogenicity of BAX 855, Baxter's PEGylated recombinant human factor VIII conjugate, in comparison to Advate, Baxter's unmodified recombinant human full-length FVIII concentrate.
Methods: The comparative immunogenicity assessment of BAX 855 and Advate included their potential modulation of both the innate and the adaptive immune system. The modulation of the human innate immune system was assessed by the potential of BAX 855 and Advate to induce pro-inflammatory cytokines in an in vitro human whole blood assay and by their potential to activate human complement in human plasma in vitro. The modulation of the adaptive immune system was assessed by the potential of BAX 855 and Advate to induce antibodies in cynomolgus monkeys and in 3 different hemophilic mouse models. The first mouse model expresses specific immune tolerance against human FVIII and mimics the situation in hemophilia patients without FVIII inhibitors. The second mouse model mimics the situation in an important fraction of hemophilia A patients with FVIII inhibitors. This model expresses a human MHC-class II haplotype (HLA-DRB1*1501) which was previously shown to be associated with an increased risk for patients to develop FVIII inhibitors. The third mouse model represents a conventional E17 hemophilic mouse.
Results: BAX 855 and Advate induced similar low levels of cytokine release and complement activation in vitro that were not different from the buffer control group. Furthermore, BAX 855 and Advate induced similar levels and incidences of antibodies against human FVIII in all animal models. Importantly, immune tolerance to human FVIII was maintained by both BAX855 and Advate in hemophilic mice that are immune tolerant to human FVIII.
Conclusion: We conclude that BAX 855 and Advate express a similar immunogenicity profile in preclinical in vitro and in vivo models.
Disclosures: The authors are full time employees of *Baxter Innovations GmbH*

PO-WE-108

The use of novel transgenic mouse models for comparative immunogenicity assessment of a new recombinant factor VIIa product

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Aim: Baxter has developed a recombinant FVIIa (rFVIIa) product for the treatment of hemophilia patients with factor VIII or factor IX inhibitors. Before entering clinical development, we assessed the immunogenic safety profile of the new product candidate using two novel mouse models that mimicked specific aspects of the situation in patients.
Methods: Several comparative preclinical immunogenicity studies were conducted to assess the immunogenicity profile of Baxter's rFVIIa in comparison to a licensed recombinant FVIIa product. Three different mouse models were used for this purpose. The first model expresses specific immune tolerance against human FVIIa and, therefore, mimics the situation in both hemophilia A and hemophilia B patients. Using this model, we asked if Baxter's rFVIIa is able to maintain immune tolerance to human FVIIa. The second model is a hemophilia A model that mimics the situation in an important fraction of hemophilia A patients with FVIII inhibitors. This model expresses a human MHC-class II haplotype (HLA-DRB1*1501) that was previously shown to be associated with an increased risk for the development of FVIII inhibitors. The third model represents a normal wildtype C57BL/6 mouse. All mice were treated with 8 weekly doses of either Baxter's rFVIIa or a licensed rFVIIa product. Total anti-FVIIa antibodies were analyzed prior to the first dose as well as after the 4th and the 8th dose using ELISA assays.
Results: Baxter's rFVIIa and the licensed rFVIIa product induced similar titers of anti-FVIIa antibodies in C57BL/6 wildtype mice and in hemophilic HLA-DRB1*1501 mice. In addition, both Baxter's rFVIIa and the licensed rFVIIa product were able to maintain specific immune tolerance in a novel mouse model that is immunologically tolerant to human FVIIa.
Conclusion: Based on the data obtained we conclude that both Baxter's rFVIIa and the licensed rFVIIa product have a similar immunogenicity profile. *Disclosures: The authors are full time employees of Baxter Innovations GmbH*

PO-WE-109

Regulatory T cell quality and FVIII inhibitors in hemophilia

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The generation of inhibitory antibodies against FVIII complicates treatment of hemophilia. There are several studies in animal models that attempt to explain which mechanisms are involved in this process. There is agreement that this process, which depends on T cell help, is suppressed by CD4+ regulatory T cells (Treg). Also, Tregs are an important component for the success of immune tolerance induction therapy (ITI) and for the prevention of inhibitor formation. Strong evidence for a similar regulatory process in humans is missing. The aim of this work was to assess the quality of Tregs in hemophilia A patients. In addition we evaluated the levels of IL-10, an important cytokine for Treg function. We studied 16 patients with active inhibitors (PI), 12 without inhibitors (P), and 11 healthy donors (HD). We also included 4 patients during or after ITI (ITI-PI). Treg subsets were identified by flow cytometry using anti-CD4, anti-CD25, and anti-FOXP3 monoclonal antibodies. IL-10 was measured by ELISA in plasma.

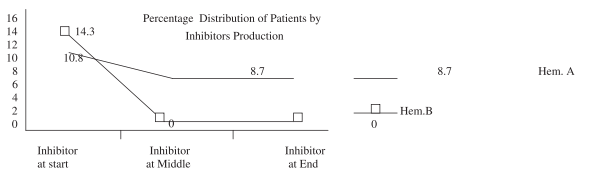

Fig. 1. Percentage Distribution of Patients by Inhibitors Production

Plasma IL-10 values were higher in PI than in HD and P, although the differences were not significant. PI had decreased Tregs (CD4+FOXP3+) compared to HD (P=0.01). However, the proportion of $CD4+CD25^{hi}FOXP3+$ was higher in PI than in P (P=0.005) and HD (P=0.03). In a patient who failed ITI, values of $CD4+CD25^{hi}FOXP3+$ decreased (1.45, 0.88, 0.79%) in accordance to the level of inhibitors (22, 13, 10.4 BU ml^{-1}). In an ITI-PI with successful treatment, $CD4+CD25^{hi}FOXP3+$ were reduced to normal levels. In 2 ITI-PI, who were studied during ITI, the values were intermediate. These results suggest that in patients with FVIII inhibitors, activated Tregs ($CD4+CD25^{hi}FOXP3+$) are increased, probably to help suppress antibody production. As ITI progresses and inhibitory antibodies decrease, these cells tend to normalize their values.

PO-WE-110

Frequency of inhibitors in 53 Colombian hemophilic patients treated with plasma derivatives between November 30, 2008 and December 1, 2011

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Fifty-three patients, 26.4 years-old average age (SD = 113,3) treated with plasma derivatives: Hemofilm M®, Emoclot®, Koat®, Fandhi®, BeriateP®, Factor VIII Behring®, Immunine®, Aimafix®. They were administered a dose as recommended by the WFH. Monitoring over 3 years to measure inhibitors at the start, middle, and end of the study was performed. 86.7% of patients with hemophilia A, 60.9% severe (28/46), 36.9 (17/46) moderate, and 2.1% (1/46) mild. 95.6% (44/46) received secondary prophylaxis. 14.2% (4/28) of severe hemophilia A patients demonstrated inhibitors at the monitoring start, 14.2% (4/28) in the middle, and 7.1% (2/28) at the end. Average age of hemophilia A patients demonstrating inhibitors was 33.2 years old (SD = 7.7). 85.7% (6/7) received secondary prophylaxis and 14.2% (1/7) on-demand treatment. 50% (1/2) of severe hemophilia B patients demonstrated inhibitors at the monitoring start, no patient demonstrated inhibitors in the middle or end. 10.8% (5/46) of hemophilia A patients demonstrated inhibitors at the program's start, 14.3% (1/7) for the hemophilia B group. Over the 3 years, 13.0% of hemophilic A patients developed inhibitors, 50% (3/6) high-responding and 50% (3/6) low-responding. 33.3% (1/3) of high-responding patients had a history of being carriers since 7 years ago. Only 8.6% (4/46) are inhibitor-carriers to date, 25% (1/4) previously known high-responding and 75% (3/4) low-responding. 14.2% (1/7) of hemophilia B patients had high-responding inhibitors. None of the patients has it to date, and none is receiving on-demand treatment. Our patients demonstrated a 1.84% frequency of inhibitors in those with hemophilia A and 0.07% in hemophilia B. Prospective studies to corroborate these results are suggested. Plasma derivatives of human origin are an alternative for developed countries.

PO-WE-111
Radioactive synoviorthesis in hemophilic children with inhibitor
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Background: Radioactive synoviorthesis (RS) has been shown to decrease the frequency of hemarthrosis, unresponsive to prophylactic treatment with factor concentrates in patients with hemophilia, particularly in those with inhibitors. Here we report our experience with RS in children with hemophilia who had high-titer inhibitor and developed target joints despite adequate treatment with bypassing agents.
Patients: The first case is a 15 year-old boy with severe hemophilia A with high-titer inhibitor and severe attention deficit disorder who developed target joints at both knee and elbows despite proper treatment with rVIIa or FEIBA. He underwent five RS procedures using Yttrium-90 for both knees (twice injected into right knee) and for both elbows using Rhenium-186 during a 7-year period, between the ages of 5–12 years. According to the WFH grading system, one joint was in grade III and the other joints were in grade II before RS. The first bleeding episodes occurred 18 months after the RS in the right elbow. A bleeding-free interval of more than 2 year following RS was obtained in other joints. At the long-term follow up, one joint was rated good, two joints were fair, one joint was poor. The second case is a 16 year-old boy with hemophilia B and high-titer inhibitor who developed target joint on his left knee despite on-demand treatment with rVIIa. He underwent RS with Yttrium-90 only once and has not experienced hemarthrosis in the same joint over the next 30 months. His joint bleeding score was rated good. No side effects were observed during or after RS in both cases.
Conclusions: Our experiences confirm that RS is the best choice for the treatment of recurrent hemarthrosis that cannot be controlled with bypassing agents in patients with inhibitor.

PO-WE-112
The results of immune tolerance induction in polish children with severe hemophilia A complicated by factor VIII inhibitor
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The development of factor VIII inhibitor (FVIII) is a serious complication in hemophilic patients. We describe results of immune tolerance induction (ITI) used in Polish children. From 1993 – 2011 ITI was used in 22 children with severe hemophilia A and high titer of FVIII inhibitor. The median age of patients was 18.5 months (ranged from 5 – 81 months) at the time of inhibitor detection. Inhibitor was detected within 3–100 exposure days to FVIII concentrates (median 18.5 exposure days). Titers of FVIII inhibitors ranged from 3.1–151 BU ml^{-1} (median 17 BU ml^{-1}) at the initiation of ITI regimen. All patients except one were treated with plasma derived FVIII concentrates, medium or high-purity, and one with cryoprecipitate before inhibitor occurred. In 15 children ITI was started with a single daily dose of ≥100 IU kg^{-1}, in 2 patients a daily dose of 50 IU ml^{-1} was given, and in 3 children FVIII concentrate in a dose of 100 IU kg^{-1} was administered twice a day. In the 2 remaining patients, doses of 50 IU kg^{-1} 2–3 times a week were repeated. Total elimination of factor VIII inhibitor was achieved in 17 patients. In the other 1 patient, the ITI was partially effective and the recurrences of low-titer inhibitor below 1 BU ml^{-1} was observed. In another 2 patients, immune tolerance was not achieved and ITI regimen was discontinued after 15 and 18 months. ITI is ongoing in 2 patients. ITI was administered in the period ranging from 2–83 months (median 11.5 months). After achievement of complete ITI FVIII concentrates were continued 2 or 3 times a week in a dose of 20–50 IU kg^{-1}. Only 1 boy was treated on demand. High efficacy of ITI was found in young children with severe hemophilia A.

PO-WE-113
Cell-mediated immune response to recombinant factor VIII-Fc in hemophilia A mice
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Objectives: Identifying cell-mediated immune responses to recombinant factor VIII is of interest in designing better therapeutic management of hemophilia A (HemA). Herein we have investigated the splenic lymphocyte response to recombinant factor VIII (rFVIII) when linked to either human Fc (hFc, IgG1) or mouse Fc (mFc, IgG2a) in comparison with commercially available full-length rFVIII (Advate®) and B-domain-deleted rFVIII (Xyntha®/Refacto AF®).
Methods: HemA mice were injected with 4 weekly doses followed by 2 every other week doses of 50 or 250 IU kg^{-1}. At the end of 8 weeks, four mice from each group were euthanized and splenic lymphocyte immunogenicity profile was determined by testing for intracellular cytokines, markers for regulatory T cells and dendritic cells using flow cytometry.
Results: Among the tested cytokines that promote immune responses, in mice injected with the 50 IU kg^{-1} of rFVIII-hFc or rFVIII-mFc, there was a significant inhibition in the levels of IL-4, and TNF-α. Conversely, the levels of these cytokines and IL-2 were higher in groups receiving 250 IU kg^{-1} of these molecules. Mice injected with 50 IU kg^{-1} of either Xyntha or Advate did not exhibit any inhibition, whereas the 250 IU kg^{-1} group showed an increase in intracellular content of IL-2, IL-4, and TNF-α. In addition, there was a higher percentage of foxp3 positive T cells in mice injected with 50 IU kg^{-1} of rFVIII-mFc compared to other treatments. Mice receiving 50 IU kg^{-1} of rFVIII-hFc and rFVIII-mFc had a higher percentage of splenic dendritic cells positive for PD-L1 (CD279), an inhibitory signal for T-cell activation and proliferation. These groups also had a higher percentage of immature dendritic cells as illustrated by a decrease in CD80 staining.
Conclusion: These results indicate that at 50 IU kg^{-1} both FVIII-mFc and FVIII-hFc have lower immunogenicity and may promote lower antibody production (see abstract by Liu, T et al) or immune tolerance, which is currently under investigation.

PO-WE-114
Inhibitor development in patients with mild hemophilia A: An Irish perspective
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Introduction: Inhibitor development in patients with mild Hemophilia A may be associated with certain mutations. We reviewed the Irish national database to assess the incidence of inhibitors and risks for their development in patients with mild hemophilia A.
Methods: One hundred sixty-two patients with mild hemophilia A are registered with the national centre for hereditary coagulation disorders. Baseline demographics, virology, factor VIII exposure, mutation, and inhibitor screens were reviewed. Patients with inhibitors and risks for development of inhibitors (family history, prolonged use of factor concentrate, and factor VIII mutation) were retrospectively assessed.
Results: Four patients with mild factor VIII deficiency had inhibitors (2.5% of all patients); one had a peak inhibitor of >5BU (patient A); the remaining three inhibitors identified were <5BU (patients B,C,D); none had a family history of inhibitors. In patient A the inhibitor peak was 80BU, associated with clinically significant bleeding and reduced endogenous factor VIII levels. It developed 8 weeks after a 5 day continuous infusion of factor VIII concentrate and was treated with cyclophosphamide and steroids. Median age at inhibitor development was 33 years old (range 11–54). Treatment with factor VIII concentrates in patients with inhibitors <5BU was for trauma or surgical prophylaxis and of <2 days duration. Certain mutations have been identified as high risk for inhibitor development (R612C, R2169H, W2248C Y2124C, and missense). Overall, two patients (1%) have a high-risk mutation but have not developed inhibitors to date. None of the mutations identified in patients with inhibitors (D186G, Q2106H, L203Q, and G489R) have previously been associated with high risk of inhibitor development.
Conclusion: Improved tools for risk assessing patients with mild factor VIII deficiency are required to aid prevention of inhibitor development. Continuous infusion of factor concentrate is a known risk, but further understanding of the impact of mutations on clinical outcome is necessary.

PO-WE-116
Genetic factors influencing inhibitor development in a cohort of South African hemophilia A patients
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A critical complication of factor VIII (FVIII) concentrate replacement therapy in hemophilia A (HA) treatment is inhibitor development. Inhibitor predisposing genetic factors are multiple and include *F8* gene mutations, ethnicity, a family history of inhibitor development, and FVIII haplotype mismatch. Knowledge of genetic risk factors for inhibitor development is important not only in predicting inhibitor risk but also in planning exposure to rapidly evolving replacement therapy. There are currently no published studies characterizing genetic risk factors for inhibitor development in the South African hemophilia population.
Aim: The objective of the study is to characterize and correlate HA disease severity, inhibitor development, intron 22 inversion mutation status, ethnicity, and FVIII haplotype in a South African severe HA (sHA) cohort.
Methods: A cohort of sHA patients, seen at the Hemophilia Comprehensive Care Centre and Clinical Genetics Unit in Johannesburg, who had inhibitor and intron 22 inversion analysis done between 1994 and 2011 were reviewed. FVIII haplotype analysis was performed in a subset of intron 22 inversion positive patients. Disease severity, ethnicity, inhibitor status, intron 22 mutation, and haplotype mismatch were then correlated.
Results: Of the 249 sHA records reviewed, 238 were included for analysis in the study. One hundred and twenty-four (52%) were black and the remainder were white. Ninety (38%) patients had the intron 22 inversion mutation (of which 52 were black) and 30 (12%) had inhibitors (of which 22 were black). The H2 haplotype was the commonest in blacks. Preliminary data suggests a correlation exists between this haplotype and inhibitor development.
Conclusion: In this small sHA cohort comprising equivalent black and white patients, blacks had a higher frequency of intron 22 inversion, inhibitor development and H2 haplotype. These results should be confirmed in a larger study.

PO-WE-117
Incidence of inhibitors against FVIII or FIX in PTPs after switching factor concentrate during the presence of immunological danger signals
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A serious complication in the treatment of hemophilia is the development of inhibitors against factor VIII or factor IX. Several factors can contribute to the development of inhibitors, such as genetic and environmental factors (e.g., immunological "danger sig-

nals''). This study retrospectively investigates the incidence of inhibitors in a single-centre hemophilia patient cohort (n = 119; median age 38.5 years; 50% severe hemophilia) after switching the factor concentrate (mainly from plasma-derived products to recombinant products). Regular measurements of coagulation factor and coagulation factor inhibitors were carried out for at least 12 months after switching the concentrate. Forty-seven per cent of the patients switched their concentrate more than two times. Sixty-seven per cent of the overall 198 switches took place during the presence of immunological ''danger signals'' (61% surgery, mainly dental and major orthopedic surgery; 39% bleeding events, mainly joint bleeds). In none of the patients did an inhibitor against coagulation factor occur within the observation period. According to this study, switching the factor concentrate does not contribute to an increased risk of inhibitor development, even in the presence of additional immunological risk factors, such as surgery or bleeding events.

PO-WE-118
Review of the Situation of Diagnosis and Treatment of Inhibitors in Patients with Hemophilia in 13 Latin American Countries

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Objectives: Aware of the great deficiencies in hemophilia treatment since June of 2010, representatives of different hemophilia centres from Argentina, Chile, Uruguay, Venezuela, Colombia, Peru, Honduras, Guatemala, Paraguay, Dominican Republic, Bolivia, Ecuador, and Panama began to meet in order to design programs to improve different aspects of diagnosis and treatment of hemophiliac patients. One of the objectives is to analyse the inhibitor development, which is considered the most severe and costly complication of hemophilia, and immune tolerance induction (ITI).
Results: Nine of the 13 countries (69.2%) are able to measure inhibitors, but only 6 countries (41.1%) reported having a routine measurement program. Three countries (23%) can provide national data: Venezuela: 7.0% of hemophilia A patients and 1.5% of hemophilia B patients. Uruguay and Chile: 3.9%, 2.1%, respectively, for hemophilia A. Peru, Argentina, Panama, and Colombia reported from a single centre and Honduras is in the process of measuring factors and inhibitors nationwide. Six countries (46.1%) use recombinant activated factor VII (rFVIIa) and activated prothrombin complex (aPCC) to manage bleeding episodes. Five countries (38.4%) report they perform prophylaxis in patients with inhibitors, 3 with rFVII and aPCC, 1 with rFVIIa, and another with aPCC. Seven countries (53.8%) report they have already treated patients with ITI.
Conclusions: Even though inhibitor development in hemophiliac patients is considered the mayor complication, due to economic and social factors, 31% of the countries within the region do not have the possibility of measuring inhibitors. In countries where there is a possibility of measuring inhibitors, only 3 provide national coverage. When inhibitors are diagnosed, only a few patients have the possibility of obtaining the appropriate treatment. It is necessary to promote programs in this region in order to help demonstrate the economic benefits and the quality of life given by ITI.

PO-WE-119
Successful Immune Suppression Followed by Immune Tolerance Induction in a Factor IX Patient Who Had Developed an Anaphylactic Reaction to Factor IX

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Background: A life threatening complication in a small number of hemophilia B patients is an anaphylactic reaction to factor IX (FIX) replacement therapy. Once an anaphylactic episode has occurred, major therapeutic problems arise for the hemophilia B patient.
Case Description: A 26 month-old had an anaphylactic reaction following a FIX administration. Prior to this event, the patient received 23 treatments of the FIX with the first treatment occurring at 7 months of age. Due to a muscle bleed and past anaphylactic reaction, the patient was admitted to hospital to receive treatment consisting of hydrocortisone, dphenhydramine, and FVII (plasma derived). This also resulted in an anaphylactic reaction. The use of FVIIa (recombinant activated) was trialed and was successful. Initially bleeds were controlled but eventually became less responsive, resulting in multiple target joints which interfered with normal daily activities. Over 5,000,000 units of FVIIa were utilized by the patient in 1 year. Immune Suppression and Immune Tolerance Management:
At the age of 14 years (2010), a treatment plan of immune suppression followed by immune tolerance therapy was developed. It involved pre-treatments with rituximab, the use of mycophenolate, and a gradual reintroduction of FIX (plasma derived). This treatment option resulted in no anaphylactic reactions. Initially FIX treatments of ~5,000 units continued daily, after treatment was tapered to ~ 4,000 units daily and then to ~ 4,000 units every other day, which he is on at present.
Conclusion: This is one of a few documented cases of a prolonged remission in a patient with a FIX anaphylaxis. Based on the success of this regimen in our patient we recommend that it be further evaluated in a larger cohort of patients.

PO-WE-120
Plasma Exchange and Continuous Infusion of Factor VIII for Life-Saving Surgery in Hemophilia A with High-Titer Inhibitor: Two Case Reports

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Background: Bleeding control in life-threatening hemorrhage or surgery in hemophiliac patients with high-titer inhibitor is challenging. Although bypassing agents are standard treatment, their use is limited in low-resource settings. Plasma exchange with continuous infusion has been reported as an option for life-saving treatment in these patients.
Methods: We report two cases of patients with hemophilia A and high-titer inhibitor who underwent surgeries. The patients received plasma exchange with cryo-removed plasma perioperatively. High-dose (100 U kg^{-1}) FVIII concentrate was started after plasma exchange followed by continuous infusion at the rate 14 U kg^{-1} h^{-1} for 7–14 days. Recombinant factor VIIa (rFVIIa) and APCC concomitant with antifibrinolytic agent were used for breakthrough bleeding.
Results: The first case was an 11-year-old boy who presented with uncontrolled bleeding from a surgical wound. The patient had no definite history of bleeding disorder and underwent a biopsy of an osteolytic lesion at the right foot. He was later diagnosed with hemophilia A with inhibitor. The highest titer was more than 660 BU. Because of uncontrolled bleeding, he underwent right below-knee amputation. He received plasma exchange nine times and two doses of rFVIIa. The second case was a 14 year-old boy with hemophilia A and known high-titer inhibitor. He presented with marked abdominal distension after a minor fall. CT angiogram revealed large pelvic blood clots and bleeding from sigmoidal artery. He underwent surgery to relieve abdominal compartment syndrome, and a second surgery for abdominal closure. He received plasma exchange five times, three doses of rFVIIa and five doses of APCC. The highest FVIII antibody titer was 4,400 BU. Bleeding was successfully stopped in both patients and inhibitor decreased to 5.2 and 3,680 BU, respectively.
Conclusion: Plasma exchange and continuous factor VIII infusion can be considered as treatment of life-threatening bleeding in hemophiliac patients with high-titer inhibitor.

PO-WE-121
Successful Low-Dose Immune Tolerance Induction Regimen Using Multiple Plasma-Derived Factor VIII Concentrates

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There are several immune tolerance induction (ITI) treatments in use worldwide, but the high costs involved limit the ITI access in many countries. In Brazil, until recently, ITI protocols were not feasible for many patients due to product access. We report the partial results of a low-dose regimen using multiple plasma-derived FVIII concentrates carried out in the Hemophilia Unit of Hemocentro Unicamp. A total of six patients (mean age at start 13 years, range 5–35 years) were treated in the period of November/2007–January/2012. All patients presented long-standing (mean 75 months, 36–108 months) high-titer inhibitors (all >5 BU ml^{-1}), with a mean historical peak of 70.4 BU ml^{-1} (13.5–150 BU ml^{-1}) and a mean pre-ITI titer of 3.9 BU ml^{-1} (0.5–11 BU ml^{-1}). All patients received plasma-derived FVIII concentrates containing various concentrations of von Willebrand factor. The FVIII concentrate used by each patient changed three to four times during the course of the ITI, according to the product availability at each time point. The initial dosing regimen used was 25 IU kg^{-1} 3x/week in 5/6 patients. In two of these five patients, the FVIII dose was raised to 35 to 50 IU kg^{-1} due to suboptimal response. One patient started the ITI using 50 IU kg^{-1} 3x/week. Four patients have completed the ITI treatment with complete success (undetectable inhibitor level, FVIII recovery ≥66% and FVIII half-life ≥6 h). The ITI course is ongoing in two patients, and one has achieved a partial response (inhibitor titers <5 BU ml^{-1} and clinical responses to FVIII infusions). The mean time to reach an undetectable inhibitor level in these four patients was 20.2 weeks (2–52 weeks). None of the patients need central venous catheter. We believe these results are very encouraging due to the high success rate using a low-dose ITI regimen. We also highlight that the use of several FVIII concentrates did not interfere with the successful results.

PO-WE-122
IgG4 Subclass of Anti-FVIII Antibodies is Correlated to High-Titer Inhibitor, whereas IgG1 Subclass is Related to Low-Titer Inhibitor in Hemophilia A Patients

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The presence of anti-factor VIII alloantibodies in hemophilia patients compromises the replacement therapy effectiveness. The characterization of immunoglobulin (Ig) subclass has been shown to be an important role in identifying the reactivity of factor (F) VIII concentrate used in the treatment of patients with hemophilia A (HA). Recent studies showed a strong correlation between high levels of anti-FVIII antibodies of subclass IgG4 with high-titer inhibitor and immune tolerance induction (ITI) failure. The objective of this study was to evaluate the characteristics of anti-FVIII IgG subclasses in HA patients

with inhibitor. The IgG subclasses (IgG1, IgG2, IgG3, IgG4) were performed by ELISA assay using three different plasma-derived factor VIII concentrates, commonly used in Brazil. Twenty-six HA patients (mean age 23 years, range 8–49 years), of which twenty-four had severe HA, one moderate HA, and one mild HA; 20/26 (77%) were high-responding inhibitors, and four had low-titer inhibitor (<5 UB ml^{-1}) at the moment of the analysis. In 23/26 (88%) patients, the IgG1 subclass was positive, and was the only IgG subclass present in the 8/10 low-titer inhibitor patients. In contrast, in 15/16 high-titer inhibitor patients, the IgG4 was positive, and the increased level of signal intensity of IgG4 was correlated to the increased inhibitor titer. The moderate HA patient was the only one low-titer inhibitor patient with IgG4 subclass. Our results showed a considerable reduction in the reactivity of FVIII concentrate 8Y (Bio Products Laboratory, UK). This product is classified as intermediate-purity, meanwhile considerable concentration of von Willebrand factor (VWF) is in its composition. Our results suggest that the presence of VWF may in fact "hide" possible epitopes or alter the conformation of FVIII when it is binding with VWF. The evaluation of the IgG subclasses maybe become a useful alternative for monitoring the presence of inhibitor.

PO-WE-123
Genetic Risk Factors for Inhibitor Development in a Brazilian Severe Hemophilia A Population

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The formation of inhibitory alloantibodies against factor VIII (FVIII) is a severe complication of replacement therapy in patients with hemophilia A (HA). Approximately 20–25% of patients with severe HA develop inhibitors. Both genetic and environmental factors influence the susceptibility of patients to develop inhibitors. This study evaluated genetic risk factors for the development of inhibitor including polymorphisms in genes encoding immunoregulatory citokines, such as interleukin 10 (IL10), tumour necroses factor alpha (TNFA) and cytotoxic T-lymphocyte antigen 4 (CTLA-4). The single nucleotide polymorphisms (SNPs) genotyping were performed by PCR amplification and further digestion by restriction enzyme. One hundred ninety-six severe HA patients from Brazil were enrolled in this study. In this population, 47% were non-Caucasians, based on physical features and ancestry. Inhibitor was present in 32/196 (16%), with 84% high-responding inhibitor patients; 18/32 (56%) inhibitor patients were black, whereas 58/164 (35%) of the non-inhibitor patients were black (P=0.03; OR 2.35, 95% CI 1.09–5.07). In contrast, all 16 indigenous descents were inhibitor negative. The FVIII mutation was determined in 92 patients. The prevalence of nonsense mutation was statistically higher among inhibitor patients (33% vs. 9%, P = 0.02; OR 5.0, 95% CI 1.33–18.82). The prevalence of inhibitors among patients with FVIII gene intron 1 and intron 22 inversions was 16% (10/62). The analysis of the SNPs in IL10 gene (-1082 G>A), TNFA gene (-308 G>A), and CTLA-4 gene (-318 C>T, and -49 A>G) did not show a significant difference with regard to the presence of inhibitor. In conclusion, the prevalence of inhibitor in the Brazilian severe HA patients analyzed in this study was higher among black patients. The FVIII mutation analysis revealed higher prevalence of nonsense mutation among inhibitor patients. Furthermore, the preliminary analysis of polymorphisms in immunoregulatory citokines genes did not demonstrate a relationship to inhibitor development in these patients.

PO-WE-124
Sequential Therapy with Activated Prothrombin Complex Concentrate and Recombinant Factor VIIa in the Treatment of Unresponsive Bleeding in Patients with Hemophilia and Inhibitors in a Single-Centre Experience

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The development of inhibitors to factor VIII or IX is the most common, severe, challenging, and expensive complication of the treatment of patients with hemophilia. Hemophilia patients with inhibitors can develop bleeding episodes, which are refractory to monotherapy with either recombinant factor VIIa (rFVIIa) or activated prothrombin complex concentrates (APCC). Management of such bleeds is often difficult. This report describes the results of a retrospective review of 5 events of patients with severe hemophilia and inhibitors who have been treated with sequential doses of APCC and rFVIIa for refractory bleeding. Sequential therapy was defined as the administration of both rFVIIa and APCC within 12 h. In 5 events of 4 patients with inhibitor, bleeding was not controlled by initial bypassing treatment. One patient had historical peak inhibitor titer increased to 1126 BU, and during peripheral inserted central catheter insertion for immune tolerance induction therapy, bleeding was not controlled. After APCC and rFVIIa were administered sequentially, bleeding was controlled. The second and third patients had a bleeding problem after total knee replacement for hemophilic arthropathy, and two agents were administered sequentially. The fourth patient had a small bowel resection because of intestinal obstruction, and post-operation bleeding was not controlled well. Disseminated intravascular coagulation (DIC) was developed. Two agents were administered sequentially for the bleeding problem, and bleeding was controlled. The last patient had traumatic hemothorax. Sequential therapy administration alternated one APCC dose to 1–2 rFVIIa doses: dosing intervals ranged between 3 and 6 h; APCC (75–100 U kg^{-1}) was given every 12 h; rFVIIa (90 μg kg^{-1}) was given every 3–6 h. Bleeding control was achieved in 12–24 h in all patients. Sequential therapy was discontinued after 2–5 days. No clinical adverse events were observed. Sequential therapy with APCC and rFVIIa was efficacious without adverse events. A prospective clinical trial is needed to provide further evidence.

PO-WE-125
PEGylated FVIII Exhibits Reduced Immunogenicity in Hemophilia A Mice and In Vitro in Human Cells

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Objective: An immune response to factor VIII (FVIII), which results in the development of neutralizing antibodies, is the most significant complication in patients with hemophilia who are receiving FVIII replacement therapy. BAY 94–9027 is a PEGylated B-domain–deleted FVIII (PEG-FVIII) that exhibits coagulation activity equivalent to non-PEGylated full-length FVIII (FL-FVIII) but displays a longer circulating half-life and, consequently, extended efficacy in preclinical bleeding models. We evaluated the immunogenicity of BAY 94–9027 in mice and human cells.
Methods/Results: In vivo studies in hemophilia A (HemA) mice reveal reduced immunogenicity for PEG-FVIII as evidenced by a lower frequency of anti-FVIII antibody–positive mice and lower anti-FVIII antibody titers compared with FL-FVIII–treated mice. Furthermore, no anti-PEG antibodies were detected in the PEG-FVIII–treated mice. Ex vivo analysis of the activity of T cells derived from the PEG-FVIII–treated mice also showed a correspondingly reduced FVIII-induced T-cell response. The weak T-cell activity, and ultimately the reduced antibody response against PEG-FVIII, can be attributed to poor antigen uptake as splenic dendritic cells (DCs) from naive HemA mice failed to internalize the PEG-FVIII protein. Extending this study to human cells, PEG-FVIII also exhibited reduced DC uptake, which was manifested in an abrogated proliferative and cytokine response of FVIII-specific T-cell lines generated from inhibitor-positive patients.
Conclusions/contribution to the practice/evidence base of hemophilia and bleeding disorders: Originally rationalized as an approach for extending protein half-life in vivo, PEGylation of FVIII appears to provide the added benefit of reducing immunogenicity. These findings will have significant clinical implications if this observation is borne out in trials currently using PEG-FVIII.
Conflicts of Interest: Drs. Paz, Xie, Liu, Koellnberger, Laux, Murphy, and Aswad are employees of Bayer HealthCare LLC, as are Mr. Fuelle, Mr. Shiroma, and Mr. Wu. Drs. Jacquemin and Lavendhomme have received research support from Bayer.

PO-WE-126
Successful Immune Tolerance Induction in Patients with Hemophilia A and Inhibitors Treated with a Plasma-Derived FVIII Product Containing von Willebrand Factor: A Large International, Multicentre, Retrospective Study

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Background: Immune tolerance induction (ITI) is probably the best therapeutic strategy for resolving the development of inhibitors against FVIII. ITI eradicates the inhibitors and subsequently induces recovery of FVIII to normal levels. Some small studies suggest that von Willebrand factor (VWF)-containing, plasma-derived FVIII products (VWF/pd-FVIII) are more successful for ITI than those lacking VWF.
Objective: To study the ITI outcome in HA patients treated with a highly purified VWF/pd-FVIII product not previously treated with FVIII (primary ITI), or patients who had failed ITI, while treated with another FVIII concentrate without VWF (rescue ITI).
Materials and Methods: CRFs of HA patients (FVIII <2 IU dl^{-1}) and inhibitors, from 35 centres in Spain, Italy, Germany, and the U.S.A., who completed primary or rescue ITI with a VWF/pd-FVIII product, were collected retrospectively and evaluated. Outcome was assessed following the criteria for complete/partial success and failure of the 2006 ITI International Workshop Consensus.
Results: Ninety-five patients were evaluated (Spain: 26, Italy: 19, Germany: 17 and U.S.A.: 33) who followed ITI protocols using Fanhdi® (61 patients) or Alphanate® (34 patients). Seventeen patients were not Caucasian (10 Hispanic/Latino, 3 African-American, 1 Native American, 2 Asian, and 1 not specified). Primary ITI success was achieved in 85% of the patients (28 complete success and 12 partial success out of 47), and 7 (15%) failure/loss of follow-up were reported. Rescue ITI success was achieved in 60% (17 complete success and 12 partial success out of 48), whereas 19 (40%) failure/loss of follow-up were reported. A wide variation in treatment dose was observed (3×47 IU kg^{-1} $week^{-1}$—2×300 IU kg^{-1} day^{-1}), and a dose-outcome relationship could not be established.
Conclusion: This retrospective study represents the largest international, multicentre, cohort of HA patients with inhibitors treated with a VWF/pd-FVIII concentrate for ITI. The high success rate reported supports the effectiveness of Fanhdi® and Alphanate® in primary and rescue ITI.

PO-WE-127
Resolution of Nephrotic Syndrome Following Rituximab Therapy in a Patient Undergoing Immune Tolerance Induction

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Inhibitors develop in approximately 1.5–3% of hemophilia B patients. Immune tolerance induction (ITI) in these patients is often unsuccessful. Anaphylactic reactions and nephrotic syndrome are complications associated with inhibitors to factor IX. Our patient was diagnosed with severe hemophilia B at birth, secondary to a family history of severe hemophilia B, high-titer inhibitors, and anaphylaxis. Following 5 doses of on-demand recombinant factor IX, our patient developed anaphylactic reactions and was found to have an inhibitor (maximum titer 3.5 BU). ITI was initiated using Alphanine (200 U kg^{-1} day^{-1}), as well as mycophenolate mofetil (MMF), immunoglobulin (IgG) and steroids. Treatment was well tolerated and his inhibitor and reactions to factor infusions resolved. With apparent successful ITI, the IgG and steroids were discontinued. Attempts to decrease his MMF and/or Alphanine resulted in small increases in inhibitor titer (1–2 BU) and recurrence of intermittent mild reactions to factor infusions. After 18 months of ITI, he developed proteinuria with a significant decrease in serum albumin. Renal biopsy revealed stage I membranous glomerulonephritis consistent with an immune complex mediated process. Following his biopsy, ITI was continued and rituximab was added. With the addition of rituximab, he had prompt resolution of the nephrotic syndrome and renal function returned to baseline. He has been closely monitored for over 6 months without recurrence of his nephrotic syndrome. Information on ITI in severe Hemophilia B patients is limited. When ITI is attempted, response may be poor and the risk of nephrotic syndrome is a concern. With development of nephrotic syndrome, the standard of care has been to discontinue ITI due to concern for irreversible renal damage. This case highlights the importance of close monitoring for this complication and the potential for successful resolution of nephrotic syndrome and control of the inhibitor with more aggressive immune modulation.

PO-WE-128
Impact of HLA and Cytokines Polymorphisms on Inhibitors Development in Children with Severe Hemophilia A

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The type of FVIII gene mutation and also HLA alleles and cytokines polymorphisms are included among genetic predisposing factors for FVIII inhibitors development in children with severe hemophilia A (HA).

Aim - Materials/Methods: To investigate any possible correlation among FVIII gene intron-22 inversion, HLA, and cytokines polymorphisms with the risk for inhibitors development in 52 Greek children with severe HA, exclusively treated with recombinant products, we performed long range PCR for detection of intron-22 inversion and PCR-SSP and PCR-SSO for genotyping of HLA A, B, C, DRB1 and DQB1 alleles and also of cytokines polymorphisms TNFα, TGF-β1, IL-10, IL-6, INF-γ. X^2 test and Fischer's exact test were used for statistical analysis.

Results: On the whole, 28 children had developed inhibitors (Group I), 71.4% high responding, while 24 had not (Group II). No statistically increased intron-22 inversion frequencies were found in Group I as compared to Group II: 15/28 (53.5%) vs. 9/24 (37.5%), respectively. Comparison of HLA frequencies between the two groups showed statistically significant differences in the following genotypes i) promoting inhibitors development: DRB1*01(*P*=0.014, OR= 10.9), DRB1*01:01(*P* = 0.011), DQB1*05:01 (*P* = 0.005, OR = 12.8), and ii) possibly protecting from inhibitors development: DRB1*11 (*P* = 0.011, OR=0.2), DRB1*11:01 (*P*=0.031, OR=0.15), DQB1*03 (*P*=0.004, OR=0.15), DQB1*03:01 (*P*=0.014, OR=0.22). The difference between the two groups regarding the cytokines polymorphisms was not statistically significant in all but in homozygocity of the genotypes ACC and ATA for IL-10 -1082G>A, -819C>T and -592C>A polymorphisms, where a trend was revealed for development of inhibitors.

Conclusion: FVIII-specific tolerance and immunity in patients with HA follow complex processes where a variety of genetic and non-genetic factors contribute to the formation of FVIII inhibitors. The data reported in our study, focusing on specific genetic factors, highlight the promoting or protective role of HLA molecules in inhibitor formation. On the contrary, neither intron-22 inversion nor cytokines polymorphisms were correlated with FVIII inhibitors development. However, these issues could be investigated in a larger cohort in order to obtain more clear results.

PO-WE-130
Experience of Surgery in Patients with Hemophilia with Inhibitors

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Introduction: Inhibitor development is one of the most challenging complications of hemophilia management. Hemostatic control in patients with hemophilia with inhibitors can be difficult, and is especially risky in those undergoing surgical interventions. We present our clinical experience of 49 orthopedic surgical procedures in ininhibitor patients during the last 10 years.

Patients and Methods: There were 32 major surgeries and 17 minor surgeries. All patients had severe hemophilia A, 40 patients with a high-titer inhibitor (from 5–463 IU). There were 16 with knee replacements (3 of them were re-endoprosthesis), 1 with hip replacement, 5 with pseudotumour removal, 4 with osteosynthesis, 2 with amputation of the leg, 4 patients with epicondylar osteotomy of the hips, 2 achilloplasty, 1 knee arthroscopy and 14 synoviorthesis with rifampicin. Thirty-six patients received rFVIIa and 13 patients received FEIBA. The doses and intervals of rFVIIa and FEIBA treatment used varied depending on the type (major or minor) or site of surgery.

Results: All cases achieved good hemostasis. Two patients required removal of the prosthesis 6 months and 1 year after knee endoprosthesis due to reactivation of endogenous infection. Fourteen patients with chronic synovitis received intra-articular injections with rifampicin, 1 patient developed an intramuscular hematoma, and 1 patient developed hemarthrosis. In all cases of synoviorthesis provided good results (i.e., cessation of hemarthrosis was achieved).

PO-WE-131
Clinical and laboratory efficacy of the new rFVIIa biosimilar coagil VII in inhibitor hemophilic patients

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Introduction: The development of inhibitors against FVIII/FIX is a serious challenge in patients with hemophilia. rFVIIa has been used as a treatment for such patients. Recently, a new biosimilar of rFVIIa, Coagill VII (CVII), has been developed. The aim of the study was to evaluate the efficacy of CVII for bleeding control during orthopedic surgery in inhibitor hemophilic patients.

Methods: Five inhibitor hemophilic patients were included in the study. All patients had orthopedic surgery: total hip replacement (1), total knee-joint replacement (3), reamputation of the distal portion of thigh (1). Patients received 120 mcg kg^{-1} of CVII (Generium, Russian Federation) before surgery and then every 2 h for 2 days. On the third day, patients received 90 mcg kg^{-1} of KVII every 2 h; from the fourth day, time intervals between CVII administrations were gradually increased to 3–8 h. Blood loss, activated partial thromboplastin time (aPTT), prothrombin time (PT), plasma activities of FVII, parameters of thromboelastography (TEG), and endogenous thrombin potential (ETP) were measured.

Results: In OR median blood loss was 2100 ml (ranges 700–2500 ml); after surgery median drain blood loss was 490 ml (ranges 0–1550 ml). ETP did not change significantly after CVII. Administration of CVII significantly increased plasma activity of FVII, shortened PT, shortened but did not correct APTT. Before administration of CVII patients had no clotting detectable by TEG. After administration of CVII TEG parameters became subnormal.

Table 1. xxx

Parameters	Before	After 15 min	After 1 h	After 2 h
FVII, %	155.2 ± 118.5	5238 ± 1440*	3274 ± 1083*	1839 ± 617.1*
PT,s	10.5 ± 1.7	7.4 ± 0.2*	7.6 ± 0.4*	7.8 ± 0.5*
aPTT	117.3 ± 27.5	69.1 ± 4.6*	71.8 ± 6.2*	75.3 ± 4.5**
R min	NA	34.7 ± 16.73	44 ± 34.1	47.2 ± 29.3
K	NA	13.3 ± 8.7	13.2 ± 10.5	15.5 ± 11.9
MA	NA	52.1 ± 18.2	47.2 ± 25.3	52.6 ± 20.1

NA- Not Available, * significant differences between levels before and after CVII administration.

Conclusion: New biosimilar of rFVIIa Coagil VII may be useful to control bleeding in inhibitor hemophilic patients during orthopedic surgery.

PO-WE-132
Identification of Potential T-Cell Epitopes in Factor VIII Using Peptide Microarrays

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MHC Class II epitopes consist of 9–12 amino acid residues in a protein antigen that can bind effectively to Class II receptors, e.g. HLA-DR and HLA-DQ. Reasonably high affinity binding is necessary for T-cell stimulation. The development of neutralizing anti-factor VIII (FVIII) antibodies ("inhibitors") is a major cause of complications in hemophilia A patients. Only several FVIII epitopes have been identified to date. Our laboratory is identifying HLA-restricted T-cell epitopes in FVIII in order to better understand the stimulation of CD4+ T cells that leads to inhibitor development. This task is rather daunting when one considers the diversity of the HLA-DR and HLA-DQ repertoire and the size, hence the number of potential epitopes, in the 2332-residue FVIII protein. In order to reduce the dimensionality of this problem, we are characterizing potential epitopes recognized by 10 recombinant proteins corresponding to the extracellular domains of HLA-DR proteins that are common in the American population. Previous studies from our laboratory and others have identified T-cell epitopes using synthetic peptides spanning the sequences of protein antigens, and peptides containing epitopes were identified by their ability to stimulate T cells. To avoid carrying out T-cell assays with irrelevant peptides, we are investigating the use of microarrays in which peptides spanning the FVIII sequence are immobilized on glass slides. These arrays are incubated with soluble recombinant HLA-DR proteins at several dilutions, followed by a fluorescent-labeled anti-DR antibody. Slides are then read on a microarray scanner. Affinities of MHC Class II/peptide complexes are then estimated by quantifying the fluorescent signals. Twenty-forty per cent of the FVIII peptides, including several verified T-cell epitopes, bound with significant affinity to each HLA-DR protein tested. Tetramer staining and T-cell proliferation assays using HLA-specific subsets of peptides are now being carried out to identify immunodominant T-cell epitopes in FVIII restricted to these HLA-DR alleles.

PO-WE-133
A Canadian Survey on the Incidence and Risk Factors for Inhibitor Development in Severe Hemophilia A PUPs: 2005–2010
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Objective: Assessment of inhibitor development (ID) in severe hemophilia A PUPs over a five-year period. Methods:
All Canadian hemophilia centres were approached. Eighteen centres had eligible patients and filled a questionnaire on their patients with severe hemophilia A (<0.02 IU ml^{-1}) born between September 2005 and August 2010.
Results: One hundred and nine PUPs were identified. Eighty-nine of these had had at least 20 exposure days (EDs) to factor VIII (FVIII) or had developed an inhibitor (27/89, 30%) with high titer (≥ 5 BU) in 19 and low titer in 8. Inhibitors developed in 15/38 (39%) patients with an intron 22 inversion mutation vs. 4/21 (19%) with low-risk mutations. Dose-intensity (U kg^{-1} day^{-1} X days) at first ED was a strong predictor of ID (P=0.02). Hemarthrosis and intracranial bleeding as an indication for treatment at first ED were associated with a 69% (9/13) and 63% (5/8) incidence of ID. Following the first ED, if patients were maintained on on-demand treatment, they had a 36% (17/47) incidence of ID, while if they were commenced on prophylaxis, they had only a 20% (8/40) incidence. ID according to FVIII used was: Advate 16/50 (32%), Kogenate FS 10/28 (36%), Wilate 0/10, and Xyntha 1/1. Although the lowest incidence was with Wilate, it should be recognized that patients placed on Wilate were, for the most part, treated differently in other respects: vaccination was not administered during their first 20 ED, and they were put on prophylaxis at time of first ED.
Conclusion: Cumulative incidence of ID during the first 20 ED to FVIII in an unselected Canadian population of severe hemophilia A PUPs was 30% with wide variations apparently related to environmental factors (choice of FVIII, intensity of exposure, early initiation of prophylaxis). Further studies with careful attention to environmental factors are warranted.

PO-WE-134
F8 Genotype and not Polymorphisms in IL10, TNFA, and CTLA4 Influences Inhibitor Development in Argentine Patients with Severe HA
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Development of FVIII inhibitors (INH) is a severe treatment complication that affects ~20% of patients with severe hemophilia A (HA). Both genetic and environmental factors have been implicated in inhibitor formation. The objective was to characterize genetic factors associated with inhibitors in Argentine patients with severe HA. We characterized the HA-causative mutation in 170 patients classified by INH status by application of a laboratory algorithm including inverse shifting-PCR for *F8* inversions, 37 PCR-amplifications for gross deletion detection, and for small-mutation screening by CSGE, and DNA-sequencing. To explore other genetic factors, we studied DNA polymorphisms in the genes encoding for interleukin-10 (*IL10*) (-1082:A/G), tumour necrosis factor-alpha (*TNFA*) (-308:G/A), and cytotoxic T-lymphocyte antigen-4 (*CTLA4*) (-318:C/T) that have been implicated as inhibitor risk factors in other populations. An unbiased series of 119 Argentine patients with severe HA with an absolute inhibitor prevalence of 17.6% (21) was analysed to show the natural distribution of *F8* mutation type/location. We classified this mutation series in three INH risk groups: high-risk (8/14=57%) including multi-exon deletions (5/7=71%) and nonsense in the FVIII light-chain defects (3/7=43%); intermediate-risk (13/88=15%) including nonsense in the heavy-chain (0/6), frameshifts Ins/Del (3/19=16%), Intron 22 inversions (9/55=16%,), splicing defects (1/4) and single-exon deletions (0/4); and low-risk (0/17=0%) including in-frame-Ins/Del (0/2), Intron 1 inversions (0/2) and missense mutations (0/13=0%). In contrast with previous studies from other populations, we found no significant differences in the inhibitor risk of polymorphisms in the genes for *IL10*, *TNFA*, and *CTLA4* in Argentina, suggesting other ethnical or environmental differences. In agreement with the literature, our population showed enhanced INH risks in severe HA patients with gross *F8*-rearrangements and nonsense mutations in the FVIII light-chain, and low risks in patients with missense mutations, highlighting the importance of F8 genotype as the first conditioning for INH formation in HA.

PO-WE-135
Circumcision Experience in Severe Hemophilia Patients with Inhibitors
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Between 2002 and 2012, a total of 7 severe hemophilia A patients with inhibitors (aged between 1 and 17 years) were circumcised in Çukurova University, Medical Faculty, Hemophilia Center, Adana, Turkey. Five patients had high-responder and 2 patients had low-responder inhibitors. In 5 hemophilia patients with inhibitors, recombinant factor VIIa was given 90 μg kg^{-1} before and after circumcision every 2 h. In 2 hemophilia patients with inhibitors, activated prothombin complex concentrates were given a loading dose of 75 U kg^{-1} and followed by 150 U kg^{-1} day^{-1} in two divided doses every 12 h. Two of 7 patients had no complications; nevertheless 5 of 7 hemophilia patients with inhibitors had 2 moderate and 3 mild bleeding complications. After being discharged from the hospital, oozing occurred in two patients 7 and 11 days after circumcision. These patients were admitted to hospital again and received additional bypassing agents. Two of seven patients with inhibitors had concurrent surgeries performed, including inguinal hernia repair and cataract extraction. In one patient inguinal hematoma occurred. With the introduction of bypassing agents, surgical interventions can be performed safely in hemophilia patients with inhibitors. Severe bleeding was not seen in our hemophilia patients with inhibitors. But, after being discharged, we observed late bleeding in 2 patients with inhibitors.

PO-WE-136
Influence of Type of Amino Acid Change on Inhibitor Formation in Hemophilia A
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Objective: Missense mutations are the most common type of mutations in hemophilia A (HA) patients. They represent 43.1% of all mutations. Our study aimed to investigate the influence of different missense mutations on inhibitor formation in patients with respect to physicochemical differences between replaced and new amino acids.
Materials and Methods: Seven hundred and twenty-two patients with known inhibitor status have been included in this study. To evaluate the severity of amino acid change, amino acids were grouped into four different classes: small/hydrophobic amino acids, neutral amino acids, acidic amino acids, and basic amino acids. If the wild-type amino acid is replaced by an amino acid of the same class (intra-amino acid class switch), properties of both amino acids are very similar; if the new amino acid amino belongs to another group (inter-amino acid class switch), properties are different.
Results: Comparison of all intra- and inter-amino acid switches showed that only 1.8% intra-amino acid substitutions were associated with inhibitor formation. In contrast 5.8% were observed in the case of inter-amino acid substitutions (p=0.04). The most significant risk of inhibitor formation exists when inter-amino acid class switches occurred out of small/hydrophobic acids.
Conclusion: This observation may be important towards improved individually personalized treatments to prevent inhibitor formation in patients with missense-mutations.

PO-WE-137
Prospective Advate Immune Tolerance Induction Registry (PAIR) in Hemophilia A Patients with Inhibitors: Interim Report
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Background/Aims: Prospective Advate Immune Tolerance Induction Registry (PAIR) is an ongoing, non-interventional, post-authorization safety surveillance registry designed to collect treatment information on the safety and efficacy of Advate (rAHF-PFM) in ITI therapy.
Materials and Methods: Subjects with hemophilia A of any severity and an inhibitor were eligible for study. Investigators determined dosing regimens and monitoring schedules. Maximum observation period for ITI was 33 months with a twelve-month follow-up period.
Results: As of 15 September 2011, 44 subjects were enrolled; 40 subjects had sufficient data to be included in the interim analysis. Thirty-five (87.5%) subjects had FVIII ≤ 1%. Median (range) age at ITI initiation was 1.5 (0–56) years. Median (range) titer in BU at diagnosis was 4.7 (0.5–173), at peak prior to ITI was 12.5 (0.7–225.2), and immediately prior to ITI was 4.0 (0–91.7). At the time of data transfer, 26 subjects had completed ITI therapy and were analyzed: 13 had general/partial success, 2 relapses*, 5 failures, and 6 were un-assessable. Kaplan-Meier estimated cumulative success rate was 70.8% (asymptotic 95% CI: 50.4%–88.6%) after 9 months of therapy in the 20 subjects evaluable per-protocol. Median time to first negative titer after ITI initiation was 3.45 months, and median time to second negative titer was 5.91 months. ITI duration ranged from 1 to 25 months. Initial ITI dose varied between 50 IU kg^{-1} QOD–200 IU kg^{-1} day^{-1} (most common: 100 IU kg^{-1} day^{-1}). No rAHF-PFM-related serious AEs were reported. *The 2 relapse cases were successful ITI completions as defined by protocol, but became partial successes with low-titer inhibitors at the 12 month follow-up visit. The 6 un-assessable cases were considered successful by investigator but were missing confirmatory inhibitory titer levels at time of ITI completion.
Conclusions: PAIR results appear to be consistent with previously reported experience with rAHF-PFM in ITI. PAIR continues to prospectively document the safety and efficacy of Advate ITI therapy.

PO-WE-138
Allele Polymorphisms of Immune Response Genes in Severe Hemophilia A Patients with Inhibitors in Ukraine
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Background: The reason that inhibitor factor VIII develops in only a fraction of patients with hemophilia A remains unclear. In the Ukraine, where resources are limited, an increase in the incidence of inhibitor development demonstrates the importance of preventing this severe complication. Several risk factors for the development of these antibodies have been discussed, but studies of genetically related subjects with hemophilia

have shown that the immunological outcomes are mainly determined by patient–related risk factors; but this data is controversial.
Aims: To establish allele and genotype frequencies of IL10 1082G/A, TNF-α 308G/A, CTLA-4 318 C/T and 49 A/G in hemophilia A inhibitor-positive and inhibitor-negative patients from the Ukraine.
Methods: The IL10 1082G/A, TNF-α 308G/A, CTLA-4 318 C/T, and 49 A/G single nucleotide polymorphisms (SNPs) were analyzed by ARMS-PCR technique among 71 hemophilia A patients (26 inhibitor-positive patients and 45 inhibitor-negative patients) and a control group (n=50) from the western Ukraine population.
Results: We revealed a significantly higher frequency of CTLA-4 318T allele (OR=5,35, CI 95%=2,19-13,6) and TT-genotype (OR=19,6, CI 95%=2,22-172,81) in hemophilia A patients compared to control; 23.3% of inhibitor positive patients have CTLA-4 318TT, 49AA genotype compared to 13.3% in inhibitor-negative patients and 2% in control subjects. This genotype could be discussed as a predisposing genetic risk factor of inhibitor development. The differences in distribution of IL10 1082G/A, TNF-α 308G/A allele and genotype in the studied groups of patients were not significant in contrast to reports on the association of certain polymorphisms with inhibitors in other populations.
Conclusions: This is the first report from the Ukraine on the association of allele polymorphisms of immune-response genes with inhibitor development in hemophilia A patients. This could provide useful insights into the immune response to FVIII in inhibitor-positive hemophilia A patients and possibly influence the timely prediction and prevention or treatment of FVIII antibodies.

PO-WE-139
Case Series Report: Low-Dose Immune Tolerance Induction (ITI) In Iran

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Introduction: The development of inhibitors to FVIII in hemophilia A patients can make control of bleeding difficult and expensive. Immune tolerance induction (ITI) is currently the best treatment for the eradication of inhibitors. A variety of protocols are employed, but selecting a cost-effective option in developing countries is difficult.
Methods: Five severe hemophilia patients with inhibitors were selected for ITI. Their median age was 21 months, and inhibitors developed after 11 (5 – 20) exposure days. At the start of ITI, the average inhibitor titer was 7.4 BU. Immune tolerance was initiated with pd FVIII at 50–100 IU kg^{-1} twice weekly. Treatment of bleeding was solely with rFVIIa. Inhibitor titers were measured monthly to 3 months, and 2-monthly to recovery. Clinical recovery was declared when inhibitors decreased below 0.6 BU, and no anamnestic response to FVIII occurred. Genotypes were determined for all these cases: 2 patients showed an intron 22 inversion; a further 2 had a frameshift in exon 14, and one patient had a frameshift mutation in exon 1. The highest inhibitor titers were seen in the 2 patients with an intron 22 inversion, reaching peaks of 54 and 15 BU, respectively. Earlier inhibitor eradication occurred in the 2 patients with exon 14 frameshift mutations.
Results: One patient with an inhibitor titer of >5 BU had to be excluded after 16 weeks because of uncooperative parents. The remaining patients recovered after 9, 26, 64, and 103 weeks, respectively. They have since remained inhibitor-free for 2 years.
Conclusion: Low-dose ITI even twice weekly, without recourse to CVC, can be effective in eradicating FVIII inhibitors, despite the presence of unfavourable mutations. This protocol is particularly appropriate and cost-beneficial for use in developing countries.

PO-WE-140
The Challenging Treatment of Bleeding Episodes in Non-Severe Hemophilia A Patients with Inhibitors

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Introduction: The development of neutralizing factor VIII antibodies (inhibitors) is a major complication of treatment with factor VIII (FVIII) concentrates in persons with non-severe hemophilia A. These inhibitors may neutralize the endogenous FVIII, thereby increasing the bleeding tendency to the phenotype of a person with severe hemophilia A. Currently, no firm data are available on approaches to treat bleeding episodes. The aim of this study was to evaluate the treatment of bleeding episodes in persons with non-severe hemophilia A and inhibitors.
Methods: All persons with non-severe hemophilia A (FVIII:c 2–40%), who developed a clinically relevant inhibitor between 1980 and 2011 in the participating centres of the INSIGHT study, were included. Of these patients, additional treatment data of bleeding episodes were collected.
Results: In total, 109 persons with non-severe hemophilia A from 30 centres in Europe and Australia developed an inhibitor at a median age of 38 years (IQR 16–60). A high-titer inhibitor (HT) (> 5 BU ml^{-1}) was present in 59%; the others had low-titer inhibitors (LT) with median peak titres of 20 BU ml^{-1} (IQR 9–65) and 2 BU ml^{-1} (IQR 1–3), respectively. Treatment for bleeding episodes was needed in 88% (91% of the persons with HT inhibitor and 83% of persons with LT inhibitor). More than half of the persons (53%) with HT inhibitors received FVIII bypassing agents, 49% received high doses of FVIII concentrates and 17% desmopressin. Of the persons with an LT inhibitor, 61% received FVIII products, 38% FVIII bypassing agents, and 14% desmopressin.
Conclusion: In a large cohort of persons with non-severe hemophilia A and inhibitors, 88% needed treatment for bleeding episodes. FVIII bypassing agents were used more frequently in HT patients and high doses of FVIII concentrates were more often used in LT patients.

PO-WE-141
Inhibitor Eradication Therapy in Non-Severe Hemophilia A

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Introduction: Development of neutralizing factor VIII antibodies (inhibitors) is a serious complication of clotting factor replacement in non-severe hemophilia A. There are limited data on the therapeutic approach to eradicate inhibitors in this group. The aim of this study was to identify therapeutic approaches for inhibitor eradication treatment in a large international cohort of persons with non-severe hemophilia A and inhibitors.
Methods: All persons with non-severe hemophilia A (FVIII:c 2–40%) who developed a clinically relevant inhibitor between 1980 and 2011 in the participating centres of the INSIGHT study were included. Treatment data on inhibitor eradication therapy were collected and analyzed.
Results: In total, 109 persons with non-severe hemophilia A from 30 centres in Europe and Australia were included. Inhibitors occurred at a median age of 38 years (IQR 16–60), with a median peak titer of 7.6 BU ml^{-1} (IQR 2.0–31.0). A high-titer inhibitor (HT, > 5 BU ml^{-1}) was present in 59%. In 69 persons (70%), of whom 56% had HT inhibitors, no eradication therapy was started. The inhibitor disappeared spontaneously in 47% of the HT inhibitors and in 64% of the low titer inhibitors (LT). Eradication treatment was given to 30 persons (30%), and the regimen consisted of immune tolerance induction (ITI) in 23 persons. The majority of these (n=13) had HT inhibitors. ITI was successful in 77% of the HT inhibitors and in all LT inhibitors. Immunosuppressive treatment was given to 11 persons, of whom 8 had a HT inhibitor and 3 had a LT inhibitor. This was successful in 4 of the HT patients and in all LT patients.
Conclusion: In this cohort of non-severe hemophilia A patients with inhibitors, 70% received no eradication therapy, and in 56% of these untreated patients, the inhibitor disappeared spontaneously. ITI and immunosuppressive treatment were successful in all LT patients, and in 65% of the HT patients.

PO-WE-142
Identification of 18 High Risk F8 Mutations for Inhibitor Development in 2,700 Non-Severe Hemophilia A Patients

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Introduction: Inhibitor development is a major complication of the treatment with factor VIII (FVIII) concentrates in patients with non-severe hemophilia A. Current hypothesis suggest that the mutation in the FVIII gene (F8) is an important predictor of inhibitor risk in these patients, however identification of high-risk patients is limited by the absence of absolute inhibitor risk of individual F8 mutations. The aim of this study was to assess inhibitor risk of F8 mutations in a large unselected cohort of non-severe hemophilia A patients.
Methods: The INSIGHT cohort included 2,711 non-severe hemophilia A patients (FVIII 2–40%) who were treated with FVIII concentrates between 1980 and 2011 in 34 centres in Europe and Australia. Absolute inhibitor risk of F8 mutations was assessed in 1,112 patients located in 14 centres in which genotyping was universally performed; these were calculated as cumulative Kaplan-Meier incidences with inhibitor as the event and cumulative number of exposure days (ED) as time variable.
Results: During 117,700 ED, 109 patients developed an inhibitor (absolute risk, 8.9%, 95% CI 7.1–10.6) after a median of 28 ED (IQR 14–68). F8 genotype was available in 898 patients (81%) among whom 236 different F8 mutations were identified. Eighteen mutations (L412F, R531C, R593C, P1761Q, F1775V, R1781G, P1854L, R1997W, D2074G, F2101C, Y2105C, R2150H, R2159C, E2228D, W2229C, V2232A, H2309D, Stop2333C) were classified as high risk mutation (n=274 patients; 50 inhibitors) with absolute inhibitor risks between 7 and 100%, the other 218 mutations were classified as low-risk mutation (absolute risk <5%).

Conclusion: In this unique cohort we identified 18 high risk F8 mutations for inhibitor development in non-severe hemophilia A. The incidences in high-risk F8 mutations were comparable to inhibitor incidences observed in severe hemophilia A. These findings highlight the substantial risk of inhibitor development in non-severe hemophilia A that has previously been underestimated.

PO-WE-143
The Role of von Willebrand Factor in the Outcome of Immune Tolerance Therapy in Persons with Severe Hemophilia A with Factor VIII Inhibiting Antibodies: A Systematic Review

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Introduction: Development of factor VIII (FVIII) inhibiting antibodies (inhibitors) is a serious complication of treatment with clotting factors in persons with hemophilia (PWH) A. To eliminate the inhibitors, PWH are treated with immune tolerance induction (ITI): an intensive regimen of high-dose factor VIII concentrate. One of the controversial issues in the management of PWH with an inhibitor is the choice of product used for ITI. It has been suggested that there might be a benefit to using a FVIII concentrate containing von Willebrand factor (VWF). The aim of this study is to compare the efficacy in inhibitor eradication of VWF-containing FVIII concentrates to non-VWF-containing FVIII concentrates.
Methods: We performed a comprehensive literature search, by using Medline, EMBASE, and the Cochrane databases (1986 to 2011), to identify studies in which the success of ITI in severe hemophilia A patients was reported.
Results: We included 26 studies reporting ITI procedures in persons with severe hemophilia A. Only three of the included studies were of adequate quality and described the product used for ITI. One study described 16 persons treated with VWF-containing FVIII products for ITI, of which 9 (57%) had a successful outcome. The other two studies evaluated 52 persons treated with non-VWF-containing FVIII products, 27 (52%) had a successful outcome. Pooled unadjusted OR for success of ITI in PWH treated with VWF-containing FVIII products was 1.19 (95% CI, 0.39 – 3.68) compared to ITI with non-VWF-containing FVIII products.
Conclusion: We did not find an association between VWF-containing products and an increased success rate of ITI in persons with severe hemophilia A with inhibitors. Because of heterogeneity in prognostic factors and outcome definitions, these results should be interpreted with care. We plan to perform individual patient analysis to be able to adjust for confounders in a multivariate analysis.

PO-WE-144
ITI in Adult Hemophilia A Patients with Long-Lasting FVIII Inhibitors: Single-Centre Experience

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The development of inhibitory antibodies to factor VIII (FVIII) is currently considered the most devastating complication of replacement therapy in hemophilia A. It occurs in 20–30% of patients with a severe form of this disease. The ultimate goal for treatment of patients with inhibitory antibodies is to permanently eradicate the inhibitor by immune tolerance induction therapy (ITI). Since ITI is usually initiated in childhood (success rate >50%), there is a shortage of literary data on the efficacy of such therapy in adult patients with long-standing FVIII inhibitors. Over the last 7 years we performed an ITI course in 24 severe hemophilia A patients, aged 22–59 years. They had never had ITI before and the interval between inhibitor diagnosis and ITI start was well over 5 years. The median immediate pre-ITI FVIII inhibitor titer was 9 BU ml^{-1} (0.5–90), and the median maximum historical inhibitor titer was 125 BU ml^{-1} (8–819). FVIII ITI dosing ranged from 50 IU kg^{-1} every other day to 100 IU kg^{-1} daily, and all patients were administered plasma-derived FVIII concentrates only. In 7/24 (29%) patients the inhibitor titer decreased below detection limit after 6–36 months of treatment, but in none of these patients did the FVIII pharmacokinetics become normalized entirely. The success was therefore partial (partial success). Neither those patients, nor two others (in their case the FVIII inhibitor titer dropped to the level 0.5–1.5 BU and they are currently on prophylactic FVIII infusions 3 times weekly) experienced any bleeding episodes. In 4 patients, the treatment was stopped prematurely due to poor compliance. Nine patients failed ITI. In the remaining 2 patients, the ITI regimen is continued. The median maximum historical inhibitor titer in patients with partial success 135 BU (8–380) did not differ significantly from that in patients with treatment failure—110 (15–819). In contrast, there was a significant difference between both groups with respect to pre-ITI inhibitor titer: 0.5–26 (median 2.2) in the partial success group vs. 3–90 (median 14.5) in the failure group.

PO-WE-145
Genotype-phenotype correlation in hemophilia A and risk of inhibitors of F8 gene mutations

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Objectives: Inhibitor development is one of the most serious complications of hemophilia A (HA). It has been suggested that some types of mutations of the F8 gene predispose to inhibitor development. We aimed to investigate the genotype-phenotype correlation in HA and risk of inhibitor development according to the mutation type of F8 gene.
Methods: We analyzed data from a mutation data base (Kohemgene) of 251 unrelated Korean HA patients having identified mutations. Mutations were detected as follows. Genomic DNA was extracted from peripheral blood leukocytes. Firstly, we conducted Inv(22) test by long-distance PCR. To identify the causative mutations other than Inv(22), we performed DNA sequencing of F8 by 3130 DNA Analyzer (Applied Biosystems). If no mutation was detected, Inv(1) and gene dosage test using the multiplex ligation-dependent probe amplification were done sequentially.
Results: Results follow in the table.
Almost all of the mutations showed severe phenotypes except missense mutation; 47.9% (105/219) of Severe HA patients had Inv(22) and 15% of those with Inv(22) have developed inhibitors. Although Inv(22) is the most common mutation of inhibitors of HA, large deletion, frameshift, and nonsense were also high risky mutations in inhibitor developments (35.5%<16/45>).

	Total	Severe	Moderate	Mild	Inhibitor(%)
Inv(22)	105	105			16 (15)
Inv(1)	1	1			1
Point mutation					
Nonsense	32	31	1		6 (18)
Frameshift	38	38			11 (28)
Missense	58	28	19	11	3 (5)
Splicing	7	6	1		
Large deletion	9	9			7 (77)
Large insertion	1	1			
Total	251	219	21	11	45 (17)

Conclusions: Genotypes were closely correlated with clinical severity. Although Inv(22) was a well-known risk factor in inhibitors, it seems to be essential to evaluate the risk of inhibitor development in the HA patients with null mutations such as large deletion, frameshift and nonsense mutations.

PO-WE-146
Environmental Risk Factors for Inhibitor Development in 215 Chinese Patients with Hemophilia A: A Retrospective Review at a Single Hemophilia Treatment Centre

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Objective: To investigate the environmental factors for inhibitor development in 215 Chinese persons with hemophilia from the hemophilia treatment centre at Nanfang Hospital.
Method: This single-centre retrospective study investigated 215 patients whose mean age was 26 years. The outcome was clinically relevant inhibitor development, de?ned as the occurrence of at least two positive inhibitor titers combined with a decreased recovery.
Results: Twenty-five patients (11.6%) developed clinically relevant inhibitors (7 high titer). Age at ?rst exposure was not associated with inhibitor development (P=0.881). Early regular prophylaxis decreased inhibitor risk, compared to on-demand treatment (relative risk[RR], 0.037;95% con?dence interval [CI], 0.002–0.616). We also found that severe hemophilia was associated with a higher risk than moderate/mild ones (RR, 6.443; CI,1.227–32.514), and less exposure/less intensive treatment increased inhibitor risk (RR, 32.622; CI, 4.120– 258.330). Furthermore, Surgical procedures, or peak treatment moments, was a great risk factor for inhibitor development (RR, 117.045; 95% CI,19.333–708.617). However, there was no difference between the inhibitor group and the inhibitor-free group for such putative risk factors of inhibitor development as breastfeeding, treatment during infections/vaccinations, concentrate types, infusion forms.
Conclusion: The development of inhibitor in Chinese patients with hemophilia A appeared to be associated with early regular prophylaxis, hemophilia severity, treatment intensity, and surgical procedures/peak treatment moments.

PO-WE-147
Prolonged Plasma Half-Life and Hemostatic Efficacy of a Recombinant Fusion Protein Linking Activated Coagulation Factor VII with Albumin (rVIIa-FP)

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Recombinant factor VIIa (rFVIIa) is approved to control bleeding in hemophilia A and B patients who have developed inhibitory antibodies to replacement therapy. rFVIIa is rapidly eliminated with a terminal half-life of approximately 2.5 h in humans. This short half-life necessitates frequent injections and considerably limits prophylactic use. A recombinant fusion protein linking activated factor VII with human albumin (rVIIa-FP) was developed to extend the half-life of rFVIIa. The aim of the present studies was to gather data about the pharmacodynamic and pharmacokinetic profile of rVIIa-FP in a mouse model mimicking the clinical conditions of severe hemophilia A to enable a more precise prediction of its kinetic properties and hemostatic efficacy for human dose finding. Single intravenous doses of rVIIa-FP or the marketed comparator NovoSeven® were administered to hemophilia A mice. Blood loss was determined for a 30 minute period, starting 2 minutes after drug application. Plasma concentrations were determined using an anti-human FVII ELISA. In hemophilia A mice, bioavailability and terminal half-life of rVIIa-FP were significantly better in comparison to NovoSeven®. The 11–fold higher AUC was accompanied with a 4-fold longer terminal half-life, while

clearance was decreased 11-fold. In vivo recovery of rVIIa-FP exceeded that of NovoSeven® by at least 100%. In addition, the kinetics of FVIIa activity parallels the trend for FVII:Ag. In the tail bleeding model, rVIIa-FP exhibited the same efficacy as NovoSeven® when measuring total blood loss. Ex vivo TGA studies showed that its prolonged systemic availability in plasma translates into sustained FVIIa activity recorded as thrombin generation. The recombinant albumin fusion technology was successfully applied to human recombinant FVIIa for improvement of pharmacokinetic parameters. Future clinical studies can prove whether the observed improved kinetic characteristics translate into a significant half-life extension and prolonged hemostatic effect in hemophilia patients.

PO-WE-148

Pre-clinical characteristics of a recombinant fusion protein linking activated coagulation factor VII with albumin (rVIIa-FP)

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Recombinant factor VIIa (rFVIIa) is approved to control bleeding in hemophilia patients who have developed inhibitory antibodies to replacement therapy. The short half-life of rFVIIa necessitates frequent injections and considerably limits prophylactic use. A recombinant fusion protein linking activated factor VII with albumin (rVIIa-FP) was developed to extend the half-life of rFVIIa. The present studies were conducted to gather knowledge about the procoagulant effect of rVIIa-FP in a venous stasis model and to assess the safety profile in different species enabling a more precise prediction of the tolerability and efficacy of rVIIa-FP for clinical use. During acute or subchronic toxicity studies in pre-clinical species, the allergic or prothrombotic potential of rVIIa-FP, its impact on safety pharmacology variables, and systemic toxicity parameters, as well as its local tolerance were assessed. When investigating dose responses or duration of effect, rVIIa-FP and NovoSeven®, a licensed rFVIIa, were administered intravenously to normal rabbits before induction of venous stasis. Clot formation and systemic hemostasis parameters were determined to assess procoagulant effects. Plasma concentrations were determined measuring FVIIa antigen. Overall, the toxicology program showed that administration of rVIIa-FP was well tolerated with no findings indicative of adverse systemic toxicity or allergic reaction and without any safety pharmacology or local intolerability concerns. Intriguingly, the immunogenicity of rVIIa-FP proved to be very low in rodents as well as non-rodents. The procoagulant effect of rVIIa-FP was not different from NovoSeven® and the prolonged systemic availability of rVIIa-FP translated into sustained hemostatic activity. Therefore, the pre-clinical toxicology and safety program conducted points to a good tolerance and favourable safety profile of CSL Behring's rVIIa-FP. The presented investigations did not reveal any safety concerns and support the evidence necessary for proceeding into human trials.

22-LABORATORY SCIENCE

S-WE-04.4-1
Development of standards as a tool in bleeding-disorders investigations during the fifty-year development of the WFH
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From the early days of investigations of bleeding disorders, laboratory measurements have played a crucial role in both diagnosis and control of optimal treatment regimens, and it is important that these measurements be both accurate and reproducible in different laboratories. In particular, the availability of concentrates on a global basis from a wide variety of sources in the 1970s and onwards necessitated the standardization of the measurement of factor (F)VIII and factor IX activity in various products, because recommended dosages are in units of factor activity. The ability to measure factor levels accurately in patients' plasma is also important both for diagnostic purposes and to follow the effects of treatment with concentrates. It has now been over 40 years since the establishment of the 1st International Standard in the field of bleeding disorders, i.e., that for FVIII; this was a concentrate standard designed to calibrate therapeutic materials. A similar concentrate was established for factor IX some 5 years later. It was soon realized that these concentrate standards were unsuitable for standardization of measurements in patients' plasma, and in 1981, a separate International Standard was established for FVIII plasma: this was calibrated both for FVIII activity and antigen, and also for von Willebrand factor (VWF) activity and antigen. In subsequent years international plasma standards have been established for factors II, V, VII, X, XI, XIII, fibrinogen, protein C, protein S, and antithrombin, and concentrate standards for factors II, VII, VIIa, X, XIII, vWF, fibrinogen, protein C, and antithrombin. It has been shown in international collaborative studies that the availability of these standards has greatly improved the accuracy and precision of measurements of these clotting factors.

S-MO-04.5-1
Thrombin generation in bleeding disorders: Current state of the art
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Despite tremendous improvements in the field of diagnosis, the assesment of the individual bleeding or thrombosis risk of a given patient still remains challenging. The measuring of thrombin, the final product of the whole coagulation mechanism, has been suggested to be a better indicator of the individual hemostatic capacity of patients with coagulation disorders. In hemophilia patients, several groups reported a correlation between circulating plasma factor VIII (FVIII), FIX activities, and thrombin generation parameters, such as endogenous thrombin potential (ETP) and the rate of thrombin generation. More importantly, a certain correlation between the thrombin generating capacity of patients with severe hemophilia and their clinical bleeding phenotype was also reported. A laboratory assay which can accurately predict the bleeding risk of each severe hemophilia patient may be highly interesting for the determination of antihemophilic prophylaxis. Such a laboratory test may also open new perspectives for individually tailored prophylaxis regimens adapted to the individual needs of each single patient. Promising results were also reported in patients with FXI deficiency. The monitoring of bypassing therapy is one of the main interests of this global approach in the field of hemophilia. The optimal use of bypassing agents in surgery is hampered by a lack of laboratory assays to monitor therapeutic efficacy and determine adequate dosing. The capability to determine the most effective therapeutic option and the optimal dose of bypassing agent for a given surgical situation would represent a major advance. Recently, we reported the first prospective clinical assessment of the thrombin generation assay for monitoring bypassing therapy in surgical settings, which demonstrated that the thrombin generation test was a promising laboratory tool that could help physicians to individually tailor and monitor hemostatic treatment in inhibitor patients undergoing surgical procedures. However, much work remains to be done to validate, standardize, and implement thrombin generation measurement in clinical laboratories that could lead to improved management of patients with bleeding disorders.

S-TU-04.5-3
Laboratory diagnosis of VWD: The role of collagen binding assays in the diagnosis of VWD
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Von Willebrand disorder (VWD) is the most common inherited bleeding disorder and arises from deficiencies and/or defects in the plasma protein von Willebrand factor (VWF). VWD is classified into 6 different types, with type 1 identified as a (partial) quantitative deficiency of VWF, type 3 defined by a (virtual) total deficiency of VWF, and type 2 identifying 4 separate types (2A, 2B, 2M, 2N) characterized by qualitative defects. The classification is based on phenotypic assays including FVIII, VWF:Ag, and VWF activity, typically by ristocetin cofactor (VWF:RCo), but also increasingly by collagen binding (VWF:CB). Phenotypic testing may be supplemented by multimer analysis, ristocetin-induced platelet agglutination (RIPA), and VWF:FVIII binding. Although genetic analysis is not required to diagnose VWD or to define a classification type, it may be useful in discrete situations. This talk will review this diagnostic process, with a particular focus on the VWF:CB assay. In brief, although the VWF:RCo and VWF:CB can be performed well by individual laboratories, the VWF:CB tends in general to provide for more favourable and comparative data in cross-laboratory studies, including a lower level of inter-laboratory variation. Moreover, the VWF:CB tends to be more sensitive to loss of high molecular weight VWF, important in the context of the identification of types 2A and 2B VWD. Finally, exclusion of the VWF:CB will lead to an inability to properly differentiate individuals with type 2M VWD. Nevertheless, optimal laboratory investigation of VWD requires the use of extended test panels including both VWF:RCo and VWF:CB, and is facilitated by additional strategies such as the use of data from desmopressin challenges as a diagnostic tool.

S-TH-01.5-2
Genetic analysis in bleeding disorders: What is the state of the art?
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Many enhancements to processes used in genetic analysis of inherited bleeding disorders are available. Laboratory information management systems provide "paperless" sample management and reporting. Genomic DNA is obtained using automated extraction. Several genetic analysis techniques are available, generally utilizing genomic DNA as a template. PCR and DNA sequencing can be streamlined through use of single amplification conditions and robotic processing. Tailed PCR primers facilitate sequencing using common, rather than exon-specific primers. Sequence analysis software rapidly identifies variants that differ from reference sequence. Large deletions/duplications are analysed using multiplex ligation-dependent probe amplification, micro-array, or custom-designed gap-PCR. F8 intra-chromosomal inversions amplified through long/inverse PCR can be analysed using gel electrophoresis or sizing on a DNA sequencer. Previously "missing" intronic mutations are detected by RT-PCR from mRNA, gel electrophoresis, and sequencing. Guidelines from CMGS, EMQN etc. recommend standards in areas including sequencing, quality control, pathogenicity prediction and disease-specific issues. Laboratory accreditation ensures common standards of practice while quality management (QM) software facilitates organization of QM documents. Variants under amplification primers can be sought with each new dbSNP release using tools including SNPCheck and primers redesigned where necessary using online software. Reference genetic materials are available for common mutations through NIBSC. Human Genome Variation Society sequence nomenclature use reduces errors in documenting variants identified by different laboratories. Variant interpretation software integrates pathogenicity prediction for amino acid and splice variants with literature searching for previously reported variants, while locus-specific mutation databases, HGMD and dbSNP, catalogue previously reported sequence variants, facilitating pathogenicity interpretation. External quality assessment monitors and facilitates improvement in clerical, genotype, and variant interpretation in genetic analysis reports. Sharing best practice and provision of backup laboratory analysis is made possible by laboratory networks e.g., UKHCDO Genetic Testing Network. Next generation sequencing will contribute to identification of exonic and currently "missing" intronic and transcriptional sequence variants.

S-TH-01.5-4
Reference materials for genetic tests in hemophilia and allied bleeding disorders
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The frequency of genetic testing is increasing, and the accuracy of this testing is of paramount importance in the diagnosis and treatment of patients and the counselling of affected families. Hemophilia A is a hereditary genetic bleeding disorder occurring in about 1 in 5000 to 10 000 male births, with intron 22 inversion mutation of the F8 gene accounting for 50% of severe hemophilia A. Genetic analysis of the intron 22 inversion is challenging, involving technically demanding methods such as Southern blotting and long-distance PCR. External quality assurance schemes have shown that errors in genotyping for this mutation do occur. Most laboratories use as their in-assay control DNA samples extracted from patients known to carry the intron 22 inversion mutation. However, these are not well characterized and are usually available only in limited amounts. Few certified and commercial genetic reference materials for hemophilia and other bleeding disorders are available. In 2008, the World Health Organization (WHO) established a stable reference panel of genomic-DNA (gDNA) (NIBSC Code, 08/160) to support the genetic testing of intron 22 mutation. This panel of 4 preparations was produced from gDNA extracted from immortalized cell lines produced by Epstein-Barr virus (EBV) transformation of lymphocytes from blood samples of consenting donors. The samples were obtained from two normal individuals (male and female), an intron 22 inversion positive female carrier and an intron 22 inversion positive male. This panel has been distributed worldwide and has proven to be useful, aiding laboratories in setting up and validating their methods. The success of this panel establishes the basis for the future production of genetic reference materials for bleeding disorders.

S-MO-04.5-4
Diagnostic usefulness of adenosine triphosphate release assays and aggregation tests with native or platelet-count-adjusted, platelet-rich plasma
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Assays of platelet aggregation and dense granule adenosine triphosphate (ATP) release are among the most common tests performed in clinical laboratories to evaluate platelet function disorders. Recent data from prospective cohort studies of individuals referred for bleeding disorder assessments indicate that these assays have important diagnostic utility. Furthermore, comparative analysis of data for light transmission platelet aggregometry (LTA), with platelet count adjusted (A) and native (N) platelet-rich plasma (PRP), using sample-type specific reference intervals, indicate that both sample types are

useful to detect impaired platelet function from bleeding disorders. Several prospective studies have demonstrated that reduced maximal aggregation with a single agonist often represents a false positive, whereas abnormalities with multiple agonists are associated with bleeding disorders (odds ratios ≥23). Assays of ATP release, using Chronolume® (a commercial luciferin-luciferase reagent containing magnesium) are also helpful to detect impaired platelet function from common bleeding disorders (odds ratio 17), even if aggregation reponses are normal (odds ratio 12). Accordingly, laboratories should consider testing for dense granule release defects to detect and help subclassify platelet function disorders. Some recommended performing aggregation and ATP release tests as separate assays, because the addition of Chronolume® can potentiate submaximal human platelet aggregation responses, and this significantly alters the aggregation findings for some disorders. To optimize testing for bleeding disorders, laboratories should consider the recent evidence and guidelines on platelet function testing, including the procedures, agonists, and strategies that help detect common defects in platelet function.

S-TU-04.5-1
Introduction: Historical perspective
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For a long time, congenital bleeding diathesis and hemophilia were synonymous. However, in 1926, the Finnish physician Eric A. von Willebrand changed the perspective when he described a large family, living on the Åland Islands in the Baltic Sea, with bleeding diathesis that could not be classified as true hemophilia. It had an autosomal dominant inheritance, affected both sexes, and displayed a different bleeding profile. He came to the conclusion that the disease was distinct from hemophilia and called it hereditary pseudohemophilia. Today, the disease is called von Willebrand disease (VWD) and is considered the most common inherited bleeding disorder. The pathogenesis remained controversial for many years, but in the 1950s, it was clear that it was caused by a missing plasma factor, first described as the factor VIII related antigen and later called the von Willebrand factor (VWF). During the decades since its discovery, it has become evident that VWD may be highly variable with different clinical and laboratory features. Currently, VWD is divided into 2 quantitative variants, type 1 with partial deficiency and type 3 (rare) with a complete absence of VWF. Approximately 25–30% of VWD cases have a qualitative deficiency that can be further subtyped depending on the type of defect. Classical hemophilia and VWD make up the majority (>95%) of bleeding disorders, and deficiency of other procoagulant factors, e.g., fibrinogen, factors II, V, VII, X, XI, and XIII (or combinations thereof) are classified as rare bleeding disorders (RBDs). The prevalences of RBDs are about 1 in every 500 000 – 2 million and are inherited in an autosomal recessive way. The detection of VWD and RBDs is challenging, and only specialized laboratories have the capacity to correctly identify all VWD subtypes and possible RBDs.

S-TU-04.5-2
Laboratory diagnosis of VWD: Role of VWF activity assays with and without ristocetin
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The precise diagnosis of von Willebrand disease (VWD) requires careful assessment of the patient's bleeding symptoms, family history, and laboratory phenotype. Several laboratory tests are necessary for VWD type and subtype identification. In addition to the determination of von Willebrand factor (VWF) antigen, it is important to determine the "activity" of VWF, as up to 30% of VWD cases have a qualitative defect that is best assessed with a functional characterization. One of the most important VWF activity assays is the VWF ristocetin cofactor activity (VWF:RCo), which utilizes the glycoprotein antibiotic ristocetin sulphate that agglutinates normal platelets in the presence of VWF under static conditions. VWF:RCo represents a measure of the interaction between VWF and platelet receptor GPIbα and is used for diagnosis and monitoring; it also the recommended activity assay to assign the potency of replacement products. However, the VWF:RCo assay can be performed in many different ways, and a major drawback is the high variability between assays. In later years, several automated assay protocols have reported improved assay characteristics and are now replacing the conventional aggregometry assays in many clinical laboratories. Alternative ristocetin-based assays involve flow cytometry or ELISA procedures with recombinant GPIbα bound to a specific antibody that are used to capture VWF in plasma. Pure immunobinding assays, independent of ristocetin, are based on monoclonal antibodies directed against the functional epitope of VWF that contain the binding site for GPIbα. These can be performed by ELISA or latex immunoassay but have not yet been fully evaluated and therefore cannot replace the traditional VWF:RCo assay. Novel, ristocetin-independent assays, that only utilizes GPIbα, has recently been published. There are several variants of this assay and one latex-enhanced assay appears easy to perform on common coagulometers with good reproducibility and sensitivity. If the initial evaluation results are valid in clinical routine settings, the ristocetin-free assay has the potential to replace the classical VWF:RCo assay.

S-WE-04.4-2
Potency labelling of clotting factors
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Since establishment of the first World Health Organization International Standards (WHO IS) for factor VIII (FVIII) and factor IX (FIX) concentrates in the 1970s, all plasma-derived and recombinant therapeutic concentrates have been labelled in International Units (IU). This approach facilitates comparison of the clinical efficacy of different products and simplifies dosage calculation where the IU represents the amount of analyte in 1ml of pooled, normal plasma. Whereas the potency labelling of FIX concentrates currently relies on a single method (1-stage clotting), the situation for FVIII is more complex through the availability of both 1-stage clotting and chromogenic methods, which are preferred for product labelling in the USA and Europe respectively. The choice of FVIII potency method for labelling is irrelevant when both methods agree, but is crucial when there are significant discrepancies as exemplified by the discordance in the IU applied to B-domain deleted recombinant FVIII licensed in the USA and Europe. The development of new products, with novel properties introduced through structural or chemical modifications (e.g., truncation, pegylation, Fc fusion), will further challenge the traditional approach to potency labelling. However, continued labelling in IU, traceable to the WHO IS, should remain a possibility if statistically valid assays are achieved in terms of linearity and parallelism of the dose-response relationships. Where IU labelling is not possible, it will be necessary to consider "product-specific units" defined by *in vitro* biological activity relative to product references. Maintenance of a harmonized therapeutic approach, in the face of different possible routes of potency labelling, will require the implementation of agreed-upon principles by licensing authorities and manufacturers at the global level.

S-TU-04.5-5
World Federation of Hemophilia EQA program
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The World Federation of Hemophilia (WFH) External Quality Assessment (EQA) program was established in 1993 to support and improve performance of laboratories in the diagnosis and treatment of hemostatic disorders. Over 160 centres from 74 different countries have participated in the program. Regular distribution of samples for PT and APTT measurement and assay of FVIII, FIX, and VWF has been supplemented by distribution of samples from patients with rare bleeding disorders (FV, FVII, FX, FXI) together with samples from patients with FVIII inhibitors, and cryoprecipitate samples for FVIII and fibrinogen assay. The WFH cohort is comprised of both emerging and established centres; assay performance among the latter is generally seen to be better, confirming the expert status of these laboratories; links between International Hemophilia Training Centres (IHTCs) and emerging centre laboratories have been forged to promote education and aid improvement in laboratory performance, with additional regional support provided through workshops and regional program managers. Interestingly, when challenged with an exercise to perform assays on cryoprecipitate, performance among emerging centre laboratories was comparable to IHTC's—this may reflect experience with use and evaluation of this material in these centres. Challenges exist in the repertoire of tests provided by emerging centre laboratories—in a questionnaire, less than 2/3 of centres perform assays for rare bleeding disorders. Participation in the WFH EQA program can help identify assay design and performance issues, and has been shown to lead to increased between-laboratory agreement. Addressing quality assurance issues and the resources required to perform a full repertoire of assays is necessary to ensure improvements in the diagnosis and care of patients with bleeding disorders.

S-TU-04.5-4
Diagnosis of FXIII deficiency
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Coagulation factor XIII (FXIII) is a protransglutaminase that circulates in plasma as a tetramer (FXIII-A2B2) consisting of two catalytic A subunits (FXIII-A) and two carrier/protective B subunits (FXIII-B). Severe congenital FXIII-A subunit deficiency is a rare autosomal recessive inherited disease, with 1 patient in 1–3 million, that affects all races and both sexes equally. More than 70 causative mutations in the FXIII-A gene have been published. Untreated, severe congenital FXIII-A subunit deficiency causes bleeding events, with intracranial hemorrhage being the major cause of death, impaired wound healing, and abortion. The first and most characteristic symptom is bleeding from the umbilical cord several days after birth. Because of the potentially fatal bleeding complications, the possible diagnosis of severe congenital FXIII deficiency should not be delayed in any individual with an unknown bleeding tendency. The usual screening tests for coagulopathies—prothrombin time, activated partial thromboplastin time, and thrombin time—do not show prolongation in cases of FXIII deficiency. Therefore, if clinical symptoms indicate a bleeding diathesis, full evaluation of the clotting system should include a test that detects FXIII deficiency. Quantitative functional FXIII activity assays and specific ELISA tests should be used. FXIII deficiency was traditionally diagnosed using the clot solubility test. However, the use of clot solubility tests as a screening test for FXIII deficiency is not recommended. If the diagnosis of severe congenital FXIII deficiency is confirmed, prophylactic replacement therapy is mandatory because of the sometimes fatal or severely disabling bleeding complications after only minor trauma.

S-TH-01.5-3
The U.K. NEQAS hemophilia molecular genetics quality assurance scheme
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The analysis of the causative mutation in families with inherited bleeding disorders is common practice. Experience from external quality assessment (EQA) schemes for other genetic disorders has highlighted the errors that may occur in genotyping and its subsequent interpretation. The U.K. NEQAS scheme was designed to assess genotyping, clerical accuracy, and the interpretation of genetic analysis reports for inherited bleeding disorders. A pilot EQA scheme to examine F8 gene mutations was established in 1998. Subsequent exercises have included F8 linkage studies as well as point mutations in the F8, F9 and VWF genes. Participants in the scheme are provided with a clinical scenario and whole blood or DNA isolated from cell lines and requested to seek a familial mutation in a limited part of the relevant gene and to report on the mutation in the

patient, its presence/absence in relative(s), and the implications for each individual analysed. Reports are scored in three areas: clerical accuracy, genotyping, and interpretation by a panel of scientists/clinicians with expertise in this area. The scheme is open to laboratories from all countries, and currently 22 laboratories participate. Two exercises per annum are circulated with a 6 week turnaround time, and to date 19 exercises have been circulated. Since its inception the scheme has seen a significant improvement in the quality of laboratory reports. Reports are confined to a single page; participants include essential information, adhere to international recommendations on gene and mutation nomenclature, and include relevant reference sequences. Despite a requirement for laboratories to participate in EQA schemes, the NEQAS scheme for inherited bleeding disorders remains the only global EQA scheme for this group of disorders.

S-MO-04.5-3
Clot waveform analysis: Does it have a role?

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Clot waveform analysis (CWA) is a convenient global clotting function test based on the continuous monitoring of the transmittance or absorbance during the routine coagulation assays, such as activated thromboplastin time (aPTT) and prothrombin time (PT). CWA technology was originally developed by Organon Teknika with the MDA-II system, and this technology and application were limited to the users of this system. However, the increasing number of current automated clotting machines can be applicable to CWA . Therefore, if the raw data of the transmittance or absorbance can be extracted from the clotting machine, it is possible to figure the waveform. According to the waveform pattern, qualitative evaluation of various clotting factor deficiencies and monitoring of the anticoagulant effect of various drugs can be easily performed. Furthermore, several parameters, such as coagulation velocity and acceleration, can be measured by mathematical processing with standard Excel software. There are several advantages in this assay. The first is the convenience that the CWA can be performed simultaneously with routine aPTT and PT tests. This means that everyone who has such an automated clotting machine can perform CWA. No special apparatus is required. Furthermore, quantitative evaluation can be performed. The useful parameters are maximum coagulation velocity and maximum coagulation acceleration. We applied CWA to the detection of low levels of factor VIII the hemostatic effect of FVIII in the presence inhibitor, monitoring the hemostatic effect of bypassing therapy, diagnosis of antiphospholipid antibody and acquired hemophilia A, and diagnosis of sepsis–related DIC. For a wider application of CWA, standardization of the assay and reagents is essential.

S-MO-04.5-2
Whole blood thromboelastometry

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Patients with severe hemophilia A (factor VIII) or B (factor IX) with or without inhibitors suffer from an incapability of establishing the propagation of thrombin generation and from developing fragile clots with reduced resistance to fibrinolysis. There is considerable interindividual variation in the response to substitution therapy and bypassing agents. This calls for individually tailored treatment regimens. Standard laboratory assay, such as the APTT of PT, cannot be used to optimally monitor factor substitution or bypassing agents. Whole blood thrombelastometry and thrombin generation are attractive global assays that provide complementary information on hemostatic capacity. This presentation will review current standards for running whole blood thromboelastometry in patients with bleeding disorders, focusing on pre-analytical and analytical variables. Thromboelastometry has demonstrated considerable heterogeneity in the baseline whole blood coagulation patterns amongst patients with verified factor VIII levels <1%. In vitro and in vivo studies have demonstrated the ability of thromboelastometry to predict the clinical response to bypassing agents in patients with inhibitors. A small clinical study has shown that thromboelastography may be used to individualize therapy and provide more judicious use of bypassing agents as well as more convenient treatment regimens. Recently, thromboelastometry has been utilized to correct the hemostatic performance of recombinant factor VIIa during surgery by showing the need for fresh platelet concentrate to secure the effect of recombinant factor VIIa. New studies on clot stability in hemophilia and various options for adjunct clot stabilizing intervention will be reviewed, including the effect of tranexamic acid, activation of TAFI with solulin, as well as the potential use of FXIII in hemophilia.

S-TH-01.5-1
Development of genetics as a tool in bleeding disorder investigations during the 50-year development of the WFH

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In 1962 little was known about the genetics of the conditions grouped as hemophilia except that the commonest disorders were X linked recessive. In that (now distant) era, molecular genetics had barely got started. By 1981 we still had only the family tree and the factor VIII to factor VIII related antigen ratio to go on when ascertaining carrier status. We used to calculate betting odds of being a carrier using an algorithm validated against a group of known carriers and normal controls. The first molecular-genetic advance came when a polymorphic restriction fragment length marker (RFLP) near the locus of the F8 gene was described, and we were able to establish that it had utility in carrier tracing. However, not being intragenic there was an inevitable risk of misdiagnosis due to meiotic crossover. Cloning the factor VIII and IX genes in 1984 and 1982, although undertaken with the purpose of enabling synthesis of the respective clotting factors, had an immediate spinoff in genetics. With Jane Gitschier we proved the utility in carrier tracking of a polymorphic variant producing an RFLP in Intron 18 of the factor VIII gene itself. The ratio of alleles in females is 40:60, giving an informative rate which accorded with Hardy-Weinberg equilibrium at 48%. With Southern blotting we could now give a definitive status of carriership or, just as importantly, non-carriership to over a third of consultands, depending on family structure, availability of critical family members, and heterozygosity. Meanwhile in the Factor IX gene, a series of informative polymorphisms were found within the gene that could be used for most families segregating Hemophilia B. Polymorphisms in the factor VIII gene are much less frequent and harder to find than in the factor IX gene. That remains an unexplained observation. A breakthrough came when we started to look for the highly polymorphic variable number tandem repeats (VNTR) in the factor VIII gene using the clones that Gitschier had isolated when mapping the gene. One was quickly within intron 13, which had at least 6 variants such that 90% of carriers are heterozygous and therefore informative. Another turned up not long after within Intron 22, and the pair became the standard for carrier tracking until the advent of direct mutation detection by means of sequencing the entire coding sequence using PCR-based techniques. This approach now dominates, since carrier status can be determined without reference to heterozygosity or intervening family members. It also contributes to genotype/phenotype understanding. There has thus been a complete revolution in the place of genetics in hemophilia during the past 50 years, from an afterthought to its rightful place at the centre of our understanding of these disorders.

PO-MO-114
Decrease of microparticles (MP) after treatment in hemophilia A patients: coincidence or causation?

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Background: Microparticles (MPs) are small membrane vesicles (0.1–1 μm) released from various cell types after activation and/or apoptosis. There are limited data about their role in hemophilia A.
Patients and Methods: Samples were taken before and 30 minutes after FVIII injection in 18 patients with severe hemophilia A treated on demand. Flow-cytometric determination of total MP (TMP) using lactadherin, platelet MP (PMP) (CD42a), endothelial MP (EMP) (CD 144), and leukocyte MP (LMP) (CD 45) was performed. The mean fluorescence intensity (MFI) was translated into molecules of equivalent soluble fluorochrome (MESF) and results were presented as 10^6 events L^{-1}. The results were compared with endogenous thrombin potential (ETP), overall hemostatic potential (OHP), fibrin gel permeability (presented as Ks), and thrombin activable fibrinolysis inhibitor (TAFI) (those results were part of a larger study).
Results: TMP and PMP decreased after the treatment 1015 ± 221 and 602 ± 134 in comparison to the values before the treatment, 2373 ± 618 and 1316 ± 331 ($P < 0.01$). EMP also decreased after the treatment (78 ± 12 vs. 107 ± 13, $P < 0.05$). Very low level of LMP (21 ± 1) was not influenced by the treatment (20 ± 1). Both TMP and PMP inversely correlated moderately but statistically significantly with OHP, ETP, and TAFI/TAFIi (r=−0.30, −0.32, −0.32 for TMP and r = −0.28, −0.32, −0.30 for PMP; $P < 0.05$ for all). TMP and PMP also correlated with Ks (0.34 and 0.32, $P < 0.05$). EMP correlated only with ETP ($r = -0.29$, $P < 0.05$), while LMP did not express any correlation. TMP and PMP also correlated with the FVIII level ($r = -0.29$, $P < 0.05$).
Interpretation: TMP, PMP, and EMP decreased after on-demand treatment with FVIII concentrate in hemophilia A patients. Decrease of circulated MP which inversely correlated with hemostatic activation and fibrin gel tightness (and also TAFI activation, which is well known to be placed within the thrombus) may potentially implicate that those MP may be incorporated in the hemostatic plug formed after FVIII substitution on the site of injury.

PO-MO-115
Characterizing global hemostasis throughout the FVIII prophylaxis dosing interval: A pilot study

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Introduction: Hemophilia A patients receiving FVIII prophylaxis have a wide interindividual variation in clinical bleeding phenotype that may not be well characterized by changes in FVIII:C. A potential alternative may be to guide FVIII dosing by global hemostasis markers (TEG and Hemodyne). To quantify inter-individual dose-response variation in FVIII response, we conducted a study that characterized global hemostasis throughout a 48 h FVIII prophylaxis interval.
Methods: Nine non-bleeding severe FVIII deficient patients received prophylactic FVIII (mean dose 32.1 IU kg^{-1}) and blood was collected at baseline and 0.5, 1, 2, 4, 8, 12, 24 and 48 h post-dose to assess FVIII:C, platelet function markers (platelet contractile force [PCF], clot elastic modulus [CEM], force onset time [FOT]) and TEG (reaction time [R], kinetics time [K], maximum amplitude [MA]).

Parameter (Mean)	Time Following rFVIII Dose								
	0	0.5	1	2	4	8	12	24	48
FVIII:C (IU dL^{-1})	0.6	88.2	78.4	71.1	61.2	42.1	29.7	16.2	3.4
PCF (kdyne)	0.3	6.7	7.4	5.7	5.9	3.5	3.9	3.1	0.6
CEM (kdyne cm^{-2})	0.0	22.1	24.5	19.5	20.8	10.7	16.5	12.6	1.6
FOT (min)	18.1	6.7	6.1	7.5	7.5	9.8	10.5	12.2	18.0
R (min)	22.5	7.2	6.4	7.3	7.5	9.8	8.5	12.2	19.6
K (min)	7.1	2.2	2.1	2.2	2.4	2.6	2.4	3.3	5.2
MA (mm)	53.5	62.2	63.0	61.0	60.0	59.2	61.2	58.9	54.2

Conclusions: The mean FVIII:C remained above 1 IU dL^{-1}throughout the dosing interval. By 8 h, however, the PCF, CEM, and R were sub-therapeutic, indicating increased bleeding risk despite FVIII:C >1 IU dL^{-1}. Therefore, there is 40 h of sub-therapeutic platelet function and clot initiation during the prophylaxis interval. R and K may be more sensitive to low FVIII:C compared to PCF/CEM. These data may suggest FVIII:C is not an adequate monitor for global hemostasis.

PO-MO-116
A circulating heparin-like anticoagulant with no bleeding complications: Case report

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Circulating heparin-like anticoagulant has been associated with different disorders, such as hematological malignancies, solid tumours, chronic renal disease, hepatic failure, and acquired immunodeficiency syndrome. To date, only a few case reports of patients with heparin-like anticoagulant have been published, with bleeding severity ranging from severe to nearly asymptomatic. We report the case of a circulating heparin-like anticoagulant in a 70 year-old man with an unexplained prolongation of the thrombin time (TT), found as the only pathological result of screening assays on several occasions during his pre-operative laboratory workup. No history of bleeding had been recorded during his lifetime. The patient had a normal concentration of fibrin(ogen) degradation products and D-dimers. The presence of abnormal fibrinogen and abnormal fibrin polymerization was excluded as normal reptilase time; a normal amount of clottable fibrinogen and a concentration of fibrinogen antigen were determined. Due to prolonged TT, the mixing study was performed with normal plasma with several dilutions (1:1, 1:4 and 1:9) and with the in vitro addition of heparinase I (Hepzyme, Siemens Medical Solutions, Marburg, Germany), and protamine hydrochloride. TT was not corrected with the addition of Hepzyme, whereas the correction of TT was observed with increasing dilution of normal plasma and with the addition of protamine hydrochloride. Furthermore, TT was performed with 2 different assays with bovine and human thrombin that both yielded the prolonged TT with partial correction after mixing with normal plasma in a proportion of 1:1. As TT was corrected with the addition of protamine hydrochloride, this suggested that the cause of the prolonged TT was the presence of a heparin-like anticoagulant. During the follow-up of the patient, it was observed that he became and remained lupus anticoagulant– (LA) positive in a 2 year period.

PO-MO-117
Development of a parallel-line-based assay for the assessment of factor VIII inhibitor Bethesda titers

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The Bethesda-Nijmegen modification is currently the standard method for detecting FVIII inhibitors in patients. However, this method is labour-intensive and lacks specificity, especially in the lower range, resulting in unreliable data and spuriously positive results. The variability associated with these inhibitor assays is high (22–128% CVs), indicating the need for standardization and development of new assays to measure inhibitors accurately with reproducibility. The aim of this study was to assess if a parallel line–based bioassay could be carried out to accurately determine Bethesda titers in comparison to the routine clinical single-point Nijmegen-Bethesda assay. Anti-FVIII (monoclonal /polyclonal) antibody samples were diluted with FVIII-deficient plasma to create inhibitor test samples ranging from approximately 0.1 – 10.0 BU ml^{-1}. Equal volumes of the test samples and imidazole-buffered normal plasma (0.1 M, pH7.4) were mixed and incubated for 2 h at 37 °C. A mixture of imidazole-buffered normal plasma (0.1 M, pH7.4) and FVIII-deficient plasma was similarly prepared as the reference standard. Chromogenic potency assays were carried out on these samples to determine the % residual FVIII activity, using multiple dilutions of 1/50, 1/100, and 1/200 in a parallel line–based methodology. A single-point Nijmegen-Bethesda assay was also carried out concurrently for comparison. The inhibitory activity for both methods was determined according to the definition of the Bethesda titer. Sixty-nine percent of the assays were parallel ($P > 0.05$), and the inter-assay variation for each sample tended to be either equivalent or lower with the parallel-line method compared to the single-point method, with Bethesda titer samples of ≤ 0.2 BU ml^{-1} showing the highest variation. This parallel line–based assay was also used to assess patient samples which gave similar results. The data suggest that parallel line–based bioassays can be used to accurately determine the factor VIII inhibitory activity (Bethesda titer) of inhibitor samples.

PO-MO-118
Hemophilia: A prenatal diagnosis by factor VIII clotting activity using percutaneous umbilical blood sampling

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Objectives: Prenatal diagnosis of pregnant hemophilia A carrier or putative carrier, using phenotypic diagnosis with percutaneous umbilical blood sampling (PUBS).
Methods: Seventy-five hemophilia A carriers or putative carriers, aged 21–42 years, with male fetuses at risk of hemophilia were tested at 20–34 weeks gestation. We obtained fetal blood samples by percutaneous umbilical blood sampling (PUBS) and performed fetal hemoglobin alkali denaturation testing, discarding the first 0.5 ml of the blood sample to avoid amniotic fluid contamination. We then spun the samples at 2500 rpm for 20 min at 4 °C for coagulation factor testing. Immediately after spinning, we measured factor VIII and IX coagulant activities in an automated coagulometer by the 1-stage assay method.
Results: In the 75 male fetuses at risk for hemophilia we found 29 abnormal prenatal tests (FVIII:C <10 u dl^{-1}) and 44 normal prenatal tests (FVIII:C >25 u dl^{-1}). All the blood samples showed FIX:C <20 u dl^{-1}; if fetal blood samples had high FIX:C, there might have been maternal contamination. Only 2 fetuses fell in the FVIII:C 10–25 u dl^{-1} group; there was 1 fetus with FVIII:C 10 6u dl^{-1}, and we recommended testing again 1 month later, but the pregnant woman insisted on termination of gestation. The other fetus with FVIII:C 21.3 u dl^{-1} at 25 weeks became FVIII:C 50.2 u dl^{-1} 1 month later. All normal prenatal tests were followed up in all children, and there were no misdiagnoses.
Conclusion: When the linkage of factor 8 gene mutation is not informative or if patients are referred to the laboratories late in their gestation, testing factor VIII clotting activity using percutaneous umbilical blood sampling offers a quick and robust diagnosis method.

PO-MO-119
Hemophilia: A missed diagnosis

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A missed diagnosis of hemophilia can prove disastrous. To determine the extent of wrong or misdiagnosis among patients with hemophilia, we analyzed records of patients referred to our hemophilia centre since May 2008. Among 1026 hemophilia patients registered during this period, we come across 9 instances in which patients were wrongly diagnosed and received wrong treatment for some other disease. All patients visiting our hemophilia centre, irrespective of previous laboratory results, were subjected to fresh investigations after careful clinical work-up as per our protocol before being given a confirmed diagnosis of hemophilia. Nine instances of wrong diagnosis are presented in this paper. Two patients of hemophilia A were wrongly diagnosed as coagulation factor IX deficiency, whereas 1 hemophilia-B was receiving treatment as factor VIII deficiency case. In one, the wrong treatment lasted as long as 25 years of his life. Hemophilia A was misdiagnosed in 1 patient each with coagulation factor VII deficiency and von Willebrand disease. One patient was being treated as hemophilia A with factor VIII infusion alone, even though he had multiple coagulation factor deficiencies. One patient of hemophilia A was wrongly diagnosed with rheumatoid arthritis and treated as such for over a decade, including the unwarranted use of methotrexate. One patient of hemophilia B with pseudotumour was wrongly diagnosed with villonodular synovitis with septic arthritis. There was 1 instance of a patient with hemophilia A with old thigh bleeds and hematoma wrongly given a suspected diagnosis of sarcoma. These patients were not responding to the treatment being given to them. A diagnosis of hemophilia should be considered in patients presenting with chronic multiple joints or muscle disabilities. Reconfirm the type or the diagnosis of hemophilia if patient does not show the expected response to antihemophilic factor or the other treatment. A wrong diagnosis may breed avoidable morbidity.

PO-MO-120
Investigation of a prolonged aPTT: Data from a UK NEQAS for blood coagulation exercise

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The activated partial thromboplastin time (aPTT) is a useful screening test in the investigation of hemostatic abnormalities. A prolonged aPTT may be indicative of specific or multiple factor deficiencies, the presence of a factor-specific or non-specific inhibitor, or lupus anticoagulant. In the laboratory investigation of an abnormal aPTT, there are many algorithms, which may in some examples be guided by the clinical history of the patient. Proficiency testing program commonly assess 1 specific analyte in an external quality assessment (EQA) challenge. Such exercises rarely challenge a laboratory to determine their own course of investigation. We describe here a study in which participants were asked to investigate a prolonged aPTT and suggest a clinical diagnosis based on their investigation. A sample from a patient with severe hemophilia A was distributed with no clinical details, and participants were instructed to investigate the cause of the abnormal aPTT. One hundred eleven centres returned results, with 103 providing an overall diagnosis. Of these, 94 (91%) reported hemophilia A for the sample (1 of which reported a mild defect). A further 5 centres reported hemophilia A together with a lupus anticoagulant, 2 centres reported hemophilia A with a borderline or mild FXII deficiency, and 1 centre reported hemophilia A with a mild FIX deficiency. One centre reported the presence of a FVIII inhibitor. A wide range of approaches to investigation were observed (99 different patterns or combinations of tests were employed by laboratories in this exercise), with 71 centres (69%) performing FVIII, FIX, FXI, and FXII assays; 58 centres (56%) performing VWF assays; and 61 centres (59%) performing aPTT correction tests. The large majority successfully identified the deficiency in this patient, despite variation in reported results (for example, FIX:C range 29–94 u dl^{-1}, FXI:C range 56–93 u dl^{-1}). Further challenges of the abilities of laboratories in real-life scenarios will support improvement in diagnostic accuracy of hemostatic investigations.

PO-MO-121
Can thrombin generation (TG) be used as a predictive tool for guiding treatment in hemophilia patients with inhibitors?

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Therapy for hemophilia patients with inhibitors is still a challenge. The large inter- and intrasubject variability detected following treatment with various bypassing agents may require individually tailored protocols. Recalcification-induced thrombin generation (TG) is a highly sensitive method for monitoring hemostasis in hemophilia plasma. Thus,

in order to individually define the best hemostatic regimen for our patients with inhibitors and further assess therapy, we conducted a TG-guided study.
Patients and Methods: Platelet poor plasma (PPP) from 18 patients (aged 0.5–62 years) with severe hemophilia A and inhibitors (1–300 BU) was spiked with FVIII (up to 200%), rFVIIa (0–6.8 μg ml^{-1}), and FEIBA (0–0.8 U ml^{-1}). TG was induced by recalcification of PPP. Based upon TG parameters measured, an algorithm for future individually tailored therapy was suggested. Response to the suggestive treatment was monitored.
Results: No measurable TG was detected in any patients prior to the addition of any bypass agent or FVIII. Ex vivo spiking of patients' PPP with increasing concentrations of rFVIIa and/or FEIBA yielded individual TG responses. In some patients, low-dose combination of FEIBA and rFVIIa induced the highest TG. Spiking with up to 200% FVIII alone failed to induce any TG in most patients, yet surprisingly, in some high-responding inhibitor patients, addition of FVIII alone to the plasma induced TG that was augmented in the presence of rFVIIa. All patients responded well to therapy regimens based upon their ex vivo TG assays. No severe adverse events or any clinically significant complications were noted.
Conclusions: Based upon our experience, we suggest that recalcification-induced TG assays, used for monitoring hemostatic response to FVIII, rFVIIa, and FEIBA in hemophilia A patients, may be applied as a beneficial predictive tool for clinical decision making and individual therapy tailoring of inhibitor patients.

PO-MO-122
New quantitative aPTT waveform analysis on Behring coagulation system

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Coagulation tests, such as prothrombin time (PT) and activated partial thromboplastin time (aPTT), measure clot formation as endpoint, when only 5% of all physiologically relevant thrombin is formed, i.e., the whole coagulation process is not assessed. Advanced automated photo-optical coagulometers measure the entire process of clot formation over time and collect optical data in a reaction curve. This advantage offers the possibility of obtaining additional information, because the shape and slope of the reaction curve reflect the function of the ensemble of plasmatic pro- and anticoagulant factors. A new quantitative aPTT waveform analysis was developed from a single aPTT measurement (Actin FS as reagent on the Behring coagulation system, Siemens Medical Solutions, Germany), with 2 different evaluation modes (drifting baseline [DB] and point-of-inflexion [PI]) that enabled the calculation of 3 quantitative parameters: DELTA (aPTT-PI minus aPTT-DB), RATIO-1 (aPTT-PI/aPTT-DB), and RATIO-2 (DELTA/aPTT-DB). The performance of the waveform analysis was examined in 101 healthy male subjects and 100 hemophilia A patients (56 severe and 44 non-severe), by comparing the results with those obtained for FVIII clotting (FVIIIclot) and chromogenic activity (FVIIIch). Significant differences ($P < 0.001$) were found for all 3 parameters between healthy subjects and patients, as well as between severe and non-severe hemophilia A patients. Very good correlation of 3 quantitative waveform parameters was obtained for FVIIIclot and FVIIIch in all examined samples and all patients (r from -0.682 to −0.882 and from −0.712 to −0.872, respectively), whereas no correlation was found in healthy subjects. According to ROC analysis, all 3 waveform parameters allowed distinguishing between healthy subjects and patients (AUC 0.942–0.994), as well as between severe and non-severe hemophilia A patients (AUC 0.731–0.768). We can conclude that this new waveform analysis derived from the routine aPTT assay could be an excellent laboratory tool for assessing the coagulation process, as well as for obtaining additional information about hemophilia patients.

PO-MO-123
Utility of new quantitative aPTT waveform analysis in laboratory management of hemophilia A patients

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Diagnosis of hemophilia A is usually made by the direct measurement of FVIII, using either the clotting (FVIIIclot) or chromogenic assay (FVIIIch). The obtained activity allows categorization of the disease severity, but it has a relatively poor correlation with the clinical phenotype. In contrast, waveform analysis as a global coagulation assay seems to display a relatively good correlation with the bleeding tendency. In this study, we compared a newly developed quantitative aPTT waveform analysis with standard laboratory assays (FVIIIclot and FVIIIch) in hemophilia A patients divided into 2 groups (37 severe, 44 non-severe), and correlated these results with known clinical parameters (age at first joint bleed, number of joints with hemophilic arthropathy, number of annual joint bleeds, and annual FVIII consumption). Quantitative aPTT waveform analysis was performed with Actin FS on the Behring coagulation system (Siemens Medical Solutions, Germany) by using 3 parameters (DELTA, RATIO-1, and RATIO-2) obtained from the single aPTT measurement with 2 evaluation modes. The best correlation in all patients was obtained for DELTA and FVIIIclot/FVIIIch (r = -0.850 and −0.858, respectively), whereas correlation coefficients for RATIO-1 and RATIO-2 were −0.685 and −0.697, respectively. Similarly, the best correlation with clinical parameters was obtained for DELTA, especially for the number of joints with hemophilic arthropathy (r = 0.689) and annual FVIII consumption (r = 0.667). The cut-off value of >9.7 s for DELTA, obtained by ROC analysis, allowed the division of patients into two groups that statistically differ in all clinical parameters, with sensitivity and specificity of 97.3% and 93.2%, respectively. The results obtained by new quantitative aPTT waveform analysis were at least equivalent to those obtained by standard laboratory methods (especially for DELTA). The simplicity of this new analysis, as well as the cost benefit of measuring routine aPTT, make this approach a reasonable and promising tool for assessing coagulation in hemophilia patients.

PO-MO-124
Validating the role of thrombelastography and the thrombin generation assay for routine clinical care in children with hemophilia

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Bleeding patterns in hemophilia patients vary markedly, even within the group of patients with comparable factor VIII and IX levels. While laboratory assays play an essential role in the clinical management of patients with hemophilia, no single assay has been shown to reliably monitor therapy. Current available hemostasis assays measure levels and/or activities of individual factors and have largely been disappointing. The biologic factors that underlie this phenotypic variability remain poorly understood, but evidence is being reviewed that supports a role for platelets and platelet-related factors in modifying bleeding tendency. Global coagulation tests may show a better correlation with phenotype in hemophilia than traditional coagulation tests. These include the calibrated automated thrombin generation assay (CAT) and modified thromboelastometry (TEG) using low tissue factor. The present study evaluates dynamic coagulation profiles and thrombin generation in whole blood (WB) and platelet-rich and -poor plasma from children with hemophilia before (mean ETP[PPP] 1002 nmMmin, ETP[PRP] 526 nMmin) and after FVIII substitution (ETP[PPP] 1220 nm min, ETP[PRP] 1296 nm min). The correlation of thrombin generation parameters for PRP and PPP show significant differences between patient groups (hemophilia A patients before [n = 76] and after substitution [n = 24] and control samples [n = 74]). TEG parameters before and after substitution are compared. Significantly, differences are seen for clotting time, clot formation time, and the maximum of the first derivative of the clot curve. The data suggest that thrombelastography and the thrombin generation assay may be helpful for predicting individual bleeding risk and for providing individually tailored regimens. Extensive evaluation in clinical practice is required.

PO-MO-125
Modified inverse shifting-PCR (IS-PCR) to investigate intron 22 inversion

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It is well known that F8 intron 22 inversion is the most important causative mutation in approximately 45% of severe hemophilia A patients. Intron 22 inversion occurs as a result of homologous recombination between copies of a repeated DNA sequence, the intron 22 homologous region (int22h), 1 copy located within the F8 intron 22 (int22h-1), and the other 2 extragenic distal inversely-oriented copies (int22h-2 and int22h-3). The frequency of this chromosomal rearrangement suggests that in families with severe hemophilia A, the affected male(s) should first be tested for the presence of the inversion. Since 1993, when Lakich described this mutation for the first time, many methods have been developed to identify it. The inversion is detectable by Southern blotting or by long polymerase chain reaction (PCR); more recently Rossetti (*JTH* 2008) developed an inverse-shifting PCR method that has proved to be reliable in a diagnostic setting. It comprises BclI restriction enzyme digestion of genomic DNA, followed by self-ligations of restriction fragments and multiplex-PCR analysis. Products are then visualized by standard gel electrophoresis. Our study suggests some modifications of the original protocol that seem to improve the PCR performance. The quality of blood samples and DNA is fundamental. DNA extraction is made with Gentra Puregene Kit (Qiagen). We amplified circularized DNA with 1 U of AmpliTaq Gold Polymerase (Applied Biosystems). Thermalcycling conditions involved the use of touchdown PCR, a modification of conventional PCR that may result in a reduction of non-specific amplification. We tested IS-PCR modifications on 10 new cases of severe affected hemophilia A patients; in 4 of them, we identified intron 22 inversion. We also tested DNA samples extracted from old blood samples conserved at -80 °C for at least 2 years, but with unsuccessful results. We also performed the protocol on 4 suspected carriers: 2 were confirmed with intron 22 inversion in heterozygosis.

PO-MO-126
Molecular analysis of mild hemophilia patients: The experience of a single centre

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According to the Scientific and Standardization Committee of the International Society on Thrombosis and Hemostasis (ISTH), mild hemophilia A or B is defined as a reduction of clotting factor VIII (FVIII) or factor IX (FIX) levels to >0.05–0.40 IU Ml^{-1}. Although 50% of affected hemophilia patients have a mild phenotype, published data on these patients are nowadays insufficient, and mutations are occasionally described. In our study, we characterized mild hemophilia patients followed at Hub Haemophilia Centre of Parma: 74 patients (40 index cases) with hemophilia A and 7 (5 index cases) with hemophilia B. We performed molecular analysis on the DNA extracted from EDTA peripheral blood samples; polymerase chain reaction (PCR) was performed on all 26 F8 exons, including intron/exon boundaries as well as 5' and 3' regulatory gene regions. Amplicons analysis was performed with denaturing high performance liquid chromatography (DHPLC) and then with direct sequencing on samples with a DHPLC profile different from that of a normal control. One hundred wild-type chromosomes from healthy control subjects, without bleeding defects but from the same ethnic background, were investigated to exclude that a new variant could represent a common polymorphism. Exon 13 duplication was performed according to Acquila (*Haematologica* 2004). Mutations were classified as suggested by Oldenburg (*Haemophilia* 2002). Causative mutation was identified in 35 of 39 families with hemophilia A (detection rate 87%). The molecular analysis has not yet been terminated. We have found 22 different mutations

(20 missense, 1 in promoter region and [?] exon 13 duplication). Some of them are involved in inhibitor development (R550C, R612C, R2169H, and V2251A). All 9 patients with mutation in the promoter region show DDAVP resistance. In conclusion, genetic screening is a useful tool for a clinical overview of patients with mild hemophilia.

PO-MO-127
Screening of bleeding disorders using a thrombelastometric thrombin generation assay

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Aim: Thrombin generation tests (TG) measure the overall potential of the coagulation system. There are many open questions regarding the practicability of different tests and interpretation of the results. TG is a complex and time-consuming procedure, and the required equipment is not available in all coagulation labs. Based on this, we will verify the hypothesis that the results from platelet-poor (PPP) or platelet-rich plasma (PRP) measured as classical TG can be transferred to whole blood measurements at rotational thrombelastography (ROTEM) using a different measuring principle. This comparison is provided by the use of one reagent in all measuring systems.
Methods: TG was measured using a modified endogenous thrombin potential (ETP) (Siemens Healthcare Diagnostics) in PPP, Technothrombin® thrombin generation assay (TGA) (Haemochrom) in PPP and PRP, and modified ROTEM (Tem International) using reagents from the TGA assay in PPP, PRP, and whole blood. TG results in samples from patients with hemophilia A (n = 182) or B (n = 18), hemorrhagic disorders (n = 30), and thrombophilia (n = 61) were compared to those of healthy donors (n = 38).
Results: The ETP assay (low tissue factor, TF) allows discrimination between patients with bleeding tendency and healthy donors for the area under the curve and the thrombin peak. TGA shows differences between both groups with all reagents (low and high tissue factor) and all parameters (lag phase, Vmax, time to peak, velocity index). Using the TGA reagents at ROTEM showed the same pattern for clotting time, angle, and time to peak; maximum clot firmness is not usable for this application. Additionally, in most cases the results correlated with the severity of the underlying defect.
Conclusions: The adaptation of the TGA assay on the ROTEM analyzer enables a simple and reliable method to measure TG. The data allow discrimination between patients with bleeding disorders, especially hemophilia, and healthy controls. Furthermore, it is possible to discriminate between patients with different severities of the underlying defect. The effect of platelets on the results was lower than expected. In patients with hemophilia B we measure a higher contribution of platelets to TG than in hemophilia A patients.

PO-MO-128
Comparison of immunologic and coagulometric FVIII inhibitor assays

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Introduction: The determination of inhibitors is an ongoing problem in our daily routine. The Bethesda and Nijmegen tests are coagulometric tests for describing an immunological reaction. The tests are positive in cases of inhibiting antibodies against FVIII. To recognize inhibiting and non-inhibiting antibodies, we need immunological tests such as enzyme-linked immunosorbent assay (ELISA). Therefore, we tested the first commercial available assay and compared the results with classical tests.
Methods and Patients: We investigated 75 patients from our centre with the GTI FVIII antibody screen test (GTI Diagnostics Waukesha, USA), and the Bethesda and Nijmegen assays. All patients had severe or mild hemophilia A (6 of them with inhibitors) and 2 patients with acquired inhibitors against FVIII. In cases with positive inhibitors, we measured both methods for the whole observation period.
Results: We found comparable results in both assays. All 8 inhibitor patients were recognized in both assays; all patients without inhibitor were negative in both assays. One patient with hemophilia A had a borderline value in the GTI test. But we obtained differences in the sensitivity of the test systems with lowest sensitivity for the BE assay and the highest sensitivity for the immunological assay. The immunological assay measured the antibody before it was detectable in the BE assay (1 patient) and the immunological assay showed a prolonged positive result in the 2 patients with acquired inhibitor.
Conclusions: We should reevaluate our tests measuring inhibitors against coagulation factors. Immunological assays are not influenced by von Willebrand factor. A further advantage is a higher sensitivity. But immunological assays are influenced from the antibody bound on the microtiter plate, a major disadvantage. Acquired inhibitors show different kinetics in comparison with inhibitors in patients with hemophilia.

PO-MO-129
Evaluation of hemostatic effect of BAY 86-6150, a recombinant FVIIa variant, in antibody-induced hemophilic whole blood under flow conditions

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BAY 86-6150, an activated recombinant factor VII (rFVIIa) variant, is currently in clinical development as a therapeutic agent for patients with hemophilia and anti-FVIII inhibitors. Our previous studies have shown that BAY 86-6150 exhibits enhanced activated factor X (FXa) generation on the surface of activated platelets in vitro and increased circulation time resulting in prolonged efficacy in vivo. To further investigate the antihemophilic properties of BAY 86-6150, we evaluated the effect of BAY 86-6150 on thrombus formation under whole blood flow conditions with a high shear rate (1500 s^{-1}) using an in vitro perfusion chamber system. Whole blood was perfused over a collagen-coated glass plate in a parallel-plate flow chamber, and the thrombus formation process on the collagen surface was monitored by confocal laser scanning microscopy. The intrathrombus fibrin deposition was detected by fluorescently-labelled antifibrin-specific monoclonal antibody. The ability of BAY 86–6150 to promote clot formation in whole blood from healthy donors rendered hemophilic by antifactor-VIII antibody was investigated. Both BAY 86–6150 and wild-type rFVIIa increased the fibrin deposition within hemophilic thrombi in a dose-dependent manner, nearly normalizing at concentrations >0.3 mg ml^{-1} (~6 nM). Immunostaining of platelet thrombi with anti-FVII antibody detected a 5–10-fold higher amount of FVII in thrombi generated in the presence of BAY 86–6150 relative to thrombi generated by wild-type FVIIa under such flow conditions. This is consistent with the higher affinity of BAY 86-6150 for activated platelets. Furthermore, the fibrin deposition and platelet thrombi induced by BAY 86–6150 in antibody-induced hemophilic blood are independent of tissue factor under flow conditions. Our results demonstrated that BAY 86-6150 is a unique FVIIa variant with enhanced efficacy, particularly at sites of vascular injury where hemostatic platelet thrombi are formed.
Conflicts of Interest: Jian-Ming Gu, Ji-Yun Kim, Derek S. Sim, Volker Laux, John E. Murphy, and Timothy Myles are employees of Bayer HealthCare LLC.

PO-MO-130
Investigation of mechanisms of hemophilia A bleeding phenotype formation using thrombin generation, thrombodynamics, and thrombelastography

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Objectives: To explore the possible mechanisms of different bleeding hemophilia A (FVIII<1%) phenotype formation, using various types of modern coagulation tests.
Methods: Ten severe-bleeding patients (SB) on FVIII concentrate therapy and 10 mild-bleeding patients (MB) with episodic FVIII injections were included in the research. The wash-out period was 5 days. Thrombelastography was performed on whole blood in the presence of tissue factor (TF). TF or kaolin-induced thrombin generation (TG) was investigated in platelet-poor plasma (PPP). We also measured TG in PPP with thrombomodulin addition. We used platelet-rich plasma (PRP) to investigate platelet-dependent TG with our original technique. In this modification, the TG curve has 2 peaks. The first one is formed mostly by plasma phospholipids and the second by platelets. This effect is reached by increasing the DMSO amount (1.6%), which prolongs platelet activation, allowing separation of the platelet and plasma contribution to TG. Thrombodynamics (spatial clot growth) was made in platelet-free plasma with or without thrombomodulin. Also aPTT and FVIII:C were measured.
Results: The second peak amplitude in PRP TG in MB was significantly higher (42 ± 11 nm) than in SB (28 ± 10 nm, $P < 0.02$). Only 3 of the SB this parameter had more than 30 nm, while it was the lower boundary for MB. Other parameters of this and other tests did not differ between MB and SB.
Conclusion: Our results can testify that the most patients with mild bleeding have higher platelet procoagulant activity than severe-bleeding patients. Other hemostasis mechanisms like clot density or plasma coagulation might not play any role in formation of hemophilia phenotypes.
Contribution to the Evidence Base of Hemophilia and Bleeding Disorders: Our research can help in better understanding the compensatory mechanisms of hemophilia that probably will predict the manifestation of the disease in hemophilic children to determine the tactics of future therapies.

PO-MO-131
Stability of clotting factors in fresh frozen plasma in the University Teaching Hospital of Yaoundé, Cameroon

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Background and Objectives: In most hospitals of Cameroon, household freezers are frequently used for the storage of blood products, including fresh frozen plasma (FFP). This study investigates the stability of clotting factors in FFP under these storage conditions.
Materials and Methods: The study was conducted in the University Teaching Hospital of Yaoundé. In 10 units of FFP, clotting factor levels were measured in duplicates on the day of collection (D0), then on D30, D60, and D90, using the STart4 coagulometer and reagents (Diagnostica Stago, Asnière, France).
Results: All factors except FVII showed a statistically significant drop in values between D0 and D30. FXI maintained more than 70% of the mean initial value until D30, while FVIII levels dropped to lower than 70% of the initial value (111.43 ± 27.01% to 60.87 ± 32.79) by D30 (Table 1).

Table1: Mean levels of clotting factors at various intervals (D=Day)

Factors	Mean Levels D 0	Mean Levels D 30	Mean Levels D 60	Mean Levels D 90
Factor I(g L^{-1})	2.27 ± 0.34	1.66 ± 0.53	1.69 ± 0.53	1.63 ± 0.52
Factor V (%)	81.18 ± 14. 69	56.91 ± 10.95	64.35 ± 15.89	66.04 ± 17.13
Factor VII (%)	75.37 ± 21.32	69,72 ± 17,84	64.63 ± 15.54	75.64 ± 17.95
Factor VIII (%)	111.43 ± 27.01	60.87 ± 32.79	67.32 ± 21.48	49.92 ± 19.79
Factor IX (%)	118.34 ± 30.45	87.97 ± 22.47	97.96 ± 12.97	76.75 ± 14.98
Factor XI (%)	116.41 ± 29.35	90.40 ± 11.96	74.02 ± 9.12	66.53 ± 17.37

Conclusion: FVII alone showed stability throughout the study period, but there was significant perturbation of the other clotting factors. Factor VIII, on the other hand, deteriorated rapidly under these conditions. The indications of these products must be adapted according to the conditions of storage in our settings.

PO-MO-132
Thrombelastography as screening test for the diagnosis of Scott syndrome
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Background: Scott syndrome (SS) is a rare bleeding disorder, characterized by impaired platelet procoagulant activity (PCA). The laboratory tests for its diagnosis are available in specialized laboratories, and sometimes only for research purposes.
Case Report: A 35 year-old male patient was referred to our centre for diagnosis of hemostasis disorder. He had a history of bruises and hematomas since childhood. Blood transfusion was required after postectomy and crural hernioplasty. His family history for bleeding was negative. Laboratory investigation showed normal measurement of all coagulation factors, including VWF antigen/activity, normal evaluation of fibrinolytic system (alpha2-antiplasmin, plasminogen, and euglobulin lysis time), as well as platelet aggregometry (ADP, ADR, arachidonic acid, collagen, and ristocetin). Thrombelastography (TEG) was hypocoagulant (prolonged R and K; reduced angle MA, G, TG, MRTG, and TMRTG), which led us to consider abnormality of PCA. Then a series of TEGs was performed, mixing total blood (patient and control) with platelet-poor plasma (PPP) and platelet-rich plasma (PRP) of the patient and control. When PRP (control) was added to patient's total blood, TEG was normalized, suggesting PCA dysfunction, and the hypothesis of SS was made. A PCA test was performed using washed platelet and activated prothrombinic complex, resulting in reduced PCA. After that, we performed the phosphatidylserin expression by flow cytometry, using annexin V and a thrombin generation assay (TGA) with control PRP, confirming the diagnosis of SS.
Conclusion: SS is a rare disease, and usually confirmatory tests are not part of the routine, even in specialized laboratories. TEG using mixtures of total blood and PRP of patient and control can be a simple and less expensive alternative method for screening impaired PCA in patients with bleeding disorders. In this case, such an approach helped in elucidating the diagnosis when sophisticated tests such as annexin V and thrombin generation were not promptly available.

PO-MO-133
Discrepancy of recombinant factor IX potency estimates between clotting and chromogenic assays
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Several recombinant FIX (rFIX) or modified rFIX products are being produced, and accurate potency estimation of these is important for comparability between products. Results from the collaborative study for the replacement of the 3rd International Standard (IS) for FIX Concentrate suggested there was a discrepancy in potency estimates by clotting and chromogenic methods, when the rFIX candidate was assayed against the plasma-derived FIX (pdFIX) IS. This study explores the potential differences between methods used for potency estimates for recombinant and plasma-derived FIX. Five batches of rFIX (BeneFIX), each paired with a batch of pdFIX, were evaluated against the 4th IS FIX concentrate by activated partial thromboplastin time (aPTT) clotting assay and specific functional chromogenic assays. The potency of BeneFIX measured by Hyphen chromogenic assay was consistently about 70–75% of the clotting potency (average 78 ± 4.0 and 108 ± 6.0 IU ml^{-1}, respectively, for the Hyphen chromogenic and clotting assay). A similar trend for BeneFIX was observed using another chromogenic assay kit (Rossix). These differences were not observed with pdFIX, which had similar potencies (averages of 96–100 (±3.6–7.6) IU ml^{-1}) regardless of assay method. These vast differences in rFIX potencies between methods could have an impact on both potency assignment of products and patient dosing regimens. A further investigation was conducted by re-assaying one batch of BeneFIX by both methods, using either the 4th IS or an NIBSC rFIX reference material. When the IS (a pdFIX) was used, the potencies were 117 and 87 IU ml^{-1} for the clotting and Hyphen assays, respectively. When the rFIX reference was used, the potencies were 115 IU ml^{-1} in each case. This clearly demonstrates that a pdFIX standard may not be appropriate when assaying rFIX and suggests that a rFIX standard may be useful to minimize potential assay discrepancies in potency estimates of rFIX.

PO-MO-134
Measurement of post-infusion recombinant factor IX activity by clotting and chromogenic assay
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Debates are ongoing regarding the appropriate reference standard for measurement of FIX activity in post-infusion plasma. To explore this, plasma samples were obtained from patients after infusion with recombinant FIX (BeneFIX, $n = 3$) or plasma-derived FIX (Replenine, $n = 1$). Potency estimates were carried out using 1-stage clotting or chromogenic assays (Hyphen and Rossix) and using either the 4th International Standard (IS) FIX concentrate, the 4th IS Factors II,VII,IX,X Plasma, or an NIBSC recombinant FIX (rFIX) preparation as the standard. Plasma from the Replenine-treated patient showed reasonably good agreement in potency, regardless of method or standard used. This was in contrast to the BeneFIX post-infusion plasma, which differed according to method and standard used. In this case, the potency estimates from the chromogenic assays were lower than the clotting potency (65 ± 8% and 46 ± 8%, respectively, for Hyphen and Rossix assays) when using the Concentrate IS. Using the Plasma IS, there were still differences between the methods (percentage of clotting potency being 76 ± 11% and 54 ± 8% for Hyphen and Rossix, respectively) and very little overlap in potency between any methods. However, using NIBSC rFIX as the reference, the differences between methods were reduced, with potencies around 81 ± 9% and 85 ± 15% of the clotting potency for Hyphen and Rossix chromogenic assays, respectively. Overall, there was closer agreement between the methods than when the Concentrate IS or Plasma IS were used as the standard. This study clearly demonstrates that in plasma from patients treated with rFIX, better agreement between methods is found when using an rFIX reference material. It also shows the importance of choice of method and standard when monitoring patient therapy ex vivo, to ensure consistency of measurement. Further investigation is required to determine the usefulness of an rFIX standard.

PO-MO-135
Enzymatic release and detection of galactose-alpha-1,3-galactose (a-Gal) in recombinant FVIII products
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A recombinant factor VIII-Fc fusion molecule (rFVIIIFc), comprising a single molecule of B-domain deleted FVIII linked to the N-terminus of the Fc domain of IgG1, is a long-lasting FVIII that is currently being investigated in a registrational study in hemophilia A patients. The current commercially available recombinant FVIII products are manufactured in either Chinese hamster ovary (CHO) or baby hamster kidney (BHK), hamster-derived cell lines. In contrast, rFVIIIFc is manufactured using the human cell line HEK293. Therefore, it is of interest to compare the FVIII post-translational modifications (PTMs) of products derived from the various cell lines. The terminal galactose-alpha-1,3-galactose (a-Gal) antigen is produced by all mammals except humans, Old World monkeys, and apes. Antibodies against this antigen constitute ~1% of all circulating antibodies in humans[1]. Recently, it was reported that CHO cell lines are able to produce a-Gal[2]. Since rFVIIIFc is produced in a human cell line, rFVIIIFc is not expected to contain this antigen. The goal for the current study was to determine the presence or absence of a-Gal in various commercially available recombinant FVIII products as well as rFVIIIFc. The a-Gal moieties were released from FVIII using a-(1–3,4,6)-galactosidase, labelled by 2-aminobenzoic acid (2-AA), and then quantified by reversed-phase **high-performance liquid chromatography** (RP-HPLC), using fluorescence detection. Purified galactose was used to generate a calibration curve. The limits of quantitation (LOQ) and detection (LOD) of a-Gal were determined to be 0.2 pmol and 0.1 pmol respectively. As expected, a human glycosylation pattern was detected in rFVIIIFc. In contrast, a-Gal was detected in Xyntha®, Advate®, and Kogenate®. The impact, if any, of the presence of these antigens on the immunogenicity profile of FVIII is not currently known.
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23-MILD HEMOPHILIA

PO-TU-120
Caring for mild hemophilia: A challenge to comprehensive hemophilia treatment centres

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Background: Persons with mild hemophilia face challenges which are distinct from those of severe or moderate hemophilia, due to differences in bleeding phenotype and treatment. An optimal approach to providing care for mild hemophilia has many uncertainties for comprehensive hemophilia treatment centres (HTC).
Objective: To explore patients' attitudes to and experiences of living with mild hemophilia.
Methods: Forty-two adult males with mild hemophilia registered with the Southern Alberta Rare Blood and Bleeding Disorders Program were invited to participate in semi-structured interviews. Ten individuals consented, with 8 transcripts available for analysis. Two raters reviewed and coded the data.
Results: Common themes identified included the perception that while mild hemophilia does not affect daily lives, it paradoxically influences career choices and quality of life; that regular follow-up at HTC is not needed unless surgery is required; that treatment is needed only for invasive procedures. There was also uncertainty about treatments for mild hemophilia. HTCs were identified as the primary source of disease education. One participant recognized the importance of a multidisciplinary approach to care.
Conclusions: Themes identified in this study suggest a disconnect between patients' attitudes toward living with mild hemophilia (generally positive and not impacting their lives) and actual life experiences or choices. With additional research efforts focused on the challenges experienced by the mild hemophilia population, HTCs will be better equipped to develop effective education and treatment programs to target these patients. As the primary source of education for persons with mild hemophilia, HTCs must ensure that these individuals have the knowledge and tools needed to improve disease ownership and coping. With better understanding of their condition, relationships between persons with mild hemophilia and HTCs may be strengthened, leading to more consistency with follow-up and earlier involvement of the clinic during bleeding episodes as well as prior to invasive procedures.

PO-TU-121
A new self-assessment pathway tool for young men with mild hemophilia A and B who experience musculoskeletal bleeds

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Purpose: We undertook this study to develop and evaluate a new self-assessment tool for people with mild hemophilia (PWMH) to apply to the management of musculoskeletal injuries and thus potential bleeds.
Relevance: In our previous qualitative study involving 18 young men with mild hemophilia from across Canada, we found that young men with mild hemophilia were missing key information about how to recognize serious bleeds and were resistant to conferring with their hemophilia care team about potential bleeds. Often, individuals presented only several days after known trauma and onset of symptoms, which can result in the use of large amounts of clotting factor concentrates, significant impairment, and lengthy rehabilitation. Evidence and clinical experiences suggest that these consequences could be avoided if treatment were initiated sooner.
Methods: The printed tool was mailed to and evaluated by participants of the previous study and others who volunteered to participate. Using telephone interviews, we sought feedback about their impressions of the tool.
Analysis: Commonly raised participant feedback was used to revise the tool. Suggestions for ways to encourage tool accessibility and use were explored.
Results: Feedback from participants led to the refinement of the self-assessment tool. This tool can be adapted as an application for a smartphone or tablet to further enhance accessibility.
Conclusions: Our overall project outcome is the creation of a user-friendly, relevant tool to help PWMH to perform self-assessment and manage their injuries and bleeds in a timely fashion. Future studies are planned to evaluate the long-term effectiveness of this tool.

PO-TU-122
Determinants of the response to DDAVP in mild hemophilia A patients

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Background: (DDAVP) is a cheap and potentially safer alternative to FVIII concentrate for the treatment of bleeding in persons with mild hemophilia A. There is a great inter-individual variation in DDAVP response. The aim of this study is to identify clinical and genetic determinants that can predict the DDAVP response.
Method: In this cross-sectional multicentre study, performed by the INSIGHT consortium, we aimed to collect data on potential determinants and DDAVP response. ''Good clinical response'' to DDAVP was defined as FVIII:C>50 IU ml^{-1}, ''no response'' as FVIII:C<30 IU ml^{-1} 1 hour after DDAVP. Data was analyzed by univariate logistic regression. We present the results of the first 244 persons, treated in 3 centres in the Netherlands.
Results: Median age at test was 31 years (IQR 15–47), median FVIII:C baseline level 18 IU ml^{-1} (IQR 12–26). Good response was associated with age >18 years (unadjusted OR 2.4; 95%CI 1.4–4.4), FVIII:C baseline level >15 IU ml^{-1} (unadjusted OR 10.8; 95%CI 5.7–20.4) and good response in family members (unadjusted OR 22.1; 95%CI 8.4–58.1). F8 genotype (location missense mutation) was associated with DDAVP response: the largest proportion of good responders was present among persons with a mutation in the A2 domain (75%), and the smallest proportion of good responders was present among persons with a mutation in C1 domain (40%). The group with a mutation in C2 domain had the largest proportion of non-responders (40%). The smallest proportion of non-responders (4%) was present in the group with a mutation in the A2 domain. A mutation at the von Willebrand factor binding site (Pro2300Leu, Arg2159Cys, Arg2150His, Asn2129Ser) was associated with poor response, unadjusted OR for good response: 0.2, 95%CI 0.07–0.52.
Conclusion: Good response to DDAVP in persons with mild hemophilia A is associated with higher age, higher basal FVIII:C, location of F8 missense mutation in the A2 domain, and good response in family members.

PO-TU-123
A novel mutation for factor XI deficiency in a Dutch family

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Introduction: Factor XI (FXI) deficiency is an autosomal inherited coagulation disorder characterized by bleeding mainly associated with injury or surgery. Most of the FXI gene mutations are found in Ashkenazi Jews. We describe here a 70 year-old Dutch woman with a FXI level of 30%, consistent with a mild, heterozygous deficiency. She was diagnosed after bleeding following ophthalmic surgery and hip replacement. Total bleeding score was 10 (Tosetto, 2006). Although it is generally believed that the hemostatic level of FXI is between 15 and 20%, there is also a weak correlation between the FXI level and the bleeding tendency.
Purpose: To determine the molecular background of factor XI deficiency in a Dutch family.
Methods: FXI levels were determined by a plasma clotting assay (Siemens). Direct sequencing analysis of all 15 exons and flanking introns of FXI gene was performed to detect causative mutations. The patient, 2 sisters, 2 daughters, and 1 niece were tested.
Results: The proband, her dizygotic twin sister (FXI 45%) and her niece (FXI 27%) were all affected with a novel heterozygous missense mutation resulting in a threonine to proline substitution at position 42 within exon 3. The other 3 family members were asymptomatic, had normal FXI levels and were not affected with a mutation in FXI gene. Multiple alignment analysis showed that threonine is highly conserved among other species. A computer-based model (2f83) was used to evaluate the effect of the novel mutation on the molecular structure of FXI. Threonine 42 interacts with phenylalanine 12, serine 78, and valine 59 through strong hydrogen bonds. After substitution, only an interaction remains with valine 59. Furthermore, proline could result in steric hindrance with phenylalanine 41.
Conclusions: We have identified a novel mutation that was associated with factor XI deficiency in a Dutch family.

24-MOLECULAR GENETICS OF BLEEDING DISORDERS

PL-TH-02.1
Gene therapy for severe hemophilia B
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A non-pathogenic, non-integrating adeno-associated virus (AAV) was used as the vector to introduce therapeutic DNA. Progressive dosing according to response was given to 2 subjects at each of 3 levels: low, intermediate, and high. The first subject was treated in April 2010 and has maintained factor IX 2% with cessation of prophylaxis. The next subject, although achieving a similar factor IX level, was older with badly damaged joints and has had to continue prophylaxis, but at wider intervals than before treatment with the vector. The third subject has been able to stop twice-weekly prophylaxis, and on average now treats himself once every 5 weeks with a baseline level of 2%. The fourth subject's factor IX level rose to 4 IU dl^{-1} and was maintained for 3 months, but has subsequently declined to 3%. He is able to play competitive sports now without prophylaxis or bleeding. The fifth subject developed elevated AST and ALT at 8 weeks post infusion. This responded to a short course of steroids and the subject maintained a factor IX level of 3% for 10 weeks with no further prophylactic therapy but subsequently the level has fallen to 1% with a return of spontaneous bleeding episodes. The sixth subject developed elevation of AST and ALT from baseline at week 9, at levels within the normal range. He was started on a short course of steroids. He has been off prophylaxis since January 20, 2011, plays vigorous sports, and is bleed free. His factor IX level was 4 IU dl^{-1} at 10 months after gene therapy. Further subjects are being recruited to a modified treatment protocol.

S-MO-03.1-1
Personal reflections on the discovery and the clarification of von Willebrand disease
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In 1924, a woman visited Dr. Erik von Willebrand in the Diakoni Hospital of Helsinki with her two little girls, 5 year-old Hjördis and 3 year-old Greta, both of whom suffered from severe bleeding tendencies. The family came from Föglö of the Åland Islands. The mother had by then already borne 11 children; of these, 3 girls had died of severe bleeding before the age of 4. Greta died at age 5 of uncontrolled bleeding, and Hjördis died of menstrual bleeding at age 13. Of the woman's further children, 4 boys and 1 girl had some bleeding symptoms, and only one, a girl, never had any bleeding symptoms. Von Willebrand investigated the whole family (and related families) and in 1926 wrote a beautiful paper about the bleeding symptoms, the hemostatic findings, and the inheritance: In the two girls the bleeding time was much prolonged, the coagulation time and the clot retraction, however, normal. The capillary resistens assay was positive; von Willebrand was not sure what this meant but suggested that it was due to platelet dysfunction. The inheritance was dominant sex-linked. The disease was named "hereditary pseudohemophilia" and, in the 1960s, "von Willebrand's disease." Further investigations by von Willebrand and researchers from Åland, Germany, and Sweden explained the pathogenesis with regard to von Willebrand Factor (VWF) and platelet dysfunction found in this and other Åland families, and in 1993 the discovery of a mutation in exon 18 of the VWF gene clarified the inheritance.

S-MO-03.1-4
Mouse models of von Willebrand disease
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Von Willebrand disease (VWD), caused by quantitative or qualitative abnormalities in von Willebrand factor (VWF), is considered the most common inherited bleeding disorder in humans. Mild and severe quantitative defects in VWF cause VWD type 1 and 3 respectively, whereas qualitative abnormalities induce VWD type 2. VWD has also been diagnosed in a number of animal species such as dogs, pigs, cats and horses, as a result of naturally occurring mutations. However, mice remain the model of choice in research. Their small size, along with their well-defined genetic background, makes them ideal tools for studying the in vivo function of VWF. The most commonly used model is the VWF-deficient mouse engineered through homologous recombination. However, models resulting from changes in modifier genes indirectly affecting VWF have also been described. More recently, murine models resulting from in vivo transfection using hydrodynamic injection have been generated. In these mice, the high-pressure injection of VWF cDNAs wild type or mutated leads to the production of transient murine models expressing any desired VWF mutant. This model allows for an expression of VWF by hepatocytes, which stays stable for a minimum of 2 weeks. Hepatocyte-derived VWF is correctly multimerized and is functional in that it can correct the hemorrhagic phenotype of the knockout mice. This approach allows generation of mice reproducing the different types of VWD. Indeed, type 1 or type 2B VWD mice have been recently generated and shown to reproduce the human phenotype. These various murine models have proven very useful in elucidating some aspects of VWF biology not easily addressed through in vitro approaches.

S-MO-03.1-2
Weibel-Palade body formation
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Weibel-Palade bodies (WPBs) are endothelial, cell specific, elongated, secretory organelles that contain von Willebrand factor (VWF) and a variety of other proteins that contribute to inflammation, angiogenesis, and tissue repair. These organelles, with a diameter of 0.1–0.3 micrometers and a length of 1–5 micrometers were first described in 1964 by Ewald Weibel and George Palade. VWF is the major constituent of WPBs and is required for the biogenesis of WPBs. During posttranslational modifications in the trans-Golgi network, VWF multimers are formed, which subsequently are condensed into tubules that are targeted to WPBs. Those tubules can be recognized by electron microscopy as the characteristic longitudinal striations in the WPBs. Many secretagogues mediate release of WPBs, either by increasing intracellular free calcium (thrombin and histamine) or cAMP (epinephrine and vasopressin). Upon exocytosis, the VWF tubules unfurl into VWF strings that dock on the endothelial cells to adhere the platelets. Three different modes of regulated exocytosis of WBPs have been described: conventional exocytosis, in which single WPBs fuse with the plasma membrane and release their content; lingering-kiss exocytosis, in which single WPBs fuse with the plasma membrane via a small fusion pore and selectively release small molecules only but retain VWF; and multigranular exocytosis, in which several WPBs coalesce before exocytosis into large vesicles termed secretory pods. The effects of missense mutations in VWF on the formation and regulated secretion of WPBs is currently being studied, and defects in the intracellular storage and regulated secretion of VWF seem to be a common mechanism underlying VWD.

S-MO-03.1-3
ADAMTS13 cleavage of VWF
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Von Willebrand factor (VWF) is a large adhesive glycoprotein multimer with established functions in hemostasis. It serves as a carrier for factor VIII and acts as a vascular damage sensor by attracting platelets to sites of vessel injury. VWF size is important for this latter function, with larger multimers being more hemostatically active. Functional imbalance in multimer size can variously cause microvascular thrombosis or bleeding. The regulation of VWF multimeric size and platelet-tethering function is carried out by ADAMTS13, a plasma metalloprotease requiring Ca^{2+} and Zn^{2+} for its activity. ADAMTS13 is constitutively active and, unusually, its protease activity is controlled not by natural inhibitors but by conformational changes in its substrate, which are induced when VWF is subject to elevated rheological shear forces. These forces transform VWF from a globular to an elongated protein. This conformational transformation unfolds the VWF A2 domain and reveals cryptic exosites as well as the scissile bond. To enable VWF proteolysis, ADAMTS13 makes multiple interactions that bring the protease to the substrate and position it to engage with the cleavage site as this becomes exposed by shear. These interactions may be remote or proximate to the cleavage site and to the active centre of the protease. Recent literature on the interaction between these two multidomain proteins will be discussed and a summary model will be proposed that explains proteolytic regulation of VWF by ADAMTS13.

PO-MO-137
Addition of short fragments of the B-domain eliminates the discrepancy of factor VIII activity of B-domain deleted factor VIII between clotting and chromogenic assays
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Objective: To evaluate the role of the factor VIII (FVIII) B-domain on FVIII expression, activity, and activation, we expressed FVIII plasmids (pMT2) with various lengths of the B-domain transiently as well as stably. FVIII activity (FVIII:C) was assessed in culture medium; FVIII antigen (FVIII:Ag) was assessed in culture medium and cellular lysates.
Methods: B-domain deleted recombinant FVIII (BDD-rFVIII) was generated from the full-length FVIII-cDNA by ligating (on the protein level) Ser743 to Arg1634. In a following step, cDNA-fragments of different lengths (on the protein level: 101, 202, 292, and 394 amino acid long fragments of the B-domain starting from its amino terminal) were cloned between Ser743 and Arg1634. Constructs were then transiently expressed in COS-7 cells and stably in CHO-DHFR(-) cells by methotrexate selection and amplification. FVIII proteins were then assessed for activity by the clotting assay and the chromogenic assay and for antigen by enzyme-linked immunosorbent assay (ELISA).
Results: Expression studies revealed that the constructs containing added lengths of the B-domain show a higher FVIII: C (~1.1–2.5-fold) and higher antigen concentration in medium and cellular lysates (~1.1–3-fold) compared to BDD-rFVIII. The functionality of the expressed proteins in terms of FVIII-specific activity was higher in all constructs in comparison to the BDD construct. When comparing FVIII:C values between the clotting and the chromogenic assay, all constructs containing added lengths of the B-domain showed approximately similar values in both assays; however, the BDD construct showed a significant discrepancy. Activation of purified FVIII proteins by thrombin revealed that the BDD-rFVIII showed a faster generation of the A2 domain than the constructs containing added lengths of the B-domain.
Conclusion: Generally, our data could show that the addition of various B-domain lengths is able to eliminate the assay discrepancy of BDD-rFVIII protein and increases the overall expression and functionality of FVIII protein.

PO-MO-138

Various genetic mechanisms resulting in phenotypic expression of hemophilia A in three females

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Hemophilia A (HA) is a recessive X-linked disease that affects 1 in 5000 males. Females are carriers of the disease and usually exhibit normal or slightly decreased factor VIII activity (FVIII:C>25%). Females have occasionally been described as having hemophilia A, and various genetic circumstances can explain such phenotype. We report three cases of mild or severe HA in females. The first case occurred in an 18 month-old baby girl suffering unexplained knee hemarthrosis without any family history of bleeding disorders. Blood coagulation study disclosed a severe factor VIII deficiency (FVIII:C< 1%). The FVIII:C level was normal in her parents and brother. The karyotype was normal. Molecular analysis showed heterozygous intron 22 inversion inherited from her mother. The entire sequencing of *F8* coding regions and flanking splicing sites were normal. Two genetic mechanisms affecting the paternal allele are under investigation: skewed X-chromosome inactivation and *de novo* large deletion or duplication. The second case was a 24 year-old woman who had a maternal male cousin with severe HA. She only suffered bruising. The FVIII:C was 10%. Her sister presented with the same profile. Family study disclosed an unknown mild HA in her father (FVIII:C = 25%) in whom the p.Ser2011Asn mutation was identified. Both sisters were compound heterozygous: they inherited the missense mutation from their father and the abnormal X-chromosome from their mother, with a preferential X-chromosome inactivation of the paternal X-chromosome. However, thorough molecular analysis (including cGH arrays) in the maternal family failed to identify the underlying molecular mechanism responsible for the severe HA. The third case was a 28 year-old woman. Her male cousin was recently diagnosed with a mild HA. She suffered bruising and epistaxis. The FVIII:C was 19%. Karyotype revealed the X-monosomy of a Turner syndrome. These cases of HA in females resulted from various underlying mechanisms, which need to be highlighted in order to provide an adapted genetic counselling.

PO-MO-140

Duplications XQ28 and hemophilia are questionable for genetic counselling

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Severe hemophilia A is frequently caused by inversions involving intronic sequence of the F8 gene (int22h1) and 1 of 2 remote, distal copies (int22h2 and int22h3). The inversed orientation of the 2 distal copies suggests that interchromosomal recombination should produce more deletions and duplications than inversion rearrangement. Reciprocal deletion and duplication of the F8 gene have been suggested. Though several F8 gene deletions have been described, the few duplications reported are most often associated with moderate hemophilia. Here, we describe severe hemophilia A patients with F8 gene duplication. All these duplications involve the centromeric or the telomeric part of F8 gene. They all have been suspected because of unusual patterns when testing for intron 22 inversion with the modified standard long-distance PCR assay used in our laboratory. Indeed, the use of the standard test is misleading, showing a false positive inversion result. These duplications were further identified by multiplex ligation-dependent probe amplification (MLPA) and some of them were investigated by comparative genomic hybridization (CGH) array. The analysis revealed a telomeric duplication that covers 0.5Mb, affects several genes and part of the F8 gene from the int22h1 copy to a locus lying between the distal int22h2 and int22h3 copies. These observations confirm the hypothesis of interchromosomal recombination involving these repeat copies. This same duplication has been recently reported in 3 patients with intellectual disability without low factor VIII levels. However, we show here that this kind of duplication involving the F8 gene is associated with (1) isolated hemophilia, and (2) severe hemophilia, contrary to the initial hypothesis that F8 gene duplication has no consequences, which then do not justify prenatal diagnosis. These new data are important for genetic counseling. Further investigations are necessary to understand why the same duplication might be associated with such different phenotypes. This is of particular interest when such duplication is identified in a pregnant woman.

PO-MO-141

Spectrum of mutations in 345 unrelated hemophilia B patients

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Hemophilia B is 6 times less frequent than hemophilia A, and characterization of deleterious mutation is less reported. We present here the result of molecular studies performed in 345 unrelated hemophilia B patients. Severity of the disease was defined by the FIX:C level: <1 U dl^{-1} severe (HB n = 180), 1–5 U dl^{-1} moderate (HB n = 68), >5 U dl^{-1} mild (HB n = 97). The functional region of the F9 gene, including the 8 exons with the 5' and 3' flanking splice junction, the promoter, and part of the 3' untranslated region surrounding polyadenylation site were studied by denaturing gel electrophoresis (DGGE) and DNA sequencing. In all patients negative after complete gene sequencing, search for duplication was performed using quantitative fluorescent multiplex-PCR (QFM-PCR) of all exons, promoters, and polyA regions. A causative mutation was identified in 328/345 (95%) patients, mainly point mutations, a whole F9 gene deletion in 6 patients, a large F9 gene deletion encompassing 1 or several exons in 12 patients, a LINE sequence insertion in 1 patient, and a mutation located in the Leyden region in 15 patients. No duplication has been identified, unlike the F8 gene, where this kind of rearrangement is now reported. Thirty-eight (11%) of the identified mutations have not been reported so far. The strategy used to predict the deleterious consequences of these new variations will be presented. Collection on the international database of the mutations responsible for all hemophilia B cases, whatever the severity, is particularly helpful to improve genetic counselling, especially for pregnant women with low FIX:C level, no family history of hemophilia, and discovery of unknown mutation. To conclude, only 5% of the patients had no mutation identified after extensive gene analysis. New technology such as next-generation sequencing will probably help us to solve these cases.

PO-MO-142

Spectrum of mutations in a majority of patients with hemophilia A in Slovenia

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The high mutational heterogeneity of hemophilia A is a challenge in the provision of genetic services. Our aim was to create a confidential national database of mutations for the improvement of genetic services in Slovenia. The factor VIII gene (F8) was analyzed in 150 of 179 hemophilia A patients in Slovenia. The mutations were identified by testing inversions of intron 22 and 1 (IV22 and IV1), sequencing part of the promoter, whole coding region, and exon/intron boundaries of the F8 gene. There are 126 families with patients with hemophilia A in the Slovene registry for hemophilia. We determined that the mutations in 81/82 patients were severe, 15/18 moderate, and 54/79 a mild form of hemophilia A, representing approximately 80% of the families in the Slovene hemophilia registry. Genetic mutation was determined in all analyzed patients: 40/150 have inversion of intron 22 (48.8% of severe cases), and another 110/150 have 54 different mutations in the F8 gene which cause hemophilia A. Of these, 21 are so far found only among Slovene patients. Inversion of intron 1 was not detected in the Slovene population of hemophilia A patients. Interestingly, there were no large deletions and insertions. Thirty percent of the small deletions and insertions occurred at stretch of adenines, codons 1191-1194 (8As). In a patient with mild phenotype, a missense mutation in 5'UTR, creating a novel translation initiation site, was found. The spectrum of mutations in Slovenian hemophilia A patients was comparable to that found in the Italian and Austrian population, as expected. We report a wide spectrum of mutations in the national database. The type of mutation is one of the predictors of clinical phenotype. The database is a powerful tool for genetic counselling and medical care of families with hemophilia A in Slovenia.

PO-MO-143

A third rearrangement caused by homologous recombination between inverted repeats at XQ28 causes severe hemophilia A

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Intrachromosomal homologous recombinations between inverted repeats account for about half of the severe hemophilia A cases. Namely, repeats in intron 1 and intron 22 of F8 can recombine with external identical inverted repeats 5' and 3' to the F8 and cause the inversion of intervening sequence and splitting of the F8 gene in 2 opposite directions. As a result, no functional protein could be produced. Here, we report on a third homologous recombination between a repeat in intron 1 of F8 that we designate Int1R-1 and 1 inverted copy Int1R-2d in intron 2 of a duplicated IKBKG gene-region about 386 Kb upstream. The rearrangement caused the failure of amplifications across the Int1R-1 region and was detected in the index patient and 2 female carriers (his mother and his sister). One junction of the rearrangement was confirmed by both Southern blot and by inverse PCR. This rearrangement explained the absence of F8 transcription that we had previously reported for the affected chromosome in this family. We further developed a PCR-based method to detect this rearrangement that could be used to screen for this rearrangement in severe hemophilia A cases without known mutations.

PO-MO-144

Direct mutation detection in Indian cases with hemophilia A

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Objectives: To apply direct mutation detection strategy for screening genetic mutations in Indian cases with hemophilia A (HA).

Methods: Study group included 100 unrelated cases with HA. Clinical records, pedigree, and FVIII bioassay were assessed. Mutation detection was carried out in this serially for intron 22 inversion by inverse PCR, intron 1 inversion, and small mutation detection,

using PCR in 36 sets for the 26 exonic regions of the gene. Single-strand conformational polymorphism (SSCP) was used for detection of shift. DNA sequencing was done in cases showing shift, and sequences analyzed.
Result: Forty cases were intron 22 inversion, 4 were intron 1 inversion positive. SSCP showed a shift in 21 samples, of which causative mutation was confirmed in 13 cases (Table 1). Cases showed a severe phenotype in 39, moderate in 52, and mild HA in 9.
Conclusion: Inversion 22 can be conveniently detected with inverse PCR. Intron 1 has a frequency of 4% in our population. SSCP did not work very well in our hands for detection of small mutations. Denaturing gel electrophoresis (DGGE) or denaturing high-performance liquid chromatography (dHPLC) can be used instead. Complete sequencing of amplified exonic regions may be more effective.
Contribution: Study elicits frequency and type of mutations in HA in north Indian population. SSCP has low sensitivity for screening small mutations.

Table 1:

S. No	Severity	Exon	Domain	Nucleotide change	Amino-Acid change
1	Moderate	4	A1	GAT>GGT	Asp → Gly
2	Moderate	4	A1	AGT>AGG	Ser → Arg
3	Severe	4	A1	TGG>AGG	Try → Arg
4	Severe	4	A1	TGG>AGG	Try → Arg
5	Moderate	12	A2	CGA>GGA	Arg → Gly
6	Moderate	12	A2	CGA>GGA	Arg → Gly
7	Moderate	15	A3	ATG >ACG	Met → Thr
8	Moderate	16	A3	AGA >AAA	Arg → Lys
9	Moderate	16	A3	CGT >CAT	Arg → His
10	Moderate	16	A3	CGT >CAT	Arg → His
11	Moderate	16	A3	CGT >CAT	Arg → His
12	Mild	24	C2	CCT >TCT	Pro → Ser
13	Moderate	14H	B	GAG>AAG	Glu → Lys

PO-MO-145
Inversion 22 in hemophilia a in the North Indian population: a new CDNA-based protocol

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Objective: To assess the frequency of Intron 22 Inversion Mutation (Inv 22) in North Indian population and to develop and evaluate a new protocol for Inv22 mutation detection.
Method: Clinical assessment; family history was obtained in all cases. Genetic studies included assessment of frequency of the Inv22 in a group (n = 181) of 102 severe cases and 79 moderate cases with hemophilia A from North Indian population by using Inverse PCR assay (Rosetti et al.). A new cDNA-based method was designed and evaluated to assess Inv 22.
Result: Seventy- seven of 181 cases were positive for Inv22 mutation. The observed frequency was 42.5%. Phenotypic evaluation revealed that in moderate hemophilia A, Inv 22 positive cases (n = 29) had a mean FVIII bioactivity of 1.74% (SD ± 0.27, range 1.2–2%) while cases without Inv 22(n = 50) had a mean FVIII bioactivity of 3.5% (SD ± 0.99, range 1.5–5%). The mean age of onset of bleeding in Inv22 + cases was 19 months (SD ± 29.46, range 0–76 months), while negative cases had a mean age of onset of 50 months (SD± 44.68, range 0–130 months). Onset of bleeding episodes at birth was observed in 43/181 cases with Inv 22 mutation, while negative cases had bleeding at birth in 25/181 cases. Overall joint bleeding was most frequent, followed by oral/gum bleeds. No difference in the site of bleeding was observed in Inv 22 positive versus negative cases. The annual requirement for FVIII infusion in Inv 22 positive cases was also higher. The new cDNA-based method was validated against the Inverse PCR and long-distance PCR in 20 cases, and complete correlation was observed with both methods.
Conclusion: We conclude that Inv 22 mutation leads to a very severe form of hemophilia A in our population. It can be conveniently detected using the Inverse PCR method. It is easy to standardize and lowest in cost. The new cDNA-based method is short, involves 3 short segment amplifications, and is easy to reproduce. Appropriate genetic counselling on the basis of severity of the disease associated with causative mutation in the family and prevention of birth of cases with Inv22 mutation can decrease the morbidity of hemophilia A in the population.
Contribution: This new method yields quick results. In our hands, the results are unambiguous and provide a definitive diagnosis with no failure rate.

PO-MO-146
Intron 22 homologous regions are implicated in non-deleterious duplications of the factor 8 gene

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The factor VIII (F8) gene intron 22 inversion is the causative mutation is the causative mutation in approximately 45% of severe hemophilia A patients. It results from homologous recombination between copies of a repeated DNA sequence, the intron 22 homologous region (int22h), one copy located in intron 22 of FVIII, the other two copies distal and telomeric to FVIII. By contrast with the intron 22 inversion, duplications comprising 1 or more exons in the F8 gene represent only 1% of causative mutations. Duplications of the F8 gene have been associated with varying phenotype, depending on the localization and length of engaged exons. We identified 2 patients with moderate and severe phenotypes[1] harbouring extensive duplications and studied the underlying molecular mechanisms. Array comparative genomic hybridization (CGH) was used to appreciate the expanded region of these rearrangements. Fine-mapping and breakpoint analyses by CGH array indicate that these duplications are delimited both on one side by the intragenic int22h-1 repeat and the other side by int22h-2 for the moderate case, or by the int22h-3 copies for the severe patient. This finding supported by the results of long-distance PCR, Southern blotting, and multiplex ligation-dependent probe amplification (MLPA) suggests that these rearrangements should have occurred during DNA replication during the female meiosis between 2 normal chromatid sisters or between 1 normal chromatid and another chromatid with inversion of intron 22 in a carrier female by a non-allelic homologous recombination (NAHR) mechanism. Of note, the same duplication was found in a non-hemophilic patient, which supports the concept that exons 1 to 22 duplication in F8 gene should be considered as a non-deleterious polymorphism masking the true HA causal mutation. Indeed, triplication comprising exons 2 to 14 for the first case and classical intr22 inversion for the second of the *F8* gene have also been identified which were definitively associated with their hemophilia phenotype. This study demonstrates for the first time that partial segments of the F8 gene can be duplicated by mechanisms which involve the same DNA repeats as those involved in intron 22 inversion. These duplications are, however, not deleterious and should not be considered as causal. This study provides new insight in the understanding of the complexity of the molecular mechanisms of hemophilia A.
1. Lannoy N, Abinet I, Bosmans A, Lambert C, Vermylen Ch, and Hermans C. *Haemophilia 2011* Aug. 26

PO-MO-147
Hemophilia B families with the same mutation are often related: A survey of the Swedish population

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Aim: To study if families with hemophilia B in Sweden carrying the same mutation are identical by descent (IBD) or the result of independent mutations (RM).
Study group: A total of 77 presumed unrelated and unselected Swedish families with hemophilia B comprising all clinical severities (total and large deletions not included). Control group of 256 healthy individuals.
Methods: Haplotyping was performed using 90 SNP markers (11 within the F9 gene) and 1 microsatellite marker. The frequencies of shared haplotypes were determined in the control group, and the ages of the shared haplotypes will be determined using the program ESTIAGE.
Results: Analysis of the mutations gave the following results: 5 small deletions (<10bp), 2 small insertions (<10bp), 3 splice site mutations, 14 nonsense mutations, and 53 missense mutations. A total of 30 mutations (39%) occurred in a single individual only, whereas the remaining 47 mutations occurred in 2 or more individuals; 7 mutations occurred in 2 individuals, 4 mutations occurred in 3 individuals, 2 mutations occurred in 4 individuals, 1 mutation occurred in 6 individuals, and 1 mutation occurred in 7 individuals each, i.e., 47 mutations out of 77 (61%) were either IBD or recurrent mutation. Haplotyping and comparisons with the control group classified 21/47 mutations as IBD and 25/47 as RM. The phenotypes of the 21 IBD individuals were mild (17), moderate 2), and severe (1); those of the 25 RM individuals were mild (7), moderate (7), and severe (12). Age estimation of the mutations is ongoing.
Conclusion: Many families with hemophilia B, in particular those with milder forms, carrying the same mutation are IBD, i.e., revision of ''hot-spots'' for mutation is needed.

PO-MO-148
Hemophilia A families with the same mutation are often related: A survey of the Swedish population

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Aim: To study if families with hemophilia A in Sweden carrying the same mutation are identical by descent (IBD) or the result of independent mutations (RM).
Study group: A total of 284 presumed unrelated and unselected Swedish families with hemophilia A comprising all clinical severities. Control group of 254 healthy individuals.
Methods: Haplotyping was performed using 90 SNP markers (18 within the F8 gene) and 5 microsatellite markers. The frequencies of shared haplotypes were determined in the control group and the ages of the shared haplotypes determined using the program ESTIAGE.
Results: Analysis of the mutations gave the following results: inversions in introns 1 or 22 were detected in 71 cases, large deletions in 5, small deletions/insertions in 4, and substitutions in 204 patients. For substitutions, a total of 107 mutations occurred in a single individual only, whereas the remaining 35 mutations occurred in 2 or more individuals; 20 mutations occurred in 2 individuals, 9 mutations occurred in 3 individuals, 4 mutations occurred in 4 individuals, and 2 mutations occurred in 7 individuals each, i.e., 97 mutations out of 204 (47%) were either IBD or recurrent mutation. Haplotyping and comparisons with the control group classified 51 of the 97 mutations as IBD. The phenotypes of the 51 individuals were mild (31), moderate (5), and severe (8), and the corresponding mutations had age estimates varying between 150 and 700 years. Inhibitors occurred in both RM and IBD families. One IBD family with mild hemophilia (2105 Tyr>Cys) had 3 members who developed inhibitors.
Conclusion: Many families with hemophilia A, in particular those with milder forms, carrying the same mutation are IBD, i.e., revision of ''hot-spots'' for mutation is needed. Few ''clusters of inhibitors'' were found.

PO-MO-149
Intracellular trafficking analysis of C111Y and C111S mutations identified in factor IX from Mexican patients with severe hemophilia B
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A group of punctual recurrent mutations out of CpG sites were previously identified in Latin-American populations. They involve cysteine sites with functional relevance in the FIX protein. We studied 2 of these mutations at 17,747 nucleotide in the second-like epidermal growth factor (EGF2) of factor IX gene (FIX). We had previously presented 3-repeat results and for confirming we are showing their integration with 2 additional repeats.
Objectives: To study the intracellular trafficking of C111S and C111Y mutations to identify their effect in the structure–function relationship of FIX.
Methods: Wild-type (wt) C111 and C111S and C111Y mutations were inserted by directed-site mutagenesis into an expression vector (pcDNA 3.1®) containing the FIX (wt) gene. Transfection on Cos-7cells by Fugene6® after 48 hours was tested with a control plasmid containing the green fluorescence protein (pGFP) with a good efficiency (64.5%) evaluated by flux-cytometry. The intracellular and secreted FIX was quantified by enzyme-linked immunosorbent assay (ELISA). Transfected cells were incubated in the presence of inhibitors like brefeldin A, which blocks protein transport from endoplasmic reticulum (ER) to the Golgi complex; N-acetyl-leu-leu-norleucinal (ALLN) and clasto-lactacystin beta-lactone; proteasomal inhibitors NH_4Cl and Leupeptin; and lysosomal inhibitors.
Results: With respect to wt FIX, the mutations showed a decreased FIX secretion (21%) and intracellular accumulation 138% (C111Y) and 166% (C111S). The effects of the inhibitors caused a higher intracellular accumulation of the mutants, which led to a degradation, mainly in lysosomes (NH_4Cl) and secondly in proteasomes (ALLN).
Conclusions: After 5 reproducible 5-repeat trials, we conclude that the disruption of the disulfide bond in the mutants have an important effect on the native folding of FIX, evident by the effects on their transport through ER and the degradation mechanisms, with a predominant degradation at proteasomes when the ER transport is blocked and a higher degradation at lysosomes when the transport from ER to Golgi complex is adequate.

PO-MO-150
Genetic defects in von Willebrand disease
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Introduction: Von Willebrand disease (VWD) is the most common congenital bleeding disease. Its diagnosis is based on clinical and laboratory findings. However, the variability in analytical assays due to environmental and acquired factors makes diagnosis difficult. In cases of uncertain diagnosis, genetic analysis plays an important role. The aim of this study was to determine genetic variations in 12 families with VWD.
Materials and methods: We studied 11 unrelated families previously diagnosed with VWD: 3 families with VWD type 3; 5 families with VWD type 2B; 2 families with VWD type 2A; and 1 family with VWD type 1. Mutation screening was done by PCR and direct sequencing of the coding VWF exons 2–52 including flanking intron sequences.
Results: Two families with VWD type 2B simultaneously showed R1315H and R1341Q mutations. This combination had not been previously reported. The others families with VWD type 2B presented R1306Q mutation in homozygosis and R1306W, R1308W mutations in heterozygosis. Two families with VWD type 2A were heterozygous for R1374H and C1272G mutations. The family with VWD type 1 presented simultaneously P1266L and V1279I mutations in heterozygosis. The 3 families with VWD type 3 were homozygous for Q1311X. All these mutations were located in exon 28 and were previously described in the ISTH-SSC VWF Online Database.
Conclusions: Genetic analysis of the VWF gene by exon 28 is useful in patients with VWD type 2A, 2B, and 3. Simultaneous R1315H and R1341Q mutations can be found in patients with VWD type 2B.

PO-MO-151
Absence of active F8 protein despite high F8 mRNA expression levels in a severe hemophilia A patient
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Hemophilia A (HA) is caused by a wide spectrum of mutations in the F8 gene, leading to a decreased or total loss of F8 activity. Inversions are the most common mutations causing a severe HA phenotype; in addition, small and large deletions, insertions, or point mutations lead to either altered or truncated protein. In the current study, we investigated the causative mutation in a severe HA patient without detectable mutation in the F8 cDNA. Fluorescent in situ hybridization (FISH) analysis showed normal chromosomal location of F8 at Xq28, excluding translocation of the F8 gene or gross chromosomal rearrangements. Quantitative mRNA analysis showed an unexpected high (>100 fold) F8 mRNA expression level in comparison to healthy individuals in the index patient. Multiple ligation-dependent probe amplification (MLPA) analysis revealed duplication of exons 1–4 and 23–26 and a large triplication comprising exons 5–22 of F8 gene. Comparative genomic hybridization (CGH) analysis confirmed these results and showed that the span of the duplication/triplication is carried over the intronic regions of F8. In conclusion, we report a so far undescribed duplication/triplication pattern comprising most genomic regions of F8 locus leading to a severe HA phenotype, despite high F8 mRNA expression levels.

PO-MO-152
Identification of mutations associated with hemophilia A: A French Caribbean experience
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Hemophilia A (HA) is a rare X-linked recessive bleeding disorder, associated with partial or complete absence of clotting factor VIII (FVIII) and heterogeneous mutations for the corresponding gene. Studying HA in Martinique is of clinical interest because its prevalence is twice as high as in continental France. HA population included 94 men with 37.65% +/– 21.67% age distribution and with severe, moderate, or mild phenotypes. In Martinique, clinical HA prophylaxis treatment reduced arthropathy and hemarthrosis. Severe HA represents 6% of the HA cohort of patients and is associated with a risk factor to develop inhibitors against FVIII. The FVIII gene was disrupted with intrachromosomal intron 22 recombinations in 33% of severe HA cases. This frequency is significantly lower than that observed in literature. From our cohort, new specific ethnic mutations associated with HA were identified by direct sequencing. Two patients with severe HA developed inhibitors against FVIII with abnormalities in exon 24 and exon 25. Genetic alterations (large deletions, frameshift, base replacement, or premature termination codons) were identified within FVIII coding sequences and promoters: all this information predicts clotting factor deficiencies. Polymorphism segregation analyses were performed for carrier diagnosis, and all patients were tested for dDAVP reactivity test. Several patients had multiple mutations. Studying family linkage and the evolution of treatments allowed the determining of risk factors associated with these mutations in a mixed population with African origins. In relation to a previous report (Viel et col., 2009, *N Engl J Med*) showing that patients with African heritage could have higher risk factors for experiencing inhibitors as compared to Caucasians, we analyze the genetic predisposition to this disease. The appearance of inhibitory antibodies is a costly complication for the therapy. We wish to demonstrate the importance of evaluating FVIII haplotype (H4, H3, H2, H1), in order to select the most appropriate treatments for our patients.

PO-MO-153
The Canadian "National Program for Hemophilia Mutation Testing" database: A ten-year anniversary review
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A reference genotyping laboratory was established in 2000 at Queen's University, Ontario, to provide genetic testing for hemophilia A (HA) and B (HB) and create a Canadian database. Hemophilia treatment centres and/or genetics clinics provided DNA and clinical information from November 2000 to March 2011. The factor VIII (F8) gene was analyzed in 1,192 patients (44% of total HA population) and 787 female family members, and the factor IX (F9) in 271 patients (41% of total HB population) and 123 female family members, using Southern blot (intron 22 inversion), PCR (intron 1 inversion), conformation-sensitive gel electrophoresis (CSGE), and/or direct sequencing. The F8 and F9 mutations identified are summarized in Table 1. Within the F8 and F9 cohorts, 39% and 45% of females who had a factor level provided (n = 314 and n = 47, respectively) had an abnormal level (<0.50 IU ml^{-1}). Five percent of samples sent were for prenatal diagnoses or carrier status during pregnancy. In conclusion, the Canadian F8 and F9 mutation spectrum reflects the heterogenic basis of HA and HB, and is similar to previously described populations. The laboratory plays an important role in the care of hemophilia patients, genetic counselling, and perinatal care. Demand for testing has remained consistent throughout this ten-year period.

Table 1: Distribution of F8 and F9 mutation types according to clinical phenotype.

Hemophilia A	All, n=1192 (%)	Severe, n=413 (%)	Moderate, n= 168 (%)	Mild, n= 521 (%)
No mutation identified	10	5	5	10
Intron 22 Inversion	11	31*	0	0
Intron 1 Inversion	1	2	0	0
Missense	57	16	67	86
Nonsense	6	13	8	0
Large Deletion	2	4	1	0
Frameshift	11	24	13	0
Splice Site	3	4	5	2
Other (includes ≥2 mutations, VWD or Hereditary parahemophilia)	1	1	1	1
Hemophilia B	**All, *n* = 271 (%)**	**Severe, *n* = 104 (%)**	**Moderate, *n* = 75 (%)**	**Mild, *n* = 56 (%)**
No mutation identified	8	1	0	16
Missense	65	57	83	64
Nonsense	9	17	4	0
Large Deletion	1	4	0	0
Frameshift	6	12	3	2
Splice Site	6	7	5	7
≥2 mutations	1	2	0	0
Hemophilia B Leiden	5	1	5	11

*Two Canadian centres perform intron 22 inversion testing locally: therefore, this number will not accurately reflect the prevalence of intron 22 inversion in the Canadian severe HA population.

PO-MO-154
MLPA assay in hemophilia: Additional tool in mutation detection both in males and in females

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Multiplex ligation-dependent probe amplification (MLPA) is a method to detect gene copy number variations. Several kits are available from MRC Holland for detection of genomic deletions and duplications in a variety of genes. We present results from analysis on hemophilia A (HA) and hemophilia B (HB) patients or females at risk for being carriers. MLPA requires denaturation of genomic DNA, hybridization with specific probes, linking of fragments by ligase, and PCR reaction with universal primers. PCR fragments are then separated by capillar electrophoresis. In our centre, 370 HA and 307 HB unrelated patients were studied; we suspected a deletion because of PCR failure in 11 and in 9 patients, respectively. MLPA confirmed the deletion in all HA patients, while 7 HB patients had total or partial F9 gene deletions; in the 2 remaining patients, poor DNA quality probably caused PCR failure. Other 26 HA/HB patients were further investigated by MLPA as first DNA analysis before PCR screening, saving time and finding 1 large deletion/duplication and 4 duplications. MLPA was also used on females at risk for carrier status both for familiarity for HA/HB and for unexpected low FVIII or FIX levels without certain familiarity. Fifteen HA and 22 HB females were studied, resulting in 11 carriers and 26 non-carriers for deletions or duplications. Among these non-carriers, some had a gene defect found by other methods; 2 have intron 22 inversion, 3 missense mutations, and 2 splicing mutations. For 19, no mutation was found at all. For a carrier HB pregnant female, MLPA was performed on chorionic villi DNA. The deletion was confirmed, demonstrating the feasibility of the test on fetal sample.

In our laboratory, MLPA has been used as the second-line test to confirm deletions in suspected cases, both in males and in at-risk females. Now it is also used in males as first line for eventually saving time on PCR screening. In females with low levels, MLPA should be used to perform carrier status definition or exclude a second defect in known mutation carriers.

PO-MO-155
Update of genetic counselling for hemophilia A at Castelfranco Veneto, Italy

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Our centre has been working for nearly 14 years in genetic counseling for patients and families with hemophilia, which displays a wide range of different molecular defects in both the F8 and F9 gene. For hemophilia A (HA), the F8 gene inversions involving intron 1 (InvInt1) or intron 22 (InvInt22) are the only recurrent mutations. Mutation detection based on PCR has been used worldwide. Direct sequencing of suspected gene fragments would be the gold standard, as it shows the specific gene defect; however, in routine laboratories its extensive use is not yet possible because of the cost. Recently, multiplex ligation-dependent probe amplification (MLPA), detecting genomic copy number variations, has been introduced for detecting large deletions or duplications on the F8 gene. Most of the 550 HA patients' DNA so far collected have been investigated for causative mutation. InvInt22 and InvInt1 detection has been done in 488 severe patients and was found in 229 (47%) and 11 (2.2%) respectively. Severe patients negative for the inversions (209) and all patients (62) suffering from mild/moderate disease have been further investigated using conformation-sensitive gel electrophoresis (CSGE) screening. MLPA was used in 11 identified deletions. Among the 511 HA characterized patients, 229 (44.8%) have InvInt22; 11 (2.1%) have InvInt1; 191 (37.4%) have point mutations; 19 (3.7%) have large deletions; 1 (0.2%) has large duplication; 59 (11.5%) have small deletions or insertions; and 1 (0.2%) has duplication of exon 13. Most patients (45%) have InvInt22; missense mutations show a different distribution in severe (17%) and in moderate/mild (79%) patients. Large deletions and nonsense mutations were found only in severe patients. Genetic counselling of 496 related females led to 54 prenatal diagnoses. DNA testing by sequential approaches is reliable for HA patients: F8 inversions investigation in severe cases, PCR and mutation screening, MLPA, and finally DNA sequencing led to mutation identification in most cases. Later, genetic counselling for related females should make possible more responsible decisions about conception.

PO-MO-156
Clinical implementation of clinician-oriented locus specific mutation detection and deposition system

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Objectives: The F8 gene contains 26 exons, 186 kb long. Not only sequencing but also interpretation is time consuming and labour intensive. So we developed an automated mutation detection software for DNA sequencing called Kohemgene (COMUS: clinician-oriented locus-specific mutation detection and deposition system). This software uses the University of California, Santa Cruz (UCSC) Genome Browser as a reference and is loaded in the Korean hemophilia mutation database (www.kohemgene.org). This study is designed to compare Kohemgene and Sequencher® in terms of time saving and accuracy of interpretation.

Methods: With a desktop computer (Pentium® IV, 512Mb), we analyzed 59 unrelated hemophilia A patients without intron 22 inversion mutation. The time from the loading of data into software to completion of interpretation was recorded in seconds. Kohemgene and Sequencher® were used for the same patients. While processing by Sequencher® is composed of 5 steps (input reference sequence, input data file, trimming, data analysis, and report) that of Kohemgene are 3 steps (input data file, data analysis, and report). Two researchers with more than 5 years' experience performed analysis and interpretation.

Results: The results from 59 patients' F8 DNA sequences were compared in the 2 programs. Kohemgene could shorten the analysis time to 1/30th in comparison with Sequencher®. Mean analysis time by Kohemgene was 56 seconds and Sequencher® 30 minutes on average. There was no disagreement in the interpretation of mutations between the 2 programs. With Kohemgene, the researchers could identify automatically whether the mutation was known or novel.

Conclusion: The Kohemgene provides an easy, time-saving, and accurate DNA sequence analysis system. Also, the Kohemgene can automatically identify the variation, whether known mutation or novel mutation in the Human Gene Mutation Database (HGMD) and Hemophilia A Mutation, Structure, Test and Resource Site (HAMSTeRS). Moreover, the software can deposit the mutation profiles and easily sort data according to specific conditions.

25-MUSCULOSKELETAL ISSUES

S-TH-01.4-1
Conservative management—splinting
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Splinting of the elbow remains a mainstay of conservative management following or between bleeding episodes. It holds the unique position amid, other more invasive approaches such as surgery, of being the only method of management in theory if not in practice of being available to all people with hemophilia. Within the domain of splinting, there are different designs of orthoses—static, dynamic, compressive, and hinged locking devices that offer a variety of beneficial effects. This presentation will briefly discuss all available options and the most appropriate instances for their implementation, but will focus on splint design that spares mobility and proprioception to the greatest degree possible. The use of splints will be linked to studies dealing with motor performance and proprioceptive feedback, and the utilization of splints not only to restrict motion but also to encourage its return will be addressed. Splinting to limit or eliminate angular joint motion will be discussed in the context of research dealing both with the deleterious effect of blood and immobilization on cartilage, and the effect of immobilization on the degradation of motor control and kinesthetic sense. Feed forward and feedback mechanisms affected by short- and long-term immobilization will be addressed, in addition to the impact that splinting and limb immobilization can have on balance—an issue of great importance to any ageing population.

S-TH-03.3-7
The importance of patients' body awareness, auto-evaluation, empowerment, and of allowing self-help when things go wrong
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Knee surgery of patients with hemophilia is frequent. Complications of all kinds are not exceptional. Patients pathologies and their physical-psychological profiles can also complicate rehabilitation "when things go wrong …" Rehabilitation must be effective without being harmful. The physiotherapist has to integrate a notion of benefit/risk with full knowledge of patients medical and surgical indications and also their physical and psychological capacities, as well as the environment. We present here, as an example, the protocol of care for 2 patients with hemophilia presenting major surgical and infectious complications of the knee. Through these examples, we detail the importance of patients' body awareness, auto-evaluation, and empowerment, and of allowing self help. This leads us to integrate and respect patients' choices in the adaptation of recuperative exercises. In this way, they are recognized as being actors and partners with the professionals in their health program. The evaluation of their quality of life and their level of satisfaction confirm the worth of this professional option: "when things go wrong … but also when they go well…"

S-MO-01.3-5
Bone defect (tissue engineering)
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Bone is one of the most commonly transplanted tissues of the human body. Contemporary skeletal reconstruction incorporates bone transfers in the treatment of osseous discontinuity, defects subsequent to congenital malformation, traumatic injuries, tumour surgery, and in failures of osteosynthesis. Bone grafts can be applied in contour augmentation and in strengthening and stabilization roles in various conditions. The osseous healing process is dynamic and unique, for the skeleton is one of the few organ systems capable of regeneration without the formation of scar tissue. The current understanding of the process of bone allograft integration is mainly based on cell biology, biomechanical studies, immunobiological approach, and clinical applications. The incorporation of cortical bone grafts proceeded very slowly in comparison to that of cancellous bone grafts; a large cortical allograft is remodeled extremely slowly by host bone, though osseous union at the host-graft interface occurred within a few weeks. Because the osteoblasts progenitor cells and vessels, originated from host bone, are provided to allograft extremely slowly, microfractures of allograft cannot be healed adequately and result in gradual weakening of the graft. The incorporation of a bone graft is the result of creeping and substitutional events that reduce the grafted bone and replace it by newly formed bone from the host bone. A challenge of orthopedic surgery involves attempts to stimulate bone healing, mostly using bone grafts. Tissue engineering promises that bony defects can be repaired by supplying cells, growth factors, and bone substitutes, alone or in combination, to achieve bone healing. Bone morphogenetic proteins (BMPs) induce mesenchymal stem cells differentiation (mature) into bone- and cartilage-forming cells. As such, they induce both direct (intramembranous) and endochondral (through a cartilage intermediate) bone formation. The end result is woven bone, which remodels and becomes populated with hematopoietic bone marrow. Growth factors, such as platelet-derived growth factor (PDGF) and TGF-β, are osteo-promotive factors, able to cause cells to divide, but not to differentiate. They produce expansion of the number of cells, and may cause cells to augment production of cellular products such as extracellular matrix proteins. Platelet rich plasma (PRP), a major source of PDGF and TGF β, may be used to enhance bone graft. The rationale for the local application of PRP in bone surgery is the release of growth factors present in the platelet. It has the advantage to be autologous without risks of disease transmission or immunogenic reaction. Tissue engineering and gene therapy could provide a useful tool to produce a tissue capable of maintaining the mechanical and biological functions of the original bone. Some techniques introduce an implant at the site of the injury, consisting of a 3-dimensional structure (bone substitutes) in which the cellular component is seeded. This generally consists of cells from the patient's own bone, which can be modified in the laboratory so that they express growth factors.

S-WE-01.4-3
Physio and EOS Review
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Although practice continues to advance in terms of preventing and treating bleeding episodes, arthropathy persists as a complication in persons with hemophilia (PWH) and PWH with inhibitors (PWHWI). Progression of arthropathy to a severe stage may be an indication for elective orthopedic surgery (EOS) to address resultant pain and functional limitations. Although it is not without challenges and requires careful planning, EOS is fairly common in PWH in countries where it is available. In addition, with the use of bypassing agents and accruing experience in hemophilia treatment centres (HTCs), EOS is now being performed in PWHWI. In both instances, it is critical that PWH and PWHWI are cared for by medical professionals that understand the fundamental differences in the treatment particularities of PWH and PWHWI, versus working with patients in the general population who are undergoing these EOS procedures. The physiotherapist is an integral member of the comprehensive, multidisciplinary team from the planning through recovery phases, and provides intervention during all stages. Physiotherapists working with orthopedic patients commonly treat patients before and after EOS. However, the type of treatment provided to a PWH or a PWHWI can be quite different than that of a patient in the general, non-bleeding-disorders population. Standard treatment methods could prove hazardous and pose threats in terms of increased musculoskeletal bleeding complications and delayed healing. For example, typical interventions such as early mobilization and return to functional mobility, the use of ice, continuous passive motion machines, and post-operative exercise protocols may need to be modified to promote healing and prevent bleeding in this patient population. Common approaches to post-operative EOS rehab in the general population will be compared to modified application of these typical physiotherapy interventions in PWH and PWHWI.

S-WE-01.4-6
The ethics and economics of inhibitor surgery
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No one would deny that wanting to live a life free of pain is rational, reasonable, and ethically justified. Advances in the hematologic control of inhibitors have made surgery a reality, but the cost remains high. Our resources are not unlimited and vary at different hemophilia centres and countries. This paper will attempt to explore our fundamental values of life, the quality of life, and how we try to equitably maximize and allocate these resources. It has been estimated that new and improved medical technologies contribute 40–50% of the annual increase in medical costs. Economists, hospital administrators, and legislators evaluate these advances by a cost/effectiveness ratio. Patients and most physicians are only interested in effectiveness. Patients expect to benefit from the advances, and physicians are trained to utilize them. To complicate the issue, industry profits from them and needs some of these profits to make additional advances. How to evaluate conflicting values is the realm of philosophy and ethics. Isaiah Berlin has pointed out that "the ends of men are many and not all of them . . . compatible. The necessity of choosing between absolute claims is the inescapable characteristic of the human condition. No person with an inhibitor should be denied life-saving or emergency surgery. The choice becomes more difficult in quality of life procedures, e.g., joint arthroplasties. One study estimated the average cost at US$694,000–855,000. A major review of knee arthroplasties showed a 7-year survival of 44% and a 14% need for removal of the prosthesis. Our job as physicians is to improve these outcomes; that of the person with hemophilia is to demand them. After all, as the English poet said in "No man is an island," "He is a part of the main . . . therefore never send to know for whom the bell tolls; it tolls for thee."

S-WE-03.5-4
Rehabilitation in young people with hemophilia: Developed countries
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In developed countries, some form of factor prophylaxis has become the standard of care for most children with severe hemophilia. Many studies have demonstrated that prophylaxis significantly reduces bleeding and limits the development of joint damage. Tailored prophylaxis appears to offer certain benefits such as decreased cost and less-frequent venous access but relies on early/accurate bleed detection. The issue of microbleeding was raised in the US Joint Outcome Study as MRI findings were seen in some patients in the absence of reported joint bleeding. More recent studies have pointed out the detrimental effects on cartilage of weight bearing on a joint with blood in it and the role of inflammation in increasing the risk of re-bleeding. Key issues in preventing arthropathy include early bleed detection and treatment, rest non-weight bearing initially and slow gradual progression to minimize risk of re-bleeding. A significant challenge faced in treating toddlers is their natural instinct to run and jump as soon as pain subsides, thereby increasing the risk of re-bleeding. Older children and adolescents may be reluctant to use crutches at school or to miss school. Children treated with prophylaxis are participating in a wide variety of sports activities at competitive as well as recreational levels. Early return to sports/activities may result in re-bleeding or persistent synovitis. Patients with mild hemophilia often come to clinic several days to weeks following an acute bleed, prolonging their rehabilitation. Significant muscle bleeds such as iliopsoas can be very problematic. A key physiotherapy role is patient/parent education in bleed detection, early bleed management, risks of re-bleeding, and monitoring of swelling. Short-term immobilization or use of a support brace may be useful to reduce

the risk of re-bleeding, especially in toddlers. Close monitoring of the patient post initial bleed helps to limit long-term musculoskeletal changes.

S-MO-01.3-2
Wound healing in bleeding disorders
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Wound healing involves a number of physiologic mechanisms including coagulation, inflammation, formation of granulation tissue, and tissue remodelling. Coagulation with robust thrombin generation leading to fibrin formation is necessary for wound healing. We have studied wound healing in mice with genetic defects in both the initiation (low tissue factor) and propagation (hemophilia B) phases of hemostasis. We also have preliminary data from mice given anti-coagulants. Others have studied the effects of warfarin on healing in rabbits. Based on our own and others' work, it appears that any treatment or deficiency that impairs thrombin generation also impairs wound healing to some degree. Mice lacking fibrinogen have a less severe defect in wound healing than mice or rabbits with defects in thrombin generation. Thus, it appears that thrombin plays roles in healing beyond producing a hemostatic fibrin clot. In addition, restoring thrombin generation only at the time of wound placement did not normalize wound healing in hemophilic mice. Coagulation function needs to be maintained for 5–7 days to support normal wound healing in this model. Angiogenesis that is an essential part of healing also increases the risk of bleeding. The delicate new developing vessels are easily damaged and also are not surrounded by the normal "hemostatic envelope" of tissue factor. If hemostatic function is not maintained during the period of angiogenesis, bleeding occurs and leads to iron accumulation in the tissues, increased inflammation, and an increased stimulus for continued angiogenesis.

S-MO-03.5-3
Rehabilitation in young people with hemophilia: Developing countries
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The availability of replacement therapy has revolutionized approaches to the management of people with hemophilia in developed countries. Unfortunately, there are still many developing countries where this effective therapy is not the standard. The World Federation of Hemophilia recommends treating patients with hemophilia in comprehensive care centres, but there is only 1 centre in Romania, in the western part of the country, too far away for many of our patients. Moreover, the lack of prophylaxis and home treatment, no access to care, and little to no availability of factor VIII replacement therapy in many parts of the country explain the presence of severe musculoskeletal complications, disability, and restriction of participation in very young patients. Also, many young people with hemophilia underwent surgical interventions such as synovectomy, and most of them get total joint replacement before the age of 30. Therefore, rehabilitation remains an inexpensive and efficient treatment option to minimize the detrimental effects of joint and muscle bleedings and to increase the functional independence and quality of life for these patients. The compliance for rehabilitation programs is poor, due to the difficulty of ensuring adequate supplies of factor VIII concentrates, and because of insufficient education of patients, their families, and healthcare professionals. Fortunately, in the last years, the National Members Organization had an active implication and developed specific rehabilitation programs for children with hemophilia, coordinated by trained physical therapists. Real support comes from the clinical trials regarding secondary prophylaxis, which offer factor VIII supply, therefore increasing the confidence and participation in specific rehabilitation programs. There is still need for evidence coming from well-conducted clinical studies in order to appreciate the real long-term effects of physical therapy and rehabilitation in young people with hemophilia

S-TH-01.4-5
Radial head resection
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Elbow pathology in a person with hemophilia typically involves flexo-extension and pronosupination. The distinction between these 2 different dimensions of joint pathology is paramount: while structural limitation of flexo-extension is often intractable, recuperation of pronosupination is possible with minimal surgical discomfort. The limitation of pronosupination results from hypertrophy of the radial head, a pathognomonic musculoskeletal manifestation of hemophilia in elbows that have had long periods of exposure to untreated synovitis. The mechanical consequence of the hypertrophy of the radial head is its impingement or locking against the radial notch of the ulna. The clinical presentation involves varying degrees of limitation of pronation and/or supination, or the absence of movement. The semiology of the lesion includes the elevation of the elbow with abduction of the shoulder in order to obtain pronation, or the anteposition of the elbow to the chest with the shoulder in flexion and external rotation to achieve supination. The indication of surgery results from the magnitude of the limitation due to the mechanical impediment. Skeletal maturity is a requirement. The surgical procedure consists of the resection of the radial head via a posterolateral approach following the internervous plane between the anconeus and the extensor carpi ulnaris muscle. The approach and osseous resection should be performed with the forearm in pronation, to protect the posterior interosseous nerve. The resection of the radial head will not improve flexo-extension significantly. While radial head spacers are required in non-hemophilia patients with radial head pathology to avoid elbow instability, for example, following trauma, this is not the case with persons with hemophilia. Physiotherapy may be started the day following surgery, with emphasis on recuperating pronosupination, which will predictably progress. A high level of functional recovery and satisfaction is associated with the resection of the radial head to improve pronosupinantion in persons with hemophilia.

S-TH-03.3-5
Total knee arthroplasty—infection
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Total knee arthroplasty, or replacement (TKR), is now the most commonly performed surgical procedure performed in adults with hemophilia. It is indicated when end-stage hemophilic arthropathy results in intractable pain and reduced function. In patients with hemophilia, however, there has always been a concern about the high risk of infection, which carries with it potentially catastrophic consequences. The aims of this study were to review the case series of TKR for hemophilic arthropathy published in the medical literature, comparing the published infection rates and the differing clotting factor replacement regimes employed. Nineteen case series were identified, representing 556 TKRs in 455 patients, with an overall infection rate of 7.9%. Case series which maintained a high level of clotting factor replacement throughout the first 2 postoperative weeks, however, had an infection rate of 2.15%, significantly lower than that of case series using the clotting factor replacement regime currently recommended in the World Federation of Hemophilia guidelines (9.22% $P = 0.00545$). We believe this study supports the use of a high level clotting factor replacement regime, replacing clotting factors to maintain them at a higher level for a longer period of time than currently recommended in international guidelines.

S-TH-03.3-4
Stiff knee: Developed countries
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Arthrofibrosis is the result of a process that occurs to severely limit motion around a joint, secondary to the formation of fibrous scar tissue and adhesions. This scar tissue can limit both flexion and extension as well as excursion of the patella in the knee joint. This creates a scenario of pain, poor post-operative function, and ongoing mobility issues, which can give a poor overall outcome. An understanding of the processes underlying the development of joint stiffness is important. This helps recognize early changes and initiate timely and effective interventions to limit the effects of joint stiffness on pain and function, and, where able, prevent further change. Pain relief and anti-inflammatory agents, used appropriately, are important adjuncts to therapeutic intervention. Prevention of stiffness is the most important, with factor replacement and rehabilitation as soon as possible after surgery. In early stages, physiotherapy, including stretching and strengthening of the muscles at the knee and manual therapy, should be instituted, with special attention to mobility of the patellofemoral joint. Splinting and serial casting can be useful if ROM loss is more severe. Following manipulation under anaesthetic or surgical release of soft tissues, aggressive rehabilitation (under factor cover) is instituted immediately to try and maintain increases in ROM. Continuous passive movement is used alongside the inpatient physiotherapy regime. Hydrotherapy and gym-based rehabilitation are utilized to improve overall muscle strength and function. Patient compliance is vital, as treatment is ongoing and time consuming. Education and support from the whole MDT throughout the process should be considered key to input and success.

S-WE-03.5-5
Surgery in young persons with hemophilia in developing country
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The main problems faced by developing countries in dealing with hemophilia are product shortages, inhibitors, and immunodeficiency states. In developing countries, surgical skill is more widely available than hematologists or hematological laboratories. The requirement for factor concentrate can be reduced drastically with fibrin glue, antifibrinolytic therapy, and continuous infusion. Major hemarthroses is treated with factor infusion to 50%, aspiration, short term splinting, and early mobilization. Chemical synoviorthesis in synovitis have shown improvement. Arthropathy requires a more conservative approach. Excision of radial head and synovectomies improve range of motion (ROM). Arthrodesis may be carried out in presence of severe destruction of joint surface. Hip aspiration is done to prevent loss of vascularity to immature hip. In gross destruction, arthroplasty is indicated. Tendon release and cast correction for knee contracture makes people with hemophilia (PWH) ambulatory. End stage arthritis requires arthrodesis, which puts stress on the other weight-bearing joints, which in turn leads to recurrent bleeds and synovitis. Knee replacement, though technically challenging, gives a more predictable outcome. Equinus and varus deformities may require triple arthrodesis to provide lasting relief in the event that conservative treatment fails. Early surgical excision is required in pseudotumours and done at selected tertiary care centres with better laboratory backups and factor concentrates. Percutaneous treatment is less often practised, as these tumours are large enough for surgical intervention. Most PWH with fractures require early treatment. Conservative treatment needs to be observed closely and surgical stabilization needs to be done as and when required. Surgery in PWH, although requiring a higher level of technical expertise, is as effective and safe (under cover of factor supplementation) as similar procedures in other patients.

S-MO-01.3-1
Inflammation as a therapeutic target to reduce the sequelae of hemophilic joint bleeding
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In the hemophilic joint exposed to hemorrhage, inflammatory proliferative and pro-angiogenic changes that have a place in normal wound healing occur out of proportion to underlying tissue injury, proceed upon a disordered and prolonged timeline, and lead to extended pathology rather than repair. Standard therapy using replacement clotting factor concentrate to halt the intra-articular accumulation of blood is essential to abbreviate these processes, however achieving hemostasis cannot be expected to arrest inflammation once initiated. Recent additions to the therapeutic armamentarium used to address other resistant inflammatory arthritides (e.g. rheumatoid arthritis) include agents that oppose inflammatory cytokines such as tumor necrosis factor alpha and interleukin-6. Monitoring hemophilia A and B mouse models following induced hemarthrosis, these same agents can provide adjunctive benefit when combined with replacement clotting factor to avoid early pathologic changes that follow severe haemarthrosis. The implications and limitations of the animal models should be considered in the context of the very limited human data that evaluates whether adjunctive therapy with anti-inflammatory agents can augment hemostatic support to improve outcomes in joints.

S-WE-01.4-2
In the middle: Conservative management before elective orthopedic surgery
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Physical Therapists in the developed world have become spoiled by the availability of factor replacement: patients can infuse factor prior to therapy sessions "just in case" and therapists can treat them as they would a person with normal coagulation. In the event that a bleed does occur due to physical-therapy techniques, treatment with factor can stop the bleeding quickly. The presence of inhibitors, however, creates extra challenges for physical therapists. Because achieving adequate coagulation in patients with inhibitors is extremely expensive, and the role of bypassing and other agents in *preventing* bleeds is still being explored, these patients may be more likely to develop target joints, chronic synovitis, and degenerative arthropathy. Therapists in the developing world are quite used to operating without the safety net of factor and must rely on safe application of assessment and treatment techniques as well as close cooperation with the patient. We can learn a lot from them. This session will explore the options and the precautions that should be considered by the physical therapist when assisting patients who have inhibitors. Conservative measures, applied correctly and in a timely manner, may be able to preserve patient functioning and delay (or avoid) the need for orthopedic surgery.

S-TH-03.3-2
Stiff Knees: Physiotherapy in Developing Countries
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The knee joint consists of the patellofemoral and tibiofemoral joints. The quadriceps muscle extends the knee and the hamstrings flex the knee. The knee joint is a major synovial, weight-bearing joint of the body. It is under constant biomechanical stress with little protection against unstable rotational forces. Stiff knees are a common problem in people with hemophilia (PWH), particularly in developing countries due to various factors. The flexion contracture of the knee is a common deformity. Valgus, external rotation deformity, and posterior subluxation of the tibia may exist alongside the flexion contracture of the knee. Early treatment of knee flexion tightness is recommended to prevent fixed flexion contracture and bony ankylosis of the knee joint (Rahiminejad, 2002). Physiotherapy is of great importance in not only treating stiff knees but preventing them, particularly in developing countries where there is a paucity of factor replacement therapy. This presentation is about the physiotherapy management of stiff knees in the developing-country scenario. It will give an overview of the cause of stiff knees in PWH, touching briefly upon the pathophysiology of contracture formation. Evaluation of joint health using standard assessment and outcome measures in PWH is important for timely and appropriate intervention—be it conservative or surgical management of stiff knees. It will highlight the importance of early management of acute knee bleeds, appropriate use of splints and orthotics, the role of CPM, traction, and exercises in preventing and treating stiff knees.
References: Rahiminejad, MS, Continuous Passive Motion (CPM) in the treatment of knee flexion contracture in hemophilic patients. Hemophilia, 2002, Vol: 8, Page 478.

S-WE-03.5-6
Surgery in young PWH: Developed countries
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Boys with hemophilia are exposed to clinical and subclinical joint bleeding, leading to joint damage. Some damage may already occur after a few hemarthroses and sometimes even without any visible bleeding event. In developed countries, where large amounts of factor concentrates are available, surgery should be performed in order to stop or delay this natural history when non-surgical treatment failed. Arthroscopic synovectomy has demonstrated good results with a decreased number of joint bleedings and improved function post-operatively. Associated musculoskeletal disorders (e.g., flat foot, axial deviation of lower limbs) have to be treated as soon as possible in order to reduce the likelihood of secondary joint disease. More frequently, orthopedic surgeons working in developed countries have to deal a new challenge: the management of hemophilic pediatric patients with severe joint involvement coming from countries where factor replacement therapy is not available. Corrective surgical treatment (e.g., arthroscopic release, epiphysiodesis, osteotomy) or, as a last resort, replacement surgery, could be performed in such patients in order to improve functional results and quality of life.

S-WE-01.4-1
Treating a patient with no factor available
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Primary prophylaxis is the goal standard for the management and prevention of hemophilic arthropathy. In many situations this is not possible, with secondary prophylaxis and on-demand treatment as the alternative therapy. Unfortunately, in many settings the access to factor is severely limited. We know that regular or primary prophylaxis can mitigate the harmful effects of bleeds and also prevent bleeds. The lack of factor or the presence of inhibitors should not condemn a person with bleeding disorder (PWBD) to live a life of painful joints, severe disability, or decreased quality of life. Physiotherapy has an important role to play in the management of patients with arthropathy. Many physiotherapy modalities can be implemented to achieve various goals, including improving range of movement, improving muscle power, and decreasing pain. Exercise is the mainstay of management of the PWBD. The use of electrotherapy modalities like transcutaneous electrical nerve stimulation can successfully manage the symptoms of pain, electrical muscular stimulation (EMS) and biofeedback helps with retraining muscles and muscle sequencing. Orthotics, functional bracing, and strapping can also be used to improve function and allow for added joint protection. The timing and progress of therapy needs to be more cautious in order to prevent bleeds induced by over exertion and muscle fatigue. The purpose of this presentation will be to look at various physiotherapy modalities and how we can implement them successfully in patients with inhibitors or with no access to factor concentrate.

S-TH-01.4-2
Arthroscopic synovectomy of the elbow in hemophilia
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Elbow arthroscopy (EA) represents around 1% of all arthroscopies performed in non-hemophilic patients, and its indications are the following: synovectomy, debridement of joint surfaces or adhesions, excision of osteophytes, loose-body removal, and capsular procedures. In our centre, arthroscopic synovectomy is indicated in hemophilic patients after the failure of 3 consecutive radiosynovectomies with a 6 month interval. In a 35 year period (1975–2010), we have performed 427 elbow arthroscopies in non-hemophilic patients. In the same period of time, 64 hemophilia patients who had synovitis of the elbow (94 elbows) were treated by synovectomy. Radiosynovectomy was performed on 77 elbows; 15 had a resection of the radial head and partial open synovectomy, and 2 had arthroscopic synovectomy. Synovectomy (by any method) significantly reduced bleeding episodes. Radiosynovectomy is the best choice for patients with persistent synovitis of the elbow. If 3 consecutive radiosynovectomies with 6 months intervals are ineffective, an arthroscopic synovectomy or open synovectomy must be indicated. Arthroscopic synovectomy of the elbow, while providing similar pain relief to open synovectomy, may place patients at higher risk for recurrence. The rate of complications following arthroscopic synovectomy ranges from 1.6% to 11% (infection, temporary nerve palsy). The most significant risk factor for the development of temporary nerve palsy is a contracture (very common in hemophilia). The primary predictor of outcome is the degree of pre-existing degenerative changes within the joint.

S-TH-03.3-1
Hemophilic knee arthropathy in developing countries
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Hemophilic arthropathy of the weight-bearing joints, such as the knee, is quite common. The low literacy rate, poor awareness, and lack of education in general – specifically among the patients and their immediate care providers – are important factors in the lack of realization of the importance of hemarthrosis. Non-availability of adequate therapeutic factors results in development of the knee as a target joint. Apart from degenerative changes in the knee, there are also associated soft-tissue contractures, which result from periarticular capsular fibrosis, the shortening of tendons and ligaments. Hemophilic knee arthropathy is no different in its pathological process and progress. The only difference is that the presentation in developing countries is late, when the joint has already developed into Pallazzi grade 3 and 4. The younger patients before closure of epiphyses present growth disturbance with resultant angulatory deformities. Because of financial constraints, inadequate therapeutic factors availability corrective procedures have to be tailored to individual patient requirement and the facilities available. In grade 1 and 2, rifampicin synoviorthesis gives very good functional results in 85% of patients. In advanced arthropathies, tendon lengthening osteomies and joint arthrodesis offer economical and functional outcome. Joint replacement surgery is available, but because of the high cost, it is not very frequently carried out.

S-MO-01.3-3
Translation of results from animal cartilage to human cartilage
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Cartilage is composed of chondrocytes embedded in an extracellular matrix. Chondrocytes are responsible for maintenance of the matrix. The cartilage matrix consists of 2 major components: collagen providing shape and tensile strength, and proteoglycans responsible for the negative charge. This causes high osmotic pressure, thereby attracting water and resisting compressive forces in a joint. Previous in vitro research showed that a single blood-exposure of cartilage leads to persistent damage. Monocytes/macrophages together with red blood cells are responsible for chondrocyte apoptosis and thus for irreversible inhibition of matrix synthesis. When choosing an animal model to study the effects of blood on cartilage in vivo, there are several aspects one needs to take into account. First, cartilage of smaller animals is more cellular than cartilage of larger animals (including humans), thereby having a higher matrix turnover rate. Especially in studies investigating treatment modalities, a fast turnover in smaller species could bias the results, since a faster turnover is expectedly related to a faster cure. Second, the thickness of cartilage varies between species; femoral condyle thickness of mice is around 0.05 mm and of humans 2–3 mm. This will have an influence on the impact of a joint hemorrhage on cartilage. Third, biomechanics of the animal joint should mimic those of a human joint as much as possible. We found that canine knee joints meet these prerequisites to a great extent, although canine joints also have their restrictions. For example, the clearance of blood from a joint is several times quicker than observed in mice and humans. As such, it is important to select the correct animal model for each study for proper translation of results from basic science to clinical practice.

S-MO-01.3-3
The use of ice in acute bleeding
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Repeated hemarthroses and the consequences of blood in the joint are known to contribute to joint degeneration in people with hemophilia (PWH). One primary goal to help maintain musculoskeletal health in PWH is to prevent or decrease hemarthoses and, hence, blood entering the joint space. Less blood volume in the joint space will cause less swelling, pain, spasm, movement loss, weakness, and, ultimately, less blood-induced arthropathy and morbidity. Factor replacement—when available, is the standard treatment recommendation for the management of acute hemarthroses in PWH, while ice application—as a part of RICE (rest, ice, compression, elevation) or on its own—is commonly recommended as an adjunct treatment. RICE is proposed routinely following acute musculoskeletal injuries in sports and the general population as a first aid measure to help decrease bleeding, pain, tissue metabolism, edema, and inflammation. The use of ice as an adjunct treatment for acute hemarthroses may essentially be a "copy-paste" type of recommendation, borrowed directly from sports or the general population and applied "as-is" for PWH. Published studies have consistently demonstrated experimental cooling of tissue and/or whole blood—both in vivo and in vitro animal or human models—can significantly impair coagulation and prolong bleeding. Interestingly, notwithstanding the established negative effects of cooling upon coagulation, ice application as a first aid measure for hemarthroses continues to be recommended and applied in PWH virtually universally. This presentation will investigate whether commonly used methods of ice application following acute hemarthroses in PWH can adversely affect coagulation, thereby potentially leading to increased blood volume in the joint, particularly in situations where factor infusion is delayed or unavailable.

FP-TU-04.4-1
Ankle fusion in patients with hemophilia
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Introduction: Ankle fusion in patients with hemophilia is a well-accepted treatment for end-stage arthropathy. However, long-term outcome data has been lacking, with many studies reporting findings based on very small sample sizes. The objective of this study was to evaluate the long-term results of ankle fusion in a large group of hemophilic patients treated at a single institution.
Methods: The results of 57 ankle fusions performed on 45 patients between 1971 and 2010 were reviewed retrospectively with a mean follow-up time of 6.6 years. Data was gathered for type and severity of hemophilia, HIV status, fixation technique, postoperative complications, and requirement of additional surgeries. A pain score and modified American Orthopaedic Foot & Ankle Society (AOFAS) hindfoot score was calculated for 20 ankles available for follow-up.
Results: There were no intra-operative or immediate post-operative complications related to fusion of the ankle. While the overall non-union rate was 10.4% for tibio-talar fusion and 8.3% for sub-talar fusion, this rate was reduced to 3.7% and 5.6%, respectively, after the introduction of newer surgical techniques in 1995. None of these non-unions required revision surgery. Subsequent sub-talar fusion was required in 3% of ankles that underwent primary tibio-talar fusion. The modified AOFAS scale demonstrated that 75% of patients had no pain in the operated ankle a mean of 7.2 years following surgery. The remaining 25% scored their average pain as 3 out of 10. The functional portion of the score suggested that patients have minimal activity limitations, the ability to walk for long distances, little or no gait abnormality, and overall good alignment.
Discussion/Conclusion: Ankle fusion is an excellent alternative for end-stage hemophilic arthropathy of the ankle. It successfully relieves pain and provides a good functional outcome. While the incidence of non-union is relatively high, it appears to be similar to that in the non-hemophilia population.

FP-MO-03.3-3
Pseudotumour Surgery in Hemophilia A Patients: Comparative Results between Inhibitor and Non-Inhibitor Patients
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Introduction: Hemophilic pseudotumour is a rare complication in hemophilia, occurring in 1–2% of all patients, and may be the cause of additional morbidity. Treatment relies on replacement therapy, radiotherapy, and surgery. In patients with inhibitors, surgery is usually seen as a last resort due to the risk of bleeding. We want to demonstrate that surgery for this complication has a similar evolution in both inhibitor and non-inhibitor patients.
Patients and Methods: We compare 14 cases of hemophilic pseudotumour: 7 cases in patients with severe hemophilia A without inhibitors (NIP) (mean age: 38 years, range 29–55 years) and 7 cases in patients with severe hemophilia A with inhibitors (IP), (mean age: 23 years, range 12–61 years). All patients were treated with the same surgical approach. The baseline characteristics of both groups were similar, only differing in mean age at the time of surgery and the presence of an inhibitor. During and after surgery, coverage for NIP was performed with factor VIII and coverage for IP was preformed with rFVIIa. Patients were evaluated for use of factor in the post-operative period, duration of surgery, PRBC transfusions, and days of admission after surgery. All data was analysed using the Mann-Whitney test for non-parametric independent samples.
Results: All variables analyzed were comparable in both groups. Mean duration of surgery was 3.86 hours for NIP and 3.0 hours for IP ($P = 0.44$). The number of days requiring factor after surgery was 15.86 days for NIP and 10.9 days for IP ($P = 0.06$). The number transfusions required was 8 for NIP and 8.40 for IP ($P = 0.7$). No difference was noted between groups in the days of admission (NIP: 43.71 and IP: 38.29, $P = 0.61$). One patient from each group died in the post-operative period due to sepsis, the remaining patients had a favourable evolution and no thrombotic events were detected in the follow up.
Conclusions: Our results show that given the proper hemostatic coverage, pseudotumour surgery in inhibitor patients is feasible and presents a post-operative evolution that does not differ from that of non-inhibitor patients.

FP-MO-03.3-2
The Potential Role of Synovial Thrombomodulin in the Pathophysiology of Joint Bleeds in Hemophilia
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Introduction: Hemophilic arthropathy is one of the main complications of recurrent bleeding episodes in patients with severe hemophilia; however, the precise reasons that the joints are the predilected site of bleeding in patients with hemophilia are not fully understood.
Aim: The objective of this project was to study the potential effect of synovium-derived thrombomodulin (TM) on the pathophysiology of hemarthroses.
Methods: The concentration of TM and TFPI was measured in knee synovial fluid of patients with hemophilia and controls. We used these concentrations of TM and TFPI in a thrombin generation model to analyse the in vitro effects on coagulation in plasma of 6 male controls and 6 patients with severe hemophilia. The expression of TM in synovial tissue was also studied in controls and hemophiliacs.
Results: Patients with hemophilic arthropathy had significantly higher synovial fluid TFPI and TM levels, with mean concentrations of 47 ± 27 ng ml^{-1} ($P = 0.033$) and 56 ± 25 ng ml^{-1} ($P = 0.031$) respectively, compared to the control group which presented lower concentrations of synovial fluid TFPI (26 ± 9 ng ml^{-1}) and TM (39 ± 21 ng ml^{-1}). Thrombin generation capacity was significantly reduced in the presence of TM at 56 ng ml^{-1} ($P = 0.02$), concentrations observed in the synovial fluid of patients with hemophilic arthropathy. The concomitant addition of TM 56 ng ml^{-1} and TFPI 47 ng ml^{-1} induced a highly significant inhibition of thrombin generation in the same samples ($P = 0.008$). No significant inhibition of thrombin generation was observed in the presence of control synovial concentration of TM ($P > 0.05$).
Conclusion: Our results showed increased TM levels in synovial fluid and dramatically impaired expression of TM on synovial cells. This suggests a massive release of TM into the synovial fluid, induced by a concerted action of neutrophils and cytokines on synovial cells as previously described in patients with rheumatoid arthritis.

FP-MO-03.3-5
Compartment Syndrome in Patients with Inhibitors
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There is little in the literature regarding inhibitor patients and compartment syndrome. Scattered case reports and a few studies assess surgical outcomes with the use of factor bypassing agents, within which compartment syndrome is mentioned. Hematological outcomes and successful cessation of bleeding are frequently quoted but functional outcome is generally overlooked. In literature on patients with inhibitors, the management of compartment syndrome is controversial and often anecdotal. We aim to review the literature and outcomes of patients with inhibitors who develop compartment syndrome in an effort to determine the best treatment modality. We identified 10 cases where blood products and inhibitor bypassing agents failed to normalize clotting

abnormalities and fasciotomy or amputation was performed for compartment syndrome. Six were managed with fasciotomy and 4 with primary amputation. In the fasciotomy group, prolonged bleeding (median: 14 days) was seen in 50% of cases. One patient was intubated and paralysed in an effort to control post-operative bleeding. In two cases where the patient underwent amputation, no details were given except that bleeding was controlled after an unspecified amount of time. The other two both bled persistently and required prolonged inhibitor bypassing agents and blood products for 32 days and 15 days, respectively, post-operatively. No mention is made of functional outcome on any of the patients. Compartment syndrome in patients with inhibitors is fortunately rare. When surgery is undertaken there is significant morbidity and firm justification is warranted: 40% of patients had an amputation, 50% bled significantly post-operatively. There is no mention of functional or long-term outcome in any of the patients. In compartment syndrome from other causes, delayed fasciotomy (>12 hours) is ill advised due to poor outcomes and a high amputation rate. Whether this is applicable to inhibitor patients needs further study before treatment guidelines can be ascertained.

FP-MO-03.3-1
Using the hemophilia joint health score (HJHS) in adult patients: Testing inter-rater reliability

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Introduction: The hemophilia joint health score (HJHS) is an adaptation from the former WFH orthopedic/clinical joint score, designed to pick up early signs of hemophilic arthropathy in children. In addition to the items of the orthopedic score, the HJHS also scores duration of swelling, extension loss, strength, and gait. These items are not age-specific, and therefore our hypothesis was that the HJHS is also suitable for use in adults, especially those with good joint health due to early prophylaxis.
Aim: To test inter-rater reliablility of HJHS in adult patients for use in comparative studies.
Methods: Two studies were performed: one (I) during several days in a skiing camp, and another (II) in a single day. Only one physiotherapist attended both sessions. After discussion between the physiotherapists and performing one patient together, the HJHS 1.0 was performed according to the manual, 3–4 times in all patients. Normal values for range of motion (ROM) in adults were used. Mean scores per patient, per joint, and overall inter-rater coefficients (ICC) were calculated and compared to the pediatric results by Hilliard et al.
Results: The HJHS was easy to perform in about 30 min. Results are shown in Table. Although the adult patients had a generally more favourable outcome than the children tested by Hilliard, the ICC of study I was good. The ICC of study II was much lower, probably due to a mathematical effect caused by the lack of variance in the study population. The joint scores in adults showed fewer with differences (>=4 points) than in the Hilliard study.

	Study I (n = 12)	Study II (n = 8)	*Hilliard et al (n = 8)*
Nr of physiotherapists	3	4	*4*
Severe hemophilia	67%	50%	*100%*
Age (median, range)	17.8 (14–30)	21.4 (17–31)	*7 (4–13)*
On prophylaxis	58%	38%	*100%*
Range of scores measured	0–38	0–11	*0–43*
Patients with mean score>3	11%	6%	*21%*
Overall ICC of total scores	0.80	0.59	*0.86*
Joints scored with >=4 points difference	16%	8%	*38%–40%*

Table 3: Description of all scores per joint for each patient mean values (min score- max score)

Pt	LE	RE	LK	RK	LA	RA	total
1	0 (0–1)	0 (0–1)	0.5 (0–1)	0.5 (0–1)	0	0 (0–1)	**2 (0–4)**
2	0	0	0.5 (0–1)	1 (0–1)	7 (3–9)	0	**8 (4–10)**
3	0	0	0	0	0	0	**0**
4	0	0	0.5 (0–1)	0 (0–1)	1 (0–2)	1 (1–2)	**3 (0–5)**
5	0	0	0.5 (0–1)	0 (0–1)	0	0	**1 (0–2)**
6	0	0 (0–1)	0	0	0	0 (0–1)	**0 (0–2)**
7	0 (0–1)	0	0.5 (0–1)	0	4 (2–6)	2 (1–5)	**7 (3–11)**
8	0	0	0 (0–1)	0.5 (0–1)	0	5 (1–9)	**5 (1–10)**

Table 3a: Summary of scores per physiotherapist

	Copenhagen	Utrecht	M alm o	Stockholm
Mean	4.6	3.0	3.0	2.1
Med (IQR)	3.0 (0.25 - 9.75)	0 (0–7.5)	2.5 (0.25–4.75)	2.0 (0.25–3.75)
Range (max 164)	0–11	0–10	0–9	0–5
% zero	25%	63%	25%	25%
% < 4	50%	63%	50%	75%

Conclusion: The HJHS 1.0 generally performed well in adults. In comparative studies, small differences may be due to inter-rater variability.
References:
1. Gilbert MS. Prophylaxis: musculoskeletal evaluation. Semin Hematol 1993;30:3–6.
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Extra data:

FP-MO-03.3-4
Arthroscopic Ankle Arthrodesis for Hemophilic Arthropathy

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Introduction: In the second decade of life, the ankle may be considered the most common site for hemophilic arthropathy. To the best of our knowledge, no detailed reports have been published regarding arthroscopic ankle arthrodesis for hemophilic arthropathy. The aim of this follow-up study is to investigate the outcome of arthroscopic ankle arthrodesis for hemophilic arthropathy.
Materials and Methods: We performed six arthroscopic ankle arthrodeses in five patients between 2004 and 2011. All patients had severe hemophilia A. The average patient age during the operation was 28 years. Following ankle joint debridement and preparation of the bone surfaces, ankle joint stabilization was accomplished by internal fixation using canulated screws placed under fluoroscopic control. The American Orthopaedic Foot and Ankle Society (AOFAS) ankle-hindfoot scale was used to assess the preoperative and postoperative functional levels.
Results: The mean operation time was 149 minutes. The mean AOFAS ankle-hindfoot score improved from 43 points preoperatively to 83 points postoperatively. Union was obtained in all 6 ankles. No major complications were observed. Perioperative pain was mild and no opioid was used postoperatively.
Discussion: Our cases achieved high satisfaction levels for pain relief. The arthroscopic technique represents an attractive method for achieving ankle fusion in hemophilic arthropathy. First, little articular cartilage remains in hemophilic arthropathy and cartilage debridement can be carried out easily. Second, varus or valgus malalignment and anterior or posterior tibiotalar translation are usually mild and it is possible to correct the ankle alignment arthroscopically. Third, arthroscopic arthrodesis is less invasive and requires less periosteal stripping, which has positive influences on bone union. Fourth, arthroscopic ankle arthrodesis is associated with reduced postoperative pain and decreased complications, leading to shortened hospitalization and recovery time.
Conclusion: Arthroscopic ankle arthrodesis is a useful technique for hemophilic arthropathy.

FP-TU-04.4-2
Association of Hemophilic Arthropathy with Genetic Markers Related to Bleeding Tendency, Joint Inflammation and Structural Cartilage

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Objective: The objective of this study was to identify the prothrombotic genes [*FVLeiden, FII20210A, MTHFR C677T,* and *A1298C* (hemorrhagic tendency)]; joint inflammation genes [pro-inflammatory (*TNF α -308 A/G, -238 A/G*) and anti-inflammatory (VNTR *IL-1RN**2)]; and cartilage structure variants (VNTR *CS1*) in Mexican pediatric patients with hemophilia A (HA) and B (HB) and to associate these gneers with the arthropathy state by international criteria.
Methods: We studied 50 HA and HB patients between 5 and 16 years of age: 50% were severe, 41% were moderate, and 9% were mild. Clinical assessments of hemorrhagic tendency were previously performed in all patients; 74% were evaluated by the World Federation of Hemophilia (WFH) physical joint examination instrument (WFHPEI) and 36% had magnetic resonance imaging (bilateral knee joint) evaluated with the progressive and additive magnetic resonance imaging (MRI) score. PCR-RFLP was performed for genotypes identification.
Results: In 55% of patients, the knee joint showed no damage (score 0), while 16% showed highest damage (maximum score possible for each instrument). The statistical analysis between instruments and measuring by different specialists showed no difference. The *677TT* genotype of *MTHFR C677T* polymorphism showed association with less clotting activity and with a higher number of damaged joints. The effusion phenomenon was associated with the heterozygote *C1298A* of *MTHFR*. Heterozygote *TNF-G308A* polymorphism showed an increased tendency for onset of symptoms at earlier age, a higher number of damaged joints, and greater subchondral cysts and hemarthroses. No association was found between clinical variables and the presence of the VNTR's of *IL1RN**2 and *CS1*; the rest of the markers had a low frequency for their analysis.
Conclusions: *677TT* genotype of *MTHFR* is associated with low levels of clotting activity and a higher number of damaged joints. The MTHFR *A1298C* enzyme mutation in heterozygote state is associated with greater knee effusion. This study highlights the importance of future associations between genetic markers and clinical variables assessed by MRI.

FP-TU-04.4-3
A Population-Based Longitudinal Study of Musculoskeletal Disorders in People with Hemophilia, and their Matched Controls
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Background: Musculoskeletal disorders are the most common manifestations of hemophilia and are responsible for the greatest long-term morbidity and cost. Accordingly, the primary goal of hemophilia therapy is to prevent or ameliorate the musculoskeletal manifestations of this disease.
Objective: To evaluate the long-term outcome of musculoskeletal disorders in people with hemophilia.
Methods: A population-based cohort study including 1430 patients with hemophilia (383 with severe disease) enrolled from local-, in-, and out-patient registries compared to 7,150 age- and sex-matched controls. Using international classification of diseases (ICD) diagnostic codes, 7 categories of musculoskeletal disorders were evaluated. Cox proportional hazard regression models were used to estimate the risk of musculoskeletal disorders.
Results: The mean follow-up for the 1,431 patients was 44.2 years. The relative risk of hemoarthrosis and joint stiffness among patients with hemophilia compared to controls was 6.18 ($P < 0.001$); soft tissue disease 1.73 ($P < 0.001$); and musculoskeletal deformities 3.91 ($P < 0.001$). No significant differences were observed in relative risk for osteoporosis, 1.67 ($P = 0.07$), synovitis and tenosynovitis 1.84 ($P = 0.07$), or knee joint damage 1.45 ($P = 0.08$).
Conclusions: This long-term follow up study has, for the first time, provided extensive and detailed information regarding the incidence of musculoskeletal disorders in people with hemophilia living in Sweden. It shows that the risk of muscle atrophy, hemoarthrosis, joint stiffness, and soft tissue disease as well as musculoskeletal deformities are higher in patients with hemophilia compared to matched controls. However, there were no significant differences in the risk for osteoporosis, synovitis and tenosynovitis, and knee joint damage.

FP-MO-03.3-6
^{186}Re radiosynovectomy for chronic synovitis in children with hemophilia
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Aims: To assess the clinical effectiveness of radiosynovectomy (RS) using ^{186}Re colloid in children with severe hemophilia A and B considering reduction of bleeds into joints, improvement of joint activity, and progression free survival (PFS).
Methods: Eighty-two children aged 7–18 years (mean age 14.6 years) were included in the study. Seventy-three had hemophilia A (4 with inhibitor factor VIII), 4 had hemophilia B (1 with inhibitor factor IX), and 5 had von Willebrand disease. There were 88 therapies including injections into the following joints: knee 32, elbow 36, ankle 16, and shoulder 4. In 49 cases, this was initial therapy and in 6 cases repeat therapy due to recurrence or deterioration. Injected activity of ^{186}Re colloid was dependent on type and size of joints, range: 60–180 MBq. Post therapy imaging was performed in each case 1 hour after injection of radioisotopes, and then on day 2 and 3. The number of bleedings into joints per month, improvement of joint movements, and other clinical changes were evaluated before and after therapy in 3 month intervals. US images were used to assess changes in joint effusion and synovial overgrowth. PFS in terms of significant clinical improvement within joints was assessed using standard Kaplan Meier methods. The prognostic significance of selected parameters was tested using discriminate function analysis.
Results: No leakage of isotope from joints was observed in post-therapeutic examinations in all cases. The average number of bleeds was reduced ($P < 0.001$). A significant clinical improvement was noted in decrease of circumference of joint, mobility, and pain reduction (P,0.05).
Conclusions: Three years after start of RS therapy a significant improvement in the treatment of arthropatic hemophilia in children can be observed.

FP-TU-04.4-4
IL-6 Receptor Antagonist as Adjunctive Therapy for the Prevention and Treatment of Bleeding-Induced Arthropathy
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Background: The major cause of morbidity in patients with hemophilia is bleeding-induced joint damage. Once hemophilic arthropathy is established, prophylactic clotting factor replacement may not completely interrupt degeneration.
Objectives: IL-6 receptor antagonists have proven effective for the treatment of rheumatoid arthritis in humans and for decreasing the inflammatory changes of autoimmune diseases in mouse models. We investigated combining therapy using MR16-1, a rat IgG blocking antibody directed against mouse IL-6 receptor (anti IL-6R), with factor VIII (FVIII) replacement to protect against inflammatory sequelae of hemarthrosis in hemophilia A mice.
Methods: Factor VIII knockout mice received needle punctures to the left knee joint capsule on days 0, 7, and 14 to induce recurrent hemarthrosis. The mice were assigned to one of 4 treatment groups: no treatment; FVIII 150 IU kg^{-1} following induction of bleeding; FVIII 150 IU kg^{-1} following hemorrhage with MR16-1; or with non-specific control antibody (rat IgG). On day 0, 8 mg was administered intraperitoneally and 0.5 mg was administered on days 7, 14, and 21. Joint diameter was measured serially. Plasma for FVIII inhibitor antibody was evaluated on days 14 and 42. Joint tissues were harvested on day 42 and stained using H&E, Safranin-O. Histopathology was scored for synovitis using the Valentino score, cartilage integrity using the Modified Mankin's score, and for macrophage infiltration (CD68 immunostain).
Results: Despite equivalent rates of inhibitor formation between groups, mice receiving anti IL-6R had better survival, less joint swelling, and the synovitis (Valentino) and Modified Mankin's scores were lower ($P < 0.05$). The major effects of anti IL-6R on synovium were decreasing synovial hyperplasia and hemosiderin deposition, and diminishing persistent macrophage infiltration. Cytokine analysis showed anti IL-6R group maintained higher serum IL-6 level compared to FVIII ± control antibody groups, consistent with reports that state IL-6 receptor blockade decreases serum IL-6 clearance.
Conclusions: Anti IL-6R adjunctive therapy decreased inflammatory changes after bleeding in hemophilia joints; further evaluation of long-term benefit is justified.

FP-TU-04.4-5
Plasmin-Induced Proteoglycan Release in Human Cartilage is PAR-Dependent
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Introduction: Hemophilic arthropathy (HA) is characterized by synovitis and degradation of the cartilage. We recently observed, in a murine model of acute hemarthrosis, an increase in synovial fibrinolytic activity and synovial plasmin levels following hemarthrosis. It is known that proteases of the fibrinolytic system, such as plasmin, are able to induce cartilage degradation. Cross-talking between coagulation and inflammation is mediated by protease-activated-receptors (PARs). The aim of this study was to investigate if plasmin-induced cartilage damage is PAR-dependent.
Method: Full-thickness human articular cartilage tissue was obtained during total knee surgery. Slices of cartilage were cut aseptically from the articular surface. Within 1 hour of dissection the slices were cut into square pieces, weighed aseptically (range: 5.0–15.0 mg), and each sample was individually placed into culture. The cartilage was cultured for 4 days in the presence of different concentrations plasmin (10, 30, or 100 nm). In addition, the cartilage was transfected with PAR1-4 small interfering RNA (siRNA) (600 nm) or control siRNA (600 nm) and cultured with plasmin (100 nm). Cartilage matrix turnover, in terms of proteoglycan release, was determined at day 4. To investigate the silencing effect of the siRNA transfection, RNA was extracted and PAR1-4 mRNA expression was analyzed with RT-PCR.
Results: Plasmin increased proteoglycan release in human cartilage in a dose-dependent and statistically significant manner (217% for plasmin at 100 nm). Plasmin-induced proteoglycan release was statistically significantly reduced with PAR1-4 siRNA (54% for plasmin at 100 nm). Control siRNA failed to reduce plasmin-induced proteoglycan release. Transfection with PAR1-4 siRNA resulted in complete suppression of PAR1-4 mRNA expression, whereas no effect of control siRNA on PAR1-4 mRNA expression was noted.
Conclusions: These results demonstrate for the first time that plasmin-induced proteoglycan release in human cartilage is PAR-dependent and offers promise for the use of siRNA as a new strategy for therapeutic intervention in HA.

FP-TU-04.4-6
A Diagnostic, Cross-Sectional Evaluation of Joint Status Using Magnetic Resonance Imaging in Patients with Severe Hemophilia A Treated with Prophylaxis versus On-Demand Therapy
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Objectives: In children with hemophilia A, factor VIII (FVIII) prophylaxis reduces joint damage and bleeding frequency compared with on-demand therapy. This investigation used magnetic resonance imaging (MRI) to evaluate bone and cartilage damage following prophylaxis begun at different ages during childhood versus on-demand therapy.
Methods: This cross-sectional multinational investigation enrolled patients (age range: 12-35 years) with severe hemophilia A and no history of FVIII inhibitors. Patients were assigned to 1 of 5 groups: primary prophylaxis started at age <2 years (group 1), secondary prophylaxis started at age 2-<6 years (group 2), 6-<12 years (group 3), or 12-18 years (group 4), or on-demand treatment (group 5). MRI was performed on 4 index joints (2 ankles, 2 knees). Efficacy was assessed using compatible additive MRI scoring (maximum ankle [primary variable], mean ankle, and mean and maximum index joint scores) and Gilbert scores in the per-protocol population ($n = 118$).
Results: Compatible additive MRI scores generally increased in prophylaxis groups with current age and age of prophylaxis start. All prophylaxis groups (groups 1–4) displayed better joint status than group 5. In patients aged 27-35 years, the maximum ankle score medians were 0.0, 17.0, and 18.0, and the mean index joint score medians were 0.0, 8.1, and 13.8 in groups 1, 4, and 5, respectively. Physical examination (Gilbert score) revealed outcomes similar to, but less pronounced than, MRI scoring.
Conclusion: MRI scores identified pathologic joint status and indicated that prophylaxis was clearly beneficial compared with on-demand therapy. Joint-protective effects were

enhanced with primary prophylaxis versus secondary prophylaxis. Higher maximum ankle scores versus index joint scores showed that ankles were the leading indicator of hemophilic arthropathy and could be used to evaluate joint disease progression.
Contribution to the practice/evidence base of hemophilia and bleeding disorders: MRI scoring is highly sensitive in evaluating joint status in patients with hemophilia.
Conflicts of Interest: Dr. Theodossiades is a member of the ADVANCE working group sponsored by Bayer. Dr. Zanon has acted as a paid consultant for Bayer, Baxter, Novo Nordisk, Pfizer, and Grifols. Dr. Kellermann is an employee of Bayer Vital GmbH. Dr. Lundin received funds for conference participation from Bayer. Drs. Katsarou and Zimmermann have no conflicts of interest to declare.

PO-WE-155
Radioactive synovectomy of the shoulder joint in patients with hemophilia
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The shoulder joint is affected relatively infrequently in people with hemophilia (PWH). The relatively deeper positioning of this joint as opposed to knee, shoulder, or ankle joints renders it technically more difficult to access via percutaneous interventions. In this study, we report our mid-term results of performing radioactive synovectomy (RAS) on shoulder joints in PWH. Over a 10-year period, we performed 8 RAS on shoulder joints in 7 patients and they constituted 2.1% of all RAS we perfomed. All cases except one had hemophilia A and three had inhibitors. The average age of patients at the time of RAS was 19.3 (range 14–25). One patient received a second RAS on the same shoulder joint after a one-year interval. We performed RAS on 5 right and 3 left shoulder joints. We used 2 mc Rhenium 186 (Re-186) in 6 cases and Yttrium 90 (Y-90) in 2. All procedures were performed under topical anaesthesia and sedation using spinal-type longer needles. Intra-articular placement of the needle was confirmed by image intensifier. After the procedure, patients' arms were placed in a sling for three days and then formal physiotherapy was initiated. No specific problems were encountered either immediately after the RAS or in the long run. In only one case, hemarthrosis attacks persisted after Y-90 RAS and we had to repeat the procedure one year later, again using Y-90. This patient was the first case in this series. After the second RAS, joint bleeding attacks discontinued. In all other cases (n = 6), a single use of Re-186 RAS was sufficient to stop (n = 4) or significantly diminish (n = 2) bleeding attacks. RAS on shoulder joints resulted in a complete response in 57% and a partial response in 43% of PWH. Performing RAS with Re-186 on shoulder joints in PWH is an effective treatment modality and yields similar results to RAS procedures on other joints.

PO-WE-156
The management of domiciliary acute hemarthrosis by ultrasonography: Experience in a single centre
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Introduction: Hemarthrosis is the most common bleeding disorder and a major cause of morbidity in hemophilia. There is no standardization for the dose and duration of on-demand treatment monitorized by clinical data. We used ultrasonography to assess and monitor the treatment of hemarthroses.
Material and methods: During 2011 we performed a domiciliary ultrasound protocol consisting of several ultrasound explorations every 3–4 days until joint bleeding disappeared. When a patient suspected he or she might have a hemarthrosis, we were called in to perform a domiciliary ultrasound exploration. We evaluated clinical findings, joint bleeds, and synovial inflammations, and treatment was adjusted according to these findings.
Results: We had 16 patients with a median age of 30 (range 7–46). On day 0, ultrasonagraphy showed that 5 symptomatic patients had no joint bleeding. Eleven patients were symptomatic and had joint bleeds (3 elbows, 3 knees, 6 ankles). On day +3, we detected 8 joint bleeds, although 7 of them were already asymptomatic and only 4 of them were symptomatic. On day +7, 5 joint bleeds were registered (7 asymptomatic and 1 symptomatic); on day +10, 3 joint bleeds were registered (6 asymptomatic and 0 symptomatic); on day +14, 2 joint bleeds were registered (3 asymptomatic and 0 symptomatic); on day +17, 0 joint bleeds were registered (2 asymptomatic and 0 symptomatic). In symptomatic patients, 25 IU kg^{-1} every 24 hours were administered while symptoms persisted. In asymptomatic patients where a joint bleed was detected, 30 IU kg^{-1} were administered twice per week until it disappeared. There was no rebleeding 10 months after the first bleeding episode was detected.
Conclusions: We recommend performing protocol ultrasounds for the maintenance of intensive replacement therapy while joint bleeding persists, regardless of whether the patient is symptomatic or not, in order to avoid rebleedings and target joints. We have reported 4 no-bleeding episodes when patients called us believing they had a hemarthrosis. Ultrasonography is a useful radiological tool for assessing the evolution and monitoring treatment of hemarthrosis.

PO-WE-157
Autologous stem cell treatment in hemophilic arthropathy
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The most typical manifestation of hemophilia is articular bleeding (hemarthrosis). The consequences of recurrent bleeding into a joint are chronic synovitis and destruction of the articular cartilage and subchondral bone. This condition, called chronic hemophilic arthropathy, is characterized by destructive changes that lead to severe pain, deformity, loss of motion, and functional disability. The knee is the most common site of hemophilic arthropathy. At the present time the therapeutic possibilities of stem cells are one of the most interesting subjects of modern medicineand have been used for several treatments. This report presents the results of a long-term follow-up (one year post-operative) analysis of two patients who received a percutaneous implant, into a chronic hemophilic knee arthropathy, of autologous mononuclear cells that included hematopoietic and mesenchymal stem cells. The cells were derived from bone marrow and mobilized to peripheral blood by granulocyte colony-stimulating factor. Patients' informed consent was obtained. Routine blood tests, X-rays, and ultrasonography studies were performed. A volume of 5 ml, containing $110x10^6$ cells (viability 99%), was injected into the affected joint of the first patient and $910x10^6$ cells (viability 97%) into the affected joint of the second patient. Relative rest for two weeks followed the procedures. Follow-up included: state of joint involvement, pain, motility, requirements of antihemophilic factors, corticoids, or analgesics. The follow-up evaluation demonstrated an increase in joint motion, diminished pain, and less requirement and frequency of the use of anti-hemophilic factors in 80% in both patients. As far as we know, these are the first reported cases of hemophilic arthropathy treated successfully with autologous cell therapy. This option is a low-cost and relatively easy-to-perform procedure that opens new ways to treat hemophilic arthropathy.

PO-WE-158
Knee on Flexion: Osteotomy of Femoral Extention in Pediatric Patients with hemophilia
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Objective: Present the experience with the use of femoral osteotomy in inverted "V" for the correction of deformities in flexion of the knee. Distal metafisiary osteotomy with a wide contact surface and a minimal internal fixation.
Methods: A total of 8 patients diagnosed with knee flexion contracture, carriers of severe hemophilia A, treated between 2006 and 2010, were examined. The averaged age was 11 years (range 8–15 years). They presented knee flexion contracture between 40° and 70° (5 cases: 40°–50°, 2 cases: 51°–60°, 1 case: 70°). All had pain in active-passive mobility and gait. The average number of instances of hemarthrosis was 13.5 per year (range 12–15 times per year). The 8 cases (5 right-sided and 3 left-sided) were treated with inverted "V" distal femoral osteotomy. The internal fixation was with crossed Steinmann wire and the external immobilization was with a long cast. Factor VIII was also post-operatively administered for 3 weeks on average. There was one patient with high response inhibitors whom we treated with FEIBA.
Results: The bone healing was achieved in an average of 9.1 weeks (range 8–10 weeks). The follow-up was an average of 2.8 years (4 maximum and 1 minimum). Post-operative patients were sent to physiotherapy for muscle strengthening and gait training. Extention was achieved in 100% of the cases. The average active motion was 80° (range 60°–100°). No patient had painwalking or moving. The average number of instances of hemarthrosis was 1.7 per year (range 1–3 times per year).
Conclusions: The inverted "V" osteotomy is very stable and easy to perform. The operation requires minimal internal fixation that is removed at the time of removal the external immobilization. This operation would be useful in scarce-resource countries, because its requirements are minimal.

PO-WE-159
Abnormal inter-extremity difference (AIED) of quadriceps muscle strength and relationship to patellar tendon thickness and joint status in PWH
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Introduction: Significant complications of hemophilia are intra-articular bleedings, which occur more frequently in joints of the lower limb. Recurrent joint bleedings eventually lead to hemophilic arthropathy. In some cases, recurrent intra-articular hemorrhages occur predominantly on one side of the body. Theconsiderable joint destruction of the affected side results in detrimental consequences for strength symmetry of the lower extremities. In this context, an asymmetry of muscular strength greater than 20% has been described as almost certainly abnormal. It has to be assumed that such a strength-specific abnormal inter-extremity difference (AIED) has direct implications for the related tendon system. The aim of this study was to investigate the relationship between an AIED of the quadriceps femoris, patellar tendon thickness (T-PT), and joint status in people with hemophilia (PWH).

Methods: T-PT was measured in both legs by ultrasonography in 14 PWH (age: 47 ± 8 years) with a verified AIED of the quadriceps strength. Ten had severe hemophilia A, two had severe hemophilia B, one had moderate hemophilia A, and one had mild hemophilia A. Isometric quadriceps strength was evaluated with a knee extensor device (SCHNELL, Germany) at a defined device angle of 75° flexion. The WFH-recommended Physical Joint Examination score was used for the description of knee joint status. T-PT and WFH score values were compared between the weaker (MIN) and stronger (MAX) side with a paired student's t-test.
Results: For T-PT, a difference of 15% was detected between the extremities (T-PT-MIN vs. T-PT-MAX [mean ± SD]: 3.67 ± 0.49 mm vs. 4.30 ± 0.92 mm, $P < 0.01$). The WFH score of the knee joint also differed remarkably between the extremities (Score-MIN vs. Score-MAX: 5.9 ± 3.4 vs. 2.4 ± 3.0, $P < 0.01$).
Conclusion: Our data show that AIED of quadriceps muscle strength is linked to a reduction of patellar tendon thickness and more severe destructions of the knee. The considerablly thinner patellar tendon corresponds to reduced mechanical loading capacity and potentially to an increased injury risk during daily activities.

PO-WE-160
Is the surgical treatment for flexum knee in patients with hemophilia still necessary?

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Introduction: Flexum knee continues to be a frequent pathology in boys and young men with hemophilia, mainly in developing countries, limiting the quality of life of patients. Even flexion contracture from 10° to 15° produces alterations in the biomechanics of the knee, predisposing the early development of arthropathy.
Objective: To evaluate the efficacy of conservative treatment of flexum knee with botulinum toxin in patients with hemophilia.
Materials and Methods: Fifteen knees belonging to 12 patients (mean age: 19) underwent this treatment. They were divided into three groups depending on the degree of flexion contracture: 0°–30° (n=9); 31°–60° ($n = 2$); and 61°–90° ($n = 4$). The mean follow-up was 8 months, with a range of 6–14 months. Two patients with 4 knees with flexion over 60° were not able to walk before treatment. Joint range of motion, posture, and patient's gait were assessed before the application of the botulinum toxin, done after 50% replacement factor therapy. An average dose of 6 to 12 units a muscle was used in the hamstrings and/or Fasciae lata tensor to produce an inhibition of the same, to facilitate rehabilitation. A pre- and post-treatment questionnaire about everyday life activities was distributed. In cases where flexion contracture was between 15° and 30°, physiotherapy treatment was based on the pattern of gait and normal posture recovery; while in more complex cases we had to include work on the lumbopelvic region and core stability exercises.
Results: In group 1 (with a flexion contracture of less than 30°), all patients improved their extension and gait. In group 2 they improved the extension without reaching 0° and their gait. The two patients in group 3 were able to walk again, improving the extension, without reaching 0°.
Conclusion: Conservative treatment of flexum knee with botulinum toxin is a useful method to diminish flexion contracture and improve the quality of life of patients.

PO-WE-161
Pseudotumours in patients with inhibitors

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Introduction: Pseudotumours are a major complication in patients with hemophilia and can be especially devastating in the presence of inhibitors. Only a few cases have been reported in the literature and all were treated in different centres.
Objectives: The aim of this paper is to show the experience, complications, and possible treatments in patients with hemophillia and inhibitors whose pseudotumours were treated at one centre.
Materials and Methods: Six patients with 7 pseudotumours were treated. All the patients suffer from severe hemophillia A. The mean age was 21.4 years (range: 13–60 years). One patient presented soft tissue (15%) pseudotumours in the arm. The most frequent locations of the bone pseudotumours were the femur (3, 50%), tibia (2, 33.3%), and calcaneus (1, 16.6%). Two patients (33.3%) had a pathological fracture, one in the femur and the other one in the tibia. One patient simultaneously had a pseudotumour of femur and calcaneus on the same lower limb. Both pseudotumours were embolized before surgery for bleeding control. The rFactor VIIa bypassing agent was used in all patients. All patients with bone pseudotumours were treated surgically and the soft tissue pseudotumour was not necessary because it responded to conservative treatment.
Results: Five true pseudotumours (83.3%) were recovered with surgical treatment. One patient (16.6%) who had a large femur pseudotumour with a pathological fracture died of sepsis secondary a necrotizing fascitis. The patient with the soft tissue pseudotumour was healed with conservative treatment. Two patients (33.3%) required aditional surgery for injuries secondary to the additional surgery.
Conclusions: Our results show that pseudotumours in patients with inhibitors can be treated with surgery and bypassing agent.

PO-WE-162
Incidence of Hemophiliac Arthropathy in Moderate and Mild Hemophilia Patients: A Retrospective Study from Paris-Bicêtre Hospital

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The hemophilic arthropathy is the major functional complication in severe hemophilia. Patients with moderate hemophilia (modh) or minor hemophilia (minh) may also present such a complication but are rarely reported in literature. We report a retrospective monocentric study on incidence and characteristics of arthropathy in a cohort of 237 patients with modh ($n = 70$) or mild ($n = 167$) hemophilia. All patient files and X-rays were reviewed on a systematic basis. Clinical arthropathy was defined by a limited range of motion or a synovitis, lasting over 2 years, with functional impairment, with or without abnormal X-ray. Arthropathy occurred in 14 (20%) patients with modh and in 5 (3%) patients with minh. For these cases the median (range) age at study entry, first joint bleed, diagnosis of clinical and radiological arthropathy was 39.5 years (20–56 years), 7 years (2–16 years), 24 years (7–38 years), 26.5 years (7–48 years) for patients with modh and 47 years (15–69 years), 19 years (8–38 years), 41.5 years (26–57 years), 39 years (26–52 years) for patients with minh, respectively. A joint replacement was necessary in 6 patients with modh (3 knees and 3 hips) and in 1 patient with minh (hip). The number of hemarthrosis prior to discovery of arthropathy was ≥5 for knees, ankles, and elbows and ≤ 3 for hips. A delay higher than 48 hours between onset of hemarthrosis and treatment was observed in all patients at least once. Only 2 patients received prophylaxis. All patients had factor VIII:C or IX:C levels lower than 12%. Correlation between clinical and radiological findings was not always found. In conclusion, this study shows that some patients with modh and minh develop arthropathy. Specific education of patients with modh and minh is particularly essential to help early diagnosis and treatment of joint bleeds. Close monitoring is also warranted to avoid repeated recurrence of hemarthrosis and prevention by prophylaxis should be discussed if appropriate.

PO-WE-163
Validity of Ultrasound for Assessment of Hemophilic Arthropathy: MRI, X-Ray and Physical Examination Correlation

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Objective: To determine the convergent and discriminant validity of ultrasound (US) for assessing hemophilic knees and ankles as compared with magnetic resonance imaging (MRI), radiography, and physical examination.
Methods: Ankles ($n = 34$) or knees ($n = 25$) of hemophilic/von Willebrand boys (median age: 13 years, range: 5–17 years) with a history of prior joint bleed were examined by US, MRI, X-ray and physical examination in Toronto, Canada and Vellore, India. US scans were performed by two operators: one blinded to clinical/MRI data and one unblinded. US scans were read by 4 blinded reviewers and then unblinded to corresponding MRI findings according to a proposed 0–14 item US scale. MRI scans were blindly and independently read by 2 readers according to a 0–17 item scale. Physical examinations were scored by the Hemophilia Joint Health Score (HJHS) and radiographs were scored by Pettersson scores.
Results: X-rays of knees presented with higher Pettersson scores than examinations of ankles (P=0.03). US poorly correlated with MRI in ankle studies (unblinded: $r = 0.33$, $P = 0.05$) and highly correlated in knee studies (blinded: $r = 0.85$, $P < 0.0001$; unblinded: $r = 0.83$, $P < 0.0001$). Correlations between US and number of lifetime bleeds in the study joint were poor for ankles ($r = 0.35$–0.42, $P = 0.01$) and moderate ($r = 0.48$–0.51, $P = 0.01$) for knees. US did not correlate with HJHS scores in ankle examinations but did correlate substantially with these scores in knee studies ($r = 0.72$, $P < 0.0001$). Correlations between US and X-rays were moderate in knee studies ($r = 0.55$–0.60, $P = 0.001$), but non-significant in ankle studies. In ankle studies, blinded- and unblinded-operator US (same AUC = 0.81) and Pettersson scores (AUC = 0.67) had excellent and substantial diagnostic performances, respectively, to discriminate mild from moderate/severe arthropathy, but study joint HJHS scores (AUC = 0.50) were non-diagnostic. In knee studies, blinded- and unblinded-operator US (AUC = 0.94 and 0.96, respectively), HJHS (AUC = 0.86) and Pettersson (AUC = 0.91) scores all demonstrated excellent discriminative diagnostic accuracy.
Conclusion: US is useful for assessing soft tissue changes and late osteochondral abnormalities (peripheral joint changes) in hemophilic joints, but has limited value for evaluating mild osteochondral changes. *Funding: Bayer Healthcare Inc., Canada.*

PO-WE-164
MR Imaging as a Screening Tool for Early Detection of Arthropathy in Hemophilic Children: Systematic Review and Recommendations

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Objectives: To determine whether magnetic resonance imaging (MRI) can accurately detect hemophilic arthropathy in young hemophilic children and whether MRI screening of early intra-articular soft tissue bleeds improves the functional status of joints over time. The purpose of this study is also to identify areas that require further research in order to improve medical management of hemophilic arthropathy in the future.
Methods: An electronic literature search using an optimal search strategy was conducted to identify studies pertaining to the diagnostic accuracy of MRI in assessment of the

ankles, knees, and elbows of children with hemophilic arthropathy. Bibliographic references of the retrieved studies were assessed for additional relevant reports. The reporting quality of the included studies was assessed using a semi-quantitative approach based on the STARD tool, developed to improve the reporting of studies on diagnostic accuracy. The reviewers independently analysed every study to assess and score the quality of the description of each STARD item.
Results: The electronic literature search retrieved 153 and 242 unique citations from MEDLINE and EMBASE, respectively. A total of 29 studies were chosen for inclusion from the results of the search and from the review of bibliographic references. Using the STARD criteria, the average score for the quality of reporting was 11.5 out of a possible 25 points. This indicates a relatively poor quality of reporting. Preliminary findings suggest that MRI performs better for discriminating early changes, but not for differentiating stages of arthropathy as compared to radiography and clinical scores.
Conclusion: There is no direct evidence that screening of early intra-articular soft tissue bleed with MRI improves the functional status of joints over time. Moreover, there is "poor" to "fair" evidence in quality and quantity of studies to suggest that MRI has a role in diagnosing early changes in hemophilic arthropathy.

PO-WE-165
Frequency, Risk Factors and Consequences of Decreased Bone Mineral Density in Children with Hemophilia A and B

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Introduction: A hemophiliac patient in his most .This study assessed the frequency and risk factors associated with decreased bone mineral density and its impact on quality of life during childhood, the period of life when bone density should reach its maximum level, with little study result as yet.
Materials and Methods: 37 children with severe hemophilia A and B, referred to Mofid Children's Hospital in 2010, were selected as continuously available. Joint score, body mass index (BMI), bone mineral density (BMD) by Dual energy X-ray absorptiometry, level of inhibitor and serological viral tests were measured in all patients. Short forms of Haeamo-QoL questionnaire were used to assess their quality of life. The entered data was statistically analyzed by Kolmogorov-Smirnov Z, Mann Whitney ? t-test, Fisher's Exact, and χ^2 tests as needed.
Results: In this study the overall prevalence of low bone density was 35%. 32 out of 37 patients (86.5%) had lower than normal BMI. Although 13 of the patients (40%) had low but none of the children with normal BMI had low BMD, this difference was not statistically significant. Factors that related significantly to the frequency and severity of decreased BMD included age, presence of inhibitor antibodies, and reduced joint range of motion. Decreased BMD was found in 43.3% of children with on-demand treatment but in just 12.5% of patients who were on prophylaxis. Total quality of life score, and scores of "others" and "attitude" dimension of it were decreased significantly in patients with decreased BMD.
Conclusion: BMI should be maintained by appropriate nutrition and exercise to prevent loss of BMD in children with hemophilia. Close Orthopedic observation, a prophylaxis regimen, and early detection of inhibitors and its management in early childhood are important in the maintenance of bone density and quality of life.

PO-WE-166
Pseudotumours in Mild Hemophiliacs - A Rare Pathology

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Objectives: Availablity of clotting factor concentrates in developing countries should prevent disastrous consequences in hemophilia patients, such as hemophilic arthropathy and pseudotumour formation. We looked at pseudotumours, a rarity (1–2%), in our hemophilia cohort to see whether this dreaded complication is still a problem in the developed world. The best noninvasive investigation to differentiate pseudotumours from sarcomas was undertaken.
Methods: A radiological retrospective study of our tertiary referral centre database over the past 10years (2001–2011) was performed. Clinical presentation, management, and complications were analysed and various imaging modalities were compared.
Results: A total of 6 patients with possible psuedotumours were identified and 2 of these psuedotumours were sarcomas. Magnetic resonance imaging (MRI) is the best imaging modality to differentiate pseudotumours from sarcomas. All of the patients had mild hemophilia A. Complications included bowel obstruction, neurovascular compromise, bone erosion, renal and respiratory failure. These led to lengthy hospital intensive care stays and 2 deaths.
Conclusions: No severe hemophiliacs or inhibitor patients with pseudotumours were found in our centre. Nonsevere hemophilia patients differ from their severe counterparts in that they tend to ignore their bleeding problems, present late, are unable to self-treat, and do not attend regular follow-ups. Late diagnosis of soft tissue hematomas and lack of compliance in mild hemophiliacs leads to pseudotumour formation. Radiological knowledge enabling differentiation of pseudotumours from sarcomas is very important.
Contribution to practice: Compliance and active management following soft tissue bleeds in mild hemophiliacs is extremely important. Sarcomas must not be forgotten in hemophiliacs and specific radiological features should be used to differentiate them from pseudotumours.

PO-WE-167
Clinical Utility of Joint Assessment by the Hemophilia Joint Health Score (HJHS) at an Academic Pediatric Hemophilia Center

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Background: Hemophilia Joint Health Score (HJHS) assessment, a sensitive and validated method for monitoring joint change during annual hemophilia comprehensive exams, is a labor-intensive measure completed by an expert physiotherapist (PT). The objective of this study was to assess the clinical utility in a "real world" setting of current methods of joint assessment in a large pediatric hemophilia centre.
Methods: One hundred patients (pts) with hemophilia were identified from Children's Hospital Boston Hematology records with an HJHS exam at an annual comprehensive visit between March 2009 and August 2011. One hundred fifty-eight visits included an evaluable, 40 minute HJHS exam. HJHS version 2 was performed by the centre PTs. An HJHS joint abnormality was defined as a total HJHS score >0, >5, or >10; an individual joint score >0; or a global gait score >0.
Results: Of the 100 hemophilia pts, 52% were severe, 6% were moderate, 42% were mild, 18% had a history of inhibitors, and 19% had hemophilia B. The mean age was 11.9 ± 5.3 years (range: 3–22 years) with a mean BMI of 20.4 ± 5.8 kg m^2. Of the severe pts, 89.6% received prophylaxis. The incidence of total HJHS scores >0, >5, and >10 were 68.4%, 25.9%, and 12.7% respectively. The incidence of ankle score >0 was 51.9%, knee >0 was 30.4%, elbow >0 was 28%, and global gait >0 was 27.9%. In contrast to the high prevalence of abnormalities, only 13.9% (15 of 108) of pts with HJHS scores >0 and 13.4% (11 of 82) pts with of ankle scores >0 led to referrals for further management of joint findings.
Conclusion: In our population of relatively well-controlled children with hemophilia, joint abnormalities are found in most pts using the HJHS exam's most sensitive criteria. A small minority of "abnormal" findings at a sensitive threshold generated clinical action, suggesting that although HJHS is a sensitive assessment, it may not be helpful in management decisions in a clinical setting. HJHS may therefore be best reserved for research studies; more limited assessments might be clinically adequate, improve clinic flow, and decrease costs.

PO-WE-168
Sensitivity and Specificity of Joint Health Measures: Comparative Study of Referrals Generated by Joint Abnormalities Detected by the US-CDC "Universal Data Collection" Range Of Motion Assessment (UDC) versus the Hemophilia Joint Health Score (HJHS) at Annual Hemophilia Visits

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Background: HJHS was developed as a sensitive, reproducible assessment of hemophiliac joints compared to prior methods (Hilliard, Hemophilia 2006; Feldman, Arthr Care Res 2011). We compared the sensitivity and specificity of joint abnormalities by a routine US measure (UDC) and HJHS for joint-related referrals.
Methods: One hundred hemophilia patients at Children's Hospital Boston had an HJHS exam at annual comprehensive visits from March 2009 to August 2011. UDC joint abnormality was defined as joint angle >3 standard deviations (SD) from normal mean for age, parallel joint (i.e. right vs. left ankle, knee, elbow) asymmetry >5 degrees, or asymmetry >15 degrees. HJHS joint abnormality was defined as total HJHS score >0, >5, or >10.
Results: The 100 subjects had 250 annual visits with UDC evaluation and 158 visits with HJHS evaluation. A total of 12.4% (31 of 250) of visits resulted in referral for physical therapy, surgery, radiology, or pain clinic. Using the UDC joint exam, parallel joint asymmetry >5 degrees in any joint was found in 20 examinations of the 31 referrals and 65 examinations of the 219 non-referrals (sensitivity 64.5%, specificity 70.3%; Table 1).
Conclusion: Similar to other screening tests, joint abnormalities detected by either UDC or HJHS measures can be rendered highly sensitive to joint changes but with low specificity for those compelling treatment changes (i.e., referrals). Conversely, with increased stringency these measures are more specific but have lowered sensitivity. Isolated from other clinical evaluations, there is no optimal cutoff for these scoring systems.
Table 1. Sensitivities and specificities of UDC and HJHS joints measures for referrals related to joint health

	Sensitivity	Specificity
UDC * Joint Angle > 3 SD from normal mean	90.0%	23.8%
Joint asymmetry > 5 degrees	64.5%	70.3%
Joint asymmetry >15 degrees	22.6%	92.7%
HJHS * Total Score > 0	100%	35.0%
Total Score > 5	60.0%	77.6%
Total Score > 10	46.7%	90.9%
*"True positive": Abnormal finding yields a referral. "False positive": Abnormal finding yields no referral.		

PO-WE-169
Total Knee Replacement in Patients with Hemophilia - A Follow-Up of 30 Patients
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Introduction: Hemophilia may lead to a severe destruction of the target joints. Besides the clinical and radiological signs of arthrosis, severe fibrosis of the soft tissue leads to a decrease of joint motion and a reduction in patient mobility. The results of arthroplasty on patients with hemophilia are inconsistent. Infection and early loosening after total knee arthroplasty are reported in the literature.
Objectives: The purpose of this study was to evaluate patients' results after total knee arthroplasty. The focus of this study was laid on the function of the joint, mobility of the patient, loosening of the implant, and infection of the joint.
Methods: Thirty patients with hemophilia who underwent total knee replacement between 1987 and 2005 were included. We used the clinical and radiological Knee Society Score and the Petterson and Arnold and Hilgartner score were applied.
Results: The mean age at the time of surgery was 43.2 years (range: 27–66 years). At the time of follow-up examination, the mean age was 51.6 years (range: 30–82 years). The mean follow-up was 7.1 years (range: 2–20 years). Preoperative, the mean Arnold and Hilgartner score was 4.17 ± 0.59 and the mean Petterson-Score was 9 ± 2.29. Compared to the preoperative deficiency in knee function (KSS: 88.17 ± 33.58) an improvement with 166.67 (±22.73) points was seen. One patient showed an aseptic loosening after 11 years.
Conclusion: Total knee replacement in patients with hemophilia improves knee function and quality of life. The results of our study present results in earlier published studies. Compared to a non-hemophilic normal population, the rate of perioperative complications was not increased.

PO-WE-170
Autologous Chondrocyte Implantation in a Patient with Severe Hemophilia
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Introduction: Hemophilia leads to the severe destruction of target joints. A consequent prophylaxis treatment may prevent early damage of the joint. Therefore, common pathologies that have not been seen before in hemophilia patients, and are not implicitly traced to the underlying disease, are now in the forefront of our treatment. osteochondritis dissecans leads to local damage of cartilage and the subchondral bone. A repetitive mechanical overload seems to be the main pathophysiological cause for the osteonecrosis of the underlying bone.
Objectives: To report on a 35-year-old patient with severe hemophilia and osteochondritis dissecans in the knee joint in which we performed a Autologous Chondrocyte Implantation (ACI).
Methods: In a two-stage surgical procedure, we assessed the knee joint and its defect and harvested a cartilage biopsy. Three weeks later, after culturing the chondrocytes, an arthrotomy of the knee with implantation of the synthetic collagen-membranes, including the cultivated chondrocytes, was performed.
Results: We allowed partial weight-bearing using crutches and passive knee motion for3 months after. Then, full weight-bearing was allowed. During this period, consequent physiotherapy was performed. Sporting activity, especially sports with jumping or excessive axial loading of the knee joint, were prohibited for 12 months. The patient remains pain-free in his daily activity and regained full range of motion in the knee joint.
Conclusion: To our knowledge, this is the first report of ACI in a patient with hemophilia. The intraoperative findings showed that prophylaxis can prevent severe destruction of the cartilage. Nevertheless, young and physically active patients will suffer from other common pathological changes in the joint, such as osteochondritis dissecans, which need adequate therapy.

PO-WE-171
Is Joint Hypermobility of Clinical Relevance in Children and Adolescents with Severe Hemophilia?
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Introduction & Aim: Hypermobile joints display an excessive range of movement. When associated with symptoms such as myalgia and arthralgia, these joints can be termed benign joint hypermobility syndrome (BJHS). It has been suggested that hypermobility plays a role in excessive joint bleeding or joint damage in hemophilia, but there is no conclusive evidence. A retrospective clinical notes review aimed to establish the incidence of joint hypermobility in individuals attending two hemophilia centres and evaluate any correlation between hypermobility and joint damage.
Method: The musculoskeletal assessment notes from routine review appointments for children and adolescents with a diagnosis of severe hemophilia were reviewed. Information documented included age, recent bleed episodes, hemophilia joint health score (HJHS), the Beighton score, and the presence of symptoms from the Brighton criteria—the latter two together are widely accepted as measures to assess joint hypermobility/BJHS.
Results: A total of 34 patients were reviewed (age range: 6–16 years). The Beighton score ranged from 0 to 7 (mean score: 2.01) out of a total available score of 9. The HJHS ranged from 0 to 16 (mean score: 2.6). Eight patients reported the presence of arthralgia; 6 in their ankles. The Beighton score for these 8 patients ranged from 0 to 5 (mean score: 1.5) and the HJHS ranged from 0 to 16 (mean score: 5.62). None of the 34 patients met the criteria for BJHS. Although 7 of 34 (20.5%) patients had a Beighton score >4 (indicating hypermobility), the trend seen was that these patients had a lower HJHS.
Discussion/Clinical Relevance: This snapshot from patients' routine assessments highlight that some individuals may have signs of hypermobility; however, this does not necessarily correlate with joint damage. It appears that hypermobility may be an important clinical observation but may not in actual fact be responsible for joint damage secondary to bleeding.

PO-WE-172
Iliopsoas Hemorrhage in Patients with Hemophilia
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Iliopsoas hematoma (IPH) in hemophilia is one of the most serious and potentially life-threatening conditions. In our centre we follow 150 hemophilia patients annually. The clinical course of 18 patients with IPH observed in a 20 year period was evaluated. IPH was confirmed by CT and ultrasonography in 7 hemophilia A patients (6 severe; 1 moderate; two with inhibitors) with on-demand treatment at 44.4 ± 15.7 years of age. Twelve episodes were posttraumatic and 6 episodes involved recurred bleeds. Two patients accounted for 12 cases of IPH. Typical symptoms (e.g. hip and/or groin pain, flexion hip contracture, and femoral nerve paresthesia) were present in 13 episodes. Five patients with IPH presented with abdominal pain. All patients experienced a significant drop in hemoglobin (mean: 8.6 ± 1.7 g dl^{-1}) and 7 episodes required 2–7 red blood cell transfusions. Therapy included intensive replacement with a minimum factor VIII (FVIII) level of 43.8 ± 9.8 IU dl^{-1} during the first week, absolute bed rest for 7 days, prudent mobilization of the leg, and prolonged physical therapy. Fourteen episodes in 5 non-inhibitor patients were treated during 18.0 ± 6.0 days with a total FVIII dose of 525 ± 195 IU kg^{-1}. Four episodes in 2 inhibitor patients were treated during 24.0 ± 5 days. Mean FVIII consumption for 3 patients with IPH in the low-titre inhibitor patient was 1725 ± 130 IU dl^{-1}. The high-responder received continuous infusion of recombinant FVIIa (3.0 mg/kg) followed by FEIBA (2000 IU kg^{-1}). Four patients continue permanent prophylaxis. Complete IPH resolution occured in 2–8 months. Conclusion: IPH is now relatively rare bleeding manifestation in patients with hemophilia. It has the tendency to recurrence and high demands on treatment and management, especially in patients with inhibitors.

PO-WE-173
Validation of an In Vivo Model of Hemarthrosis in Hemophilia A Mice to Study the Short and Long-Term Regulators of Blood Induced Joint Damage
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Hemophilic arthropathy results from recurrent joint bleeds (hemarthrosis) in patients with severe hemophilia. Inflammatory processes in the synovium and the subsequent effect on the joint cartilage contribute to this condition. The precise pathogenetic mechanisms are not fully known and have been difficult to evaluate in the absence of suitable models. Understanding them can be crucial to designing interventions that can prevent such damage. To investigate this phenomenon, we have used the murine model of hemarthrosis (Valentino *et al.*, 2008) to generate the histomorphologic features seen after single- or multiple-articular bleeds. Groups (n = 7) of eight to twelve week old hemophilia A mice were injured at the right knee as described previously; the left knee joint served as the uninjured control. Injury was then repeated every 15 days (day 0, 14, 30, 45, and 60) in different groups of mice. Mice were then euthanized at the abovementioned time points for gross examination, histological analysis, and for evaluating mediators of inflammation. The amount of residual blood, synovial hyperplasia, vascularity, hemosidrin deposition, villus formation, and cartilage erosion were scored in the injured and control joints (based on a 0–3 degree of severity scale for synovial hyperplasia and 0–1 for other factors) by a pathologist blinded to experimental conditions. Our data (Figure 1) demonstrates a significant increase in histological scores from single- (day 1) to multiple-bleeding (day 30 or 60) over a maximum possible score of 8. In conclusion, our data validates the single-injury hemarthrosis model and further shows the effects of multiple injuries in this model. This is now being used to study the molecular mediators responsible for the pathogenesis of hemophilic arthropathy.
Figure 1: Total histological scores of joint tissue isolated from control (C) or injured (I) joints from the single- or multiple- injury hemarthrosis model.

PO-WE-174
ETPS: An Effective Modality for Synovitis
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Introduction: Synovitis results in recurrent bleeds in hemophilia. The cycle of bleeds and synovitis is vicious; it is important to break this cycle to prevent early joint disintegration and disability for therapeutic outcomes. Literature review reveals methods like chemical ablation, radio isotopic ablation, arthroscopic, and surgical synovectomy in management of synovitis. Conventional occupational therapists use methods like rest in splints, ultrasound, e-stim, joint protection techniques, and exercises for management of synovitis. Electrotherapeutic point stimulation (ETPS), a low-voltage direct current (DC) used to treat inflammatory and infective conditions, was used to treat synovitis in this study. This noninvasive technique, conceptualized on the Chinese acupuncture principles, offers stimulation to acupuncture (points away from the problem areas) and trigger points (points around the problem area), as recommended by the Yin-Yang principles of acupuncture. The goal of intervention is preventing long-term complications of synovitis: limitations in function, joint disintegration, and dysfunction.
Aims and objectives: The objective of this study was to observe the effect of ETPS on objective parameters (viz.ROM, joint swelling, pain during activities and at rest, number

of bleeds, and consumption of factor) and subjective parameters (feeling of well-being, task endurance, improvement in ADL tasks, and dependency on assistive devices).
Methods: The ETPS stimulator was used to stimulate the trigger points used for acupuncture. In this study we randomly selected 30 patients with hemophilic synovitis. Patients were treated with ETPS and a regulated exercise protocol vs. ultrasound, acupressure, and regulated exercises in the other patients who attended the centre. Parameters were validated after converting into scores and subjected to statistical analysis. There was significant improvement ($P < 0.01$) in scores after 8 weeks of treatment with ETPS and exercise.
Conclusion: ETPS is a safe and effective therapeutic measure in the treatment of hemophilic synovitis and control of complications.

PO-WE-175
Factor IX (FIX) Deficiency and a Swollen Knee: Not Always a Bleed

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Objective: The objective of this study is to describe an unexpected diagnosis in a patient with severe factor IX (FIX) deficiency and a swollen, painful knee.
Methods: A 45 year-old HIV+ male with severe FIX deficiency, advanced bilateral knee arthropathy, and no history of trauma developed acute onset of severe right knee pain, swelling, and loss of range of motion.
Results: The symptoms did not respond to immediate factor IX infusions and he went to a local hospital. He was afebrile with a grossly swollen, warm, tender right knee. His factor IX level was 77%. After admission he continued to receive FIX and intravenous pain medications, yet the knee remained painful and swollen despite therapeutic FIX levels. Radiographs showed severe narrowing of the tibiofemoral and patellofemoral joints with joint effusion and without acute fracture. An arthrocentesis on the second hospital day yielded 180 ml of pink-tinged fluid. Analysis of the joint fluid revealed intra- and extra-cellular calcium pyrophosphate crystal deposition (CPPD), diagnostic of pseudogout. The patient obtained immediate pain relief after the aspiration and was discharged on day 4 of therapeutic doses of FIX. The subsequent outpatient treatment consisted of naproxen, short course of oral steroids supplemented with intra-articular steroid injections, and colchicine. He did not have a recurrence of the pseudogout and 10 weeks later underwent a successful bilateral total knee arthroplasties. Seven months posthospitalization he is doing well, without colchicine therapy, and with no pseudogout recurrence.
Conclusion: Inhibitor formation and joint infection are the primary considerations in the differential diagnosis of a swollen joint in hemophilia unresponsive to factor replacement. Gout and pseudogout are generally not considered. However, if not properly diagnosed and treated these conditions may result in significant morbidity.
Contribution to the practice/evidence base of hemophilia and bleeding disorders: Pseudogout presents most frequently in middle-age patients and >50% of cases affect the knee. As the hemophilia population ages, providers should include this disorder in their differential diagnosis when evaluating a hemophilia patient with a swollen joint unresponsive to factor replacement. Joint aspiration is controversial in hemophilia but is required for establishing this diagnosis.

PO-WE-176
Safety Profiles of Radioisotope Synovectomy in Hemophilia: Izmir Experience for More Than 10 Years

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Radioisotope Synovectomy (RS) is defined as intra-articular injection of radioisotopes for target joints. Satisfactory responses have been reported in the past, however safety concerns have arisen due to latest acute leukemia reports in the U.S.A. We have long-term experience in RS in patients with hemophilia using Yttrium90 (Y-90) and Rhenium186 (Re-186). We aimed to evaluate safety records in patients. We performed 374 RS for 176 pts. Mean age was 15.5 ± 6.6 yr (3–53). One fifth of cases (21%) were <10 yr. Joints were knees (189), elbows (92), ankles (84), shoulders (8) and wrist (1) for patients with hemophilia A (HA) (146), hemophilia B (HB) (27), VWD (2) and FVII deficiency. (1 girl). 20 cases (12%) had inhibitors. Mean target joints per patient was 1.3 (1–3). Over 11 years, the mean RS applications was 2.2 per patient (1–9). In 12 patients (7%), 3 joints were performed in same session. In 10 patients, 3 consecutive RS were needed to perform for the same joint. By 2005, Y-90 was used for all joints. As of 2005, Re-186 started for elbows and ankles, however Y-90 continued for knees. During the >10 years of observation, we have not had any patients with malignancy (0/176). One patient with HA with inhibitors was diagnosed with aplastic anemia after 8 months (Re-186 for ankle)(1/176; 0.6%). The patient was evaluated as co-incidence. Radioisotope leakage to skin was observed in 3 cases (3/374; 0.8%).Y-90 was a responsible agent for knee and elbow. Re-186 was responsible for other elbow. Acute inflamatory reaction was observed in 2 patients (2/176; 1.1%). 14 year-old boy with HA and inhibitors complained of severe pain after 2 hours of Re -186 injection for elbow. He was treated with steroids and rFVIIa. Another case in ankle joint had a mild reaction and colour change in skin. Y-90 was used this 4 year-old boy with HA. As a conclusion, after >10 years of observation radioisotope-mediated malignancy has not been seen. Serious safety problems were not observed. Radioisotope Synovectomy has been evaluated as a safe procedure for treating target joints of young hemophiliac patients.

PO-WE-177
Efficacy of Synoviorthesis with Rifampicin and Phonophoresis with Pyroligneous Naphthalanum in Hemophilic Patients in Azerbaijan

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Introduction: Chemical synoviorthesis with rifampicin is successfully used in patients worldwide for the treatment of chronic synovitis within more than ten years. This method is based on the proteolytic and antifibrinolytic properties of rifampicin to achieve synovial sclerosis and fibrosis. The procedure was repeated once a week for 5 weeks. As a complex treatment, we used a phonophoresis with pyroligneous naphthalanum on area of the injured joint. Naphthalan oil has no analogues in the world and it possesses analgesic, anti-inflammatory, vasodilator, and anti-allergic effects and activates the intensity of metabolic processes.
Methods: Forty-four patients who fulfilled the selection criteria were included for synoviorthesis; more than 4 hemorrhagic episodes in 6 months, at least a stage II hemophilic arthropathy (Arnold and Hilgartner classification), chronic synovitis. Hemostatic therapy was realized by concentrates of factors VIII and IX.
Results: We performed synoviorthesis and naphthalanum therapy on 37 knee, 6 elbow, and 1 ankle joint(s) of 44 patients with a mean age 10.6 (range: 6–27) years. The average follow-up period after procedure was 2.4 years. Thirty-five patients (79%) showed improvements: decrease or disappearance of pain syndrome, increase in amplitude of movement to 15–20°, decrease in hemorrhagic frequency; 9 patients (21%) had adverse results.
Conclusions: Synoviorthesis with rifampicin and phonophoresis with pyroligneous naphthalanum appears to be an effective treatment modality to control recurrent hemarthrosis and prevent the progression of hemophilic arthritis.

PO-WE-179
Radiosynovectomy in Chronic Recurrent Hemophilic Hemarthrosis: The Northeast Experience

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Radiosynovectomy is used to manage recurrent hemophilic hemarthrosis. The primary aim of this study was to observe the effectiveness of radiosynovectomy in reducing the incidence of hemarthrosis in target joints. The secondary aims were to assess benefits in pain reduction, joint movement, and duration of improvement and to assess complications related to the procedure. We performed 24 radiosynovectomies in 14 patients with recurrent hemarthroses. Intra-articular injection with Yttrium(3) or Rhenium(21) was performed under local or general anaesthetic. All the patients were males with an age range of 8–37 years (median: 17 years). Twelve patients had hemophilia A and two had hemophilia B. Thirteen patients had severe hemophilia and one had mild hemophilia. Twelve of the patients were receiving biweekly to twice-weekly prophylaxis of factor replacement. Two patients had circulating inhibitors. One patient had ankle arthrodesis 2 years after the radiosynovectomy. The rate of bleeding episodes in the target joint was 8.3 per person per year prior to radiosynovectomy. This reduced by 70%–2.75 after treatment, which was maintained up to five years later (2.5) (Fig.1). Improvement in elbow extension (20ordm;) and flexion (6°) was observed. Similar improvement was observed in ankle plantar flexion (5°) and dorsiflexion (7°). Two patients had repeat radiosynovectomy at 1 and 3 years and adequate reduction in bleeding rate was achieved. One patient had ankle arthrodesis for painful advanced degenerative changes 2 years after radiosynovectomy. No complications of radiosynovectomy were observed in this study. Radiosynovectomy improves joint function and appears to be a safe and effective procedure in the reducing rate of hemophilic hemarthrosis and joint pain. Following radiosynovectomy there was a reduced need for therapeutic factor replacement. Longer-term benefits in terms of joint preservation remain to be demonstrated, but the short-term benefits justify continuation of radiosynovectomy for the target joints in hemophilia.

PO-WE-180
Results of Ankle Prosthesis in Patients with Severe Hemophilic Arthropathy: Follow Up

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Introduction: Arthrodesis is predominantly used in cases of hemophilic arthropathy of the ankle joint. The prosthetic replacement surgery can offer a new therapeutic option for ankle arthropathy and is a well established operation in patients with rheumatoid arthritis and in posttraumatic arthritis. Few cases are published about ankle replacement in hemophilic arthropathy. The aim of this study was to evaluate the efficacy of ankle prosthesis in patients with severe hemophilic arthropathy.
Patients and methods: Five patients with hemophilia A (4 severe, 1 mild; 30–44 years of age) and 1 female with von Willebrand disease type 3 (VWD) (45 years of age) showed an advanced state of joint destruction of the ankle evaluated by magnetic resonance imaging (MRI)/X-rays. The presence of severe pain, radiological joint damage (MRI score/Pettersson score), and a sufficient residual condition of mobility were the main indications for ankle replacement therapy. Surgical interventions were performed under factor VIII (FVIII) or FVIII/von Willebrand factor (VWF) replacement therapy and the daily monitoring of the substitution.
Results: No complications (infection or intra-articular ankle bleeding) or side effects were documented in any patient. Typical lymphatic edema was resolved after 6 months. Three years after ankle replacement, the patient with VWD required revision surgery due

to a progressive decrease in mobility. After follow-up of 2–5.5 years, all prostheses were still in place and did not show any signs of loosening. Clinical scores showed a good (n = 2) to excellent (n = 3) results in the patients.
Conclusion: The ankle prosthetic replacement surgery represents a therapeutic option in patients with hemophilic arthropathy. Prospective studies are needed to confirm the efficacy of ankle replacement compared with that of ankle fusion.

PO-WE-181
A Web Based Integrated System for Recording Health Events and Musculo-Articular Assessments and Scoring for Hemophilia Patients
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Recording data from bleeding and treatment episodes, musculoskeletal assessments and scores, and radiological findings is crucial for follow-up of hemophilia patients. These data are necessary to ensure a proper follow-up and adapted treatment for each patient. In 2010 we presented our paper forms-based recording and presenting system at the World Federation of Hemophilia (WFH) meeting in Buenos Aires, Argentina. This tool is now entirely computerized and on a web based system with online capture and recording of any information with tablet (3G or Wi-Fi internet connected) or computer. We presented this system, which allows online data entry by clinician, nurse, or physiotherapist during the visit or the physical assessment. Data entry is also feasible from the patient logbook or institution charts. Our system captures data on bleeding episodes, treatments, hospitalizations periods, radiological examinations, and physical assessment with an automatized calculation of Hemophilia Joint Health Score (HJHS). Recapitulative data are presented on "year at a glance" view and specific views allow the user to focus on bleeding episodes (muscular and articular) or clinical orthopaedic status. This tool may easily be widely used by any hemophilia treatment centre and prospective computerized data collection will be useful for clinical studies. Moreover, presentation to the patients with visual, modern media and communication tools is useful for the understanding of their condition and, hence, the adhesion to treatment, thus participating in a therapeutic education program.

PO-WE-182
Joint Preservation Post Ankle Arthrodesis in Hemophilia: A Review
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Background: Hemophilic arthropathy of the ankle leads to severe pain and, ultimately, ankylosis. Surgical ankle arthrodesis (AA) is performed to eliminate the patient's pain. Patients report concern for long-term health of joints adjacent to the foot/ankle post-AA.
Objective: The purpose of this paper is to provide recommendations for preservation of adjacent joints post-AA, based on a review of both the hemophilia and nonhemophilia literature.
Methods: A literature search was conducted using various electronic databases and focused on articles published between 1980 and 2010 reporting outcomes related to long-term prognosis, gait, and physical activity post-AA. Fourteen articles consisting primarily of case reports and gait studies were reviewed.
Results: Hemophilia literature outcomes included elimination of pain/recurrent hemarthroses, restoration of joint position, improved quality of life, and concern for stress on adjacent joints. Nonhemophilia literature outcomes included hind-foot arthritis developed in 15–60% of patients. During gait, hindfoot limitations were compensated for by increased motion in joints adjacent to the foot/ankle, decreased soleal activity from loading response to terminal stance biased the foot toward eversion, and improved hip/knee kinematics. Shoes with a heel rise of ≥2.5 cm improved foot dynamics.
Conclusions: This review of the literature suggests hemophilic patients undergoing AA will have good pain relief early and risk for deterioration of adjacent joints of the foot/ankle long-term. Strengthening available plantar flexion/inversion as well as using a shoe with a heel-rise may reduce stress on joints adjacent to the foot/ankle.
Contribution to practice: Though joints adjacent to the foot/ankle following AA are at risk for degenerative changes, actions may be taken to prolong the health of the joints. Patient education focusing on reducing everyday stresses on the foot/ankle should include avoiding running and jumping and limiting exercise, recreation, and work-related activities to those with minimal impact on the foot/ankle.

PO-WE-183
Outcomes in Activity, Participation and Body Structure Following Ankle Arthrodesis in Persons with Hemophilia: Analyses Using the Universal Data Collection Surveillance Project
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Background: In persons with hemophilia (PWH), repeated ankle hemarthroses lead to pain, loss of joint range of motion (ROM), and limitations in activity and participation. PWH consider surgical ankle arthrodesis (AA) to eliminate pain. In our experience, PWH are hesitant to proceed with AA due to concerns of gait anomalies, functional decline, and complete loss of ROM.
Objective: Report outcomes in activity [activity scale/use of assistive device (AD)], participation (work/school absenteeism), and body structure (ROM) for participants in the Centers for Disease Control and Prevention's Universal Data Collection (UDC) surveillance project pre- and post-AA.
MethodsMales with hemophilia with first report of AA between 1998 and 2010 were enrolled in the UDC surveillance project. Descriptive statistics were calculated using data from the annual study visit pre-AA and the second visit (2 years later) post-AA.
Results: The 68 subjects (68 AA) identified had a mean age of 36.9 ± 12.9 years. 85.3% were white; 85.3% had hemophilia A; 72% severe, 20.6% moderate; 10.3% with an inhibitor at least once during the study period. On a self-reported activity scale, 11.8% of patients improved, 8.8% worsened, and 79.4% did not change post- compared to pre-AA. Absence from work/school (mean days missed) decreased from 2.7 ± 6.4 days pre- to 1.5 ± 6.4 days (P = 0.26) post-AA. For 85.3% of patients there was no change in use of an AD for ambulation post-AA. Mean ankle ROM post-AA was -1.63° ± 7.17° dorsiflexion to 14.57° ± 15.01° plantarflexion with a loss in mean total arc of motion of 17.02° ± 21.8° (P = < 0.01) post-AA.
Conclusions: These data suggest that, post-AA, most individuals experienced maintenance of physical activity, decreased work/school absenteeism, and no change in use of AD for ambulation. Ankle ROM was significantly reduced, but within a functional range for ambulation.
Contribution to practice: Patients considering AA should expect maintenance of activity and participation with some loss in ankle ROM.

PO-WE-184
Intra-Articular Hyaluronic Acid in Treating of Hemophilic Knee Arthropathy
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Introduction: Repeated hemarthroses results in synovitis and destructive arthropathy in hemophilia patients. We conducted a prospective study to investigate the efficacy, safety, and synovial response of an intra-articular hyaluronic acid (HA) injection for hemophilic knee arthropathy treatment.
Methods: From August 2010 to December 2011, 15 hemophilic patients who had painful arthropathy of knee joint with synovitis were enrolled at our hemophilia centre. Patients received three weekly intra-articular injections of 2 ml HA (Hyalgan). Synovial thickness and vascularity were assessed by ultrasonography. Visual analogue pain scale (VAS), range of motion (ROM), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and SF-36 were compared before treatment and at 1, 2, 3, and 6 months after the first injection.
Results: There were 14 hemophilia A and one hemophilia B patients. The median age was 41 years (range: 21–58 years). Twenty knee joints were given HA viscosupplementation therapy and the average Pettersson score was 8.4 ± 3.66 (range: 1–13). Significant improvement in VAS (F = 20.48, P < 0.001), WOMAC score (F = 10.77, P < 0.001), SF-36 score (F = 14.24, P < 0.001), thickness of suprapatellar recess synovium (F = 16.49, P < 0.001), and synovial hyperemia (F = 12.96, P < 0.001) as compared to baseline values were noted at all follow-up visits from 1 to 6 months after the intra-articular HA injection. No severe injection-related adverse events or hemarthrosis was observed.
Conclusion: This study demonstrates that 3 weekly intra-articular HA (Hyalgan) injections are safe and effective in treating of hemophilic knee arthropathy with synovitis. It can not only improve quality of life, relieve pain, and restore function of knee in hemophilia patients with painful arthropathy, but also decrease synovial thickness and hyperemia. HA viscosupplementation therapy could be an alternative therapy if conservative treatment fails or could be an adjunctive therapy before surgical interventions, such as arthroscopic synovectomy and total knee arthroplasty, are performed.

PO-WE-185
Hemophilic Arthropathy and Health-Related Quality of Life in Hemophilic Patients
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Introduction: Repeated hemarthroses results in destructive arthropathy and functional impairment in hemophilia patients. The aim of this study was to assess the correlation between hemophilic arthropathy and health-related quality of life (HRQoL) in hemophiliacs.
Methods: A total of 86 patients who had been followed at our hemophilia centre were studied. We collected clinical information including age, hemophilia type, disease severity, factor inhibitor, HBV, HCV, HIV, liver function, and SF-36. Bilateral shoulders, elbows, hips, knees, and ankles were evaluated by X-ray in terms of range of motion and Pettersson score. The relationships between SF-36 and clinical variables were assessed using Spearman's correlation coefficient.
Results: Eighty-one hemophilia A and 5 hemophilia B patients were enrolled. The mean age was 30.64 ± 14.1 years (range: 6–66 years). The most common affected joint was ankle (57 patients, 66.3%) followed by elbow (46 patients, 53.5%) and knee (41 patients, 47.7%). The SF-36 scores of hemophilic patients were worse in comparison with Taiwanese normative values. The significant correlations between the summary score of SF-36 and Pettersson score (r = -0.560, P < 0.001), ROM (r = 0.538, P < 0.001), and age (r = -0.426, P < 0.001) were noted. There was no significant correlation between other clinical variables and SF-36.
Conclusion: Advanced Pettersson score, reduced ROM, and older age were related to low HRQoL in hemophilic patients: the worse the arthropathy, the lower the HRQoL. If hemophilic arthropathy can be managed appropriately to prevent ROM deterioration, there is a substantial quality-of-life improvement for hemophiliacs.

PO-WE-187
Megaprosthetic Knee Replacement at Patients with Hemophilia
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Objective: There are situations when, because of deficiency of a bone fabric or the deformations of proximal part of tibia and distal part of femur, primary total knee replacement is impossible. Modular prosthesis or megaprosthesis allows us to solve this problem. The design of these artificial limbs supposes a resection of proximal part of tibia and distal part of femur, restoring (if necessary) the length of an extremity and its function. It also can be used in case of complex periprosthetical fractures.
Methods: Since 2008 in our branch, 23 similar operations have been executed in 15 patients. Twelve patients had severe hemophilia A, 1 had inhibitor hemophilia, and 2 had severe hemophilia B. In patients with hemophilia A and B, hemostatic therapy with a concentrate of the factor VIII and IX, respectively, was administered. Hemostatic therapy in the patient with inhibitor was administered with the concentrate of the activated recombinant factor VII. In all cases, prophylaxis antibacterial therapy was administered to 7 days after the operation. Within 3 days after the operation, an extremity was in plaster. Functional rehabilitation of the joint began 4 days after the operation.
Results: In 15 of the 23 cases, the average result was good. In 2, there was septic instability (then revision arthroplasty with good result), in 6, there was aseptic instability (then revision arthroplasty with good result).

PO-WE-188
Subperiosteal/Intramuscular Pseudotumour- Surgical Treatment by Intralesional Currettage or Wide Excision
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Introduction: Management of the hemophilic pseudotumour is complex and carries a high rate of potential complications. Surgical excision remains the only curative treatment. However, there is no consensus on the type of excision for a particular type of pseudotumour.
Materials &_methods: Out of 21 pseudotumours operated at our centre, 11 were not associated with any kind of fracture or impending fracture of the adjacent bone, but there were pressure effects causing erosion or periosteal reaction of the bone. All patients had a preoperative MRI to confirm and investigate the extent of the lesion. Out of these, 4 pseudotumours were classified as subperiosteal, where the periosteum of parent bone was contiguous with the capsule of the tumour. The other 7 pseudotumours were intramuscular, where periosteum was adherent to the parent bone. Complete excision of the subperiosteal group was not possible and hence the wall of the tumour was excised after the evacuation of its contents. In the latter group, a complete excision was possible as the pseudotumour could be well dissected from the adjacent bone. Calcium phosphate cement granules were applied when required depending upon the size of the bone defect.
Results: The average age of these patients was 22.5 years (range: 12–48 years). The average follow up was 2.5 years (range: 6 months–7 years). The disability limitation score improved from average 60.8 to 45.3. There was no evidence of recurrence and incorporation of bone substitute, where used, was good. One patient died after 2 years of treatment due to medical causes unrelated to hemophilia.
Conclusion: We suggest surgical excision is planned according to type of pseudotumour discovered from the MRI findings. Intralesional curettage is the treatment of choice for a subperiosteal variety and a wide excision is required for intramuscular types of pseudotumour. The use of calcium phosphate cement granules is a useful modality in the surgical treatment of hemophilic pseudotumours where significant bone defect persists.

PO-WE-189
Hemarthrosis Results in an Increase in Synovial Fibrinolytic Activity in Hemophilia Mice
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Introduction: It is unknown why the joints are so vulnerable to bleeding in hemophilia patients. The aim of this study was to test the hypothesis that hemarthrosis results in an increase in synovial fibrinolytic activity, making joints more vulnerable for subsequent bleedings.
Method: FVIII deficient mice (n = 114) and matched control mice (n = 105) were anesthetized. The knee joint diameter and visual bleeding score (VBS) were determined and the right knee was punctured—the left knee served as an unaffected control joint. After 24 hours, blood was collected and the mice were euthanized. Knee joints were examined and a patella-synovial washout was performed. Levels of urokinase Plasminogen (uPA), Plasminogen Inhibitor 1 (PAI-1), and plasmin were measured from plasma and washout supernatants. In a subset of mice, knee joints were isolated, sectioned (4 μm), and stained for synovial uPA expression.
Results: Plasma uPA, PAI-1, and plasmin levels were statistically significantly higher in hemophilic mice as compared to control mice. In control mice, puncturing the right knee did not result in hemarthrosis or alterations in synovial uPA, PAI-1, and plasmin levels. In hemophilic mice, puncturing the right knee resulted in hemarthrosis. Following hemarthrosis, a statistically significant increase in joint diameter, VBS, and synovial uPA expression was observed. In addition, synovial uPA levels were statistically significant higher in the right knee (0.016 ng ml^{-1}) as compared to the left knee (0.01 ng ml^{-1}). No difference in the levels of PAI-1 between the right and left knee was observed. The net result was a statistically significant increase in synovial plasmin levels in the right knee (0.52 μg ml^{-1}) as compared to the left knee (0.44 μg ml^{-1}).
Conclusions: This study demonstrates that hemarthrosis in a murine hemophilia model of acute joint bleeding induces the synovial fibrinolytic system and suggests an explanation for joint susceptibility to subsequent bleedings.

PO-WE-190
Identification - and Differences in Expression - of the Iron Regulators Ferroportin, Hepcidin, Hemoglobin Scavenger Receptor CD163, Heme Carrier Protein 1, and Heme Exporter FLVCR in Healthy, Osteoarthritic, Rheumatoid, and Hemophilic Synovium
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Introduction: Recurrent joint bleeding is the most common manifestation of hemophilia resulting in hemophilic arthropathy (HA). Iron plays a central role in the two main features of HA: synovitis and cartilage damage. The aim of this study was to investigate the synovial expression of the iron regulator proteins: ferroportin (FPN), hepcidin, hemoglobin scavenger receptor CD163 (CD163), heme carrier protein 1 (HCP-1), and feline leukemia virus subgroup C (FLVCR) in HA, healthy control (HC), osteoarthritis (OA), and rheumatoid arthritis (RA).
Method: Synovial tissue samples from HA, HC, OA, and RA (all n = 6) were processed for immunohistochemical staining for FPN, hepcidin, HCP-1, CD163, and FLVCR. Synovial expression of the iron regulator proteins was quantified by two blinded observers and was determined as the percentage of positive synovial cells out of total cells. In addition, the percentage of positive cells in the lining, sublining, and blood vessels was determined.
Results: Synovial tissue was found to express all of the investigated iron regulator proteins. The percentage of positive cells out of total cells of all iron regulator proteins, except hepcidin, was statistically significantly higher in HA synovium as compared to HC, OA, and RA synovium. Expression of FPN, FLVCR, and HCP-1 was statistically significantly higher in the synovial lining, sublining, and blood vessels in HA synovium as compared to HC, OA, and RA synovium. For CD163, synovial expression was statistically significantly higher in the synovial lining in HA as compared to HC, OA, and RA.
Conclusions: In this study we demonstrate for the first time the synovial presence of the investigated iron regulator proteins. Expression of the iron regulator proteins was enhanced in HA in comparison to HC, OA, and RA synovium. These findings indicate the presence of iron regulator proteins in the synovium and suggest synovial adaptation occurs to maintain synovial iron homeostasis in hemophilic arthropathy.

PO-WE-191
Open Synovectomy of the Ankle in Young Hemophiliacs: Long Term Results of a Monocentric Series of 32 Procedures
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Thirty-two ankles in 21 patients (20 severe and 1 moderate hemophiliacs) underwent a complete open synovectomy with safety margins between 1982 and 1999. Two patients had an inhibitor. Mean number of target joints was 3.3 per patient corresponding to a severe bleeding phenotype. Mean age at time of surgery was 8.4 ± 5 years. Median follow-up was 15 years (range: 1–27). Indication for surgery in most patients was recurrent bleedings in the joint. Petrini score, at clinical evaluation, and the Peterson score for radiological changes were used preoperatively at 1 and 5 years after surgery and at the last follow-up. Spearman and Wilcoxon tests were used to compare evolution of clinical and radiological scores. No complications occurred during surgery and in the postoperative period. The mean Petrini and Peterson scores at surgery were 6.25 and 2.46, respectively. The median Petrini score was improved from 6.00 (range: 3–12) preoperatively to 2.00 (range: 0–5) at 5 years. The median Peterson score was 2.00 (range: 0–8) preoperatively and 4.5 (range: 0–12) at 5 years. A correlation between Petrini and Peterson scores was observed at 5 years (P = 0.001). Three patients required an ankle fusion at 1, 2, and 11 years. For the other patients, the mean Petrini score was 4.70, 5.38, and 5.80 with respectively 10, 15, and 20 years of follow-up. Therefore, open synovectomy with a complete removal of synovial tissue gives good long term results. This retrospective study emphasizes the role of the local control of synovitis on joints' functional prognosis. With better comprehensive medical care of hemophiliacs, the synovectomy's indications are now rare. However, this procedure, performed with open or rather by arthroscopic way, has to be considered in case of patients with inhibitor and target joint, in case of a bad response to medical treatment in hemophiliac without inhibitor, or in countries with a limited access to products.

PO-WE-192
Diagnostic, Cross-Sectional Evaluation of Joint Status Using Magnetic Resonance Imaging in Patients with Severe Hemophilia A: Biomarker Analysis
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Objectives: Although biomarkers are useful diagnostic tools to assess joint damage in osteoarthritis and rheumatoid arthritis, few data exist for biomarkers of hemophilic arthropathy. This analysis evaluated the association of biomarkers with compatible additive magnetic resonance imaging (MRI) scores in patients with severe hemophilia A using clinical data.
Methods: Patients aged 12-35 years with no history of factor VIII (FVIII) inhibitors were enrolled into a controlled, cross-sectional, multinational investigation. Patients received primary or secondary prophylaxis or on-demand treatment with FVIII and underwent

MRI on 4 index joints (2 ankles, 2 knees). Plasma was collected to assess soluble biomarkers of cartilage and bone degradation, inflammation, and angiogenesis [i.e., C-terminal telopeptides of type-1 collagen (CTX-I), cartilage oligomeric matrix protein (COMP), chondroitin-sulfate aggrecan turnover 846 epitope (CS846), matrix metalloproteinases 3 and 9 (MMP3, MMP9), tissue inhibitor of metalloproteinase 1 (TIMP-1), or vascular endothelial growth factor (VEGF)]. Relationships between biomarkers and MRI scores were evaluated using Spearman rank correlation.
Results: Biomarkers were assessed in 117 of 118 per-protocol patients. Mean and median CTX-I, COMP, TIMP-1, MMP3, MMP9 and VEGF values were within normal ranges (the reference range is not available for CS846 in healthy volunteers). No correlations between biomarkers and MRI scores were found with the exception of CS846, which showed significant correlation in the 22 on-demand patients ($r = 0.436$; $P = 0.04$).
Conclusions: Compatible additive MRI scores did not show clear correlations with any of the biomarkers assessed in the overall population. However, increased CS846 levels were significantly correlated with worse MRI scores in on-demand patients.
Contribution to the practice/evidence base of hemophilia and bleeding disorders: MRI joint status scores did not correlate with potential biomarkers of hemophilic arthropathy except for CS846 in on-demand patients.
Conflicts of Interest: Dr. Theodossiades is a member of the ADVANCE working group sponsored by Bayer. Dr. Zanon has acted as a paid consultant for Bayer, Baxter, Novo Nordisk, Pfizer, and Grifols. Dr. Kellermann is an employee of Bayer Vital GmbH. Dr. Lundin received funds for conference participation from Bayer. Drs. Katsarou and Zimmermann have no conflicts of interest to declare.

PO-WE-193
Prospective Evaluation of Safety and Efficacy of Radioactive Synovectomy with ^{90}Yttrium-Hidroxyapatite and ^{153}Samarium-Hidroxyapatite in Chronic Hemophilic Synovitis

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In countries where primary prophylaxis is not a widely available, the radioactive synovectomy (RS) is sometimes the best treatment option for patients who develop chronic synovitis. The aim of this study is to evaluate the efficacy and safety of radioactive synovectomy with ^{90}Yttrium-hydroxyapatite (^{90}Y-HA) and ^{153}Samarium-hydroxyapatite (^{153}Sm-HA) in the treatment of hemophilic arthropathy. Eligibility criteria included the diagnosis of hemophilia and signs of synovitis. Efficacy was determined by comparing the frequency of bleeding episodes in the treated joint, 6 months before and after RS. Safety was analyzed for the presence of adverse events and extravasation of the radiopharmaceutical. All patients underwent 3-phase bone scintigraphy before and 72 hours and 6 months after the procedure. Sixty-five joints (50 patients) underwent RS. Thirty-eight joints (33 knees and 5 ankles) received ^{90}Y-HA and 27 joints (1 knee, 19 elbow and 7 ankles) received ^{153}Sm-HA. At the 6 month follow-up, it was observed that the frequency of joint bleeds per month in the treated joint decreased from 1.44 ± 0.64 (range of 0.33–3.33) to 0.45 ± 0.41 (0–1.67) ($P < 0.0001$, paired Wilcoxon). Adverse events included transient synovitis worsening in the first 14 weeks after treatment in treated joints (12%), among these, 5 patients treated with ^{90}Y-HA and 9 patients treated with ^{153}Sm-HA. One patient treated with ^{153}Sm-HA presented extra-articular leakage in the lungs without evidence of clinical change. The reduction of episodes of hemarthrosis in the whole group resulted in a potential cost reduction in the use of clotting factor of 1,084,950 IU, equivalent to about US$220,000 during the period of 6 months follow-up. The analysis of 65 joints treated with ^{90}Y-HA and ^{153}Sm-HA demonstrated that RS is an effective and safe procedure and was able to signifficantly decrease the number of joint bleeds and clotting factor consumption.

PO-WE-194
Conservative Treatment of Severe Knee Flexion Contracture in Two Patients with Severe Hemophilia A Patients with High-Responding Inhibitors

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Knee flexion contracture is a common finding in patients with hemophilia and is the result of recurrent intra-articular and intramuscular hemorrhage. This complication affects the gait pattern and activities of daily living. Patients with inhibitor are more prone to develop articular contractures and progressive arthropathy. The usual treatment for severe cases of knee contracture with more than 30 degrees of flexion is surgical soft tissue release and/or extension osteotomy. Several complications of surgical treatment are described, such as vascular compromise and scar tissue formation. We describe our approach of two children with severe hemophilia A with high-responding inhibitors who developed flexion contracture and underwent conservative treatment with progressive extension and serial casts. Case 1 was a 7 year-old patient with a 55 degrees flexion contracture of the right knee. Functional independence score in hemophilia (FISH) was graded as 22 at initial evaluation. The first cast was applied after gentle manipulation under anesthetic sedation. Wedging and serial casting were performed in the following weeks and cast was removed after 5 weeks. Flexion contracture was reduced to 25 degrees and FISH was graded as 26 after treatment. Hemostasis was achieved during the treatment with aPCC. Case 2 was a 7 year-old patient with 85 degrees flexion contracture of the right knee and FISH graded as 17 before treatment. Same protocol was used and, after serial casting, flexion was reduced to 28 degrees and FISH was improved to 22. This patient was under immune tolerance induction during this treatment. Both patients were included in a program of intensive rehabilitation after orthopedic treatment. We observed no articular subluxation or other complications with this method. So far we are not able to correct all the flexion contracture with this method in these patients; however, there was significant improvement in function.

PO-WE-195
Surgical Treatment of the Hemophilic Pseudotumour: A Single Center Experience

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Objectives: Hemophilic pseudotumour was defined by Fernandez de Valderrama and Matthews as a progressive cystic swelling involving muscle, produced by recurrent hemorrhage and accompanied by roentgenographic evidence of bone involvement. The radiographic changes resemble malignant bone tumours, which is why this rare but severe complication of hemophilia is called pseudotumour. The most common site for the hemophilic pseudotumour is the proximal skeleton around the femur and pelvis.
Methods: We retrospectively reviewed all clinical histories of 87 patients with bleeding disorders who were treated because of musculoskeletal affection due to congenital bleeding disorders at the Department of Orthopaedic Surgery, Vienna Medical University between 1967 and 2004. We identified 6 patients with a hemophilic pseudotumour who were treated at our department.
Results: The mean age at surgery was 46.9 years (range: 40–60 years). The iliac bone was affected in 3 patients (one, right; two, left), the right distal tibia in 1 patient, the right femur in 1 patient, and the right proximal ulna in 1 patient. One patient developed, additionally to the left iliac bone, a hemophilic pseudotumour of the right gluteal muscle; one, additionally to the right iliac bone, a massive muscle bleeding of the ipsilateral thigh. At the latest follow up after 8.4 years (range: 5–24 years), normal healing with no recurrence were observed. In 3 cases, the postoperative course was complicated by deep infection. In these patients, revision surgery was necessary.
Discussion: The hemophilic pseudotumour is a rare but severe complication of hereditary bleeding disorders. In the international literature, the resection and postoperative course is described as demanding and difficult and requires detailed preoperative planning. Operation done in specialized centres with close cooperation between surgeons and hematologists is feasible.

PO-WE-196
Safety of Joint Injections in the Treatment of Hemophilic Arthropathy

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Introduction: There is little recent evidence regarding the use of joint injections in adult hemophilic arthropathy. A prospective case series of injections performed over the last 12 months at the Ronald Sawers Hemophilia Centre in Melbourne, Australia is presented.
Methodology: A pre-injection and post-injection assessment was performed on consecutive patients who had an intra-articular joint injection over a 12 month period: January 2011–January 2012. On initial presentation, patients reported pain (measured by VAS), functional impairment (on FSPS scale), and decreased range of motion (standard goniometric measurement) all 28 joints (100%). Patients were given factor replacement prior to the joint injections.
Results: Intra-articular injections were performed in 28 joints on 23 patients. Twenty (71%) corticosteroid and 8 (29%) Yttrium injections were performed. Of the joints injected, 15 (54%) were ankles, 6 (21%) were elbows, 6 (21%) were knees, and 1 (4%) was a shoulder. Three joints (11%, 2 patients) had hemophilia with inhibitors and 1 joint (4%) had von Willebrand type III. Of these there were no incidences of septic joints or infection. There was 1 reported case of a crystal flare, 1 case of Yttrium leakage detected on scanning but with no adverse clinical sequelae, and 1 case of a suspected joint bleed post-injection.
Conclusion: Intra-articular joint injections in patients with hemophilia are safe and offer a potentially useful adjunct to management of joint disease. Work is currently underway to determine whether they are effective.

PO-WE-197
A Case Series of 7 Hemophilic Joints Assessed with Microbubble Contrast Enhanced Ultrasonography and MRI

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Introduction: Hemophilic arthropathy includes a secondary synovitis that is amenable to treatment interventions such as cortisone injections and yttrium synovectomy. In most cases, the diagnosis of secondary synovitis is clinical, but further imaging is sometimes required. Magnetic resonance imaging (MRI) with gadolinium contrast is the current investigation of choice at our centre; however, there are issues with cost, claustrophobia, contraindications to gadolinium, and delay to investigation. Microbubble contrast-enhanced power Doppler ultrasonography has been used to detect synovitis in the non-hemophilia population. We present a case series of patients at the Ronald Sawers Haemophilia Centre in Australia who have had both microbubble contrast-enhanced ultrasound and MRI within a 1 month time frame from June 2010 to June 2011.
Methodology: A retrospective audit was done of all patients with hemophilia A that had both an MRI and a microbubble contrast enhanced ultrasound.
Results: A total of 87 adult patients seen over a 12 month period with hemophilia A, hemophilia B, von Willebrand disease, and Factor V Deficiency were seen at our hemophilia multidisciplinary clinic. Of these 87 patients, 7 target joints (hemophilia A 6/7, B 1/7) were evaluated with both MR and ultrasound for the presence of synovitis (3 ankles, 2 knees, 1 elbow, and 1 shoulder). In 4 of the 7 joints, both ultrasound and MR diagnosed synovitis. Of the 7 MR examinations, 2 were performed without gadolinium administration. No adverse events were reported.

Conclusion: Microbubble contrast-enhanced ultrasonograhy appears to be safe in the hemophilia population. Further evidence for use in hemophilic arthropathy is required and a randomized controlled trial comparing the technique to MRI with gadolinium is currently being submitted to ethics at our institution.

PO-WE-198
A Review of DEXA Studies Done on Patients with Severe Hemophilia – Should They Be Routinely Ordered?

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Introduction: Osteoporosis and osteopaenia are associated with severe hemophilia. Patients with severe hemophilia have known risk factors for osteoporosis such as viral co-infection and reduced weight bearing activities. As dual-emission X-ray absorptiometry (DEXA) is not currently undertaken in our centre, we performed an audit of patients attending the Ronald Sawers Haemophilia Unit in Australia.
Methodology: Over a 2 year period, all consecutive patients presenting to the hemophilia musculoskeletal clinic who previously had not had a bone mineral density performed were referred for this procedure. The DEXA scans were examined to see which proportions were abnormal.
Results: Twenty-two patients with severe hemophilia were identified as having had a recent bone mineral density test. Of these, 16 had hemophilia A and 6 had hemophilia B. The average body mass index was 26 kg/m^2 (range: 17–34 kg/m^2) and the average age was 48 years (range: 25–83 years). At the lumbar spine, osteopaenia was present in 12 (55%) cases and osteoporosis in 4 (18%). At the femoral neck, osteopaenia was present in 12 (55%) cases and osteoporosis in 8 (36%). Of the cases of osteoporosis, 50% were positive for human immunodeficiency virus (HIV).
Conclusion: Although many of the cases of osteoporosis or osteopaenia could be linked to patients with HIV infection and/or older age, there were still several patients with osteopaenia and osteoporosis with no obvious risk factors other than severe hemophilia. Many patients with severe hemophilia have not yet been assessed, particularly those under the age of 30 and those without co-existant hemophilic arthropathy. Until further evidence is presented, our centre will offer bone mineral density testing to all patients with severe hemophilia.

PO-WE-199
Ultrasonography Protocol for Diagnosis and Control of Acute Hemarthrosis in Hemophilic Patients

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Introduction: In patients with hemophilia (HP), intra-articular blood – basically hemarthrosis of repetition – inevitably leads to hemophilic arthropathy. Factor replacement therapy, especially the primary prophylaxis, has proven its effectiveness in reducing the frequency of bleeding, but has not eliminated the risk of accidental traumatic events involving evidence of effusion, including subclinical hemarthrosis. Ultrasound has proven its validity in the diagnosis of musculoskeletal pathology. Its use in hemophilia has been widely recommended, but its standardization as the first option tool is still debated. The diagnosis and management of acute hemarthrosis with ultrasound scanning is readily available at any hospital. Ultrasound scanning can optimize the treatment of HP and improve patient outcomes, to achieve a satisfactory state of health. The aim of this paper is to show an ultrasound exploratory protocol: a simple protocol, from routine use, to minimize inter-subjectivity browser, show the disruption of normal patterns, and guide the hematological treatment in acute hemarthrosis.
Methods: Exploratory Protocol: ELBOWS in longitudinal scan (LS), with reference in triceps tendon insertion and elbow flexion to 90°; KNEES LS, reference in patella and quadriceps tendon insertion, 20–30° knee flexion; ANKLE LS, reference hallux extensor tendon, tibia and talar neck, ankle plantar flexion of 10–20°. Routine ultrasound examination always includes the two joints (healthy and affected).
Results: In our centre (Total of 371 HP), 147 patients with hemarthrosis were detected (n = 100 HP) in the last 12 months: (33 elbows [n = 22 HP], 57 knees [n = 41 HP], 30 ankles [n = 24 HP] and 27 in other articulations [n = 20 HP]. 100% of the cases were followed up by clinical and ultrasound control. In 72% of knee hemarthrosis cases, effusion was identified with ultrasonography imaging protocol (whether full exploration includes other scans). Effusion was demonstrated in 100% of the ankles and 100% of the elbows by our ultrasound protocol.
Conclusions: The specific anatomical landmarks and protocols for ultrasound scanning minimize the operator-dependent concept in musculoskeletal ultrasonography. The disappearance of clinical symptoms doesn't match the ultrasound evidence of the persistence of the effusion. For this reason it is necessary to further study the hematological treatment.

PO-WE-200
Does Prophylaxis Have an Effect on Bone Strength Beyond Physical Activity?

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Objectives: Previous studies have demonstrated that children with severe hemophilia who receive prophylactic treatment have less joint damage related to bleeding than those without. With prophylaxis, bleeding in patients with severe hemophilia is less likely to occur spontaneously, allowing the patients to participate in physical activities. Several studies have demonstrated that boys with hemophilia are at risk of suboptimal peak bone mass and low bone mineral density. As the clinical significance of this is unclear, we sought to evaluate bone strength in children with hemophilia who receive prophylaxis compared to on-demand treatment.
Methods: The study group comprised 29 children with hemophilia (mean age: 12.2 years) and 46 age-matched controls. One-fourth (7) of patients had mild or moderate hemophilia and received on-demand treatment while 75% (22; 2 moderate and 20 severe hemophilia) were on prophylactic treatment. Their bone strength was assessed by peripheral quantitative computed tomography (pQCT) at the radius. Physical activity was evaluated by a questionnaire.
Results: There were no significant differences in physical activity or number of joint bleeds between patients receiving on-demand treatment and prophylaxis. Though no differences were observed in physical activity between patients and controls, the intensity of physical activity was significantly lower in patients (P = 0.03). However, the pQCT-derived bone strength parameter SSI Z-score was significantly lower in patients with on-demand treatment when compared with patients on prophylaxis (P = 0.005), even after adjusting for age and muscle cross-section area. Bone strength at the radius of patients receiving prophylaxis was equal to healthy children while patients with on-demand treatment had inferior bone strength when compared to controls (P = 0.013).
Conclusion: Boys with severe hemophilia and prophylactic treatment have normal bone strength at the radius when compared with healthy controls. Prophylactic treatment seems to have a beneficial effect on bone health beyond the effect on physical activity.

PO-WE-201
The Effects of Pulsed Ultrasound and Low Level Laser Therapy on Joint Friction and Biomechanical Parameters of Articular Cartilage in Experimental Hemarthrosis Model

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The use of pulsed ultrasound (PUS) and low level laser therapy (LLLT) in patients with hemophilia has been recommended for supportive treatment of acute and chronic phases of hemarthrosis, but its role has not been supported by experimental evidence. The purpose of this study is to evaluate the effect of these modalities on joint swelling, friction, and biomechanical parameters of articular cartilage. An experimental rabbit knee hemarthrosis model was used to to test the hypothesis that LLLT and PUS favourably impacted on the biotribological and biomechanical properties of cartilage after joint bleeding. To test this, 35 male albino rabbits weighing 1.5–2 kg were used. The left knee of 30 rabbits was injected with 1 mL of fresh autologous blood 2 times per week for 4 consecutive weeks to simulate recurrent hemarthrosis; 5 rabbits served as non-bleeding controls. Ten rabbits were treated with PUS, 10 with LLLT, and the remaining 10 were not treated. The treatments were started after 2 days and the treatment duration was planned for 5 days (sessions) in ultrasound and laser groups. A low level Ga-Al-As laser was applied with an 810 nm wavelength, 25mW power, and 1 J/cm^2 dosage for a duration of 200 seconds. The pulsed ultrasound treatment was applied with a duty cycle of 1/9, frequency of 1 MHz, and power of 0.4 W cm^{-2} for 150 seconds. Joint perimeter was measured at the beginning of therapies and after cessation of the procedure. Friction and biomechanical parameters were measured immediately after euthanization. The results demonstrate that PUS was more effective in reducing knee joint swelling than LLT. Moreover, PUS had the unique ability of reducing the joint friction below normal values. However, it was not successful in returning the articular cartilage force and stiffness to normal state. LLLT was more effective in increasing equilibrium force of the articular cartilage than PUS; however, neither therapy normalized this parameter. From these data, we conclude that PUS—but not LLLT—is effective in reducing joint swelling and articular joint friction after experimental hemarthrosis.

PO-WE-202
The international classification of functioning, disability, and health (ICF) core set for osteoarthritis: A useful tool in the follow-up of patients with hemophilic arthropathy

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Background: The importance of addressing the patient's perspective and the patient's experience of functioning, disability, and health is now commonly accepted. However, this topic is quite innovative in hemophilia research.
Aim: The aim of this study was to verify the applicability of the ICF core set for osteoarthritis (OA) as an outcome tool for hemophilic arthropathy, in order to describe the profile of functioning and to compare the changes in the profiles among patients.
Methods: Three hundred twenty-five joints were retrospectively evaluated in overall 111 patients with moderate and severe hemophilia with both a sonography score and Gilbert score mapping both scores with the ICF core set for OA as a frame of reference.
Results: All concepts from both scores were linked within the 55 categories of the ICF OA core set using Body Functions (BF= 47%), Body Structures (BS= 41%), and Activity and Participation (A&P= 12%) with the exception of environmental factors (EF). Out of 325 joints examined (115 ankles, 210 knees), the functional profile identified damages of BS (s750 structure of lower extremity) and BF (b710 mobility of joint functions) in 50% of ankles and 33% of knees in overall 111 patients. Abnormalities in the structure of ankle (s75022) and knees (s75011) were the most frequent observations (88% in ankle and 76% in affected knees, respectively). There was scarce information or an absence of information about the A&P and EF components since the two scores systems do not require data about these components.
Conclusion: The ICF core set for OA resulted in an interesting outcome tool for hemophilic arthropathy, even if more research is needed, mainly on data reliability and category definition. The use of the ICF core set should be encouraged because it permits us to define the level of functioning of patients and allows us to focus on aspects of the patient's everyday life usually not taken into account in the traditional assessments.

PO-WE-203
Bone Mineral Density in Hemophiliac Patients
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Objectives: Patients with hemophilia have several risk factors for reduced bone mineral density (BMD), including arthropathy and resulting immobility. Recent studies have shown variable frequency of low BMD in this group of patients. We conduct this study to assess prevalence of low BMD (osteoporosis and osteopenia) and associated risk factors.
Methods: Patients with moderate or severe hemophilia A underwent BMD-measurement by dual energy X-ray absorptiometry in the Imam Khomeini hemophilia centre at Tehran, Iran. BMD results were correlated with other variables including physical activity, calcium intake, and demographic data.
Results: Forty-two patients with mean age 31 years (range: 18–72 years) completed the study. The prevalence of osteoporosis in spine and left femoral neck were 23.8% and 14.6%, respectively, by World Health Organization T-score criteria; osteopenia in spine and femoral neck were seen in 45.2% and 31.7%, respectively. We found only cigarette smoking to be significantly related to reduced BMD ($P = 0.00$). We had two cases of pathologic fracture at femoral neck and forearm (2 of 42 patients, 4.8%).
Conclusion: Reduced BMD is very common in patients with hemophilia. Appropriate assessment of BMD in this group and control of predisposing factors such as prophylactic factor replacement to prevent hemarthrosis and cessation of cigarette smoking is warranted.

PO-WE-204
A Prospective Study of Non-Animal Stabilized Very High Molecular Weight Hyaluronic Acid (NASHA) Intra-Articular Injections in Hemophilc Patients with Ankle Arthropathy
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Background: Hemophilic arthropathy is the consequence of recurrent joint bleeds in patients affected by severe hemophilia A or B or von Willebrand disease, leading to functional limitations and chronic pain with negative impact on quality of life. Main target joints are knees, ankles, and elbows. Few therapeutic options are available for ankle arthropathy. Temporary symptom improvements have been reported by repeated (i.e., 3–5) intra-articular administrations of hyaluronic acid (HA). A non-animal stabilized very-high molecular weight HA formulation (NASHA) has been proven to achieve long-term benefits in patients with knee and hip osteoarthritis.
Methods: Patients with ankle arthropathy undergoing a single NASHA (Durolane® 0.5 ml, Smith & Nephew) injection were prospectively studied. Clinical assessment, including Gilbert Score (Pain, PGS, and physical examination, PEGS), pain scores (Visual Anologue scale, VAS and McGill Score, MGS), generic quality-of-life evaluation (EQ5D), and magnetic resonance imaging (MRI) were performed at baseline (T0) and 1 (T1), 6 (T6), and 12 (T12)months after NASHA injection.
Results: Fifteen ankles in 9 patients (7 severe, 2 moderate; age: 21–45 years) were treated. A significant improvement of symptoms and functional outcome was reported at T1 compared to T0 (PGS: 0.5 ± 0.6 vs. 1.7 ± 1.0, $P = 0.03$; PEGS: 2.2 ± 2.8 vs. 4.7 ± 3.3, $P = 0.001$; VAS: 18 ± 19 vs. 71 ± 26; MGS: 0.8 ± 0.7 vs. 2.8 ± 1.1; $P < 0.001$; EQ5D: 80 ± 14 vs. 54 ± 25, $P = 0.015$). Data were not statistically different at T6 versus T1, suggesting long-term benefits after NASHA injection. Only 4 patients reached T12 at the time of this paper. The positive-experienced outcomes led to repeat treatment in these 4 patients 13 months (mean) after the first injection. No significant change in the European magnetic resonance imaging Score was found throughout the study.
Conclusions: NASHA viscosupplementation enabled long-lasting clinical benefits and improvements of quality-of-life in patients with ankle arthropathy. This single-injection treatment provides an approach reducing risks and costs of multiple intra-articular injections, is well accepted by patients, and has a favourable cost-utility ratio.

PO-WE-205
Interest of the Baropodometry Record in Post Surgery and Follow Up of Ankle Prosthesis in Bleeding Parient
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Since 2002, we've treated hemophiliac ankle pathology almost exclusively with ankle prosthesis AES and HINTEGRA. We have tried different methods to estimate our results in the most objective manner. The Fluoroscopy record was not sufficient, so instead we have chosen the Baropodometry study.
Description of the Equipment and Technical: The patient walks on a special platform of 2m in length and 70 cm in width, equipped with manysensors in order to register foot pressure. The sensors are connected to a computer with "Win track" software. Static and gait analysis is then conducted on this walkway (using the sensitive sensors) with total freedom in stance and motion acquisition. On the screen we can estimate 2 studies Static foot pressure mapping with different color corresponding to the variation of pressure calculations per area. Multiple visualization options Dynamic: roll off animation, global dynamic picture calculations and graphs simultaneous displays of each step, calculations of space time parameters multiple characteristics of gait timing foot pressure mapping and timing of the stance and complete time pressure analysis medio lateral analysis. This study has been made on 10 bleeding patients, before and after surgery. Rehearsal of records was made, next to 3 month, 6 month, and 1 year after surgery.
Results: The result gives us static and dynamic information's: *Static:* design of the foot print, specific points of loading and their value, geometric centre of gravity and its variations in posturology. We explain the results of that series and compare some examples of records after ankle prosthesis TAR one side versus Arthrodesis other side Bilateral TAR. TAR and Knee prosthesis 2 TAR and 2 Knees prosthesis.
Conclusion: The Baropodometry record is a reliable, faithful and reproduced technical to estimate the surgical results to the lower limb in hemophilic patients.

PO-WE-206
Thermography in Children with Hemophilia: A Sensitive Tool to Predict the Future of Hemophilic Joints?
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Introduction: Early detection of inflammation is crucial in patients with hemophilia. Subclinical bleedings may cause subclinical inflammation and early hemarthropathy. Silent symptoms, such as tender points on joints, are early signs before the patient becomes symptomatic.
Material and methods: Ten children from 4 to 17 years-of-age with a mean age of 10.3 years were examined physically for tender points and with digital themography (Varioscan high resolution 3201 ST, Jenoptic Laser, Jena, Germany). Temperature, 21.9 °C (range: 21.7–22.2°C), and air humidity, 62.3% (range: 59–63.7%), were constant. Elbows, knees, and ankles were examined. Digital RGB images were taken with patients in same position for anatomical comparison. Clinical findings were compared to temperature hot spots and to relevant left/right discrepancies (>0.5 °C).
Results: We found a mean of 7.2 silent symptoms, 9 relevant right/left differences in temperature, and 18.5 hot spots in thermography per patient. Elbows constituted 23.6% of all silent symptoms, 23.3% of right/left temperature differences, and 27.1% of the hot spots; knees, 27.8% silent symptoms, 40% side differences in thermography, and 44% of hot spots; ankles, 48.6% of clinical findings, 28.9% of right/left differences, and 34.6% of hot spots. All silent symptoms correlated with a hot spot. Thermography showed more relevant hot spots than clinical findings; this was more evident in the knee than in the ankle.
Conclusion: Thermography is a very sensitive method for detecting temperature differences in anatomical locations. It was possible to detect all silent symptoms by thermography correlating with increased blood flow like in local inflammation. Thermography is more sensitive than clinical examination in detecting early inflammation. The knee seems to hide early inflammatory signs, much more than the ankle and the elbow. The ankle is the joint with the highest number of silent symptoms.

PO-WE-207
Curricula Adapted Inclusion for Children with Hemophilia into Sport Lessons at School - A New Approach within the "Fit For Life" Project
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Inclusive pedagogic thinking and acting is an important topic in school sports for teachers, parents, and students. The new European guidelines enable inclusion, especially for students with chronic illnesses like hemophilia. Within our project—Fit for Life—where we advice children and young adults with hemopilia to find the right sport, we developed a new approach for an optimized inclusion of children with hemophilia into sport lessons with the cooperation of the German Sport Teachers Association (Hessen). We analysed and rated the actual curricula for the different school years and looked at the specific needs, risks and necessary abilities for patients with hemophilia. For all 500 typical movement exercises in school sports, we developed individual advice and adapted exercise solutions for the sport lessons. The advice is dependent on the degree of illness, the patient's individual restrictions (joint status), and his or her actual fitness status. The fitness status is measured by a 5-station test (testing for coordination, strength, flexibility, aerobic fitness, and body fat). The results are discussed with children parents and teachers (USB stick). The teachers receive detailed information about the patient's illness and individual fitness abilities, and will learn which movements during sport lessons are safe for hemophiliac students, which are borderline, and which should not be performed. In addition, the teacher will receive individualized training programs with specific exercises for basic fitness that are configured by the results of the 5-station test. This is the first approach in literature to establish a good correlation between chronic illness, individual fitness, and the demands of an age-specific sport curriculum at school.

PO-WE-208
Long-Term Studies of Hemophilic Arthropathy by Pettersson's Score – Evidences that Joint Damages in Hemophiliacs Occur Predominantly in Early Years of Life
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Introduction: Minimal or no treatments were given in the care of hemophiliacs in Taiwan before 1980. The year 1984 was the most important turning point, when the first hemophilia treatment centre was established and adequate treatments began to be implemented. The influence of the difference in treatment on the development of hemophilic arthropathy will be evaluated in this study.
Methods: Pettersson's score was used to study the hemophilic arthropathy of ankles, knees, and elbows in 107 cases of severe hemophiliacs from 1984 to 1986; 104 cases from 1997 to 2000; and 63 cases from 2007 to 2010. The mean score was obtained by averaging the scores of 6 joints of the patient.

Results: Multivariate analysis of the mean score was performed by fitting multiple linear regression model with the stepwise variable selection method, and by fitting a multiple generalized additive model with the smoothing technique applied to the effects of age at the measurement and age in 1984. The results of this analysis revealed that the mean score would increase at the rate of 0.1574 per year of age at measurement ($P < 0.0001$); patients who were between 7 and 36.75 years of age in 1984 had a mean score 0.8004 higher than those who were less than 7 years old in 1984; patients who were born before 1984 would receive minimal or no treatments and their mean score increased from 0 to 7 years of age (in 1984) and steadily increased through 10 and up to 25 years old, slowed down until 36.75 years of age and then went down; and patients who were born after 1984 would receive adequate treatments and their mean scores were stable and much smaller.
Conclusion: Minimal or no treatment in hemophiliacs would cause serious joint damage, which occurred predominantly in early years of life through 7 years of age and from 25 to 36.75 years of age.

PO-WE-209
The Impact of Hemarthropathy on the QoL of Korean Patients with Severe Hemophilia A: The Critical Level of Hemarthropathy for the QoL

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Objectives: It is acknowledged that as the degree of hemarthropathy approaches a certain critical level, the disabled physical state may markedly affect the quality-of-life (QoL) of hemophiliacs. However, the critical level of hemarthropathy may be different in different countries because the QoL could be influenced not only by the physical state but also by sociocultural environments across countries. For these reasons, the impact of hemarthropathy on the QoL in Korean hemophilia A patients were investigated to find out the critical level of hemarthropathy in these patients.
Methods: This study was conducted in 27 severe hemophilia A patients over 17 years of age who were registered at a single hemophilia treatment centre. Depending on observed Pettersson scores at the start of study, the patients were divided into 3 groups: Pettersson score ($P \leq 10$), P 11–19 and ($P \geq 20$). The QoL of each patient, assessed by the SF36 (Korean version), was compared between the groups. In addition, a correlation analysis was conducted between Pettersson scores and scales of the SF36 to assess the impact of hemarthropathy on the patients' QoL.
Results: In the present study, Pettersson scores were significantly correlated with physical health scales (PF, BP, GH) and physical component summery (PCS). None of the scores of the SF36 scales were different between the ($P \leq 10$) and P 11–19 groups. In contrast, the scores of PF and MH scales were significantly different between the P11–19 and ($P \geq 20$) groups. When changes in the scores of each scale in the SF36 were observed according to changes in Pettersson scores, the average P score of 13.0 ± 2.7 was thought to be the critical level of hemarthropathy because above that level hemarthropathy and physical and mental health of the patients rapidly deteriorated.
Conclusion: The progression of hemarthropathy to the critical level should be delayed as long as possible to prevent or delay a rapid deterioration of the QoL of Korean patients with hemophilia.

PO-WE-210
Age-Related Changes of Joint Status in Adults with Severe Hemophilia in Germany

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Introduction: People with hemophilia (PWH) are often affected by recurrent bleedings into joints, commonly ankles, knees, and elbows, which entail hemophilic arthropathy. Along with an increasing immobility, the disorder leads to limited movements and malposition of joints accompanied by significant pain. Due to recurrent bleedings during the patient's lifespan, it can be assumed that orthopaedic joint status worsens with age. However, to date, few data are available that show a coherency of the orthopaedic joint status and age in PWH. The aim of this study was to analyse the age-dependent orthopaedic joint status of PWH.
Methods: One hundred eight-two (182) adults (age: 40 ± 12 years; range: 18–67 years) with severe hemophilia (A or B) and 81 non-hemophilic control patients (age: 40 ± 14 years; range: 20–68 years) underwent an orthopaedic examination. For assessment of the joint status of ankles, knees, and elbows, we used the World Federation of Hemophilia (WFH) joint physical examination instrument (WFH score); a higher score implies more distinct structural and functional joint deficits. Correlations were determined using spearman rank correlation (rs).
Results: The total WFH score was 24 ± 13, whereby ankles were the most affected joints in PWH. A significant correlation was found between total WFH score and age ($rs = 0.77$, $P < 0.001$). Moreover, the analysis of each joint also revealed a significant correlation with age (left ankle: $rs = 0.54$; right ankle: $rs = 0.58$; left knee: $rs = 0.58$; right knee: $rs = 0.62$; left elbow: $rs = 0.55$; right elbow: $rs = 0.48$; ($P < 0.001$). In contrast, no significant correlations were detected for the WFH score and age in control patients.
Conclusion: Our data clearly show that the orthopaedic joint status in PWH highly correlates with age in contrast to people without hemophilia. Furthermore, the most pronounced structural and functional joint deficit was found in the ankle, which became increasingly important for today and in the future. (This study was conducted in cooperation with HaemArthroGroup and Baxter.)

PO-WE-211
The Early Biomechanical Manifestations of Ankle Joint Hemarthrosis?

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Advances in treatment that involve regular prophylactic rather than episodic administration of coagulation factor concentrates have resulted in reduced bleeding frequency; however, intermittent joint bleeding remains a concern. The aim of this study was to evaluate biomechanical differences between a group of hemophilic boys with a history of hemorrhage into the ankle joint and typically-developing age-matched boys. Twenty-six boys aged 6–12 years with severe hemophilia from 3 hemophilia centres in the United Kingdom (U.K.) (G1) and 26 age-matched, typically-developing boys (G2) were recruited into the study. Maximum isokinetic muscle strength of the knee flexors (KF) and extensors (KE), ankle dorsi (ADF) and plantar flexors (APF) was measured at 60 °/second. To determine muscle anatomical cross sectional area (ACSA), thickness, width, fascicle length and pennation angle, ultrasound images of vastus lateralis (VL) and lateral gastrocnemius (LG) were recorded. An 8-camera 3-dimensional motion-capture system (Vicon, Oxford Metrics Ltd, U.K.) and 2 embedded force platforms (Bertec, Model MIE Ltd, Leeds, U.K.) were utilized to determine joint angles and movements at the hip, knee and ankle together with EMG to record activity patterns of specific lower-limb muscles. Clinical scores for G1 were evaluated with the Colorado Physical Examination (CPE) instrument. Despite normal clinical CPE scores, muscle strength of the KE, ADF and APF was significantly lower in G1 when compared to G2 ($P < 0.05$). ACSA of VL and LG were significantly smaller in G1 compared to G2 ($P < 0.05$). Boys in G1 walked with significantly ($P < 0.05$) greater vertical ground reaction forces accompanied by greater knee flexion and ankle dorsiflexion angles, hip, and knee flexion moments and EMG activity of lateral gastrocnemius. Key findings from this study could be used to develop quantitative monitoring of musculoskeletal status and to identify boys at risk of developing chronic joint arthropathy.

PO-WE-212
Osteochondral Lesions of the Ankle Joint in Patients with Hemophilia A: A Retrospective Case Series

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Introduction: Despite the early use of prophylaxis, arthropathy remains an issue for some persons with hemophilia.[1] Research has demonstrated a shift in the pattern of joint bleeding with the ankle replacing the knee as the most frequently affected joint.[1,2]
Methods: This retrospective case series included patients who met the following inclusion criteria: age of 25 years or younger; moderate/severe hemophilia A; patient at a Canadian hemophilia treatment centre since birth and currently followed by the McMaster clinic; prescribed prophylaxis; complaints of ankle pain; and recent computed tomography (CT) scan/magnetic resonance imaging (MRI) of the ankle.
Results: Five of 41 (12%) screened patients met the inclusion criteria. The mean age of patients enrolled in the study was 18.4 ± 4.1 years (range: 15–25 years), The mean modified hemophilia joint health score (MHJHS) was 6.6 ± 7.4 (range 0–16) for the total score and 6.2 ± 6.8 (range: 0–14) for the ankle component, with higher scores indicating more joint damage (maximum total score: 106, maximum ankle score: 34). Only 1 patient demonstrated positive physical findings in a joint other than the ankle. One patient studied had a total MHJHS and ankle component of 0, indicating no joint changes. Forty per cent (40%, 2 of 5) of patients had no history of ankle joint bleeding; however, 100% of the cases complained of ankle pain and CT scan/MRI demonstrated multifocal osteochondral lesions in the ankle joint.
Conclusion: This study supports the notion that patterns of bleeding are changing and that prophylaxis is able to prevent arthropathy in the elbow and knee, but less able in the ankle. The total MHJHS is not sensitive to detect individual joint pathology. The use of a joint specific score over time and a pain assessment may be more relevant and sensitive when assessing joint status. Furthermore, a lack of documented bleeding episodes does not rule out the possibility of significant arthropathy. In conclusion, total joint score alone does not adequately assess individual joint status.
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PO-WE-213
Contrast-Enhanced Colour Doppler Ultrasound Scan (CEUS) in the Evaluation of Hemophilic Arthropathy

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Introduction: Hemophilic arthropathy (HA) is the most serious complication of intra-articular bleedings and imaging has become an important tool for the evaluation of joint condition. Recently Doria, in his review appeared in *Haemophilia* (2010 16, 107–11), has proposed the intravenous microbubble echo-contrast agents as the potential to increase the sensibility of Doppler ultrasound scan since it can be of additional value for the assessment of vascular synovial changes.

Objective: The objective of this study is to evaluate the diagnostic value of contrast-enhanced colour Doppler ultrasound scan (CEUS) in the joints of a cohort of hemophilic patients.
Materials and methods: We evaluated 15 joints in 12 hemophilic patients: 6 affected by hemophilia A and 4 affected by hemophilia B. Three HA patients were characterized by high titre antibodies to factor VIII (FVIII). Eight patients received on-demand replacement therapy while 2 were on secondary prophylaxis. The mean age of the patients was 33 years (range: 8–69 years). All patients suffered persistent joint pain and swelling. US examination of 2 knees, 9 ankles, 2 shoulders, and 3 elbows were obtained after intravenous injection of mdc. In 5 ankles and 1 shoulder, this technique was able to detect increased local blood flow. Other cases did not detect significant changes in microvascular blood flow.
Conclusions: In patients with hemophilia, a meticulous evaluation of joint condition is essential and CEUS may allow earlier and accurate quantification of arthropatic changes over time. In patients in whom CEUS demonstrated an increased local blood flow in target joint, we utilized more intense concentrates and/or local therapy as radiosynovirtesis. In our opinion, contrast-enhanced colour Doppler imaging holds promise for the detection of active synovial vascularization. It is cost-effective (no replacement treatment was used for the technique, including the 2 inhibitors patients) and easy for a correct and cheap therapeutic approach in the field of hemophilic arthropathy.

PO-WE-214
Radioactive Synoviorthesis for Advanced Stage Hemophilic Arthropathy

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Introduction: Synoviorthesis is the intra-articular injection of chemical or radioactive substances able to produce fibrosis of hypertrophied synovium. A more aggressive approach than on demand or primary and secondary prophylaxis has reduced largely the development of chronic synovitis in children and teenagers. Synovitis may be present in a proportion of patients undergoing primary prophylaxis and a larger proportion of adult hemophiliacs suffer from arthrosis. Radioactive synoviorthesis with 198Au, 90Y, 186Re, and 31P has proved effective in a series of inflammatory and degenerative joint diseases like reumatoid arthritis, spondiloarthritis, and osteoarthritis. Indications of RSO include the treatment of chronic hemophilic synovitis and have been used in hemophiliacs with recurrent hemarthrosis and chronic synovitis. The results, obtained by different experiences, show a definite diminution of hemarthroses in nearly 90% of cases.
Methods: Since 2006, we have selected 28 patients, most of who were treated on demand but 2 were treated with on secondary prophylaxis. 23 were patients with hemophilia A (3 with inhibitors) and 5 were patients with hemophilia B. All were suffering from severe pain in the joints despite the intensive on demand or prophylaxis treatment. The major part not refer recurrent hemarthroses; for some patients total joint replacement was already prescribed. The mean age of the patients was 36 (range 9–72) and the joints involved were 10 knees, 6 elbows, 10 ankles, 1 shoulder, and 1 wrist. The radioactive treatment was a single injection with $Yttrium^{90}$ for the knee and $Renium^{186}$ for the other joints. The mean follow up is now 14 months (range 3–52) and the first evaluation was done after 3 months from the initial injection. The results in terms of recurrent hemarthrosis, pain, and range of motion were excellent/good in 18 out of 20 cases. No procedure-related side effects were observed, though in 2 patients we did not observe any improvement.
Conclusions: Our results suggest that radiosynoviorthesis offers local and relatively non-invasive therapy for treating hemophilic arthropathy. It may be suitable also in a subgroup with advanced/end-stage arthropathy reducing pain and postponing, in some cases, the prosthetic procedure.

PO-WE-215
Arthroscopic Synovectomy with Joint Distraction Using a Patella Tendon Bearing Brace for Severe Hemophilic Ankle Arthropathy

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Introduction: Although arthrodesis is a gold standard for severe ankle arthropathy, we would like to avoid it, especially for young patients. We devised treatment with joint distraction using a patella tendon bearing (PTB) brace after synovectomy. The purpose of this study was to evaluate the clinical results of our procedures.
Methods: Nine patients (males, age 5–18 years, mean 10 years) with progressed ankle arthropathy were treated. Careful arthroscopic synovectomy was performed and defected cartilage areas were treated with bone marrow stimulation technique. The PTB brace was applied for 1 year postoperatively. Clinical results and radiographic finding using weight-bearing views were evaluated. Follow-up durations were from 29 to 84 months with an average of 61 months.
Results: Pain and disturbance of ADL were dramatically improved. The average AOFAS score was improved from 59 points to 88 points. Episodes of intraarticular bleeding were significant decreased after the treatment. Erosive changes were repaired and narrowing of joint space was recovered to nearly normal. The Arnold stages also were improved. The average of Pettersson score was improved from 7.7 to 4.7. One patient's autism was cured postoperatively and he now plays drums in his band.
Conclusion: Arthroscopic synovectomy is an established therapeutic option for hemophilic ankle arthropathy; however, it is well known that synovectomy could not improve existing joint degeneration. Our devised treatment could improve radiographic stages for progressed ankle arthropathy, and should be done before indicating arthrodesis for young patients.

PO-WE-216
Radioactive Synovectomy with Yttrium and Samarium Hydroxyapatite in Hemophilia: Epidemiologic Report on Radiation Safety

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Introduction: Radioactive synovectomy (RS) is a useful treatment for hemophilic synovitis. However, the safety of RS in terms of risks of ionizing radiation still causes concerns which need to be addressed. *Aim:* In this study, we report the preliminary radiation safety evaluation of the radiopharmaceuticals used for RS in Brazil. *Methods*: A retrospective survey of data for patients treated with RS since 2003 at 3 Brazilian centres was analyzed for untoward effects. A validated questionnaire was provided to the participant hemophilia centres and the results are reported in this article.
Results: A total of 488 patients (age 3–51 years old) were treated with RS using either ^{90}Yttrium (^{90}Y) Citrate, ^{90}Y Hydroxyapatite, or ^{153}Samarium (^{153}Sm) Hydroxyapatite. Four patients died from circumstances not related to radiation (acute pulmonary edema, liver cirrhosis due to viral hepatitis, homicide, and intracranial bleeding). One patient, aged 14 years, was diagnosed with soft tissue Ewing sarcoma (ES) in the right scapular region 11 months after receiving RS. He achieved satisfactory response to the treatment of the tumour, through surgery and chemotherapy.
Conclusion: RS with ^{90}Y Citrate, ^{90}Y Hydroxyapatite or ^{153}Sm Hydroxyapatite was safe in nonarticular organs in this set of patients. A causal association of ES and RS in this case is improbable, mainly because of the short latency period between the two events. Long term surveillance, ideally performed at multiple centres, is required to fully evaluate the safety profile of RS performed with the available radiopharmaceuticals. This is part of an ongoing study, thus more cases are added to the authors' database after each new RS treatment. The authors have no interests which might be perceived as posing a conflict or causing bias.

PO-WE-217
Blood Coagulation Aggravates Joint Damage after an Experimental Hemorrhage in a Canine Knee

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Objectives: Joint bleeding due to trauma, major joint surgery, or hemophilia leads to joint damage. However, it is unclear if there are differences between coagulating blood and anticoagulated blood with respect to joint degeneration, especially *in vivo*. In a canine *in vivo* model we evaluated whether intra-articular blood exposure is more destructive in case of coagulating blood compared to anticoagulated blood and whether inflammation plays a role in the cartilage damaging process.
Methods: In 7 dogs, left knees were injected with coagulating blood 4 times per week in weeks 1 and 4 and the right knees were injected with saline. In 7 other dogs, anticoagulated, heparinized blood was similarly injected with heparinized saline as control. Ten weeks after the last injection, cartilage matrix turnover and synovial inflammation were analyzed. To study inflammation-independent cartilage damage, human cartilage explants ($n = 6$) were exposed *in vitro* to coagulating and anticoagulated blood, plasma, and serum for 4 days. Cartilage matrix turnover was determined on day 16.
Results: Canine knees injected with coagulating blood showed a more disturbed proteoglycan turnover (higher proteoglycan release and a lower -content; ($P < 0.02$) than knees injected with anticoagulated blood. Statistically significant synovial inflammation was only present after intra-articular injections with coagulating blood ($P < 0.01$). Coagulation of blood *in vitro* resulted in more cartilage damage compared to anticoagulated blood (more reduction of proteoglycan synthesis rate and higher -release; ($P < 0.05$), while plasma and serum did not alter cartilage matrix turnover.
Conclusion: This study shows that coagulating blood causes more long-lasting *in vivo* joint damage, directly on cartilage and via inflammation, than anticoagulated blood. Nevertheless, since anticoagulating blood also causes cartilage damage, the best way to treat blood-induced joint damage is to aspirate blood from the joint.

PO-WE-218
Four-Day Continuous Blood Exposure Leads to Prolonged Joint Damage in a Canine In Vivo Model, Whereas Intermittent Blood Exposure Does Not

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Objectives: Blood exposure leads to irreversible cartilage damage *in vitro*. In a canine model, intra-articular blood injections twice a week for 4 weeks resulted in transient damage only. In this study it was evaluated whether continuous blood exposure is more harmful than intermittent blood exposure in a canine model of knee arthropathy.

Methods: Seven dogs received 2 series of 4 once-daily blood injections (continuous exposure) with 2 weeks in between. Seven other dogs received a total of 8 intra-articular blood injections, intermittently over a 4 week period with at least 1 day in between. Contralateral knees served as the controls. Ten weeks after the last injection, cartilage matrix turnover and synovial inflammation were evaluated.
Results: In the blood-exposed joints of both groups, proteoglycan synthesis rate was increased (both $P \leq 0.02$) as an attempt to repair cartilage. This mimics early features of joint degeneration. Only in the continuous blood-exposed knees, the release of newly formed and total (resident) cartilage matrix glycosaminoglycans (GAGs) was increased ($P = 0.04$ and $P = 0.01$, respectively). Furthermore, in the animals with continuous exposure, cartilage GAG content was decreased ($P = 0.01$), but no decreased was noted in the animals with intermittent exposure. Mild synovial inflammation was observed in both groups (both $P < 0.0001$), but was not different between groups.
Conclusion: In contrast to intermittent exposure, a 4 day continuous blood exposure twice in 4 weeks leads to prolonged cartilage damage, independent of the level of synovial inflammation. This model is of use to study treatment modalities preventing blood-induced arthropathy.

26-NURSING ISSUES

S-MO-01.4-2
Cultural/Ethical Sensitivity in Rare Bleeding Disorders
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Rare bleeding disorders (RBDs) are quite common in emerging countries, particularly in the countries where marriages between relatives are quite high. It is common to refer to these societies as consanguineous societies. Through marriages between relatives, these disorders can be filtered and become more visible, even though they are normally recessive. There is a big concern in these emerging societies over disclosing these disorders or even talking about them since discovering one disorder in the family is going to affect the future marriages in the family particularly among the females of this family. This is a big cultural concern and health professionals, particularly nurses, usually find it quite sensitive to talk about the problem either when diagnosis is made or during educational activities. At the same time, a much larger ethical concern manifests here, either on selecting some treatment options like bone marrow transplantation in some disorders, or on giving advice on marriages and future pregnancies. Health professionals in remote areas are put in a very delicate situation if they advise families on the necessity to break the cycle and have marriages outside the family. This presentation is going to identify most of these challenges, highlight the ways to address them, and provide some suggestions on how to respond to questions from the general public.

S-TU-01.4-2
Hemophilia nursing in the surgical setting
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In countries where clotting factor is readily available, acute and elective surgical procedures for people with hemophilia are common place and are usually successful. However, surgical procedures, such as circumcision, that are performed for cultural or traditional reasons, are challenging, as they are often performed in developing countries who do not have ready access to clotting factor. Safe, cheap, and practical methods to reduce bleeding are being developed so that people are able to practice their society's beliefs. Tattooing and piercing are not only popular ways of being individualistic and creative but are also symbolic in many cultures. In New Zealand, the Maoris and the large Pacific Island population traditionally have their family stories and history tattooed on their arms and legs. But, tattooists are not licensed or regulated, so apart from the risk of oozing blood, local and blood borne infections are a risk. For patients on regular prophylaxis, tattooing and piercing are not such a bleeding concern, but we often see people who are on demand after the event with bleeding wounds. As nurses, we acknowledge that social and cultural practices are important to people's wellbeing, so we embrace new and innovative methods to reduce mortality in this area.

S-MO-01.4-3
Rare bleeding disorders in women
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Bleeding disorder is a dysfunction of the coagulation system that causes spontaneous or post-traumatic bleedings in humans, or prolongs the bleeding time. The incidence of bleeding disorders is one in 1,000 to 20,000 inhabitants. Bleeding disorders may be underdiagnosed as in some patients the bleeding disorder can be mild and can therefore be unrecognized (i.e. patients with von Willebrand disease). Main symptoms for mild bleeding disorders are: Mild or long-lasting nose bleeds, prolonged bleeding time in smaller skin injuries or major traumas, heavy menstrual bleedings, postpartum or postoperative bleedings, and the occurrence of similar symptoms in other family members. There is a major impact on quality of life for a woman with a rare bleeding disorder is depending on the status of the disease – either she is a carrier of hemophilia and having problems with prolonged bleeding time, or she is already diagnosed with a bleeding disorder caused by coagulation factor deficiency. In patients with rare bleeding disorders, it is important to know about family anamnesis, current situation and quality of life (occurring symptoms and problems), and to what extent medical support is needed. From the nurse's perspective it is important to have skills to provide psychological support for rare bleeding disorder patient in regards to treatment and quality of life. This requires a good knowledge about diagnosis, treatment, and the relief of the symptoms of bleeding disorders from the nurse.

S-WE-04.5-3
The prevalence of stomatology in Chinese people with hemophilia
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Background: Hemophilia is a group of hereditary hemorrhagic diseases that cannot currently be radically cured, and the major clinical manifestations are spontaneous bleeding or bleeding from injured arthroses (constitutes of 70–80% of all bleeding symptoms) muscular/soft tissues (10–20%), oral cavity/gingivae/nasal cavities, urinary system, etc. At present, compared with the international standards, the levels of treatment and attendance to the people with hemophilia in China still have a large disparity, for example, the levels of the oral hygiene and the treatment of the people with hemophilia. For the people with hemophilia, it is particularly important to keep the oral cavity healthy and prevent dental diseases, which not only concern their quality of life, nutrition, and health, but also minimize the risk of dental surgery.
Objectives: To investigate the oral health of people with hemophilia in Beijing and other provinces.
Methods: Randomly selected 180 people with hemophilia in Beijing and other provinces from Beijing Hemophilia Management Centre to investigate their healthy conditions of the oral cavity, resorting to the self-designed questionnaire and oral cavity examination by specialists.
Results: It was found, through the investigation, that people with hemophilia lacked the knowledge to prevent the dental caries and periodontal disease with 20.6–45% of the correct rate on the related questions; lacked the positive performance of visiting doctors on the oral cavity healthcare, with 9.4% patients regularly resorting to teeth cleaning and 10.6% patients regularly examining the oral cavity, with 25% and 30% respectively of taking medical treatment for gingivae bleeding and dental caries; 66.7% of people with hemophilia suffered from the spontaneous gingivae bleeding, which differed from the normal people whose gingivae bleeding resulted from the oral cavity disease, and had something to do with the hemophilia itself as hemorrhagic disease; with 100%, 100% and 94.89% of plaque, dental calculus and bleeding detected respectively in the oral cavity examination.
Conclusion: People with hemophilia lacked the professional knowledge related to dental caries and periodontal disease, lacked the positive performance of visiting doctors, mostly had the spontaneous daily gingivae bleeding and had higher rate of plaque, dental calculus and bleeding than normal people in the examination, so they were in need of education and intervention.

S-TH-03.5-2
Inhibitors in pediatrics
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Inhibitors are antibodies that develop as a result of exposure to factor VIII in patients with severe hemophilia A. These circulating anticoagulants inhibit the activity of infused clotting factor concentrate. Inhibitors present a very serious complication in hemophilia. Inhibitors are suspected in patients with hemophilia when factor replacement therapy appears to be less or ineffective. Confirmation of inhibitor is established in the laboratory by performance of a Bethesda assay. Inhibitors mostly develop in the first 20–50 exposures to exogenous factor concentrate. There are several treatment options for patients with inhibitors, but none can guarantee the same good outcome as specific factor VIII or factor IX replacement. The best intervention at present is immune tolerance therapy (ITT), which is successful in 80% of inhibitor patients with inhibitors to factor VIII. Factors to consider prior to commencing immune tolerance therapy are the severity of the inhibitor; the duration of the inhibitor; the treatment of acute bleeding episodes; venous access; type of product; availability of factor; safety and affordability of the product; duration of treatment; frequency of clinic/hospital visits; compliance. To illustrate these challenges, I will describe and discuss 2 pediatric patients, from different socio-economic backgrounds, with inhibitors undergoing ITT, taking into account the major and minor challenges to treatment of inhibitors in a developing country. The question is, is it justified to embark on immune tolerance therapy in a developing country with limited resources?

S-TH-03.5-1
Enhancing the nurse's role for subjects with inhibitors
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There are few specialized programs for the care of patients with hemophilia who have developed inhibitors or who have acquired hemophilia. The Quebec Reference Centre for the Treatment of Patients with Inhibitors in Canada is an example of a specialized interdisciplinary program created to dispense quality care and services to this group of patients. The specialized clinical nurse plays a central role in the functioning of such a centre in coordinating nursing, medical, and interdisciplinary care. She assumes a leadership role and must make sure that the objectives of the team are clear and coherent to ensure the well-being of patients and families. The nurse's main priority is on education, and she takes into account the expertise of each member of the interdisciplinary team. Their professional observations concerning the different challenges of living with inhibitors are, therefore, an invaluable source of knowledge in the development of quality care and services for this clientele. The nurse's experiences with patients and families, as well as the themes that emerge within the team, also offer outstanding opportunities for research not only at the interdisciplinary level but more importantly for nursing. The constant evolution of the clinical nurse-specialist role responds to recognized needs of the clientele. We would like to describe the role of the clinical nurse-specialist in order to set grounds for further discussions on the need to support the development of the nurse's role in this sphere of intervention.

S-WE-04.5-1
History, need, and benefits of hemophilia camps
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Objectives: Discuss areas where nurses provide care, advocacy, and support to patients outside the treatment centre setting. Educate the audience on the successful use of camp for patients with bleeding disorders. Define at least three types of camping programs. Expose audience members to the Health Centre Guidelines developed for camps serving those with bleeding disorders. Examine educational opportunities nurses may have in areas outside the centre.

Methods: Using research in the area of camping and chronic diseases, we will discuss how nurses in hemophilia treatment centres can impact the level of understanding, quality of life, and self-esteem of children with bleeding disorders. We will explore the historical use of camps for this patient population and discuss how providing a camping experience will benefit the individual patient.
Results: Condition-specific camps have been able to show benefits to children affected by a chronic illness including: decreased anxiety, increased understanding of their illness, emotional support, self-advocacy development, and the establishment of positive and life-long social interactions.
Conclusions: Nurses are often utilized outside the treatment centre walls to provide professional services to their patients and families. School and home visits, surgical/dental settings, camps and government meetings are just a few of the areas nurses expand their roles for patients with bleeding disorders.

S-TH-03.5-4
Inhibitors in hemophilia – adverse condition in treating and care for patients from the nurses' perspective: Case report
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Introduction: In healthy persons, control of bleeding is achieved quickly and without the need for medical intervention. However, some persons suffer from chronic bleeding disorders that decrease their ability to reach hemostasis. Many of these disorders are hereditary. Hemophilia is the most common hereditary coagulation disorder, caused by complete or partial lack of factor influencing the normal blood coagulation. The lifelong tendency for bleeding leads to a more passive lifestyle and various levels of invalidity, depending on the degree of factor deficiency. This represents an important social problem in society. The people with hemophilia are treated by the administration of coagulation factors VIII or IX, produced from plasma or through recombinant technology. One of the complications in treating hemophilia is the development of inhibitors. The concentrate of factors is destroyed before it manages to stop the bleeding. The inhibitors are usually recorded when the patient does not respond to the standard therapy. As a member of a multidisciplinary team, the nurse is participating in the application of the assigned therapy, care, and health education of patients with hemophilia and inhibitors.
Conclusion: The imperative for treating patients with hemophilia and inhibitors is to stop bleeding, prevent new bleeding, and remove the inhibitor that prevents the expected result. The treatment of these patients demands an individual approach and a specific field of work for both physicians and nurses.

S-WE-04.5-2
Self-infusion: Education outside of the hemophilia centre
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Education is one of the keywords used in our hemophilia centre, where we serve adults and children, totalling 198 patients with hemophilia A and hemophilia B (HA and HB). 80% of this people are trained to do self-infusion and/or their parents or other relatives are also prepared to do this. Training, with this objective, is to make these individuals independent and able to participate in their daily activities without fear. In 2000, a Ministry of Health program called Domiciliary Dose was implemented in our country and a factor dose was given to the patient to take home, with the purpose of raising the factor level to 30–40%. However, one of the conditions necessary for people to have this dose at home was that they were trained for vein puncture. Then, we began to give greater focus to the training of patients, particularly children who began to be invited to participate in this program from the age of 3. Nothing would have been possible if we did not work in a multidisciplinary group, where each professional opinion is always respected. Today, 12 years later, our country is starting the Primary Prophylaxis Program and, fortunately, most of the patients in our centre are prepared to participate in this program.

S-TH-03.5-5
Case study: Mild hemophilia and inhibitor - Nurses challenge in the care of the elderly
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History: People with mild hemophilia are often not knowledgeable about their hemophilia and the management of it. Moreover, in a lot of healthcare settings, there exists the risk of being 'underserved' for mild hemophilia. Our patient was diagnosed in 2001 at the age of 50, without antecedents in the family. The genotype of this patient is Intron 22. He had several bleeds after the extraction of teeth during youth and a life-threatening bleed after operation of ductus parotis (left). In April 2009, the patient had symptoms of amourosis fugax and had to undergo a bilateral carotisendarterectomy with substitution of rFVIII.
Inhibitor history: The general practioner of the patient called our centre reporting subcutaneous bleeds, macroscopic hematuria, and anemia. Lab results showed: FVIII inhibitor 12 BU; Immune tolerance induction. 1st episode: High dose plasma derived FVIII 200 IU kg^{-1}: 10000 IU per day; Medrol 32 mg d^{-1}; 4 × Rituximab. 2nd episode: DDAVP pn 2 × per week; 4 × Rituximab. Complications: Cardia ischemia due to anemia with admission on CCU. Cardiovascular risk factor: Obesitas; Hypertension; Smoking; hypercholesterolemia. Venous access: At the start, venous access was obtained by peripheral IV catheter. Due to a major extravasation in the patient local hospital and rise of FVIII inhibitor, but also due to poor venous access, a PICC catheter was inserted in the Vena Sephalica right with catheter tip in the Vena Cava superior. Treatment of bleeds: Recombinant FVII for major bleeds; DDAVP for minor bleeds; Educational aspects patient concerning mild hemophilia and inhibitor; Educational aspect colleagues in- and extramuros

PD-SU-NUR-1
Improving hemophiliac care by engaging nurses in clinical research
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Aim: Clinical research should form a core component of the role of hemophiliac nurse specialists and offer the opportunity to further the quality of care delivered to patients and their families. The U.K. Haemophilia Nurses Association sought to determine the barriers that prevent nurse specialists from engaging in research and to seek ways to promote clinical research by nurses.
Method: Web-based survey with subsequent workshop discussion.
Results: Responses were received from 32 nurses (a 50% response rate). All agreed that hemophilia nurses should be actively involved with nursing research, although only 21 had actually participated in research specifically related to hemophilia practice. Of this, most research had been related to educational programs or (less commonly) was limited to data collection as part of multidisciplinary studies. Nurses' involvement in research rarely resulted in publication. Survey respondents identified systematic (time and managerial support), professional (lack of support and guidance, and opportunities to collaborate), and personal (lack of confidence and motivation) barriers to involvement in nursing research and subsequent publication. Respondents identified key practice areas that warranted nurse-based research. These included carriership and antenatal decision-making, along with the role and impact on care of the specialist hemophilia nurse, education, and empowerment.
Conclusion: Nurses engaged in the "sharp end" of clinical practice will frequently be the first to identify areas of practice in which new approaches are needed and in which questions need to be answered to improve evidence-based care for patients and their families. In order to overcome the barriers to engaging in research and publishing, nurses require dedicated research time, mentorship, and collaboration with more experienced hemophilia nurse researchers. The HNA-endorsed Haemnet social-network-based website (www.haemnet.com) offers an online forum in which nurses can share their experiences of research and discuss, collaborate, and promote their own initiatives.

PO-MO-161
The role of nurse in improving hemophilia care
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Introduction: The hemophilia nurse has a dynamic, comprehensive, and extensive function; he contributes to improving and maintaining the quality of life for patients.
Objectives: Our objectives are to a) provide quality care for people with hemophilia (PWH), and b) strengthen the link between care givers and patients.
Methods: In this paper, we report the functions performed by the nurse specialist in hemophilia at the unit of hemophilia and congenital bleeding disorders of the Hematology Department (role of communication, of care, of training, and administrative function).
Results: The hemophilia nurse was trained abroad to acquire the skills necessary to provide quality care to PWH. One hundred sixty-seven PWH were followed regularly in consultation; they frequently call the hemophilia nurse who tries to manage their stress, analyze their needs, and advise them. He also manages patient records, updates their information, and includes the new patients in the national register. He coordinates appointments for follow-up visits (130 people with severe hemophilia were followed every 3 months, 25 with moderate hemophilia every 6 months, and 12 with minor hemophilia every 12 months), orthopedic consultations (10 per month), dental consultations (15), and physiotherapy. He manages inventory and controls the anti-hemophilic factor. During follow-up consultations, he welcomes PWH and their parents and provides blood collection. He supports the bleeding complications. In addition, he participated in the therapeutic education program (4 training sessions since 2009) for PWH: 77% of adults and 50% of parents have acquired self-infusion.
Conclusion: The nurse specialist in hemophilia has improved the management of hemophilia.

PO-MO-162
Inherited bleeding disorders: The nursing experience of patient and family care needs in the pediatric setting
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Background: This qualitative study aims to assess the perceptions of nursing staff who care for patients with severe bleeding disorders and their families. Are we meeting their needs? Do we as nurses have more to offer in service development?
Aim: Our aim is to determine how nurses perceive their role now, and identify, if possible, their perception of the future role of the ward nurse in the care of these patients.
Methodology: A questionnaire was designed addressing components of "in hospital" nursing care for patients' with inherited bleeding disorders. The questionnaire addresses the following: identification of specific care needs for patients; evaluation of whether the service is perceived by nurses to be meeting those needs. If not, why not?; definition of the nurse's perception of his/her role in the multidisciplinary care of these patients; and do nurses have more to offer? Staff were given a 2-week timeframe in which to anonymously answer the questionnaire. Questions were limited to 5 to increase the likelihood of staff responding.

Results: Findings have not yet been collated and therefore cannot be presented at this time. Results will be qualitative in nature and, therefore, may be open to interpretation and debate.
Conclusion: The nursing process must be continually assessed and evolve to incorporate the skill base of staff, develop and build on past nursing experiences, in order to provide optimum care for our patients. Qualitative data has been effective in providing a platform from which to continue.

PO-MO-163
The needs and support measures of Japanese hemophilic carrier (JHC): Discussion from literature review

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Introduction: There has not been few reports which medical care providers focused on hemophilic careers (HC) in Japan. We reviewed and analyzed literature on the support of Japanese hemophilic carriers (JHC) to clarify the contents of support measures needed for JHC.
Method: The literature was investigated using a search engine for medicine and nursing using the basis of key words "hemophilia," "carrier", or "nursing", and 10 papers were the subject of our study. Sampling needs of carriers or support situation, they were compared with them in developed countries in the field of hemophilia.
Results: From the literatures, it was disappeared that many nurses wanted to have the knowledge of genetics, pregnancy, delivery in HC to receive the consultation from hemophiliacs and their families. A half of HC had not known whether they were carriers or not till their deliveries from the results of the investigation for HC. There are 6 institutions which can support HC in Japan. However, some HC tended to have excessive anxiety by the information from the internet services. Although there were 58 institutions which department of genetic medicine was settled at the time of 2006, most of them were urban areas.
Discussion: As there are only several institutions which can provide a special care for hemophiliacs, it was suggested that HC did not have the opportunity of the counseling about their unique problems even though they had troubles or anxieties in Japan. In their needs about genetics, pregnancy and delivery, it can be seemed to deal with them at the department of genetic medicine in the institutions. There is still lacking in a viewpoint which HC should be cared as potential hemophiliacs in Japan. It was important to spread the knowledge of HC to the field of medicine or nursing in order to improve the present situation.

PO-MO-164
Improving nurse care in hemophilia and other coagulopathy: Development of a self-treatment protocol and patient guidance

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Introduction: Spanish law considers the self-treatment of hemophilia from April 28th, 1982. This self-treatment is regulated and indicated in the case of moderate or severe hemophilia. Self-treatment must be requested by patients or their guardians, and health professionals should provide technical training to the patient or the guardian/s and under-age patients. Moreover, early training of pediatric patients is encouraged. The Spanish health system provides the materials needed, and the patient is supervised and the evolution of this treatment is followed by health professionals.
Aims: Our aim was to develop a nursing protocol to unify treatment criteria and improve patient training, so our service could provide high quality self-treatment support.
Results: Patient training and guidance protocols were standardized, updated, and improved to offer better self-treatment support to our patients with hemophilia. The final protocol followed the formal structure in our centre and covers the following aspects: definition, objectives, staffing, materials used, detailed procedure adapted to patient-information needs, precautions and suggestions, observations, and evaluation criteria.
Conclusions: The practice of this new protocol resulted in increased satisfaction for both patients and professionals. The proper development of nursing protocols is necessary since the staff is essential in providing personal care to our patients.

PO-MO-165
Evaluation of methods of identifying carriers of hemophilia

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In South Africa the identification of carriers of hemophilia has been unsuccessful. Previously undiagnosed carriers present to a medical facility at delivery of a boy child. The lack of prenatal planning has resulted in various degrees of morbidity. Letters given to people with hemophilia to pass on to female relatives inviting them to contact the hemophilia or genetic clinic were not responded to. In order to establish a better way of reaching the carriers in our population, a general literature search was done asking the question, "What methods have been used in the past in other communities and how successful have they been." These different methods of approaching carriers were looked at and evaluated to assist us in choosing an appropriate method. This literature search and evaluation will be discussed. Early analysis differentiates between compliant societies and those where basic necessities are a daily struggle. Other key factors were level of education and cultural background. Through this process we hope to identify carriers who are at risk, more patients in the South African population which remain under diagnosed at an early age, and improved care from the prenatal stage onwards for people with hemophilia.

PO-MO-166
The implementation and evaluation of an oral health risk assessment by non-dental personnel for patients with bleeding disorders

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Introduction: Oral care and the prevention of dental problems are of significant importance in ensuring optimum physical health and quality of life for people with bleeding disorders. The economic costs of providing treatment for patients who have extensive dental disease can be high, and the personal cost of dental neglect can involve life-threatening bleeding; yet dental disease is preventable, and the risk factors are known.
Aims and Objectives: To develop an oral health risk assessment tool for use by non-dental personnel (such as nursing and medical staff) for patients with bleeding disorders. To evaluate and audit a triage process for use when patients contact the hemophilia centre with a dental problem or request advice when they are in pain or have a dental emergency.
Method: The risk assessment tool includes general information about patients' perceptions of their oral health; their pattern of dental attendance, including barriers to care; their previous dental experiences, such as bleeding episodes, trauma, and phobia; and their individual risk factors for oral disease. The tool is intended for use at initial patient appointments, hemophilia annual review, and nurse-led clinics. The triage process includes a flow diagram which can be used to assess the urgency of the dental problem, indicate the appropriate pathway of care, and provide an aide memoire for appropriate advice and guidance regarding common dental emergency situations. Both tools will be made available on the hemophilia electronic patient database.
Findings: The implementation of an oral health risk assessment and a triage tool by non-dental personnel will highlight individuals who are at high risk of oral disease and should optimize communication within the multidisciplinary team, so that a safe, efficient, and appropriate pathway of oral care for persons with bleeding disorders is ensured and their dental experience improved. To measure the success of the new tool, monthly audits will be conducted to measure tool adoption and assess data quality.
Conclusion: Within the context of a comprehensive care centre, it is of paramount importance that the medical and nursing teams unite with the dental team via seamless pathways of care, to ensure that the promotion of good oral health is an integrated part of the healthcare plan for the person with a bleeding disorder.

PO-MO-167
How much factor are we really using? Observations about adherence to prophylaxis in an interdisciplinary setting

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Background: Severe hemophilia is often managed by prophylactic factor infusions in developed countries. The benefits of secondary prophylaxis in adult patients are currently being studied, and adherence to their prescribed prophylactic factor regimen is vital to decreasing bleeding episodes. We sought to understand patterns of adherence in our clinic population.
Objective: To measure discrepancies between the physician prescription for prophylactic factor usage and the actual factor usage obtained through self-reported infusion logs.
Methodology: Subjects with severe hemophilia A or B (FVIII or FIX $\leq$ 2%), from a single hemophilia clinic with complete medical and infusion records from July 01, 2009 to June 30, 2011, were evaluated. Continuous prophylaxis≥4 weeks was included in the analysis. A scoring system for adherence to prescribed dosing and frequency was developed. A global scale of adherence was performed by 2 independent nurses' (RN1 and RN2) using visual analogue scales.
Results: Thirty-one subjects, all with hemophilia A, with a median age of 26 years (range 18–56), were included. The median (IQR) adherence rate to prescribed frequency and dosage, respectively, was 76% (67–85%) and 92% (66–98%). In multivariate analysis, only the length of time on prophylaxis during the study period showed a positive correlation with adherence, whereas age, number of co-infections, and number of joints with chronic arthropathy did not. Global nursing assessments were in general agreement with the score, with median adherence rates for RN1 of 78% (64–98%) and 99% (0.89–1.0) to prescribed frequency and dosage, respectively, and RN2 was 83% (31–96%) and 95% (79–97%), respectively.
Conclusion: We observed a moderately good level of adherence based on score and by the nurses' global assessment. Better adherence was found in subjects with longer exposure to prophylaxis. Our clinic will continue to explore methods of measuring discrepancies in prophylaxis between prescribed and recorded infusion logs.

PO-MO-168
Forging partnerships between hemophilia treatment teams and local health networks to optimize health outcomes for children living with hemophilia in rural communities

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Aim: To demonstrate the importance of establishing partnerships between hemophilia treatment centres (HTCs) and local health network providers to improve care provision and health outcomes for children living with hemophilia in rural communities.
Discussion: It is well documented that the further children live away from specialist treatment the poorer their health outcomes, and with vast distances in Australia, meeting

the needs of children with hemophilia in rural areas can be arduous. Overcoming barriers in each community is important, and identifying key personnel to partner with families is vital in establishing a local health-professional network to provide optimal support and care. Achieving improved health outcomes for children with hemophilia requires an adaptive and collaborative approach, and in the South East of South Australia we took up this challenge. The primary goal initially was to facilitate prophylaxis and subsequently evolved to include a treatment plan for bleeds, education for families, carers, and education providers. In addition, improving knowledge of hospital staff in the recognition and treatment of bleeds in emergency situations and ongoing education for key community nursing staff was undertaken. With education and information sharing provided through a variety of formats, our knowledge and understanding of hemophilia increased, allowing us to broaden our care to meet both short- and long-term goals and lead to early recognition and treatment of bleeds and, importantly, independence of families to manage and prevent bleeds. The key to achieving optimal care was the close and open communication between specialist nursing staff in the HTC, the local community nursing team, and family networks.
Conclusion: Ongoing partnerships between specialist hemophilia staff and local health network providers is essential to improved knowledge of hemophilia and key to supporting and providing optimal care to children with hemophilia in rural Australia.

PO-MO-169
Hemophilia: Transition from pediatric to adult care
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Adolescence may be considered a phase of enormous physical and emotional change and instability. At the same time, adolescents have to learn to be responsible for their life, including any chronic medical condition. They also face the transition from pediatric to adult care during this period. There is an increased risk for adverse health events if the transition from isn't smooth or effective. Practice and literature show a lack of transition programs. Transitions are often abrupt and parents often feel lost. Therefore our pediatric Hemophilia Reference Centre developed a transition program for adolescents. Previously, research using past literature was done. The developed transition program is based on two nursing diagnoses (NANDA, 2010) and a published protocol by Kennedy et al. (2007). The purpose of the program is tailored in a step-by-step program so that education and counselling towards self-management is achieved. Furthermore, parents and adolescents should have seen the adult care centre and met the hematologist prior to transition. Finally, transfer is planned at a time of patient readiness.

PO-MO-170
A survey of trainee's perceptions of the hemophilia nurse specialist vein-training program
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Background: Intravenous (IV) prophylactic coagulation factor concentrate (CFC) is best practice for patients with severe hemophilia and for patients with problematic moderate hemophilia and type 3 von Willebrand disease (VWD). The hemophilia clinical nurse specialist (CNS) is responsible for educating parents and patients to administer CFC via peripheral veins.
Aims and Objectives: To determine how well parents and patients understand the reasons for peripheral IV access; to evaluate how well parents and patients are educated/supported in administering CFC's via peripheral veins; to evaluate perception of support after training; and to identify areas in need of development to optimize parent and patient satisfaction.
Method: An anonymous questionnaire was distributed to 11 children and 19 parents who had completed the training program, inviting them to evaluate satisfaction in relation to preparation for vein training; education and training regarding the administration of CFCs via peripheral veins; advice and support post-discharge.
Results: This survey is currently in progress. Results will be analyzed using descriptive statistics. Conclusion:
The hemophilia team is responsible for providing comprehensive information and support. The hemophilia CNS has a pivotal role in empowering parents and patients to facilitate home treatment.

PO-MO-171
Need for Shared Experience among Girls with Inherited Bleeding Disorders
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Background: Many females with bleeding disorders, including up to one third of hemophilia carriers, experience heavy and/or prolonged menstrual bleeding, or bleed after dental work, surgery, injury, or childbirth. In most cases, symptoms can be treated leading to full and active lives. Nevertheless, girls and women with inherited bleeding disorders frequently suffer with bleeding difficulties for many years before being diagnosed.
Methods: Two focus groups, one for known/potential hemophilia carriers and one for girls with other bleeding disorders, were held in 2011. They consisted of moderated discussion of living with a bleeding disorder, its management, and the coping strategies that women find helpful.
Results: Despite attending clinics, these teenage girls had poor recall of the educational leaflets and information offered, frequently relying on Internet-based resources. They stated that the majority of "talking and educating" had been done with their parents and that it was assumed they also knew this information. Clinic literature was thought too academic, and failed to address "real" and relevant questions regarding sex, heavy (and prolonged) periods, pregnancy and childbirth, the pill, tattoos/piercings, etc. In addition, girls said medical consultations too often offered only bland reassurances regarding issues such as fertility and pregnancy outcome. Girls rarely met others with bleeding disorders, but expressed a desire to hear about and share real-life experiences from older women.
Discussion: The SixVibe social network and website (www.sixvibe.com) will provide information and self-management skills for girls with bleeding disorders, focusing on issues relevant to everyday life, not generally addressed by medical services (disclosure of diagnosis to friends and extended family, sexuality, tattoos and body piercing, recreational drug use, depression and so on). Internet-based social networking may be of particular value to girls with bleeding disorders who are unable to seek help from traditional medical services due to religious or other cultural barriers.

PO-MO-172
Using motivational interviewing techniques to enhance therapeutic relationships with adult and pediatric hemophilia clients
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Objectives: To explore ways in which motivational interviewing (MI) can improve communication between hemophilia nurses and their clients.
Methods: A group of six hemophilia nurses participated in an introductory program about MI in the fall of 2011. The nurses were encouraged to use MI techniques with their clients for two months, and to meet again to share their experiences.
Results: This poster summarizes the outcomes of five of the nurses' experiences using MI in their practices. The nurses felt the MI technique had allowed them to do the following: 1) *Use the autonomy component of MI to improve therapeutic relationships*: MI helped create a more relaxed atmosphere where clients spontaneously suggested ways to change behaviour to improve bleeding outcomes. 2) *Avoid the expert trap*: when the nurse asked patients for their permission before providing advice, patients felt like they had been heard, and collaborated with the nurse to develop realistic action plans. 3) *Enhance hemophilia nursing practice:* using MI helped the nurse to feel more authentic in her role; increase her job satisfaction; uncover information; and feel more relaxed and effective in difficult conversations. 4) *Enhance therapeutic relationships with patients transitioning from pediatric to adult treatment centres:* in working with young adults, MI facilitated client engagement and the transition to an adult treatment centre. 5) *Make implicit permission explicit:* requesting, rather than presuming, consent resulted in greater trust and openness between the nurse and patients. It helped patients take ownership of their health and relieved the nurse of the burden of "fixing the problem."
Conclusion: Motivational interviewing provides a valuable tool for hemophilia nurses in supporting and enhancing their nursing practices.

PO-MO-173
A successful model of a nursing short-message system (SMS) for improving hemophilia care in South China
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Background: In 2004, the Hemophilia Centre at Nanfang Hospital was designated as the referral centre for South China. Since 2009, a nursing short-message system (SMS) has successfully established frequent contact with 700 patients with hemophilia.
Methods: We established an electronic medical record and communication system: the Nursing-SMS. China-Telecom provided one phone number and region-wide coverage to send and accept SMS messages. Patients' names, cell-phone numbers, and other information were inputted. Patients then had access to services like health management, medical education, and activity notices. It was designed at a very low cost, about US$1.50 per 100 SMS messages sent, and free for accepting.
Results: Data from December 2010 to November 2011 revealed a total of 652 (93%) patients kept in touch with their nurses through the Nursing SMS. Approximately 270 (38.5%) patients used the Nursing SMS from the remote regions (over 350 km from our centre). Approximately 11,320 messages were received and were comprised of acute emergent care (24%), general consultation (46%), reports of bleeds and injections (28%), and other (2%). Nurses sent approximately 15,000 messages including medical counselling (34%), follow-up care (13%), event/meeting notices (31%), and general notices (22%).
Conclusion: Nursing-SMS provides a powerful tool in hemophilia care. Patients contact nurses anywhere, anytime, without nurses bound to the telephone. Most notably, the Nursing SMS provides a real-time tool for patients to deal with bleeding events under the medical guidance of the hemophilia centre. This could reduce serious complications especially with patients living in remote rural areas. For non-urgent messaging, Nursing-SMS provides timely communication between the patient and the nurses, possibly improving health care and education of the patient. The low-cost of the SMS makes it accessible and affordable. The demonstrated benefits of using this Nursing SMS should be implemented as a country-wide program improving hemophilia care in China.

PO-MO-174
A survey of parents' perceptions of support received from a hemophilia nurse specialist during their child's portacath insertion
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Background: Prophylactic coagulation factor concentrate (CFC) is best practice for children with severe hemophilia and for some children with type 3 von Willebrand disease (VWD). However, difficult peripheral venous access often necessitates a CVAD. The hemophilia clinical nurse (CNS) specialist is responsible for supporting and educating parents in the care of this device and administration of CFC.
Aims and Objectives: To determine how well parents are educated about CVADs prior to their insertion. To evaluate how well parents are educated/supported in accessing CVAD and administering CFCs. To evaluate parents' perception of support after discharge from hospital. To identify areas in need of development to optimize parent and patient satisfaction.
Method: An anonymous questionnaire was distributed to parents of children with severe bleeding disorders who had a CVAD inserted between January 2008 and January 2012 to evaluate satisfaction in relation to preparation for surgery; education and training on administration of CFCs; advice and support post-discharge.
Results: This survey is currently in progress and is due to be completed on March 15, 2012. Results will be analyzed using descriptive statistics.
Conclusion: The hemophilia team in collaboration with the surgeons is responsible for providing comprehensive information and support prior to and after insertion of CVAD. The hemophilia CNS has a pivotal role in empowering parents.

PO-MO-175
New service development: Nurse-led telephone clinic for patients with mild/moderate bleeding disorders
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The Royal London Haemophilia Comprehensive Care Centre has 1,248 registered patients with inherited bleeding disorders; 894 of these are adult patients with mild/moderate bleeding disorders. Nursing staff currently run a telephone clinic as a follow-up option for these patients. There are several important aims and objectives: to review adult patients at least annually; to increase skills and practice for the hemophilia nursing team; to maintain patient satisfaction; to improve on current outpatient clinic DNA rates; and to reduce pressure on clinics. Inclusion patient criteria includes: patients over the age of 18 years; mild inherited bleeding disorder/some moderate bleeding disorders; patients seen annually in outpatients; patients without severe arthropathy or other significant comorbidities; good command of spoken English; and access to a landline or mobile phone. Prior to starting the clinic, a specific competency assessment tool was prepared, to ensure a standard of practice was followed by all nurses running the clinic. A formal standard operating procedure (SOP) was produced and circulated among the team, covering both the clinical and administrative steps required to ensure good, consistent practice and a smooth-running clinic. A questionnaire was developed for the nurses to use as the basis of the consultation, to ensure all areas were covered consistently. Clinic documentation is made on the hospital computer system CRS (Care Records Service). The hemophilia centre now successfully runs the telephone clinic twice a month, and would anticipate reviewing approximately 70–80 patients per year. Patient feedback has been positive. Any significant issues are fed back to the MDT. The clinic is under regular review using an electronic audit tool to record patient feedback. It is anticipated this will be reviewed every 6 months, and changes made as necessary.

PO-MO-176
Networking in hemophilia and other bleeding disorders care: The Canada-Germany nurse experience
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Background/Purpose: Hemophilia nurses are vital to the care of patients with hemophilia and other bleeding disorders. They are involved in nearly every aspect of the patient's care. Networking among hemophilia nurses in bleeding disorders care is a valuable opportunity to provide nurses, caregivers, and patients with a forum to expand their knowledge and skills, share joint experiences, understandings, and resources. Networking can assist in improving access to timely patient care, safety, and the patient's overall experience with the bleeding disorders team. As a result of the "Bayer European Hemophilia Nurses Scholarship," a networking opportunity arose for the nurse coordinator of the Saskatchewan Bleeding Disorders Program (Canada) to travel to the hosting hemophilia centre in Heidelberg, Germany.
Objective: The scholarship objectives were to have two hemophilia nurses meet, work, and develop a network between a well-trained and skilled nurse coordinator and an inexperienced nurse coordinator. Knowledge gained would be implemented in each of the practice areas, with the hope of improving and optimizing the provision of appropriate care and treatment for all people living with bleeding disorders.
Results: Learning and teaching opportunities related to the diagnosis and management of hemophilia and related bleeding disorders patients were exchanged by both nurses. Common and unique barriers were discussed leading to conversation regarding how change could occur in each of the current clinical practice areas to overcome these barriers.
Discussion/Conclusions: Networking provides the most productive, most efficient, and most enduring tactic to build relationships. The collaboration of bleeding disorder nurses on an international level promoted the creation of connections and enabled the building of an enduring, mutually beneficial rapport. This relationship resulted in both nurses gaining knowledge, experience, and inspiration to implement change and a new found friendship.

PO-MO-177
Client Satisfaction with a Nurse-Led Hemophilia Carrier Testing Clinic and Counselling Service
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Background: Genetic counselling for females with a family history of hemophilia has long been advocated. However, there is little research on the satisfaction of clients with existing counselling models.
Aims and objectives: The purpose of this study was to determine if clients were satisfied with a nurse-led carrier testing clinic and counselling service.
Method: The clinic provides education and counselling to clients when they attend for carrier testing and also when they re-attend for results. The educational counselling includes a discussion on the inheritance of hemophilia and the significance of hemophilia carriership. Clients' satisfaction and perceived knowledge was assessed using an anonymous questionnaire in a retrospective quantitative survey. This was distributed to all clients who had attended the clinic in the previous 12 months ($n = 42$). Analysis was performed using PASW version 18.
Results: The response rate was 71%. Two-thirds of the respondents were 35 years of age or younger. Ninety-three per cent had a family history of hemophilia, and 56% were diagnosed as carriers. The majority of clients were satisfied with the knowledge relayed during the session. Perceived understanding and knowledge increased significantly between the first and second appointments ($P < 0.001$). A small proportion of clients, some of whom were non-carriers, felt that they did not receive enough information on prenatal diagnosis, delivery, management of the newborn child, and raising a child with hemophilia.
Conclusions: This study identified high patient satisfaction with a nurse-led carrier testing clinic and counselling service.
Relevance to clinical practice: The results and findings provided clear indicators on how to further improve the service, such as providing additional education on prenatal diagnosis, delivery, management of the newborn child, and raising a child with hemophilia.

PO-MO-178
Self-modification of regimens by hemophilia patients in Japan
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Objectives: Hemophilia patients' self-care and lifestyle are closely related. Our previous study demonstrated that patients modified their original regimen, which their doctors had prescribed, to fit their respective lifestyles. This study was undertaken to elucidate patterns of self-modification in original regimens using qualitative analyses.
Methods: Twenty-three participants with hemophilia living in a home setting were selected using theoretical sampling from a self-help group or snow-bowl sampling (Jul. 2009–Nov. 2011). The first interview was based on life narratives. The second was semi-structured to obtain more detailed information.
Results: All participants were male and aged 20–60 years. Individuals with HIV and HCV were 15 and 16, respectively. The degree of modification by patients themselves of the original regimen tailored by a physician shows a gradation from low to high. Modifications to their regimen patterns were classified according to patients' level of self-direction, as passive or active. Low self-modification showed closer adherence to the original regimen than high self-modification. Passive participants who showed low modification of regimens reported that they had no choice because of their vulnerable condition and that they do not want to give their caregivers trouble. Active participants with low modification used the original regimen at first in circumstances such as a clinical trial and later reverted from the high-modified regimen to the original one because of some trouble. Active participants with high modification customized the original regimen to fit their lifestyles, satisfied even with incomplete health, and sometimes remained on their prescribed medicine. Passive patients with high modification or those who refused treatment felt powerless or lacked knowledge and accessibility, and experienced economic vulnerability.
Conclusion: Several patterns of patient behaviour exist according to their respective levels of self-modification and autonomy.
Contribution to the practice: Understanding self-modification patterns is helpful to provide appropriate medication and communication for individuals with hemophilia.

PO-MO-179
The BayCuff®: A useful tool for learning self-infusion
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Throughout the world, prophylaxis (when available) is the standard of care for boys with severe hemophilia and, depending upon the patient's bleeding patterns, for boys with moderate hemophilia as well. Very rarely are boys with mild hemophilia placed on prophylaxis. The BayCuff® is a small, compact, reusable device that attaches to the arm or hand with Velcro straps and allows an individual to learn the skill of self-infusion safely, without the pain or discomfort of repeated needle sticks when confidence and skills are not yet developed. The device has a washable "skin-like" surface with an artificial vein underneath that is filled with a red liquid. When the "vein" is pierced by an infusion needle, a realistic back flash of the red liquid occurs, just as if a vein had been successfully accessed. The BayCuff® was used with great success to help a needle-phobic, 15-year-old boy with mild hemophilia A to learn to self-infuse. This individual had rarely required treatment throughout his entire life. A blow to his thigh while playing bas-

ketball was not properly managed over a course of 6 weeks, resulting in a large muscle bleed that developed into a pseudotumour. The treatment for this bleed/pseudotumour has been long-term prophylaxis. With the use of the BayCuff® and expert instruction and support, this patient learned to self-infuse and is confident and compliant with his ongoing treatment.

PO-MO-180
Experience in venous central catheter (portacath) in pediatrics, for treatment of hemophilia and von Willebrand disease in Panama
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The experience of the management of venous central catheter is presented in 12 pediatric patients. This child presenting difficult vein access and all has cares at the clinic of Coagulopathies in the Hospital del Niño. All cases are children with Severe CONGENITAL COAGULOPATHIES type hemophilia and von Willebrand disease, which mostly placed them CENTRAL CATHETER (**PORT-A-CATH**) before the one year old, greatly facilitating the secure and reliable access to ensure optimal treatment. Intravenous therapy with FACTOR plays a key and important role in the success of the treatment of patients with hemophilia and other severe CONGENITAL COAGULOPATHIES. The need for the deficient factor applied depending on the severity, treatment lowers greatly the risk of bleeding, damage joints, and the severity of the bleeding and complications of the disease. For the benefit of the patient, intravenous therapy must begin before two years old or with the first event of join hemorrhage in severe cases, which sets out it from very small to intravenous therapy. To perform a successful intravenous therapy in patients with difficult venous access is used with great benefit central venous catheter with subcutaneous reservoir known as **PORT-A-CATH.**

PO-MO-181
Experience of the use of Veinviewer® for DIVA patients with hemophilia
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Objectives: In Korea, central venous administration of factor concentrates is rarely performed due to a lack of insurance coverage for the central venous catheterization procedure. So the majority of the pediatric patients with hemophilia use peripheral veins for the injection of factor concentrates. If patients are smaller and younger, they, as well as their caregivers and healthcare personnel, are often subjected to great stress. We evaluated the reliability of Veinviewer® which is a device that delineates subcutaneous veins using near-infrared light with DIVA (difficult intravenous access) scores in hemophilic patients younger than 4 years old.
Methods and Results: Thirty-nine patients younger than 4 years old visited the Korean Hemophilia Foundation Clinic from September 2011 to December 2011. The distributions of the patients by age younger than 1, 2, 3and 4 years were 1, 22, 7, and 9 respectively, and the mean age was 1.61 years old. The DIVA scores according to the age subgroups were 3, 2.27, 1.85, and 1.22 points respectively, and the mean score was 1.97 points. After the tourniquet application, 17 out of 39 patients had the veins palpable but not or the veins neither palpable nor visible. Their mean DIVA score was 3.41 points. For them, we have used Veinviewer® for intravenous access. The mean number of intravenous attempts before success was 1.06. The remaining 22 patients, without the use of the Veinviewer®, had 0.86 points of DIVA, and 1.09 attempts.
Conclusion: While we could not explain the clinical significance of this outcome, the Veinviewer® will be helpful especially for young children and infants who have difficult intravenous access. Further research is necessary to demonstrate the role of the device in DIVA patients with hemophilia.

27-OTHERS

PL-TH-02.2
Inherited bleeding disease research: Opportunities for the World Federation of Hemophilia

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Improvements in clinical care rely upon the generation and subsequent translation of new knowledge. The World Federation of Hemophilia (WFH) recognizes and supports the merits of knowledge generation and discovery, and has highlighted this commitment through its current strategic plan. In this document, two of the themes that pertain to the support of research activities concern a commitment to share knowledge and building capacity through information exchange and training, and secondly, promoting access to safe and improved treatment and cure-related research. These formal statements of support for research initiatives by the WFH have been further strengthened by the establishment of a WFH Research Committee that is currently in the process of developing an initial research agenda for the organization. Over the past 30 years, the global inherited bleeding disease community has witnessed dramatic advances to clinical care that have resulted from a combination of outstanding basic, translational, and clinical research. We are now witnessing a growing incorporation of genetic information into the diagnosis and clinical management of these patients, and the era of personalized medicine is fast becoming a reality for patients with these conditions. Furthermore, the treatment of these conditions, which is already very safe and effective, is currently undergoing significant changes to further improve the convenience and long-term benefits of clotting factor replacement. These clinical management enhancements are being accompanied by corresponding research into the improvement of the quality of life of these patients. Overall, the inherited bleeding diseases represent excellent paradigms for the application of a wide range of knowledge discovery. The aim of the WFH is to provide support for these research initiatives and to ensure that knowledge discovery and translation benefits the bleeding disease community worldwide.

FP-TU-01.4-3
Experience of circumcision using low quantities of factor concentrates

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Introduction: Circumcision is very important for social integration of hemophiliac patients in Senegal. However, it is a real challenge when considering hemorrhagic risks and the lack of availability of factor concentrates in a country with limited resources. The present work aimed to evaluate a circumcision protocol using small quantities of factor (F) VIII concentrates.
Methods: The medical protocol was as follows: 30 IU kg^{-1}per day of FVIII concentrates over three days in association with 20 mg kg^{-1} per day of tranexamic acid in two doses intravenously. Additional injections of FVIII concentrates were used whenever hemorrhagic complications occurred over the following days. Circumcision was practised under local anesthesia. The cutting of the prepuce was done with an electric lancet 2 mm underneath the balano-préputial track, followed by an additional hemostasis with simple stitches separated with Vicryl 60.
Results: Twenty-six (26) patients were involved with a mean age of 9.6 years (1–30); severe hemophilia represented 8 (31%) cases, moderate hemophilia represented 10 (35%); and minor hemophilia represented 8 cases (34%). Four patients (15.3%) were positive to FVIII inhibitors screening with low level (<3 Bethesda units). Mean number of hospitalization days was 13.5 days (13–15 days) in adults and 3.6 days (2–10) among children (p = 0,0000). Mean days of exposure to FVIII concentrates was 10.7 in adults and 6.9 in children (p = 0,0049). Recovery period was 25.2 days (20–40) in adults and 26.4 in children (p = 0,697). Hemorrhagic episodes occurred in 10 patients (42%) and infections in 1 patient (4%).
Conclusion: Circumcision of hemophiliacs is possible with low quantities of FVIII concentrates, but needs to be performed by an experienced surgeon.

PO-TU-124
Small mutations in hemophilia A: identification of 3 novel mutations in Indian cases

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Objective: Screening of small mutations in hemophilia A: 3 novel mutations identified.
Method: Mutation analysis of the F8 gene was performed in 23 unrelated cases with mild and moderate hemophilia A and screened with single-strand conformational polymorphism (SSCP) for mutations in the F8 gene. Sequencing was done in cases showing shift, using ABI-XL3130 Genetic Analyzer (Applied Biosystem, U.S.A.), and sequences analyzed with Set-Scape Software. Structural change in FVIII gene was predicted using modelling with Sybyl 7.1(Tripos).
Result: A total of 8 different disease-causing mutations were found in cases, 3 of which were described for the first time (Table 1).
Protein-modelling studies in Exon 4 showed that the original Trp138 is surrounded mainly by hydrophobic residues Ile76, Val84, Ile86, Leu98, Ala100, Val137, and Leu176. Silico mutational analysis revealed that mutation to Arg at this position may result in the lack of some important hydrophobic interactions. In Exon 16, Arginine is replaced by Lysine, showing that the mutation probably disrupts the H-bond between Arg 1803 and Glutamate 1801, which can't be formed due to the larger distance between the Lysine 1803 and Glutamate 1801 residues in the mutated protein. In Exon 24, mutation of Proline 2221 present at the loop region in the outer surface of protein with Serine 2221 showed loss of loop flexibility with formation of one hydrogen bond, with residue Val 2223 present in the surrounding environment.

Table 1: Novel mutations in F8 gene in Hemophilia A

S.No.	Exon	Codon	Domain	Nucleotide change	Amino-Acid change	Severity
1	4	138	A1	TGG > AGG	Try → Arg	Severe
2	16	1803	A3	AGA > AAA	Arg → Lys	Moderate
3	24	2221	C2	CCT > TCT	Ser → Pro	Mild

Conclusion: We report 3 novel disease mutations not previously reported at the HAMSTeRS. Protein modelling helps predict the structural and functional changes in the structure, explaining the possible mechanism for phenotypic disease express that defining causing mutation.
Contribution: The outcome of this study would enable us to give an accurate diagnosis in affected cases with hemophilia A by direct mutation analysis.

PO-TU-125
The royal family: A project to increase awareness of hemophilia in Slovakia

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Objectives: The aim was to create a unique piece of artwork: a symbol to remind Slovak people with hemophilia that their individuality is an important aspect of hemophilia. The artwork also provides a communication strategy for the Slovak Hemophilia Society, drawing public attention to this rare disease and inviting debate between professionals and the lay public. The project presents the possibility of recombinant coagulation factors as a treatment for hemophilia. Joint activities with the Slovak Hemophilia Society were arranged throughout the year, showcasing the patient organization.
Design Idea: In August 2011, a group of children with hemophilia and Slovak painter Darina Berkova created a unique piece of artwork. This image resembles a tapestry describing a family tree from the 18th century. Through the image, the public can learn more about congenital bleeding disorders. This image is used for various promotional purposes.
Method: Painter Darina Berkova spent two months preparing the concept and design of the image, which features Queen Victoria sitting on a tree trunk: a symbolic royal throne. Children drew the tree leaves, which symbolize their feelings and life stories. Twenty children aged 8–18 participated in the project.
Exhibitions: The picture was exhibited in the eight Slovak cities. The first exhibition took place on 9 September 2010 in a shopping centre in Nitra. The travelling exhibition culminated in April 2011 on World Hemophilia Day at the International Hemophilia Congress in the capital city Bratislava. The image was installed in the main foyer of the Slovak National Theatre from 14 April until 6 May. Guests (healthcare professionals, people with hemophilia, journalists, and Bayer employees) were each given a badge to wear: a symbol of a royal crown.
Conclusions: The creation of this unique image created much interest in the Slovak media. Slovak TV broadcast the project on the main news, and there were many interviews on the radio and articles published. This project was followed by a theatre "Best Practice Award" at the Bayer EU PR Summit 2011 in Vienna. The Royal Family Project was supported by the National Hemophilia Centre, in particular the Centre's President, Professor Angelika Batorova, MD, PhD. The project increases awareness of hemophilia throughout Slovakia and demonstrates the possibility of treatment with recombinant coagulation factors.

PO-TU-126
Cerebral hemorrhage in a Malagasy with hemophilia B

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Background: The treatment of hemophilia in Madagascar is still difficult in cases of hemorrhagic stroke, due to the unavailability of factor concentrates.
Objective: Describe the management of a cerebral hemorrhage in a patient with severe hemophilia B in Madagascar.
Clinical Signs: Two months ago, a 15-year-old Malagasy with severe hemophilia B complained of frontal headache without notion of trauma. He presented a disturbance of consciousness with seizures. The CT scan performed urgently showed a massive intracerebral hemorrhage invading the circle of Willis.
Support and Monitoring: In the Universitary Hospital of Antananarivo, neurosurgical intervention was urgently needed; an anesthesiologist immobilized the patient with sedation. The Association Support Santé Internationale managed to get FIX concentrates on humanitarian grounds from LFB laboratory in France and with the help of the French Haemophilia Association (AFH), 40 000 IU Betafact® could be sent to Antananarivo from Central Pharmacy in Reunion Island within a few hours. The intervention was carried out under FIX concentrate perfusion at a rate of 2000 IU first injection and then 1000 IU every 12 hours for 10 days. Hematological analysis showed levels of FIX to 80% with a normal APTT. Sedation was continued for 3 days. After 10 days, a second

batch of Betafact® was chartered. Betafact® was continued with a dose of 500 IU every 12 hours for another 10 days with 25% level factor IX.
Results and Comments: With efficient multidisciplinary medical cooperation and international help, the Malagasy child with hemophilia was saved. The intracerebral hematoma has been evacuated, and resuscitation was carried out properly; some memory problems still remain that are gradually receding. No other bleeding problem occurred after replacement therapy.
Conclusion: This great solidarity between hemophilia associations and partners supporting hemophilia saved the life of the Malagasy patient with hemophilia B residing in a country where FIX concentrates remain unaffordable.

PO-TU-127
Development of a circumcision poster for people with hemophilia
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Approximately 1,000 young Xhosa men in the Eastern Cape undergo a tribal circumcision as part of the ''right of passage'' from boyhood to manhood. Unfortunately, as many as 5% of initiates will develop complications such as infection, sepsis, and gangrene. For any young person, especially a person with hemophilia, to undergo a tribal circumcision is a major challenge. The nurses and the National Department of Health (DoH) have recognized that well-trained Circumcision Nurse Coordinators have the ability to implement the policy guideline from the 2001 DoH Circumcision Act. This policy could change the way people with hemophilia are treated during this ''rite of passage'' and is key to the provision and maintenance of appropriate hemophilia treatment. The idea has provided the motivation to plan and implement a training program for nurses on circumcision. Most nurses and physicians had little knowledge on the management of this uncommon disorder that resulted in increased mortality and the mismanagement of known and unknown people with hemophilia in the Eastern Cape Province. This poster has been designed with the DoH to inform initiates of the correct procedure to follow when embarking on this rite of passage so as to improve the outcome for young men with bleeding disorders.

PO-TU-128
Bile acid deficiency as cause of VKCFD in a newborn
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Case Report: Although the incidence of intracranial hemorrhage resulting from vitamin K-deficiency has decreased since the introduction of vitamin K-prophylaxis, spontaneous intracranial hemorrhages are still present in infants. Here we report a 3-month-old male infant suffering from spontaneous fever (39.5 °C), recurrent vomiting, and paleness. Laboratory investigations showed Quick <10%, aPTT >200 sek, and vitamin K-dependent coagulation factor activity <5%. X-ray computed tomography (CT) revealed an acute subdural hematoma and intracerebral hemorrhage. He was administered with vitamin K (1 $\mu g\ kg^{-1}$ i.v.) resulting in Quick >40% after 90 min. After additional administration of PPSB concentrate Quick normalized to 100%. Due to continuous decrease of Quick over the next two days, vitamin K was substituted once a week resulting in normalized coagulation factor activity. As no signs of cholestasis were seen, genetic analysis of VKORC1 and GGCX, the enzymes responsible for vitamin K recycling and gamma carboxylation, was initiated, but did not reveal any mutation. Therefore, we took a closer look at bile acids. Here, high serum levels of bile acids (241 $\mu mol\ l^{-1}$, normal value <8 $\mu mol\ l^{-1}$) combined with low fat soluble vitamins but regular bilirubin and liver enzymes were diagnosed. Absence of phytosteroles in serum confirmed malabsorption disease due to lack of secreted bile acids.
Conclusions: Since the introduction of vitamin K prophylaxis, intracranial hemorrhage in infancy has decreased from ~ 34 per 100,000 to less than a tenth of this number. Although prophylaxis routinely is applied, in some cases vitamin K deficiency can be considered as causation. Often defects in the vitamin K cycle due to mutations in VKORC1 or GGCX resulting in VKCFD1 or VKCFD2 can be diagnosed. In rare cases, malabsorption of fat soluble vitamins including vitamin K can be seen. Therefore, measurement of serum bile acids and fat soluble vitamins should be considered in infants with vitamin K deficiency bleeding.

28-OTHER TREATMENT MODALITIES

FP-MO-03.2-1
Pro-coagulant peptides as potential novel therapeutics for FVIII deficiency
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Objectives: Restoration of hemostasis in hemophilia A patients often depends on factor VIII (FVIII) replacement. Adherence to this regimen is challenging, in part due to the appearance of FVIII inhibitors, venous access requirement, and dosing frequency in prophylaxis. In order to develop alternative treatment options, we have previously reported on using phage display to identify a family of FIXa-enhancing peptides as a novel class of therapeutics that partially mimic FVIII pro-coagulant functions. These peptides enhanced FIXa catalytic activity, as reflected by enhanced FXa and thrombin generation rates, and improved aPTT and ROTEM parameters. Here we describe the optimization and further characterization of these molecules.
Methods: Focused phage libraries were constructed based on the peptide sequence of the FIXa-binding peptide hits by extending the core flanking sequences. Pro-coagulant candidates were identified based on enhancement of FXa generation assay, thrombin generation, and ROTEM parameters. Additionally, peptides were chemically modified to understand the structure-activity relationship (SAR) and improve plasma stability.
Results: A number of isolates were identified from focused phage libraries based on binding to FIXa. Peptides encoded by these isolates were ranked based on their FXa generation profile. Active peptides exhibited enhanced thrombin generation profiles in both purified systems and in FVIII-deficient plasma. Additionally, when assayed by ROTEM these peptides improved the clotting parameters of hemophilia A plasma and whole blood. In hemophilia A plasma, the clotting parameters were improved in the presence of FVIII inhibitory antibodies. We used SAR to map out residues of functional importance and made a number of modifications, such as introducing unnatural amino acids in place of non-essential residues that improved these molecules' activity and plasma stability.
Conclusion: A family of peptides with pro-coagulant properties was optimized to restore normal hemostatic parameters in FVIII-deficient plasma and whole blood. These peptides may lead to a novel hemophilia A therapy.

FP-TU-01.1-6
GlycoPEGylated rFVIII (N8-GP) has prolonged hemostatic effect in hemophilia A mice
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Introduction: The development of a rFVIII derivative with prolonged circulating half-life could provide hemostatic coverage with less frequent dosing, thereby improving compliance. N8-GP, generated by specific PEGylation of a naturally occurring O-glycan in rFVIII, has been shown to have an increased half-life in several animal species. The aim of these studies was to investigate if this translates also into a prolonged duration of hemostatic effect in hemophilia A mice.
Methods: The acute effect of N8-GP and rFVIII (Advate®) in hemophilia A mice was compared by thromboelastography (TEG) after spiking whole blood and in a tail bleeding model (transection of 4 mm of the tail) after IV administration. Furthermore the duration of the effect was compared in a ferric chloride injury model (carotid artery) and in a needle induced joint bleeding model.
Results: The potency of N8-GP was comparable to that of rFVIII (Advate®) when determined by TEG (EC_{50} (clot formation) 0.01 ± 0.003 U ml^{-1} for both compounds) and in the tail bleeding model (ED_{50} (bleeding time) 16.6 ± 5.9 and 18.7 ± 5.7 U kg^{-1}; $p = 0.67$, N8-GP and rFVIII respectively). In the duration of action studies, both compounds normalized the hemostatic response 5 min after dosing, however, the effect of Advate® declined faster than the effect of N8-GP in all models. Thus, 24 hours after treatment, the bleeding times in the tail bleed were 286 ± 33 and 1201 ± 316 s for N8-GP and Advate® ($p < 0.01$), respectively. In the ferric chloride model, the occlusion times were 9.6 ± 2.5 and >25.0 min ($p < 0.001$), and in the joint bleeding model, the mean visual bleeding score was 0.71 ± 0.19 and 2.4 ± 0.18 ($p < 0.001$) 60 hours after treatment with N8-GP and Advate®, respectively. The prolonged duration of effect was further supported by TEG.
Conclusion: GlycoPegylated rFVIII (N8-GP) and rFVIII (Advate®) had comparable potency and efficacy following acute administration. The duration of hemostatic effect in hemophilia A mouse was significantly prolonged for N8-GP compared to Advate®.

PO-TU-131
Clearance pathways of rFVIIIFc in hemophilia A mice
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Objectives: Recombinant fusion of a single factor VIII (FVIII) molecule to the constant region of IgG1 Fc (rFVIIIFc) has been shown to decrease clearance compared to rFVIII in a FcRn dependent manner (Dumont et al. 2012 Blood), using a natural pathway that recirculates antibodies into the blood stream. A phase 1/2a clinical trial in hemophilia A subjects demonstrated that rFVIIIFc has a 1.5- to 1.7-fold longer half-life than recombinant full-length FVIII (Advate®) (Powell et al. 2012 Blood). In the current study we sought to identify the cell types and organs that contribute to the protection of rFVIIIFc and to assess the relative contributions of the FVIII and Fc domains to the biodistribution and clearance of rFVIIIFc in mice.
Methods: The clearance of rFVIIIFc and rFVIII was compared in genetically engineered knockout mouse models deficient in either factor VIII (HemA) or von Willebrand factor (VWF). Intravenously dosed clodronate-containing lipid vesicles were used to deplete Kupffer cells and monocytes/macrophages in these mouse models. The effectiveness of depletion was quantitated by immunohistochemistry and FACS analysis. Pharmacokinetic analysis was performed with a FVIII-specific Coatest assay following intravenous injection of rFVIIIFc or rFVIII.
Results: Kupffer cell depletion in HemA mice increased rFVIIIFc clearance. Furthermore, in the absence of VWF (HemA/VWF double knockout mice), the depletion of Kupffer cells and macrophages increased the clearance of rFVIIIFc to levels similar to that of rFVIII, indicating significant contribution of Kupffer cells to the difference in clearance between rFVIII and rFVIIIFc in this model.
Conclusion: These studies suggest that Kupffer cells may contribute to the FcRn-mediated recycling of rFVIIIFc. Studies using bone marrow transplants with FcRn KO mice are in progress to verify this mechanism. These studies, combined with *in vitro* cellular uptake experiments will elucidate the role of Kupffer cells and other FcRn-expressing cell types, including endothelial cells in the recycling of rFVIIIFc.

PO-TU-132
Mode of action for anticoagulant activities of non-anticoagulant sulfated polysaccharides
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Fucoidans are sulfated polysaccharides extracted from brown seaweeds. They are described as non-anticoagulant sulfated polysaccharides (NASPs) and improve clotting in FVIII-deficient plasma (Liu et al., 2006), making them good candidates for hemophilia therapy. However, fucoidans have also been studied for their anticoagulant effects (Pereira et al., 1999), which occur at much higher concentrations than the procoagulant activity. Different anticoagulant mechanisms are activated by NASPs. Branched brown algae fucoidans have been shown to directly inhibit thrombin, while linear fucoidans from echinoderms activated antithrombin III (ATIII) or heparin cofactor II (HCII)-mediated thrombin inhibition (Pereira et al., 1999). In this study, we analyzed fucoidans from several brown algae species for their anticoagulant properties and mechanism to identify the candidate with the best procoagulant and lowest anticoagulant activity. Different anticoagulant activities were observed for NASPs from the brown algae species *L.j.*, *F.v.* and *U.p.* in an aPTT assay. *U.p.* fucoidan increased clotting time by 50% at 4 μg/mL, which represents a two-fold higher anticoagulant effect than the other fucoidans. NASPs were also analyzed in ATIII- and HCII-thrombin model assays. ATIII-mediated thrombin inhibition was only activated by *L.j.* fucoidan. However, all fucoidans clearly increased HCII-mediated thrombin inhibition at concentrations below 1 μg/mL. Our data suggest that HCII is the main target for the anticoagulant activity of fucoidans, which was confirmed by clotting assays in ATIII- and HCII-deficient plasma. Overall, we observed substantial differences between individual fucoidans which can be correlated to their structural properties. Our work describes the assessment of anticoagulant activities of different fucoidan species to better understand their intertwined pro- and anticoagulant effects. Important insights gained from these data will support the development of hemophilia therapies.

PO-TU-133
BAX 499 restores clot formation to normal levels and reduces fibrinolysis in lysis-induced FVIII-inhibited whole blood
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Tissue factor pathway inhibitor (TFPI) is the physiological inhibitor of the extrinsic pathway of coagulation. Blocking TFPI activity is a potential approach to treat bleeding disorders such as hemophilia. BAX 499 (formerly ARC19499) is a nucleic acid aptamer that binds to and inhibits TFPI. In this study, the impact of BAX 499 on hemostasis and fibrinolysis was determined with low-tissue factor-triggered rotational thromboelastometry (ROTEM®) in FVIII-inhibited, tissue plasminogen activator (tPA)-induced human whole blood. FVIII activity was antibody-inhibited in citrated whole blood from a healthy donor to generate a model of hemophilia blood. ROTEM® analyses were performed in the presence of saturating BAX 499 and the magnitude of each ROTEM® tracing was calculated by the area under the curve (AUC). In the absence of exogenous tPA, BAX 499 caused a 2-fold increase in the overall coagulation potential (OCP) of FVIII-inhibited whole blood, restoring coagulation to normal levels. The hemostatic effect of BAX 499 was further increased to 20-fold in lysis-induced FVIII-inhibited whole blood, reflecting its overall hemostatic potential (OHP). The overall fibrinolytic potential (OFP) was calculated as a percentage of the difference between the OHP and OCP. The OFP of FVIII-inhibited whole blood was 94%, while the addition of BAX 499 decreased the OFP to 43%, indicating reduced fibrinolysis. We have established a global whole blood method to determine the hemostatic activity of molecules that modulate coagulation, like BAX 499. This TFPI inhibitory aptamer restored coagulation of FVIII-inhibited whole blood to normal and reduced fibrinolysis. The procoagulant effect of BAX 499 on clot formation, particularly in the absence of FVIII, has been demonstrated previously. Our data suggest that BAX 499 may also impact hemostasis by increasing clot stability, which could be an important mechanistic feature for the treatment of hemophilia.

PO-TU-134
Use of alternative medicine by people living with hemophilia (PWH): Evidence from India
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Background: Hemophilia represents a rare genetic disorder having the second highest burden of disease in India following U.S.A. Documentation of alternative usages of medicine and its cost is imperative among these rare groups of patients in the light of AYUSH policy of the government of India (GOI).
Objectives: (1) To determine the prevalence of alternative medicine usage along with allopathic medicine among PWH. (2) To explore the types of alternative medicine used, their costs, socio-demographic factors associated with them, and reasons for usages.
Methods: One hundred sixty severe hemophilia A patients visiting the Hemophilia Society were recruited purposively, and data on sociodemographic, economic, clinical parameters, usage of alternative medicine, and cost were collected using a semi-structured interview schedule.
Results: Out of 160 PWH, 43.1% have used alternative medicine, and among them 24.4% used Ayurvedic medicine, 18.8% used homeopathic medicine, 2.5% used combined alternative medicine with traditional healers, and all of them have used allopathic medicine. The highest utilization of alternative medicine was found among higher and middle MPCE (Monthly Per Capita Consumption Expenditure) class (39.1%, 37.7%, respectively) than lower MPCE class 23.2% ($P = 0.019$). Qualitative data indicates that the use of traditional healers is reported to be associated with myth, stigma, and superstitions attached with the disease and its utilization is associated more during earlier years of life immediately after diagnosis of disorder. Usage of alternative medicine for more than a year to control bleed episodes or pain management suggests that many of these patients perceived some continuing benefits from these alternative treatments.
Conclusions: The study gives insights that alternative medicines cannot be considered irrelevant in the management of hemophilia in India. Qualitative data reflect the subtle differences in the counters of alternative medicine practices among PWH. Further research is warranted in multi-institutional and collaborative settings to determine the veracity, efficacy, supportive role, and limitation of alternative medicine for PWH in India.

PO-TU-135
Local clot formation after a monoclonal TFPI antibody, mAB 2021, is prevented by a low molecular weight heparin (LMWH) in a venous stasis injury model in rabbits
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Introduction: A monoclonal TFPI antibody (mAb 2021) has been developed to improve coagulation in hemophilia patients by blockage of the inhibitory action of TFPI on the initiation of the extrinsic pathway. Previous data from our laboratory have shown that mAb 2021 effectively reduces blood loss in a transiently hemophilic nail bleeding model in rabbits. The present study examined whether a standard anticoagulant, LMWH, was able to attenuate the procoagulant effects of mAb 2021.
Methods: Rabbits were anaesthetized with pentobarbital and the facial veins were exposed. A 2 mg kg^{-1} dose of mAb 2021 was injected followed 5 minutes later by injection of saline or 500 anti-FXa IU kg^{-1} of LMWH. Injection of an isotype antibody 2 mg kg^{-1} followed by injection of saline served as control. At 10 min, the facial veins were clamped, where after vessel wall injury was induced by squeezing the veins by use of a needle forceps holder. At 40 min, any clots formed were removed and weighed. Blood samples were obtained for platelet counts and for global coagulation assays.
Results: The clot weights in the injured facial veins were found to be (mean ± SEM): 15.3 ± 2.5 mg and 4.4 ± 1.5 mg following mAb 2021 and isotype antibody injection, respectively ($P < 0.001$). No clots were found when mAb 2021 injection was followed by LMWH. There was a small 5% decrease in aPTT after mAb 2021 injection. No differences were found in platelet and WBC counts, PT, and fibrinogen levels between mAb 2021 and isotype antibody. As expected, LMWH influenced the global coagulation assays towards an anticoagulant state.
Conclusion: Procoagulant activity of a monoclonal anti-TFPI antibody, mAb 2021, was demonstrated by induction of local clot formation after vessel wall injury without any disturbing effects on the coagulation system. This clot formation could be completely prevented by LMWH.

PO-TU-136
Evaluation of desmopressin testing in patients with hemophilia A and hemophilia carriers: Results of a multicentre survey
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Introduction: Published data about desmopressin testing (DT) in patients (pts) with hemophilia A (HA) and female HA carriers (CHA) are limited. Furthermore, DT is not standardized. The aim of study was to evaluate results of DT in pts with HA and CHA carried out between 1996 and 2010 in centres participating in the "Competence Network Haemorrhagic Diatheses East."
Methods: Data were obtained by personal centres visits using a standardized protocol. The defined criteria for complete response (CR) were an increase of the factor VIII (FVIII) above 50% or up to twofold of the initial value within 120 min after desmopressin application.
Results: In 12 centres data from 80 pts including 31 children (mean: 8.9 years, range: 2.2–17.6) and 49 adults (19.9 yrs; range: 18 to 65.5) were evaluated. Sixty-four pts suffered from HA (moderate form with FVIII 1 to ≤ 5%, $n = 2$; mild form - 5 to ≤ 15%, $n = 14$; sub-hemophilia - 15 to 40%; $n = 48$) and 16 were CHA. In 34 pts desmopressin was given IV at a dose ranging from 0.26 to 0.6 μg kg^{-1} (mean: 0.33), in 31 intranasally (300–600 μg) and in 15 s.c. (15–40 μg). Coagulation parameters including FVIII and aPTT, were determined at different time points after desmopressin application ranging from 15 minutes to 24 hours. The mean increase of FVIII after IV desmopressin application was 3.1 fold (range: 1.3–9.1), after intranasal administration 2.1 fold (1–3.7) and after s.c. application 2.4 fold (1.1–4.7). A CR was detected in 71 pts (89%) and a non-response in 9 (11%). Mild side effects such as flush, headaches, nausea during DT were observed in 10 pts (12.5%).
Conclusion: The detection of a non-response in 9 pts underlines the necessity of a standardized DT in pts with HA and CHA.

PO-TU-137
Dose-response of a monoclonal TFPI-antibody, mAB 2021, in transient hemophilic rabbits after intravenous administration
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Introduction: Tissue factor pathway inhibitor (TFPI) down-regulates the initiation of coagulation by inhibition of FVIIa-TF-FXa and FXa. Consequently, inhibition of TFPI may facilitate thrombin generation even in the absence of the prothrombinase complex. In order to further examine the potential use of a TFPI antibody as hemostatic agent in hemophilia, a high-affinity monoclonal, humanized antibody against the Kunitz-2 domain of human TFPI was produced, mAb 2021. Previously, mAb 2021 was shown to be efficacious in reducing bleeding in hemophilic rabbit after intravenous (IV) administration[1]. However, in that study no significant difference in effect between the doses 0.5–8 mg kg^{-1} was observed. Consequently, the effect of lower doses of mAb 2021 was examined in the present study.
Methods: Rabbits were made hemophilic by IV administration of a monoclonal anti-human FVIII-antibody. After 10 min, the rabbits received doses from 0.125 to 1 mg kg^{-1} mAb 2021 (IV, $n = 6$–8) or isotype control antibody ($n = 12$). After another 35 min, cuticle bleeding was induced and observed for 60 min.
Results: mAb 2021 dose-dependently reduced cuticle blood loss in hemophilic rabbits reaching maximum effect at 0.375 mg kg^{-1} and above, with an estimated ED50 of 0.23 mg kg^{-1} (0.14–0.38 mg kg^{-1}).
Conclusion: The monoclonal TFPI-antibody, mAb 2021, was able to dose-dependently reduce bleeding in hemophilic rabbits after intravenous administration with an estimated ED50 of 0.23 mg kg^{-1}.
References: 1. Lauritzen B. et al. A monoclonal anti-TFPI-antibody, mAb 2021, reduces bleeding in haemophilic rabbits after intravenous and subcutaneous administration. The XXIIIrd Congress of the International Society on Thrombosis and Haemostasis (ISTH 2011). Kyoto, Japan, 23.–28. July, 2011.

PO-TU-1381
Conformational radiotherapy in the treatment of recurrent bleeding of the arthropathic knee in hemophilia
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Frequent bleeding in the knee significantly destroys the cartilage and produces a painful arthropathy and disability in patients with hemophilia. There are numerous therapeutic methods to stop the bleeding, however, they are not ideal. Conformational radiotherapy aims to prevent abnormal synovial angiogenesis and destroy existing in the fibrous tissue. We treated four knees (of four patients) from July 2009 to November 2010. Three patients had hemophilia A and one hemophilia B, aged between 14 and 23 years old. The clinical assessment criteria were number of bleeding months, pain, range of motion and radiological classification. The degree of arthropathy according to the Arnold and Hilgartner classification was type II and III; two of them failed the Middle genicular artery embolization previously. All patients bled on average twice per month, consuming large quantities of replacement factor and representing high economic costs and further bone destruction. Pain 9–10 (VAS) during bleed and 7 whithout bleed, limited range of motions. Radiotherapy protocol includes MRI and CT Scan to locate in third dimension the synovium that will receive the radiation. Included factor replacement application (40 units per kilogram) .The total radiation dose is 35 Grays units divided into 15 sessions. A week after treatment, patient begins a rehabilitation program to improve muscular strength and range of motions. Any patient has bleeding again since the end of the treatment until today. Pain decreased and improves range of motion.
Discussion: There are worldwide patients with significant arthorpathy since they were not treated with opportunity in childhood. Besides disability clothing factors consumption is very high and therefore a high cost to health services. Conformational radiotherapy in third dimension has been shown to suppress bleeding in this sample of patients which represents hope for acting at an early age in countries of low resource economy.

PO-TU-139
Frozen autologous platelet-rich gel used for treatment of hemophilic pseudotumour: A report of two cases

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Frozen autologous platelet-rich gel (FAPRG) contains numerous therapeutically active growth factors beneficial for wound healing and tissue reconstruction. Hemophilic pseudotumours (HP) are an uncommon hemophilia complication reported in patients with severe forms of this disease. Pseudotumours that occur in muscles may progress to cause severe pressure erosion in the adjacent bone. The aim of the study was to present our own experience with FAPRG used in the treatment of two hemophilia A patients subjected to surgical procedures for hemophilic pseudotumours.
Case 1.A 55-year-old man with severe hemophilia A was admitted to our department with diagnosis of recurrent HP of the left retroperitoneal region and cutaneous fistula. Twelve years earlier he had surgery for HP in the same localization. CT scan revealed a 33×21 cm tumour which caused damage to the left pelvis bone as well as in the hip joint region. Surgery was performed under factor VIII replacement therapy. The hemophilia tumour mass was almost completely removed, the abscess cavity was drained and filled with FAPRG. Replacement therapy was continued for 90 days and a total of 190,000 units of factor VIII were administered. In all, 18 FAPRG applications into the HP tumour cavity were performed. The HP dimensions were reduced to 15×8 cm and the fistula was closed.
Case 2.A 41-year-old man with severe hemophilia A with inhibitor (0.7 BU) was admitted to our department for hemophilic pseudotumour (HP) of left iliolumbar muscle infiltrating the hip bone. Surgery was performed; the HP mass was removed and the tumour cavity was drained. Replacement therapy was continued for 78 days with a total of 60,000 U of factor VIII administered. In all, 23 FAPRG portions were applied to the tumour cavity, which resulted in significant reduction of cavity dimensions.
Conclusion. In our opinion, application of FAPRG following HP surgery is an effective therapeutical procedure worth recommendation.

PO-TU-140
Differences in the bleeding phenotypes of hemophilia A and B

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Background: The phenotype of severe hemophilia B (HB) is described to be different to severe hemophilia A (HA). Patients with HB show a milder bleeding type with respect to joint and muscular bleeds. However, currently it is discussed that HB patients are at higher risk for intracranial bleeds.
Methods: All patients with severe HA or HB (<1% FVIII/FIX) treated at the hemophilia care centre in Muenster were included. Regimens of replacement therapy, factor concentrate consumption, and bleeding episodes within the past three years were evaluated. Intracranial bleeds were captured over the whole life span of the patients. Prerequisites for inclusion were complete documentation and absence of a second bleeding disorder other than HA or HB. Data were calculated per patient and per kg body weight (bw), given as means ± sem.
Results: A total of 95 HA patients and 20 HB patients were included. Initially 33 HA (4 HB) patients were treated on demand, 62 HA (16 HB) patients were medicated prophylactically. Body weight of patients increased by about 7% during the investigation period from 61.5 ± 3.1 to 66.3 ± 3.0 (HA cohort) and from 66.6 ± 7.1 to 70.8 ± 6.7 (HB cohort). HA patients experienced 38 ± 3 and HB patients 23 ± 4 bleeds per patient during the investigation period. HA patients consumed per year 2,515 ± 150 and HB patients consumed per year 1,712 ± 267 IU kg^{-1} bw. Cerebral bleeds did not occur more frequently in HB (0.05 bleeds per patient) than in HA patients (0.08 bleeds per patient). Subgroup analyses revealed equal bleeding frequencies and consumption of concentrates during prophylaxis but a lower bleeding frequency and factor consumption of HB patients when treated only on demand.
Conclusion: Data confirm a milder bleeding type of patients with severe HB compared to severe HA, which cannot be explained by the longer half-life of rFIX compared to rFVIII, but suggest that HB patients are not at higher risk for intracranial bleeds.

PO-TU-141
A monoclonal antibody mAB 2021 blocks tissue factor pathway inhibitor (TFPI) and enhances hemostasis in whole blood under hemophilia A- and B-like conditions equally well

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Introduction: Tissue factor (TF) in complex with factor VIIa (FVIIa) initiates coagulation by activating factors IX and X. Tissue factor pathway inhibitor (TFPI) forms complexes with FXa, and TFPI/FXa binds and inhibits FVIIa/TF. Blockage of TFPI with a monoclonal antibody may facilitate hemostasis initiated by FVIIa/TF thereby compensating for impaired FIX/FVIII-dependent coagulation in hemophilia. A monoclonal antibody mAb 2021 which binds the Kunitz 2 domain of TFPI with high affinity (K_D = 25 pM) was spiked into human whole blood under hemophilia A- and B-like conditions. Clotting was analyzed by thrombelastography.
Methods: Thrombelastography (TEG) analysis was performed using normal blood incubated with neutralizing antibodies to either FVIII (sheep anti-FVIII IgG) or FIX (anti-FIX IgG, mAb) to mimic hemophilia A or B. The antibodies were added to a final concentration of approximately 10 Bethesda U ml^{-1}. A concentration range of mAb 2021 from 1 pM to 500 nM was tested. TF (Innovin®, 0.03 pM) was added to re-calcified blood to initiate the clotting. The concentration-response curve for "clot time" (min) and "clot development" (mm*100 sec^{-1}) was generated and the EC_{50}-values estimated by curve-fitting.
Results: mAb 2021 shortened the clot time and increased clot development in both hemophilia A- and hemophilia B-like human blood in a concentration-dependent manner. The EC_{50}-values for clot time were 0.43 ± 0.13 nM in hemophilia A-like blood and 0.44 ± 0.13 nM in hemophilia B-like blood. For the clot development, the EC_{50}-values were 2.5 ± 0.2 nM and 2.9 ± 0.4 nM, respectively.
Conclusion: Thrombelastography in human whole blood showed that the mAb 2021 improved hemostasis with similar high efficacy whether hemophilia-like conditions were obtained by neutralizing either FVIII or FIX. This is in line with a supposed FVIII/FIX-independent MoA of mAb 2021 and suggests that mAb 2021 will be equally efficacious in treatment of hemophilia A and B patients.

PO-TU-142
Sclerotherapy in secondary prophylaxis of esophageal variceal bleeding in hemophilia patients

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Patients after hemorrhage from esophageal varices are exposed to a high risk of recurrent bleeding and death. The aim of the study was a prospective evaluation of the effectiveness of repeated sclerotherapy procedures on prevention of recurrent esophageal bleeding in hemophilia patients.
Material and methods. From 2001 to 2011, all hemophilia patients with a history of endoscopically documented hemorrhage from esophageal varices were enrolled into the study. The group included 15 hemophilia A patients (9 severe, 2 with low-titer inhibitor, 4 mild) and 2 hemophilia B patients, aged 21–58 (mean age 42.6). All were cirrhotic; 8 were A, 6 were B, and 3 were C according to Child-Pugh classification. Repeated endoscopic sclerotherapy procedures with intravariceally injected 5% ethanolamine oleate were performed. All patients received replacement therapy for 3 days to secure each sclerotherapy procedure; factor VIII/IX activity was maintained at a level of 80–100%.
Results. In 17 patients a total of 102 sclerotherapy procedures were performed, from 4 to 8 per patient. Complete eradication of esophageal varices was achieved in 15 (88%) patients. The average number of procedures required for eradication of varices in one patient was 5.4 (±1.5). Recurrent variceal bleedings were recorded in 3 (17.6%) patients. In two patients bleeding was ceased with sclerotherapy and one patient died in another hospital. Complications were observed in 4 patients (deep esophageal ulcer in 1, exudative pleuritis in 2, Mallory-Weiss tear bleeding in 1), which subsided after conservative treatments or injection therapy. No mortality was associated with this procedures. In the average 5-year follow-up (range 15–88 months), a total of 3 (17.6%) deaths were observed; two related to liver insufficiency and one to hemorrhage.
Conclusion. Endoscopic sclerotherapy is a valuable method of secondary prophylaxis of esophageal variceal bleeding, effective for eradication of varices and reduction of recurrent bleeding rate.

PO-TU-143
Development of ALN-APC: a novel RNAi therapeutic for treatment of hemophilia

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Despite the progress made in hemophilia treatment with the advent of recombinant factor replacement therapy, there remains significant unmet medical need. While prophylactic therapy is effective, it is hampered by the short half-life of factor, which makes therapy both costly and often having vascular access complications. Of greater consequence still is the development of inhibitors to replacement factor, representing the area of greatest unmet medical need in hemophilia management. We are pursuing a novel therapeutic approach for the treatment of hemophilia by using RNA interference (RNAi) to target protein C, a major natural anticoagulant. The anticoagulant effect of the activated protein C (APC), which is formed by limited proteolysis of the zymogen protein C, is due to subsequent inactivation of both activated factors V (FVa) and VIII (FVIIIa). The important role of APC in coagulation is highlighted in both inherited protein C deficiency and FV Leiden (FVL), the most common inherited form of thrombophilia. FVL is caused by a mutation in the FV gene at the primary APC cleavage site, leading to lower rate of FVL inactivation, thus resulting in higher thrombin levels and a procoagulant state. Several clinical studies have suggested that the severity or onset of bleeding phenotype in hemophilia patients is substantially reduced in association with the coinheritance of protein C deficiency or FVL. Transgenic animal studies also show that hemophilic mice, carrying FVL, have improved clotting times, supporting the role of the FVL mutation in enhancing hemostasis. Therapeutic strategies aimed at reducing the level of protein C and activated protein C, thereby increasing levels of FVa and thrombin, could thus prove efficacious in hemophilia A and B. Here we investigate the systemic administration of lipid nanoparticle (LNP) formulated small interfering RNA (siRNA) directed against protein C (encoded by *PROC*) in wild type animals and hemophilia mouse models. We demonstrate robust and durable suppression of the target gene in liver and depletion of protein C in plasma. We also demonstrate thrombin generation potential as a result of different levels of protein C suppression and investigate the effects on clotting.

29-OUTCOME ASSESSMENTS

S-TU-03.1-3
Quality of life in the assessment of hemophilia
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Quality of life (QoL) is a ubiquitous term used to describe general well-being. The World Health Organization has provided a useful definition. Quality of life should take into consideration an individual's subjective meaning of experience, in the context of that individual's goals and desires—as well as allowing for autonomy of choice. Health-Related Quality of Life (HRQL) is a term often used synonymously with 'health status.' The International Classification of Functioning, Disability and Health (ICF) provides a framework for discussing the broad domains of health. A good HRQL measure should adequately assess the ICF domains of health, while accounting for subjectivity and autonomy. Many disease-specific and generic HRQL questionnaires have been used in hemophilia research, and most have very good measurement properties. Further investigation should be made into the incorporation of subjectivity and autonomy of choice in the measurement of HRQL.

S-TU-03.1-2
Radiological assessment of haemophilia
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Radiological assessment has been one of the oldest clinimetric tools used to measure the progression of joint arthropathy. With newer imaging modalities, it has been possible to detect changes in joints before they are clinically apparent. It is therefore an important tool for evaluating the effectiveness of different prophylaxis regimes. The Pettersson scoring system based on the radiologic (X-ray) changes seen in the six most commonly affected joints (i.e., the knee, elbow, and ankle joints) has so far been the standard for long-term outcome measurement in hemophilia. The introduction of more intensive prophylaxis has enabled joints to be maintained at a stage where no radiologic changes can be detected. As it became evident that conventional radiographs were insensitive to early changes in the hemophilic joints, newer scoring systems based on magnetic resonance imaging (MRI) were developed. The Denver scale, the European scale, and the one developed by the International Prophylaxis Study Group (IPSG) are all examples of scores based on MRI changes. While MRI imaging picks up several early changes before they are seen on plain radiographs, the implications of these minor changes in terms of individual joint function remain to be determined. MRI is also expensive, time consuming, sometimes requires sedation, and may involve inevitable long waiting periods. Ultrasonongraphic assessment (US) is useful to detect changes in the soft tissues, and attempts are being made to establish an imaging protocol, as well as a scoring system, to correlate with MRI findings. However, this tool requires expertise in interpretation and is user dependant. Although imaging has helped our understanding of the integrity of the joint reasonably well, the scoring system is probably still in an evolutionary phase. The challenges in the use of radiological tools include availability, cost, expertise, the long durations required for the studies, and waiting periods. A better understanding of how the radiological changes correlate with the progression of joint arthropathy is also essential.

S-TU-03.1-1
Clinical assessment of musculoskeletal outcome
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It is essential to have a core set of validated clinimetric instruments to assess different treatment strategies, document the impact of the disease on individuals, and assess musculoskeletal outcome in hemophilia. Disease-specific assessment tools, based on the International Classification of Functioning, Disability and Health (ICF) help capture the different domains of health. To assess the domain of "structure and function," the World Federation of Hemophilia (WFH) score was developed in the 1980s. This has never been formally validated, and has been improved on by several authors. One such instrument, the Hemophilia Joint Health Score (HJHS), was created to detect early changes in hemophilia. It takes into account normal childhood variants, and its validity and reliability have been studied by the developers. Its reliability in larger populations with more extensively damaged joints needs to be assessed. The radiological tools X-rays, MRI, and more recently, ultrasonography, have also been used to assess structure and function. The domain of "activities" has been assessed objectively by the Functional Independence Score in Hemophilia (FISH), which has been found to be valid, reliable, and responsive, and is widely used in different cultures. Its use in early arthritis with minimal functional deficits is, however, limited. The HAL is a reliable, valid, and subjective assessment tool for adults that not only covers the domain of ''activities'' but also includes aspects of 'participation.' The Paed HAL has been described to assess the same domains in children. While useful in certain cultures, its use is limited in others, as several questions related to 'participation' are very culture specific. The domain of 'participation' has not been explored much in hemophilia, due to several social, cultural, and economic differences. Consensus on a core set of assessment tools that are reliable and valid, able to pick up changes in early arthritis, and applicable across different cultures has been a difficult challenge.

PO-TU-146
A New Clinical Tool to Measure Balance and Mobility in Hemophilia: the Community Balance and Mobility Scale
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Background: To date, no study has explored the use of a single measure of balance and mobility in persons with hemophilia (PWH). The Community Balance and Mobility Scale (CBM) is an instrument evaluating static/dynamic balance and mobility skills necessary for community participation. Normative values have been established for ages 8–11 and 20–69. In adults, a score of 50/96 is considered a threshold below which community participation may be reduced.
Objectives: To explore the scoring patterns of PWH using the CBM and to determine the feasibility of using the CBM for evaluating function of PWH.
Methods: The CBM and Hemophilia Joint Health Score (HJHS) were administered to 42 PWH (mild, moderate and severe) ages 8–69. Descriptive statistics, correlation coefficient and independent t-tests were conducted to determine scoring patterns.
Results: A significant correlation was observed between CBM and lower extremity items on the HJHS ($r = -0.473$, $P < 0.05$), while no correlation was observed with upper extremity items. Knee HJHS ($r = -0.524$, $P < 0.05$) was more strongly correlated with CBM than ankle HJHS ($r = -0.352$, $P < 0.05$). CBM score was correlated with a diagnosis of severe hemophilia ($r = -0.753$, $P < 0.001$). Subjects with severe hemophilia aged 40–49 and 50–59 scored lower than norms ($P< 0.001$), however lower age groups scored within range of norms. Of all adult subjects, 20.7 percent scored below the cut point of 50/96. Administration of CBM took a mean of 15 min/subject.
Conclusions: This study is the first to suggest the Community Balance and Mobility Scale (CBM) as a valid measure for use with persons with hemophilia (PWH). Balance impairments and mobility limitations may be barriers to participation in PWH, particularly with advancing age. The CBM can be used by the hemophilia care team to quickly and easily assess balance and mobility across the lifespan, and to identify those at risk of limited community participation.

PO-TU-147
Development and validation of a classification algorithm for prophylactic versus on-demand factor VIII therapy in patients with hemophilia A
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Objectives: Health insurance claims databases are well-suited to study rare diseases such as hemophilia, but lack specific codes for classifying prophylactic (PRO) vs. on-demand (OD) factor VIII (FVIII) regimens in hemophilia A (HA) patients (pts). The authors sought to develop and validate a classification algorithm from specialty pharmacy data with an aim to identify these treatment approaches in claims data.
Methods: Prescription records from a US specialty pharmacy dispensing database from July 2010 to June 2011 were used. Males aged ≥2 years with a HA diagnosis, ≥1 prescription for FVIII, no anti-inhibitor agents, and no mixed PRO/OD FVIII regimens were included. Three variables common to specialty pharmacy and standard claims databases were used to develop the algorithm: age at initial dispensing was used as a proxy for weight; vial potency (IU/vial) and number of vials dispensed were used to calculate total units of FVIII (TUFVIII) dispensed (IU/vial*number of vials dispensed). Different specified TUFVIII thresholds per age groups 2–12, 13–16, 17–24, and 25+, together with pts' estimated weights, formed the algorithm. Several TUFVIII thresholds for each age group were iteratively tested over various observation lengths for pts classified as on PRO (vs. OD) regimen. Finally, each algorithm was assessed against actual regimens prescribed based on physician notes using sensitivity, specificity, positive and negative predictive values (PPV & NPV).
Results: One hundred seventy-two pts met study selection criteria with 70% on PRO FVIII regimens. Mean age (years) across the OD and PRO cohorts was similar (OD: 23.3 ± 16.2; PRO: 23.7 ± 13.0). The majority of OD pts had mild to moderate HA (65%), whereas most PRO pts had severe HA (88%). The best-performing algorithm was based on TUFVIII thresholds of 49,600 (age group 2–12), 74,400 (13–16), 100,000 (17–24), and 66,000 (25+), over the first 5 months of observation. Sensitivity, specificity, PPV, and NPV of this algorithm were .86, .85, .95, and .66, respectively.
Conclusion: The best-performing algorithm showed promising performance validity with PPV>.90 for ascertainment of PRO FVIII regimens in HA patients. Further refinement of the classification algorithm is needed.
Contribution to the practice/evidence base of hemophilia and bleeding disorders: The development of a classification algorithm will allow for the identification of PRO vs. OD FVIII regimens among HA patients in claims databases, thereby enabling the assessment of these treatment approaches in real-world settings.
Conflict of interest disclosure: This study was funded by Bayer HealthCare Pharmaceuticals, Inc. (Bayer). F Vekeman, W Cheng, A Trahey, S Sarda, and MS Duh are employees of Analysis Group, Inc., which has received research grants from Bayer. J Pocoski, S Valluri, and R Preblick are employees of Bayer.

PO-TU-148
Qualitative and quantitative assessment of sexual intimacy in adult patients in the hemophilia experiences results opportunities (HERO) study

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Background: Scarce information is available about sexual intimacy in patients with hemophilia.
Objectives: To evaluate patient experiences and perceptions around sexual intimacy with long-term partners. Methods:
The web-based HERO study was conducted in 10 countries (ARG;CAN;CHN;-DEU;DZA;ESP;FRA;GBR;ITA;USA) targeting 600 patients ≥age 18.
Results: Of 592 patients, 339 were in relationships, of whom 285 (84%) agreed to answer specific questions related to intimacy. Patients with inhibitors were less likely to participate (59% vs. 87%, $P < 0.05$). Mean (median) duration of marriage or relationship was 14 (11) years. Overall, 77% reported being satisfied with sexual relationships over the last month. Specifically, 76% reported satisfaction with the quality of their sex life, 63% with the number of times having sex, 77% with the way they/their partner show affection, 71% with the way they communicate about sex, and 82% with all other aspects of the relationship. Number of sexual engagements in the last month was reported as: 0 (12%), 1–2 (24%), 3–4 (27%), 5–6 (14%), 7–10 (11%), 11+ (7%). Fifty-four per cent reported that hemophilia affected the quality of their sex life with 60% of those reporting limitations in movement and 51% issues related to HIV/HCV; more inhibitor than non-inhibitor patients reported being afraid of causing a bleed during sex (36% vs. 17%). Sixty-nine percent didn't talk to their doctor or his/her team about sexual intimacy, and 48% didn't feel it would be helpful.
Conclusion: HERO participants provided the first-ever large-scale evidence base about sexuality in hemophilia. Overall satisfaction with their partners and frequent intimacy, but also impact of limitations in movement, viral transmission, and intercourse-related bleeds, were reported. Respondents reported infrequently sharing concerns with healthcare professionals; further research might identify potential roles for HTC psychologists, social workers, and physical therapists in the comprehensive care setting.

PO-TU-149
Association of prophylaxis regimen with FVIII and treatment outcomes in Latin America patients with severe hemophilia A

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Introduction: Primary prophylaxis treatment with factor VIII (FVIII) in patients with severe hemophilia A has been associated with better joint outcomes. The objective of this analysis was to understand the association of prophylaxis with bleeding and patient-reported range of motion (ROM).
Methods: This cross-sectional survey of severe hemophilia A patients≥18 or older, or the parent/caregiver of patients aged 2–17, was administered in collaboration with hemophilia associations or hemophilia treatment centres in Argentina, Chile, Colombia, and Mexico. Eligible, consenting patients completed a detailed questionnaire in two phases: from October to November 2009 (Argentina) and June–August 2011 (Chile, Colombia, Mexico). Regression modeling was utilized to measure the relationship between treatment regimen and outcomes related to bleeds and ROM. Age and country were included as control variables.
Results: Four hundred and forty-four patients participated in this study (258 adults; 186 children) with 10.6%, 36.0%, and 53.4% on primary prophylaxis (PP), secondary prophylaxis (SP), and on-demand (OD) treatment, respectively. Nearly all patients on PP were children. PP was associated with a 68.7% reduction in annual total bleeds and a 82.6% reduction in annual joint bleeds versus OD treatment ($P < 0.00001$). SP demonstrated a 17.2% and 14.9% reduction in annual total bleeds and joint bleeds, respectively (not significant). A significant association was found between the amount of time on prophylaxis and the number of annual total bleeds and joint bleeds. The odds of having severe limited ROM was 4.42 and 1.39 times higher for those on OD versus PP and SP ($P < 0.0064$ and $P = 0.26$, respectively). Additionally, the longer amount of time spent on a prophylaxis regimen, the lower the probability of reporting severe limited ROM.
Conclusions: A strong association was found between time spent on prophylaxis and the reduction in bleeds and improved ROM among Latin America patients. Primary prophylaxis may limit future joint damage by mitigating bleeding complications.

PO-TU-150
Advate hemophlia a outome database (AHEAD): A long-term registry focusing on joint health outcomes and health-related quality of life

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Background/Aims: Non-interventional studies have certain advantages over controlled interventional studies, including higher number of enrolled patients, better transferability of results to routine clinical practice, and low subject-selection bias. However, most registries only focus on the first 6–12 months of treatment and are therefore are unable to ascertain changes in health-related quality of life (HRQOL) and joint health over a longer observation period.
Materials and Methods: AHEAD study was initiated to capture long-term results in terms of joint health, HRQOL, hemophilia-related co-morbidities, efficacy, and safety in subjects treated with Advate (rAHF-PFM) within the scope of their clinical routine treatment (i.e., primary prophylaxis, secondary prophylaxis, on-demand treatment, or immune tolerance therapy). Collected data will include a variety of methodologies to assess joint health status and standard post-authorization safety and efficacy parameters.
Results: German AHEAD is supported by an interdisciplinary steering board and intended to yield data from 500 patients in up to 35 hemophilia treatments centres (HTCs) in Germany. Patient recruitment was started in June 2010 and will continue until the end of 2012; the observation period for each patient will be 4 years. Twenty-eight German centres have been initiated; 214 patients have enrolled as of January 13, 2012. Additionally, data from approximately 200 patients from European HTCs outside of Germany will be collected, increasing the number of patients available for a planned integrated analysis. Twenty-three centres in Belgium, Greece, Hungary, Spain, Sweden, Czech Republic, Italy, Denmark, and Switzerland have been initiated. Startup activities are ongoing in Norway, Portugal, Finland, and the U.K. Twenty-six subjects have been enrolled as of January 13, 2012.
Conclusions: It is anticipated that the AHEAD study significantly contributes to our knowledge of long-term joint health outcomes and hemostatic effectiveness, safety, and HRQOL outcomes in subjects using rAHF-PFM under the conditions of routine clinical practice. The study is now open for enrolment.

PO-TU-151
The safety and efficacy surveillance study of full-length plasma and albumin-free recombinant factor VIII for previously treated patients with hemophilia A in Taiwan

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Objectives: This surveillance aims to collect treatment-related data to evaluate the safety and efficacy in previously treated patients (PTP) with hemophilia A (HA) who received the third generation full-length plasma and albumin-free recombinant factor VIII (Advate®) therapy as prophylaxis or on-demand therapy over a one-year period. The primary objectives were to assess the incidence of serious and other adverse effects that were possibly related to Advate, such as inhibitor formation. The secondary objective was to assess the hemostatic efficacy in these HA patients treated with Advate.
Methods: This was a prospective, uncontrolled, observational study. Coagulation laboratory data including baseline FVIII clotting activity, FVIII inhibitor screening and titer assayed by Bethesda unit were determined once every three months during the study. Treatment efficacy was assessed according to the relief level of pain scores or symptoms scored by patients themselves. SF-36 questionnaire was used to evaluate patients' quality of life (QOL).
Results: From Dec. 2009 to Oct. 2011, there were 40 consecutively PTP with HA (32 severe, 8 moderate type) recruited. There was no FVIII inhibitor development in this cohort of patients and no drug-related serious adverse effects over one year. Among 1178 bleeding events, with the majority being joint and muscular bleeding, 386 patients (32.8%) had excellent, 382 (32.4%) had good, and 344 (29.2%) had fair rating in efficacy assessment. Sixty-six patients (5.6%) had poor rating.
Conclusion: Our study demonstrates that Advate can provide good safety and efficacy for PTP with HA in Taiwan.

PO-TU-152
Estimated annual infusion volume reduction with a 2mL reconstitution volume for Advate

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Introduction: Advate recently received approval for a 2 ml reconstitution volume for potencies up to 1800 IU in the United States. Reducing the reconstitution volume for factor VIII (FVIII) products may increase convenience, such as reduced time to infuse, for patients with Hemophilia A.
Objective: Estimate the infusion volume reduction associated with this 3 ml decrease in the reconstitution volume for dosage strengths of Advate <1800 IU using real-world prescription data.
Methods: Retrospective analysis of a large, US-based, hemophilia homecare database was conducted using data between July 2010 and June 2011. All prescriptions filled for Advate were selected. The average annual reduction in infusion volume for each patient was calculated assuming 2 ml vs. 5 ml reconstitution volume for potencies up to 1800 IU.
Results: Six hundred sixteen Advate patients were identified for this analysis. The average patient was 21 years old and weighed 60 kg. 404 (66%) patients had at least one potency dispensed below 1800 IU and would thus receive smaller reconstitution volume. Specifically, 228 (37%) patients had all of their prescriptions filled with vials less than 1800 IU and on average, would have infused 278 ml (60%) less if they had used vials with the 2 ml reconstitution volume over the 12-month period. Another 176 (29%) patients had prescriptions filled with a combination of vials above and below 1800 IU and would have infused 221 ml (28%) less over the 12-month period. For the total Advate sample, patients on average would have infused 170 ml (30%) less if the 2 ml reconstitution volume would have been available.
Conclusion: A majority of Advate patients would potentially benefit from the introduction of a 2 ml reconstitution volume. These patients could see a reduction in the infusion volume up to 60%, which may subsequently reduce the amount of time to infuse.

PO-TU-153

Estimated potential vial reduction with the availability of a proposed Advate 4000 IU dosage strength

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Introduction: Factor VIII manufacturers offer different selections of dosage strengths to meet individual patient needs. Offering more dosage strengths may improve patient convenience if fewer vials are required to fill the prescribed dose.

Objective: Estimate the potential amount of vial reduction and the percent of patients who could be single-vial users assuming availability of a proposed 4000 IU dosage strength for Advate.

Methods: Retrospective analysis of a large, US-based, hemophilia homecare database was conducted using data between July 2010 and June 2011. All prescriptions filled for Advate were identified. The number of vials dispensed per dose and the percent of users who had at least a single-vial dose option during this time period was compared to estimated results assuming a 4000 IU dosage strength was also available during this time period.

Results: Out of a total of 616 Advate patients, 591 had all information necessary for this analysis. An estimated 95 (16%) patients could benefit from a 4000 IU dosage strength. The average patient who could benefit from a 4000 IU dosage strength was 30.2 years old, weighed 85.3 kg, and was prescribed 4544 IU. For these patients, the average number of vials needed to meet the prescribed dose was calculated to be 1.6 and 2.2 with and without a 4000 IU dosage strength, respectively ($P < 0.001$). It was also estimated that a 4000 IU dosage strength could allow an additional 43 (7%) patients to become single-vial users. Therefore, the addition of a 4000 IU dosage strength would increase the percentage of Advate patients having an opportunity to receive a single-vial dose, from 77% currently, to an estimated 84% of patients ($P < 0.001$).

Conclusion: A 4000 IU dosage strength may improve patient convenience with fewer vials to mix. It was also estimated that the availability of a 4000 IU dosage strength may increase the percentage of Advate patients that could have a single-vial dose option.

30-PAIN MANAGEMENT

S-TU-03.2-4
Creative visualization and movement
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Seen from the perspective of psycho-neuro-endocrino-immunology, a particular approach of medicine, the interrelationship among body, mind, and spirit exists permanently, within the socio-cultural context. Through this approach, we can demonstrate the existence of an evident link between emotions and health as well as thoughts and pain. Pain is made up of memories and habits. When, for example, chronic pain caused by the after-effects of recurrent hemarthrosis in the joints is experienced, the patient tends to remember the pain that was previously perceived. That's why it is important to learn to keep the mind clean and calm. Integral therapy works to educate the patient, promoting, preserving, and restoring his quality of life in spite of chronic or acute pain. There are certain techniques used in integral therapy. Some of them are offered to patients with hemophilia, because using them successfully strengthens autonomy and self-esteem. Through creative-visualization training and movement, pain can be shifted to another place where it can be forgotten or replaced by milder sensations. Creative visualization involves thoughts in the form of images. It is a way to product relaxation. Relaxation helps release the mind from worries and allows the person to feel well for a period of time. In this way, it reduces the effects of stress and permits a certain degree of pleasure. Imagination focused toward a specific goal can therefore exert a certain effect on the body, given the power that it has over it. So, the person is transported to a state of relaxation, focusing on images that connect to wellbeing. Movement awakens and activates many of our mental capacities. Besides, movement as a result of previous training produces self confidence because it reverses the sense of incapacity.

S-TU-03.2-2
Stiff Knees: Physiotherapy in Developing Countries
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The knee joint consists of the patellofemoral and tibiofemoral joints. The quadriceps muscle extends the knee and the hamstrings flex the knee. The knee joint is a major synovial, weight-bearing joint of the body. It is under constant biomechanical stress with little protection against unstable rotational forces. Stiff knees are a common problem in people with hemophilia (PWH), particularly in developing countries due to various factors. The flexion contracture of the knee is a common deformity. Valgus, external rotation deformity, and posterior subluxation of the tibia may exist alongside the flexion contracture of the knee. Early treatment of knee flexion tightness is recommended to prevent fixed flexion contracture and bony ankylosis of the knee joint (Rahiminejad, 2002). Physiotherapy is of great importance in not only treating stiff knees but preventing them, particularly in developing countries where there is a paucity of factor replacement therapy. This presentation is about the physiotherapy management of stiff knees in the developing-country scenario. It will give an overview of the cause of stiff knees in PWH, touching briefly upon the pathophysiology of contracture formation. Evaluation of joint health using standard assessment and outcome measures in PWH is important for timely and appropriate intervention—be it conservative or surgical management of stiff knees. It will highlight the importance of early management of acute knee bleeds, appropriate use of splints and orthotics, the role of CPM, traction, and exercises in preventing and treating stiff knees.
References: M. S. Rahiminejad, Continuous Passive Motion (CPM) in the treatment of knee flexion contracture in hemophilic patients. Hemophilia, 2002, Vol: 8, Page 478.

S-TU-03.2-3
Music therapy as a complementary and alternative medicine (CAM) technique used in patients with chronic and life-altering illnes experiencing pain and anxiety
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Background: Music therapy is a complementary and alternative medicine (CAM) technique used increasingly to promote musical and non-musical communicative behaviours, positive peer interactions, compliant behaviour, emotional synchronicity, and initiation of engagement in children and young adults experiencing pain and anxiety, with promising results. The Children's Music Fund's (CMF) mission is to provide musical instruments and music therapy to children and young adults with chronic and life altering illnesses. In addition, CMF seeks to actively improve and increase the available research on music therapy within the field of complementary and alternative medical therapies.
Primary Objective: The literature continues to lack evidence-based systematic reviews and well-designed controlled studies to assess the efficacy of music therapy in facilitating prosocial and communicative behaviours with the pervasive developmental disorder (PDD). Since a higher proportion of children with PDD present to clinic with chronic pain, this study aims to assess converging reports of these benefits in a sample of children and adolescents with this condition at discrete time points.
Summary and Implementation Strategy: Parent, child, and therapist pre- and post-intervention assessents are collected and will be summarized to delineate the therapeutic effects of music therapy on various key outcomes in children with PDD, including repetitive stereoptypical behaviours, social functioning, and communication by CMF clients. CMF has provided over 300 individual music therapy sessions and donated over 100 musical instruments to date. Our findings thus far reveal that patients provided with music-therapy intervention exhibit an increase in verbal and non-verbal communication, as compared to the control group, show improvements in reciprocal social behaviours, and show a reduction in repetitive/stereotypical behaviours.
Conclusion: Although music interventions have been used to facilitate social, behavioural, and communication skills, further research is required to establish the contribution of these interventions to the development and maintenance of these skills.

S-TU-03.2-1
Introduction and overview of global models of pain management
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Primary Objective: To outline the 'language' used by patients to describe pain; describe pharmacologic and non-pharmacologic strategies utilized to control pain; to evaluate quality of life incorporating the SF-36 QOL tool.
Background: Pain is an undertreated phenomenon. Persistent pain in pediatrics and adults (general and hemophilia population) often goes unrecognized and undertreated. Inadequately/untreated acute pain can cause physical changes within the brain leading to persistent pain and many associated biopsychosocial complications. Due to joint bleeds, pain is a common occurrence and a known complication in persons with hemophilia (PWH) beginning at a young age. This is often a combination of acute pain secondary to bleeding episodes, as well as persistent pain as hemarthrosis develops, especially in those with inhibitors or as PWH age. Because of this, PWH frequently experience acute pain concurrently with persistent pain; thus they are unusual in their presentation compared to the general population. Scant literature describes the pain experience of a PWH. Where factor is readily available, it is suspected many patients self-treat what may be persistent pain with a factor replacement product when another modality would be more effective and less costly. There is no literature on what PWH do in countries where factor is not readily available.
Summary: The National Pain Study (NPS) recently published descriptions of the PWH's pain experience in the United States. Thirty-nine percent of participants reported their pain was not well treated. The average persistent pain score reported was 4.22/10. The most frequently reported word descriptors for acute pain were throbbing, aching, sharp, tender, and miserable. The most frequently reported word descriptors for persistent pain were aching, nagging, tiring, sharp, and tender. Hematologists and primary-care providers provide the majority of pain management for PWH. The most frequently reported pain strategies for acute and persistent pain included factor, rest, ice, elevation, and compression. Alcohol and illicit drugs were reportedly used to manage both acute pain as well as persistent pain. Primarily, short-acting opioids and acetaminophen were reported to treat both acute and persistent pain.
Recommendations: The NPS is an initial step in recognizing the prevalence and description of pain in PWH. Further research is necessary to develop specific pain-management guidelines that include multimodal holistic treatment plans for the bleeding disorders population.
Disclosure: This research was supported through unrestricted grants from Wyeth (now Pfizer, Inc.) and Hemophilia Health Services.

PO-TU-154
Pain in hemophilia: Assessment of type of pain, coping styles, and analgesic use
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Introduction: People with hemophilia experience recurrent episodes of acute pain due to musculoskeletal bleeding and chronic pain due to arthropathy. Few data are published on pain type, coping style, and pain management techniques used by people with hemophilia. The aim of this study is to assess pain presentation, methods used to manage the pain including analgesics, and the patients' coping styles for adults with hemophilia registered at the regional hemophilia centre. The McGill Pain Questionnaire and the Hemophilia Coping Questionnaire designed by Elander (1) were used in this assessment.
Results: Wide variations preventing statistical analysis were observed in all groups assessed. There was a higher 'usual pain score,' more use of affective and miscellaneous descriptors, and more persistent pain issues in people with severe hemophilia compared to the mild and moderate groups. Analgesic use was similar for all severity groups. Coping styles were generally similar in all groups with occasional marked outliers. Feelings of anger, isolation, and increasing behavioural activities were ranked higher in the severe group than in the mild and moderate groups.
Discussion: This on-going assessment of a single hemophilia treatment centre is showing a wide range in pain complaints and coping styles. People with severe hemophilia, particularly, appear to have coping styles that can be expected to benefit from targeted psychological services.
References: J. Elander, G. Robinson, A brief haemophilia pain coping questionnaire, Haemophilia 2008; 14, 1039–48

PO-TU-155
Pain and meaning: From the injury to the experience of pain
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Introduction: Pain is one of the human experiences known to us by individual testimonies.
It is experienced in many ways in patients with hemophilia; the purpose here is to concentrate on when it happens as an effect of hemarthrosis. Pain and joint limitations are its trademarks. With the difficult to control cycle of hemarthrosis, arthropathy, and

synovitis, different types of treatment can be offered that are fundamentally based on palliative care, ranging from pharmacology to rehabilitation.
Objectives: To develop a group of psychic-corporal activities; to try symptomatic relief; to set up a group of patients to discuss emotional tension, worries, and anxiety that appear due to the limitations they have to confront; and to promote the search for personal ways to deal with this.
Description: This work is carried out in a small group. The sessions begin with an expanded conversation concerning each person's discomfort, and as a result, the most suitable exercises are recommended for each participant. The essence of the work is to show the individual differences related to the subjective experience of pain. Once the physical work is finished, there is another opportunity for discussion, where, once again, the specific differences are explained from the previous experience.
Conclusion: This experience has brought about, in many of its participants, a change in their attitude towards pain. From considering pain as an insurmountable obstacle, the participants in the group have been able to learn gradually how to confront it, with new attitudes. From a position of impotence that reinforces distress and anxiety, the participants have been able to find other ways to refer to pain and to speak about themselves with respect to this pain. All of this orientates subjects to a position where their own experience is lived, and they take control of their own existence.

31-PEDIATRIC ISSUES

PO-TU-156
Implementation of national recommendations of early prophylaxis in boys with severe hemophilia: Results from the Pups cohort of "FranceCoag network"

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In 2002, the French society Medical Coordination for Treatment of Hemophilia (COMETH) promoted recommendations for 'early long term prophylaxis (LTP) with escalating intensification in severe hemophilia A (HA) and B (HB).' In a national study sponsored by the Ministry of Research we analyze comprehensively their implementation before the age of 3 years and we aim to identify factors that may influence the adherence. All the boys with hemophilia included in the FranceCoag Pups Cohort (FVIII or FIX level <2%) and born in the 2000–07 period are eligible for the study. Characteristics of patients, details of hemarthrosis, and treatments are being checked to ensure the absence of missing data. In November 2011, 339 boys, 295 with HA (277 severe) and 44 with HB (38 severe), were eligible. This intermediate analysis is focused on 171 boys with severe HA and fully completed forms, excluding cases with intracranial bleeding (n = 15) and/or inhibitor (n = 24) that occurred before a first hemarthrosis. A LTP regimen was implemented in 97 boys (56.7%) before 3 years, at a median age of 1.7 years (range: 0.5–3.0), not later than after the second hemarthrosis for 87.6% of them. LTP started according to a weekly infusion schedule (step 1) in 62.9% of cases and twice weekly (step 2) in 15.5%. The median duration of step 1 was 1.2 years (range: 0.03–3.9) in cases with escalation to step 2. During this period, not more than two hemarthroses occurred in 78.4% of patients. We can assume that this national study joined to the FranceCoag Pups cohort will confirm with a remarkable exhaustiveness that the 'COMETH' recommendations of prophylaxis have had a major impact on clinical practice in France. The escalating pattern with a weekly first step appears as a reasonable option. Further results will be helpful in the analysis of factors that may be associated with the adhesion.

PO-TU-157
FEIBA prophylaxis in children: A single-centre experience

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Background: Inhibitors occur in ~ 30% of children with severe hemophilia A. Of these, 10–20% are high titer/high-responding inhibitors, whose management involves attempts to eradicate the inhibitor by a process of immune tolerance therapy (ITT) using injections of FVIII of varying dose and frequency. The management of children with inhibitors resistant to high-dose ITT is controversial. In order to minimize and prevent bleeding episodes and subsequent joint damage, there has been an increase in the use of FEIBA as a prophylactic agent.
Methods: Five boys aged between 2 and 9 years old with resistant FVIII inhibitors who had failed immune tolerance (ITT) after 2 years to 5 years and one boy who remained on high-dose immune tolerance but with a target ankle joint, were commenced on FEIBA prophylaxis at an average dose of 50 U kg^{-1} alternate daily. All 6 boys were on plasma derived FVIII concentrate for ITT prior to commencing FEIBA.
Results: Four out of 6 boys experienced an overall reduction in bleeding rate, a significant improvement in HJHS scores, a reduction in days off school and a general improvement in QOL as reported by themselves and parents. Two families opted to switch their sons back to low-dose plasma derived FVIII within a year of starting FEIBA due to an increased frequency of minor soft tissue and muscle bleeds compared to when on ITT. These boys are closely monitored from a clinical and musculoskeletal point of view and have a reduction in bleeds, which is supported by physiotherapy, observation, and clinical assessment.
Conclusions: On evaluation 4/6 boys showed improvement in clinical outcome. In conclusion, FEIBA is a useful prophylactic as well as adjuvant therapy in children with complex inhibitors, to date there are no adverse side effects in this cohort.

PO-TU-158
One diagnosis, two babies, three hospitals, four hours apart: No definitive consensus on the mode of delivery for babies with hemophilia A

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Cases: We present 2 babies born on the same day 4 h apart at 2 obstetric units in London; both babies planned to be managed at our centre. Baby 1 was prenatally diagnosed with severe hemophilia A in a known carrier during screening for another genetic condition. The mother of baby 2 was also a known carrier of severe hemophilia A with an affected son; the family declined prenatal diagnosis but fetal sexing confirmed a male. Both deliveries were planned at obstetric centres affiliated to hemophilia centres and MDT decision was for planned Caesarean section for baby 1 at term and a trial of spontaneous labour for baby 2.
Outcome: Baby 1 was born by elective Caesarean section at 38/40 weeks gestation; no neonatal intervention was required. Baby 2 was born by spontaneous vaginal delivery at 41^{+4}/40 weeks gestation complicated by malpresentation and a large cephalhematoma requiring recombinant factor VIII and tranexamic acid shortly after birth, followed by a further 2 doses of factor VIII in the next 24 hours after confirmation that the child was affected. The child was well at discharge with no evidence on intracranial abnormality. There were no immediate maternal complications in either case.
Conclusion: There are many issues when deciding the delivery plan for babies known to be affected or at risk of being affected by hemophilia. These cases highlight why it is difficult to mandate a clear consensus for the mode of delivery. Imposing constraints on monitoring and delivery could prove unnecessary and potential dangerous to both mother and fetus in a woman at risk of having a child affected by hemophilia. However, in our case a planned Caesarean section may have eliminated the need for treatment with factor concentrate on day 1 of life and the concerns surrounding early treatment exposure.

PO-TU-159
Central venous line insertion and factor replacement therapy in patients with hemophilia A: A local experience

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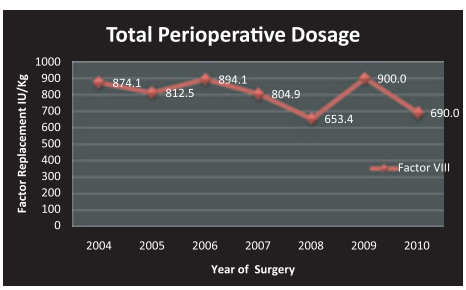
Introduction: Central venous line (CVL) insertion is one of the most common procedures performed on pediatric hemophilia patients. There are no clear guidelines outlining the optimal dosing schedule of factor VIII (FVIII) and duration of treatment required to achieve adequate hemostasis during and after surgery. In this paper, we present our experience of using the factor replacement therapy in 14 children with severe hemophilia A at McMaster Children's Hospital over the course of 4 years, from 2004 to 2010, which could be used as a framework for developing evidence-based guidelines.
Methods: This is a retrospective institutional chart review. The study was approved by the Hamilton Health Sciences research ethics board. Patients between 0 and 18 years of age with severe hemophilia A that underwent CVL insertion at McMaster Children's Hospital in Hamilton, Ontario, from 2004 to 2010, were identified and charts were reviewed. Data collected included patient demographics, length of stay in hospital, factor replacement therapy, and timing in relation to the surgical procedure. Data was then extracted and plotted for analysis.
Results: A total of 14 CVL insertion surgeries were reviewed. The average age at which CVL was inserted was 2.1 years, (0.9 to 6.1 years). The total average pre-operative dose of FVIII was 84.7 IU kg^{-1} (68.7 IU kg^{-1}–115.38 IU kg^{-1}). The total average post-operative dose was 706.3 IU Kg^{-1} (431.8 IU kg^{-1}–962.9 IU kg^{-1}).The total perioperative dose was 790.9 IU kg^{-1} (500 IU kg^{-1}–1032 IU kg^{-1}). See Apendix 1.



Year surgery	*Number of cases*	*Pre op dose IU/Kg*	*Post op dose IU/Kg*	*Total dose IU/Kg*
2004	3	89.3	784.8	874.1
2005	1	78.1	734.4	812.5
2006	2	102.7	791.4	894.1
2007	2	87.1	717.8	804.9
2008	3	78.8	574.6	653.4
2009	1	75.0	825.0	900.0
2010	2	74.1	615.9	690.0
Total average		84.7	706.3	790.9
Range		68.18-115.38	431.82-962.96	500-1032

Conclusion: The current study attempts to find an optimal hemostatic coverage during CVL surgeries and describes the experience at McMaster Children's Hospital. For insertion surgeries at McMaster, the average factor dose administered has slightly decreased over the years. These results may be of help in developing an optimal treatment schedule to achieve adequate hemostasis with the minimal optimal factor dosage.

PO-TU-160
Obesity management in boys with severe hemophilia: What works?

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Objective: Investigate number of obese boys and current obesity management in severe hemophilia. Obesity is a concern in the child/adolescent population. In the hemophilia population, maintaining joint health is vital, as excess body adiposity can reduce movement in weight bearing joints, increase difficulty in venous access and amount of clotting factor for prophylaxis, and hence a rise in health dollar.
Methods: Clinical chart review of boys with severe hemophilia in 2011 at a pediatric tertiary care hospital. Severe hemophilia: normal factor activity in blood <1%. BMI calculated using 2000 CDC growth charts (USA) (kg m^{-2}) with overweight>85th per-

centile, obese>95th percentile. If overweight/obese, boys and families received weight-loss management by their consultant.
Results: Severe hemophilia was identified in 72 boys (mean 10.8 years, range 3–19). There were 8 cases of obesity (mean 10.6 years) and 8 overweight (mean 6.6 years). Of concern 5 overweight and 2 obese boys were <6 years. Of the obese boys: 3 were 7–11 years and 3>12 years. All had weight management included in their consultations. In the last 3 years, 2 obese boys had accelerated weight loss (14 year BMI percentile 98–52/15 m; and 16 year BMI percentile 94–16/7 m) and diagnosed with an eating disorder requiring referral to eating disorder clinic. Comparison of data from 2001 will ascertain trends of increasing BMI in this population.
Conclusion: There is a relationship of high BMI in childhood and adulthood and obese children becoming obese adults. Boys with severe hemophilia are now being diagnosed as overweight/obese before school-age. Current weight management may lead to morbidity of developing an eating disorder. Early referral to weight management clinics should be considered and in extreme cases possible discussion of gastric banding/bypass.
Contribution: Awareness of overweight/obese boys with severe hemophilia before school-age and risk of eating disorder with current weight loss management suggesting new strategies need to be employed.

PO-TU-161
Re-bleeding and septic arthritis following arthrocentesis in hemophilia patient with inhibitors

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Children with hemophilia and inhibitors are at particular risk of recurrent hemarthroses. Treatment of those patients is expensive and the control of repeated bleeds is inadequate because of persistent swelling and pain in affected joint. Arthrocentesis is an alternative therapeutic procedure, and it is recommended for major hemarthrosis. We are presenting a fifteen-year-old boy with sever hemophilia A and history of inhibitors who has developed right knee hemarthrosis. Arthrocentesis in order to evacuate residual blood and at the same time to inject betamethasone as an attempt to prevent further joint damage was performed under the coverage of rFVIIa and antibiotics. Two weeks later, pain and swelling in the treated knee, associated with fever occurred. At the admission, anemia (Hgb 88 g L^{-1}) and elevated levels of inflammatory parameters (CRP 168 mg L^{-1}, fibrinogen 6.2 g L^{-1}) were confirmed. Blood cultures were sterile. Knee CT scan reviled the presence of hematoma and empyema. The diagnosis of septic arthritis with re-bleeding was established and the treatment with vancomycin and amikacin started. As the inhibitor level was low (3 BU) and recovery test was satisfactory (maximal plasma FVIII concentration 60.5%), the treatment with FVIII concentrate was introduced (50 IU kg^{-1} twice daily) for 6 days. Anamnestic response occurred 9 days after the introduction of FVIII (inhibitor titer 660 BU). General condition and local findings have gradually improved, and the boy was discharged 16 days later. In the further period, the level of inhibitors has slowly decreased and returned to basal after 10 months, while repeated episodes of joints bleeds were treated with rFVIIa. Although arthrocentesis is a cheap and affordable method, it can be associated with severe complications, such as infections and hemorrhages. Treatment of those complications is even more complex in patients with inhibitors and can be associated with uncertain outcomes.

PO-TU-162
The use of recombinant FVIIa in two children with Glanzmann's thrombasthenia with severe bleeding after trauma

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Glanzmann's thrombasthenia is an inherited functional platelet disorder caused by quantitative or qualitative defects of the glycoproteinIIb/IIIacomplex in the platelet membrane. Activated recombinant factor VII (rFVIIa) has recently been used in the treatment of patients with Glanzmann's thrombasthenia. Platelet transfusion during bleeding episodes is the standard treatment. However, repeated platelet transfusions may result in GPIIb-IIIa and/or HLA alloimmunization causing platelet refractoriness. rFVIIa has recently been introduced for treating uncontrolled bleeding episodes refractory to platelet transfusion in patients with Glanzmann's thrombasthenia.
Case 1: A 9-year-old boy not responding to thrombocyte transfusion for excessive bleeding in the mouth and nose following trauma was successfully treated with rFVIIa (Novoseven®, NovoNordisk, Bagsvaerd, Denmark) at a dose of 90 μgr kg^{-1} per dose. The same dose was repeated one more time at a 2 h interval. The bleeding was stopped and the patient was discharged without any symptoms of bleeding.
Case 2: A 15-year-old boy with Glanzmann's thrombasthenia had a severe motorcycle accident. He was unconsciousness when he was admitted to emergency. Cranial computed tomography scan (CT) revealed an acute hemorrhage within the right ventricle without any intraparenchymal hemorrhage. He had an intracranial hemorrhage. The hemorrhage was drained by the neurosurgeons and he was concurrently given rFVIIa (90 μg kg^{-1}). Treatment with rFVIIa (90 μg kg^{-1}) repeated every 3 h for 6 doses resulted in cessation of bleeding, which was confirmed by cranial CT. rFVIIa was continued every 6 h for 10 days. Although the bleeding was under control, his conscious did not improve and he died of multi-organ failure due to severe trauma. In both patients, no complications related to rFVIIa were observed. We suggest that rFVIIa at repeated doses of 90 μg kg^{-1} can be effectively used in patients with Glanzmann's thrombasthenia having excessive bleeding.

PO-TU-163
Constraints and challenges in treating a young hemophilia patient with exceptionally high inhibitor titers

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Introduction: Inhibitor formation is currently the most challenging complication in the management of hemophilia in young patients.
Objective: To report the case of a 3.5-year-old hemophilia patient presenting with persistent and exceptionally high inhibitor titers unresponsive to conventional immune tolerance induction (ITI) therapy, and to highlight the difficulties in treating such patients.
Case report: A male patient, born to a healthy primiparous mother at 38 weeks gestation via normal delivery, was diagnosed with severe factor VIII (FVIII) deficiency (1%) soon after birth. Diagnosis was made following the formation of soft tissue hematomas at venepuncture sites and patient was promptly treated with recombinant factor VIII. During the first months of the patient's life, he presented with repeated bleeding episodes requiring substitution therapy, and by the age of 8 months, inhibitor presence was established (1 BU). At 3 months follow-up the titer was raised up to 256 BU DNA analysis revealed mutation INV22(+), known to be associated with a high risk for inhibitor development. Bleeding episodes were initially managed with recombinant activated factor VII, which subsequently became unavailable due to economic reasons at the hospital. ITI was planned, but due to poor venous access and difficulty in maintaining a central venous line (the child pulled off his Hickman catheter twice) was not started until the age of 2. Because of ITI being performed by peripheral veins, a conventional non-aggressive regiment was decided (80 IU $kg^{-1} \times 3$ $week^{-1}$). During 12 months of ITI, the inhibitor titer rose from 128 BU mL^{-1} to 2000 BU mL^{-1}, and ITI was discontinued as unsuccessful. The child continues to bleed frequently, with minimal access to factor VII. Additionally, the very young age and the non-presence of central venous line make aggressive ITI protocols that include immunosuppressant difficult to decide.
Conclusions: The case highlights the difficulties in treating young patients with inhibitors, touching on both medical and economic issues.

PO-TU-165
A survey of current Canadian practice in the care of newborn boys with hemophilia

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Background: There is no consensus regarding many aspects of the care of newborns with hemophilia, including the use of imaging tests to detect intracranial hemorrhage, the prophylactic use of factor concentrates, and the route of administration of vitamin K. We conducted a survey to describe the current management of newborns with hemophilia in Canada, and to identify differences in practice between hematologists and neonatologists/pediatricians.
Methods: A survey consisting of multiple-choice questions about the management of three scenarios involving newborns with hemophilia was sent in electronic and paper formats to members of a number of organizations of hematologists and neonatologists in Canada. Differences in response proportions between groups were analyzed using Pearson's chi-square or Fisher's exact test.
Results: Of practising physicians who were sent the survey, 28.4% responded, and the survey was completed by 29 hematologists and 29 neonatologists/pediatricians who had been involved in the treatment of newborns with hemophilia within 5 years. No consensus was observed in the route of vitamin K administration or the use of imaging tests to detect intracranial hemorrhage, but there was a consensus to withhold factor concentrates after uncomplicated delivery. Comparing hematologists and neonatologists/pediatricians, hematologists preferred a hematology consult before birth in two scenarios (90% vs. 62%, $P = 0.01$; 86% vs. 59%, $P = 0.003$), neonatologists preferred oral vitamin K in one scenario (69% vs. 38%, $P = 0.043$), and hematologists treated a baby with factor concentrate rather than other products in the presence of neurologic symptoms (90% vs. 50%, $P = 0.02$).
Discussion: The management of newborns with hemophilia is not consistent across Canada. The uniformity and the quality of delivered care may be improved by more effective communication between hematologists and neonatologists. Multidisciplinary guidelines, informed by collaborative projects to determine the optimal use of imaging tests and factor concentrates in the neonatal period, are needed.

PO-TU-166
Perinatal practices in the context of hemophilia carrier: Expert opinion from an international pediatric panel

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According to evidence-based medicine, there is a lack of high level study in the field of the care to babies born from a mother carrier or supposed carrier of hemophilia. For a long

time, vaginal delivery has been recommended but this subject remains somewhat controversial. The European Paediatric Network (PedNet) and the International Network for Pediatric Hemophilia (INPH) are informal groups with scientific, educational and networking objectives for individuals involved in the care of children with hemophilia. The members do not represent their respective countries or any national organization, but they bring extensive experience from large centres. By analyzing the published guidelines about perinatal practices and documents used by some centres, we have identified a list of items to verify to what extent they may support a consensus opinion. We have drawn up a survey with 26 questions about general issues (n = 2), the labour (n = 4), and the care of the newborn (n = 16). The questionnaire was completed by members of PedNet (n = 22) and INPH (n = 18) at a rate of 100% (n = 36; 4 members belonging to both groups) and the results were discussed during the 2011 annual meetings. We recorded the answers to the questionnaire with high consensus rate for many questions (93 to 100%), such as: the avoidance of instrumental delivery with absolute contra-indication of vacuum extraction, the availability of FVIII/FIX vial at birth, the cautious appraisal of the obstetrical trauma and emergency of diagnosis and targeted treatment, the requirement of repeated clinical examination of the newborn. 86% recommended vaginal delivery and 100% considered the anticipation of Cesarean section necessary in cases of obstetrical difficulty. Answers about some issues such as the screening for intracranial bleeding or the duration of stay at the hospital were not as homogeneous. This international pediatric survey points out some key messages where members reached consensus that may strengthen guidelines as expert opinions. The analyses of some large international databases such as the PedNet Registry may be helpful from an epidemiologic point of view.

PO-TU-167
Dose and FVIII levels during continuous infusion in children: A single-centre experience

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Objectives: In order to optimize continuous infusion (CI) treatment strategy, FVIII levels and clotting factor requirement in pediatric surgery were evaluated.

Methods: Data on all surgical procedures in children with hemophilia A covered by CI performed at the Van Creveldkliniek, the Netherlands, from 2000–10 were extracted from patient files. FVIII levels were measured 15 min after bolus injection, in the post-operative hours, and daily thereafter. Rate of infusion was adjusted according to FVIII levels. Mean and range FVIII dose and levels were calculated for each day.
Results: Ninety-one surgical interventions in 44 severe hemophilia A patients were analyzed (mean age 4.2 years, range 0–12). Seventy-five per cent of procedures were portacath insertion/removal, 8% adenotonsillectomies, and 17% other. All patients received recombinant FVIII as CI for a mean of 5.5 days (range 3–9). FVIII was administered as initial bolus of mean 58 U Kg^{-1} (15–158) and CI started with a rate of 5.7 U kg^{-1} h^{-1} (2.1–12). Two procedures required high doses of FVIII due to the presence of low-titer inhibitor. Mean FVIII levels and mean FVIII doses are shown in Table 1. To maintain adequate FVIII levels, an extra bolus was required on the day of surgery for 21/91 procedures, 8/91 on day 1, and 6/91 after day 2. Median consumption of FVIII was 114 U kg^{-1} day^{-1} (range 43–594). There were no bleeding complications, thrombosis, or infections.

	After bolus	Post operative hours	Day 1	Day 2	Day 3	Day 4	Day 5
Mean FVIII levels (U dL^{-1})	104	76	101	104	104	106	92
Mean FVIII doses (U kg^{-1} h^{-1})	5.7	7	6.5	6.1	6.2	6.1	6.3

Conclusion: FVIII levels decreased during the first post-operative hours and therefore FVIII infusion rate had to be adjusted in order to maintain hemostatic efficacy. FVIII levels and rate of infusion remained constant from the first day after surgery. These results suggest standardization of post-surgery FVIII evaluation in order to detect unexpected through levels that could induce break-through bleeding.

31-PHARMACOVIGILANCE

PO-TU-169

Pharmacokinetic and pharmacodynamic modelling of rFVIII and glycoPEGylated rFVIII (N8-GP) in hemophilia A dogs support less frequent dosing

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Introduction: N8-GP is a new recombinant FVIII derivative with a site specific glycoPEGylation on the B-domain. The site-specific conjugation leads to an active molecule which is similar to native FVIIIa. A two-fold prolongation in half-life has been shown in rodents. The present study reports both pharmacokinetic (PK) and pharmacodynamic (PD) results from hemophilia dogs, and demonstrates a substantially prolonged effect of N8-GP as compared to unmodified rFVIII.
Methods: N8-GP and rFVIII (turoctocog alfa) were administered intravenously to hemophilia A dogs at a dose of 125 U kg^{-1}. Pharmacokinetic (PK) parameters based on the plasma FVIII:C measured by one-stage clotting assay were evaluated by standard methods, and the pharmacodynamic (PD) profiles were evaluated using whole blood clotting time (WBCT). A direct effect model was used to characterize the relationship between the PK and the PD.
Results: After intravenous administration, the clearance was estimated to be 3.8 and 6.4 mL h^{-1} kg^{-1} for turoctocog alfa and N8-GP respectively. The terminal half-life was close to two-fold longer for N8-GP as compared to turoctocog alfa. Both turoctocog alfa and N8-GP were able to normalize whole blood clotting time in hemophilia A dogs.
Conclusion: GlycoPEGylated rFVIII (N8-GP) demonstrated close to two-fold prolongation of half-life as compared to rFVIII and reduced clearance in hemophilia A dogs. Simulations of a multiple dosing regimen in dogs suggest that to maintain WBCT at a level known to prevent bleeding (<20 min), N8-GP can be dosed less frequently than turoctocog alfa. Data therefore support N8-GP as an alternative to standard rFVIII replacement therapy, with a more convenient dosing regimen.

PO-TU-170

Pharmacokinetics and efficacy of on-demand treatment with human-cl rhFVIII in previously treated patients with severe haemophilia A

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Introduction: The pharmacokinetics (PK) and efficacy of on-demand treatment was studied with the first Human-cl rhFVIII, a B-domain deleted recombinant factor VIII (rFVIII) expressed in Human Embryonic Kidney 293F cells, in previously treated patients with severe haemophilia A.
Methods: The PK of Human-cl rhFVIII was compared with that of the full-length rFVIII Kogenate FS using a crossover design, followed by on-demand treatment with Human-cl rhFVIII for ≥6 months and ≥50 Exposure Days (EDs). For PK evaluation, patients received a single IV nominal dose of 50 IU kg^{-1}. Blood samples were collected over 48 h. FVIII coagulant activity was measured by validated chromogenic substrate (CHR) and one-stage (OS) assays in a central laboratory, which also assigned drug potency with the same assays. Inhibitor activity was determined using the Nijmegen modification of the Bethesda assay before the first Human-cl rhFVIII administration and at defined intervals thereafter. Efficacy of treating bleeding episodes was judged as 'excellent', 'good', 'moderate' or 'none' by taking into account the number of infusions and time until bleeding signs improved.
Results: Twenty-two patients between 12 and 65 years of age were recruited from 9 centres in the United States and Europe. PK parameters (mean ± SD) of these patients are shown below.
Human-cl rhFVIII and Kogenate FS were bioequivalent as the 90% confidence interval of the ratio of the geometric mean values of the AUC fell within 80–125% for both assays. A total of 451 bleeding episodes treated with Human-cl rhFVIII have been documented so far. Treatment efficacy was rated as 'excellent' or 'good' in 91.8% of cases. Human-cl rhFVIII has been safe and well tolerated and no FVIII inhibitors have been observed.

Parameter	Kogenate FS (CHR)	Human-cl rhFVII (CHR)	Kogenate FS (OS)	Human-cl rhFVII (OS)
AUC_{norm} (hr*IU mL^{-1}/(IU kg^{-1}))	0.38 ± 0.09	0.39 ± 0.14	0.38 ± 0.10	0.37 ± 0.11
Clearance (mL hr^{-1} kg^{-1})	2.75 ± 0.64	2.94 ± 1.18	2.82 ± 0.72	2.96 ± 0.97
In-vivo recovery (% per IU kg^{-1})	2.49 ± 0.32	2.51 ± 0.37	2.03 ± 0.28	2.15 ± 0.27
Terminal half-life (hr)	16.1 ± 5.9	14.7 ± 10.0	18.8 ± 5.9	17.1 ± 11.2

Conclusion: The data indicate that Human-cl rh FVIII is bioequivalent to a licensed rFVIII concentrate and that it is safe and efficacious in treating bleeding episodes in persons with haemophlia A.

PO-TU-171

High-purity, plasma-derived, pasteurized factor VIII concentrate in the treatment of patients with hemophilia A: Update of a long-term pharmacovigilance

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Comprehensive, non-interventional, large-scale pharmacovigilance studies are effective tools to collect data on products in the post-authorization period. This study assessed the long-term efficacy, tolerability, and safety of a high-purity, plasma-derived, pasteurized FVIII concentrate (Beriate® P, CSL Behring GmbH, Marburg). Previously untreated and previously treated patients at any age with hemophilia A, who had received Beriate® P and who fulfilled the inclusion criteria, were enrolled. Based on the proceeding at the centres, patients were routinely screened every 3 to 12 months. Parameters documented comprised efficacy-, safety-, pharmacoeconomic- and pharmacokinetic data. Up to now, 84 patients were included into this study (median duration: 44 months [0–102]), and data from 770 visits were available for analysis. Sixty-nine patients suffered from severe-, 10 patients from moderate-, and 4 patients from mild hemophilia A. In one patient, the information on severity of hemophilia A was missing. Median patient age was 19.3 years (0.1–74.6). Eighty-two percent of the patients (n = 67) received prophylaxis with at least one infusion per week. Median average number of bleeds per year was 3.23 (0–42.98), and a median of 1.0 (0–83.0) infusion per bleeding was administered. Seventy-four percent of patients (n = 72) experienced no major bleeding, and 11% experienced no bleed at all with regard to all sorts of bleeding. The efficacy of Beriate® P was judged to be excellent to good ranging from 93.7 to 98.4% in all visits. Only two cases of inhibitor development were reported; one inhibitor was transient, and the second inhibitor was treated with immune tolerance therapy. There was no virus transmission for hepatitis A, hepatitis B, hepatitis C, or human immunodeficiency virus. The results included in this interim analysis confirm the very good efficacy, tolerability and safety of Beriate® P.

PO-TU-172

Recombinant FVIII-FS for the treatment of hemophilia A: Update of a long-term pharmacovigilance project

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This multinational (Austria, France, Germany, Italy, Sweden) project is assessing the long-term efficacy, tolerability, and safety of recombinant factor VIII-FS (Helixate® NexGen, CSL Behring, Marburg) in the post-authorization period. PUPs and PTPs with hemophilia A at any age treated with recombinant FVIII-FS (Helixate® NexGen) are eligible for enrollment. Patients are routinely screened every 3 to 12 months. The following parameters, as determined routinely for these patients (non-interventional design), were documented: overall clinical response, bleeding events, adverse drug reactions including the incidence of inhibitors, laboratory safety and virus safety parameters, relevant concomitant diseases, and relevant concomitant medication. Pharmacokinetic data were also collected if available. Treatment modalities including average factor consumption per month and exposure days were recorded. Data from a total of 218 patients with a total of 2,064 visits were available for this update. The majority of the patients (82%) had severe hemophilia A. The median age was 23.5 years (range: 15 days to 68 years). Exposure to recombinant FVIII-FS during the pharmacovigilance ranged from one day to 104.9 months. Median time between visits to the respective centre was 4 months (range: 0–48 months). Most of the patients (79%) received prophylaxis with at least one infusion per week. The median number of bleeds per year was 2.48 (range: 0–70) per patient. Eighty-two per cent of the patients had no major bleeding, and 14 % experienced no bleed at all. A median number of 2 infusions was administered per bleeding. During the up-to-10-year observation period, only 3 cases of inhibitor development were reported. Efficacy of Helixate® NexGen was assessed as good or excellent in 97 % of all documented bleeding events. The results included in this interim analysis confirm the very good efficacy, tolerability, and safety of Helixate® NexGen.

PO-TU-173

Preclinical safety pharmacology of a PEGylated variant of recombinant factor VIII

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Baxter and Nektar have developed a PEGylated form of Baxter's recombinant FVIII (rFVIII) product based on the Advate manufacturing process, BAX 855. The product is derived from a Chinese hamster ovary (CHO) cell line using a plasma-protein-free method and a virus inactivation step. In this preclinical study program, the objective was to evaluate the safety of Baxter's longer acting rFVIII in different species. The rabbit stasis model, developed by Wessler, was used to study the thrombogenic potential of BAX 855. To demonstrate the consistent safety between different batches, two lots of BAX 855 were used and Advate served as the control item. The effects of BAX 855 on body temperature, heart rate, blood pressure, respiratory variables or QT, QTcf, and PR and/or QRS intervals and respiratory system (intra-thoracic pressure) was evaluated in

conscious telemetered cynomolgus monkeys. BAX 855 was given at 150 and 600 U kg^{-1} day^{-1} to male monkeys by intravenous administration. BAX 855 showed no thrombogenic potential in the Wessler model at a dose of 900 U kg^{-1}. There was no evidence of thrombogenic potential after intravenous treatment with either the test item or Advate, the active reference item. Furthermore, BAX 855 did not cause any adverse clinical, respiratory, or cardiovascular effects and was very well tolerated at all dose levels tested. In conclusion, Baxter's longer acting rFVIII did not cause any thrombogenic events or adverse clinical, respiratory or cardiovascular effects and was very well tolerated at all dose levels.

PO-TU-174
Pharmacokinetics of a recombinant factor VIIa in factor VIII ko mice, rats, and macaques

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The aim of the studies was to assess the pharmacokinetic profile of Baxter's new rFVIIa in comparison with a licensed rFVIIa after a single intravenous bolus injection at a dose of 0.6 mg kg^{-1} in mice and rats and 2.7 mg kg^{-1} in cynomolgus monkeys. The $AUC_{0\text{-tlast}}$ (area under the concentration vs. time curve from 0 to the last time point) was evaluated as primary endpoint. Secondary endpoints were total clearance (CL), terminal half-life (HL), and mean residence time (MRT) for FVIIa protein and clotting activity. In cynomolgus monkeys only FVIIa clotting activity was evaluated. Blood was sampled at baseline and each of the time points after a single intravenous bolus injection of Baxter's new rFVIIa or the commercially available rFVIIa. The citrated plasma samples were analyzed for FVIIa activity using a FVIIa clotting assay and FVII protein (antigen) using a FVII ELISA. By using a serial sacrifice design, 10 (5m/5f) FVIII ko mice per time point were bled by cardiac puncture under anesthesia 5–200 min after a single intravenous bolus injection of the test or reference item. In rats and monkeys, a single animals design was used. In rats (5m/5f) and cynomolgus monkeys (2m/2f), blood samples were drawn before and 5–270 min (rats) and 5–900 min (cynomolgus monkeys) after administration. In all species, bioequivalence of Baxter's new rFVIIa and the reference item could be shown for the primary endpoint ($AUC_{0\text{-tlast}}$). Additionally, secondary endpoints of FVIIa activity (CL, HL and MRT) were similar for Baxter's new rFVIIa and the reference item. In mice, CL was 245 mL kg^{-1} h^{-1}, HL was 0.64 h, and MRT was 0.80h for Baxter's new rFVIIa. Values for the secondary endpoints in rats were 102.6 mL kg^{-1} h^{-1} for CL, 1.17 h for HL, and 1.29 h for MRT. In cynomolgus monkeys, CL was 33.6 mL kg^{-1} h^{-1}, HL was 2.00 h, and MRT was 2.45 h. In summary, the pharmacokinetic profiles of Baxter's new rFVIIa and the commercially available rFVIIa were similar in all species studied.

PO-TU-175
Single-dose pharmacokinetics of a PEGylated variant of recombinant FVIII in factor VIII ko mice, rats, and macaques

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Baxter and Nektar are developing a recombinant FVIII (rFVIII) modified with polyethylene glycol (PEGylation) to achieve longer circulation (BAX 855). The aim of the presented studies was to assess the pharmacokinetic profile of BAX 855 in mice, rats, and monkeys compared with that of Advate, a licensed rFVIII. The test items were administered as an intravenous bolus injection. Mice and rats received 200 IU kg^{-1}, and monkeys received 350 IU kg^{-1} rFVIII of either BAX 855 or Advate. Mean residence time (MRT), terminal half-life (HL), total clearance per kg body mass, $AUC_{0\text{-tlast}}$ (the area under the concentration vs. time curve from 0 to the last measured time point), and in vivo recovery (IVR) were evaluated. Citrated plasma samples were analyzed for FVIII activity (chromogenic assay; mice and monkeys), FVIII–bound PEG (PEG-FVIII ELISA; all species), and/or FVIII antigen (FVIII ELISA; rats). By using a serial sacrifice design, 16 FVIII ko mice (B6;129S4-*F8*^{tm2Kaz}) for BAX 855 and 8 FVIII ko mice for Advate per time point were bled by cardiac puncture under anesthesia 5 min–48 h after a single intravenous bolus injection. A single animal design was used in rats and monkeys. 16 (BAX 855) and 8 (Advate) CD rats were bled via the tail artery before and 5 min–48 h after dosing. 8 (BAX 855) and 4 (Advate) cynomolgus monkeys were bled from a suitable vein before and 5 min–96 h after dosing. A prolongation in MRT of BAX 855 compared with Advate could be demonstrated in all species. FVIII activity analysis showed an increase in MRT from 4.9 to 7.9 h in mice and from 7.5 to 11.5 h in monkeys. This prolongation was also reflected in the terminal HL (4.3 to 5.9 h in mice; 5.7 to 9.4 h in monkeys). A lower clearance for BAX 855 than for Advate could be observed consistently. Similar pharmacokinetic results could be shown for FVIII-bound PEG in all three preclinical models and for FVIII antigen in rats. These pharmacokinetic data provide evidence that PEGylation of human rFVIII increases the circulation time.

32-PHYSIOTHERAPY AND REHABILITATION

S-MO-03.4-4
Home adaptations and devices to help with movement: Emerging country
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In countries where long-term prophylaxis is not widely available, hemophilic arthropathy is one of the most frequent complications for persons with hemophilia (PWH). Impaired functional skills interfere with movement, autonomy, and independence to perform daily life activities (DLA). Likewise, there is an intense deterioration to quality of life, jeopardizing the self-esteem and social adjustment of PWH. Therefore, the following are part of a multidisciplinary therapeutic intervention: a) to identify environmental factors facilitating or hampering the performance of DLA and b) to develop strategies enabling structural adaptations. Thus, the ultimate outcome is to facilitate and stimulate the development of skills and other potentialities. Assistive technology (AT), such as arm supports, adapted bath seats, orthotics for upper and lower extremities, and button and socks aids is an essential resource to promote independence. Sometimes, with creativity, some adjustments can be done at home by patients themselves, to facilitate recovery or adaptation for movement. AT compensates joint limitations, but during acute bleeds, it can be difficult to use those devices, mostly for self-care and self-infusion. Using the non-dominant side is an instinctively applied resource, but it is not usually emphasized as an interesting psychomotor technique to train these skills. Pain and limitation of movement are frequent problems of PWH's lives. Studies developed for other disorders have shown that pain affects body scheme in a negative way, and movement is essential to constructing body image. Thus, training the non-dominant side can become an impacting tool for social, psychological, and physical rehabilitation. There are few studies addressing this topic for PWH and, therefore, it is essential to develop more studies to achieve better understanding.

S-MO-03.4-3
Home adaptations and devices to help with movement: Established country
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The objective of this presentation is to give some ideas about home adaptations and devices available in an established country like Finland. With the advent of today's electronic entertainment devices, such as video-based, motion-sensing input devices; balance boards; or hand-held motion detectors, there are new opportunities to engage patients with hemophilia in physical activities. Simulated sports offer a safe way to experience the thrill of competitive sports. Software has been developed to allow individual, goal-oriented, progressive training to be incorporated into rehabilitation. In high-resource countries where sedentary office work offers the best career opportunities, many patients with hemophilia feel that the opportunities for physical activity are limited. That is why every possibility should be used to encourage movement, and of these tools, the new home-entertainment systems are both affordable and safe. Due to World War II, Finland is a country with lots of people experiencing varying degrees of ambulatory challenges. As the population ages, the need for independent transit outside the home increases. In Finland, efforts have been made to develop and create easy accessibility for everyone. This is true especially in the public transportation system. In most commuter buses, there are low floors, big doors, and ramps for wheelchair access. Most bus stops allow for levelled access. Buses also have the possibility of kneeling to allow easier entrance. Trains and trams also have low floors, allowing for easy accessibility. The Arctic climate in Finland also poses unique challenges. As the roads and pavement are covered with ice or thick snow, moving about is difficult. Different aids for moving about have been developed. Sleigh-like devices work better then wheels in deep snow. Different kinds of spikes that can be attached to shoes or canes are also available. Still, the winter severely hampers movement, especially with wheeled devices.

S-MO-03.4-2
Bringing movement back into daily lives
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Movement is the essence of everyday life. We have many goals and milestones to achieve throughout our lives starting from the day we born. Every stage of life has specific movement goals and purposes. The important aspect of achieving and maintaining successful movement programs and targets is that it has to be goal orientated and purposeful. A baby learning to roll only does it out of necessity, in this situation, to reach for a toy. To be a competent task, it also needs to have meaning. Learning to drive is an important 'right-of-passage' and a step closer to autonomy. Though structured exercise programs are beneficial and achieve great results when adhered to, they are often time consuming and sometimes require special equipment and so are not always practical. Incorporating and emphasizing movement during activities of daily living will also allow for the benefits of a structured exercise program but may save time. With so many technological advances being made to make life easier for us, we don't have to move as much as we used to, leading to a more static and sedentary life, which has its own set of health related problems attached to it. The purpose of this presentation is to provide practical ideas on how to bring movement back into our lives, to keep active, and to improve health and general well-being.

S-MO-03.4-1
Making good use of the body
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Many adult patients with hemophilia have some resistance or even reluctance to our physiotherapeutic approach in which sometimes exercises and programs are offered to them that are too inconvenient. Their bodies often lose much of the spontaneity, the harmony, and the effort-saving principles that should govern their movements. As our willingness to re-educate disturbs the body layout they have gradually set up with every bleeding, and because we try to link their adapted tonic structure back to the natural but long-forgotten coordination schemes, we might put them off and be unable to convince them of the absolute necessity of regular exercise. We, as physiotherapists, must understand that and draw a line of action aimed at giving patients support and advice concerning the everyday movements that will preserve their mobility, help them avoid some 'sensorimotor amnesia,' and revive their creativeness by developing their sense of movement. To that end, we must be able, outside acute bleeding episodes, to put forward other approaches—known as 'body consciousness techniques'—for better use of the body, so that all patients, according to their type and psychomotor habits, may try one technique or other: one emphasizing the sensory aspect (such as eutony), one based on the analysis and representation of movement (such as kinesiology), one relying on 'adequate' movement (such as the Alexander, Feldenkrais, or Hanna methods), or one using the rhythm and music of movement in a collective and more entertaining way (such as 'contact improvisation'). The experiment carried out in Lyon of 'contact improvisation' illustrates how moves that are simple, efficient, pleasant to make, and, as such, adequate, can become possible. Following warm-up and stretching exercises, this proprioceptive activity restores self-confidence and so stimulates the creative spontaneity of patients' motor capabilities and makes them want to take regular exercise and appreciate it.

FP-TU-01.2-4
Aerobic capacity in Egyptian adults with hemophilia
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Background and aim of work: It is well known, that physical activity is very important for hemophilic patients and can contribute to better quality of life. Physical training also reduces the risk of bleeding episodes and prepares the body to manage hemophilia better. In spite of the benefits, participation in physical activity for children with hemophilia was discouraged in Egypt. So it wise to know where we are to start implementation of this modality in management of hemophilic patients. The purposes of this study were to investigate the feasibility of maximum cardiopulmonary exercise test (CPX) to evaluate aerobic capacity of hemophilic patients, also to determine the maximum oxygen consumption (VO_{2max}) and total work load (TWL) in adult Egyptian patients with hemophilia A.
Methods and results: VO_{2max} and TWL obtained during CPX test (breath by breath) from thirty subjects with hemophilia A (16 moderate and 14 severe); their mean age was 17.6 ± 1.92 years; were compared with normal matched for anthropometric data and age. All subjects were able to perform at maximal or near maximal level on exercise tests and none of them reported bleeding or other adverse events. The aerobic capacity indices: the VO_{2max} and TWL were less for hemophilic subject by 56.5% and 32.5% respectively than normal peers. There is non-significant difference between moderate and sever hemophilic subjects.
Conclusion: It was concluded that maximum exercise test was safe and useful for hemophilic subjects. Egyptian adults with bleeding disorders have impaired aerobic capacity compared with their peers. This may be attributed to lack of appropriate treatment, patient's overprotection, and socioeconomic factors. The severity of bleeding disorder did not contribute to aerobic capacity deficiency.

FP-TU-01.2-5
Development of physical therapy practice guidelines for persons with bleeding disorders: Outreach to community providers
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The Physical Therapy Working Group (PTWG) of the National Hemophilia Foundation (NHF) emphasizes the importance of patient care coordination through the comprehensive care team model at regional hemophilia treatment centers (HTC). The PTWG does recognize, due to medical, economic, and geographical factors, individuals are seeking out physical therapy services from community-based providers who may not be associated with an HTC. In order to have a standardized approach to service provision, the PTWG objective was to develop practice guidelines to educate and guide physical therapists who are providing community-based, direct-patient-care services to individuals with bleeding disorders.
Method: The PTWG arranged a series of therapist group discussions and workshops, format design, and content review and revision sessions during NHF annual and mid-year meetings from 2008–11. The practice guidelines were developed through consensus of therapists working with patients with bleeding disorders, including PTWG members from across the United States. The guidelines were further reviewed for medical accuracy by a physician member of the NHF Medical and Scientific Advisory Council (MASAC).

Results: In January 2011, The PTWG completed the development of practice guidelines in the following four areas: (to be displayed on poster): Muscle Bleeds, Joint Bleeds, Iliopsoas Bleed, Cryotherapy. A corresponding bibliography and glossary were completed. Each guideline presents information on acute, subacute, and chronic-stage interventions, signs/symptoms, other treatment considerations, precautions/contraindications, and differential diagnoses. The practice guidelines were presented for review and approved by the NHF MASAC in the spring of 2011.
Conclusion/Future Direction: Physical Therapy Practice Guidelines have been posted on the NHF website and made available to all healthcare providers at HTC's to distribute electronically. PTWG ongoing efforts include completing practice guidelines for synovectomies and joint replacement, and poster presentations at international meetings to foster discussion and collaboration with other international organizations.

FP-TU-01.2-6
Ambidexterity training program for patients with hemophilia

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Recurrent joint and muscle bleeding affecting upper limbs in patients with hemophilia (PWH) due to limited access to regular prophylaxis lead to compromise of activities of daily living (ADL). Furthermore, acute bleeding episodes and chronic arthropathy in dominant upper limb lead to high rate of absenteeism and compromise work and school productivity. To minimize these negative effects, we established a training program to develop the ambidexterity of PWH. Ambidexterity is the state of being equally adept in the use of both hands. The training program consists of educating the patients to regularly practice ADL using their non-dominant hand. In addition the patients are stimulated to write small texts with their dominant and non-dominant hands. Two to four times per month, the patients have sessions in the hemophilia centre with psychological educative activities such as games, paintings, and writing involving the non-dominant hand. The training program started in 2009 and so far 12 patients (mean age: 21.5 years, 11–42 years) have been included. One of the included patients was left-handed. We classified the success rate of the program as partial when the patients achieved the ability of ADL with the non-dominant hand, or total when they can also write with both hands. All of the patients achieved partial success and three achieved total success. The estimated time to reach the objectives was 30 to 90 days. The major factor determining the level of success was the motivation and dedication to regular practice of the training activities. The age of the patients did not influence the results. This is the first time that this type of ambidexterity training program was developed focusing on PWH. We believe that mixed handedness could bring great beneficial effects to patients in their daily activities, self-infusion, school progress, and work productivity, resulting in improved quality of life.

PO-WE-236
Strength training and stretching muscles of lower limbs in patients with hemophilia and arthropathy of the ankle: A pilot study

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Introduction: The functional limitation caused by the ankle arthropathy produces a shortening of the dorsal musculature of the leg and a loss of periarticular muscle strength. Over time, this contraction joint, further limiting joint range dorsiflexed ankle and causes pain in the march.
Objectives: To assess the effectiveness of a treatment facilitation proprioceptive, exercises against resistance with Thera-Band, and functional massage in patients with hemophilia and ankle arthropathy.
Methods: We selected 17 patients with hemophilia and chronic ankle arthropathy, and nine of them applied a intervention for 10 weeks, two sessions a week lasting 45 min per session. Treatment consisted of proprioceptive facilitation of ankle, exercises against resistance of twins and tibial compression, and functional massage-stretch-relaxation. The rest of patients formed the control group. Before and after treatment the perimeter of twin with tape measure, manual muscle balance, and perception of pain with VAS were assessed.
Results: Table 1 show the descriptive data of patients in both groups. It found improvements in muscular balance of both legs ($P < 0.05$) and perception of pain in the ankles ($P < 0.01$). There is a tendency to significance in improving the perimeter of twins in both legs ($P = 0.075$). No significant differences are noted in the control group. During the treatment period, there was no ankle hemarthrosis in subjects from the intervention group.
Conclusions: With proprioceptive facilitation therapy, massage exercises against resistance and functional, there is improvement in muscle strength in the legs of patients with ankle arthropathy. With strength training improves the perception of pain in the ankle. There was not ankle hemarthrosis with this technique of Physiotherapy.

PO-WE-237
Efficacy and safety of traction articular ankle arthropathy: A pilot study

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Introduction: Ankle arthropathy in patients with hemophilia is characterized by the limited range of motion (ROM), pain, and gait disturbance. Over time, ankle arthropathy produces disabilities that restrict the activities of daily life for the patient. The joint-drive manual therapy is a technique of physiotherapy effective for the treatment of limited joint mobility.
Objectives: Assess the effectiveness of joint traction, grade I and II, in limiting the ROM in patients with hemophilia and chronic ankle arthropathy.
Methods: We selected 18 patients with hemophilia, and adults diagnosed with an ankle arthropathy. Nine patients participated in a manual therapy treatment for 6 weeks with two sessions per week, and a duration of 60 min per session. We did an articulate traction of ankle with proximal fixation of the ankle, in the highest range of dorsal flexion and plantar flexion without pain, and applying heat surface before the technique and cold at the end. The other nine patients formed the control group. All patients were measured with a universal goniometer ROM, and the perception of pain with VAS, before starting treatment and at the end of it, 6 weeks later.
Results: There was significant improvement in dorsal flexion ($P < 0.02$) in both ankles, and plantar flexion, and the perception of pain in his right ankle ($P < 0.05$). We found significant tendency in plantar flexion ($P = 0.062$) left ankle. No significant differences in control group. There was no bleeding in patients in the experimental group during the treatment.
Conclusions: The joint traction is a valid technique for the treatment of joint limitation in ankle arthropathy. With a good management technique, the likelihood of ankle hemarthrosis is lessened.

PO-WE-238
Clinical improvement of chronic arthropathy of the knee with manual therapy: A pilot study

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Introduction: The knee is the most commonly affected joint arthropathy in patients with hemophilia. The loss of range of motion (ROM) and joint pain affect the progress and activities of daily life for a patient. Over time, functional impairment of the knee can affect the ankle and hip. So it is important to try to improve the limitations of the knee as soon as possible.
Objectives: To assess the effectiveness of joint drive to improve the mobility of the knee and pain perception, and to note the improvement in the clinical assessment of knee arthropathy.
Methods: Twenty patients with hemophilia and arthropathy of the knee participated in this study. Twelve patients were treated with grade II articular traction for 8 weeks with 1 session per week, 30 min each session. Treatment consisted of joint traction at the highest ranges of flexion and knee extension with proximal and distal fixation. The other eight patients formed the control group. An external evaluator assessed before and after treatment, knee flexion and extension using a goniometer, the perception of pain with VAS, and clinical assessment scale with Gilbert.
Results: The experimental group had significant improvement in knee flexion and extension, in the clinical assessment ($P < 0.01$), and the perception of pain ($P < 0.05$). There were no significant differences in the control group between the two assessments. There was no knee hemarthrosis in the experimental group during the treatment of physiotherapy.
Conclusions: The joint traction technique gives a clinical improvement in ROM, pain perception, and clinical assessment of the knee. It needed more studies with greater cohort and follow-up period to assess the effectiveness of traction articular knee arthropathy.

PO-WE-239
In-hospital rehabilitation after multiple joint procedures (MJP) of the lower extremities in persons with hemophilia (PWH)

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People with hemophilia (PWH) often suffer from hemophilic arthropathy in more than one joint. Pain in joints of the lower extremities, especially, keeps them from functioning in their society in an adequate way. From 1995 till today, 53 PWH underwent 56 MJP of their lower extremities. MJP is defined as any combination of total knee (TK), total hip (TH) or ankle arthrodesis (AA) during one in-hospital stay, performed during one session or staged. All PWH were rehabilitated in the UMC Utrecht, the Netherlands, during their in-hospital stay. A literature search revealed that no guidelines or protocols exist on rehabilitation of this particular group of PWH. This project aimed to define subgroups, to describe these subgroups, and to use the data to develop guidelines during their in-hospital stay. Objectives are also needed to decide the proper moment of surgery, and to perform a proper follow-up, both short- and long-term. This is needed to detect the benefits and to optimize the results for these PWH, after their enormous investment. Since 1995 a total of 56 MJP were carried out in 53 patients. Subgroups defined are: TK both sides ($n = 10$), TK both sides combined with AA both sides ($n = 10$), AA both sides ($n = 9$), TK and AA both sides ($n = 7$), TH and TK homo lateral ($n = 5$), TK and AA homo lateral ($n = 5$), TK and TH hetero lateral ($n = 2$), TH and AA hetero lateral, ($n = 2$), TK and AA hetero lateral ($n = 2$), TK and AA hetero lateral ($n = 2$), and TK both sides and AA ($n = 1$). In-hospital rehabilitation schedules of all subgroups will be given, as well as data on body and activities level both pre- and post-operative as well as their profile at discharge. Because this specific group is very heterogeneous it can only be used to develop an onset towards guidelines. Case studies will be used to give more insight into the intensive rehabilitation, as well as complications met during this very intensive period.

PO-WE-240

The use of a carbon-fiber ankle foot orthosis and therapeutic exercise for managing pain in an adolescent with severe blood-induced ankle joint arthropathy secondary to type 3 von Willebrand disease

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Objective: Type 3 von Willebrand disease (VWD) is a hemophilia-like bleeding disorder, which can have severe bleeding symptoms, including recurrent joint bleeding, leading to arthropathy and target joint development. This report describes physical therapy intervention for managing chronic ankle pain, weakness, and balance/gait impairments with bracing, exercise, gait training, and education in a 12-year-old boy with severe ankle arthropathy secondary to type 3 VWD.
Case Description: Ankle bleeding resolved with open synovectomy. However, pain increased and musculoskeletal impairments, including ankle varum deformity, loss of ankle dorsiflexion, ankle and core weakness, and balance and gait abnormalities, persisted. This led to weight gain and limited participation and quality of life. Intervention included lower extremity and core strengthening exercises combined with balance activities, gait training, and use of custom-fitted functional foot orthoses combined with a carbon-fiber, ankle foot orthosis (AFO). Education on adherence to prophylactic clotting factor infusion and implementation of family dietary changes were included.
Outcomes: Ankle pain decreased from FACE 3 to FACE 1 on the Wong-Baker Faces Pain Rating Scale. Activity for Leisure/Sport and Leg Function increased by 67% and 250%, respectively, as measured on the Pediatric Hemophilia Activities List. Quality of life, measured on the Canadian Hemophilia Outcomes-Kids' Life Assessment Tool, showed 14% improvement on the child score and 26% improvement on the parent score. The 6-Minute-Walk Test distance increased 80 m. BMI decreased, and strength in core musculature and lower extremities increased. Participation, measured on the Children's Assessment of Participation and Enjoyment, increased only in the domain of enjoyment. The Hemophilia Joint Health Score remained unchanged.
Discussion: Identifying impairments affecting daily activities and implementing interventions help manage pain and restore function in children with arthropathy due to joint bleeding. These outcomes may provide support for this intervention with other adolescents with blood-induced ankle arthropathy and chronic pain.

PO-WE-241

Recovery of the gait ability after total knee arthroplasty

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Objective: The aim of this study is to investigate early gait ability recovery factors after total knee arthroplasty (TKA) for patients with hemophilia.
Patients and methods: Twelve hemophilic arthropathies (10 severe hemophilia patients: hemophilia A8 (inhibitor 1), hemophilia B2 (inhibitor 1), average age 49 ± 15 years) had been operated on TKA (revision 1) from May 2010 to June 2011. They were divided into two groups based on post-operative 80 m maximum gait speed (MGS) at the discharge day (average discharge day was 30 ± 9.5 day). Group A was recovered to pre-operative MGS until discharge, group B was not. Several factors were analyzed so that the two groups could be compared: maximum gait speed, 30-second one-leg stands, quadriceps and hamstrings muscle strength, knee joint range of motion, static standing weight-bearing balance, length of the displacement of the centre of gravity, a centre of gravity movability range, and knee extension rag.
Results: Pre-operative MGS of Group A and B were 1.38 ± 0.18 m s^{-1} and 1.36 ± 0.19 m s^{-1}, and post-operative MGS of Group A and B were 1.55 ± 0.18 m s^{-1} and 0.99 ± 0.41 m s^{-1}, respectively. Pre-operative operation side quadriceps strength (Group A 153.4 ± 45.1Newton (N), Group B 58.3 ± 48.9N), pre-operative operation side hamstrings strength (Group A 131.6 ± 62.1N, Group B 52.3 ± 53.0N), and post-operative opposite operation side hamstrings strength (Group A 214.8 ± 61.9N, Group B 127.4 ± 65.3N) were significant differences between two Groups ($P < 0.05$).
Conclusion: Among various factors affecting gait ability, the results suggested that pre-operative lower limb muscle strength is an important factor to early recovery gait ability.

PO-WE-242

Proprioceptive training in hemophilic children

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Efficient movement function and the maintenance of balance during dynamic tasks are more complex than only force production it requires a primary sensory mechanism for motor control which is propioception. The objective of this work is to study alterations in proprioceptive performance to subsequently evaluate the appropriate therapeutics. The purpose of the study is to determine whether exercise intervention improves balance in children with hemophilia following the participation in a balance and proprioceptive training program on the Biodex stability system. Thirty hemophilic boys aged between 7 and 14 years with hemophilia (type A and B) participated in this study. They were classified randomly into two groups of equal number, (control and study). The control group received factor replacement as prophylactic medical management. The study group received propiceptive training program and factor replacement. Proprioception parameters were assessed using Biodex stability system in both groups with eyes opened and with eyes closed, before and after three months of the application of the treatment program. The results of this study revealed statistically highly significant improvement in nearly all of the measuring variables of the study group ($P < 0.01$) when comparing its pre- and post-treatment results, and when comparing the post-treatment results of the control group. From the obtained results of this study, it can be concluded that proprioceptive training is a beneficial modality that may be used to improve standing postural control with minimal stress to the joint in hemophilic children.

PO-WE-243

Use of the exergaming (Nintendo Wii) in the rehabilitation of patients with hemophilia

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The evaluation of musculoskeletal deficits in patients with hemophilia (PWH) emphasizes some disability that interferes in global health and functional capacity of these patients. These conditions affect the static and dynamic balance. Identify these deficits is important for the establishment of training programs that can improve the balance. The aim of this study is to analyze the influence of an exercise protocol through therapeutic modality 'exergaming' (Nintendo Wii®) in controlling the balance of PWH. Two patients with severe hemophilia A were evaluated in this study. The activities were performed twice a week for 50 min during 2 months. In each treatment session, the software automatically generated graphics performance with the score after exercise that was compared to previous sessions. The exercise protocol included activities of balance, proprioception and postural correction. The activities included several exercises programs, such as Balance Buble, Penguin Slide, Tilt Table, Soccer Heading, and others. Patients started the exercise protocol in the beginner intensity, progressing based on performance. Balance, and musculoskeletal status were assessed at the beginning and at the end of the exercise protocol, using the Berg Balance scale, Tinetti Test score and the Functional Independence Score in Hemophilia (FISH). The outcomes are in the table 1. There was improvement of balance, gait and functional independence in the evaluation. Currently, features that use virtual reality has become prominent in the rehabilitation of patients allowing new experiences and sensations can be achieved. The therapeutic modality 'exergaming' can help to stimulate proprioceptive and musculoskeletal capacity in PWH.

Table 1. Scale score of Berg, Tinetti Scale and FISH.

	Berg		Tinetti (Gait)		Tinetti (Balance)		FISH	
Patient	before	after	before	after	before	after	before	after
1	34	40	04	07	08	12	22	26
2	38	46	10	12	11	14	28	32

PO-WE-244

Postural control in children with hemophilia

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Introduction: Sensory information from visual, vestibular, and proprioceptive systems are necessary to control posture and balance. Impairment in proprioception due to repetitive joint bleedings may lead to a deficit in postural balance, which, in turn, leads to high joint stress and risk of bleeding recurrence. Despite the increase of attention in this field during the last years, there is still scarce data on how these bleeds can affect postural control of children with hemophilia (CWH) without arthropathy.
Objectives: To evaluate postural balance under different sensory conditions in CWH.
Methods: Twenty children with hemophilia (HG) and 20 age-paired children (CG) were recruited to this study. A force plate was used to record centre of pressure displacement (COP) under four different postural sensorial conditions during quiet standing: (cond1) eyes-open on firm surface, (cond2) eyes open on foam surface, (cond3) eyes-closed on firm surface, and (cond4) eyes-closed on foam surface. Variables of COP as sway area, velocity (VM), and the root mean square (RMS) and in anterior-posterior (x) mediolateral (y) direction were processed, and for each variable quotients of vision (cond2/cond1), proprioception (cond3/cond1), and vestibular(cond4/cond1) were calculated and compared between groups.
Results: No differences were found in visual and vestibular quotients' variables between groups. Higher value was found in sway area variable on proprioception quotient in HG when compared with CG ($P = 0{,}042$).
Conclusion: CHW without gross joint damage showed a difference in postural balance when compared with non-hemophiliac children.
Contribution: The identification of early balance impairments in CWH can help us to understand better the effects of bleeds inside joints on postural control and plan a more effective rehabilitation treatment.

PO-WE-245

Successful treatment outcome for an eight-year-old hemophilic boy with chronic regional pain syndrome (CRPS)

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Background: Complex regional pain syndrome (CRPS) or reflex neurovascular dystrophy (RND) is a chronic neuropathic pain disorder with autonomic features which typically develops in an extremity after acute tissue trauma. Neuropathic pain such as burning, hyperalgesia, and allodynia may occur. CRPS may have local edema, altered sweating, skin temperature and skin color, loss of strength, decreased active range of motion, and tremor.
Case description: An 8-year-old boy with severe hemophilia B presented with a painful left ankle. Examination showed limited range of motion, allodynia, and minimal weight

bearing. Physical therapy treatment consisted of ultrasound, soft laser, active movement, kinesiotape placement, and exercises to improve weight bearing. Three weeks following his first presentation, the patient's symptoms worsened. The entire foot was edematous, the skin shiny and pale, allodynia was severe, no active movement was obtained, and there was no weight bearing. The patient refused to wear shoes and socks. He ambulated with a walker. The quality of the pain and objective findings were consistent with the diagnosis of CRPS.
Treatment: Physical therapy treatment consisted of the Reflex Neurovascular Dystrophy Philadelphia program. Treatment includes intense exercise to the area affected by the pain syndrome. It promotes increased strength, endurance and agility, reduces hypersensitivity, and helps return full functionality to the affected area. The main goal is to return to full daily activities. Each child is educated on how to progress their activities and home exercise program once discharged from the program. Exercises and activities include hopping, wheelbarrow races, steps, jumping like a frog, and hydrotherapy. Each activity must be performed faster and better than the time before.
Results: The patient's treatment lasted 6 weeks. He improved in all the activities, desensitization, and hydrotherapy. He ambulated with full weight bearing, donned socks and shoes, and returned completely to his daily activities.

PO-WE-246
Gait analysis of 20 hemophilia adolescents using the Zebris Interactive FDM-T treadmill system

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Background: The Interactive FDM-T Treadmill System from the Zebris Medical Company consists of a treadmill with over 5,000 force sensors integrated underneath the treading surface and a large screen on which a virtual running environment is depicted, for example, in the form of a path running through the forest. The runner sees his own footprints live on the screen and gains direct feedback on his movements. Obstacles then occur such as puddles that have to be jumped over or avoided. An evaluation system awards points according to how successfully this is achieved.
Participants: Twenty adolescents with hemophilia A and B with mild, moderate, or severe hemophilia.
Methods: Each participant practised the use of the treadmill. He then walked at a comfortable speed, walked at an increased speed, and walked at an increased speed with an increased incline.
Results: Walking speeds, kinetic, and kinematic outcomes were compared between the participants who were of different hemophilia severities. Weight distribution of the foot during each of the walking speeds was also compared. The results were also compared to healthy participants of the same age group. Differences of between 20–50% in weight distribution were found both between the groups of the hemophilia participants and between the hemophilia participants and healthy peers of the same age. Kinetic and kinematic differences were also found to be significant.
Conclusion: Due to the changes seen in the gait characteristics of young hemophilia patients, a different approach should be considered in treatment and education. This should include a more intense and active exercise and stretching program and possibly more properly fitting insoles and shoes.

PO-WE-247
The effect of 8-week aquatic exercise on strength, balance and gait speed in hemophilia

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Objectives: It has been reported that aquatic exercise improves deep muscle strength and prevents falls through the improvement of muscle strength and balance. In this study, 8 weeks (from August to November in 2011 in the Korea Hemophilia Foundation Clinic) of aquatic exercise was conducted for patients with hemophilia to validate the effectiveness of aquatic exercise.
Methods: We enrolled 11 patients and divided them into two groups. The aquatic exercise group was composed of 5 patients and the control group of 6 patients. The control group got regular exercise at home. The average age of patients in both groups was 40.2 years (median age: 39 years). The Pettersson score of 6 joints was 26.3 and 21.8 for aquatic exercise group and control group, respectively. The aquatic exercise consisted of 40-minute sessions, 2 or 3 sessions a week for 8 weeks. The depth and temperature of the pool was 110 cm and 31°C. We compared before and after study period muscle strength of thigh, one-legged-stance test with eyes closed, Timed Up & Go (TUG) test, 10 m gait speed, and VAS in both groups.
Results: The aquatic exercise groups showed improved results such as muscle strength (left: 11.3%, right: 8.4%), one- legged-stance time (left: 3.79 s to 4.58 s, right: 4.02 s to 6.87 s), TUG (13.11 s to 10.93 s), 10 m gait speed (13.05 s to 10.77 s), and VAS (3.2 to 2.4). However, there was no change before and after exercise in the control group.
Conclusion: The 8-week program of aquatic exercise could improve muscle strength, balance, VAS, and gait speed in patients with hemophilia. To determine more concrete protocols of aquatic exercise, it is necessary to include more patients and investigate various methods of exercise.

33-PLATELET DISORDERS

S-WE-01.1-2
Diagnosis of inherited platelet disorders
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In platelet disorders caused by a reduction in platelet number (thrombocytopenia) and/or platelet function (thrombocytopathies), bleeding occurs immediately after injury, primarily in skin, mucous membranes, nose, and gastrointestinal tracts. The diagnostic approach to a suspected inherited platelet disorder includes a careful history and physical examination of the patient as well as different laboratory investigations such as the Ivy bleeding time, platelet aggregation tests, ATP secretion, platelet adhesion by the platelet function analyzer (PFA100), and platelet morphology by electron microscopy. This review will deal with classical thrombopathies/thrombocytopenias and also will discuss the less commonly known relation between platelet research and disorders with a broader clinical phenotype, including neurological, endocrinological, and metabolic diseases. Platelets are easily accessible cells, and different techniques are possible to study platelet function under basal and activated conditions. Defects in platelet adhesion, G protein signalling and secretion can result from mutations in platelet-specific genes (leading to isolated thrombopathies) or from mutations in widely expressed genes (leading to a broader clinical phenotype including a platelet defect). Therefore, it is important to recognize how platelet research becomes an important tool to improve our knowledge in broad phenotype mendelian disorders, of which some will be discussed in further detail. Recently, novel methods in sequencing, epigenetics, proteomics, and transcriptomics, plus unprecedented large-scale cooperative efforts, led to the generation of novel insights into the complexity of inherited platelet disorders of which the pathology was known long before the responsible underlying genetic causative factor was found. Especially medical DNA sequencing is expected to give clinicians important information regarding the genetic phenotype of the inherited platelet disorder in their patients to improve early diagnosis and prognostication.

S-WE-01.1-1
The molecular basis of inherited platelet bleeding disorders: an update
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Genetic defects of platelet function and/or production give rise to muco-cutaneous bleeding of varying severity. Platelets fail to fulfil their hemostatic role after vessel injury. The most studied function disorders are deficiencies of glycoprotein (GP), mediators of adhesion (Bernard-Soulier syndrome), and aggregation (Glanzmann thrombasthenia [GT]) affecting the GPIb-IX-V complex and the integrin αIIbβ3 respectively. Leukocyte adhesion deficiency-III combines GT with infections due to abnormalities of kindlin-3, a mediator of integrin activation. Agonist-specific deficiencies in platelet aggregation and abnormalities of signalling pathways are common and are beginning to be understood. Deficiencies of primary receptors for stimuli include the ADP (P2Y12), thromboxane A2 (TXA2R), and collagen (GPVI) receptors. Inherited defects of secretion from dense granules are accompanied by pigment defects in the Hermansky-Pudlak and Chediak-Higashi syndromes and concern multiple genes and protein complexes involved in secretory organelle biogenesis. Deficiencies of α-granule biogenesis largely concern NBEAL2 defects and the grey platelet syndrome, while the Quebec syndrome is linked to a tandem duplication of the urokinase plasminogen activator (PLAU) gene. Mutations in transmembrane protein 16F (TMEM16F) cause a defective procoagulant activity and phosphatidylserine expression in the Scott syndrome. Associated anomalies of platelet production (with platelet size changes) and platelet function group the Wiskott-Aldrich syndrome with small platelets and a wide spectrum of macrothrombocytopenias, including the MYH9-related diseases, filamin A deficiency, or GATA-1 defects. Mutations of ANKRD26 result in thrombocytopenia without macrocytosis. This presentation will illustrate the above with selected examples of recent advances in understanding their genetic basis and diagnosis, with emphasis on next-generation technology.

S-WE-01.1-3
Treatment of inherited platelet disorders
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Treatment modalities for patients with inherited platelet disorders can be derived from the substantial experience gained in treating patients affected by Glanzmann thrombasthenia. Therapy is needed for arresting spontaneous bleeding episodes and securing hemostasis during surgery or trauma. Bleeding episodes that are frequently difficult to manage include epistaxis, menorrhagia, primary and secondary post-partum hemorrhage, and gastrointestinal bleeding. Preventive measures are essential for minimizing morbidity, e.g., regular dental care, iron therapy when iron stores are depleted, the avoidance of non-steroidal anti-inflammatory drugs, vaccination against hepatitis B and A, and non-participation in contact sports. Treatment modalities include (1) topical measures such as fibrin sealants, plastic splints for dental extractions, compression and packing for epistaxis; (2) antifibrinolytic agents (tranexamic acid or epsilon aminocaproic acid) that are useful in cases of menorrhagia and mucosal bleeding and as adjuncts of other modes of therapy; (3) female hormones, such as continuous oral contraceptives, depot medroxyprogesterone acetate, levonogestrel-releasing intrauterine devices for menorrhagia; (4) platelet transfusion (This modality should be used only if deemed essential or when other modalities have failed. Platelets should be leukocyte depleted, or HLA-matched and ABO-matched; single platelet donors are preferable); and (5) recombinant (r) factor VIIa that was shown to induce thrombin generation independently from tissue factor and augment platelet adhesion and aggregation. R-factor VIIa in repeated doses of 90 μg kg^{-1} can be given during major surgery or excessive post-partum bleeding, and should be given when patients are refractory to platelet transfusion or have developed antibodies against glycoprotein (GP) αIIbβ3 or GPIbα.

PO-WE-252
The oxidative stress and antioxidant status at children with immune thrombocytopenic purpura: Endothelial nitric oxide synthase Glu298Asp gene polymorphism
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Aim: Pathogenesis of idiopathic thrombocytopenic purpura (ITP) include autoimmune mechanisms resulting in cellular damage with formation of hydrogen peroxide, which is an oxidant yield. Oxidative stress and free radicals could be responsible in the pathogenesis of ITP. High doses of nitric oxide result in the formation of toxic molecule peroxynitrite in the presence of cellular superoxide anion. Peroxynitrite may cause cellular injury with lipid peroxidation, DNA fragmentation, and depletion of plasma antioxidants. Polymorphism of endothelial nitric oxide synthase (eNOS) gene, which supplies nitric oxide synthesis, changes the functions of this enzyme. This study investigated the role of eNOS Glu298Asp gene polymorphism in etiopathogenesis, course and treatment of ITP.
Material and Methods: Sixty-six patients including 51 acute and 15 chronic ITP and 60 healthy controls were enrolled in the study.
Results: In all patients with ITP and in the groups with acute, chronic ITP and healthy group, the frequency of GG genotype was found as 40.9%, 39.2%, 46.7% and 21.7%, respectively. The frequency of GT genotype was 48.5%, 51%, 40%, 70% and TT genotype were 10.6%, 9.8%, 13.3% and 8.3%. Most common genotype in all patients with ITP, acute ITP group, and control group was GT genotype, while GG genotype was found predominantly in patients with chronic ITP. Most common allele in all patients with ITP, acute ITP group, and control group was G allele.
Conclusions: A significant correlation was found between ITP and eNOS Glu298Asp gene polymorphism. eNOS Glu298Asp gene polymorphism might be a risk factor in the etiopathogenesis of ITP. Patients with GG genotype were thought to have a high intention for having a chronic disease. Patients with acute, chronic ITP and GG genotype, responded effectively to medical treatment with IVIG therapy mainly. Presence of G allele was observed to have a positive effect and T allele to have a negative effect in the medical treatment of patients with chronic ITP.

PO-WE-253
Normal platelet parameters in childhood period from newborns to adolescents
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Aim: There are few studies on normal values of platelet parameters as mean platelet volume (MPV), plateletcrit (PCT), and platelet distribution width (PDW) in children.
Material and Methods: The aim of this study is to determine the normal values of these platelet parameters in healthy Eastern Turkish children. This study occured in Healthy Child Clinic of University Hospital on a total of 1005 children, between 0 to 14 years old, who have normal growth and developmental features. Their blood samples were collected by venipuncture of the arm. Platelet values determined in an automatic counter (Advia 120, Japan) were used in the statistical analysis to calculate the mean and standard deviation. To determine the differentiations between age groups one way, Anova was used and $P < 0.05$ was accepted as significant.
Results: Platelet count and PCT values are decreased in the neonatal period. These values are increased slightly in the infantile period and are decreased again in the adolescent period. For MPV extremely low values are in the neonatal period, and after, these values increase from the infantile to the adolescent period. However PDW values are apparently increased in the neonatal period and then keep to a constant interval.
Conclusions: The values of platelet indices obtained in this study were similar to different reports and may be used as referential values in pediatric patients with clinical problems related to these cells.

PO-WE-262
Five-year treatment report of hospitalized children with Glanzmann's thrombasthenia in a comprehensive hemophilia care centre (2006–2011)
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Objective: In this retrospective study we report on 5 years of experience (from 2006 to 2011) of a defined step-by-step treatment protocol for bleedings in admitted children with Glanzmann's thrombasthenia (GT) due to sever bleedings or elective surgery in a comprehensive care centre in Iran, a developing country.
Method: Patients, in addition to antifibrinolytics and local hemostatic agents, were treated at first step with Platelet Concentrates (PC) in order of availability: Apheresis derived (ADPC), Leukoreduced pooled (L.R.P.P.C) and Non-Leukoreduced random donor PCs (RDPC) respectively. Recombinant-activated factor VII (rFVIIa) was used as the next step according to the severity of bleeding and response to the first step. The main variables we were looking for included age, type of bleedings, number and types of used

PCs, usage amount of rFVIIa, rate of response of bleedings and patients to PCs, rFVIIa, or both, and the cause of treatment decision (including availability of products, responsiveness, and severity of bleeding). Finally, we defined some indices for treatment requirements.
Results: In all, 15 cases of children were admitted with GT (mean age of 3.5 years) for 52 bleeding events (79%) or elective surgeries (21%). Total amount of used $rFVIII_a$ was 137 mg and infused PCs were 68 units, among them 35, 29, and 4 units were ADPC, LRPPC, and RDPCs, respectively. Four patients (29%) received only PC and 50% of bleedings were controlled only with PCs. Two out of 11 patients (18%) who received rFVIIa were non-responder to PCs. Two cases (18%) did not respond to rFVIIa. Leukoreduced PCs (LRPC) were available in 84% of bleedings when needed. Mean admission per Patients, Mean LRPC units per patients and Mean $rFVII_a$(mg) per patients were 3.46, 4.26,and 9.13 mg respectively.
Conclusion: Availability of ADPC and LRPPC in the meantime of preventing alloimmunization leads to control of most of the bleeding events and save cost in children with GT.

PO-WE-254
Successful management of central venous line associated thrombosis in a child with Glanzmann's Thrombasthenia
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Glanzmann's Thrombasthenia (GT) is a severe bleeding disorder characterized by mucocutaneous bleeding due to a quantitative or qualitative defect of the platelet αIIbβ3 integrin resulting in abnormal platelet aggregation. We present the case of an 11-year-old girl, diagnosed with severe phenotype GT, who developed a thrombosis associated with a peripherally inserted central catheter (PICC). Thrombosis is a very rare complication of severe bleeding disorders and management guidance is limited to case reports. To our knowledge, this has not previously been reported in the pediatric population. Our patient was admitted for management of severe epistaxis, unresponsive to local measures. This was managed with tranexamic acid, HLA-matched platelets and recombinant factor VIIa. A PICC was inserted to facilitate administration of these products in view of difficult venous access. One month following insertion of the PICC, swelling and pain of the left arm was noted. Doppler ultrasonography demonstrated an occlusive thrombus in the brachial vein adjacent to the PICC. Apart from regular oral tranexamic acid to control menorrhagia, she had not received any hemostatic agents in the previous 4 weeks. The PICC was removed and she was commenced on 100 U kg^{-1} dalteparin twice daily. Other than bruising at the site of the dalteparin injections no new bleeding occurred. The anti-Xa level was maintained at the lower end of the recommended range (0.5–1.0 U mL^{-1}) for 4 weeks. At this stage a repeat Doppler ultrasound showed that the thrombus had completely resolved and in view of her bleeding risk, dalteparin was discontinued. As this thrombosis fully resolved and there has been no evidence of further thrombus generation, we propose that a short course of therapeutic anticoagulation is appropriate in this situation.

PO-WE-255
Hemarthrosis an unusual presentation of Glanzmann's Thrombasthenia
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Glanzmann's thrombasthenia (GT) is an extremely rare autosomal recessive coagulopathy disease. It characterized by significant prolonged bleeding time and normal platelet count. The cause of disease is the quantitative or qualitative defect of the platelet glycoprotein IIb–IIIa. As a result, the aggregation processes via fibrinogen bridging of platelets to other platelets cannot occur properly. The disease characteristically presents as mucosal bleeding such as epistaxis, gum, dental extraction bleeding, menorrhagia, and increased bleeding post-operatively. Hemarthrosis usually associated with abnormalities of the plasma coagulation factors such as classic hemophilia.
Purpose: The present study aims to present the hemarthrosis and other clinical manifestations of 53 patients with GT from southwest Iran.
Materials and Methods: The diagnosis was made in 53 (27 male, 26 female) patients in the range of one to 50 years old in the presence of a normal platelet count, prolonged bleeding time (BT), decreased or absent clot retraction, and absent platelet aggregation to ADP, epinephrine, collagen, and thrombin. A comprehensive evaluation such as clinical manifestations and demographic data were recorded. This is a descriptive cross-sectional study that was conducted at Ahvaz Jundishapur University of Medical Sciences in Khuzestan province. Data were collected by a questionnaire form. Statistical analysis was done by using Statistical Package for the Social Sciences version 17.
Results: Hemarthrosis was the first presenting symptom among 9 cases (17%). Three patients had recurrent hemarthrosis, hemophilic-like arthropathy. Target joint in two patients was the knee (one patient with both knees involved) and the elbow was the occurrence of another chronic arthropathy. The former patients were women and the latter was man. The other first usual clinical manifestations of this disorder among the 53 patients were as follows: gum and dental manipulation bleeding in 16 patients (30.2%), bleeding after circumcision surgery in three patients (5.7%), epistaxis in 19 patients (35.8%), and menorrhagia in 6 patients (11.3%).
Conclusion: Hemarthrosis is distinctly unusual presentation in GT. The review of literature is noted only a few GT patients with hemarthrosis. Some occurred after major trauma, but our patients had hemarthrosis after minor trauma and three of patients had repeated hemarthrosis. The optimal treatment of patients was done by single-donor platelet transfusion and/or recombinant factor VIIa (Novo Seven). This brief report may have some clinical points for the clinicians and health sector providers.
Acknowledgement: The author gratefully thanks the Novo Nordisk company for the supporting the patients diagnosis and registration.

PO-WE-256
The efficacy of rituximab for pediatric refractory chronic Immune thrombocytopenia (ITP) in Korea
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Background: Some children with chronic immune thrombocytopenia (ITP) do not respond to the conventional treatments such as intravenous immunoglobulin, corticosteroid, anti-D immunoglobulin, and splenectomy. Rituximab, monoclonal anti-CD20 antibody, demonstrates promising effect on adult refractory chronic ITP. However, there are little data and some limitation in use for children under Korean National Health Insurance coverage system. The authors try to evaluate the efficacy of rituximab for children with refractory chronic ITP in Korea.
Methods: A retrospective study was performed for 21 children with chronic ITP by reviewing questionnaires and medical records. Complete response was considered if the platelet count is over 150,000 uL^{-1} and is maintained on this level.
Results: Twelve female and nine male children received rituximab treatment 23 times for refractory or relapsed chronic ITP. Median age was 4.3 years (range, 0.1 ~ 15.6) and median platelet count at baseline was 8,000 uL^{-1} (range, 1,000~46,000). Three patients were lost to follow-up and one has too short a time period to evaluate the response. Finally, seventeen children with chronic ITP including one Evans syndrome were evaluated. Median follow-up duration was 2.8 years (range, 0.7–7.5). Complete response was obtained in 5 of 17 children (29.4%). Time to complete response from the start of rituximab was 3.9, 4.7, 5.7, 6.0, and 9.7 weeks, respectively. Among 5 children, two are in remission for 4.0 and 4.6 years and three children relapsed after 21.4, 26.4, and 34.9 weeks of follow-up. One interesting finding was that two relapsed children were retreated with rituximab and achieved complete response again. There were no severe adverse events to discontinue the rituximab.
Conclusions: Rituximab is a useful and tolerable treatment for children with refractory chronic ITP. Also, rituximab can be a therapeutic alternative for delaying or saving splenectomy in childhood chronic ITP who may have the chance of spontaneous remission.

PO-WE-257
Prospective evaluation of a diagnostic algorithm identifies the spectrum of defects in primary hemostasis in a tertiary-care pediatric centre
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The diagnosis of defects of primary hemostasis presents many challenges. A diagnostic algorithm has recently been published by Israels et al. (*Pediatr Blood Cancer* 2011;56:975) for platelet function disorders, and also includes von Willebrand disease (VWD). The algorithm begins with clinical evaluation (including the determination of a bleeding score) and laboratory testing that is generally available, proceeding to specialized testing for specific diagnoses. In this study, we are prospectively evaluating the usefulness of this algorithm as a standardized approach in the identification of patients with defects in primary hemostasis. Any child referred to our tertiary-care pediatric bleeding disorders clinic with mucocutaneous bleeding and/or a family history of platelet dysfunction or VWD is eligible for the study. To date we have enrolled 48 children with a median age of 8.1 years (range: 0.5–17.8 years); the median PBQ (Pediatric Bleeding Questionnaire; Bowman et al., J Thromb Haemost 2009;7:1418) score of these children is 3 (range: 0–8; normal score <2). Twenty children have completed laboratory evaluations of VWF and platelet function (aggregation testing) as required according to the algorithm. Their median age is 10.3 years (range: 2.9–17.3), and median PBQ score, 3 (range: 0–8). Four children had a normal PBQ score (either 0 or 1) and normal laboratory results. The other 16 children had an abnormal PBQ score, 8 having normal laboratory results (median PBQ score: 4 [range: 2–8]), and 8 having abnormal laboratory results leading to a diagnosis of VWD (n=4; median PBQ score: 3.5 [range: 2–8]) or a platelet function disorder (n = 4; median PBQ score: 5.5 [range: 3–7]). Thus, no child who was diagnosed with VWD or platelet dysfunction had a normal PBQ score. Interestingly, 1 of the children with a normal PBQ score had a slightly elevated INR and was determined to be heterozygous for FVII deficiency. This prospective study of a published diagnostic algorithm for platelet disorders is allowing us to work-up children referred to a tertiary-care bleeding disorders clinic with mucocutaneous bleeding and/or a family history of platelet dysfunction or VWD in a standardized fashion to recognize the incidence and spectrum of disorders of primary hemostasis in these children.

PO-WE-258
Identification of five new mutations in nine Glanzmann's Thrombasthenia patients
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The glycoprotein (GP) IIb/IIIa is a calcium-dependent, non-covalently associated heterodimer on the platelet surface, binding fibrinogen. The GPIIb/IIIa is expressed exclusively on platelets and is the most abundant integrin on the surface of platelets. Patients with Glanzmann's thrombasthenia (GT) show a diminished, total lack, or dysfunction of GPIIb/IIIa often suffer from severe bleeding complications. Platelet expression of GPIIb/IIIa was performed by flow cytometry using mAbs (fibrinogen binding: PAC-1 binding). Platelet function was analyzed using agonist induced platelet aggregation (ADP, collagen, ristocetin). Molecular analysis of genomic DNA, respectively the exons of the GPIIb- and GPIIIa-genes, was performed using polymerase chain reaction and a cycle

sequencing system. Patient G.E. is suffering from GT type I. Agonist induced platelet aggregation in response to ADP or collagen and PAC-1 binding after platelet activation was not inducible. Flow cytometric analysis revealed a lack of GPIIb/IIIa (<2%) on the platelets' surface. Molecular analysis of the GPIIb- and GPIIIa-genes unveiled two heterozygous missense mutations, both in the GPIIb-subunit: exon 2: p.71 Pro>Arg and exon 22: p.684 Leu>Arg. A family analysis was performed subsequently. Further, in two siblings (both compound heterozygous) suffering from GT type I we could detect one new missense mutation (p.76 Pro>Ala; GPIIb exon 4) and one formerly described splicing site mutation (c.3092 + 2 T>C) in exon 29 of the GPIIb subunit. In two other individuals we could identify two new homozygous missense mutations p.42 Cys>Trp (GPIIIa exon1) and p.314 Asp>Ala (GPIIIa exon 7). In conclusion, our investigation of several patients, and in two cases including first degree relatives, revealed a number of different mutations within the α_{IIb} and β_3 subunits associated with causing GT. This vast number of different mutations indicates the genetic heterogeneity in the studied group, respectively in GT.

PO-WE-259

Re-evaluation of the defect in platelet calpain in Montreal Platelet Syndrome patients with type 2B von Willebrand disease

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In the mid-to-late 1900s, the Montreal Platelet Syndrome (MPS) was described as a rare platelet disorder inherited in an autosomal dominant fashion and characterized by mucocutaneous bleeding, macrothrombocytopenia with spontaneous platelet clumping, abnormal platelet shape change upon stimulation, and a defect in platelet μ-calpain. In a re-evaluation of the MPS kindred, it was recently determined that MPS patients have type 2B von Willebrand disease (VWD) with the V1316M mutation in the von Willebrand factor (*VWF*) gene (Jackson et al., *Blood* 2009;113:3348). As a platelet calpain defect has not previously been reported in type 2B VWD, we re-examined the content of this Ca^{2+}-dependent cysteine protease in platelets of 2 of the originally-described 'MPS' patients. Washed platelets were isolated from blood samples of the 2 patients (P1, P2) and a family member shown not to have 'MPS'/type 2B VWD (control). Platelet lysates were prepared in the presence of protease inhibitors, and Western blotting was performed using a monoclonal antibody to the 80 kD catalytic subunit of μ-calpain. Calpain was detected in all samples, with no lower molecular weight autoproteolytic products in evidence. Films were subjected to densitometry, and results are expressed as the mean ± SEM (n = 6) of the ratio of calpain:actin (internal control) band density. No difference in calpain content in the patients vs. control was observed (P = 0.32, 1-way ANOVA). Thus, we were unable to detect a calpain defect in platelets from patients with 'MPS'/type 2B VWD with the V1316M *VWF* mutation.

PO-WE-260

Neurosurgery in a patient with Bernard-Soulier Syndrome

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We report here the case of a 68-year-old woman with Bernard-Soulier Syndrome (BSS) who underwent two neurosurgical operations. To the best of our knowledge, this is the first report of neurosurgery in a patient with this condition. The patient is part of a large kindred with multiple family members affected by BSS. She was herself diagnosed with the syndrome based on characteristic blood counts, platelet morphology, and platelet function testing by lumiaggregometry. She does not experience spontaneous bleeding, but does bleed excessively with challenge if not pre-treated with hemostatic agents. In October of 2010 the patient presented to an ophthalmologist in our hospital complaining of transient monocular visual loss of her right eye. Opthalmologic evaluation revealed a unilateral elevated swollen optic nerve in the right eye. This was further evaluated with MRI of the brain that showed a 4 cm cerebello-pontine angle meningioma. On January 10, 2011, she underwent craniotomy for dissection of the tumour. Approximately 30 min pre-operatively the patient received a transfusion of one adult dose of apheresis platelets and an infusion of tranexamic acid was begun. Intra-operatively, a small amount of excess bleeding was encountered, and the patient received additional therapy with 2 U of packed red blood cells, 1 adult dose of cryoprecipitate, one adult dose of frozen plasma, and an additional unit of apheresis platelets. On the morning prior to surgery her platelet count was $49 \times 109\ L^{-1}$, which is close to her baseline. Following the surgery she had a platelet count of $62 \times 109\ L^{-1}$ and hemoglobin 110 g L^{-1}. Post-operatively she was continued on tranexamic acid 1 g IV every 8 h. Post-operative MRI revealed no evidence of intra-cranial bleeding and no further transfusion was required. She did, however, continue to experience blurred vision believed to be due to obstructive hydrocephalus and required repeat operation for placement of a ventriculoperitoneal shunt. This second surgery was done on January 26, 2011. Pre-operatively, she had a platelet count of $59 \times 109\ L^{-1}$ and was transfused one unit of apheresis platelets and post-operatively she was again treated with tranexamic acid. No excess bleeding was encountered, and the patient was discharged home in stable condition shortly after the surgery. Platelet antibody testing was undertaken in May 2011 and revealed no evidence of allo-immunization to platelet glycoproteins. This case highlights several of the salient features of managing patients with BSS in the peri-operative period. Patients with BSS are at risk of allo-immunization to GP-1b when they receive platelet transfusions. Consequently, transfusion therapy should be reserved only for life-threatening bleeding or procedures with very high bleeding risks. Though craniotomy for tumour is not a high-risk surgery with respect to bleeding, any excessive bleeding in the operative field can seriously compromise the patient's outcome. Consequently we elected to transfuse platelets pre-operatively. Tranexamic acid therapy was added to further minimize bleeding and avoid the need for additional transfusion. Given that this is the first reported case of neurosurgery in a patient with BSS, we would recommend use of the described hemostatic therapy for other similar cases.

PO-WE-261

Predictive score for the diagnosis of inherited platelet dysfunction

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Introduction: Von Willebrand disease (VWD) and inherited platelet dysfunction (IPD) are common inherited bleeding disorders. They both can have similar presentation and initial laboratory results of normal platelet count and coagulogram, and either prolonged or normal bleeding time (BT). Therefore, specific investigations of VWD study and platelet function test (PFT) are required. Because PFT is time consuming and costly, the test should be performed in suspected patients.

Objective: To determine the predictive factors of IPD in patients presented with symptoms of mild bleeding disorder.

Materials and methods: This retrospective study enrolled patients aged <18 years who presented with mild bleeding disorder. Patients were divided into two groups according to the diagnosis IPD and non-IPD (such as VWD) groups. We excluded patients with platelet count <150,000 μL^{-1} and PFT defect to adrenalin, which can be found in 50% of healthy volunteers. The 22 items of bleeding history, 3 items of physical examination, and 4 items of initial investigation were collected. For any incomplete data, patients will receive telephone contact or appointment to come to the clinic.

Results: Of the total of 87 patients, 23 were IPD and 64 were non-IPD. The early age of onset (<3 years), history of ecchymosis, petechiae, positive tourniquet test, and prolonged BT were significantly different between the two groups. After multivariate logistic regression analysis was performed, 3 parameters of onset age <3 years, petechial hemorrhage and BT >15 min were selected for further identification of predictive score. The calculated predictive score was 1(age <3 years) + 1(BT >15 min) + 3(petechial hemorrhage). The cutoff score ≥2 had specificity of 95% and sensitivity of 39% for the diagnosis of IPD.

Conclusion: Any patient who has mild bleeding disorder and predictive score ≥2 is suggestive of IPD. Therefore, PFT should be included in the earlier step of investigation.

34-PRENATAL DIAGNOSIS

PO-TU-178
Evolution of management of pregnancies at-risk for hemophilia in France this last ten years: Impact of non-invasive fetal sex determination
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Management of pregnancies at-risk for hemophilia was traditionally based on ultrasound and/or invasive prenatal diagnosis (PND). PND was generally offered to families with severe hemophilia, and mainly based on chorionic villus sampling (CVS) for fetal karyotype to determine sex, and if the foetus was male to seek for familial mutation. Alternatively, a less invasive amniocentesis was proposed in cases of *de novo* mutation, as the risk of recurrence is low (mosaic and/or germinal mosaicism). Overall, fetal sex determination is a key point to manage and guide the offer of invasive testing in pregnancies with a male fetus. Non-invasive prenatal diagnosis (NIPD) for fetal sex determination on maternal blood has been introduced in France in 2001; the first year, PND for hemophilia was reduced by 25% to reach the expected 50% (male-gender pregnancies only) in 2005. This approach is now well established in a routine diagnostic setting in France and the assay reimbursed by the social security health insurance. Data available from the 'Agence de la Biomédecine' show that most pregnant carriers benefit from this approach; 40% of them choose for PND of which only 50% of women with affected fetuses asked for termination of pregnancy (compared to the nearly 100% for Duchenne muscular dystrophy). This attitude is probably related to the newly positive perception of management of hemophilia. The next step is moving towards complete NIPD of hemophilia itself, which is the major challenge. Clinical studies are currently in progress in France to evaluate new strategies for the management of pregnant women with *de novo* hemophiliacs, based on maternal blood examination. While it remains difficult to detect fetal alleles that are inherited from carrier mothers, new technologies have been recently described, giving opportunity in the near future to extend NIPD of hemophilia.

PO-TU-179
Prenatal diagnosis of hemophilia in Sweden: A ten-year follow-up
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Objective: Previous Swedish studies have shown that carriers of hemophilia experience psychological difficulties when undergoing prenatal diagnosis (PND). The aim of this study was to gain more knowledge on how Swedish carriers perceive the procedure in order to improve PND in the future.
Study group: Women who underwent PND of hemophilia in Malmö, either by amniocentesis or chorionic villus sampling, during 1997–2008. Seventeen women were identified, comprising >95% of the total in Sweden at that time, and all agreed to participate in the study.
Method: Semi-structured personal interviews were used.
Results: Twenty-eight PNDs were performed on 17 women, and in ten of these, the fetuses had hemophilia. Of these, 5/10 were terminated and the remaining 5 led to birth of a boy with hemophilia. Of those terminating their pregnancy due to hemophilia, 3/5 felt that the months following were difficult, and one regretted the decision; 2/5 later gave birth to a boy with hemophilia. For 11/17, being a carrier had a negative effect on the decision to become pregnant, and in 11 cases, PND had influenced their decision to conceive. Ten of the 17 chose PND in order to terminate the pregnancy if the fetus had hemophilia, 4/17 to prepare themselves psychologically for having a boy with hemophilia, and 3/17 mainly to find chromosomal abnormalities. Prior to the PND, 13/17 received genetic counselling, and 7/13 felt that the information fully corresponded to what they later experienced. The PND procedure was unexpectedly distressing for 11/17 and 8/17 described it as physically very painful.
Conclusions and contribution: A fourth of the women chose PND to prepare themselves psychologically, and not to terminate the pregnancy. The women accepted PND rather well, but care can be further improved by better information before the procedure. Women who decide to terminate a pregnancy following PND should be offered psychological support.

PO-TU-180
Prenatal diagnosis of hemophilia in Serbia: Evolution from phenotypic to molecular methods
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Introduction: Prenatal diagnosis is possible by coagulation testing on blood samples after cordocentesis in the second trimester of pregnancy. The most reliable method for prenatal diagnosis is genotype assessment, detection of the mutation, or informative genetic markers on a chorionic villi sample obtained in the 11th–12th week of pregnancy.
Objective: To present results of prenatal diagnosis in our Centre and evolution from coagulation to molecular methods.
Methods: Since 1988, a total of 63 pregnant carriers of hemophilia (60 HA, 3 HB) were referred to our Centre for prenatal diagnosis in 81 pregnancies (77 HA, 4 HB). Coagulation phenotype was based on factor VIII/IX assay. DNA analysis included examination of restriction fragment length polymorphisms (RFLPs) in factor VIII (BclI) and IX (XmnI, TaqI and HhaI) and mutation detection.
Results: Coagulation prenatal investigation was initiated in 53 carriers (HA 50, HB 3) in 67 pregnancies (HA 63, HB 4). Female gender was detected by ultrasound in 16 fetuses and investigation was discontinued. One woman had a miscarriage soon after unsuccessful cordocentesis. Coagulation testing was performed in 50 fetuses (45 male, 5 unidentified gender). Forty per cent were fetuses with hemophilia (20/50), while 60% were unaffected (30/50). Ninety per cent (18/20) of women diagnosed as having a hemophiliac fetus decided to have a therapeutic abortion, while 10% (2/20) went on with pregnancy. Molecular prenatal diagnosis was performed in 10 HA carriers in 14 pregnancies. Eight fetuses were female, and prenatal diagnosis was performed in 6 male fetuses. Five of 6 male fetuses were hemophilic, and those pregnancies were terminated.
Conclusion: At present, molecular prenatal diagnosis is commonly used in Serbia, as it greatly improves the assessment of carrier status and prenatal diagnosis for hemophilia. Coagulation tests are applied for prenatal diagnosis in the second pregnancy trimester or to avoid risk of invasive procedures in female fetuses.

PO-TU-181
Reproductive choices in pregnant carriers of hemophilia
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Background: Genetic counselling of pregnant hemophilia carriers includes discussion on two reproductive options: 1) accept the risk, 2) perform prenatal diagnosis (PD). With improved standards of hemophilia treatment in the western world, performing PD might have become less appealing. Studies on the status quo of reproductive choices in pregnant carriers of hemophilia should be undertaken as a first step towards determining the validity of this assumption.
Objective and Methods: A retrospective cohort study on reproductive choices in pregnant carriers of hemophilia was performed at the Academic Medical Center-Hemophilia Treatment Center (AMC-HTC). Reproductive choices were retrieved from the AMC-HTC genetic counselling database for all pregnant hemophilia carriers between 2005 and 2012. In order to evaluate the reproductive choices in a current generation of hemophilia carriers, percentages of PD versus non-PD cases were calculated for pregnant carriers of severe and non-severe hemophilia.
Results: Between 2005 and 2012, 56 pregnancies in 44 unique hemophilia carriers were observed. In 30% of the pregnancies, the couple opted for PD. Of the 17 pregnancies with PD, 15 mothers-to-be proved carriers of severe hemophilia (88%). In carriers of severe hemophilia, PD was performed in 75% of all pregnancies. The results of PD's showed that 7 fetuses were female and 10 male, of which 4 were affected. In 3 cases, pregnancy was terminated.
Conclusion: The result of this study showed that although treatment options are improved, PD is still a favored choice in the group of carriers of severe hemophilia.

35-PROPHYLAXIS

PL-TU-02.2
Personalized prophylaxis
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Prophylaxis is the recommended treatment for people with severe hemophilia. It is unlikely that a single prophylactic regimen, for example based on weight, would be optimal for all patients and, therefore, each individual should have a personalized regimen, agreed between themselves and their hemophilia centre. This regimen should take into account the individual's bleeding pattern, the condition of their musculoskeletal system, level and timing of physical activity, and measurement of coagulation factor in their blood. It is important to recognize that prophylactic regimens are likely to need to change with time as the circumstances of an individual changes. For example, activity may change with age or with the season and an individual's factor VIII pharmacokinetics varies with age. Knowledge of a patient's pharmacokinetics is likely to help personalize prophylaxis when combined with other information. Factor VIII pharmacokinetics are simple to measure in routine clinical practice and can be adequately calculated from 2–3 blood samples combined with a simple-to-use and free-to-download computer program. Prophylaxis is expensive and, in countries with a limited healthcare budget, ways to improve its cost effectiveness need to be considered to allow increased access to this treatment. For example, increasing the frequency of prophylaxis can dramatically reduce the amount of treatment required to sustain measureable factor levels and hence reduce cost. The introduction of longer-acting coagulation factors may necessitate a change in concepts about prophylaxis because, while these agents may sustain an apparently adequate trough level with fewer infusions, the length of time a person spends at a low level will be increased, and this could increase the risk of bleeding, especially at the time of increased physical activity. There is convincing evidence that prophylaxis is the optimal therapy for severe hemophilia; optimizing treatment for each individual and increasing access are important goals for the future.

S-TU-03.1-1
History of prophylaxis
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Studies conducted in Sweden by Ramgren and Ahlberg during the 1960s showed that persons with hemophilia (PWH) with FVIII or IX levels above 1% of normal rarely developed severe disabling arthropathy. They hypothesized that it was logical to increase the level of factor activity in severe hemophilia to at least 1% by continuous prophylaxis. Several attempts at prevention of bleeding with prophylaxis were documented during the late 1960s and the 1970s, both in Europe and North America. Most studies were of short duration in small cohorts and used bleeding frequency as the outcome measure, but their designs were, in some cases, of high quality. The results indicated that prophylaxis was superior to treatment on demand and that frequent dosing was superior to dosing at longer intervals. The first and largest long-term joint outcome study was published in 1992 by Nilsson and colleagues. In this 25–year follow-up of 60 patients, it was concluded that starting prophylaxis early and preventing the factor level from falling below 1% could virtually prevent joint disease and allow patients to lead normal lives. The results were confirmed by Aledort et al. in 1994 in a large international study of joint outcome. Focus during recent decades has been on more cost-effective dosing regimens, the tailoring of prophylaxis, the improvement of outcome measures, compliance, and quality of life. International collaborations have been implemented addressing these issues. The well-designed study by Manco-Johnson and colleagues published in 2007 finally convinced most treaters that prophylaxis is the choice of treatment in severe hemophilia.

S-TU-03.1-3
Economic justifications for prophylaxis
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Introduction: Prophylaxis with clotting factor is considered to be the clinical treatment of choice, but it is costly to provide. Information on cost effectiveness is generated by performing economic evaluations, where the costs and benefits of health technologies are compared. However, health economics as a discipline is not solely about efficiency: it is concerned with the allocation of resources. Indeed, economic evaluation should be viewed as a component of the broader concept of health technology assessment (HTA).
Aims: To suggest where uncertainties in the cost-effectiveness literature exist; to suggest improvements to it; and to debate issues of equity regarding the provision of prophylaxis, using a recently recommended framework.
Methods: A literature review, and use of the 2011 Culyer framework to identify areas of equity that are particularly pertinent to hemophilia and the provision of prophylaxis.
Results: The results suggest that results differ mainly because of different definitions of prophylaxis, clotting factor price, discount rates, choice of outcome measures, and time horizon. Domains on the equity framework that are particularly relevant to hemophilia include 'implicit stereotyping,' 'special circumstances,' and 'cumulative effects.'
Discussion: The existing evidence based on the cost effectiveness of prophylaxis is of variable quality and is inconsistent in terms of reported cost-effectiveness ratios. The availability of lower clotting prices; lower rates at which future health outcomes are discounted; and consideration of broader health benefits, such as those that relate to carers, would significantly improve cost-effectiveness estimates. A more systematic approach to considering equity would also help to provide stronger economic arguments for prophylaxis.

FP-TU-04.3-3
Modelling life-long hemophilia treatment: Dose and discontinuation
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Introduction: To compare outcomes of different treatment strategies for severe hemophilia, a computer simulation model was developed based on individual patient data (Fischer et al., *Haematologica* 2011). This model suggested that some adult patients may discontinue prophylaxis, but criteria for optimal switching between treatments were not studied.
Aim: To determine the optimal strategy for continuing on-demand treatment (OD) and restarting prophylaxis (PR) in those who discontinued prophylaxis in adulthood, and explore the effects of prophylactic dosing.
Methods: Using a formal expert elicitation procedure, 18 experts provided information on 1) natural bleeding frequency according to age and onset of bleeding, 2) treatment of bleeds, 3) time needed to control bleeding after starting PR (effectiveness) according to bleeding frequency, 4) PR dose needed according to onset of bleeding, and 5) life-expectancy. For each parameter experts provided their quantitative estimates (median, P10, P90). The model was expanded to include the combined expert estimates. Switching criteria were determined such that the % of patients with a life-time Pettersson score <15 was maximized while minimizing the clotting factor consumption.
Results: Bleeding frequencies for patients treated OD with an average onset of joint bleeding (1.7 years) were estimated at 11 joint bleeds/year (3–29) for patients ≤ 18, and 13 (1–56) for adult patients. The model suggested that a mean dose of 2000 IU kg^{-1} yr^{-1} provided the most cost-effective PR regimen. After having received early PR during childhood on this dose, adult patients with ≤ 1 joint bleed in the last 2 years can switch to OD treatment. The models' criteria for restarting PR are: suffering ≥8 joint bleeds in any year, ≥6 in 2 years, or ≥4 in 3 consecutive years of OD treatment.
Conclusion: Computer models can support designing prophylactic regimens by determining optimal criteria for switching between prophylaxis and on demand treatment.

FP-MO-04.4-3
Adherence to prophylaxis in the Netherlands: A multicentre study
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Objectives: To assess adherence, reasons for, and frequency of deviation from prescribed treatment in hemophilia patients on prophylaxis by self-infusion.
Methods: In 3 Dutch treatment centres, semi-structured interviews were embedded in the regular nursing consultation, including questions concerning timing of infusion, deviation, forgetfulness, and knowledge. Hemophilia patients on prophylaxis using home treatment for minimally 1 year were eligible. Full adherence was defined as a minimum of 90% adherence rate; i.e., no deviation from the prescribed schedule and skipping prophylactic infusion no more than once per month.
Results: In total, until now 197 patients were included (46% of the total population on prophylaxis; Utrecht N = 133, Amsterdam N = 51, and Rotterdam N = 13). The median age was 14.3 years (range 2.3–77.5), with 88% hemophilia A, 9% B, and 3% other bleeding disorders. Most patients (96%) had severe hemophilia. Of all respondents, 60% (n = 118) were ranked as fully adherent. Ninety-four per cent knew that they had to infuse in the morning as advised. However, only 53% did infuse in the morning (med: at 8:00 h). Only 4.3% of patients changed the prophylactic dose on their own initiative. Seventy-two per cent of all patients never forgot their prophylaxis or skipped an infusion. Parents who infused their child deviated significantly less than patients who infused themselves (fully adherent: 69% vs. 55%, P = 0.02). The main reported reasons for deviation from prescribed prophylaxis were difficulties in combining prophylaxis with daily routines (34%), the absence of symptoms (23%), or the absence of a fixed routine (14%).
Conclusion: In this study, only 60% of all patients were full adherent, which is comparable to other chronic diseases. Deviations are mainly in timing of infusion, instead of skipping infusions.
Contribution to the practice: Quantification of adherence to prophylaxis provides a first step towards the design of interventions to promote adherence.

FP-MO-04.4-4
Prophylaxis versus on-demand therapy through economic report (POTTER) study: Preliminary data from the final five-year analysis
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Introduction: Prophylaxis is the evidence-based treatment of choice, enabling healthy joints and improved quality of life (QOL) in children with severe hemophilia. Most

retrospective data support similar benefits for secondary prophylaxis versus on-demand (OD) treatment in adolescents/adults.
Objectives: To evaluate efficacy, safety, pharmacoeconomic impact, and QOL of long-term secondary prophylaxis compared with OD in adolescents/adults with severe hemophilia A treated with sucrose-formulated recombinant factor VIII (FVIII).
Methods: An observational, prospective study (2004–2010) enrolled 58 patients (29 prophylaxis; 29 OD) in 11 Italian hemophilia centres. Patients were evaluated every 6 months. Joint bleeding rate was estimated through a negative binomial regression model.
Results: Preliminary 5-year follow-up data are shown in the table.
Table. The prophylaxis group showed better QOL than the OD group (data not shown).

		Prophylaxis		On-Demand	
		12–25 y (n=14)	26–55 y (n=13)	12–25 y (n=11)	26–55 y (n=15)
Age at start of prophylaxis, y*		11.50 (4.09)	27.69 (5.50)		
Rate of joint bleeds: n bleeds/pt-y (CI 95%)		1.91 (1.16–3.16)§	3.88 (1.81–8.30)§	16.04 (10.16–25.32)	19.91 (13.10–30.26)
Orthopaedic score (pain + physical examination) *N pts*		13	11	9	13
*Value at fifth year**		3.91 (2.39)	11.50 (14.74)	9.29 (1.80)	25.38 (13.33)
*Change last evaluation vs. baseline**		−0.67 (3.03) §	−4.20 (9.60)§	3.63 (4.78)	4.67 (6.50)
Pettersson score *N pts*		6	6	4	5
*Last evaluation value**		5.50 (4.85)	20.33 (17.15)	4.25 (4.79)	31.40 (16.79)
*Change last evaluation vs. baseline**		1.33 (1.51)	2.50 (2.59)	1.25 (1.50)	5.80 (26.01)
Consumption rFVIII (IU/kg/y)*		3795.77 (1030.70) §	3664.49 (763.83) §	1367.70 (1330.08)	2080.28 (1300.51)
Treatment costs (€/patient-y)**	Secondary Prophylaxis	179,748.46	188,542.10	11,822.00	35,064.65
	On-demand (hemorrhages)	9,152.98 §	11,894.55 §	41,450.65	56,704.78
	Surgery and other reasons	1,352.31 §	4,384.80 §	7,322.10	11,095.77

**Mean (SD); **IU recombinant factor VIII (rFVIII) cost=0.69 €; § p<0.005 prophylaxis vs. on-demand treatment regimen*

Conclusions: These results show a significant lower number of joint bleeds/year and better joint outcomes and QOL in patients treated with secondary prophylaxis versus OD. Against higher short-term treatment costs, secondary prophylaxis may ensure longer-term benefits even in terms of costs of treatment (e.g., hemorrhages, surgery, and other procedures).

PO-TU-182
Observational study for improving adherence with prophylaxis in hemophilia

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Introduction: Regular replacement therapy (prophylaxis) has become a standard therapy for adolescent patients with severe hemophilia in Japan. The primary goal of prophylaxis is to prevent the development of chronic arthropathy. Some reports show that adolescents with hemophilia have a lower adherence with prophylaxis and indicate that measures to improve adherence during adolescence are critical, as adolescents often take responsibility for self-infusion. One of the reasons for the lower adherence rate is the lack of patients' knowledge on the disease and its treatment. The aim of this study is to evaluate whether education can improve adherence with prophylaxis. The questionnaire "Assessment Checklist for Patients" was prepared as the educational material. We present the current status of the correlation between the knowledge level and adherence at entry time point as the interim report.
Method: This was a prospective multicentre study performed in seven hemophilia treatment centres in Japan. Self-infused persons with hemophilia (PWH) were enrolled. Patients answered the questionnaire to check their knowledge level. Afterwards, patients were educated thoroughly by healthcare workers. This procedure was performed three times: at entry time point and post 6 and 12 months. Statistical analysis was used by Chi Square Test.
Result: One hundred fifteen self-infused PWH were enrolled from April to October 2011. Eighty-four patients (hemophilia A: 74, hemophilia B: 10) with prophylaxis was evaluated for their adherence rate. Sixty-eight patients were in the good adherence group (more than 80%) and 16 patients were in poor group (less than or equal to 80%). There was no significant difference between adherence groups in answering the questions correctly. It should be noted that even in the good group, the rate of correct answers to the question about "long-term benefit with prophylaxis" was very low at 21%.
Discussion: Results show that the patients did not understand the disease and its treatment well. Investigation will continue to determine whether it is possible to improve adherence rates by re-education using the Assessment Checklist.

PO-TU-183
The use of prophylaxis in the hemophilia A patients

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Prophylactic treatment for severe hemophilia A is likely to be more effective than treatment when bleeding occurs; however, prophylaxis is costly. Whereas the benefits of primary prophylaxis are well documented, data related to secondary prophylaxis is limited. We are presenting the data from 113 males diagnosed with hemophilia A, aged between 11 months and 27.1 years. Patients were separated into four groups according to their frequency and their target joint involvements were recorded. Patients' responses to prophylaxis treatment were also recorded. Patients with radioactive synovectomy were evaluated for both response and treatment complications. In 55 (49%) of 113 patients, there was target joint involvement, and in 29 patients, 2 joints were affected. Among patients with target joints, 5 had grade I, 14 had grade II, 18 had grade III, and 10 had grade IV arthropathy. In 4 patients there were target joints but no arthropathy had developed. Of all the patients, 40 (35.4%) were under secondary prophylaxis and 3 (2.7%) were under primary prophylaxis. While 32 patients (80%) under secondary prophylaxis had their bleedings controlled, 8 (20%) had recurrent bleedings. Three patients under primary prophylaxis had no significant bleeding. In 28 patients that had radioactive synovectomy, 24 had no complications, 2 had extra-articular leakage, and 2 had intra-articular hemorrhage. Nineteen patients (64%) had controlled bleeding after procedure, but 5 were accepted as unresponsive. Four patients were lost from follow-up after procedure. Failure of prophylaxis may be related to underlying status of the joints, poor compliance, and participation in high-risk activities. The cost of secondary prophylaxis in adolescents and young adults is likely to be higher, as larger doses of factor concentrate are required because of patient weight, but the potential benefits of reduced absence from school, increased work-based productivity, and reduced need for orthopedic surgery may be significant.

PO-TU-184
Secondary prophylaxis in adult severe hemophilic patients: A prospective study in a single centre

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Introduction: In 2001, the Medical and Scientific Advisory Council recommended prophylaxis as the optimal treatment in patients with severe hemophilia at any age. There are retrospective studies showing the efficacy of prophylaxis compared to on-demand treatment in adults with severe hemophilia. However, there is not enough evidence to start secondary prophylaxis (SP) in patients that have developed hemophilic arthropathy. Regarding SP in adults, only three prospective studies have been published. We designed a prospective study in our unit to establish the efficacy of SP in 15 adult patients with severe hemophilia who have previously been on on-demand treatment and have completed 10 months on prophylaxis.
Methods: We analyzed on-demand treatment retrospectively 10 months and prophylaxis (starting at 35 IU kg^{-1} twice per week, and subsequently adjusted with FVIII:C levels at 72 and 96 h post-infusion until reaching minimal levels without hemorrhage) prospectively during a similar time frame. We measured the following parameters: frequency of hemarthrosis, musculoskeletal function, imaging diagnosis (X-ray, ultrasound, MRI, and densitometry), health-related quality of life (Hem-Qol questionnaire A), absenteeism, economic costs, and possible adverse effects.
Results: SP showed an increased efficacy: a significant reduction in the number of bleedings and hemarthroses per patient (22.24 episodes while on on-demand compared to 1.38 episodes under prophylaxis) as well as chronic pain. An improvement in the musculoskeletal function and quality of life was observed. Possible effects of prophylaxis in hemophilic arthropathy will be evaluated long-term. For this, X-ray, ultrasound, and MRI have already been performed. The economic cost of prophylactic treatment was 1.7 times higher than on-demand treatment.
Conclusions: These preliminary results highlight the efficacy of SP in adult patients with severe hemophilia after 10 months of follow-up. The consumption was only 1.7 times higher in patients on prophylaxis instead of an on-demand regimen. We have to evaluate the long-term economic viability and efficacy of this treatment.

PO-TU-185
Pharmacokinetic-pharmacodynamic (PK/PD) modelling of factor VIII (FVIII) using its plasma concentration and global hemostasis biomarkers

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Objective: To determine the pharmacokinetic-pharmacodynamic (PK-PD) relationships between FVIII plasma concentrations and *ex-vivo* platelet function/viscoelastic coagulation measures. This information could assist in therapy optimization.
Methods: Nine non-bleeding, severe FVIII-deficient patients received prophylactic rFVIII (mean dose: 32 IU kg^{-1}). Blood was collected pre-dose and for up to 48 h post-dose for assessment of FVIII:C, and *ex-vivo* platelet function markers (platelet contractile force [PCF], clot elastic modulus [CEM], force onset time [FOT]), and TEG markers (reaction-time [R], kinetics-time [K] and maximum amplitude [MA]). PK-PD modelling using a one-compartment model was performed by nonlinear regression.
Results: Mean (SD) FVIII:C volume of distribution at steady state (Vd_{ss}), total clearance (CL_{tot}), terminal half-life ($t_{1/2}$), and maximum concentration (C_{max}) were 3.1 (0.6) L, 0.24 (0.10) L h^{-1} 11.6 (6.2) h, and 88 (4) IU dL^{-1}, respectively. Plasma concentration-dependency of PCF and CEM vs. FVIII:C was best described by a direct linear model, while FOT, R, and K were fit by a direct sigmoidal E_{max}-model. The slopes were 0.0083 (0.0036) kdynes dL IU^{-1} and 0.0316 (0.0160). kdynes dL IU^{-1} cm^{-2} for PCF and CEM, respectively.

PD Endpoint	E_{max} (% Reduction)	EC_{50} (IU dL^{-1})
FOT	70.1 (16.9)	87.9 (31.4)
R	74.9 (26.0)	68.5 (28.4)
K	73.3 (36.4)	67.2 (29.0)

Conclusions: FVIII:C PK was consistent with previous studies with wide variability in CL_{tot} and $t_{1/2}$. All pre-dose platelet function markers were sub-normal. After dosing, this platelet function impairment was almost completely reversed, but only temporarily; the effects were still measurable after 48 h. For reasons yet to be identified, there was considerable variability in platelet function marker responsiveness to FVIII:C as shown for PCF and CEM versus FVIII:C slopes and EC_{50} for FOT, R and K. EC_{50} values for the latter markers were similar and approached C_{max} values achieved on therapeutic doses. These results may be used to dose-optimize rFVIII therapy in patients.

PO-TU-186
Comparison of two laboratory assays in monitoring efficacy of different prophylaxis regimens for severe hemophilia

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Objectives: The objective of this study was to compare the validity of two laboratory assays: rotating thromboelastometry (ROTEM) and endogenous thrombin potential (ETP) in monitoring and evaluating different prophylactic treatment regimens in patients with severe hemophilia.
Methods: This study included 20 adult patients with severe hemophilia, without inhibitors. Five patients with hemophilia A received prophylaxis with factor VIII (FVIII) concentrate in standard dose 20 IU kg^{-1} three times per week; five patients with hemophilia A received low doses of FVIII concentrate as prophylaxis, 10–15 IU kg^{-1} three times per week. Seven patients with hemophilia A and 3 with hemophilia B received FVIII/IX concentrate only on-demand. In patients on prophylactic therapy, ROTEM and ETP were done initially before starting prophylaxis, and in addition, 20 min after application of first prophylactic dose and again after 3 months, before receiving next prophylactic dose. In patients treated only on-demand, ROTEM and ETP were done twice per three-month period. In ROTEM, clotting time (CT) in intrinsic system (INTEM) was measured, whereas in ETP, calculated values of area under the thrombin generation curve (ETP.AUC2.cal) and calculated values of maximal clotting (ETP.C-max.cal) were estimated.
Results: In the group on standard prophylactic dose, CT in ROTEM/INTEM ($P = 0.025$) and ETP.AUC2.cal ($P = 0.042$) were significantly improved after 3 months in comparison with patients with low prophylactic dose ($P = 0.042$). ETP.Cmax was not significantly changed between these groups. In patients treated only on-demand, ROTEM and ETP values were not changed.
Conclusion: Prophylaxis with a standard dose of 20 IU kg^{-1} three times per week provides adequate hemostasis in comparison with a low prophylactic dose. ROTEM and ETP enable appropriate monitoring of therapy's efficacy.
Contribution to the practice: ROTEM and ETP can be useful for treatment's modalities monitoring and evaluation in patients with hemophilia.

PO-TU-187
Successful secondary prophylaxis in hemophilia with inhibitors using rFVIIa three times per week

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Introduction: Since the introduction of prophylaxis with rFVIIa, there have been numerous reports of success with different regimes. In 2010, an expert consensus from the Argentinean Haemophilia Foundation published a recommendation of 90 μg kg^{-1} three times per week as the initial dose and to escalate dosage according to the response obtained. Here, we report the experience of 5 centres with secondary prophylaxis using rFVIIa three times/week.
Patients and Methods: Twelve patients (11 HA and 1 HB), mean age 12 years (2–43 years), from a five different hospitals received prophylaxis therapy with rFVIIa thrice a week. The indication for prophylaxis was recurrent bleeding episodes for 9 patients and CNS bleeding in the remaining three. All patients were initially put on 90 μg kg^{-1} three times per week. Nine out of eleven continued with this dosing during the follow-up period and 2 had the dose increased to 270 μg kg^{-1} in order to reduce the number of bleeding episodes. Patients were followed for a mean of 21 months (4–40) after the initiation of prophylactic therapy. To assess the efficacy of the thrice weekly schedules, we compared the number of bleeding episodes and the admission days before and after prophylaxis was instituted.
Results: The mean number of bleeding episodes was reduced from 26 (range: 9–64) for on-demand therapy to 7 (range: 2–15) for prophylaxis (p: 0.003). As a group, this represented an overall reduction of 63% of bleeding episodes. When we analyzed the need for hospitalization, the mean admission days were 6.92 (range: 0–45), while on-demand therapy was reduced to 0.77 days (range: 0–7) on prophylaxis (p: 0.014). It is noteworthy that no thromboembolic events were detected despite the prolonged and continued exposure to rFVIIa.
Conclusions: Our results suggest that prophylaxis with rFVIIa three times per week effectively reduces bleeding episodes in inhibitor patients. Furthermore, this reduction was accompanied by a significant reduction in admission days, which can be considered an improvement in the quality of life for these patients.

PO-TU-188
Bleeding patterns in severe hemophilia A infants and toddlers on prophylaxis vs. on-demand therapy: A prospective randomized observational study

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Objective: To compare prospectively the bleeding patterns in severe hemophilia A children younger than 6 years on prophylaxis vs. on-demand therapy.
Patients and Methods: After the first joint bleed, 75 patients were randomized into two groups in (1:2) ratio and followed for 2 years; twenty-five children received prophylaxis therapy with initial dose of 50 IU kg^{-1} $week^{-1}$, then an escalated dose if needed, while the rest ($n = 50$ patients) were treated on-demand on a dose of 15–25 IU kg^{-1} for 1–3 doses/joint bleed.
Results: Median dose of FVIII consumption in prophylaxis therapy was 57 IU kg^{-1} $week^{-1}$; while the median dose for those on on-demand median dose was 18 IU kg^{-1} $week^{-1}$. Overall, a total of 67bleeds/year were observed in 22/25 patients on prophylaxis vs. 282 bleeds/year in 50/50 patients on on-demand. Out of all children, 28 (37%) were first diagnosed during the first 40 days due to post circumcision bleeding; all of them had a negative family history of hemophilia. Patients on prophylaxis for 6–12 months had a median of 2.2 bleeds/year – predominantly oral cavity bleeding, mostly due to tooth eruption (89%). None had intracranial hemorrhage (ICH), nor bleeding orifices, four developed target joints (8%) (predominantly knee joint bleeding [63%] as well as muscle bleeding into the buttocks, thigh, and forearm, one intracranial hemorrhage [2%]) vs. 4.8 bleeds/year for those on on-demand therapy; 12 (24%) children had target joints (40% knees, 33% ankles, and 27% had elbows or more than one joint) and 6 muscle bleeds over the 2 year follow–up period.
In conclusion: Both frequency and pattern of bleeding were different among patients either on primary prophylaxis or on on-demand therapy, with prophylaxis being the favourable option. It seemed appropriate to begin primary prophylaxis in children with severe hemophilia A after the first joint bleed at an early age to minimize the development of target joints.

PO-TU-190
Application of prophylactic treatment in patients with severe and moderately severe hemophilia A in Azerbaijan

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Prophylactic treatment is recommended by the World Hemophilia Federation and WHO as the most optimal treatment for hemophilia patients. We investigated treatment results of 20 hemophilia A patients of 10–34 years old who admitted to the Hemophilia Treatment Centre, Baku, for secondary prophylactic treatment. These patients often visited the Centre during the previous year with complaints on different bleedings (from 6 to 10 visits yearly). Prophylactic treatment schedule was selected depending on the patient's age, body weight, and disease severity. All patients passed clinical investigation (including aPTT and factor VIII activity % values) before treatment start. According to laboratory analysis, it was determined that 11 (55%) patients had severe and 9 (45%) had moderately severe Hemophilia A. For selection of correct prophylactic-injection dose, blood samples of each patient were analyzed three times according to Sven Björkman 2008 protocol: 1) at least 5 days before any coagulation medicine injection; 2) 4–6 h after injection of ≥40 IU kg^{-1} of factor VIII; 3) 24–34 h after a factor VIII injection. Results showed individual differences in the half-life period of factor VIII and 24 h elimination values. Depending on above mentioned criteria, 6 patients received 3 times weekly injections while 14 patients received 2 times weekly injections. The yearly number of admissions to the Centre because of spontaneous bleedings was reduced by four times. One patient developed hematuria during prophylactic treatment, for which we had to increase the FVIII dose by 500 IU. One patient had a traumatic cut wound on the right arm, but the bleeding was not intensive and recovery was quite fast and successful (like in healthy people). We used X-ray investigation before and after prophylactic treatment to analyze target joint bleeding. Due to prophylactic treatment, the rate of recurrent bleedings was reduced, and adding curative gymnastics, massage, and physiotherapy improved treatment results. We did not reveal inhibitor titer in any patient, recurring bleedings to target joints and spontaneous bleedings diminished to minimum. Psychological status of patients became significantly better and mental, emotional and social functioning increased.

PO-TU-192
Adherence to prophylaxis treatment regimens among persons with severe hemophilia A and B: Results from a one-year, single-institution study

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Introduction: Adherence to a physician-prescribed treatment regimen is an important dimension of clinical care and joint preservation among persons with hemophilia.
Objectives: To assess prophylaxis treatment adherence and selected demographic characteristics among patients attending the Gulf States Hemophilia and Thrombophilia Center.
Methods: All patients with a confirmed diagnosis of severe hemophilia A or B, who utilized the centre's pharmacy, and were prescribed a prophylaxis treatment regimen by their physician between January 1, 2011, and December 31, 2011, were included in the study. A retrospective evaluation of pharmacy and medical records were utilized to determine a patient's adherence to their treatment plan.
Results: Medication adherence was evaluated using the medication refill adherence (MRA) measure, which was calculated for each patient using the time intervals between refills. During the observation period, 64 patients who utilized the centre's pharmacy were prescribed a prophylaxis treatment regimen. The majority of the sample had severe

hemophilia A (84%), were 18 years of age or younger (65%), were of Hispanic origin (61%), and were covered by some form of government health insurance program (61% had Medicaid and 6% had Medicare). The overall adherence measure for the centre was 88.8% ±27.5 (mean ± standard deviation). No significant differences were observed between patients' MRA values and any of the following variables that were examined: age, race, type of hemophilia disease, and insurance status.
Conclusions: The majority of patients at our centre had greater than an 80% adherence rate to their prescribed treatment regimen. Further research regarding whether treatment was used appropriately and factors influencing treatment adherence need to be examined, as this study relied solely on a single measure of adherence that was based on whether a patient obtained a refill before their supply was exhausted.

PO-TU-193
Prophylaxis with increasing doses: Our experience in eight cases
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Introduction: Prophylactic treatment of severe hemophilia A is likely to be more effective than on-demand treatment, but is more expensive considering the higher amount of units necessary to treat patients.
Objective: Reduction of the bleeding frequency and prevention of hemophilic arthropathy.
Methods: We recruited 8 patients with severe hemophilia A with an age range of 21 months to 9 years over a 7–22 month period, (the length of the period depended on the availability of recombinant FVIII, to ensure full protocol compliance). They were first treated with once-a-week infusion, and the frequency was increased step-by-step, if the occurrence and frequency of unacceptable bleeding escalated (Canadian Protocol). We followed up with the patients every 3 months during outcome visits with the hemophilia team to assess the frequency of bleeding and to determine the development of a target joint.
Results: All the 8 boys with severe hemophilia A exhibited a decrease in the monthly frequency of bleeding following the initiation of prophylaxis. The average monthly bleeding frequency decreased from 0.66 bleeding episodes/month before prophylaxis to 0.41 bleeding episodes/month after the start of prophylaxis. One patient did not report a single bleed event since the start of prophylaxis, and 2 others met the criteria for escalation to step 2. During bleeding events, all patients with severe hemophilia A on prophylaxis required less factor VIII than before. The average monthly consumption of FVIII decreased from 646 IU month^{-1} before the start of prophylaxis, to 287 IU month^{-1} after the start of prophylaxis. No patients developed inhibitors against FVIII, and the radiological evaluation of the joints was unchanged.
Conclusion: Young patients with severe hemophilia A on prophylaxis exhibited a decreased bleeding tendency that is associated with the preservation of joint structure and function.

PO-TU-194
Thromboembolic prophylaxis in hemophilia patients undergoing total joint arthroplasty is safe and effective
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Introduction: Total joint arthroplasty (TJA) is the most common surgical procedure performed on hemophilia patients. Standard of care for thromboprophylaxis for TJA in non-hemophiliacs is low molecular weight heparin (LMWH) to prevent venous thromboembolism (VTE). In persons with hemophilia, the use of factor replacement to normal levels of coagulation may increase the risk of VTE similar to that of individuals without coagulation disorders. Though the incidence of VTE is low in this population generally, there have been reports of fatal pulmonary embolism (PE) in hemophilia patients following TJA.
Objective: To elucidate the safety and efficacy of thromboembolic prophylaxis during TJA in hemophilia patients who receive factor replacement.
Method: The clinical records of thirty-five patients with severe hemophilia A or B who had TJA in our hemophilia treatment center (HTC) were retrospectively analyzed. Following surgery, all patients received low molecular weight heparin (LMWH) for thromboprophylaxis while receiving full factor replacement. Standard dosing of LMWH was used. Factor replacement was dosed to maintain trough levels greater than 50% for 10 days to 2 weeks. Evidence of VTE and PE were objectively assessed through signs and symptoms exhibited by the patients and confirmed by Doppler ultrasound or computed tomography (CT) scans.
Results: The mean age at the time of surgery was 35 years (range of 32–67). All thirty-five patients received LMWH post-operatively. There was no unexpected bleeding in these patients while on thromboprophylaxis. During the 3 months following TJA, the incidence of clinically apparent VTE was 8.6%, and no patients experienced PE.
Conclusion: There is need for evidence based guidelines in the prevention of VTE for patients with hemophilia. Here we report our experience with VTE prophylaxis. Our data indicates that standard dose LMWH is safe and effective for thromboprophylaxis in persons with hemophilia following TJA.

PO-TU-195
Severe hemophilia: Stopping and tapering prophylaxis in the second and third decade
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Objective: This study assesses treatment adherence and consequences of tapering or stopping prophylaxis, information vital in the support of life-long treatment of severe hemophilia patients.
Methods: All patients with severe hemophilia A, born 1970–88, without inhibitors and with full treatment history available at the Van Creveldkliniek in Utrecht, the Netherlands, were studied. Patient-initiated treatment changes after the start of self-infusion were assessed. Outcome was measured as joint bleed frequency in the last 3 years. Collection of joint status information is ongoing.
Results: Sixty-seven patients, with a current median age of 31.0 years, were included. Median age at start self infusion was 15.3 years. The first treatment reduction (stopping or tapering) was observed at a median age of 18.9 years, a median 2.6 years after starting self-infusion. Out of 67 patients, 13 (19%) never reduced prophylaxis. Forty-seven patients (70%) tapered prophylaxis median 2 times, with 36 reverting back to prescribed prophylaxis after median 1.0 year and 11 (16%) remaining on tapered regimen for a median of 1.1 years. Twenty-six patients (39%) stopped prophylaxis median 1 time, with 10 reverting back to prophylaxis after a median of 1.9 years, and 16 (24%) remaining on on-demand treatment for a median of 10.0 years. Preliminary analysis of annual joint bleed frequency in the last 3 years showed no significant differences between currently stopped patients (median 1.8; IQR 0.0–3.2 joint bleeds/year), patients currently on tapered prophylaxis (median1.3; IQR 0.5–2.5), and those that adhered to prescribed prophylaxis (median 0.9; IQR 0.3–2.0).
Conclusions: The presented study confirms that the majority of patients attempt to reduce treatment after starting self-infusion. Tapering and stopping prophylaxis show different patterns. Tapering is more common, while switching to on-demand treatment concerns longer periods. Current bleeding frequency was similar in all treatment groups, suggesting a milder bleeding phenotype in those who reduced prophylaxis.

PO-TU-196
Secondary prophylaxis in hemophiliac adults with arthropathy: Description of a cohort
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Primary prophylaxis is the standard of care in hemophiliac patients. This approach offers multiple benefits if started at early ages. Prophylaxis started at adulthood can prevent bleeding, improves orthopedic scores, decreases hospitalization rates, school/work absenteeism rates, and improves quality of life. Description of a cohort is being performed at a centre in a developing country.
Methods and Results: Twenty-four adult hemophiliac patients treated and followed during six months are described at a centre in Bogotá- Colombia. Age: 30.5 years (mean - range: 18–63 years. Patients: 19 (79%) with hemophilia A and 5 (21%) with hemophilia B. Seventy-five per cent is given with plasma-derived factor, 21% is given with recombinant factor. Two patients have inhibitors and are receiving prophylaxis with FEIBA. All patients have severe arthropathy, 37% refers permanent or most of the time joint pain and 21% are completely disabled. Fifteen patients presented 37 bleed events (2.4 bleedings per patients in 6 months), 8 (33%) patients presented no bleeding of any type. Most of bleedings were hemarthrosis. There were no life-threatening bleedings. There were no hospitalizations due to hemorrhage. Prophylaxis dose was (IU kg^{-1} week^{-1}) 15.1 (6.6–49.1). Prophylaxis frequency (number/week): 2.5 (1–3) for hemophilia A and 1.8 (1–2) for hemophilia B. Quality was assessed with SF-36. Emotional role and social function were the higher-scored dimensions.
Conclusions: Secondary prophylaxis is feasible in a developing country. Most importantly, observed results display the decrease in bleeding rates, and the decrease in the number of complications and hospitalization rates. We are performing a cost-effectiveness study that will compare this approach with on-demand treatment.

PO-TU-197
Secondary prophylaxis with anti-inhibitor coagulant complex (AICC): From anecdote to reality
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Background: Evidence of the benefit of prophylaxis treatment in patients without inhibitors to reduce hemarthrosis and severe bleeding has not been demonstrated in patients with hemophilia A (HA) and inhibitors; however, we could assume the reduction in bleeding episodes. Several publications have shown good results using secondary prophylaxis with AICC agents to safely reduce the number of bleeding episodes. We report the results in hemophilia treatment centres in two cities in a developing country, with access difficulties because of the high cost of this therapy to the health system.
Objective: To describe the frequency of hemarthrosis and other bleeding episodes in patients with HA with inhibitors under AICC (FEIBA®) prophylaxis.
Methods: Case series study.
Inclusion criteria: HA patients with high inhibitor title (>5UB), severe bleeding or frequent hemarthrosis or target joint, at least 6 months of prophylaxis with AICC.
Results: Seven patients, median age 19 years (7–38): 6 patients with severe HA, one with moderate HA. Inhibitor title at diagnosis between 4 and 104 IU/B, peak title 1178 IU/B, median 80 IU/B (25.6 to 1178). Average time with AICC prophylaxis 2.8 years (7 months–6 years), range dose 40–75 IU kg-1 2–3 times/week. Before AICC prophylaxis: all type bleeds 5/year, target joint 6/7 patients, severe bleeding 2/7, hemarthrosis 7/7 patients. Associate factors with occurrence of inhibitors: not established 4/7, severe mutation 1/7, surgery 1/7, trauma 1/7. Bleedings after starting AICC: 1.5/year. No patient had thrombotic events during the time of prophylaxis with FEIBA. Compliance with AICC schedule was over 80%.
Conclusions: Use of AICC prophylaxis showed a 70% reduction in all bleeding episodes. The cost can be considered a limitation for its use in a country with limited economic resources for health. Questions such as how long prophylaxis should be maintained and

when to adjust therapy schedule while attempting eradication of inhibitors remain unresolved.

PO-TU-198
Tailored primary prophylaxis with dose-escalation in Iranian hemophilia A

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Primary prophylaxis (PP) provides the best standard of treatment for children with severe hemophilia, reducing the frequency of hemarthrosis and arthropathy. Yet prophylaxis is not available everywhere. Finding a cost-effective regimen is therefore a priority. Nineteen boys with severe hemophilia A (FVIII <1%), aged <5 years (median 26 months) with no inhibitor or target-joint history, were randomized to receive prophylactic pdFVIII 30–50 IU kg^{-1} once a week with escalation to 2–3 times a week (25 IU kg^{-1}) as required. Seven on-demand treatment (ODT) patients were investigated retrospectively. Numbers of bleeds, hemarthrosis frequency, and physical and radiological scores were evaluated at the ICHCC for 54 months. Our patients received treatment only via peripheral veins. Three patients developed a low-titer inhibitor, but 2 returned to prophylaxis after ITI. Median times to dose-escalation were as follows: from step 1 to 2, 27 months; from step 2 to 3, 13 months. At the end of the study, 8 patients (44.4%) remained on step 1; 7 (38.8%) on step 2, and 3 (16.6%) on step 3. Children on prophylaxis had fewer hemarthroses compared to ODT children (4.1 vs. 6.2 per person/year, respectively). At 54 months, follow-up showed a median total joint score on physical examination of 1.5 for the PPs and 3.4 for ODTs. The radiological scores were 0.05 for PPs and 0.5 for ODTs. However, even before initiation of prophylaxis, MRI already showed detectable osteochondral changes in 12/19 (65%). Target joints developed in 5 PPs (28%) and in 3 ODTs (43%). The average consumption of pdFVIII both for prophylaxis and break-through bleeds was 2868 IU kg^{-1} $year^{-1}$, while the ODT group received 2356 IU. PP was superior to ODT even in a low-dose regime. Tailored prophylaxis is suitable in developing countries for delaying disabilities. Early initiation of PP is essential to forestall joint damage detectable only on MRI.

PO-TU-199
Analysis of the outcome of limited-dose primary prophylaxis on twenty-six toddlers with severe hemophilia A or B

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Introduction: The biggest challenge for primary prophylaxis in a developing country probably is maintenance of treatment without breaks to ensure normal musculoskeletal health.
Objective: Analyse the outcome of the comprehensive care given to a cohort of children who were in need of primary prophylaxis and compare the same with existing standard primary prophylactic regimes.
Material and methods: Children who developed major traumatic bleeds like ICH or children who developed inhibitors were excluded. The team designed a local prophylactic regime that consisted of one dose of factor concentrate to raise the factor level up to about 20%, once a week. Occasional shortages were covered with calculated doses of blood components. The data retrieved and analyzed were on age and type of bleed at diagnosis, age at which primary prophylaxis was started, number of units of factor per kg year infused, number of bleeds per year and the sites, ultra sound findings of the 6 main joints of the limbs, HIV and hepatitis serology.
Results and analysis: Age at which prophylaxis was started ranged from 13–36 months. The most frequent site of bleed was the ankle joint, with the knee joint being second. Break through joint or muscle bleeds occurred in about 5%. One per cent of the patients had US evidence of hemophilic arthropathy. Mean doses of factor VIII and IX were 714 and 1202 per kg per year respectively.
Conclusions and discussion: This retrospective descriptive analysis, taking the data of day-to-day management of the cases with frequently changing vial strengths of the factor concentrates, shows that prophylactic treatment with a suboptimal dose even at a frequency of once in two weeks is advantageous over the on-demand therapy. This can be utilized as a pilot study to objectively analyze the beneficial effects of primary prophylaxis with a sub-optimal dose at wider spacing.

PO-TU-200
Prophylactic versus on-demand treatment for severe hemophilia in adults: What are the reasons for refraining from prophylactic treatment?

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Background: Prophylactic treatment has been recommended for people with severe hemophilia by the World Health Organization. Prophylaxis reduces the number of bleeds and results in a better outcome. In the Netherlands, prophylaxis is available to all patients and considered the standard of care. Yet there are people with severe hemophilia who refrain from prophylactic treatment.
Aim: To identify reasons why adult men with severe hemophilia refrain from prophylactic treatment in our centre.
Methods: This is a single-centre, qualitative study that used focus groups to capitalize on communication between research participants. We identified adult men with severe hemophilia who had not been on prophylactic therapy in the last year and invited them to focus group discussion. The invitation sent to the participants explained that the aim of the discussion was to explore motivations and barriers to the use of prophylaxis or on-demand treatment. A topic list was developed to conduct the discussion, which was held with two focus groups with 5 or 6 participants. This topic list was the basis for labelling the transcribed audio tape. Labelling and analysis were conducted independently by two investigators.
Results: Participants did not perceive themselves as having stopped prophylaxis but rather as being flexible on prophylactic medication. The most frequently cited reasons for refraining from prophylactic treatment were reduction, fluctuation, or disappearance of symptoms due to good physical condition. In addition to this, forgetfulness, lack of time, and failure to access peripheral vein were also mentioned. The reasons to refrain from prophylaxis were different according to the age of the participants, with older men citing concern about viral infection. An additional effect of this study was the sharing of opinions between peers, and participants were very positive about the project.

PO-TU-201
Long-term low-dose secondary prophylaxis for severe and moderate hemophilia in children with arthropathy: A single-centre prospective study in China

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Background: With the economic and concentrate limitation, full-dose primary prophylaxis (prophy) is difficult in China. The majority of Chinese children with hemophilia have minimal treatment and their joint status deteriorates rapidly. We have previously demonstrated the benefits of low-dose, short-term, secondary (2^o) prophy. Longer-term prophy data are needed.
Objectives: To explore the efficacy of low-dose, long-term 2^o prophy for severe and moderate children with hemophilia with arthropathy.
Methods: Single Chinese treatment centre prospective study carried out between Feb 2009 & Oct 2010. I. Prophy group (Hemophilia A (HA): 10IU FVIII/kg, 2x/week, Hemophilia B (HB): 20IU FIX/kg, weekly). II. Control group-episodic treatment as affordable (usually <5I U kg^{-1} for joint bleed).
Assessments: 1. Prophy vs. control: joint bleed frequency, clinical joint assessment, and quality of life (QOL). 2. Pre- vs. post- >1year of prophy treatment: radiological joint assessment, psychological assessment and Family Burden Scale of Disease (FBSD). 3. Break-through joint bleeds (site, timing) during prophy.
Results: 1: Compared to 10 control children, 10 children who completed prophy treatment for >1 year had significantly reduced joint bleed frequency, improved clinical joint function and QOL (P: 0.000–0.02). 2. Improvement after prophy (vs. pre-prophy): Radiologic joint assessments 8.3% (but 29.2% deteriorated), Psychological assessment 20%; FBSD 30%. 3. 89% of breakthrough bleeding during prophy occurred at the diseased joints, and 61.0% within 2 days for HA and 66.7% within 3 days for HB before next infusion.
Conclusion: This study demonstrates benefits of long-term, low-dose secondary prophylaxis in severe and moderate hemophilia children with arthropathy in China: reduced bleeding frequency in arthropathic joint, improved joint function and QOL. However, deterioration of arthropathies continued with little improvement of psychological disability and FBSD likely a result of late intervention (after development of arthropathies) and prolonged low factor trough period.

PO-TU-202
Hemophilic arthropathy in pediatric patients with hemophilia A: Comparison of early and late prophylaxis

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Objective: To evaluate the effect of early prophylaxis, we investigated the influence of prophylaxis-starting age and number of joint bleedings on the radiological score of joints in patients with severe hemophilia A who were treated at Korea Hemophilia Foundation Clinic from 2006 to 2011.
Methods: Twenty-four patients with severe hemophilia A who received prophylaxis were analyzed. Patients were divided into two groups: 12 patients in group 1 (G1) who started prophylaxis before 7 years of age and 12 patients in group 2 (G2) who started at the age of 7 years or more. All patients received low-dose prophylaxis (10–15 U kg^{-1} body weight, three times a week). The radiological alterations of joints (knee, elbow, ankle) were assessed using the Pettersson score (PS).
Results: The median age at the start of prophylaxis in G1 was 3 years (range 1–6 years) while that in G2 was 10 years (range 7–12 years.) The median age at analysis was 8.5 years for G1 and 16 years for G2. Median PS (and range) of G1 was 0 (0–5) whereas that of G2 was 5 (0–19). There was a significant correlation between the number of joint bleedings before the start of prophylaxis and the radiological outcome in both groups, while the number of bleedings during the prophylactic treatment was not correlated well with the severity of arthropathy. Two of 64 joints in G1 and 9 of 64 joints in G2 had a PS ≥4 (target joints). Elbow and ankle joints were more often affected than knee joints.
Conclusion: The number of joint bleedings before the start of prophylaxis influenced the progression of arthropathy even in patients with early prophylaxis. The prophylactic treatment in severe hemophilia should be started early, before the occurrence of joint bleeding.

36-PSYCHOSOCIAL ISSUES

S-MO-01.2-5
A shared decision
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Decisions involving taking medications are often complicated. When is it the right time to start? How will it affect my life? What might the social implications be? Is it the right time for my loved ones? It is indeed a very complex decision. Hemophilia is a disorder with many different aspects, but the unpredictable timing of bleeds is, perhaps, the most annoying. However, what we do know is when we have to treat ourselves with our replacement factor. When diagnosed with HIV in 1985, there were no choices to be made regarding any medications, as there weren't any available. There were, however, many decisions to make regarding relationships, lifestyle and disclosure, and yes, sadly, even death. Thankfully medications did start arriving as time went by. The choices were limited at first and sometimes the varying stages of my health or blood counts (T-cells, white cells etc.) dictated whether I began a treatment regime or not. The longer I lived, it seemed more decisions had to be made. Many more drugs became available, but often side effects resulted in either a drug change or an extra drug to combat the complication. When my Hepatitis C became a problem, the decision to treat seemed to be the hardest one to make, even though there was only one treatment option to take at the time. Bad geno type, awful side effects, poor success rates, and a long regime all seemed too much to bear. This changed significantly when the combination therapy of pegylated interferon and ribavirin was proving to be much more successful, even to people with co-infection. In my presentation, I will explain more about what decisions I made, how I came to make them, along with the implications and outcomes.

S-MO-01.5-1
Influence of patient education on adherence: Is teaching enough?
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Advances in medical care create the potential for individuals with chronic illness to minimize complications and attain optimal health. Many individuals find adherence to prescribed regimens challenging, with estimates of 50% adherence in chronic illness. Advances in treatment and products will not help patients achieve health goals if patients are not willing or able to follow the prescribed treatment plan. For patients with hemophilia, poor adherence results in increased joint disease, limitations of activities of daily living, and decreased quality of life. Treatment of hemophilia, by its nature, requires significant time and effort on the part of the patient and family and includes factors that have been shown to predict poor adherence. Factors that contribute to non-adherence are numerous and complex, and providers often rely almost exclusively on information and education to increase adherence. However, lack of information is only one of the factors that can negatively impact adherence to medical advice. For each plan of care prescribed, multi-dimensional strategies must be developed with the patient and family to support their ability to adhere to the plan. While patient education is a critical component of comprehensive care, education alone is not sufficient to ensure adherence to treatment recommendations. Teaching can influence adherence if the educational plan is individualized, if it includes recognition and attention to behavioural, cultural, and social factors and if plans of care are developed with patient and family participation from the beginning. Healthcare providers can assist families in identification of barriers to adherence and in developing successful strategies to promote optimal health.

S-TU-03.5-1
Ethical issues in clinical-trial participation
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Primary Objective: To address ethical issues when recruiting human subjects for clinical research trials, who do not have access to adequate treatment and/or standard of care.
Background: While persons living with a bleeding disorder have benefited from advances in and the availability of replacement therapy, the high cost of treatment and availability of comprehensive care remain a significant concern among persons with this chronic illness. Participation in a clinical research trial provides participants an opportunity to receive new therapeutic products that will continue to improve treatment and patient outcomes for this illness. For some subjects, this may be their only means of receiving treatment or health care. If clinical trials are to be ethically acceptable, participants must be given relevant information in a manner they can comprehend, and must freely consent to take part without inducement. The procedures for obtaining consent must address differences in social and cultural environments, particularly in developing countries.
Implementation: This session will illustrate the obligations of the researcher and members of the bleeding disorder multidisciplinary team to discuss all of the relevant information about the clinical research-its purpose, the procedures involved, and the potential risks and benefits-with the research candidate. Providing continuing care after the research study is completed and what standard of care should be available will be discussed.

S-MO-01.5-2
Cultural views and approaches to adherence
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Culture encompasses a broad range of backgrounds, norms, and expectations; it impacts beliefs and behaviour on many levels. Individuals' perception of their hemophilia can be influenced by religious, familial, and cultural factors. Misunderstandings between patients and providers may occur as a result of differences in language, vocabulary, and cultural and ethnic background. These misunderstandings may be compounded by assumptions, lack of familiarity, and lack of cultural proficiency and may contribute to non-adherence. For patients outside the dominant culture, adherence to treatment recommendations can be impeded at all levels of the healthcare delivery system. A study of 175 pharmacies in the United States found half were unable to provide labels or instructions in a language other than English, and two thirds of those pharmacies did not have translation services available (Bradshaw, 2007). Another US study found disparities in health outcomes for minorities, across disease states and socio-economic status (IOM report, 2003). Lack of acculturation and familiarity is likely to hinder patients from revealing their use of alternative or non-traditional treatment for their hemophilia and their willingness to adhere to traditional care and treatment recommendations. In some cultures there is a stigma attached to having a genetic disorder such as hemophilia, resulting in patients' reluctance to disclose their diagnosis even to medical providers (Sayyeheh, 2006). Strategies and techniques designed to reduce cultural barriers, enhance providers' cultural proficiency, and foster adherence will be explored.

S-TH-03.6-1
Coping with transitions in adulthood
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Transitions are a period of uncertainty-the 'in between' phase when passing from one stage of life to the next. Transitions pose difficulties as well as opportunities and require increased demands for coping and adaptation. They typically involve multiple, simultaneous events and are more challenging for those with compounding issues, including chronic illnesses, such as hemophilia. Individuals with hemophilia often experience life changes out of sequence from their peers; these out of sequence changes can make coping with transitions even more challenging. Additionally, individuals' perceptions about their hemophilia and severity of their symptoms can either positively or negatively impact their transitions thorough the lifecycle. (Triemstra, et al,1998). The ability of individuals to cope successfully and incorporate challenges they face with their hemophilia will impact the choices they make throughout adulthood, including those related to career and educational attainment, physical activities, management of their care, relationships, family planning, retirement, adjustment to physical and/or cognitive changes, and issues with grief and loss. Common life-transition issues faced by adults in their thirties, forties, fifties, sixties, and beyond will be discussed, with a focus on compounding issues related to hemophilia and its complications. Strategies aimed at strengthening individuals' internal locus of control, stress-management skills, and coping techniques will be explored.

S-TH-03.6-2
Strategies and tools for coping with hemophilia, for children and families
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When a child is diagnosed with hemophilia, the family sinks into a crisis. This situation is both a difficulty and an opportunity for the child's parents. They are confronted with multiple demands of increasing complexity in facing the condition, adapting to it, and being able to construct a new reality. We will discuss the importance of playing, not only for the children but also for the nuclear and extended families, as a way of working through the crisis triggered by the presence of hemophilia. Playing is the privileged way in which children discover the world, establish relationships with the others, socialize, and solve traumatic and conflictive situations. This experience has been implemented by the Psychological Department at the Foundation in Argentina through many activities and programs such as family workshops and psychological interviews aimed at accepting the diagnosis and building a new balance, via the working-through process. We have developed new educational material as well-a children's book collection-to facilitate the knowledge and management of the disease. Health is more than physical health. Playing, as a universal tool that promotes a healthy environment, will be explored, showing in what way this experience improves the "know how" of hemophilia in the whole family, thereby favoring and fostering a better family quality of life.

S-TU-03.5-3
Ethical issues in hemophilia: Code of ethics
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In the world of social work, psychology, and other psychosocial practices and standards, a code of ethical practice must be observed. It is necessary for the protection of the patient/client and the psychosocial professional. The social work code of ethics in the United States, as an example, provides standards of ethical practice and looks for the obligation of the psychosocial worker to follow these ethical practices to the best of their abilities. Any violation of the code of ethics or standards will constitute unethical conduct with grounds for disciplinary action. Ethics provides a guide to proper behaviour. A code of ethics is a set of rules and guidelines that set forth what are 'good' or moral actions and what is considered 'bad' or immoral behaviour. Many professions have a specialized code of ethics (http://www.journals.uchicago.edu/toc/et/). Many psychosocial professionals are expected to obtain continuing educational credits (CEU) annually to keep their licence of practice current. Depending on the country and their healthcare system regarding hemophilia care, ethical issues and conduct come into question. This seems to occur more in countries where patient product choice is available. Professionals

have their professional codes of ethics to fall back on as they navigate the ethical concerns that can arise. This session will explore the purpose of a code of ethics, how it is defined, and provide a sample of a social work code of ethics from the United States.

S-MO-01.2-3
Psychological aspects in patients with HIV, HCV, and hemophilia

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Objectives: To evaluate the psychological impact of HIV and HVC infection in patients with hemophilia in order to assess the effects on life and self-perception. The long-term objective is to improve the care of such patients.
Methods: Three dimensions have been analyzed: (I) the experience of the hemorrhagic disease, (II) the body image and personality in regards to HIV and HCV infection, and (III) the defences setting to face the distress. These items have been evaluated in six patients using individual interviews and long-term medical therapy. Also, exchanges with the hepato-enterologist who cares for these patients have been included in our analysis. These methods have been considered the most appropriate to answer questions raised by our clinical practice with people with hemophilia (PWH).
Results: With regard to the clinical elements drawn from the investigation, the following observations have been made: (I) the hemophiliac's experience creates significant shortcomings for three patients who show major defects. (II) body's image shows, especially in two patients, important defects, with an extreme difficulty to protect themselves from the corporeal and environmental excitations inducing a lot of distress (III) As a common feature, the hemophiliac in the same way as his mother or his parents does, due to an identification to our anxiety and also as a consequence of an impossible mourning of the ill body for the mother. Consequentially the disease will be handled in the hypochondriac mode, with major anxiety, repetitive medical requests, feelings of aggression…).
Conclusions: The feeling of self safety is lacking in the majority of these patients. The HIV and HCV infections strengthen and feeds upon the disorders inherent to hemophilia. The objective of the psychotherapist is to develop better defensive arrangement via mourning for the healthy ego.

S-MO-01.2-5
Effect on family, friends, and work

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Motivation: 'Trials given to people are commensurate to the courage they have; my personal experience from a developing country.'
Problem statement: How can social support and faith be utilized in living positively with co-infection [HIV/HCV]? The social stigma that surrounds HIV/HCV may have adverse effects not only for individuals, but also on their relationships with family, friends, and colleagues. I'm severe hemophilic with factor VIII deficiency and was diagnosed with both HIV/HCV when I was quite young. Upon knowing my status, the whole world collapsed around me. Hopes were shattered and life seemed to have come to a standstill. My friends started avoiding me and workmates preferred not to interact frequently. Family members may also become burdened by caregiving as the disease progresses, and they may be affected by the stigma often attached to the disease.
Approach: I visualized several things to suppress reality until finally I surrendered to God. First question that came to my mind was 'Why me?' Then I looked for answers: 'God only burdens those capable of bearing the burden.' I have gone through many trials and surely there is a reason God tested me. Then I read, trials given to people are commensurate to the courage they have. Rather than be sad, I felt proud.
Results: Having transcended my fears, with the belief that the future lies in God's hands, I live each day positively, with courage to face the uncertainty of being co-infected. I have seen life not as simply as others have; challenges I faced have given me the resolve to not only help myself but also others. Social support has helped me reconcile with my feelings of anger against those who misunderstood me. 'After gaining confidence, I have seen a positive change in my relationships.'
Conclusion: a) Social support buffers stress, improves treatment adherence and quality of life; b) faith and emotional support may also help a person to restore his reason for being and give increased self-esteem; c) implementation of non-discriminatory workplace policies may reduce stigma and discrimination; and d) depression and self-stigma should be targeted for intervention to improve various social relationships.

S-TH-03.6-3
Coping responses to hemophilia

RICHA MOHAN
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Every individual has a different style of coping when it comes to the emotional roller coaster of Hemophilia.
Objective: This study examines those aspects of bleeding disorders that children and adolescents with hemophilia find stressful. It explores the coping behaviours and strategies used to manage those stressors. It also assesses whether a standard conceptualization of coping was most applicable to the hemophilia population.
Method: A total of 80 children and adolescents with mild, moderate, or severe hemophilia were asked to complete a coping checklist in response to self-generated illness-related problems.
Results: An analysis of coping strategies revealed that some coping strategies were used equally across varying illness-related stressors, but others varied by type of stressor. Moderately consistent patterns were found among those with mild, moderate, and severe hemophilia.
Conclusions: The results suggest that coping strategies used by children and adolescents with hemophilia have some similarities but do vary across situations. The study helped to identify several children and adolescents who might need special psychological support. It can be concluded that exploring the coping-response strategies among children and adolescents will help hemophilia physicians, counsellors, and psychologists in dealing with them more adequately.

S-TU-03.5-4
Disclosure issues in hemophilia care

A. F. ROBERTS
South African Haemophilia Foundation

Disclosure is defined as 'the act of bringing to light or revealing' (Chambers Dictionary, 1983), or as 'making known' (Pera and van Tonder, 2011). The issue of disclosure is central to the work of hemophilia care, whether pertaining to patient care or organizational management. Disclosure hinges heavily on the concepts of privacy, confidentiality, volunteering of information, consent, and ethics in general. The presentation uses the case study methodology to explore these concepts from a human rights' perspective. It argues that a combination of trust and vigilance forms the basis for all aspects of disclosure.

S-TU-03.5-2
Ethical issues in hemophilia

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The Oxford Dictionary defines Ethics as 'the moral principles which govern a person's behaviour or the conducting of an activity', while the Merriam-Webster dictionary provides the following meaning, 'the discipline dealing with what is good and bad and with moral duty and obligation; a guiding philosophy.' An awareness and understanding of what constitutes ethical behaviour and decision making is an integral part of the general practice of social work, psychology and counselling. Critical reflection is a tool used to ensure that workers in the 'caring and help-giving' professions are able to make appropriate decisions in the face of conflicting choices. Students of the helping professions are taught reflective practice from the very beginning. Unfortunately, workers often face ethical issues 'head-on' in situations that are already charged with high emotion and equally 'unattractive' alternative courses of action. Most countries have developed their own codes of ethics for professional workers to give guidance and direction in such situations. An examination of these guiding statements will show that they are, not surprisingly, quite similar. People with inherited bleeding disorders frequently deal with significant life concerns based around chronic and acute health issues, many of which are extremely difficult and stressful to address. Unfortunately, there is also, for them, no immunity from all the other life stressors and problems that face the general population. Ethical issues would be identified by workers as they work in many of these situations. This session will explore the ethical issues identified by social workers, psychologists, and counsellors who work within the hemophilia community across the world. The presentation will show the results of a survey that will be conducted in the coming months. The aim of the survey is to identify ethical issues for psychosocial workers in their current workload. It will ask a range of questions related to ethics and will also seek to identify if there have been changes in ethical issues experienced in recent times. The survey responses will be de-identified to ensure anonymity. The presentation will also look at a number of ethical issues identified by workers in more detail.

PO-MO-184
The importance of summer camps for people with hemophilia

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Introduction: Medical, social and psychological rehabilitation are all part of managing and treating hemophilia. Within psychological intervention, it is important to address the emotional aspect of the support a patient receives in handling his or her illness, personal life, and social surroundings. That's why Tabasco Hemophilia A.C., based in Villahermosa, Tabasco, Mexico, organizes annual summer camps that offer education, activities, and games for people with hemophilia. This camp is directed at all people with hemophilia in the Mexican Republic who are 7 years old and up.
Objective: The camp's objective is for patients to learn skills and enjoy educational and recreational life experiences.
Material and methods: All activities take place in safe facilities and under medical supervision. Children are educated in a playful and fun way and monitored at all times. With this methodology, they acquire and internalize the values, concepts, attitudes we wish them to learn. Sports games bring children into contact with nature and give them an opportunity to be active and interact with each other.
Results: The patients learn to cooperate and work as a team, socialize and integrate, improve their communication skills, express themselves, learn team-building skills, experience freedom and some sense of independence, create and participate, have a better quality of life, and develop greater self-esteem.
Conclusion: This camp teaches children valuable life skills through education, activities, and games. They are educated within a framework of fun, respect, and values. The opportunities to socialize, experience independence, and develop a sense of individual responsibility create a better quality of life for the patient with hemophilia.

PO-MO-185
Study of adherence to prophylactic treatment in patients with severe hemophilia A
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Introduction: It has been observed that adolescent hemophilic patients exhibit a reduced adherence to prophylaxis. Geraghty in 2006 showed that 59% of children under the age of 12 had very high compliance with prophylactic treatment, reflecting the influence of parents, compared to only 13% of the adolescent age group and 6% of the young adult group. Compliance was very high in the 0–12 age group, but dropped significantly at 13 and upwards, only improving again after the age of 28.
Objectives: The main objective of the study is to assess prophylaxis adherence with factor VIII in patients with severe hemophilia A. Secondary objectives are to understand adherence and quality of life from the patient's perspective and to study the relationship between adherence and the patient's clinical status.
Material and methods: In order to assess adherence to prophylactic treatment, we considered the IU of factor VIII administered versus prescribed in the last 2 years. For evaluating the adherence from the patient's perspective, an ad hoc questionnaire on adherence has been developed. The HemoQOL Questionnaire, adapted to each age range, is administered to assess the patient's quality of life. To understand the relationship between adherence and the clinical condition of the patient, clinical variables related to the bleeding episode are considered.
Results: Eleven patients from 12 Spanish hospitals have been enrolled by January 2012. We expect to have 86 severe hemophilic patients enrolled by the end of this year. This study was initiated in November 2011 and will run throughout 2012.
Conclusions: Close adherence to prophylactic therapy regimens can reduce bleeding episodes without losing the benefits of primary prophylaxis. It is therefore important to know the level of adherence, identify the main barriers to adherence, and assess the influence of these barriers on the patient's clinical condition and quality of life. Established programs to promote adherence should be developed. Study funded by Bayer Hispania S.L.

PO-MO-186
Psychosocial consultation in a comprehensive hemophilia care centre
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Comprehensive Hemophilia Care Center, Tehran, Iran

Hemophilia is a chronic and lifelong disorder caused by a coagulation defect. Patients are usually susceptible to frequent bleedings, especially in their musculoskeletal organs such as joints. Proper treatment is not always available in developing countries. In the absence of proper treatment, people with hemophilia suffer from bleeding, pain, and arthrosis and often experience frequent hospitalizations, disability, and unemployment. As a result, people with hemophilia are usually under chronic stress and suffer from different psychosocial problems. When the first Iranian comprehensive hemophilia care centre was established in 2000, we started a psychosocial clinic to serve people with hemophilia, their parents, and their partners. The most important topics include (but are not limited to): the first case of hemophilia in a family, attention deficit hyperactivity disorder (ADHD), and marriage counselling (especially when one partner has also a viral infection and addiction). Furthermore we have visited more than 150 patients who were going to start HCV treatment with Peginterferon, in a regular interval.

PO-MO-187
Circumcision of hemophilia patients: hematological and sociocultural aspect
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Objective: Circumcision of patients with hemophilia is a controversial issue among medical professionals. Opinions vary depending on the individual's place of residence and social, cultural and religious beliefs.
Materials (subjects) and methods: This study analyzed the circumcision of 20 children with hemophilia in Gaziantep, Turkey. All of the patients were circumcised by surgical technique after factor replacement. Parents' attitudes to circumcision were evaluated with a questionnaire. Most of them thought that circumcision was an essential procedure for sociocultural, psychological, and religious reasons.
Results: All of the patients were circumcised successfully and most of the parents (85%–100%) were concerned about religious and social factors. They were worried that their children would be excluded if they were uncircumcised.
Conclusion: Circumcision is an essential procedure even for people with hemophilia because of sociocultural, psychological, and religious aspects in Gaziantep-a city in the southeast region of Turkey. As specialists for these patients, we should perform the procedure with a team including a surgeon, hematologist, and an equipped laboratory to oversee these issues.

PO-MO-188
Peer victimization and psychosocial outcomes among children with hemophilia: A comparison between English and Spanish speakers
J. VELASQUEZ, D. COOK, R. BERKOWITZ, A. FEDERIZO and J. BERNSTEIN
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Children with chronic medical conditions are a medically vulnerable population. Children with hemophilia are also at increased risk for peer victimization and need to be especially careful to avoid physical altercations. Bullying among school-aged youth is increasingly being recognized as an important social problem that affects social and emotional well-being. The purpose of this study is to explore the impact of pediatric hemophilia on peer victimization and psychosocial outcomes. Data will be obtained from youth aged 11 to 16 years old who are diagnosed with hemophilia A and B and von Willebrand disease and will be matched with non-diagnosed peers. Once demographic information, including the child/teen's medical diagnosis and socioeconomic status (SES) data, is gathered, the Multidimensional Peer Victimization Scale will be utilized to assess peer victimization and the Behavioural Assessment System for Children, Second Edition (BASC-2), will be utilized to assess psychosocial outcomes. There will be a comparison between children with a diagnosis of hemophilia and children without a diagnosis of hemophilia on peer victimization ratings. Children with hemophilia are expected to report higher levels of peer victimization than their non-diagnosed peers. We will also compare English language versus Spanish language dominance across all four groups of children to explore the influence of diversity within these populations. Further, it is expected that children with hemophilia who report peer victimization will present with elevated Composite Scores on Internalizing subscales and Behavioural Index subscales; that these children will present depressed scores on both the Adaptive Behaviour Composite Scores and subscales; and that there will be exaggerated findings in children from the non-dominant language and ethnic group. A two-tailed t-test will examine population differences while ANOVA will examine fixed, main, and special effects as well as interactions.

PO-MO-189
Multicentre study of pediatric quality of life and psychomotor development in parents of children with severe and moderate hemophilia who receive primary prophylaxis treatment in public hospitals in Chile
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Complejo Asistencial Dr Sótero del Río, Santiago, Chile

Objective: To assess psychomotor development (SMD) and quality of life (QOL) in children with severe and moderate hemophilia who are being treated with primary prophylaxis in the Chilean Public Health System. Parents' perceptions of their child's SMD are compared with an expert evaluation.
Method: In a sample of 8 children with moderate and severe hemophilia receiving primary prophylaxis treatment, we conducted two questionnaires with their parents: the Bricker and Squires Ages & Stages Questionnaires ® (ASQ) for Parents and the long version of the Hemophilia Quality of Life questionnaire (HemoQOL) designed to assess 4–7 year-olds (Bullinger and Mackensen). SMD assessment was completed with expert assessment using the ASQ criteria.
Results: The children obtained a normal SMD evaluated for age. When we analyze the differences between parents' perceptions and the expert assessment, there were differences in all areas, except the personal/social area. These differences were statistically significant in the fine motor and the communication area. Parents underestimated the motor development area, and overestimated the communication area. The parental perception of children's quality of life is high. The most problematic areas are those related to feelings (anger) and family (overprotection). Treatment administration received the lowest evaluations. Most children (90%) are not treated at home; parents do not administer the treatment. Because of their age, children are very susceptible to injuries.
Conclusions: Children with severe and moderate hemophilia receiving primary prophylaxis treatment have a normal SMD evaluated for age. The QOL reported by their parents is high. There are difficulties associated with treatment that is administered at a health centre rather than at home. Perceptions of SMD reported by parents differ from assessments by experts. Parents overestimate their children's achievements in the communications area and underestimate their achievements in the motor area; these differences are probably due to overprotective behaviour.

PO-MO-190
Impact of pediatric psychology on identification of psychosocial needs
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Background: Children with hemophilia often experience greater difficulties with emotional well-being, including symptoms of depression and low self-esteem. Early detection and management of these problems is vital, as they may have adverse effects on mental and physical health. However, psychosocial needs, especially those involving impairments that are not overtly severe, are often under-identified by healthcare providers. Multidisciplinary care teams have become increasingly common and help provide psychosocial support, but integration of psychology within those teams is limited.
Objective: To examine the impact of a pediatric psychology program embedded within a hemophilia treatment centre (HTC) on identification of psychosocial needs and access to care.
Methods: A postdoctoral psychology fellow joined the HTC at a pediatric hospital in July 2010. Data regarding referrals for psychological services were collected and compared between November 2009 and June 2010, prior to program implementation in July 2010. Between July 2010 and February 2011, the psychologist briefly screened each

patient; between March 2011 and October 2011, the psychologist was available in clinics but patient contact was based on care team referral.
Results: No patients were referred for psychological services during the period prior to program implementation, although the services were available within the hospital. Forty patients were referred when brief screening was provided to each patient, as compared to 18 patients when the psychologist was available in the clinic but only met with patients referred by the care team. Patient utilization of services after referral was 70% for July 2010–February 2011 and 89% for March 2011–October 2011.
Conclusions: Implementing pediatric psychology into the HTC increased awareness about triggers for psychological services and patient access to those services. The results also support the importance of integrating psychology within the multidisciplinary care team to ensure sufficient identification of psychosocial needs.

PO-MO-191
Pedagogical attention program: Results after 18 years

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Introduction: In 1994 a house-to-house study was carried out to find out the needs of people with congenital coagulopathies in Catalonia. On a pedagogical level, the most significant data of the 89 families visited with under age children were: 39% of parents expressed that their children had learning difficulties; 22% of pupils had repeated at least one school year; and 12% of pupils had dropped out of school without obtaining a basic level of education.
Objectives: To improve the academic and educational level of hemophiliac children and teenagers in Catalonia through the establishment of a pedagogical attention program.
Description: The pedagogical attention program designed and carried out different projects: Providing sociopedagogical grants to all the families; assessing all staff at the school attended by a child or teenager with hemophilia; setting up one monthly psychoeducative group of parents and another for children and teenagers; and providing personalized attention to children with specific educational needs. This personalized attention included psychopedagogical diagnosis, back-up classes, re-education, curricular adaptation in coordination with schools, education and professional orientation, and referrals to other professionals like psychologists or social workers, where necessary.
Conclusion: After 18 years' experience with this program, we can affirm that we have been able to improve the academic and educational levels of children with hemophilia in Catalonia. Here are the main points: Thanks to the grants, we can carry out a follow-up for each one of the 115 people who are currently studying Of the 74 children younger than 18, 10% have learning difficulties. Ten per cent of students have repeated at least one school year. Only one teenager dropped out before completing the minimum educational requirement. Forty-one people aged over 18 continue studying, and 63% of them attend university.

PO-MO-192
Social participation in boys with hemophilia

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Purpose: To determine the relationship between self-esteem and perceived social support and how it relates to social participation in boys with hemophilia. We consider activities to be tasks that one can do alone, while participation includes things that we do with others (Whiteneck & Dijkers, 2009). In this presentation, we discuss the concept of social participation and offer some preliminary data.
Methods: We have recruited 18 of a projected 50 subjects with moderate and severe hemophilia A and B between the ages of 7 and 18 (13 patients aged 7–13, 5 patients aged 14–18). Patients were recruited at SickKids Hospital as part of a study examining the burden of illness. Patients completed measures of participation (Participation Scale-Kids), self-esteem (Self-Perception Profile for Children/Adolescents), and social support (Social Support Scale for Children).
Summary of results: Eighty-nine per cent of subjects had normal participation. For children, social participation was positively related to overall self-esteem (r_s = -0.79, P = 0.0022). Self-esteem subscales of social acceptance (r_s = -0.82, P = 0.0010) and global self-worth (r_s = -0.57, P = 0.0523) were positively related to social participation, however there was no association with athletic competence. Overall social support was not related to social participation; however, subscales of classmate (r_s = -0.48, P = 0.049) and close friend (r_s = -0.56, P = 0.0184) support/regard were positively related to social participation. There were no significant findings regarding adolescent self-esteem due to the small sample.
Conclusions: These findings suggest that there may be a link between the self-esteem and social support of boys with hemophilia and their social participation. The majority of the sample was found to engage in social participation in ways similar to their peers. With this knowledge, healthcare providers may be better able to identify which patients could best benefit from increased support regarding social participation.

PO-MO-193
Between hope and tragedy

G. GOLDSTEIN and G. KENET
The National Hemophilia Center, Sheba Medical Center, Tel-Hashomer, Israel

Arabic Muslim families and religious Jewish families have a lot in common. Most of them have large families and refrain from any abortions. As hemophilia caregivers, the most important fact for us is that most of these families do not pursue prenatal counselling and diagnosis. Thus, it is possible for them to have more than one child with hemophilia. We would like to present one Muslim Bedouin family, from northern Galilee, with 4 children with hemophilia. All 4 children have now grown up. They experienced a long and complicated path, but, with the help of our comprehensive national hemophilia centre, they survived and built their lives. Traditions, genetic obstacles, and geographic distances made this journey very special. We shared the family's feelings when the father married a second wife-he had begun to build a new family with her when his first wife, who had borne four sick children, finally gave birth to a healthy son. We have accompanied this family for 17 years, going through their celebrations and tragedies, their sorrows and hopes, and it seems that today they still struggle. Nevertheless, a lot of things have improved in their surroundings, including the changing influences of tradition and modern life and even the relationships between Arabic Muslims and Christian Arabs. This case study tells us about more than just the struggle of living with hemophilia. It certainly shows how, with the help of the hemophilia centre, we can improve families' lives 'in good times and in bad, in sickness and in health.'

PO-MO-194
Achieving a significant change within a weekend

G. GOLDSTEIN, D. BASHARI and G. KENET
The National Hemophilia Center, Sheba Medical Center, Tel-Hashomer, Israel

As a social worker with the Israeli national hemophilia centre, I take care of a diverse population that is composed of new immigrants as well as native Israeli Jews, Muslims, Christians, and others. We have found that in order to improve compliance from newcomer patients, communication and cultural barriers have to be broken. We took into consideration that newcomers have economic and adjustment problems that could prevent them from joining our regular group therapy meetings, held at the centre during the evenings. We invited a group of Russian-speaking new immigrants with children with hemophilia to join us for one weekend. Ten families were invited for a full board weekend in a hotel. Being placed at a resort allowed them to listen to our doctors' lectures, take part in group therapy (all these with translation), and spend time with their children. The people made new connections with other parents and patients in the same situation. They did not feel different and isolated. They became much more compliant in treatment, understanding better, and feeling free to ask questions. Families who had previously refused central line placement have agreed to portacath operation, while others finally started sending their children to kindergarten.
Conclusion: Change may be achieved in a short time if a good target-oriented framework is built and supported by teamwork.

PO-MO-195
Childhood and subjective timings: Growing up with hemophilia

S. GRASES
Fundació Catalana de l'Hemofília, Barcelona, Spain

The diagnosis of a coagulopathy gives rise to a series of phenomena that a child with hemophilia may experience with his body: hemorrhaging, pain, functional limitations, and even the treatment for hemophilia, in the sense that this involves manipulating the child's body. The child experiences this phenomena in his body from a very young age, without being able to speak about it. The diagnosis of hemophilia for the child always comes, therefore, after his own experience. This is a priority and forces the child to embark on a psychic or subjective journey relating to everything that happens to him. Questions arise from the phenomena within his body: What is this? Why is it happening to me? The experience related to the body, the diagnosis of hemophilia, and the adults' explanations share a subjective journey of building a life with hemophilia. This way is specific for each child, because it's not about completing standard phases, but rather 'subjective or logical timings.' Each child will use elements from his own experience to form explanations about hemophilia and also to find his own way of dealing with it. Knowing that hemophilia for a child is above all, an experience, understanding the ways in which children deal with this experience, the questions they ask themselves, and how they manage to form their own explanations can all help parents and professionals to understand better the child's hemophilia experience and accompany him along this journey from childhood to adolescence.

PO-MO-196
Psychosocial issues in hemophilia: 100 case studies

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Hemophilia is a bleeding disorder that may result in chronic physical disabilities and psychosocial issues in the absence of adequate treatment facilities. Until recently, treatment facilities have been far from adequate in the northern state of Delhi in India. From the records of psychosocial counselling in our hemophilia centre, 100 cases were analyzed for the spectrum of psychosocial problems in Northern India. Among the 50 children younger than 18 years old, only nine were doing well. 21 (42%) had issues related to schooling, ranging from being unable to be attentive to studies (13 cases) to being denied school admission (two cases). Hemophilia bleeds affected schooling in three cases and was a de-motivating factor in another four cases. Undue anxiety caused problems in seven children. Parental overprotectiveness was seen in 10 instances, though it resulted in timidity in only one child with hemophilia. Amongst the 31 adults 19–45 years old, nine were doing well. Half suffered from mental stress and anxiety from employment issues (six cases), frequent bleeds (five cases), and family-related issues (four cases). Three had not disclosed hemophilia status to their spouses. One resorted to drug abuse (painkillers) and one committed suicide. Amongst the five parents, three had undue anxiety. Two parents had no faith in modern medicine, and this had negative implications for their hemophilic children. Nearly 80% of hemophilia cases in this study had psychosocial problems. Whereas schooling-related issues were the most important for children, it was the jobs and family-related issues that were most important amongst the adults. Since the psychosocial issues vary with age and social context, it is more important than the standard medical treatment to individualize their identification and management.

PO-MO-197
Psychosocial issues: support for people with hemophilia and their families in India
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The aim of this paper is to brief about psychological problems and offering counselling services to people with hemophilia (PWH) and their families. Management of hemophilia in India is difficult because of illiteracy, poverty, and the low level of awareness amongst the general public and in the medical and paramedical community. Twenty-five percent of the world hemophilia population lives in Asia; India is estimated to have about 100,000 PWH, but only 15,000 are identified and registered. For PWH, repeated bleeds cause absences from school/college, and a lack of proper education can lead to unstable employment. Depression, a sense of inferiority, feelings of guilt, and marital issues can make life miserable. As they age, PWH can experience chronic pain due to disabling arthropathy, and this can lead some people to attempt suicide. Within families, the mother is often harassed by her husband and in-laws for bringing hemophilia into their family. Daughters of carriers, the sisters of PWH, often remain unmarried because potential spouses assume that they are carriers. Carrier mothers avoid future pregnancies because they are afraid of giving birth to another child with hemophilia (CWH). The practice of consanguineous marriages has contributed to the spread of hemophilia within extended families and has even resulted in the birth of a female with hemophilia. At our centre, financial assistance to poor families through certain welfare projects has enabled children to get timely treatment and for adults to access the education they need to obtain a suitable job. Rehabilitation camps for children and young people help them to build self-confidence and accept the kind of lifestyle they need to adopt in order to live with hemophilia. Regular physiotherapy, suitable sports, and career counselling has helped youths. Engaging CWH in drawing and painting during their stays in hospital has helped to divert them from their pain. Alternative therapies like naturopathy, yoga, and acupuncture have improved patients' quality of life. Genetic counselling through Women's Group meetings has removed misconceptions and provided access to carrier detection testing and prenatal diagnosis, ultimately reducing the incidence of hemophilia.

PO-MO-198
The psychology work at Centro dos Hemofílicos do Estado de São Paulo (CHESP)
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This study presents the psychology work at Centro dos Hemofílicos do Estado de São Paulo (CHESP), located in the city of São Paulo. This institution offers assistance to people with hemophilia (PWH) and their families-mainly of low income-extending its activities to social interaction and income generation areas. In this sense, the psychologist has a wider and more diversified work, interacting widely with the patients and their families, as well as with specialized technicians and other staff. Visits are carried out in the psychology office, but more directed approaches happen in various places like the dining hall, corridors, infirmary, physiotherapy area, and others. This type of approach is due to the specificities of visits to CHESP, which require a wide participation of the family for the well-being of patients. Patients and their families don't go to the institution to receive psychological treatment, but physiotherapy. Thus, the work of the psychologist becomes more complex, as he or she has to deal with the lack of demand for psychological visits and must create bonds with patients and families through parallel activities. One of the main difficulties of the psychologist is to organize psycotherapeutical groups, due to the ambivalence of the mothers, who dedicate themselves almost entirely to the care of their sons. Their personal life is conturbed by the stress of constant and intense care, which prevents them from enjoying the normal pleasures of daily life. Mothers often experience a desire to be taken care of by the institution as well. They expect CHESP to deal with their sons' issues and relieve them of the burden of mother care. The work of the psychologist is to develop activities to stimulate autonomy of the patient, as well as of the mother and/or person responsible for care. One of the main objectives is to work on the symbiotic relationships between parents and children that result from addressing the challenges of living with hemophilia.

PO-MO-199
Demographic characteristics of adult patient respondents in the Hemophilia Experiences Results Opportunities (HERO) study
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Objectives: To describe the population of adult hemophilia patient respondents in the HERO study.
Methods: A web-based survey was conducted in 10 countries (ARG; CAN; CHN; DEU; DZA; ESP; FRA; GBR; ITA; USA) to target 600 congenital hemophilia patients ≥age 18, mostly recruited through national patient organizations.
Results: Among the 592 patients who completed the survey, the median age was 36 years (range 18–83), with 30% in the 31–40 age group. The majority had congenital hemophilia A (HA, 73%) or B (HB, 13%), with 14% reporting inhibitors (HwI). Spontaneous bleeding during the previous 12 months was reported in 95%, 76%, and 69% of HwI, HA, and HB, respectively. Most patients were treated with factor replacement (HA 97%, HB 96%) or bypassing agents (HwI 87%). The most common comorbidities associated with hemophilia were bone/skeletal problems (HA/HB 52%, HwI 40%) and HIV/HCV infection (42%). The most common unrelated comorbidity was cardiovascular disease, reported by 31% of patients. Ninety-five per cent reported having received formal education (median age when they left/finished was 21, with 77% between ages 16 and 25). Employment history included 62% full- or part-time work, with 44% engaged in office work/studying as their primary work activity. Overall, 13% reported not working due to long-term disability (46% registered as disabled for benefits claims), and 19% reported no negative impact of hemophilia on working life (40% for those with spontaneous bleeding). Low risk activities were more commonly reported than moderate or high risk ones (74%, 36%, 6%), with age-related differences noted (e.g. jogging more common in age <30 than in 41+) and increased moderate/high risk activities more common in subjects on prophylaxis.
Conclusion: HERO patient respondents represent a wide portion of the global adult hemophilia population. The unique capture of comorbidities in HERO will allow for multivariate analysis of psychosocial issues.

PO-MO-200
Demographic characteristics of parents of children/adolescents with hemophilia responding in the Hemophilia Experiences Results Opportunities (HERO) study
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Objectives: To describe the global parent respondent population in the HERO study.
Methods: A web-based survey was conducted in 10 countries (ARG; CAN; CHN; DEU; DZA; ESP; FRA; GBR; ITA; USA) targeting 600 parents of patients <age 18, mostly recruited through patient organizations.
Results: The 503 parents who completed the survey had a mean age of 38.6, with 62.4% ≤ age 40. The majority were female (75%); 84% were married, 11% divorced, and 3% single. Fifty-nine per cent had other unaffected children; 86%, 13%, and 2% had one, two, or three sons with hemophilia. Over half had an oldest affected son ≤ age 10; 76% had a son with congenital hemophilia A (HA), 16% had a son with hemophilia B (HB), and 8% had a son with hemophilia with inhibitors (HwI). Spontaneous bleeding during the previous 12 months was reported by 54%. Most patients received factor replacement (HA 99%, HB 97%), or bypassing agents (HwI 83%). Eighty-nine per cent of the parents reported formal education (the median age at which they left/finished was 22). Parents were 71% employed at full or part-time, with 39% engaged in office work/studying as their primary work activity. Thirty-five per cent reported that caring for their child did not preclude them from working; however, 28% selected their job and 25% had flexible work hours to allow them to care for their child. Overall, 61% reported that having a son with hemophilia had a negative impact on work; 31% reported a moderate/large negative impact. One-third reported their children were registered or collected disability benefits (43% inhibitors, 74% Western Europe, 14% North America). Children's peak engagement in all/high risk activities was at age 6–10. Parents of children ages 6–10 reported higher low/moderate/high risk activities compared with parents of adolescents ($P < 0.05$). Soccer, football, and martial arts were the top desired activities.
Conclusion: Parent respondents cared for young to adolescent patients with hemophilia and were largely educated and employed, but some experienced significant negative impact of caring for their sons on employment.

PO-MO-201
Patient perceptions and attitudes towards hemophilia treatment and prophylaxis among hemophilia patients with inhibitors
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Introduction: Hemophilia patients with inhibitors often suffer from significant morbidity despite the active role many take in discussing treatment options with their providers. The aim of this analysis was to gain a better understanding of patient perceptions on the impact of treatment and how often they seek optimal care.
Methods: A cross-sectional questionnaire was administered to hemophilia A or B patients with inhibitors aged 18 or older or the parent of a patient aged 2–17. Patients must have been diagnosed with inhibitors for at least one year and have been on a bypassing agent at the time of the study. Patients were recruited from hemophilia treatment centres/hospitals in the US, UK, Italy and Argentina. Participating patients completed a questionnaire from January–February 2011. Patients were asked to indicate their agreement with statements related to how active they are in discussing treatment with providers, their perceptions regarding the prophylactic treatment efficacy, and satisfaction with inhibitor treatment information.
Results: Sixty-one inhibitor patients completed the questionnaire, of which nearly half (48%) were completed by parents of patients under 18. Thirty per cent were on a prophylaxis treatment regimen with bypassing agents. The majority (82%) agreed or completely agreed with the statement 'preventing bleeds allows me to live a more normal life,' and 72% believed 'taking therapy regularly will protect my joints.' Further, 69% indicated they 'take an active role in discussing treatment options with my provider.' Despite these findings, only 58% indicated their physicians 'discussed prophylactic therapy with me to prevent bleeds' and 44% indicated their 'disability has increased since I was diagnosed with inhibitors.' Finally, only 64% felt satisfied with 'the information on inhibitors available to me.'
Conclusions: Patient perceptions of treatment benefits, coupled with the low self-reported prophylaxis rate suggest an opportunity to further educate and empower patients and clinicians on prophylaxis treatment options.

PO-MO-202
Restructuring and improving quality of life for HIV-positive Japanese people with hemophilia and their families: How do we rebuild our life with effective support?

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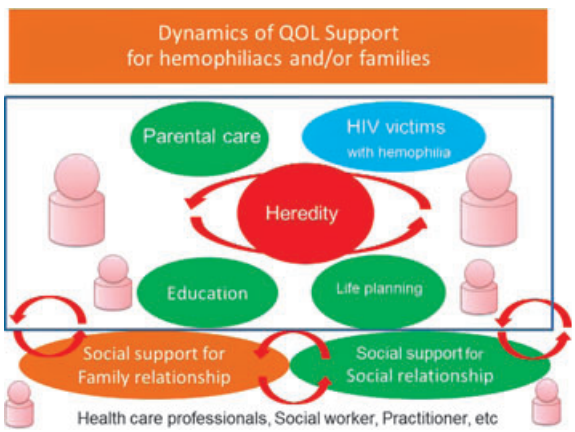
Background: About 40% of Japanese people with hemophilia (PWH) were infected with HIV through contaminated blood products in the early 1980s. This incident has affected their psychosocial aspects over a long time, thus restructuring their living is important issue. Psychological issues can have a tremendous negative impact, on not only PWH that are HIV-positive but also on the current HIV-free generation of people with hemophilia and their families.
Aim: To support the lives of people with hemophilia and HIV by: 1) clarifying their experiences and difficulties; 2) building an effective support framework; and 3) gaining practical suggestions from multidisciplinary and permanent support organizations.
Methods: Studies were carried out and analyzed using an action research (triangulation) method. Interviews were conducted with HIV-positive PWH and their families, including mothers (n = 19), fathers (n = 16), and brothers (n = 6). Interviews were also conducted with mothers of non-HIV PWH (n = 10) and healthcare professionals involved in genetic counselling and hemophilia (n = 6). Questionnaires were given to educators (n = 37).
Results: HIV victims with hemophilia and their families have experienced a heavy burden of life and been exposed to psychosocial stressors such as stigma, guilty, difficulties in family dialogue, expression of negative experiences, self-blaming, difficulties with coping, and lack of social support. They were also confronted with negative attitudes from healthcare professionals. Discussion: HIV victims with hemophilia and their families require a preliminary future plan corresponding to each life stage with permanent issues such as hemophilia heredity, parental care, education, life planning, and HIV.



Conclusion: We propose a dynamic support scheme that involves social and family relationships. It is expected that our study will contribute to restructuring and improving quality of life (QOL) for HIV-positive Japanese people with hemophilia and their families.

PO-MO-203
Prevalence of alexithymia and its association with quality of life and emotional distress, in Greek hemophilia subjects

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Objective: Alexithymia, defined as the difficulty of identifying and expressing feelings, is recognized in several chronic diseases. The objective of this study is to assess alexithymia and its association with health-related quality of life (HRQOL) and the level of emotional distress in patients with hemophilia in Greece.
Method: In total, 74 hemophilia patients of all severities, 73 male and 1 female, mean age 42.9 (range 18–70), were enrolled in the present survey. A generic HRQOL instrument, the Medical Outcome Study (MOS) Short-Form 36 (SF-36), was implemented to measure HRQOL, while alexithymia and emotional distress were measured through the Toronto Alexithymia Scale (TAS-20) and the Greek Questionnaire of Emotional Distress (SRQ), respectively. Statistical analysis was conducted in order to identify the relationship between the presence of alexythimia (defined as a total score >60), with sociodemographic parameters and levels of HRQOL, and emotional distress.
Results: Fifty-nine out of the 74 included patients (80%) had hemophilia A, and 17 (20%) had hemophilia B; 48 (65%) had severe hemophilia and only 17 (20%) of them were under prophylaxis treatment. The majority of them (78.4%) were HCV positive, while 25.5%, were HIV positive. The majority of the sample (67.5%) had secondary education, 24.3% were retired, and 40.5% are lived with parents. A total of 20 subjects (27.4%) were found to have alexithymia. The presence of alexithymia was significantly associated with PCS and MCS scores of SF-36 (P < 0.019 and <0.005 respectively) as well as the Emotional Distress Score (P < 0.005), especially anxiety symptoms. Among sociodemographic parameters, the severity of the disease and presence of viral infections were not associated with alexythymia, while subjects who had never worked were found with significantly higher alexithymia scores.
Conclusions: In our study a higher prevalence of alexithymia was observed in people with hemophilia than in healthy subjects, which was positively associated with general quality of life and emotional distress of the patients. A lack of work seemed to have a higher impact than medical parameters, such as severity of viral status.

PO-MO-204
Transition clinics for adolescents with bleeding disorders

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Background: Many adolescents with bleeding disorders and their parents express anxiety about the transition of leaving pediatric care to establish care with adult providers.
Objectives: To determine the needs of adolescent patients with bleeding disorders and to establish interventions to alleviate anxiety associated with transition from pediatric to adult care. Methods: A literature search related to transition of adolescents with bleeding disorders was conducted. Our team identified several actions we could take to alleviate the stress of transition for adolescents and their parents. We developed specialty clinics for young men and women with bleeding disorders ages 14–18 years. These clinics, 'Boyz 2 Men' and 'Diva Day,' were designed to provide education focused on issues common to adolescents with bleeding disorders as well as the comprehensive clinic visit. Each HTC team member gave a short interactive talk on topics pertinent to adolescents. Adult hemophilia providers were introduced, who welcomed attendees to adult care. After a provided lunch with open discussion, a tour was given so that attendees could preview the site of the adult clinics.
Results: Sixty-five adolescents with bleeding disorders, ages 14–18, have been invited to attend the transition clinics. Twenty-six adolescents, each accompanied by a parent, have attended the clinics. Adolescents and parents who have attended the clinics express satisfaction with the clinic, the education provided, and the opportunity to meet the adult hemophilia team. Attendees report decreased anxiety about transitioning to adult hemophilia care after attending the transition clinics.
Conclusion: Providing specialty transition clinics for adolescents with bleeding disorders and their parents leads to decreased anxiety about health care transition from pediatric to adult care in the bleeding disorders population. Efforts to develop creative methods to provide relevant education, as well as to measure the effectiveness of these interventions, are being developed.

PO-MO-205
Feelings, experiences on the sibling relationship and the perception of heredity on hemophilia by patients and siblings

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Siblings of children with chronic diseases are known to have a variety of concerns, such as loneliness, lack of information, burden of care, the potential of passing the disease to their children, and discrimination at school and within the community. Although previous studies have asked mothers and siblings about the sibling relationship, patients' perceptions about this relationship have seldom been studied. Therefore, feelings about and experiences of the sibling relationship and perceptions about the heredity of the disease were studied via interviews with two adult patients with hemophilia and three adult sisters. The following results were obtained: one) although patients felt guilty that mothers spent more time with them than with their sisters, the siblings did not report feeling loneliness; two) the sisters suffered from the stress of being responsible for taking care of parents and keeping the property; three) patients and sisters expected mothers to manage the relationship between siblings and fathers to coordinate the family dynamics; and four) patients and sisters requested to have general information on the carrier status of their offspring. These results suggest that one) special considerations are required to address succession of property and taking care of elderly parents for Japanese patients and sisters, two) information on hemophilia and the carrier status should be provided for patients and siblings on their youth, and three) empowerment programs for young parents should be provided to help them manage the family relationship.

PO-MO-206
Mind inhibitors

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As a person with hemophilia (PWH), my passion led me to conduct personal research to uncover the main cause of my drawbacks in my education, my career, and my romantic life. I have experienced unjustified conflicts in my social relations, feeling stale in mind and body, indefinite self-image, emotional instability, and successive spontaneous bleeds despite the continuous factor replacement. My research is based on my experience of living with hemophilia for 37 years, reading countless books on personal development and the mind-body relationship, and having profound discussions about these experiences with my wife.
Findings: Through my research, I uncovered that I used to suffer from what I call 'mind inhibitors'; these were the hidden cause of my life disorders and spontaneous bleeds.

These mind inhibitors are responsible for locking the body factor receptors, blocking body energy centres (like the solar plexus), discouraging the super-intelligent body cells from running their auto-healing system, and paralyzing the instinctive high-speed cellular response to external molecular treatment. Mind inhibitors originate from different sources like thinking of oneself in a victim role, anxiety about medical treatments, lack of financial stability, negative attitudes, self-rejection, and contradictory thoughts and feelings.
Conclusion: Mind inhibitors should be handled as seriously as biological inhibitors. As Dr. Bruce Lipton explains in his book, 'The Biology of Belief': DNA does not control our biology; instead DNA is controlled by signals from outside the cell. Our bodies can be changed as we retrain our thinking, since thoughts are made of energy that affects the cellular energy level, and thus everything is created twice: once in our minds and then the physical creation follows. New holistic approaches should be considered for treating PWH as a complete synchronized system of Soul, Mind, and Body; treatment should include more than just factor adjustment. Factor adjustment only treats symptoms, but a holistic approach would also address the patient's need for a subconscious paradigm shift in the person's thought and belief system.

PO-MO-207
Frankly.net: Navigating the road to adulthood with hemophilia

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Objective: Becoming an adult comes with its own challenges. However, for young men with hemophilia, there are few resources available that offer guidance on the journey. To address this need, we created an online forum that provides news, tips, and information to help them lead the lives they choose.
Method: In 2010, an editorial board was established to guide the creation of Frankly.net, an online magazine for young men with hemophilia. Board members are experts in the areas of health care, social work, and advocacy, and two are young men with hemophilia. Controlled exclusively by the editorial board and sponsored by Bayer HealthCare, Frankly.net is a daring online magazine that serves as a candid, trusted resource on real-life issues to teenagers and young adults with hemophilia worldwide. Frankly.net is optimized for smart phones, and users are encouraged to keep updated on content by following @FranklyNet on Twitter.
Results: Since its inception, the board has guided the development of more than 50 articles on topics ranging from leaving home for the first time, to 'coming out' as a person with hemophilia, to falling in love and having sex. This year, editorial board member Eviatar Weizman also chronicled the excitement and challenges of travelling around the world with hemophilia in a video series titled the 'No Limits Tour.' To date, Frankly.net has seen more than 6,300 visitors. An average of 17 weekly tweets drives users to the site. Also available for download are two informational booklets—one on psychosocial issues and another on topics that are difficult to discuss as a young person with hemophilia. More booklets on specific lifestyle topics are in development.
Conclusions: Frankly.net is a first-of-its-kind online resource that continues to break the mould in helping young men navigate the ups and downs of living with hemophilia.

PO-MO-208
A new tool to assess coping and perception of children with hemophilia: Validation and evaluation

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Objectives: How children cope with and perceive their disease is an important predictor of self-management and Health-Related Quality of Life (HRQOL). The Hemophilia Coping and Perception Test (HCPT) for children is a new tool to assess coping and perception of children with hemophilia. The HCPT is based on the Asthma Coping and Perception Test (ACPT). The aim of this study is to evaluate and validate the HCPT.
Methods: The HCPT is a board game containing a comprehensive set of 33 questions about hemophilia, including knowledge, self-management, coping, anxiety, and perception. Additional questions concern sensitive subjects or contain fun assignments. Approximately 30 children in the Netherlands between the ages of 8 and 12 who have mild, moderate, and severe hemophilia will be approached for this multicentre study (Amsterdam, Groningen, Eindhoven, Leiden, and Rotterdam). The HCPT will be validated using the Coping with a Disease questionnaire (CODI), the Hemophilia Quality of Life questionnaire (HemoQOL, short version), and a disease-specific coping questionnaire. After finishing the HCPT, both children and parents answer an evaluation questionnaire.
Preliminary results and conclusion: So far, 10 boys have played the HCPT (mean age 8.9 ± 0.7) and first reactions were positive. Both parents and children report the HCPT to be informative and entertaining. Although the sample is small, we expect HCPT to be a valid and effective tool to detect problems regarding coping, management, anxiety, and perception of children with hemophilia. Based on the results of the similar ACPT, we also expect the HCPT to increase and facilitate communication with children with hemophilia. By June 2012, 30 children will be included.
Contribution to clinical practice: To be able to provide tailored health care, it is important to get insight in children's coping and perception of their disease. The use of this new test will make it possible to get insight into these aspects in a playful, child-friendly way.

PO-MO-209
Is illness perception of parents related to severity of disease in children with hemophilia?

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Objectives: The aim of the present study was to examine the illness perception of parents of children with hemophilia, in relation to the severity of the disease.
Methods: The cohort (2007) includes 129 boys (8–18 years; mean age 12.82 ± 2.84) with hemophilia A (88%) or B treated at 5 hemophilia treatment centres in the Netherlands (Amsterdam, Utrecht, Rotterdam, Groningen, and Nijmegen). The boys have grown up with a comprehensive and high standard of health care. All boys with severe hemophilia (SeH) received prophylaxis at home. Parents' illness perception was measured using the Revised Illness Perception Questionnaire (IPQ-R). High scores on the subscales 1, 2, and 3 respectively represent negative beliefs about the cyclical nature, consequences, and number of symptoms of the illness. High scores on the subscales 4, 5, and 6 represent positive beliefs about personal understanding and controllability of the illness. Independent sample t-tests were used to compare the different severity groups on parental perception (Table 1).
Results: Parents of children with moderate hemophilia (MoH) reported significantly more negative beliefs on the cyclical nature and consequences of the disease than parents of children with mild hemophilia (MiH) and severe hemophilia (SeH). Parents of children with SeH reported a significantly more positive perception of the personal and treatment controllability of the disease compared to parents of children with MiH.
Conclusion: Parents of children with MoH believe the illness to be more chronic and to have a more negative impact on physical, social, and psychological functioning compared to MiH and SeH. Future research should focus on the relation of perception and parental distress.

PO-MO-210
Psychological aspects in patients with HIV, HCV, and hemophilia

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Objectives: To evaluate the psychological impact of HIV and HVC infections in people with hemophilia (PWH) in order to assess the impact on the patients' lives and self-perceptions. The long-term objective is to improve the care of such patients.
Methods: Three dimensions have been analyzed: (I) the experience of the hemorrhagic disease, (II) the body image and personality in regard of HIV and HCV infections and (III) the defences necessary to face the distress. These items have been evaluated in six patients using individual interviews and long-term medical therapy. Also, exchanges with the hepato-enterologist who cares for these patients have been included in our analysis. These methods have been considered as the most appropriate to answer questions raised by our clinical practice with PWH.
Results: With regard to the clinical elements drawn from the investigation, the following observations have been made: (I) The patient's experience created important shortcomings and a difficult psychological elaboration for three patients who showed major defects. (II) The patient's body image proved, especially in two patients, to be critically affected, with an extreme difficulty to protect themselves from the corporeal and environmental excitations inducing a lot of distress. (III) As a common feature, the body seemed to be considered by the PWH in the same way that his parents viewed it, due to an identification to our anxiety and also as a consequence of an impossible mourning of the ill body for the mother. Consequently the disease might be handled on the hypochondriac mode, with major anxiety, repetitive medical requests, and feelings of aggression.
Conclusions: The feeling of a lack of self safety is found in the majority of these patients. The HIV and HIC infections strengthen the disorders inherent to hemophilia. The objective of the psychotherapist is to develop better defensive arrangement via mourning for the healthy ego.

PO-MO-211
Social support and economic stability as major determinants of self-esteem among persons with hemophilia

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Previous studies have shown that persons with hemophilia (PWH) have a significantly greater tendency to develop low self-esteem than healthy persons. They have also shown that self-esteem plays a distinctly important role in the possible development of depressive disorders and/or anxiety states among PWH. For this reason, we wanted to examine which aspects of life were significantly related to self-esteem in PWH; that is, which aspects of their daily life should be encouraged to raise levels of self-esteem. An empirical survey among adults with hemophilia was conducted in Croatia (n = 135). Different measures of health, economic, and social status were used (19 items in total) while the Rosenberg scale (10 items) was used to measure self-esteem. Variables of physical health significantly correlated with the level of self-esteem, which is confirmation of earlier research findings as well as our initial assumptions. A very high correlation between self-esteem and satisfaction levels with social relations towards participants was found. The same result was obtained in relation to the quantity of social contacts. Education levels, employment, and economic status also showed a significant connection with the level of self-esteem. The results suggest several conclusions. To ensure that self-esteem is at the highest level in people with hemophilia, which would reduce the likelihood of mental disorders, there is a need to work on the availability of adequate medical care. However, besides adequate medical care, it is essential to raise awareness about activating other aspects of life. A positive correlation between economic stability

and self-esteem indicates the necessity of raising the economic well-being of people with hemophilia. At the same time, it serves as a message to society of the need to create conditions of economic independence for this population (to encourage education among young people with hemophilia, encourage orientation towards occupations where hemophilia is not an obstacle, develop recruitment strategies, etc.). Finally, it is exceptionally important to promote social engagement—not just among people with hemophilia, but also among people who make up their social environment.

PO-MO-212
The importance of social services at Centro dos Hemofilicos do Estado de São Paulo
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Brazil is situated in South America, a country of large territorial dimensions with about 190 million inhabitants. The population of Brazil is composed of a mixture of people of Indian, African, European, and Asian descent, who contribute to its rich cultural diversity. Although this country bears this cultural richness, it also has huge social disparities. This is the working environment of the Centro dos Hemofilicos do Estado de São Paulo (CHESP), a beneficent health association located in the city of São Paulo. CHESP's main function is to defend the rights of people who have hemophilia and von Willebrand disease (VWD) and provide a wide range of services: psychology, pedagogy, physiotherapy/rehabilitation, and social services. The objective of this work is to present the importance of social services in the institution. Social services at CHESP has the function of identifying and intervening on the social difficulties presented by the people who have hemophilia/VWD and their families, in an attempt to minimize and assist people to overcome these obstacles. It is important to point out that the work of these professionals starts with social research, which provides essential data for the interventions. Through this study, we have the opportunity to get acquainted to the user, his family dynamics, the socioeconomic context surrounding him, his level of knowledge about hemophilia/VWD, and the impact of the deficiency on his life and in his family. With this information in hand, the professionals provide the patient with an orientation about access to treatment and all the issues raised by the social research. They inform users about organizations that can assist them, in order to assure their rights and guarantee the exercise of citizenship. The professionals at CHESP seek to offer high quality treatment, but also to stimulate potentialities, promote access to a better quality of life, and help patients develop the necessary autonomy they need to face the various obstacles of everyday life, sensitively aggravated by the complications of hemophilia.

PO-MO-213
A ten-year follow-up of a person with hemophilia A co-infected with HIV/HCV after living donor liver transplantation
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Background: I was diagnosed with moderate hemophilia A in 1976 at the age of 4. I was infected with HIV and HCV through contaminated factor VIII. Although HIV infection had been well controlled by antiretroviral treatment, hepatitis C had progressed to the end-stage. In November 2002 (30 years old), a living donor liver transplantation (LDLT) was performed by the gift of life from my mother. The sustained viral response was achieved with peginterferon/ribavirin therapy that was started soon after LDLT. Replacement of factor VIII became unnecessary 1 week after the operation. In January 2006, Burkitt-type acute lymphoblastic leukemia (ALL) occurred, probably due to strong immunosuppression with steroids and tacrolimus. Five courses of rituximab plus a regimen of cyclophosphamide, doxorubicin, vincristine, and prednisone (R-hyper CVAD) had been given for 10 months and resulted complete remission. Although chemotherapy was successful, I suffered from severe complications, including bone marrow suppression and neurological disorders. To maintain WBC and IgG levels, repeated injections of G-CFS and replacement of immunoglobulin were required for more than 2 years thereafter. The lower extremities were paralyzed. As a result, I could not stand or even move for 6 months and only started to become better very slowly. To avoid the recurrence of ALL, I stopped taking tacrolimus. In January 2008, a compression fracture (Th12 to L4) occurred because of long-term use of steroids that made me bedridden for 4 months. After the recovery, low-dose tacrolimus was restarted to prevent GVHD in place of steroids. In addition to these complications, I repeatedly experienced bacterial infections such as chronic sinusitis, pneumonia, and bacteremia and aspergillus pneumonia over 10 years.
Conclusion: I received LDLT 10 years ago. After the operation, I suffered from many complications. However, I have been eager for life and have conquered all of them. I live in Tokyo with my wife and two children with hope for future.

PO-MO-214
At a loss as to where to go from here
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VT is a 38-year-old man with severe hemophilia A who has many complex issues including hepatitis C, chronic pain, hemophilia arthropathy, opioid addiction, non-compliance, and non-attendance for appointments. V has a family history of severe hemophilia A. He has one brother with severe hemophilia A and a sister who is a carrier. V treats himself at home on a demand regime and contacts us via his relatives when he needs more factor VIII. Unfortunately, the relationship with V becomes strained when he is asking us to prescribe his narcotics. V is restricted by an order from Medsafe under the Misuse of Drugs Act 1975, and we cannot prescribe any controlled drugs for him. In 2005, V was diagnosed with an infective lesion in his right knee; he had not attended any surgical appointments organized for him over the last 3 years. V's brother contacted us earlier this year and asked that we organize a referral for V to the local pain service; once obtaining V's permission to organize the appointment, he did not attend. V and his partner now have a young son and V wants to 'pick his health up and be here for the boy.' Unfortunately, when V did finally attend a surgical appointment a few months ago, he was told that he is not a good surgical candidate due to his general poor health and ongoing infection from the lesion on his knee. V was compliant in taking his antibiotics for a few months; however, he has stopped again. In this presentation I will discuss the ethical issues of confidentiality, autonomy, non-compliance and the potential cost of treatment due to this. How can we motivate V to take responsibility for his care? The aim of this presentation will be to 'stimulate discussion about complex hematology patients and the difficulties that arise from poor compliance.'

PO-MO-215
Oral mucosal bleeding: A nurse's view
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The most trying time for many families who have children with severe hemophilia is the second year of life (12–24 months). This is the time when children start to have more organized motor skills and so can interact with their environment more actively. In psychoanalytic theory, the oral stage is the earliest stage of psychosexual development (from birth to approximately 18 months), during which the infant's needs, expression, and pleasurable experiences centre on the oral zone. Oral mucosal bleeding is occasionally the first, but often the most visual bleeding episode in the early life of a patient with severe hemophilia and their family. As with many aspects of managing the diagnosis of hemophilia in those less than 2 year olds, *when* the family receives the diagnosis plays a huge role. In my experience, families who receive the diagnosis before or close to birth generally seem more prepared to cope with the pressures of the second year of life than those who receive a later diagnosis. Within the Wellington Haemophilia service, we had 3 children with severe hemophilia A, in separate families, born within 8 monthof one another. Diagnosis varied from date of birth to over 4 months after delivery. All 3 children have experienced oral mucosal bleeding to varying degrees. This has allowed the author to consider issues around oral mucosal bleeding from a very practical standpoint! This presentation will consider the issues related to oral mucosal bleeding from a psychosocial and a treatment perspective.

PO-MO-216
Youth with hemophilia in Pakistan
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Pakistan has a large youth population according to the UN's definition of youth. An estimated 103 million Pakistanis, or 63% of the population, fall under the age of 25 years. However, as a result of endemic poverty, the majority of youth in Pakistan do not have the opportunity to experience an enjoyable childhood. Fifty per cent of the population of Pakistan consists of youth. Youth are always considered to be the backbone of any country. But being a young person with hemophilia (PWH) in Pakistan is a taboo. Bleeding episodes may cause inconsistency in schooling, which can have a long-lasting effect on a person's career. Having troubles in studies may cause low grades, which is a barrier to admission into a reputable university. Institutional status influences job ranking and awareness of hemophilia can compel an employer to think negatively about a job candidate. Moving ahead, social stigma and discrimination must be faced in developing countries like Pakistan, for example, opposition to marriages of PWH. In some areas, social bindings do not allow marriages to occur if the man is not circumcised. Circumcision is considered to be one of the mandatory conditions to be a Muslim. There is also a misconception that a PWH could transfer the disease to his spouse and children. These factors often have many psychological impacts like: self-stigma, deprivation, isolation, and an erratic and uncoordinated approach towards life. As a volunteer hemophilia social worker, I do career counselling as a peer and always try to give hope to other PWH by presenting myself as a role model.

PO-MO-217
Predictors of intention to screen for vCJD and appropriate interventions to support this decision
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Objectives: Individuals with hemophilia and other bleeding disorders are considered to be at high risk for infection with variant Creutzveldt-Jakob disease (vCJD) and are considered to be a public health risk. Due to the current work in the UK on the development of an accurate test for vCJD, this study aimed to identify cognitive predictors of intention to be tested for vCJD once a test became available and also the services required to support this decision.
Methods: Ninety men and women with hemophilia and other bleeding disorders were recruited through the U.K. Haemophilia Society. A questionnaire evaluating components of an extended Theory of Planned Behaviour (TPB) in order to predict vCJD screening was used (attitudes towards screening, subjective norms, self-efficacy, perceived control, and anticipated regret). Several models were tested using Structural Equation Modelling (SEM).
Results: Intention to undertake vCJD screening was high with 65% intending to be screened. The tested structural models for the TPB all fitted well. Self-efficacy and a latent variable combining attitudes and anticipated regret components together (labelled *behaviour evaluation*) explained 71% of the variance in intention to screen. In terms of subjective norms, those relating to the attitudes of family and friends proved important,

and those of doctors were non-significant. The effect of subjective norms on intention seemed to be mediated by behaviour evaluation.
Conclusions: Identifying predictors means simple interventions can be developed that can be used to address these factors to help people reach a decision that is right for them. For example, the results suggest that development of educational information should address salient attitudes, subjective norms, and perceptions of control. In addition, outcome simulation role play would address anticipated emotional responses to testing. Significant others such as friends and family could be invited to be involved in the decision-making process.

PO-MO-218
Beyond surviving: An evaluation of the therapeutic benefits of making art for people living with bleeding disorders and co-infection

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Reason for the study: Following a request from within the co-infected community, the Haemophilia Society (UK) facilitated a series of workshops led by a professional photographer. The aim was to use image-making as a means to enhance reflection skills and help develop a safe space within which to consider any emerging reactions. This study represents our investigation of the benefits of using photography as a therapeutic intervention.
Methods: Fifty-two people, men and woman, were recruited through the Macfarlane Trust and the Haemophilia Society. All attended a weekend event where they explored photography as an art and photography skills. Each person chose one of their pictures and provided a short written reflection upon it. Those who provided reflections were then interviewed using an interpretive phenomenological analysis approach.
Results: Thematic analysis revealed a number of themes relating to concerns and conflicts including considerations of the distinction between life and death, expression of the fine balance between hope and fear, and feelings of uncertainty. Significantly, some participants declined the opportunity to explore the meaning of their image.
Conclusions: The process of creation can be a potent coping mechanism, but the images themselves are also powerful expressions of both unconscious and conscious feelings and thoughts. As such, they provide an opportunity for this group to make sense of their experiences and offer us valuable insights into their perspective. Unlike other approaches, there is the potential for insight gained through image-making to remain at a personal or preconscious level for those who do not at present wish to explore any insights gained.

PO-MO-219
Psychosocial issues and support for people with hemophilia and their families in India

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Objectives: To identify psychosocial pssues amongst people with hemophilia (PWH) and their families attending a Psychosocial Rehabilitation Camp.
Methods: A pre and post-camp survey was conducted on PWH and their family members attending a Psychosocial Rehabilitation Camp in December 2010. Participants were requested to fill out a structured questionnaire before and after the camp. The pre-camp questionnaire explored briefly the participants' demographic and medical background and existing psychosocial issues. In the post-camp questionnaire, participants were requested to provide feedback on what they had learnt and derived from the camp. Data was pooled and described. Survey response sheets for the pre- and post-camp surveys were coded for pairing and analysis. Anonymity was maintained throughout the survey.
Results: Fifty-five participants (PWH and their family members) took part in the survey, including 10 females, 5 children, 35 adolescents, and 5 adults.
Pre-camp Survey: When confronted, 25 participants discussed their psychosocial issues with family and friends. Twenty participants felt depressed owing to the condition. Fear of threat to life from impending bleeding plagued 20 participants, while 15 others felt that acquiring transfusion-transmitted infections was their biggest fear. Issues relating to social and financial insecurity bothered 30 participants. Five participants felt that the parents were to blame for passing the condition on to their children and also reported feeling the guilt of being a burden on their respective families. When posed with a stressful situation, 30 PWH and/or their family members felt that adopting coping mechanisms helped them.
Post-camp survey: Fifty participants found the camp to be educational and said that it had boosted their self-confidence. Psychosocial counselling provided support for 50 participants and the same number also expressed that more such camps would improve the overall quality of their lives.
Conclusion: Camps provide an important platform to identify, educate and address the psychosocial issues affecting PWH and their families. Participants felt supported and assisted in tackling psychosocial issues with more confidence.

PO-MO-220
Comparative study of family functioning in patients with hemophilia and other diseases

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Introduction: The experience of disease affects the person concerned but also the person's environment. The family is part of growth, development, and greater support for the individual, especially when the person is sick. Family functioning affects coping and adherence to treatment. A dysfunctional family can be a factor of risk, while a functioning family can be protective against the disease process.
Objective: To study family functioning in families of children with hemophilia. To Compare family functioning in patients with hemophilia and other families with disease.
Materials and methods: The studied sample was 83 people (54 families with a child with hemophilia, 15 families with a child diagnosed with an acute illness, and 14 families with children without diagnosis of disease). We used FACES III (Olson et al.). It describes 16 family typologies that are grouped into three groups: best families, normal families, and dysfunctional families.
Results: Descriptive analysis: The overall functioning of the three groups are found within the range of normal families (united cohesion and flexible adaptability). Analysis of variance according to groups shows significant differences ($P < 0.01$) in adaptability: better family functioning families with hemophilia (united cohesion and flexible adaptability) than families with acute disease (separate cohesion and flexible adaptability) and families without diagnosis of disease (united cohesion and chaotic adaptability). The variable of sex does not show significant differences. The variable number of children shows significant differences ($P < 0.01$): a son and more than 4 better family functioning and adaptability than families with 2 or 3 children.
Conclusions: The situation of disease may condition family functioning affecting adjustment and control of it. However, not always implying dysfunctional or risk (as the results indicate). It can be a protective factor.

PO-MO-221
'Schools of families' for parents of children with hemophilia

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Introduction: The Murciana Regional Hemophilia Association has among its objectives to inform, guide, and advise those affected by hemophilia and their families about the disease and its treatment. One of their activities is called 'School of families,' and it provides parents of children with hemophilia, especially parents with young or newly diagnosed children, with information and training on hemophilia and its treatment. The purpose is that the development of the child and family functioning are not conditioned by the illness and they achieve a good quality of life in spite of the disease.
Objective: To inform and educate parents through theoretical and practical workshops on hemophilia and its treatment from medical, psychosocial, and musculoskeletal points of view.
Materials and methods: The program consists of theoretical and practical workshops on hemophilia and its treatment (biopsychosocial approach): learning self-treatment techniques (4 sessions), emotional support (2 sessions), hemophilia treatment and proper use of the factor (2 sessions), and physical exercise and arthropathy prevention (2 sessions). The group is composed of 12 families who come to the headquarters of the Association. Health professionals treat the issues in theoretical and practical exercises while the children are doing recreational activities with volunteers.
Results: Participants report high levels of satisfaction with the activity. After the workshop we observed that 65% of parents have learned the technique of self-treatment, 55% show emotional stability and appropriate coping strategies, 80% have a good knowledge of hemophilia and its treatment, and 50% of children do exercise regularly.
Conclusion: This type of project is an important step in getting people with hemophilia integrated into larger society in a manner similar to any person without the disease.

PO-MO-222
Intentional and unintentional non-adherence to prophylaxis in adolescents and young adults with hemophilia: A pilot study

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Objectives: A pilot study investigating adherence to prophylaxis among adolescents and young adults with hemophilia in the UK was carried out to explore the main issues these individuals experience in relation to prophylaxis. Two types of non-adherence, intentional (i.e. skipping) and unintentional (i.e. forgetting), were considered in relation to the participants' perceptions of their condition and its treatment as well as any difficulties they experience.
Methods: Members of the Haemophilia Society were invited via email to complete an online questionnaire. Inclusion criteria were that participants were aged 13 to 25, had been diagnosed with severe hemophilia, and were following a prophylactic treatment regimen. The final sample consisted of 13 adolescents (aged 13–17) and 8 young adults (aged 18–25).
Results: Fifty per cent reported unintentionally forgetting infusions, but only 10% reported intentionally skipping infusions. Participants fully responsible for their own treatment were 3.5 times more likely to forget (OR = 3.50; CI = 0.397–35.492) and 1.25 times more likely to skip (OR = 1.25; CI = 0.028–56.038) than participants receiving help from a caregiver with their treatment. Those who sometimes forgot were also less concerned about their hemophilia and less emotionally affected by it; they also reported that they had a good understanding of their hemophilia. When asked to indicate which three things they find most difficult in managing their hemophilia, participants' most frequently reported issues were remembering whether today was the day for their prophylaxis (50%), putting the needle into a vein (40%), and logging the treatment record (40%).
Conclusion: Unintentional non-adherence (forgetting) is a bigger problem than intentional non-adherence (skipping). Interventions that encourage support for young people with their infusions and that address their levels of concern about hemophilia and any

misunderstanding they may have about the condition may reduce this level of unintentional non-adherence.

PO-MO-223

Assessing the psychological and disease-related burden in children with hemophilia and arthropathy: A single-centre study in China

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Background: Children with hemophilia (CWH) who are living in China do not have the same access to modern hemophilia care and (near) normal quality of life as children with hemophilia in developed countries.
Objectives: To assess the psychological status and disease burden for Chinese CWH with arthropathy and analyze the factors that can affect this.
Methods: We used 2 Chinese tools: Inventory of Subjective Life Quality (ISLQ) and Family Burden Scale of Diseases (FBSD) to assess the study group (CWH with arthropathy and their parents) and the control group (normal children and their parents) in a single pediatric hemophilia centre in China.
Results: (1) Psychological assessment (ISLQ): 62 CWH and 52 normal children were enrolled (patients' age $P > 0.05$). The study group showed worse results than the control group (all in cognitive, emotional, and general assessment, $P < 0.01$). Age, hemorrhage frequency, school absences per month, number of diseased joints, Bathel score and Gilbert score didn't shown as factors that potentially affected the worse result in study group (P: 0.096~0.859). (2) Disease burden (FBSD): 91 parents in the study group and 11 parents in the control group were enrolled (patients' age $P > 0.05$). The study group showed worse results than the control group (23.87 ± 10.90 vs. 5.36 ± 3.10, $P < 0.01$). Age, hemorrhage frequency were not (P: 0.141~0.858) but school absences per month, number of diseased joints, Bathel score and Gilbert score (P: 0.007~0.011) were the potential affected factors for the heavier disease burden in study group.
Conclusions: CWH with arthropathy in China have a worse psychological status and a heavier disease burden. The poor conditions of daily life and reduced functioning of diseased joints might be the causes.

37-QUALITY OF LIFE ISSUES

S-TU-01.2-3
Optimizing treatment for hemophilia: Individualization is key

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Repeated bleeding in large joints and muscles is the hallmark of hemophilia. Especially in severe hemophilia, bleeding may occur spontaneously or after minor trauma. Repeated bleeding eventually results in hemophilic arthropathy, causing joint destruction, chronic pain, and loss of quality of life. In the 1960s, Professor Nilsson from Sweden first started prophylactic infusions with clotting factor to prevent bleeding. This was very effective and prophylaxis has now become the recommended treatment for all boys with severe hemophilia in all available guidelines. Different regimes are used. The Swedish start prophylaxis before the onset of joint bleeding, at about 12 months. Infusions are started $1 \times \text{week}^{-1}$, and frequency is increased to $3–3.5 \times \text{week}^{-1}$ within 3 months. Dosages are 25–40 IU kg^{-1}/infusion. The Dutch start prophylaxis after the first joint bleed or severe soft tissue bleed. Initial frequency is once weekly, 25 IU kg^{-1}, increased after each bleed, until reaching $3–3.5 \times \text{week}^{-1}$. Dosage is adapted according to breakthrough bleeding, usually to 10–20 IU kg^{-1}/infusion. The Canadian prospective study starts prophylaxis before 30 months, with 50 IU kg^{-1}1x/week, increasing after 3 bleeds in 1 joint or 4 bleeds/3 months to 2×30 IU kg^{-1}, and 25 IU kg^{-1} every other day. Issues of cost, venous access, and acceptance still affect the introduction and use of prophylaxis in clinical practice. Although all regimens aim to prevent bleeding, patients' bleeding patterns and requirements vary widely. It is well established that prophylaxis is most effective when started early, but the optimum age should be established individually as the onset of joint bleeding may occur between 0.3 and 5.8 years. After starting, dose and frequency of prophylaxis should be adapted to the patient's bleeding phenotype and activities. Optimum prophylaxis is individually tailored, requiring experience, adherence, and multidisciplinary support.

S-TU-01.2-2
Health care utilization and cost of care: Insights from the hemophilia utilization group study (HUGS)

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Background: Hemophilia Utilization Group Study Va (HUGS Va–persons with Hemophilia A) and Vb (HUGS Vb–persons with Hemophilia B) are two prospective, longitudinal, multicentre cohort studies designed to evaluate cost of care and burden of illness among persons with hemophilia in the United States (US).
Summary: Geographically representative cohorts of persons with factor VIII or factor IX deficiency were recruited from 6 federally sponsored Hemophilia Treatment Centers (HTCs) in HUGS Va and 10 HTCs in HUGS Vb. Data were collected on sociodemographics, clinical characteristics, health insurance coverage, comorbidities, access to care, health care utilization, self-rated joint pain and motion limitation, and health-related quality of life (HRQoL) over 2 years from participants or parents of children less than 18 years. A total of 329 participants (50.2% children) were recruited in HUGS Va (enrollment ended July 2007). As of November 2011, HUGS Vb has 108 participants (54.6% children). Results from HUGS Va show that factor cost (reflecting factor use) increases with increasing hemophilia severity and is greater in those with severe hemophilia on prophylaxis (US$275,324 $year^{-1}$) versus episodic treatment (US$159,761 $year^{-1}$). However, participants with severe hemophilia on prophylaxis incurred lower non-factor healthcare costs (US$2,852 $year^{-1}$) compared to those with severe hemophilia on episodic treatment (US$16,185 $year^{-1}$). Except among those with severe disease, children and adults in the study have HRQoL scores comparable to those of the healthy US population. The physical aspects of HRQoL in both adults and children decrease with increasing severity of illness, but the scores for the mental aspects are similar across all severities.
Implications: HUGS is the largest US prospective study of persons with hemophilia, with a study population representative of the hemophilia A and B populations in the US. The findings from this study will help policymakers and payers identify and address the specific needs of individuals with hemophilia.

PO-TU-206
What do Canadian men living with hemophilia need to know to facilitate optimal disease management? A mixed methods approach

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Objectives: Objectives of this study were to determine what individuals with hemophilia need to know about the disease and its treatment from the perspectives of adults with hemophilia and healthcare professionals who treat hemophilia, to inform education strategies/interventions and to facilitate optimal disease self-management.
Methods: In Phase 1 of the study, 3 focus groups and 2 interviews were conducted with healthcare professionals ($n = 13$) to explore their thoughts on what individuals with hemophilia know and need to know about the disease. In Phase 2, the results from the analysis of the qualitative data were used to develop a survey that was sent to men living with hemophilia at 3 hemophilia treatment centres (HTCs) in Canada. In Phase 3, results from the qualitative analysis and the survey will be used to develop recommendations for educational interventions to address any gaps identified by participants.
Results: Major themes to emerge from the qualitative data in Phase 1 included: understanding the pathology of hemophilia; potential causes and consequences of bleeds; preventing, recognizing, and treating bleeds appropriately; anticipating potential complications and making lifestyle choices to minimize the risk of complications; lifestyle issues, including activity selection, career choice, sexuality, reproduction, travel, and aging; and psychological issues, including anger, anxiety and grief related to having hemophilia. Participants made recommendations about knowledge sharing and education, stressing that knowledge needs change through the lifecycle and that education should be individualized. Participants discussed the challenges they had experienced, including lack of time for education and the knowledge transfer gap between parents and adolescents. Quantitative survey data from Phase 2 will be analyzed using descriptive statistics to summarize knowledge levels and determine correlations between these and other variables.
Contributions to practice: This mixed-methods study will identify knowledge gaps and make recommendations about educational strategies/interventions contributing to optimal disease management for individuals with hemophilia.

PO-TU-207
The effect of yoga technique on quality of life in children and adolescents with hemophilia

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Background: Hemophilia is a chronic bleeding disorder that can disrupt activities and impair quality of life. Nowadays, hemophilic patients are widely advised to participate in sport and exercise to improve the quality of life, and yoga may help. So, we investigated the effects of yoga techniques on the number of bleedings, absence from school, referrals to the clinic, and quality-of-life scores of children and adolescents with hemophilia.
Methods: In this clinical trial, 27 boys between 8–16 years of age with hemophilia A or B participated. Data was collected using a Hemo-QOL questionnaire (long version). Then, intervention was done for 14 weeks of yoga practice, including 8 weeks of attendance at classes and 6 weeks of exercise at home using an educational CD.
Results: The mean number of bleeding events, absence from school, and quality-of-life scores in both age groups were significantly reduced after the intervention ($P \leq 0.001$).
Conclusion: yoga techniques, as a physical, mental, and psychological practice, can be helpful without risk for injury in reducing the number of bleedings, referrals to the clinic, and absentees from school, by improving perception of quality of life. Yoga can reduce bleeding and has benefit when factor replacement therapy is not enough or readily available, especially, in developing countries such as Iran.

PO-TU-208
Cross-cultural adaptation of the Hemo-QOL questionnaire into 28 languages

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Objectives: The Hemo-QOL questionnaire was developed to assess health-related quality-of-life (HRQOL) in children with hemophilia. Three different age-group versions (I:4–7 [21 items], II:8–12 [64 items], III:13–16 years [77 items]) are available, as well as three respective proxy versions for parents. The original questionnaire was developed in German and translated into U.K. English. Since capturing HRQOL aspects of hemophilia care has become an integrated part of clinical trials in this field, it is important to ensure that the questionnaires used are linguistically validated for international use. The objective of this study is to present the cross-cultural adaptation of the Hemo-QOL into 28 languages representing six different language families (Indo-European, Ural-Altaic, Afro-Asiatic, Japonic, Sino-Tibetan, and Austronesian).
Methods: The U.K. version was translated using a multi-step methodology: 1. Development of a concept list; 2. forward/backward translation (or adaptation step or quality check); 3. review of the backward translation and report by the developer of the original instrument; and 4. review of the translation by a clinician. Difficulties encountered during the process were categorized as Grammatical, Idiomatic, Semantic/Conceptual, and Cultural.
Results: Fifteen items raised a lot of discussions for semantic (12 items), cultural (2 items), and idiomatic reasons (1 item). For instance, the question 'What about relationships?' could not be translated as such in most of the countries. In some languages, additional wording was required to reflect the original meaning implied in 'relationships': e.g., 'relationships with girls' (Italian, French Canadian, Japanese), "personal relationships" (Malay, Polish), or "love relationships" (Croatian, Serbian). Further examples will be presented.
Conclusion: The cross-cultural adaptation of the Hemo-QOL into 28 languages required international collaboration and enabled the production of conceptually equivalent and culturally appropriate tools. The same process was used for the Hem-A-qol (for adults) and the treatment satisfaction questionnaire (Hemo-Sat). When applied, these validated tools will provide insights into an area of hemophilia not well understood in the past.

PO-TU-209
Cross-cultural adaptation of the Canadian hemophilia outcomes: Kids' life-assessment tool (CHO-KLAT) in 11 languages

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Objectives: The Canadian Hemophilia Outcomes: Kids' Life Assessment Tool (CHO-KLAT$_{2.0}$) is a disease-specific measure of health-related quality of life (HRQL) that was developed from the perspectives of boys with hemophilia. The questionnaire is available for both self-report and parent/proxy-report. The CHO-KLAT was developed in Canadian English and adapted for use in seven additional languages to facilitate use in international clinical trials as well as in the routine clinical care setting. The objective of this study is to describe the process developed to achieve rapidly the cross-cultural translations into 18 other languages corresponding to seven countries (Australia [English], Hong Kong [Cantonese, English], India [English, Hindi, Kannada, Marathi, Malayalam, Tamil, Telugu], Poland [Polish], South Africa [Afrikaans, English, Sesotho, Zulu], Turkey [Turkish], U.S.A. [English, Spanish]).
Methods: The original version of the CHO-KLAT went through a translation process involving several steps: 1. forward and backward translation; 2. clinician's review; 3. cognitive debriefing (on a minimum of five boys with hemophilia to test the child-report version and five parents of boys with hemophilia to test the proxy/guardian version). For the 'translation' into other English languages, step 1 was replaced by an adaptation step during which the suitability of the Canadian English original in the linguistic and cultural context of the target countries was verified.
Results: The cross-cultural translation process is currently on-going. Difficulties encountered during the process will be presented and categorized as follows: cultural (country-specific aspects), lexical, grammatical, idiomatic, and due to format (scripts, lay out). A selection of solutions found to overcome these difficulties will be presented.
Conclusion: The cross-cultural adaptation of the CHO-KLAT into 18 additional languages required an international collaboration and followed a rigorous methodology to ensure the production of conceptually equivalent and culturally appropriate translations.

PO-TU-210
Prophylactic versus on-demand treatment with rFVIIa in hemophilia patients with inhibitors: A decision-model analysis

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Introduction: Congenital hemophilia is a rare hereditary bleeding disorder characterized by repetitive musculoskeletal bleeding episodes. Treatment with clotting factor VIII or IX can control bleeding and prevent chronic joint disease. About 20%–30% of patients with hemophilia A will develop inhibitors rendering replacement treatment useless and leaving bypassing agents such as rFVIIa as the only alternative treatment. In recent years, prophylaxis with rFVIIa has been used as an option to improve joint health in inhibitor patients. However, the specific role of this strategy remains to be defined.
Objectives: To determine which of the two treatment strategies, on-demand or prophylaxis with rFVIIa, results in better utilities for patients with hemophilia and inhibitors.
Methods: Using probabilities of developing chronic arthropathy after 5 years of bleeding episodes, we constructed a decision model comparing on-demand and prophylaxis treatment with rFVIIa. Utilities were obtained from interviews with 5 hemophilia patients and 5 physicians using a visual analogue scale. Sensitivity analyses were performed for all probabilities between 0–1 and for all different values of quality-adjusted life years (QALYs) obtained.
Results: Using the average QALYs obtained from the interviews, the on-demand arm gave a 1.54 QALY gain in a 5 year timeline, while the prophylaxis arm resulted in a gain of 2.70 QALYs. After sensitivity analyses, prophylaxis almost always remained the better option, only reaching a breakeven point when the probability of reducing bleeding episodes was <16%. When the sensibility analyses were repeated with the QALYs that showed less difference between arms, prophylaxis was still the better choice as long as bleeding episodes are reduced ≥41%.
Conclusions: In our analysis, prophylaxis with rFVIIa appears to be a better treatment option for patients with inhibitors. This advantage is more noticeable with higher response probabilities. Prophylaxis could be offered to all patients with inhibitors, aiming for a reduction ≥40% of bleeding episodes.

PO-TU-211
Quality of life of hemophilic children on prophylactic or on-demand treatment regimens in Iran

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Background: Treating a chronic disease such as hemophilia is to improve the symptoms and quality of life (QOL) of the patients. This study aimed to assess the QOL of hemophilic children between 4–16 years old and compare it between patients receiving prophylactic or on-demand treatments in Iran, as a developing country.
Methods: In this descriptive-comparative study, we enrolled 90 patients from three main hemophilia care centres in Tehran, 60 patients in the age group 4–7 (group 1) and 30 in the age group 8–16 (group 2). Half of the patients in first group were receiving prophylactic and half were receiving on-demand treatment. Patients in second group only received on-demand treatment. The research tool used was the short form of the Hemoqol questionnaire, which assesses QOL in 9 dimensions (physical, feeling, family, friends, others, school, attitude, treatment, and behaviour). In this instrument, higher points correspond to lower QOL. All analyses used a two-sided test of significance and the level of 0.05 was considered positive. Paired and independent *t*-test, Mann Whitney, Fisher, and Chi Square tests were applied as appropriate.
Results: The mean QOL in the first group receiving prophylactic and on-demand treatments were 2.6 ± 0.3 and 3.33 ± 0.4 respectively ($P < 0.001$). Other dimensions except 'treatment' and 'feeling' were different between groups. Patients in the second group had poorer QOL than patients in first group receiving on-demand treatment ($P < 0.001$). In first age group, the highest impairment in patients, regardless of their treatment regimen, were family and physical dimension respectively. In the second age group, the highest impairment was in the sport's dimension.
Conclusion: It is necessary to pay more attention to prophylactic treatment in hemophilic children especially at earlier ages to maintain their QOL.

PO-TU-212
The place of the pictorial blood assessment chart in the appreciation of quality of life in women with inherited bleeding disorders

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Issue: The quality of life in women with inherited bleeding disorders (IBD) seems impaired by menstrual blood loss. This is difficult to quantify, hence, the use of semi-quantitative scores such as the Higham score (score ≥ 100 is equivalent to menstrual blood loss of more than 80 mL).
Objective: To assess the impact of menstrual blood loss (appreciated by the mean of a pictorial blood assessment chart PBAC) on the quality of life in women with inherited bleeding disorders.
Methods: Eighteen women with various inherited bleeding disorders were interviewed. They completed a PBAC and a quality of life questionnaire.
Results: The Higham score mean per patient per menstrual cycle was 98.5 ± 66.44. Eleven patients (61.1%) had a Higham score of <100. The rate of patients claiming to have an intense dysmenorrhea (score ≥ 4) was 16.67%. The score of the impact of dysmenorrhea on daily life averaged 2 ± 1.78. Fourteen patients (77.8%) believed that dysmenorrhea had a minimal impact on their daily lives. Six patients (33.3%) consider their general condition as moderate. Of patients with a mild general condition, 50% (3 of the 6) had a pathological PBAC. If PBAC is pathological, the mean score assessing quality of life on menstrual period was 7.14 ± 2.11, whereas it was only 3.54 ± 3.17 when PBAC is normal.
Conclusion: Alteration of individual scores of quality of life is found in women with an IBD, but given the small size of our population, we cannot demonstrate a correlation between the degree of blood loss and quality of life.

PO-TU-213
Quality of life during menstruations in women with inherited bleeding disorders (31 patients)

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Background: Menstruations, by their abundance and their duration, can be a source of impaired quality of life. Women with inherited bleeding disorders appear to be especially at risk.
Aim: To assess the impact of menstrual blood loss on the quality of life for women with inherited bleeding disorders.
Material & methods: Thirty-one women with various inherited bleeding disorders were interviewed. They completed a quality of life questionnaire.
Results: Von Willebrand disease was the most frequent inherited bleeding disorder in our population (38.7%); 54.8% of patients had a menstrual period of more than 6 days, and 61.3% of them consider their menstrual flow to be normal. The general condition apart of the menstrual period was considered medium to poor in 35.5% of patients. The average score assessing the impact of menstruation on daily life was of 5.00 ± 3.47. Only 19.35% of patients felt that dysmenorrhea significantly affected their quality of life. Impaired quality of life was seen in 64.5% of patients according to score A and in 41.9% of them according to score B. During menstruation 22.6% of the patients didn't do to work or school because of their menstrual flow. On the other hand, 48.4% of patients were hospitalized at least once for a heavy menstrual flow.
Conclusion: The quality of life during menstruation in women with an inherited bleeding disorder, according to the different scores, appears altered. Although because of the small size of our study population, we could not prove a correlation between the importance of menstrual blood loss and the impairment of quality of life.

PO-TU-214
Dissimilarity of daily lives and joint damage between young and middle-aged people with hemophilia in Japan

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Introduction: More than 30 years have passed since the approval of self-infusion and the beginning of home-infusion therapy for people with hemophilia (PWH) in Japan. We had

a questionnaire survey about self-infusion, regulatory replacement therapy (RRT), joint damage, and daily lives, and analyzed the effectiveness of self-infusion or RRT in young and middle-aged people.
Method: The survey was done at 5 institutions in Japan from 2007 to 2008. The items questioned were about RRT, history of sports, difficulty of climbing steps, walking, and so on. The questionnaires were collected and the data was divided into two groups (Group I: patients up to 34 years old, Group II: patients more than 34 years old).
Results: The number of persons in group I (GI) was 37 and in group 2 (GII) was 51. The adoption ratio of RRT in GI was significantly higher than that in GII ($P < 0.05$). People in GI had experienced more sports than people in GII had ($P < 0.05$). Most people in GI did not have problems with steps or walking, but most people in GII had some difficulty with them. Concerning the recent bleeding joints, there was no significant difference in ankles between GI and GII, though people in GII had a higher frequency of bleedings in the left elbow and both knees than people in GI.
Discussion: As most adolescents or young adults adopted RRT, they might be conscious of prophylaxis well. Since middle-aged people had rarely played sports, it was suspected that they had not been permitted to play sports or to attend physical training at school in order to prevent bleedings. There was usefulness of RTT in adolescents or young adults from the data. However, it was clear that ankle joints were easy damaged even when RRT was used.

PO-TU-215
Quality of life and satisfaction with hemophilia therapy in patients in Rio Hortega Hospital: The patient's perspective

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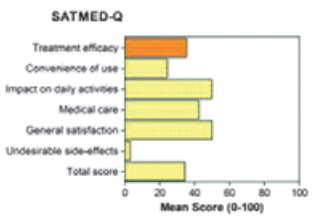
Introduction: Hemophilia Health-related quality of life (HRQOL) questionnaires provide an opportunity for patients to report their own experiences of their general functioning and well-being. In order to make continuous improvements, health professionals have to be aware of patient satisfaction. The aim of this study was to describe treatment satisfaction and HRQOL of a sample of patients attended to in our hospital.
Methods: Twenty hemophiliac patients were invited to complete a treatment satisfaction validated scale (SATMED-Q), additional questions on their satisfaction, the HRQOL questionnaire EQ5D, and A36 Hemo-QOL. Questionnaires were analyzed according to their manual.
Results: Mean age (SD) was 35.6 (17.2) and most patients were early diagnosed (12 patients). Hemophilia A was present in 69.2% and hemophilia B in 30.8%. Four persons had severe hemophilia, 3 mild, and 8 moderate. Fifty per cent were on prophylactic treatment and 50% on demand; 57.1% were self-treated, 28.6% required professional aid, and 14.3% received help from a relative. SATMED-Q results are provided in fig. 1. Only 25.5% declared feeling generally well (euroqol-5D), and 57.1% reported pain or discomfort, with EQ-VAS (SD) 68.7 (28.6). A36-Hemophilia QOl total score was 86 ± 29.28.



Additional satisfaction questions

Patients opinion	Percentage
Medicine conservationis not easy	45.5%
Medicine preparation is not easy	45.5%
Finding injection site is not easy	45.5%
Medicine administrations not easy	45.5%
Administration is not fast	45.5%
Ocasional accidental pricking	100%
Needle and material disposal is not easy	45.5%
I am not anxious during injections	91.7%
I feel comfortable doing this myself	63.6%

Conclusions: Although data collection is ongoing, these preliminary results suggest that some patients are experiencing difficulties and that patient care for hemophiliacs could be improved with good treatment planning and patient training. This information will help us improve the overall quality and delivery of hemophilia assessment and care.

PO-TU-216
Factors related to quality of life in hemophilia patients

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There are many factors that affect hemophilia patients' quality of life, intra-articular bleeding, inhibitor, synovitis, arthropathy, disability, and infection caused by transfusions using unheated blood products (but this in particular is open to some debate). This study aims to find a determinant of health-related quality of life (HR-QOL) in hemophilia patients. The subjects were 691 patients aged 16 and over who were registered with 12 hemophilia centres in Japan. The main points investigated were the subjects' biographical data, such as age, coagulation factor levels, employment, levels of satisfaction regarding physical and mental support, level of activity of daily living (ADL) accomplishment, and health-related quality of life using the RAND 36-item Health Survey 2.0 Japanese version (SF-36). Analysis focused on two SF-36 summary scores, Physical Component Summary (PCS) and Mental Component Summary (MCS). There were 259 (37.5%) valid responses. The average age was 40.9 years old. There were 65% severe cases, 18% moderate, and 17% mild or unknown; 78.2% of the subjects were HCV-positive; 35.2% were HIV-positive; 13.0% were inhibitor-positive; and 69.4% of the subjects were employed or educated. According to stepwise logistic regression analysis, the significant factors influenced on PCS were ADL and work-related problems, and the significant factors influenced on MCS were the number of bleeding episodes, HCV, satisfaction with family support, work-related problems. Comprehensive intervention is necessary to manage HCV and bleeding, improvement of ADL, vocational assistance, and both physical and mental support from family in order to improve the hemophilia patient's HR-QOL. In particular, improvement of ADL is necessary in order to improve physical aspects of HR-QOL for hemophilia patients. And vocational assistance is necessary in order to improve mental aspects of HR-QOL.

PO-TU-217
Health-related quality of life among hemophilia patients in the Northeast region of Indonesia

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Background: Patients with hemophilia face a number of psychosocial challenges that affect their family and personal life, education, employment, and their daily life as a whole.
Objectives: To know the health-related quality of life among hemophilia patients in North East region of Indonesia.
Methods: A cross sectional survey was conducted in August 2011. Patients or caretakers were asked to fill out a PEDSQL® (Pediatric Quality of Life Inventory) questionnaire that consisted of questions about physical functioning, emotional functioning, social functioning, and school functioning.
Results: Thirty-three out of 34 questionnaires were returned, with a response rate of 97%. The age among these patients has a large range. The youngest patient was 6 months old and the eldest was 43 years old. Six patients were under 3 years of age so the questionnaires were filled out by their caretakers. The average score regarding questions about physical functioning was 58.7, which meant that our patients with hemophilia suffered a great impact in their physical functioning due to hemophilia. Most of the patients had difficulty running. The average score regarding emotional functioning was 71, which showed that hemophilia does have an emotional impact on our patients; most of them frequently feel angry about their condition. Seventy-six point six was the average score for questions regarding their social functioning. Our patients stated that they cannot do things that other normal people do, which affects their emotional functioning. Regarding questions about their school/work-functioning, the average score was 63.7. The most frequent problem reported was the absence rate from school/work due to their conditions, which required them to go to the hospital to get treatments. Overall, the health related quality of life score was 67.5, which was deemed to be an unfit result.
Conclusions: Health related quality of life among hemophilia patients in North East region of Indonesia is not satisfying. Efforts should be made to improve the health quality of life among patients.

PO-TU-218
Quality of life (QOL) and well-being of hemophilia patients and parents managing hemophilia: Hero study analysis

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Objectives: To describe the QOL and impact of hemophilia on patients and their families.
Methods: Patients (≥18 years) completed euroqol-5D from which EQ-5D Index was derived to allow comparison with other chronic diseases. Patients and parents of patients <18 assessed impact on life.
Results: For 509 patients completing EQ-5D, the mean/median index was 0.73/0.76; problems were noted with mobility (58%), self-care (20%), usual activities (47%), pain/discomfort (74%), and anxiety/depression (46%). On an 11-point visual analogue scale assessing 'health,' 30% of patients reported scores ≤ 50 with midpoint 34% on-demand vs. 25% prophylaxis, $P < 0.05$). Eighty-nine percent indicated pain interfered with daily life (54% moderate/extreme interference); 50% reported constant pain. Inhibitor patients more frequently reported only bleed-related pain (59% vs. 40%, $P < 0.05$). Of 503 parents, 91% felt involved in treatment decisions and coped well, but 94% wished others understood hemophilia better. Fifty-four per cent felt disappointed their son had hemophilia. While 74% of mothers felt guilty for passing on hemophilia (inhibitors' mothers 90%), fewer fathers (54%) perceived the mother's guilt. Most parents felt their son's hemophilia did not influence their relationship (65%), did not make their son feel isolated (56%), did not prevent desired holidays/vacations (66%), and did not interfere with his relationships at school (54%). In the past 5 years, 23% of patients received treatment for psychological conditions (36% US, 17% non-US); 17% of parents reported treatment for their son. Patient/caregiver future outlook, assessed on a scale from (1)-very pessimistic to (7)-very optimistic, was mean (median) 5.0(5)/5.4(6). Key issues for patients/caregivers were "education and employment" (24%/20%), "well-being and QOL" (18%/14%), and "treatment/interactions with healthcare professionals" (18%/14%).
Conclusion: Mobility and pain interfere with QOL, particularly for patients with inhibitors, with a similar magnitude to other arthritic conditions but in a younger population. Hemophilia impacted day-to-day QOL for the patient and family.

PO-TU-219

A multi-national survey assessing the relationship between prophylaxis treatment and health-related quality of life among severe hemophilia A patients

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Introduction: Research has shown that hemophilia A patients report lower health-related quality of life (HRQOL) compared to the general healthy population. While a primary prophylaxis (PP) treatment regimen reduces bleed rates, it remains unclear if it is associated with improved HRQOL. The objective of this analysis was to determine if a treatment regimen was associated with improved HRQOL among hemophilia A patients.
Methods: This cross-sectional survey of severe hemophilia A patients ≥18 or older, or the parent/caregiver of patients aged 2–17, was administered in collaboration with hemophilia associations or hemophilia treatment centres/hospitals in Argentina, Chile, Colombia, Mexico, the United States, and Russia. Eligible, consenting patients completed a detailed questionnaire in one of two phases: from October-November 2009 (Argentina, Russia, and the U.S.A.) or June–August 2011 (Chile, Colombia, and Mexico). HRQOL was measured by the Short Form 12 (SF-12) for adults and the Pediatric Quality of Life (PedsQL) for children. Treatment regimen and other treatment characteristics were also assessed.
Results: Seven hundred twenty-eight severe hemophilia A patients participated in this study, with 56% adults. Overall, 401 (55%) patients were either on primary (13%, PP) or secondary (42%, SP) prophylaxis. An ordinary least squares regression was performed with SF-12 Physical Component Score (PCS) as the dependent variable, and PP and SP as independent variables. Age and country were also included as control variables. PP patients had on average a higher physical HRQOL score of 9.35 compared to on-demand (OD) patients after adjusting for age and country ($P = 0.0133$). A comparable analysis among children using the Physical Summary score of the PedsQL revealed a similar trend, with PP patients having a higher physical HRQOL score of 6.42 compared to OD patients after controlling for age and country ($P = 0.006$).
Conclusions: Results suggest that severe hemophilia A patients who begin prophylaxis treatment at an early age may experience improved physical HRQOL.

PO-TU-220

Assessment of prophylaxis therapy, bleed rates, and quality of life among hemophilia patients with inhibitors: A cross-sectional survey across four countries

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Introduction: Hemophilia patients with inhibitors face significant challenges in controlling bleeds and have higher risk for arthropathy, which may impact quality of life (QOL). This analysis assessed treatment patterns with bypassing therapies as well as bleed rates, treatment regimen, and QOL among inhibitor patients across 4 countries.
Methods: A cross-sectional survey was administered to hemophilia A or B patients aged 18+ or the parent of a patient aged 2-17. Patients must have been diagnosed with inhibitors for at least 1 year and on a bypassing agent (prophylaxis or on-demand) at the time of the study. Patients were recruited from hemophilia treatment centres/hospitals in the U.S.A., U.K., Italy, and Argentina. Participating patients completed a questionnaire from January–February 2011. QOL was measured by the Short Form 12 (SF-12) for adults and the Pediatric Quality of Life (PedsQL) for children. Treatment regimen and bleed rates were also assessed.
Results: Sixty-one inhibitor patients participated in the study (U.K. = 17, US = 17, Italy = 16, Argentina = 11). Nearly half (48%) were parents of patients under 18. Thirty per cent were on a prophylaxis treatment regimen. Of these patients, 72% reported <2 bleeds per month after beginning a prophylaxis regimen. Both the adult and pediatric patients in the U.K. reported the highest median bleed rates (24.8) compared to the U.S.A., Italy, and Argentina (9.4, 7.5, and 10.5, respectively). Adult patients in the U.K. reported the lowest SF-12 Physical Component scores (30.7), while Italian patients reported the highest (41.8). Among pediatric patients, the U.K. had the lowest Physical Summary scores, while US patients had the highest (44.1 and 73.8, respectively).
Conclusions: Inhibitor patients reported lower bleed rates after starting prophylaxis, and countries reporting higher bleed rates had lower physical QOL scores. Prophylaxis therapy with bypassing agents may reduce bleed rates and improve QOL in hemophilia patients with inhibitors but further studies are needed.

PO-TU-221

A comparison of pediatric hemophilia patients with and without inhibitors in the US: assessment of health-related quality of life and joint outcomes

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Introduction: The challenges of having hemophilia may be greater for those with inhibitors compared to those without due to differences in patient characteristics. This analysis compared health-related quality of life (HRQOL) and joint outcomes between inhibitor and non-inhibitor pediatric hemophilia patients in the USA
Method: Two cross-sectional surveys were conducted among US parents/caregivers of hemophilia patients aged 2–18 years. The first was in hemophilia A patients without inhibitors and the second in inhibitor patients with hemophilia A or B. Demographics, treatment characteristics, HRQOL as measured by the Pediatric Quality of Life Inventory (PedsQL), age at first joint pain, number of total and joint bleeds in the past 12 months, bodily pain and motion limitation data were collected. Non-parametric statistics were used to compare the outcomes between the two groups.
Results: Parents/caregivers of 53 non-inhibitor (mean age: 10.5 ± 3.9) and eight inhibitor patients (mean age: 12.5 ± 4.2) participated in the respective surveys; 95.9% of non-inhibitor patients and 25.0% of inhibitor patients reported receiving prophylaxis treatment. Inhibitor patients had significantly lower total PedsQL (66.7 ± 9.9 vs. 78.2 ± 15.3, $P = 0.0285$) and emotional functioning scores (65.6 ± 12.1 vs. 77.2 ± 19.6, $P = 0.0489$) compared to non-inhibitor patients. Among inhibitor patients, there were no significant differences in PedsQL scores between prophylaxis and on-demand. Inhibitor patients also experienced significantly more joint bleeds (4.8 ± 3.1 vs. 3.1 ± 4.7, $P = 0.0059$) in the 12 months prior to the survey and developed significantly more target joints (3.8 ± 0.5 vs 0.6 ± 0.8, $P < 0.0001$). More non-inhibitor patients (60.4%) reported a full range of motion compared to inhibitor patients (25.0%), although similar proportions of non-inhibitor (90.6%) and inhibitor patients (87.5%) reported none or slight bodily pain that interfered with their activities.
Conclusion: Pediatric hemophilia patients with inhibitors experience worse HRQOL and self-reported joint outcomes than non-inhibitor patients. Increased understanding of the impact of inhibitors on HRQOL and joint outcomes may guide improvements to care for inhibitor patients.

PO-TU-222

Assessment of QOL in Korean hemophiliacs: The impact of health- related factors, social state, and a treatment factor on QOL of Korean hemophiliacs

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Objectives: Health-related factors, treatment factors, and the social aspects of hemophilia patients may have an impact on their quality of life (QOL). However, the impact of these factors, especially social aspects and treatment factors, may be different among countries with different social and cultural backgrounds and treatment approaches. Therefore, identification of those factors in each country is vital to establishing potential strategies to intervene in hemophilia patients. For this reason, the impact of health-related factors, a treatment factor, and social aspects on QOL of Korean hemophilia patients were evaluated.
Methods: Data were collected from questionnaires and reviews of the medical records of Korean hemophilia patients over 17 years of age. QOL was evaluated with the standardized questionnaires of SF36. The disease- and health-related factors, such as the severity and type of disease, presence of inhibitor, HCV and HIV infection history, disability, and history of analgesic use were obtained from medical records. Arthropathy was evaluated by a patient's perception of involved major joints, both knee, ankle, and elbow joints. Socio-demographic data such as marital state, occupational state, and education years were obtained by questionnaires. Self-injection ability, as a treatment factor, was evaluated by self-injection diaries and questionnaires. Age-adjusted partial correlation analysis and multiple regression analysis were conducted to elucidate the impact of these observed data on QOL of the patients.
Results: Similar to results of other studies, the severity of hemophilia, inhibitor presence and other disease- and health-related factors were correlated only with several physical health scales of SF36. Marital status, the only social aspect correlated with QOL of hemophilia patients in Korea, also had an impact on the physical health scale. However, self-injection score, the only treatment factor surveyed in the study, was significantly associated not only with physical health but also with mental-health scales of Korean hemophilia patients.
Conclusion: Health-related factors and social state had impact only on the physical health of Korean hemophilia patients. A treatment factor, self-injection ability, had impact on both the physical and mental health of these patients.

PO-TU-223

Patient-reported outcomes in clinical hemophilia practice

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Objectives: Children with congenital bleeding disorders may experience health-related quality of life (HRQOL) problems. Two multicentre studies measuring the effect of electronic patient-reported outcomes (ePROS) in clinical pediatric practice pointed out that discussing HRQOL during consultation increases the psychosocial items discussed and the identification of emotional problems. The aim of this abstract is to describe the implementation of ePROS in pediatric hemophilia practice.
Methods: In September 2011 ePROS were introduced as part of the standard care for children at the Hemophilia Treatment Center AMC. Children (8–18 years) or their parents (if the child is <7 years) with congenital bleeding disorders completed online HRQOL questionnaires (TNO-AZL Preschool children Quality of Life; TAPQOL or Pediatric Quality of Life Inventory; PedsQL) at the website www.hetklikt.nu before regular consultation. The answers were converted into an epro, the KLIK profile, and discussed during consultation. Before multidisciplinary consultations, patients also filled in a behavioural-problems questionnaire (Strengths and Difficulties Questionnaire; SDQ), which was discussed by a psychologist, and parents completed a distress thermometer (Distress Thermometer for Parents; DTFP), discussed by a social worker.
Results and conclusion: So far, approximately 40 children (25%) with congenital bleeding disorders completed the online questionnaires and discussed the KLIK profile during consultation. Children, parents, and pediatricians are positive about the use of the KLIK profile in clinical practice. With the use of the Internet, KLIK is easy to implement in clinical practice and helpful in facilitating communication about HRQOL. Other Dutch hemophilia treatment centres (HTCs) will start using KLIK in the near future.

Interested?Log in as a doctor on www.hetklikt.nu with 'PRO' as username and 'KLIK' as password to see an example of the KLIK profile. The website is also available in English, including an informative movie about KLIK.

PO-TU-224
Income and anxiousness of working people with hemophilia in Japan

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Aim: To compare income with Japanese general male population and to describe anxiousness in Japanese hemophiliacs.
Method: In 2009 we distributed a questionnaire to Japanese people with hemophilia (PWH) or their families. The data of income and employment status of hemophilia patients, who were of the age of employment, were compared with the general male population, which had been published by the Ministry of Health, Labour, and Welfare. In addition, we analyzed who had a lot of anxiety in the workplace.
Result: Six hundred and sixty-six Japanese patients with bleeding disorders (hemophilia A: 81.7%; B: 15.1%). The operation rate of PWH was low in comparison to the general male population in all age rank groups. PWH were distributed over the low income bracket in comparison to the general male population. The ratio of irregular employment in PWH was higher than the general male population. The employee ratio of PWH with HIV infection was significantly lower than for non-infected people. The employee ratio of PWH with liver cirrhosis and/or hematoma was also low. Seventeen present of regularly employed PWH hoped co-workers would be receptive to their disease. PWH with HIV infection hoped co-workers would be more receptive (25%). In addition, PWH with liver cirrhosis and/or hematoma also had the same hopes (38%).
Conclusion: The employment rate in patients with hemophilia was low, and employment conditions were bad. PWH with HIV infection, liver cirrhosis and/or hematoma had particularly low employment rates. In addition, they also hoped co-workers would be more receptive to their disease. They particularly needed to improve the employment environment and economic support.

PO-TU-225
Treatment outcome in young adults' survey of eight countries: Preliminary results

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In 2009, the authors published the results of a survey of prophylaxis, on-demand, and combined treatment in men aged 20–35 years old with severe hemophilia in four European countries, showing that the quality of life of patients on long-term prophylaxis is significantly better than those receiving on-demand only or individuals who have changed treatment regimens over their lifetime (combined group). In 2011, the survey was repeated and extended to Canada, the Netherlands, Poland, and Romania. The survey was extended in order to further examine the effects of long-term prophylaxis using varying treatment regimens. Preliminary data is now available from 5 countries. The preliminary findings reinforce the findings from the 2009 survey. Over 90% of the on-demand group and 7% of the combined-treatment group have more than 15 bleeds per year. All respondents in the prophylaxis group reported less than 7 bleeds per year. The on-demand group has the highest reported incidence of target joints, serious bleeds, problems with recurring bleeds at the time of the survey, and invasive procedures compared to the prophylaxis or combined-treatment groups. The on-demand group also reported the highest days missed from work, with 5 respondents reporting between 50–105 days of work missed in the last year due to their bleeding disorder. In an EQ-5D questionnaire, the prophylaxis, combined, and on-demand groups had a mean utility value of 0.866, 0.784, and 0.628, respectively.

PO-TU-226
Pilot testing of a disease-specific quality of life questionnaire (Hemo-QOL) in Filipino language for children with hemophilia in a tertiary hospital in the Philippines

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Background: Consensus has been reached with regard to the main components of quality of life (QOL), namely, well-being and function in physical, social, and emotional domains. To capture the individual's perception of health conditions and treatment regimens, self-reporting by respondents is important; hence, disease-specific measures of QOL for children with chronic diseases like hemophilia were developed. The Hemo-QOL project included centres from six European countries, active in developing a pilot test version of the Hemo-QOL questionnaire, and this was linguistically validated in 33 language versions; however, none existed in the Filipino language. To meet the need for an adequate assessment of health-related (HR) QOL in Filipino children with hemophilia, translation and validation of Hemo-QOL questionnaire in our own Filipino language is recommended.
Objectives: The aim of this paper is to conduct a pilot testing of a disease-specific questionnaire (Hemo-QOL) in the Filipino language among Filipino children and adolescents with hemophilia and their parents; to describe the psychometric properties of the questionnaire with regard to reliability and validity; to understand the factors in?uencing scale scores, and to evaluate critically the potential and limitations of the newly developed questionnaire.
Methods: A validation study of the disease-specific Hemo-QOL questionnaire in the Filipino language was conducted among pediatric hemophiliac patients, ages 4 to 16, and their parents/guardians following up at the UST Hemophilia Treatment Centre from January to April 2011.
Results: Preliminary psychometric testing of all 3 revised age-group versions of the Hemo-QOL for both patients and parents have acceptable internal consistency and reliability values, as well as sufficient convergent validity. It was recommended that some of the questions and scales be removed in consideration of the item-reduction criteria.
Conclusion: The translated Filipino version of the Hemo-QOL questionnaire showed adequate reliability and validity to measure the health-related quality of life of Filipino children with hemophilia.

PO-TU-227
Health-related quality of life (HRQOL) in bleeding prophylaxis with an activated prothrombin complex concentrate (APCC): Results from the Pro-FEIBA study

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Background: Patients with hemophilia A and inhibitors are at high risk for severe bleeding and progression of joint disease with consequent deterioration of health-related quality of life (HRQOL). Prophylaxis with bypassing agents has been suggested as a potential therapeutic option in these patients decreasing the frequency of bleeding as shown by the Pro-Feiba Study (Lessinger, Gringeri, NEJM, 2011).
Methods: A prospective, randomized, crossover study (Pro-FEIBA Study) was designed to evaluate safety and efficacy of an activated prothrombin complex concentrate (APCC) for bleeding prophylaxis in hemophilia A patients with high-responding inhibitors and age >2 years. HRQOL in patients >14 years was assessed with 2 generic instruments: the SF-36 and the EQ-5D.
Results: Eighteen of 19 patients (mean age: 32.6 years; min–max: 16.1–62.8) completed the questionnaires. Twelve of these patients were considered 'good responders' (≥50% reduction in bleeding episodes), and 6 were considered 'poor responders' (<50% reduction in bleeding episodes). A general trend toward improvement in HRQOL was observed after prophylaxis for the 18 evaluable patients in all SF-36 dimensions except for 'vitality/energy' and 'mental health.' Differences between SF-36 physical component summary (PCS) variations before and after each treatment period were statistically significant in good responders ($P = 0.018$). PCS differences were statistically significant in all evaluable subjects when measured before and after prophylaxis ($P < 0.048$). The EQ-5D health profile showed a trend toward improvement, particularly for 'pain/discomfort,' 'usual activities,' and 'self-care.' The difference between EQ visual analogue scale values pre- and post-prophylaxis was 9.00 ($P = 0.064$).
Conclusion: APCC prophylaxis significantly improved HRQOL as compared with episodic treatment. Good responders to APCC prophylaxis showed an even more consistent increase of PCS and statistically significant improvements in the dimension 'role physical,' 'bodily pain,' and 'social functioning'. However, further research should include larger cohorts and longer follow-up together with the use of specific measures in order to better evaluate patients' HRQOL.

PO-TU-228
Linking quality of life measures with the ICF/ICF-CY in young people with hemophilia

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Background: The importance of addressing the patients' perspective and experience of functioning, disability, and health is now commonly accepted. However, this topic is quite innovative in hemophilia research. This study describes health and functioning in children and adolescents with hemophilia in Europe based on the results of the linkage between the hemophilia-specific health-related quality of life questionnaire for children and adolescents (Hemo-QOL) and ICF/ICF-CY classification.
Objective: To measure health and functioning of children with hemophilia in Europe using ICF/ICF-CY as a frame of reference and items from health related quality of life (HRQOL) instruments as a measurement tool within a European data set of 446 children.
Results: More than 60% of the sample reported no or only minor impairment in the area of emotional functions (Body Functions, b152) indicating high emotional well-being. More impairment was found in the area of pain (Body Functions, b 280). The major cause of pain in hemophilia is arthropathy in joints. As the level of arthropathy increases with time and with the number of joint bleeds, older children and those receiving on-demand treatment are more impaired in this area. The restriction of functioning in relation to recreation and leisure (Activity & Participation, d 920) seemed to be most affected by receiving on-demand treatment, even if they seemed to have fewer restrictions in the area of informal social relationship (Activity & Participation, d750). Finally, younger children (8–12 years) perceive more barriers in relation to the individual attitudes of immediate family members (Environmental Factors, e410) than older children (13–16 years).
Conclusion: Using items from HRQOL instruments with ICF-CY as a frame of reference proved to be a useful approach for the assessment of health and functioning in children with hemophilia. This approach should be improved in routine hemophilia assessment.

PO-TU-229
Difficulties faced by hemophilic students in Japan

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Background: Most hemophilic students in Japan opt for general education. However, after graduating from school, some of them cannot continue employment as they tend to lack teamwork, communication, and leadership skills, which are usually inculcated during school life.
Aim: To assess the difficulties faced by hemophilic students during their school life and analyze why they cannot acquire these skills and why their teachers did not support them.
Methods: Two studies were conducted to explore the difficulties faced by hemophilic students. Mothers of 27 hemophilic students were interviewed, and an open-ended research questionnaire was conducted with 37 school nurse teachers. The interview transcripts and written responses to the questionnaires were analyzed qualitatively.
Results: The mothers reported that their children were sometimes denied admission to nursery schools or elementary schools because of their medical condition. Not only mothers of children with HIV/AIDS but also those of children with hemophilia but not HIV/AIDS tended to conceal information regarding their child's medical condition from the teachers because they were afraid of prejudice and discrimination against the children. Some of the children were not allowed to participate in physical education, school trips, or athletic meets because their teachers wanted to avoid any responsibility for their injuries. Moreover, the children did not receive any educational support when they were absent from school. Their teachers did not support them because of the lack of budget, time, manpower, or knowledge of the disease.
Conclusion: Most hemophilic students do not develop close relationships with their classmates because their teachers sometimes forbid them from participating in certain school activities. At times, their academic abilities lack improvement because adequate support is not provided by their teachers. The teachers need to possess adequate and accurate knowledge of the disease to prevent prejudice and discrimination and to provide adequate support to these students.

PO-TU-230
Description of a Canadian cohort of youth and young men with hemophilia based on health-related quality of life measures.

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Objectives: Health-related quality of life (HRQOL) is an important treatment outcome in chronic conditions. Little is reported on the factors that impact longitudinal HRQOL in hemophilia A (HA). This study aims to describe the longitudinal patterns of HRQOL among youth and young adults with HA over a 3 year period. This abstract reports the baseline characteristics of the study cohort.
Methods: Males, 14 to 29 years of age, with moderate or severe HA were recruited from 6 treatment centres in Canada. Participants completed a comprehensive survey at baseline. HRQOL was measured using generic and disease-specific questionnaires: the CHO-KLAT$_{2.0}$ (youth), Hemo-QOL-A (adults) and the SF-36 (all). Joint status was measured using the Hemophilia Joint Health Score 2.0 (HJHS).
Results: Thirteen youth (mean age = 15.7, range = 12.9–17.9 years) and 35 adults (mean age = 23.5; range = 18.4–28.7 years) with moderate (6%) and severe (94%) HA were enrolled. In this group, 47 were on a prophylactic regimen and 1 was on demand. The median HRQOL scores were 78.1 for the CHO-KLAT, 87.5 for the Hemo-QOL-A, and 0.74 for the SF-36. The disease-specific HRQOL scores were weakly correlated with the generic SF36 in youth (CHO-KLAT-SF36 r = 0.23, P = 0.47) and more strongly correlated in adults (Hemo-QOL-A vs. SF36 r = 0.53, P = 0.001). This is in part due to the narrow distribution of scores and small sample of youth. HRQOL scores were not well correlated with HJHS in youth (CHO-KLAT-HJHS r = -0.08, P = 0.8), but were moderately correlated in the adults (Hemo-QOL-A vs. HJHS r = -0.36, P = 0.03). Again, this is due to the broader distribution of HJHS scores (median = 17, range 1 to 34) in the adults compared to youth (median=3, range 1 to 17).
Conclusion: Despite having hemophilia, the youth in this cohort have minimal joint disease and good HRQOL. The adults are demonstrating more joint disease and slightly worse QOL. The SF36 appears to provide a good estimate of QOL across the age range 14–29 years.
Contribution: These results form the foundation for a longitudinal study that will examine the impact of biological factors and life events on the HRQOL of youth and young men with hemophilia.

PO-TU-231
Impact of life events and transitions on health-related quality of life measurements in youth and young adults with hemophilia

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Objectives: Validated health-related quality of life (HRQOL) instruments measure the impact of disease on patients' perceptions of well-being. It is not known to what extent significant non-disease related life events or transitions may influence the results of HRQOL measurements. As part of a prospective longitudinal study describing HRQOL in youth and young adults with hemophilia A (HA), we assessed the effect of significant life events on HRQOL. We report our baseline results.
Methods: Subjects ages 14 to 29 were recruited from 6 hemophilia treatment centres in Canada. Medical and joint assessment was performed at study entry. Patients reported their HRQOL using generic (SF-36) and disease-specific (CHO-KLAT and Hemo-QOL-A) measures at entry and every 6 months. Patients were also asked to report significant life events in the preceding 6 months using a novel questionnaire listing changes in personal non-medical circumstances. In the same Significant Life Event Questionnaire (SLEQ), they also rated the positive or negative impact of these events on their life.
Results: Thirteen youth and 35 young adults with moderate (6%) and severe (94%) HA were enrolled. Eighty-six per cent of participants reported one or more significant life event or transition in the preceding 6 months. These events were assigned by the study subjects a negative or positive score that ranged from 7 to 12. At study entry, there was a weak correlation between the SLEQ score and the baseline HRQOL scores (r = 0.08 with CHO-KLAT, r = 0.06 with Hemo-QOL-A and r = 0.31 with the SF36) suggesting a possible impact of significant life events on QOL.
Conclusion: Significant life events and transitions occur frequently in HA subjects ages 14 to 29 years. These events may influence HRQOL scores. The SLEQ provides a tool to assess this interaction.
Contribution: These results form the foundation for a 3-year longitudinal study that will examine the effect of biological and life events on the HRQOL of youth and young adults with HA.

PO-TU-232
Quantitative word mapping of hemophiliac patients' opinions based on free-answer descriptions on a quality-of-life questionnaire

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Introduction: We analyzed the free-answer descriptions given by hemophiliac patients in a quality-of-life survey.
Methods: The total number of collected answer forms was 663, among which free descriptions were found in 312 cases. We used the Japanese textual data analysis software Word Miner version 1.150. Word mapping was drawn quantitatively by using the similarity measure of words appearing in the descriptions.
Results: A total of 28,705 different words were used. The average number of words in each description was 30.1. The 10 most frequently used words in descending order were as follows: 'hemophilia,' 'injection,' 'anxiety,' 'possible,' 'hospital,' 'now,' 'therapy,' 'bleeding,' 'life,' and 'patient.' Three words, 'hemophilia,' 'anxiety,' and 'medical expenses,' were connected tightly on the word mapping to the description of the medical system, whereas the phrase 'medical expenses' was surrounded by 'public,' 'eternal,' and 'support.' Regarding therapy, the word 'injection' was located near 'therapy,' 'possible,' and 'hurry.' The word 'gene therapy' was connected with 'development' through the word 'expectation.' The word 'drug' had three major satellites, 'longer,' 'efficacy,' and 'continuation.' There was a low frequency of words related to liver disease or viral hepatitis, even in the description of disease conditions. In the 2-dimensional map of words, the location of the word 'liver function' was one of the satellites of 'joint,' which had a much higher usage frequency.
Discussion: The patients' opinions based on the present mapping of words were as follows: they are anxious for continuation of the national support system. They expect the development of gene therapy and drugs that have a longer effect. Patients were less worried about viral hepatitis than the problems with their joints. Summarizing free-answer descriptions is usually accompanied by bias arising from the analyst's attitude. Textual data analysis will be helpful in obtaining quantitative comprehension of the patients' opinions without such bias.

PO-TU-233
Determination of the minimal important difference (mid) of the hemophilia-specific quality of life questionnaire (Hemo-QOL-A) for adults with severe hemophilia A

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Objective: Statistically significant changes in quality of life scores are not synonymous with clinically meaningful changes. In the context of patient-reported outcomes, minimal important difference (MID) is the smallest difference in scores that is clinically meaningful to the patient. The objective of this study was to estimate the MID for the Physical Functioning domain and total score of the Hemophilia-specific Quality of Life Questionnaire for Adults (Hemo-QOL-A).
Methods: MID estimates were derived using pooled data from 2 open-label, prospective trials. Assessments included the Hemo-QOL-A, joint evaluation (Gilbert Scale) and bleeding frequency. The anchor-based method required an external criterion (i.e., an-

chor) to compare changed scores on the Hemo-QOL-A; the distribution-based approach involved calculating the SE of measurement and 1/2 SD of the Hemo-QOL-A scores at baseline. Mean differences in Hemo-QOL-A scores between Gilbert pain categories (none, mild, moderate, severe) were examined at baseline and 6 and 12 months.
Results: Analyses included 45 males (mean age, 26.3 years; range, 13–45 years). Participants were mostly white (82%), non-inhibitor patients (84%) with severe hemophilia A (78%). Due to small numbers of patients reporting, Hemo-QOL-A changes and potential anchors ($n \leq 13$), using the anchor-based approach, was not possible. Using the distribution-based method, the MID for the Physical Functioning domain and total score ranged from 6–9 points and 5–7 points (scale, 0–100), respectively. For those reporting no pain vs. mild pain on the Gilbert Scale, mean differences in Physical Functioning domain score ranged from 11–23 points, and the mean total score difference ranged from 4–14 points.
Conclusions: A change of ≥6–9 points (Physical Functioning) and 5–7 points (total score) represents the smallest change considered clinically meaningful.
Contribution to the practice/evidence base of hemophilia and bleeding disorders: Mids for the Hemo-QOL-A Physical Functioning domain and total score were determined.
Conflicts of Interest: Drs. Valluri, Pocoski, and Sasane are employees of Bayer Healthcare LLC. Dr. Bell, Mr. Mink, and Ms. Flood are employees of Oxford Outcomes Inc., an ICON plc company, which has received research funding from Bayer.

PO-TU-234
Understanding the impact of hemophilia on the family: A pilot study of the PedsQL family impact module

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Quality of life (QOL) is an important outcome measure in clinical trials.The Canadian Hemophilia Outcomes-Kids Life Assessment Tool (CHO-KLAT) is a disease-specific measure of QOL in children with hemophilia. In addition to the impact of disease on the patient, its impact on the family is an important consideration in pediatric chronic disease. The Family Impact Module (FIM) is a companion tool to the well-established PedsQL and has been validated across a spectrum of chronic pediatric conditions (Varni *et al* 2004), but has not been applied to the hemophilia population. Our objective was to assess the relationship between the FIM and QOL among parents of children with hemophilia. A total of 44 parents of children with all severities of hemophilia (19 severe, 14 moderate, and 11 mild) completed the FIM and CHO-KLAT questionnaires. Overall, the FIM scale correlated well with the CHO-KLAT scores ($r = 0.64$, $P < 0.001$). Mean FIM score across domains was 83.1 ± 18.2. ANOVA was used to compare mean FIM scores between groups by severity but did not show any significant differences. When patients were grouped clinically, considering their need for regular infusions for prophylaxis and recent bleeding, the social functioning sub-scale of the FIM neared significance ($P = 0.06$), suggesting that needles and bleeding may impact the family. When patients were grouped by functional status as determined by physical assessment, only two patients had severe deficits. Although the group size was too small for statistical analysis, the total FIM score in these parents was substantially lower (43.3 and 44.4) and was most disparate in the sub-domain of emotional function. In conclusion, the parental FIM scores correlated with the CHO-KLAT scores, indicating that the QOL of the child and the impact on the family are related, thereby suggesting that both are affected by hemophilia and its management. However, because differences were not related to disease severity, other factors such as needles and bleeding may be responsible for the link between QOL and family impact. Additional testing of larger numbers of parents is necessary, and future analyses should consider clinical issues that contribute to burden of illness including prophylaxis, joint bleeds, and functional status by physical assessment.

PO-TU-235
Has the quality of life improved for children with hemophilia A?

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Objectives: To assess whether improvements in the treatment of hemophilia have translated into improvements in the quality of life (QOL) of children with hemophilia.
Methods: The Hemo-QOL 8–12 year questionnaire was completed by a current group of 8–12 year-old hemophilia A children ($n = 8$), and the results compared with a group of adult hemophilia patients ($n = 20$) who were asked to answer the questionnaire by recalling their lives when they were children. The mean age of the adults at the time of the study was 59 years (range 46 to 73).
Results: For all subscales, adult scores were consistently higher than child scores indicating lower QOL ratings by the adults. However, significant differences between the two groups were only obtained for the subscales 'view of yourself' ($P = 0.04$), 'friends' ($P = 0.003$), 'dealing with hemophilia' ($P = 0.05$), 'sports and school' ($P = 0.06$), and 'global health' ($P = 0.0006$). Differences between the two groups on the remaining subscales, which included 'physical health,' 'feeling,' 'family,' 'perceived support,' 'other persons,' and 'treatment,' were not significant.
Conclusions: Overall, results tend to indicate that children's QOL has improved over the years, most probably due to advancements in treatment. However, larger-scale studies would need to be undertaken in order for firmer conclusions to be reached and to enable identification of areas in children's lives where more resources will need to be directed for the currently perceived quality of life to be improved upon.

38-RARE CONGENITAL BLEEDING DISORDERS

S-TU-01P.1-2
Congenital Factor VII deficiency

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Congenital factor VII (FVII) deficiency with an estimated prevalence of 1:300,000–1:500, 000 is the most common among the rare inherited bleeding disorders. Remarkable progress of the knowledge about this disease has been achieved, thanks to extensive research on the pathophysiology, molecular genetics, and biology of FVII; and recent clinical studies in large patient cohorts from national and international registries. Our comprehensive analysis of 687 individuals with FVII deficiency collected in the International Registry of FVII Deficiency (IRF7) and in the prospective multicentre Seven Treatment Evaluation Registry (STER) confirmed significant clinical heterogeneity of disease, often with a poor correlation between FVII levels and bleeding risk. Three clinical phenotypes were defined: (1) asymptomatic, present in 37%–40% of patients; (2) mild 'platelet-like' disorder with muco-cutaneous bleedings (49%–51%); and (3) severe 'hemophilia-like' phenotype (11%–12%). Presenting phenotype at diagnosis may change during the life towards more or less severe or even asymptomatic. Intracranial, gastrointestinal and/or joint bleeds are invariably associated with homozygous and compound heterozygous gene defects and FVII:C<5 IU dL^{-1}. However, this level was also observed in 58.7% and 14.7% of individuals with a mild and asymptomatic phenotype, respectively. In females, the fertile years represent a major challenge, particularly in those with severe FVII deficiency. In the IRF7 group of 34 females with FVII:C ≤ 1.9 IU dL^{-1}, the frequency of menorrhagia (97%), ovarian cysts (47%), hemoperitoneum related to ovulation bleeding (21%), and postpartum hemorrhage (22%) was similar to that seen in women with type 3 von Willebrand disease.. The IRF7 and STER provided valuable information on the clinical picture of FVII deficiency. The results of the STER study, which focused on several issues of replacement therapy, including FVII pharmacokinetics, dose regimes, therapy monitoring, and prophylaxis, will help to optimize the management of bleeding and surgery in FVII deficiency. Prophylaxis should be considered in patients with severe bleeding phenotype, including females wishing to conceive, suffering from gynecological bleeding that does not respond to hormonal therapy.

	At Dg		Observation	Total
	n	%		
All	687	100%		686 /100%
Asymptomatic	272	39.6%	➡Asymptomatic 237, 35 new muco-cutaneous (MC)	237 / 34%
Mild	338	49,2%	➡268 new MC, 51 new severe bleeding, 12 no bleeds	338+35
Severe	77	11,2%	➡34 severe, 38 mild, 5 no further bleeds	77+51= 128/450= 28%
All symptomatic	425	60.2%	Mild: 35 from asymp+268 from mild+ 34 from severe = 337 Severe: 38 from severe+ 51 mild= 89	450 (338 at dg +35 new from asymptomatic +77severe)

At Dg			Observation		
	n	%	Asymptomatic	Mild	Severe
All	687	100%	254/36,9%	348/50,6%	85/12.3%
Asymptomatic	272	39.6%	237/87,1%	35/12,9%	
Mild	338	49,2%	12/3,6%	275/81,3%	51/15,1%
Severe	77	11,2%	5/6,5%	38/49,3%	34/44,2%
All symptomatic	415	60.2%	17/4,1%	313/75,4%	85/20,5%

SYMPTOMATIC N=415	Asymptomatic	Mild	Severe
All at dg		338/81.4%	77/18.6%
Observation	17/4.1%	313/75.4%	85/20.5%

SYMPTOMATIC	Mild	Severe
At diagnosis N=338+77= 415	338/81.4%	77/18.6%
Observation N=275+35+38+85=433	313/72.2%	85/19.6%

	Asymptomatic	Mild	Severe
Entire Follow-up (713)	237 (33%)	348 (48.8%)	128 (17.9%)

S-TU-01.1-1
Factor XI

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Factor XI (FXI) is stimulating current research interest both because of its role in hemostasis, and for the potential role of FXI inhibitors in the prevention of thrombosis. Animal experiments have demonstrated that FXI inhibitors may prevent thrombosis without increased bleeding risk, and further research is in progress. FXI has a unique structure among coagulation factors as a dimer, and participates in coagulation by reinforcement of the intrinsic pathway and inhibition of fibrinolysis. Inherited factor XI deficiency is associated with a mild bleeding tendency (and an absence of spontaneous bleeding), which is not easily predicted from the factor XI level. Bleeding characteristically occurs after accidents or surgery in areas of high fibrinolysis, particularly the mouth and genito-urinary systems. Excessive bleeding may occur in individuals with mild as well as severe deficiency. It is likely that the interaction of platelets and other coagulation factors can modulate the bleeding risk. Factor XI deficiency is particularly common in Ashkenazy Jews, but it is found in all racial groups. Mild deficiency is most commonly diagnosed after pre-operative coagulation screening, but it is important to consider screening women with menorrhagia. Treatment should be tailored to the individual situation. Close supervision without specific replacement may be sufficient; antifibrinolytic agents are very useful and sufficient for dental extractions, even in severe deficiency. Plasma (preferably pathogen inactivated) is effective; and two FXI concentrates are available in some countries, but should be used with caution, as both have been associated with an increased thrombotic risk.

S-TU-01.1-3
Congenital fibrinogen disorders

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An important body of knowledge on congenital fibrinogen disorders has accumulated these past years, particularly thanks to international collaborative studies and national registries, as well as genetic studies. Inherited disorders of fibrinogen affect either the quantity (afibrinogenemia and hypofibrinogenemia) or the quality of the circulating fibrinogen (dysfibrinogenemia) or both (hypodysfibrinogenemia). Patients suffer most often from bleeding but, paradoxically, may present severe thrombotic episodes. Pregnancy loss is another common clinical complication. Even in specialized laboratories, the precise diagnosis of some fibrinogen disorders may be difficult. Determination of the molecular defects is important, since it makes it possible to achieve a more precise diagnosis, to elaborate a diagnostic strategy, to distinguish in some cases the patients at risk of thrombosis rather than bleeding, and to enable prenatal diagnosis. However the phenotype–genotype correlation is not easy to establish. Replacement therapy is effective in treating bleeding episodes, but because the pharmacokinetics of fibrinogen after replacement therapy is highly variable amongst patients, it is important to adjust the treatment individually. Even though the number of cases studied and mutations identified are already quite substantial, the collection and comparison of molecular, biochemical, and clinical data will continue to yield valuable information on the development and course of these diseases as well as on the choice of the most appropriate treatments. A definitive cure of afibrinogenemia is already feasible through liver transplantation, although obviously this approach cannot be envisaged on a large scale. Gene therapy remains a possibility in the long term.

FP-TU-04.3-2
Pharmacokinetics, safety, and efficacy of a high purity factor X in patients with severe and moderate hereditary factor X deficiency

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Background: BPL has developed a high-purity factor X concentrate (FX) for the management of hereditary factor X deficiency.
Objectives: To assess the pharmacokinetics (PK), safety, and efficacy of FX in treating bleeding episodes in patients >12 years old with severe or moderate factor X (FX) deficiency. PK parameters for FX:C and FX:Ag were measured at baseline, with sampling time points up to 144 h (6 days) following an infusion of 25 IU kg^{-1} FX, and at 6 months. Bleeding episodes were treated with 25 IU kg^{-1} FX, repeated as necessary. Safety monitoring included: virology, FX-inhibitor screens, and thrombogenicity marker testing.
Results: Of the 12 patients enrolled, 9 had severe and 3 had moderate FX deficiency. Data from 10 baseline FX:C PK profiles gave an incremental recovery of 1.97 ± 0.12 IU dL^{-1} per IU kg^{-1} (mean ± SEM) and half-life of 30.0 ± 1.8 h (non-compartmental analysis). Currently >100 infusions of FX have been given for treatment of 34 bleeds. In the 16 bleeds analyzed to date, a median of 1 infusion was given to treat bleeding and 1.5 infusions as secondary prophylaxis. In the 14 bleeds in which efficacy of FX has been reported, FX was judged to be excellent or good in treating 100% of the bleeds. Of 20 post-dose FX inhibitor tests to date, all have been negative. Of 2 post-dose virology results to date, there were no seroconversions. No FX-related adverse events or infusion-site reactions have been reported, nor any clinical evidence of thrombogenicity.
Conclusion: Data from this study demonstrate FX to be both efficacious and safe in treating 34 bleeds to date in these FX deficient patients. PK results are similar to those from another study evaluating infusion of a prothrombin complex concentrate in healthy volunteers.

PO-TU-241
Use of thrombin generation assay in the management of hemostatic treatments in a patient with severe factor V deficiency and anti-factor V inhibitor
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Congenital factor V (FV) deficiency is a rare (1/1,000,000) bleeding disorder inherited as an autosomal recessive trait. We report a 46 year-old patient with severe FV deficiency (FV < 1 IU dL^{-1}) that was diagnosed at the age of 6 because of a major bleeding episode. Before 2009, he was treated with fresh frozen plasma (FFP) on-demand with a good efficacy. A knee arthroscopy was performed with success under FFP substitutive therapy. After 30 days, a hematuria occurred and provoked major anemia caused by severe renal hematoma An anti-factor V (FV) inhibitor was diagnosed (maximum titer at D44 = 8 BU mL^{-1}). As successful treatment by recombinant activated factor VII (rFVIIa) in patients with anti-FV inhibitor was previously described (González-Boullosa R et al., 2005), we used rFVIIa (90-120 μg kg^{-1} repeated bolus) to treat this urologic bleeding according to the classical scheme used in hemophiliacs with inhibitors. The clinical efficacy of rFVIIa was limited and transitory. So we decided to associate apheresis platelet concentrates (APC) to rFVIIa, and this association was efficient. Thrombin generation assays (TGA) could be performed on platelet rich plasma before and after infusions of rFVIIa or APC. rFVIIa only induced a slight improvement of TGA parameters whereas there was significant increase of thrombin generation after APC transfusion. During the next 6 months, the patient showed multiple hematomas responsible for repeated massive blood loss. These bleedings were solely treated with platelet concentrates with good efficacy. In conclusion, we suggested that the use of TGA allowed a good estimation of the clinical efficacy of these two hemostatic treatments and could be helpful in the management of these patients with severe bleeding risk.

PO-TU-242
Factor XI concentrates: Five years' experience in a single centre
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Introduction: Factor XI (FXI) deficiency is a rare autosomally inherited bleeding disorder, with a variable bleeding phenotype. Two plasma-derived (pd), virally-inactivated FXI concentrates are currently available. Despite initial concerns regarding the thrombotic risk of these concentrates, there have been few recent reports of thrombosis following their infusion.
Methods: A retrospective analysis of all FXI concentrate use between November 2006 and November 2011 at our centre. The primary end points were thrombosis or hemorrhage following concentrate infusion.
Results: There were 33 episodes of concentrate use in ten patients over 20 treatment episodes. The median number of infusions per treatment episode was 1 (range 1–10). The majority of these infusions (24/33) were for prophylaxis prior to a surgical procedure. The remainder were for hemostasis post-surgery (5/33), bleeding (3/33) or for a test dose prior to surgery (1/33). The median target FXI coagulant activity (FXI:C) was 60 IU dL^{-1}. The median peak FXI:C achieved was 67.5 IU dL^{-1} (range 38–104). There were six episodes of clinically significant bleeding. Three of these required additional concentrate infusion, two required Emergency Department attendance, and one required a transfusion. There was no significant difference in the dose of concentrate used, target FXI:C or peak FXI:C between the patients who bled and those who did not. One episode of thrombosis (multiple pulmonary emboli) was observed (peak FXI:C 50 IU dL^{-1}). No other complications of FXI concentrate use were observed during the study period.
Conclusion: This retrospective analysis shows continued safe usage of pd FXI concentrates. There was one thrombotic episode which occurred at a peak FXI:C of 50 IU dL^{-1} in a patient with traditional vascular risk factors. Although our experience shows this to be an isolated event, we would continue to advise assessment of thrombotic risk factors and consideration of appropriate thromboprophylaxis in all patients prior to surgical procedures.

PO-TU-243
Prophylactic treatment in factor XI deficiency patients undergoing invasive procedures
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As for many coagulation disorders, there is not a good correlation between the level of the protein and the risk of hemorrhage in factor XI deficiency. This raises the question of the indication for a systematic prophylactic substitution therapy particularly for mild deficiency. We retrospectively analyzed surgery and delivery and the correlation with bleeding complications in a cohort of factor XI deficient patients in a university hospital. One hundred fifty-three patients with factor XI deficiency of varying severity were analyzed. The factor deficiencies range from less than 5 IU dL^{-1} (n = 8), 5 to 15 (n = 5), 15 to 30 IU dL^{-1} (n = 44), and 30 to 50 IU dL^{-1} (n = 96). Also analyzed were patients with normal levels (> 50 IU dL^{-1}) who were obligate carrier of a mutation (n = 22). Two hundred eighty-six procedures were performed with a varied bleeding risk. Two patients received prophylactic fresh frozen plasma (deficiency less than 5 IU dL^{-1}), 29 specific purified factor XI (21 for deficiency less than 5 IU dL^{-1} and 8 for 5 to 30 IU dL^{-1}), 6 dDAVP infusion, 29 tranexamic acid, and 232 received no specific regimen. Thirty-two patients with a similar frequency for severe and mild deficiencies were observed for hemorrhage: 11% for less than 5 IU dL^{-1}, 10% for 5 to 30 IU dL^{-1}, and 11% for more than 30 IU dL^{-1}. Two thrombotic complications occurred during factor XI therapy for the same patient later diagnosed with essential thrombocytosis. The decision to resort to prophylactic blood products in factor XI deficiency remains ambiguous in current literature. Even if the severity of the deficiency is the main parameter, the risk of the surgery, the consequences of a bleeding, and the need for thrombotic prophylaxis may influence the decision. Further studies have to be performed to determine the hemostatic cut-off of the factor XI level or to find other coagulation tests with an improved predictive value.

PO-TU-244
Rare bleeding disorders (RBD) in the FranceCoag Network: Diagnosis circumstances and severe events in patients with severe FVII deficiency
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We report a focused analysis of patients with severe FVII deficiency defined as a basal plasma level<10%, included in the FranceCoag Network (FNC) since January 2003. By November 2011, 113 patients (54 males, 59 females) had been included by 22 centres. Among them, 37 (32.7%) are under 18 years old, 42 (37.2%) are aged 18-40 years, and 34 (30.1%) are over 40 years old. The minimal FVII level is <1% in 8 patients, [1–5%] in 70,]5–10%[in 35. The median age at diagnosis is 12.4 years (range: 0–70.9). However, patients with the most severe defect (<1%) are diagnosed earlier: 6.4 years vs. 10.3 and 16.2 for patients with a FVII between [1–5%] and between] 5–10% [respectively. The median age at inclusion was 19.9 years (range: 0.3–78.7). The median follow-up per patient was 1 year (range: 0.7–9) and the total duration was 331.64 person-years. The most frequent circumstance of diagnosis (54.8%) was an abnormal pre-operative prothrombin time (respectively 12.5% and 58% when FVII<1% or [1–10%]). In contrast, the diagnosis was secondary to a bleeding in 75% of the cases with a FVII<1% (23.8% for FVII between [1–10%] whatever the family history). Hemarthrosis (n = 8), menorrhagia (n = 3), and gastrointestinal bleedings (n = 3) occurred mostly in patients with FVII≤5%. Thirteen patients (11.5%) presented with life-threatening hemorrhages including 6 intracranial hemorrhages that occurred only in those with FVII≤5%. Regarding replacement therapy, 53.1% have been treated at least once in their lives. The median age at first treatment was 19.2 years (range: 0.01–71). Four patients had a prophylactic regimen during the study. The FCN confirms that severe FVII deficiency is one of the most prevalent rare bleeding disorders (RBD) (with FXI). The main clinical features in our registry is the variety of the clinical manifestations, and the trend of the most severe profile in cases with a FVII≤5%.

PO-TU-245
Rare inherited bleeding disorders: A single centre in Pakistan
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Background: Consanguinity remains common in several populations around the world. However, consanguinity rates vary from country to country. In Pakistan, close consanguineous unions continue to be extremely common as is the case in Southwest Asia. As a result of these marriages, autosomal recessive disorders become common. Here we describe the frequency of rare inherited coagulation bleeding disorders, their types and clinical features among patients seeking advice for bleeding tendencies from a single centre in Pakistan.
Patients & Methods: Pre-designed data sheets were filled in by incorporating patients' demographics, family history, present and past history of bleeding episodes with the associated signs and symptoms. In female cases, maternal and obstetrical history was taken. Blood samples were collected for CBC and coagulation assays, prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, VWF: Ag, RiCoF and factor assays. Urea clot solubility test was done in cases where all coagulation tests were normal.
Results: Out of 447 patients diagnosed with inherited coagulation bleeding disorders, 48 subjects had rare bleeding disorders (10.7%). Among them, 55% were male and 45% patients were female. Median age of all the patients was 9.8 years, (range 6 months to 27 years). The most common deficiency was FXIII (n = 16, 33.3%,) followed by FVII deficiency (n = 11, 23%), fibrinogen deficiency (n = 9, 18.7%), FV deficiency (n = 5, 10.4%), FX deficiency (n = 2, 4.1%), FXI deficiency (n = 1, 2.1%), respectively. There were two cases of combined FV and VIII deficiency and 2 cases of combined vitamin K depended factor deficiency (4.1% each). Clinical bleeding episodes were classified into categories according to severity. Grade III, II, and I bleeding were noted in 62.5%, 45.9%, and 10.4% patients, respectively. Gum bleeding, epistaxis, easy bruising, menorrhagia, and umbilical cord bleeding were the main clinical manifestations. Fresh frozen plasma/cryoprecipitate were used in the management of most patients.
Conclusion: The study shows that autosomal recessive disorders are common in a setting of consanguineous marriages. Further studies of the association between phenotype and genotype in this subset of patients are needed.

PO-TU-246
Mutation causing severe factor XIII deficiency in Pakistan
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Background: Rare bleeding disorders (RBDs) represent 3% to 5% of all inherited coagulation deficiencies. Factor VII deficiency is the most common among RBDs, but in Karachi, Pakistan, we have seen a high number of factor XIII (FXIII) deficiency in comparison to other RBDs. An increased frequency of this disorder was already reported in countries like Iran and India where consanguineous marriages are also common. FXIII deficiency is usually due to mutations in the factor 13A gene (*F13A*) which is located in chromosome 6, at p24-25. Up to now more than 70 mutations on *F13A* are reported.
Clinical Manifestation & Methods: In our centre, 16 unrelated patients affected with FXIII deficiency are followed. Here, we describe the case of 27 year-old man coming from Pakistan affected with severe FXIII deficiency. He was referred with a history of bleeding symptoms at circumcision, repeated nose, gum bleeds, and cutaneous bruises. Married to his first cousin, he has 2 children who also have histories of bleeding. Laboratory coagulation tests showed all normal results except FXIII activity which was undetectable in plasma using 5 M urea clot solubility test. FXIIIA antigen levels were then determined. The molecular analysis was performed by direct sequencing of the coding regions, intron/exon boundaries and 5' and 3' untranslated regions of the *F13A*. PCR products were sequenced using a Big Dye Terminator cycle sequencing kit (Applied Biosystems, Warrington, UK) on an ABI 3130 genetic analyzer (PE Applied Biosystems, Foster City, CA, U.S.A.).
Results: A novel splice site mutation c.1460 + 1G>A (IVS 11 + 1G>A) in core domain was identified in homozygous state, associated with undetectable FXIII activity and FXIIIA antigen 2%.The use of the Berkely Drosophilia Genome Project human database predicted that mutation would probably result in the complete abolition of the donor splicing site in mutant. The same mutation was confirmed in heterozygous state in wife and in homozygous state in both children. The same mutation was also found in two patients of another family.
Conclusion: This is the first gene mutation found in our FXIII deficiency patients. We will characterize all other severe affected patients of our centre to verify if this variant could be a recurrent mutation in our specific geographic area. This molecular analysis might help for prevention of these disorders in our region through prenatal diagnosis in families with already one severe affected child.

PO-TU-247
Long term prophylaxis with subcutaneous rFVIIa for congenital factor VII deficit: A case report
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Introduction: Factor VII deficiency in patients with a heavy bleeding phenotype can be challenging, and prophylaxis with rFVlla has been recommended to improve these patients' long-term outcome. However, venous access can be an obstacle to this treatment and placement of a central venous catheter is the only way to ensure continuity.
Case description: We report the case of a 22 month-old boy who presented with severe CNS bleeding and hematemesis during the neonatal period. Coagulation work-up showed a prolonged TP that corrected on mixing tests and a 4% of FVII activity and no family history of bleeding diathesis. He was initially treated with fresh frozen plasma (FFP) and prothrombin complex concentrate (PCC), stabilizing his clinical condition, without requiring neurosurgical intervention or hemodynamic support and was subsequently switched to i.v. rFVlla 30 μg kg^{-1} three times per week as a maintenance regimen. Nine months after the initial bleeding, in concomitance with an infectious episode, he presented a subdural hematoma which required drainage. Recombinant FVIIa was used for hemostatic coverage, and after the surgery he was put on long term prophylaxis with this agent. However, his poor venous access precluded the continuation with this therapy, so it was decided to switch the rFVIIa to the subcutaneous (s.c.) route. To ensure efficacy of s.c. rFVIIa, coagulation parameters and FVII activity were measured an hour and 48 h after the administration of rFVIIa. All PTs obtained immediately after the injection were hemostatic (range: 66–74%), as was the FVII activity (range: 33–42%), and fell after 48 h. He is now 22 months old and continues on subcutaneous prophylaxis with rFVIIa with an excellent evolution, good skill acquisition, mild deafness, and no major bleedings.
Conclusions: In the case presented here, subcutaneous rFVIIa proved to be an efficacious and safe manner to administrate prophylaxis to FVII deficient patients. However, due to the nature of this report, further investigation should be performed to confirm these data.

PO-TU-248
A multidisciplinary approach to managing an iliopsoas bleed in a patient with severe factor V deficiency: A case report
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Introduction: This case report describes the management and outcomes of a teenager with severe factor V deficiency but mild bleeding phenotype and an acute onset of left groin pain.
Case presentation: He presented two weeks after initial injury with increasing pain and immobility at the hemophilia centre. Initial objective findings including motor and sensory deficits were suggestive of an iliopsoas hematoma with femoral nerve compression. This was confirmed by ultrasound and CT imaging. Within 24 h his clinical status deteriorated and further investigations were required, questioning the initial diagnosis. Due to the complex nature of his condition, multiple teams were consulted on his management.
Management: Initial intensive hematological management included Octaplas platelets, tranexamic acid, and NovoSeven, with gradual reduction over a six-week period. He received regular analgesia and, subsequent to a change in his condition, intravenous (IV) antibiotics. The hematoma was aspirated under sedation and sent for culture. Following a period of initial bed rest, gradual rehabilitation was carried out with the physiotherapist.
Outcomes: Radiological resolution of the hematoma was seen at 6 weeks. Over the following eight months with continued therapy input, notable improvements in motor, sensory, and functional ability were made.
Conclusion: This case study highlights the successful management of this patient and his unusual bleed with the involvement of other disciplines and a multidisciplinary approach from the hematology team.

PO-TU-249
Menorrhagia and other gynecological symptoms in women with inherited bleeding disorders: Experience of Aziza Othmana Hospital, Tunis, (about 32 cases)
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Issue: When compared to the general population, women with inherited bleeding disorders are at higher risk to develop menorrhagia as well as other gynecological manifestations. The management of the disease is not well codified.
Objective: To study the frequency of gynecological manifestations in women with inherited bleeding disorders and provide a management plan for these patients.
Methods: A retrospective comparative study between a group of 32 women with inherited bleeding disorders and a control group of 32 women recruited at random at a local clinic.
Results: Menorrhagia was more common in women of the study group compared with the control group (78.1% vs. 3.1% $P < 0.01$), fertility was also impaired in the group of women studied (71.4% vs. 00%). Ovarian cysts were more frequently encountered in the study group (12.5% vs. 00%). The quality of life was considered poor in 43.8% of the women in the study group and anemia was diagnosed in 65.6% of them. As part of the management, combined contraceptive pills have been used firstly with a success rate of 73.7% and a satisfaction rate of 63.2%.
Conclusion: Besides menorrhagia, women with inherited bleeding disorders are at greater risk of developing various gynecological problems. Quality of life seems worse for women with inherited bleeding disorders than it does for women in the general population. The first treatment that we recommend is the combined contraceptive pills. Collaboration between the gynecologist, the hematologist, and the anesthesiologist is also required for an optimal management.

PO-TU-250
The Canadian experience: Severe factor V deficiency
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Background: Severe factor V deficiency (sFVD) is a rare congenital bleeding disorder with FV of 1 IU dL^{-1} and autosomal recessive inheritance. It is associated with spontaneous bleeding, often mucosal surfaces. The Canadian Hemophilia Registry (CHR) reports 7 patients with sFVD among the Canadian population (34 million).
Objective: To describe bleeding manifestations and treatment of sFVD in Canada.
Methods: Retrospective chart review of five patients with sFVD identified through CHR.
Results: Patient demographic information and description of bleeding manifestations are in Table 1. Majority of patients are Caucasian, none reported family history. Diagnosis of sFVD occurred after investigation of prolonged provoked bleeding or menorrhagia. Fresh frozen plasma (FFP) 15–20 mL kg^{-1} has been used as treatment/surgical prophylaxis for bleeding with adequate FV recovery. Adjuvant therapies included tranexamic acid and desmopressin. One patient received recombinant activated factor VII (rFVIIa) and prothrombin complex concentrate (PCC) due to religious beliefs. Two patients required antihistamines prior to FFP due to minor adverse events (AE).

Table 1. Description of patient demographics and bleeding manifestations.

Case	Age (Yrs)	Sex	Age at Diagnosis	Genotype	Bleeding Symptoms	Treatment	FV Recovery (IU/dL)	FFP Reactions	Procedures
1	4.5	M	2.5 years	Exon 13 deletion / Exon 22 G2060D	Traumatic Frenulum, Tongue	FFP 15-20mL/kg, TXA	31 post 22mL/kg FFP	N/A	FFP prophylaxis with dental procedures
2	21	F	13 years	Exon 15 Y1702C / Exon 17 V1813M	Bruising, Epistaxis, Menorrhagia, Traumatic Rt Calf	FFP 15-20mL/kg, TXA, DDAVP (menorrhagia)	33 post 6U FFP	HTN, nausea, headache, mild SOB	FFP prophylaxis at C-section
3	23	F	19 years	N/A	Postpartum Hemorrhage	Nil	N/A	Nil	Uncomplicated second pregnancy with no FFP prophylaxis
4	23	M	5 days	N/A	Post circumcision Spontaneous Rt Psoas, Rt Gluteal (2) Traumatic Lt Forearm	FFP 10-20mL/kg, TXA, rFVIIa, PCC	19 post 3U FFP	Nil	FFP prophylaxis with dental procedures
5	28	F	7 months	N/A	Epistaxis, Menorrhagia Multiple Spontaneous/ Traumatic Hemarthrosis, Rt Iliopsoas (2) Hemorrhagic ovarian cysts	FFP 15-20mL/kg, TXA	22 post 4U FFP	Hives	FFP prophylaxis with dental procedures

Abbreviations: M – Male, F – Female, FFP – Fresh Frozen Plasma, TXA – Tranexamic Acid, DDAVP – Desmopressin, rFVIIa – Recombinant Activated factor VII, PCC – Prothrombin Complex Concentrate, U – Units, Rt – Right, Lt – Left, HTN - Hypertension

Conclusions: The majority of bleeding symptoms in sFVD are mucocutaneous, although 2 of our patients also experienced spontaneous musculoskeletal bleeding. Females require particular attention to the management of gynecological bleeding (e.g, menorrhagia, hemorrhagic ovarian cysts, peri/postpartum bleeding). In our patients, FFP 15–20 mL kg^{-1} has been effective in achieving hemostatic levels of FV ($\geq$0.20 U mL^{-1}) with minimal AE and remains the mainstay of therapy. The development of FV concentrate to provide more optimal management of serious bleeding experienced by these patients is needed.

PO-TU-251
First Case of Inherited FXIII-A Type II Deficiency

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Background: Inherited severe FXIII-A deficiency is a rare bleeding disorder that affects one individual in 1–3 million. In contrast, heterozygous factor XIII deficiency is more common, but usually not associated with severe hemorrhage such as intracranial bleeding or hemarthrosis. FXIII-A type I deficiency is a quantitative defect resulting from decreased synthesis of the protein, whereas type II deficiency is characterized by a normal or near-normal concentration of functionally defective FXIIIA. Here we report the first case of inherited FXIII-A type II deficiency (heterozygous form).
Patients and methods: Index patient was a five-year-old boy. Mild FXIII deficiency was detected due to a scheduled surgery and bleeding history in the relatives (mother experienced delayed bleeding after tonsillectomy; grandfather had a postoperative bleeding). FXIII activity was checked using photometric and incorporation assays. Levels of FXIII-A, FXIII-B, and activation peptide (AP-FXIII) were measured by ELISA assays. All listed FXIII parameters were analysed in index patient and in three further affected relatives (one year-old brother, mother, and grandfather). *F13A* and *F13B* genes have been screened by sequencing technique (Applied Biosystems).
Results: The measured FXIII activity ranged from 29 to 35% of normal (photometric assay) and from 38 to 42% of normal measured by incorporation assay. FXIII A-Subunit antigen levels ranged from 85 to 115%. FXIII B-Subunit antigen concentration varied from 81 to 113%. AP-FXIII levels were between 39 and 66% of normal. All family members carried a single heterozygous missense mutation in *F13A* gene (Arg37Gln). No mutations have been identified within *F13B* gene.
Conclusions: The measured levels of FXIII activity and AP-FXIII correlated well with the heterozygous status of a novel missense mutation directly affecting the thrombin cleavage site (Arg37) of FXIII-A. While the FXIII A-Subunit antigen concentration was found in normal range suggesting the functional defect of FXIII-A molecule. To our knowledge this is the first case demonstrating FXIII-A type II deficiency (heterozygous form).

PO-TU-252
Molecular basis of fibrinogen deficiency in twenty-eight patients from India

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Introduction: Fibrinogen deficiency is an extremely rare hereditary bleeding disorder in ~1 million affecting secondary hemostasis. Only ~244 mutations in the fibrinogen gene cluster have been reported as being disease-causative. Identification of additional mutations is important for understanding the biology of fibrinogen as well as offering genetic testing to families affected by this disorder.
Patients & Methods: Twenty-eight patients evaluated between 2001 and 2011 were diagnosed to have fibrinogen deficiency (Afibrinogenemia, n = 25; Hypofibrinogenemia, n = 3) on the basis of prolonged clotting times and low fibrinogen levels. All these patients presented with umbilical stump bleeding at birth and history of variable skin and mucosal bleeding. Genomic DNA was screened for mutations in the fibrinogen alpha (*FGA*), beta (*FGB*), gamma (*FGG*) genes by PCR and CSGE. For ascribing causality to novel mutations identified, we performed *in silico* analysis on the structural stability (SIFT and Poly-phen scores) of aminoacids mutated and their evolutionary conservation across different species (*Xenopus tropicalis, Bos taurus, Gallus gallus, Petromyzon marinus, Drosophila melanogaster, Rattus norvegicus, Homo sapiens*). Haplotype analysis of *FGA/FGB* genes was carried out in patients with common mutations.
Results and discussion: Mutations (n = 15) were identified in all the 28 patients. These included frameshifts (53.3%) missense (33.3%), and splice site mutations (13.3%), of which 13 were novel. All patients with frameshift mutations, which predict premature translation of protein synthesis, had afibrinogenemia. The molecular pathology of the eight novel frameshifts (FGα: p.Lys575fs; p.Thr466fs, p.Asp296fs; p.Glu262_263fs, FGβ: p.Gly414fs; FGγ: p.Lys185fs; p.Ser81fs; p.Asp278_279fs) is self-evident as they resulted in truncated fibrinogen proteins. Two novel splice site mutations (*FGA*: c.364 + 1G>A, n = 5; FGG: c.851 + 1 G>A n = 1) abolished the donor splice site possibly leading to exon skipping or intron retention due to utilization of cryptic splice sites. Among the five missense mutations identified three were novel (*FG*β: p.Gly288Ser; p.Gly320Asp; p.Arg445Thr). p.Gly288 and p.Gly320 residues are highly conserved across different species and located in the five-stranded sheet that forms the major structural feature of FGβ-D domains. Mutations in this region are known to result in protein instability (SIFT score: 0.0). The p.Arg445 mutation residue lies at the C-terminal of FGβ-β polypeptide. This mutation possibly affects the extracellular secretion of fibrinogen β protein. Two common mutations (*FGA*: c.364 + 1G>A, n = 6, *FGB*: p.Arg478Lys, n = 9) affecting 15 patients were identified in this series. Haplotype analysis of these mutations suggested the possibility of a common founder.
Conclusions: The mutations identified in patients with fibrinogen deficiency is as heterogenous as reported in other populations. Two common mutations account for 54% of patients with fibrinogen deficiency in India and should be screened first for the genetic diagnosis of this condition.

PO-TU-253
Laboratory diagnosis of FXIII deficiency: Data from a U.K. NEQAS (blood coagulation) exercise

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FXIII deficiency is a rare coagulation bleeding disorder, with characteristic symptoms including delayed bleeding and intracranial hemorrhage. Traditionally, laboratory diagnosis has been carried out using clot solubility tests. However, we have previously demonstrated poor sensitivity of these tests to anything other than severe deficiency. Furthermore, a recent ISTH Scientific Subcommittee communication has recommended that the first line test in the diagnosis of FXIII deficiency should be a quantitative FXIII activity assay. Previous U.K. NEQAS exercises for FXIII investigations have demonstrated that the majority of centres screening for this deficiency employ solubility tests, and centres using assays have shown poor precision and sensitivity. In two recent exercises, we have seen a marked rise in the number and proportion of centres employing specific assays. An exercise in 2011 revealed 63/119 centres performing assays. Eight out of 59 centres performing solubility screening tests failed to correctly identify one plasma deficient in FXIII and one normal plasma. In each case, potential errors in the test method could be identified. For centres employing quantitative assays, there was a significant difference in results obtained with the two most widely used methods (method A n = 39, median 5.0 U dL^{-1}, method B n = 19, median 2.0 U dL^{-1}, $P < 0.001$). Despite this, precision was improved compared with the results from the previous exercise (from 177% to 82.1% for the deficient sample, and 21.6% to 14.8% for the normal sample).
Conclusions: Perhaps because of the ease and cost of performing a solubility test, these tests continue to be used. Our data show that this can be successful in some centres, depending on the sensitivity of the method in use. Where FXIII assays are employed to investigate suspicion of FXIII deficiency or to confirm abnormal screening test results, further standardization of these assays is required.

PO-TU-254
Genotype and phenotype report on patients with combined deficiency of factor V and factor VIII in Iran

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Objective: Combined factor V (FV) and factor VIII (FVIII) deficiency (F5F8D) is a rare autosomal recessive bleeding disorder characterized by mild-to-moderate bleeding. Epistaxis, post-surgical bleeding, and menorrhagia are the most common symptoms. Our aim of this study is to identify phenotype-genotype relationship in F5F8D Iranian patients.
Methods: A series case study was conducted in Shiraz Hemophilia Centre, southern Iran. Twelve cases, 7 males and 5 females coming from 8 families, were included in our study after completing consent forms. IL9000 coagulation was used for measuring coagulation activity and genomic DNA extraction was done using kia Gem kits. Fisher exact test and Spearman's correlation tests were used for data analysis.
Results: Our results showed age range of 6–59 years mean ± SD (25.66 ± 16.86). The clinical and laboratory findings are shown in Table 1. We identified in our Iranian cases 3 already reported mutations, all located on *LMAN1* gene (Table 1). There is a significant correlation between factor V and VIII levels, which is indicative of association with loss of function of *LMAN1* gene, and reduced plasma levels of both factors. No significant correlation was observed between clinical symptoms and the level of factors.

Table 1. Clinical and laboratory findings in F5F8D patients included in the current study.

patient	sex	age	Onset Clinical sign	FV C:%	FVIII C:%	LMAN1 mutations
1	M		post-circumcision	8	5	c.89–90insG; p.Asp31 ArgfsX102
2	M	59	post-surgery	<1	<1	c.89–90insG; p.Asp31 ArgfsX102
3	F	6	epistaxis	12	13	c.822G>A p.Pro274Pro fsX13
4	M	37	gingival bleeding	10	26	c.822G>A p.Pro274Pro fsX13
5	M	25	post-traumatic bleeding	15	18	c.822G>A p.Pro274Pro fsX13
6	F	32	post-surgery	8	18	c.822G>A p.Pro274Pro fsX13
7	M	34	epistaxis	11	27	c.822G>A p.Pro274Pro fsX13
8	M	12	epistaxis	16	28	c.904A>T p.Lys302Stop
9	F	17	post-dental extraction	7	7	c.904A>T p.Lys302Stop
10	F	19	post-traumatic bleeding	13	15	In progress
11	F	8	epistaxis	13	10	In progress
12	M	28	-	-	-	In progress

Discussion: Our study showed mucus membrane bleeding is the most common symptom and that there is no direct correlation between genotype, activity level and symptoms.

PO-TU-255
The successful use of human coagulation factor x concentrate (BPL) in a child with severe factor X deficiency

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Introduction: Severe factor X deficiency is a rare (1:500,000) inherited bleeding disorder, known to pre-dispose to intra-cranial hemorrhage. It can be treated with FFP and/or prothrombin complex concentrates (PCC), which contain factors II, VII, IX, and X. The volume of administration of PCC is smaller with less risk of blood-borne viral transmission compared to FFP. There is a potential risk of thromboembolic complications given the presence of activated forms of other vitamin K-dependent factors.
Methods: We describe the case of a 7-year-old consanguineous Caucasian girl with co-existent congenital muscular dystrophy (MD) and severe factor X deficiency. She has been treated prophylactically with PCC via central lines since diagnosis at 3 days of age, as an older sibling with severe FX deficiency died of intra-cranial hemorrhage at the age of 5 months. Her 5th portacath became occluded, thrombus was detected in the right subclavian and right brachiocephalic veins when the port was removed. Peripheral venous access was very difficult and effective prophylaxis proved impossible over a period of 6 months, partly due to large infusion volumes. She was commenced on Human Coagulation factor X concentrate (BPL) in early 2011, as this is a purer product, thought less likely to have thrombotic sequelae and due to smaller infusion volumes was easier to administer. A 6th portacath was inserted due to ongoing issues with peripheral access and FX concentrate continues.
Results: Human Coagulation factor X concentrate (BPL) has been effective in this child in maintaining measurable trough levels at 72 h post dose (~38 IU kg^{-1}), with no bleeding or thrombotic episodes to date.
Conclusion: Human Coagulation factor X concentrate (BPL) has been shown to be a safe and effective alternative to PCC's in this girl with severe factor X deficiency and immobility due to muscular dystrophy

PO-TU-256
Inherited factor VII deficiency: Perioperative replacement therapy is not necessary in most cases

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Aims: Inherited factor VII (FVII) deficiency is a rare bleeding disorder with a wide variation of bleeding symptoms less severe than in hemophilia A and B. Consistent evidence-based recommendations regarding perioperative replacement management do not exist for FVII-deficient patients. The aim of this study was to evaluate bleeding symptoms in these patients.
Methods: We collected retrospectively data of all patients with factor VII deficiency presented between 2001 and 2011 in two institutions (Vivantes Klinikum im Friedrichshain, Berlin and Zentrum für Blutgerinnungsstörungen, Leipzig). We evaluated age, sex, factor VII activity, surgical interventions, bleeding symptoms, and pregnancies.
Results: We analyzed 119 patients between 4 and 76 years old at presentation. Three patients had a FVII activity below 1% and 7 patients below 10%. Most patients showed up for a diagnostic work-up with a reduced Quick value. Most underlying molecular defects were missense mutations. Sixteen out of 119 patients had bleeding symptoms in daily life (1 patient FVII <1%, 15 patients >20%) and 11/37 had bleeding complications during surgery before diagnosis of FVII deficiency. There was no relation between bleeding symptoms and FVII activity. In 19 surgeries (10/19 major) after the diagnosis of FVII-deficiency, no bleeds occurred. All patients received tranexamic acid. One patient (FVII <1%) received one dose recombinant FVIIa before total hip replacement, and one patient (FVII <1%) received only tranexamic acid. Six pregnancies (FVII: 3% to 55%) took place without bleeding complications.
Conclusions: Patients with FVII-deficiency have a low number of bleeding symptoms in daily life and during surgery. Bleeding symptoms were not proportional to the residual factor VII activity. Even patients with severe FVII deficiencies do not need routinely perioperative replacement therapy.

PO-TU-257
Prophylaxis of bleeding by FEIBA® in a boy with severe congenital factor X deficiency

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Introduction: Congenital FX (factor X) deficiency is a very rare coagulation disorder. Although PCC (prothrombin complex concentrate) is known to be useful, it is not available in several countries. Thus we herein introduce a boy with severe FX deficiency treated with activated PCC, FEIBA®.
Case description: An 11 months-old boy was admitted due to easy bruising after birth. The initial laboratory test revealed both prolonged prothrombin time and activated partial thromboplastin time. FX activity was markedly decreased below 1%. He was managed with FFP (fresh frozen plasma) whenever he experienced minor bleedings. At 18 months of age, he was admitted due to intracranial hemorrhage. Craniotomy and removal of hematoma were done and during the surgery FFP was frequently transfused. However, his follow-up brain computed tomography (CT) revealed aggravated hemorrhage. Because PCC is not available in Korea, he was treated with FEIBA® during a second operation. After that, CT showed improvement and he was managed with FEIBA® for 2 weeks after neurosurgery. At 22 months of age, he had craniotomy again because of subdural hematoma. Removal of hematoma was performed and he also received FEIBA®. *In vivo* recovery was checked after infusion of FEIBA® (table 1). To maintain the trough level of FX over 1%, he has been managed by weekly administration of 100 IU kg^{-1} FEIBA® until the present. He is now 27 months old and shows little tendency to bleed during prophylaxis.
Table 1: *In vivo* recovery after administration of 100 IU/kg FEIBA® in a boy with severe congenital factor X deficiency

Time	0	15 min	30 min	60 min	12 h	24 h	2 days	3 days	4 days	5 days	6 days	7 days
FX (%)	<1	80	92	90	54	42	27	12	6	3	2	1

PO-TU-258
Rare bleeding disorders in the FranceCoag Network: Diagnosis circumstances and severe events in patients with severe FXIII deficiency under 10 per cent

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Analyses of the European Network of rare bleeding disorders (RBD) indicate that RBD should not be studied as a whole group but studies should focus on specific aspects of each single RBD. Severe forms of FXIII deficiency defined as a plasma level <10% have been included in the French Hemophilia Registry (FranceCoag Network) since January 2002. In December 2011, 25 patients (15 males and 10 females) were included by 13 centres. Thirteen patients (52%) are under 18 years, 8 (32%) are aged 40–18 years, and 4 (16%) are over 40 years in 2011. Twenty-one patients have a median plasma level <1% and 3 between 1–5%. The median age at inclusion was 10 years (17 days–53 years). The median follow-up per patient was 6.39 year (1–9.37 years) and total duration of follow-up is 144.12 person $years^{-1}$. Three (12%) patients had known family histories before the diagnosis. The diagnosis is secondary to a hemorrhagic event in 88% (22/25) of cases, whether or not there is a known family history: 34% due to bleeding or disorders scarring of the umbilical cord, 13% intracranial hemorrhage (5/25), 10% hematoma (4/25). Other circumstances are prolonged bleeding (8%), surgery (5%), and miscarriages (3%). Since birth, 19 (56%) severe bleedings occurred in 12 patients, including 12 (63%) intracranial hemorrhages among patients with FXIII <1%. Fourteen (56%) patients have never had a serious bleeding in their lives, 5 (20%) have had at least 1, 5 (20%) patients at least 2, and 1 (4%) patient more than 3. Regarding treatment, all the patients with FXIII deficiency have been treated at least once in their life. The median age at first treatment was 19 months (0.16–420) (no difference according to the severity): 83% received plasma-derived products, 12% of PSL, and 5% another replacement therapy. One hundred per cent of patients are treated at last visit, which dates less than 3 years in 84% (21/25). Twenty-four patients (96%) have a prophylactic regimen. Thanks to our registry, we propose a clinical description of 25 patients with FXIII deficiency less than 10%. Such a tool allows the improvement of epidemiological

knowledge and clinical management of these rare disorders and confirms the interest to focus on each rare bleeding disorder with the aim of identifying specificities of each.

PO-TU-259
Factor XIII deficiency in Sistan and Baluchestan of Iran

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Introduction: Inherited factor XIII (FXIII) deficiency is a rare bleeding disorder that can present with umbilical bleeding during the neonatal period, delayed soft tissue bruising, mucosal bleeding, poor wound healing, recurrent miscarriages, and life-threatening intracranial hemorrhage. In FXIII deficiency, all routine coagulation tests are normal. This necessitates screening for FXIII deficiency with clot solubility tests in 5 m urea or 1% monochloroacetic acid environments. Diagnosis is confirmed by measurement of FXIII activity, FXIII antigenicity, or plasma concentration of FXIII. As this disorder is autosomal recessive, it is believed to be more common in populations with a high rate of consanguinity, such as the populations of Sistan and Baluchistan. Up to December 2011, we had registered a total of 213 FXIII-deficiency of 92 unrelated families.
Material and methods: Prevalent of factor XIII deficiency is high in the Sistan and Baluchistan province, where by it is the first common disease caused by abnormal clotting factors (57%). This study aims to provide a new and quick way to diagnose the disease based on the patients' clinical manifestation such as delayed wound healing, umbilical bleeding, and recurrent abortions. In total, 213 patients were selected to participate in this study. The patients were divided into two receiver and non-receiver prophylaxis groups.
Results: The mean age of patients was 12.7 ± 8.4 years. Data analysis indicates that 33 patients have intracranial hemorrhage and 173 patients have umbilical bleeding. Finally, significant correlation was seen between intracranial hemorrhage and abortion with age ($P < 0.05$). In this study, 33 (16.1%) had an intracranial hemorrhage. The incidence of intracranial hemorrhage in this disease is more than other bleeding disorders. In addition, there are reports that indicate a very high probability of onset after 3 months, which makes the need for rapid diagnosis essential.

PO-TU-260
Frequency and clinical spectrum of rare bleeding disorders in Pakistan: A multi-centre study

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Objective: To determine the frequency of rare bleeding disorders at multiple hematology centres
Study designs: Descriptive.
Introduction: The prevalence of rare bleeding disorders is high in those countries where consanguinity is normally practised and poses significant clinical and social problems. Due to a lack of proper diagnostic facilities, most of the labs label these patients as hemophilia.
Method: This study was conducted from August 2008 to December 2011 on subjects from NIBD (Karachi), Chughtai, Children Hospital (Lahore), and Pakistan Atomic Energy Commission Hospital (Islamabad). All the subjects with bleeding tendency without any acquired causes were selected for further investigations. Screening tests including platelet counts, prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen assay were performed. Patients with prolonged aPTT were tested for factor VIII and IX. If FVIII was low von Willebrand factor antigen and Von Willebrand factor: Ristocetin cofactor activity were tested. When PT and aPTT both were prolonged then FV, FX, and FII were tested. Urea clot solubility test was done when all coagulation tests were normal. Platelet aggregation studies were done in suspected cases or when screening results were normal.
Result: In total, 732 patients were evaluated for bleeding tendency at the multiple centres and 172 (23.4%) were diagnosed with rare bleeding disorders. Out of these 172, 99 were males and 73 were females, with an age range 1 month to 60 years. Rare bleeding disorders that were found in our population included deficiency of factor VII: {n = 12 (0.58%)}, factor X: {n = 02 (1.16%)}, factor XIII: {n = 10 (5.8%)}, factor V: {n = 5 (2.9%)}, factor XI: {n = 1 (0.58%)}, Combined deficiency of factor V & VIII: {n = 3 (1.7%)}, multiple vitamin K-dependent clotting factors deficiency {n = 3 (1.7%)}, Glanzmann's thrombasthenia: {n = 35 (20.3%)}, Bernard-Soulier syndrome: {n = 04 (2.32%)}, epinephrine receptor defect: {n = 14 (8.1%)}, ADP receptor defect: {n = 4 (2.3%)}, collagen receptor defect: {n = 3 (1.7%)}, multiple platelet receptors defect {n = 55 (31.9%)}
Conclusion: Patients' awareness, clinical and diagnostic workshops for health care professionals for correct diagnosis, standardized treatment, good coordination in maintaining RBD registry on national and international level so that we can identify more new rare bleeding disorder patients and plan better management for them.

PO-TU-261
Prophylactic treatment with activated prothrombin complex concentrate in a patient with severe factor X (FX) deficiency

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Congenital factor X (FX) deficiency is a rare bleeding disorder characterized by autosomal recessive inheritance. The incidence of homozygotes in the general population is 1:1,000,000. Patients with FX deficiency may present with bleeding at any age; for example, joint and muscle-bleeding, severe postoperative hemorrhage, and perinatal intracranial hemorrhage.
Objectives: To assess the treatment effectiveness of prophylactic activated prothrombin complex concentrate (aPPC) in a patient with FX deficiency.
Case report: We describe a female child treated at our hematology service, 39 days old, who showed intracranial hemorrhage with a measured level of FX: 0.7%. After this episode, the infant presented 3 central nervous system bleedings. Prophylaxis started with fresh frozen plasma (FFP) 2 times a week, but due to allergic reactions and no in-country availability of FX concentrates, prophylaxis begins with aPCC 30 IU kg^{-1} day^{-1}, 3 times a week, achieving an FX level of 127%. The levels of factor II, VII, and IX were normal before and after administration of the aPPC. No bleeding episodes have occurred again, and the patient has normal neurodevelopment 4 years after aPCC prophylaxis.
Conclusion: Treatment options for patients with FX deficiency include FPP administration, aPCC (containing factors II, VII, IX, and X) and concentrate of plasma-derived factor X. Two first options are associated with risk of volume-overload (FFP), thromboembolism due to substitution of other coagulation factors that the patients have normal levels, and finally, transmission of viral infection due to no virus inactivation. However, aPCC can be a good alternative treatment. Currently in the literature there are few reported cases of prophylaxis in patients with aPPC with severe FX deficiency.

PO-TU-262
Phenotypic classification of the mutations in coagulation factor IXx segregate to different locations in its protein structure

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Coagulation factor IX (FIX), a zymogen synthesised in the liver, is a single-chain, vitamin K-dependent plasma glycoprotein of the peptidase S1 family and is an important factor of the intrinsic system of the coagulation cascade. Defects in the *F9* gene lead to hemophilia B, a gender-linked recessive coagulation disorder with an incidence of approximately 1 in 50,000 and occur almost exclusively in males. We have assessed 1,030 unique mutations in the *F9* gene corresponding to 3,192 patient entries that cause hemophilia B in the serine protease (SP), EGF, and Gla domains of the FIX. Of these 1,030, 63 unique mutations are novel and not published in the last update of hemophilia B mutation database in 2004. There are 36 double, 1 triple, and 1 quadruple mutants. We have developed an interactive database in which the *F9* mutations are presented in searchable formats, and viewed in conjunction with a FIX protein structure. Mutations have been reported for 308 out of the 461 residues in FIX, with activity and antigen levels reported for 162 of these. Of the 148 unique mutations in the four domains with known phenotypes, 18% (27) are quantitative type I mutations, 68% (100) are qualitative type II mutations, and 14% (21) are unclassified. In the SP domain, which is formed as two subdomains, between which lies the catalytic active site cleft, 44 of the 62 type II mutations in the SP domain are located in subdomain 2, and the majority of these lead to severe hemophilia B. In contrast, 14 of the 27 type I mutations are in the subdomain 1 of the SP domain. We conclude that the phenotype and severity of the mutations in *F9* correlate with their location in the FIX structure. The database will enable analysis of the structure-function effect of individual mutations thus informing the clinical management of patients with hemophilia B.

PO-TU-264
Genotype-phenotype correlation in families with mild factor VII deficiency

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Factor VII (FVII) deficiency (MIM 227500) is the most common among the rare congenital coagulation disorders and is transmitted with autosomal recessive inheritance. Gene polymorphisms, pathological mutations, the presence of modifier genes, and environmental factors could contribute to clinical heterogeneity, which ranges in severity from lethal to mild or even asymptomatic forms. The genotype-phenotype correlation is not always clear, and in many cases it is difficult to establish the genetic influence on clinical phenotypes. In order to define clearly the genotype-phenotype correlation and to outline a welfare management of these patients, we evaluated seven families with mild congenital deficit of factor VII, selected among all patients of Hub Hemophilia Centre of Parma (Italy). We focused our interest on these patients because we collected blood samples from all members of their families, not only from those with reduced FVII levels. The recruited families were formed by a proband, with reduced FVII:C (20%<FVII:C<40%, mean value: 33%), parents and siblings. Three probands did not show a bleeding tendency; the remaining patients showed gum bleeding or a mild but prolonged bleeding after injury. They all showed a prolonged prothrombin time (PT) carried out in occasional blood tests or pre-operative screening. The factor 8 gene, including exons, flanking, and promoter regions, was analysed by DHPLC and direct sequencing. We characterized a pathological mutation in heterozygosis in two families (one missense, c.985T>C p.Ser329Pro and one splicing, g.5120G>A c.64 + 5G>A); in one family we detected a silent nucleotidic change of uncertain phenotypic effect (c.285G>A p.Glu95Glu). In the remainder, plasma levels of FVII are affected by polymorphisms known to be associated with low FVII:C (-323CCTATATCCT insertion; −122 t/c; R353Q), but none of those patients had clinical manifestations. Mild deficiency of FVII remains undiagnosed in many patients due to a lack of significant bleeding symptoms and the surgical management of these patients remains unclear.

PO-TU-265
Surgical interventions in rare coagulation factor deficiencies
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Congenital rare factor deficiencies may present in infancy by life threatening bleedings or may not show any symptoms until adulthood. It is more commonly reported in countries that have frequent consanguineous marriages in their population. Data regarding surgical interventions of rare congenital factor deficiencies are based on case reports and records of guidelines. There are not well-documented and separately prepared directories related to pre-surgical and prophylactic approaches to surgical interventions of these deficiencies. Our retrospective study consisted of 171 cases of patients with rare factor deficiencies that were followed up with in our clinic, of whom 50 had 71 surgical interventions between 1990 and 2011. Of these patients, 35 were deficient in factor VII (FVII), 5 in factor V (FV), 4 in factor X (FX), 2 in factor XI (FXI), 2 in factor XIII (FXIII), and 2 were fibrinogen deficient. In 18 patients factor activities were under 5% (36%), 9 were between 5–30% (18%), 23 were above 30% (46%). Thirty-one were symptomatic, 19 were asymptomatic. All the asymptomatic patients were diagnosed incidentally with coagulation tests before surgery. The patient population consisted of 41 males and 9 females. The age range was between 3 months and 24 years, and the ages at the admission of 48 patients were between 2 weeks and 18 years. The rate of familial consanguinity was 48%. The surgical interventions listed in order of frequency were as follows: circumcisions with a frequency of 33.8% (n = 24), tooth extractions with a frequency of 25.3% (n = 18), and inguinal hernia in 7 patients (9.8%). We used fresh frozen plasma in 29 patients, rFVIIa in 18 patients, PCC in 4 patients, and fibrinogen in 2 patients during surgical interventions. In 13 patients antifibrinolytic agents were also used. In 18 patients surgical interventions were applied without any replacement therapy. No additional doses were required after surgical prophylaxis doses. Bleeding and thrombotic events were not observed. Antibody occurrence was not detected in these patients. In our study, we evaluated preparation before surgical interventions, factor replacement prior to surgery, and post-operative processes in patients with rare coagulation factor deficiency.

PO-TU-266
Prophylaxis in Rare Coagulation Factor Deficiencies
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In the 2000s plenty of national and international study groups propagated studies regarding diagnosis and treatment of rare coagulation factor deficiencies. With respect to the high morbidities and mortalities due to severe bleedings, prophylactic treatment approaches have emerged. In cases of the central nervous system, gastrointestinal system, and joint bleedings, prophylaxis is recommended. Experiences regarding prophylaxis were reported in a series consisting of a small number of patients with fibrinogen, factor II, factor V, factor VII, factor X and factor XIII deficiency. In our study, the demographic, clinical, and laboratory data of two factor VII deficiency, one afibrinogenemia, and one factor X deficiency cases under prophylactic treatment were evaluated retrospectively. Of the factor VII deficiencies, one (F:C = 0%) with recurrent central nervous system bleedings was under prophylaxis with activated recombinant factor VII once a week for 7 years and the other (F:C = 0%) with one episode of central nervous system bleeding was under prophylaxis for 4.5 years. Our patient with factor X deficiency (F:C = 1.75%), having recurrent central nervous system bleeding, was having prophylaxis with prothrombin complex concentrate twice a week for 5.5 years, and one with afibrinogenemia (F:C = 0%), having severe pain and inability to walk due to recurrent soft tissue bleedings, was under prophylaxis with fibrinogen product twice a week with 2.5 years. Data regarding follow-up of our patients, clinical, and laboratory findings during prophylaxis are presented.

PO-TU-267
Rare coagulation factor deficiencies presenting with severe bleeding episodes
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Rare coagulation factor deficiencies are autosomal recessively inherited disorders. Their frequency is approximately 1:500,000 to 1:2,000,000 in the general population. In this study, our purpose is to assess 171 patients retrospectively, who were diagnosed and treated with rare coagulation-factor deficiency between 1990 and 2011. One hundred and eleven (64.9%) patients were male and 60 (35.1%) were female. The ages at the admission ranged from 2 weeks to 19 years. Familial consanguinity was present in 43.3% of the patients. Of these 171 patients, 8 were diagnosed with fibrinogen deficiency, 1 with factor II deficiency, 8 with factor V deficiency, 127 with factor VII deficiency, 14 with factor X deficiency, 11 with factor XI deficiency, 2 with factor XIII deficiency. The levels of factor:C were as follows: 42 (24.5%) patients; <5%, 33 (19.3%) patients; 5–30% and 96 (56.2%) patients; >30%. Sixty-six (38.6%) patients were asymptomatic and 26 of them were diagnosed by preoperative laboratory tests, 24 were diagnosed by family histories, and 16 were diagnosed by bleeding during surgery. Among 34 severe bleeding episodes, central nervous system bleedings were the most common site (n = 18, 53%), followed by hemarthrosis (n = 12, 35.3), and gastrointestinal system bleeding (n = 4, 11.7%). Twenty-four of the patients presented with severe bleeding were under 3 months old. This result emphasized the importance of early diagnosis. In our study, we discussed the treatment of severe bleeding episodes in rare coagulation factor deficiencies and evaluated the conditions which required prophylaxis.

PO-TU-268
Thrombosis of the Abdominal Aorta in Congenital Afibrinogenemia
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Rare cases of thrombosis in congenital hypo-afibrinogenemia have been described, either in association or not with replacement therapy or thrombotic risk factors. We describe an aortic thrombosis in a 48-year-old female with congenital afibrinogenemia. She had a long-term bleeding history: hemorrhage from umbilical cord, bleeding of gums and after minor trauma, and hemoperitoneum due to rupture of ovarian cysts. She was initially treated on demand with hemotransfusions and cryoprecipitates, then with fibrinogen concentrates (FC). In 2001 she developed a spontaneous cerebral hemorrhage treated with FC, which was maintained as long-term prophylaxis (1 g every 10 days; Fibrinogeno TIM3, Baxter, replaced by Haemocomplettan P, CSL Behring, since 2004) with no bleeding events. In April 2011 she was admitted for ischemia of the 4th right toe; she reported a low-back trauma a few months before. Arterial pulses and EchoColorDoppler of lower limb were normal, as well as ECG and echocardiogram. An angio-TC of abdominal aorta showed a thrombosis from the origin of renal arteries to the carrefour with a stenosis of 50–60% and a distal floating part of 34 mm. Fibrinogen levels were undetectable; mild hypercholesterolemia and hypertension were seen, whereas diabetes, thrombophilia, vasculitis, cancer, and atherosclerosis were excluded. The patient received FC to maintain fibrinogen levels above 80 mg dL^{-1}, reduced dose of sc enoxaparin (75 IU kg^{-1} bid) and aspirin (50 mg every other day). The toe ischemia completely recovered. Antithrombotic treatment was maintained in addition to prophylactic FC, without bleeding or thrombosis recurrence. After 6 months aortic thrombus was partially reduced. We can speculate that thrombus formation might have been triggered by a traumatic lesion of aortic endothelium, whereas the role of fibrinogen prophylaxis remains uncertain. Our therapeutic approach was effective to obtain thrombus reduction. Further studies are needed to optimize treatment type and duration in this peculiar setting.

PO-TU-269
Efficacy of a recombinant ADAMTS13 in a mouse model of thrombotic thrombocytopenic purpura
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Baxter is developing a recombinant ADAMTS13 (rADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) product for the potential prophylaxis and treatment of thrombotic thrombocytopenic purpura (TTP). We established a disease model in ADAMTS13 ko mice (B6.129-ADAMTS13^{tm1Dgi}) in which the animals simultaneously and consistently develop TTP-like symptoms by challenge with a high dose of human recombinant von Willebrand factor (rVWF) containing ultra-large VWF multimers. A dose-dependent efficacy of rADAMTS13 in this model was shown in previous studies. In the present studies, the prophylactic and therapeutic efficacy of Baxter's rADAMTS13 was tested over time. Groups of 10 ADAMTS13 ko mice received a single dose of 200 FRETS-U kg^{-1} rADAMTS13 5 min–120 h before, or 15–180 min after challenge with rVWF. Buffer was used as a negative control item in both studies. Efficacy was defined as the degree of prevention of platelet drop and increase in LDH. Schistocytosis and organ damage were also assessed. Morbidity in negative controls was 100%: All animals receiving rVWF containing ultra-large VWF multimers were severely thrombocytopenic and showed increased LDH levels, schistocytosis and organ damage. Efficacy of rADAMTS13 was treatment interval-dependent in both studies. Platelet count at termination of all rADAMTS13-treated groups was statistically superior to buffer-treated controls ($P \leq 0.0001$). However, animals that received prophylactic treatment 120 h before administration of rVWF showed severe thrombocytopenia and clinically relevant protection was only seen for treatment intervals $\leq$ 72 h. Therapeutic treatment with rADAMTS13 stabilized the platelet count and prevented further development of thrombocytopenia. Other endpoints, including LDH, schistocytosis and organ damage, confirmed the treatment interval-dependent efficacy observed for platelet count. In summary, Baxter's rADAMTS13 was effective in an rVWF-induced animal model closely mimicking the situation in patients with hereditary TTP.

PO-TU-270
Delayed vitamin k-deficiency related bleeding: Is it genetically linked?
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Hemorrhagic disease of the newborn (HDN) or delayed vitamin K-deficiency bleeding (VKDB) is an uncommon disorder with potentially devastating outcomes. The bleeding is most often intracranial (IC), but can also be mucosal, cutaneous, or gastrointestinal. Despite administration of vitamin K (VK), some infants show lower activity of VK-dependent coagulation factors. Exclusive breast feeding with no or inadequate vitamin K prophylaxis, intestinal malabsorption defects (cholestatic jaundice, cystic fibrosis, α-1-antitrypsin deficiency etc.), antibiotics, diarrhea, and a history of maternal medication are some of the known acquired causes of vitamin K-deficiency in children. We studied 11 infants who presented with vitamin K-deficiency-related bleeding between 8 and 13 weeks old. Six had IC bleeding, 2 had severe epistaxis, 2 had prolonged bleeding from the site of injection, and one had excessive bleeding from the site of catheter insertion. Analysis of the 3 warfarin-sensitive polymorphisms showed that 6 out of 11 infants had some of the 3 warfarin-sensitive alleles

The present study shows a higher prevalence of warfarin-sensitive alleles in delayed vitamin K-deficiency group infants indicating a possible genetic predisposition.

VKORC1 & CYP2C9 genotypes in 11 delayed vitamin k deficient patients

WILD		
Genotype	No. of patients	Percentage
GG + *1/*1	5	45.5 %
VARIANT		
Genotype	No. of patients	Percentage
GA + *1/*1	1	9.1 %
GA + *1/*3	1	9.1 %
GA + *1/*2	1	9.1 %
GG + *1/*2	2	18.2 %
GG + *1/*3	1	9.1 %
TOTAL	6	54.5 %

PO-TU-271
Intracranial hemorrhage in an infant with severe factor V deficiency

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Factor V deficiency is a rare congenital bleeding disorder. In Canada, 50 cases have been registered in the Canadian Rare Inherited Bleeding Disorders Registry; six are classified as severe. Our patient was an otherwise healthy 4 month-old infant from a remote rural community who presented with recurrent epistaxis resulting in clinically significant anemia. The activated partial thromboplastin time (aPTT) and international normalized ratio (INR) were markedly elevated at 158 s and 2.4, respectively. She was referred to the Pediatric Hematology program for further evaluation, where a factor V level of <1% was identified. The family history did not identify relatives with significant bleeding. Following the diagnosis, the family was educated to be alert to the early signs of bleeding, particularly intracranial hemorrhage, and was provided with a Factor First information card to present to the local hospital. Two weeks later, the patient began to experience increasing irritability and decreased activity. She was taken to the local Emergency Department on three occasions and discharged with a diagnosis of viral illness. On the fourth visit, she presented with a decreased level of consciousness, and after stabilization, including fresh frozen plasma (FFP) and transfer to our tertiary care center, neuro-imaging demonstrated intracranial hemorrhage. The patient underwent emergency neurosurgical decompression under coverage with FFP. Regular transfusions of FFP continued daily for the first five days post-operatively to maintain near normal aPTT and INR. Prophylaxis with FFP, three times weekly, was initiated and will continue for the foreseeable future. No recurrent hemorrhage has occurred. A major challenge for patients with rare bleeding disorders is the lack of awareness among medical personnel. Despite her caregiver's persistence and the information card we had provided, early signs and symptoms of intracranial hemorrhage were not appreciated. Education for parents and professionals is a crucial component of the therapeutic plan for patients with rare bleeding disorders.

PO-TU-272
Factor XI deficiency: Importance of von Willebrand factor level on hemorrhagic phenotype

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In patients with factor XI (FXI) deficiency, bleeding manifestations are weakly correlated with plasmatic factor XI level. Previous studies suggested that von Willebrand factor (VWF) activity may influence bleeding tendency (Bolton-Maggs Thromb Haemost 1995; 73: 194–202). The goal of the present study is to analyze the clinical and biological characteristics of FXI-deficient patients in relationship with hemorrhagic diathesis. This retrospective observational study was conducted in the 'Multisite Grand Est Haemophilia Competence Center' (including academic hospitals of Besançon, Dijon, Nancy, and Reims). Inclusion criteria combined FXI level <40 IU dL^{-1} and a large hemostasis screening. Patients were classified in four groups of bleeding severity: none, minor, moderate, or major bleeding. Patients with deficiencies other than VWF defect were excluded. Statistical analysis was performed using ANOVA. Patients (n = 177) were analyzed. Main characteristics are: sex ratio (M/F = 0.57), median age (27 years, 3–82), median age at diagnosis (19 years, 0–79), circumstances of diagnosis (incidental = 63%), family history = 25%, bleeding (n = 12%), surgery (n = 345), invasive procedure (n = 93), pregnancy (n = 135), number of patients with FXI < 15 IU dL^{-1} (n = 25), positive family history of bleeding (48%).
The repartition of age at diagnosis, FXI level, and VWF activity according to bleeding severity are presented in Table 1:

	No bleeding n = 68	Minor bleeding n = 52	Moderate bleeding n = 40	Major bleeding n = 17	Level of significance
Median age at diagnosis	14	21	22	34	P < 0.001
FXI level (mean)	26	27	23	22	NS
VWF activity (mean ± SD)	89 ± 32	87 ± 34	72 ± 33	69 ± 27	P = 0.01

Bleeding severity was not statistically correlated with FXI level (P = 0.08). On the contrary, VWF activity was correlated with hemorrhagic manifestations (P = 0.01). In conclusion, VWF significantly influences bleeding tendency in FXI deficient patients. Thus, we suggest measuring VWF in all patients with FXI deficiency in order to predict more accurately the hemorrhagic risk.

PO-TU-273
Rare bleeding disorders in the FranceCoag Network: Circumstances of diagnosis and clinical manifestations in the French population of patients with FXI deficiency under twenty per cent

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We report a focused analysis on severe FXI deficiency defined as a basal plasma level <20%, included in the FranceCoag Network since January 2003. On November 2011, 125 patients (62 males, 63 females) were included by 22 centres. Among them, 27 (21.6%) patients were under 18 years, 36 (28.8%) were between 18 and 40 years, and 62 (49.6%) were over 40 years. The minimal FXI plasma level is <1% in 42 patients, [1–5%] in 62 and]5–20%[in 21. The median age at inclusion was 34.8 years (range: 0.1–79.3) and the median age at diagnosis was 25.5 years (range: 0–78.4). The median follow-up per patient is 1.00 year and the total duration of follow-up is 328.45 person-years. In most of the cases (n = 78, 62.4%) including the most severe forms, the factor XI defect was incidentally discovered by a systematic blood test. In 22 cases (17.6%), the diagnosis was secondary to bleeding complications following surgery (n = 10), miscellaneous bleeding symptoms (n = 6), dental extractions (n = 4), or delivery (n = 2). Twenty patients (16%) were diagnosed due to a family history. Data about diagnostic circumstances were lacking in five patients. For patients with a family history, the percentage of patients diagnosed by a systematic blood test was lower (32.1%). Twenty-one life-threatening hemorrhages occurred in 12 patients (9.6%), including 9 uterus bleeding (6 post-partum hemorrhages), 10 bleeding after surgery or traumatic circumstances, and one gastrointestinal bleeding. Regarding replacement therapy, 52 patients (41.6%) have been treated at least once in their live. The median age at first treatment was 35 years (range 0.06–78.5) with no difference according to the severity. In conclusion, in factor XI deficiencies, we observed a low rate of serious bleeding events; diagnosis was mostly incidental by a systematic blood test. Most of the bleeding episodes occurred after invasive procedures.

PO-TU-274
Molecular analysis and clinical course of factor XI (FXI) deficiency in twelve Polish families

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The gene encoding factor XI (*F11*) located on chromosome 4 consists of 15 exons and 14 introns and spreads over 23 kb of genomic DNA. Inherited FXI deficiency is a rare autosomal recessive disorder but it is frequent among Ashkenazi Jews where the carrier rate is 8–9% and about 0.2% of the general population is afflicted with severe FXI deficiency. Two mutations, type II (Glu117Stop) and type III (Phe283Leu), are the most prevalent in this population. The aim of the present study is to identify the causative mutations in Polish FXI-deficient patients registered in the nationwide data base. We have also studied the clinical manifestations of the condition. Up to date, 15 patients from 12 families with FXI deficiency were included in the study. FXI coagulation activity (FXI:C) was determined by one-stage clotting assay. The *F11* gene was examined by automated direct sequencing of all 15 coding regions and exon/intron splicing sites on ABI 3100 Genetic Analyzer. All patients had reduced FXI activity ranging from 3 to 51 IU dL^{-1} (normal range 70–140 IU dL^{-1}). We identified 6 causative mutations in 11 patients from 8 families; four (Glu117Stop (c.403 G/T), Phe283Leu (c.901 T/C), Ile197 (c.644_649delTCGACA), c.325 + 1 G>A) were previously described while two (Glu525Lys (c.1627 G>A), Ser420Stop [c.1313 C/A]) were novel. Two of 6 patients with FXI:C below 10 IU dL^{-1} were homozygous (one - Glu117Stop, one - c.325 + 1 G>A), while four were compound heterozygous (two subjects - Phe283Leu/Glu525Lys, one - Glu117Stop/Phe283Leu, one - Ser420Stop/Ile197) for the causative mutations. In these 6 patients, the first bleeding complications (easy bruising, epistaxis, oral cavity hemorrhage, menorrhagia) occurred in the first two decades of life, yet FXI-deficiency diagnosis was significantly delayed and established between 24 and 71 years of age. In two patients the diagnosis was made after excessive post-operative bleeding. In 4 patients, from 4 distinct families, with FXI:C ranging from 38 to 51 IU dL^{-1}, no mutation in *F11* was found.

PO-TU-275

Results of long-term prophylaxis in patients with factor XIII (FXIII) deficiency

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Inherited factor XIII (FXIII) deficiency is known as a rare autosomal recessive disorder, affecting approximately one out of one to three million people. It is characterized by a life-long bleeding tendency, impaired wound healing, and spontaneous abortions in females. The most common manifestations of inborn FXIII deficiency are umbilical cord bleeding and intracranial hemorrhage reported in up to 80% of cases. We report here on the efficacy of long-term prophylaxis with FXIII-containing preparations in 10 Polish patients with inherited FXIII deficiency from 8 families. Patients were born between 1945 and 1998. In 8/10 patients the causative mutations in FXIII gene were identified and described elsewhere (*Haemophilia 2007, 13, 649–657*). All 10 patients presented very severe bleeding phenotype, 8 of them experienced from one to six intracranial hemorrhages before the diagnosis was made. The prophylactic infusions of FXIII-containing products were initiated at our centre in the beginning of the 1980s. At first, patients received fresh frozen plasma (FFP) and cryoprecipitate, and then, since the first half of the 1990s, patients were administered plasma-derived FXIII (pdFXIII) concentrate Fibrogammin P (CSL Behring, Germany). The average dose of pdFXIII was about 10–15 IU kg^{-1} given every 4 weeks with no lab monitoring. Over the last 20 years such treatment regimen virtually eliminated spontaneous bleeding occurrence in our patients. The extra infusions of pdFXIII concentrate were given on several occasions; prior to major surgery (thyroidectomy) in one case and prior to two childbirths in another case. Five patients became infected with hepatitis C virus before 1991, but there were no seroconversions while on pdFXIII concentrate treatment. Our data indicate that long-term prophylaxis with FXIII concentrate is a safe and effective modality and should be considered the treatment of choice for FXIII deficient patients who present with severe bleeding tendency.

39-SEXUAL HEALTH

S-WE-04.3-3
Physiotherapist's perspective
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This presentation will address the physical stresses that intercourse places on the muscles and joints, and potential for injury due to forces involved. Advice regarding specific body positions that increase or decrease risk to individual joints and muscles will be offered, and linked to the effects of bleeding on the musculoskeletal system. As with other forms of physical activity, it is advised that you discuss concerns regarding sex with your physiotherapist. Based on your bleeding history, and the stress placed on your body in different positions, your physiotherapist may be able to recommend positions that would be best for your body. Joints and muscles may be used differently during sex, based upon body position, compared to their function in other everyday activities. As sex can be both gentle and relaxing as well as vigorous and energetic, there is potential for injury, and sex should be considered in the same way as other types of exercise when trying to decide on the risk of bleeding. This presentation will establish the link between the physicality of sex and the potential for injury, and through interaction with the audience will provide a forum to discuss strategies to counteract the risks involved. The iliopsoas muscle is significantly at risk during sexual activity. Along with the abdominal muscles, it is very active during thrusting motions of the pelvis. Due to the increased risk, and the extensive resources and time required to rehabilitate it from a bleeding episode, it will be specifically discussed during the presentation.

S-WE-04.3-1
PWH and sexuality; A Hemophilia nurse's view
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People with hemophilia (PWH) need to have a good understanding of healthy relationships, just the same as in the general population. The hemophilia nurse should be well-placed to provide this key educational role, as the relationship with the hemophilia nurse often spans both the teenage and adult years. In reality, the educational role focuses on more traditional health-management issues, and discussions and engagement around sexual health rarely take place. The important decisions that people with hemophilia need to make before they have sex is to know and to be clear with a partner about what they both want and expect from the relationship as a whole. It is important that PWH go to health professionals who deal regularly with PWH; and health professionals may, in turn, need training in how to counsel, rather than merely 'giving advice,' in order to encourage discussion about sex. People with hemophilia need to take responsibility for their lifestyle choices and need to respect their sex partners. The communication used when counselling needs to be simple and practical so that the emotional, physical, and social issues we face do not restrict two-way communication. Health professionals need to be effective communicators and attentive listeners. This presentation will describe the need for appropriately timed guidance and counselling about future relationships before relationships are formed.

S-WE-04.3-2
PWH and sexuality: A sexual health professional's view
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Rehabilitation Centre De Trappenberg, Huizen, Netherlands

To properly deal with sexuality in men with hemophilia, the professional needs a mixture of attitude and skills. On the one hand, you have to be aware of male-female differences and male identity. On the other hand, you have to be very pragmatic in approaching sexual disturbances. Hemophilia is accompanied by disturbed sexual function. Sexual desire is, for instance, easily damaged by fatigue, pain, and depression. Erection can be damaged by hypertension and its medication, whereas the ability for ejaculation and orgasm can be reduced by antidepressants. The difficult side of this is that these disturbances not only happen quite frequently, but they also are not easily discussed. The good side of this is that for nearly all sexual function and intimacy disturbances, there are solutions available. When dealing with disturbed sexual function, which solutions could or should be in the toolbox of the hemophilia professional? Especially needed is the skill to discuss various tips and tricks, with topics such as masturbation, adaptations in position, the logistics of timing and energy, the use of erotica to regain desire, and the use of a vibrator and lubricants to facilitate erection-as well as the use of interventions to deal with lost erection, including PDE5-inhibitors and medication to regain orgasm. All interventions should be embedded in the reality of the man's hemophilia and his relationship.

S-WE-04.3-4
Hematologist perspective of sexual health in hemophilia
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Sexual development in males with hemophilia is not different from other males, and hemophilia itself is no reason for sexual abstinence. However hemophilia may cause specific obstacles that vary during life, and may also be the result of side effects of treatment or ageing.
Fear: Fear has a negative effect on sexual desire. It may be caused by fear of a bleeding, fear of pain, and, in the case of hepatitis or HIV, fear of sexual transmission of the virus. Counselling and, in the case of fear of viral transmission, the use of condoms may be useful.
Pain: Pain has a negative effect on sexuality. Adequate clotting factor replacement will relieve pain caused by a bleeding. When pain is caused by arthropathy, painkillers may help.
Bleeding: Bleedings caused by sexual activity are rare. However an iliopsoas muscle bleed may be the result of sexual activity. It causes pain and functional limitations. Clotting factor replacement, rehabilitation, and education are essential to stop the bleeding.
Arthropathy: Besides pain, arthropathy may cause functional limitations and disturbing noises. Functional limitations of elbows, knees, and hips, especially, may cause problems. Alternative positions and putting on music may be of help.
Viral infections: Infections, such as hepatitis C and/or HIV, may influence a fear of transmission, and, although this is very rare, chronic hepatitis may cause sexual dysfunction. Therapy with interferon and ribavirine has a major effect on sexual desire; it increases fatigue and depression and decreases testosterone levels. which are needed for sexual desire. HAART therapy may increase sexual dysfunction in HIV positive persons due to reduced libido and erectile dysfunction.
Co-morbidity: Ageing patients with hemophilia will be confronted with (age related) co-morbidity. Hypertension is more often seen in patients with hemophilia compared to age-matched men, and more often antihypertensive drugs are used. Both may cause erectile dysfunction.
Medication for erectile dysfunction: Oral phosphodiesterase-5 inhibitors (sildenafil and tadalafil) slightly inhibit platelet aggregation *in vitro*.
Conclusion: There are many pitfalls that may negatively influence sexuality. Hemophilia care givers should be aware of this and counseling should be part of a yearly check-up.

PD-SU-PSY
Dealing with sexuality and intimacy in people with hemophilia
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Hemophilia can be accompanied by disturbances in sexuality and in intimate relationships. On the one hand, we know that strenuous sex can cause bleeding. We know, on the other hand, that sexual function can be influenced by complications of the disease (like pain and fatigue causing low desire) or by the treatment (e.g., antihypertensive treatment causing loss of erection or antidepressants causing loss of orgasm). We know, also, that for many sexual disturbances, treatment is available. The topic, however, has to be addressed first. So, since sexuality is such an important aspect of quality of life, attention to this area should be an integral part of hemophilia care. Then the question arises, who is responsible for that discussion? In spite of the fact that sexuality is important for many patients, the majority of them will not start this conversation. Most hope that the professional will open up the topic and then they happily will jump in. However, medical professionals, like other citizens, have not learned to talk about sex easily, in a professional way. This 75 min workshop will allow participants to build skills in 'talking sex' with their patients, intended both for the phase of history taking and for the phase of advice and treatment. Most of the training will consist of small-group exercises (2–3 people who can do the exercises in their own language). When such a touchy area is easily addressed, it usually improves the patient-professional relationship and subsequently, also, treatment compliance.

40-SPORTS AND HEMOPHILIA

FP-TU-01.2-1
Physical activity measured by high-frequency accelerometry in boys with hemophilia

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Background: Participation in regular physical activity (PA) is now widely encouraged for persons with hemophilia (PWH). However, PA levels among PWH have not been well studied. High-frequency accelerometry is an objective measure of PA that accurately captures children's PA levels.
Objectives: To describe PA levels in PWH using accelerometry, and to explore relationships between PA levels and age, hemophilia joint health score (HJHS), number of lifetime joint bleeds (LJB), and body mass index (BMI).
Methods: Eleven boys with moderate (n = 5) or severe (n = 6) hemophilia A or B, ages 6–18, years were recruited. Their characteristics were (mean ± SD): age, 10.3 ± 4.7 years; BMI%ile, 54 ± 26%ile; HJHS, 1.9 ± 3.9; LJB, 10.1 ± 14.0. An Actigraph accelerometer was worn for seven consecutive days, and a parent completed a questionnaire regarding the child's PA level. Participants wore the accelerometer for at least 5 h day^{-1}, 4 days week^{-1}. Data were categorized as light (LPA), moderate (MPA), moderate to vigorous (MVPA), and vigorous (VPA) using validated cut-points for intensity.
Results: Average minutes spent/week in each category were (mean ± SD): LPA (155.8 ± 37.6), MPA (34.1 ± 12.4), MVPA (61.8 ± 27.6), VPA (27.7 ± 13.8). Seventy-three per cent of parents reported their child "is as active as he should be," but only 18% of participants met Canada's PA recommendation of at least 60 min of MVPA day^{-1}. LJB (r = 0.62, P = 0.056) but not HJHS (r = 0.55, P = 0.10) was correlated with BMI%ile. Total physical activity/week (r = -0.71, P = 0.01), MVPA (r = -0.63, P = 0.04), and % of recommended MVPA (r = -0.63, P = 0.04) were correlated with age.
Conclusions: This is the first study to measure PA in PWH using high-frequency accelerometry. In our local cohort, children with severe hemophilia were less active with increasing age, and higher BMI was associated with worse joint status. All participants failed to meet recommended daily MVPA, highlighting the need for future intervention studies to improve PA levels in children with hemophilia.

FP-TU-01.2-2
Risk of bleeds associated with physical activity in children with hemophilia

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Background: It has long been thought that vigorous physical activity increases the risk of bleeds in children with hemophilia, but the magnitude of the increase in risk is not known.
Methods: A case-crossover study was nested within a prospective cohort study. One hundred and four children with moderate or severe hemophilia A or B participated. All bleeds in each participant were monitored for up to 1 year. Following each bleed, the child or parent was interviewed to ascertain exposures to physical activity preceding the bleed. Physical activity was categorized according to expected frequency and severity of collisions. The risk of bleeds associated with physical activity was estimated by contrasting exposure to physical activity in the 8 h before the bleed with exposures in two 8 h control windows on the days preceding the bleed, controlling for levels of clotting factor in the blood.
Results: The incidence rate of bleeds was 5.4 bleeds per person year. Category 2 activities (e.g. soccer, basketball) transiently increased the rate of bleeding by a factor of 2.7 (95% CI 1.7 to 4.8 P < 0.001). Category 3 activities (e.g. wrestling, rugby) transiently increased the rate of bleeding by a factor of 3.7 (95% CI 2.3 to 7.3, P < 0.001). The incidence of bleeding was reduced by 2% for every 1% increase in factor level (95% CI 1 to 4%, P = 0.004). Most bleeds caused by physical activity became apparent within one h of activity.
Conclusion: Vigorous physical activity moderately increases risk of bleeds in children with moderate and severe hemophilia. Exogenous clotting factor substantially mitigates this risk. Risk estimates can be used to inform decisions about participation in physical activity and to design optimal prophylactic schedules.

FP-TU-01.2-3
Endurance performance in adult hemophilia patients before and after a three-month sports therapy program: A randomized controlled trial (RCT)

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Introduction: Based on the increased life expectation of people with hemophilia (PWH) in the last years, age-related cardiovascular diseases (CVD) become more and more important. Endurance performance is an important tool in the prevention of CVD, but joint bleedings and hemophilic arthropathy hinder PWH to participate in endurance training.
Aim: The aim of this study was to investigate the endurance performance before and after a three-month sports therapy program.
Methods: Forty-three subjects with severe and moderate hemophilia A or B (44 ± 11, 22–67 years) were compared to 40 subjects without hemophilia (42 ± 14, 20–68 years) concerning their endurance performance. Furthermore, 18 PWH participated in a three-month sports therapy program; eight PWH performed training in terms of body awareness, muscle tone regulation, and joint mobilization (basic group, BG), and 10 PWH completed additional strength and endurance training (intensive group, IG). Submaximal endurance was measured by spiroergometry on a treadmill using modified stage protocol. VO_2 (oxygen uptake) and VCO_2 (carbon dioxide output) (L min^{-1}), HR (heart rate) (beats min^{-1}), RER (respiratory exchange ratio), f (respiratory frequency) (min^{-1}) as well as Watt, Borg scale, and numeric analog scale (NAS) were assessed during the final stage.
Results: Except for VCO_2 and f, gas exchange parameters and Watt showed impaired endurance performance in PWH compared to controls ($P \leq 0.01$). PWH reported greater exertion (Borg scale) and more pain (NAS) ($P \leq 0.001$). IG showed an increase in Watt (+18 ± 27) after sports therapy compared to BG (+1 ± 8) ($P \leq 0.05$). Parallel, gas exchange parameters, Borg scale, and NAS still remained unchanged in both groups over time ($P > 0.05$).
Conclusion: At first, endurance performance is lower in PWH as we know from other studies; therefore, cardiovascular training should be an integral component of an adequate treatment. A specific adapted and intensified sports therapy seems to have a positive influence on the endurance performance also in PWH.

PO-WE-265
Physical and psychosocial benefits of exercise for patients with hemophilia

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Objectives: To consider the beneficial effects of exercise for patients with hemophilia (PWH), with a view to developing a comprehensive set of recommendations for appropriate exercise regimens.
Methods: A literature review evaluating the medical/psychosocial effects of exercise for PWH was undertaken. Articles published in the preceding 10 years were identified by searching the EMBASE and MEDLINE databases. Search terms included hemophilia and activity/exercise/fitness/sport/athletics/cycling/football/soccer/swimming, as well as joints/protection of joints/prevention of arthropathy/musculoskeletal system/ physiotherapy/strengthening/stretching. Exercise guidelines from medical societies and patient groups were also consulted. Published findings have been summarized and interpreted in the light of the authors' clinical experience.
Results: The literature shows that regardless of the clinical treatment options available, exercise can enhance muscle strength, muscle flexibility, joint motion, and gait pattern. It is therefore important to reinforce the fact that PWH can exercise safely and experience the beneficial physical and psychosocial effects of exercise. Although not unanimous, there is evidence that appropriate physiotherapy and/or exercise programs can improve muscle tone and decrease bleeding frequency, reducing the need for medication and improving quality of life. Exercise may also moderate osteoporosis, a major problem in the ageing hemophilia population. Importantly, geographical and cultural differences impact on treatment availability and attitudes to care for PWH, which influences exercise recommendations in some regions.
Conclusion: Successfully promoting the benefits of exercise may result in PWH becoming more active, leading to improved physical performance and quality of life. This comprehensive overview of the most appropriate sports and training programs highlights the need for a positive approach to PWH on the benefits of exercise.

PO-WE-266
Hemophilia and exercise project (HEP): subjective and objective physical performance in adult hemophilia patients after one year sports therapy program

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Introduction: Bleeding events in people with hemophilia (PWH) are associated with a reduced activity level and consequently with limitations in physical performance. Up to now, there is little experience in effects of sports therapy on PWH. Within the scope of the Hemophilia and Exercise Project (HEP), PWH participated in a special model of 'programmed sports therapy' (PST).
Aim: The aim of this study was to investigate subjective and objective physical performance in PWH after annual PST.
Methods: Forty-eight adult subjects with severe and moderate hemophilia A or B were compared concerning their physical performance (PP) before and after PST. PP was assessed subjectively with HEP-Test-Q and objectively concerning mobility (range of motion), strength and coordination (one-leg stand), and endurance (12 min walk test). PST includes two collective instructive sports camps per year together with a supervised self-employed home training. Participants documented their training and evaluated their activity level. In addition, 43 controls without hemophilia and without training were examined.
Results: Out of 48 PWH, thirteen performed a regular training (active PWH). Twelve HEP participants were constant passive over time (passive PWH). Twenty-three PWH and 24 controls dropped out because of incomplete data. The activity level increased 100% in active PWH and remained unchanged in passive PWH and controls ($P \leq 0.05$). The mobility of the right knee was significantly improved in active PWH

(+5.8 ± 5.3) compared to passive PWH (-1.3 ± 8.6). The 12 min-walk test proved a significant longer walking distance for active PWH (+217 ± 199 m) compared to controls (-32 ± 217 m). Active PWH reported a significant better subjective physical performance in the HEP-Test-Q-domains 'strength and coordination,' 'endurance,' and the total score (+9.4 ± 13.6) compared to passive PWH (-5.3 ± 13.5) and controls (+3.7 ± 7.5). No change was found for the one-leg stand.
Conclusion: Sports therapy affects positively the activity level and the physical performance of PWH, whereby objective effects were not always associated with the subjective assessments.

PO-WE-267
Hemophilia 2012—London-Moscow-Dhaka: A Comparative, Observational Study of the Musculoskeletal Impact of Severe Hemophilia in Twenty Boys in Each City

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2012 is Olympic year in London, focusing on engaging young people in sport. At the outset of our Dhaka–London WFH Twinning Project, we contrast the musculoskeletal impact of severe hemophilia in 20 12 year-old boys from London (mean age 12.7 years, range 11.3–13.9) with 20 boys of equivalent ages from each of the following two cities: Dhaka, Bangladesh, and Moscow, Russia. Hemophilia joint health scores (HJHS) reflect primary prophylaxis in the UK, predominant secondary prophylaxis in Russia, and on-demand treatment with whole blood or fresh frozen plasma in Bangladeshi boys. Sixteen boys from London had a perfect HJHS score of zero compared to 11 from Moscow and only 2 from Bangladesh. Two boys from Moscow and none from London had HJHS >5. Fifteen Bangladeshi boys had HJHS scores >5 (range 6–31), including 6 individuals with a joint score >20. Nine out of 20 Bangladeshi individuals had an abnormal gait score, 3 severely so (no skills within normal limits). Gait scores were normal in all boys from Moscow and London. This study is a snapshot of the geographical inequality of health care, while giving important supporting data for each participating country to continue building sustainable services for their patients. The data is unequivocal in demonstrating the musculoskeletal protection provided by adequate treatment, offering boys a more active life with opportunities previously thought unobtainable. 2012 is a year in which the U.K. national cycling time trial champion is a professional athlete living with severe hemophilia A. As a member of the London 2012 Olympics Team GB cycling squad, he may be the first professional athlete with severe hemophilia to compete in the Olympics. 2012 is also a year in which boys in Dhaka will have immediate access to cryoprecipitate for the first time, providing their next step to more effective treatment as part of an evolving hemophilia network.

PO-WE-268
Development of a Bleeds-Risk Calculator

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We recently completed a case-crossover study which followed 104 boys with hemophilia A or B aged 4–18 years for up to one year. The study provided estimates of the effect of participation in vigorous physical activities on bleeds risk. Estimates of the effect of physical activity on bleeds risk could inform decisions about participation in vigorous physical activity. In practice, however, these estimates (exposure odds ratios) are difficult to interpret and difficult to use. Consequently, we have begun the process of developing a free, web-based bleeds-risk calculator (the 'AHCDO Bleeds-Risk Calculator'). The calculator uses information about bleeds history (past rate of bleeds) and past physical activity profile to generate person-specific estimates of the rate of bleeds that would be expected to occur in the future given a particular future physical activity profile. This makes it possible to explore, in an easily understood way, the effect of participation in a particular physical activity on the expected rate of bleeds. Such analyses might show, for example, that participation in 1 h of football per week, in addition to a child's current physical activity profile, would increase the expected number of bleeds for a child by one bleed per year. (This is only an example. In practice, the estimates will differ for each child, depending on the child's baseline rate of bleeds.) The bleeds-risk calculator will make it possible to use estimates of the effect on bleeds risk of participation in vigorous physical activities to make informed decisions about participation in vigorous physical activity.

PO-WE-269
To Play or Not to Play? U.K. Hemophilia Professionals' Views on Sport in Hemophilia

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Introduction and Aim: Advances in prophylaxis have made it safer and easier for people with hemophilia to take part in exercise and sports. Promotion of regular exercise is a fundamental part of hemophilia practice, with widely recognized physiological and psychosocial health benefits. Lists of activities and recommendations about sporting activities are available, informing how to approach advising people with hemophilia. In practice, advice varies across the world. The aim of this project was to evaluate the current attitudes of hemophilia specialists in the United Kingdom towards sporting activities in patients with hemophilia.
Method: A questionnaire was sent to 87 hemophilia centres in the United Kingdom to be completed by professionals involved in hemophilia care. The questionnaire included questions to obtain demographic information, attitudes towards sport, thoughts on sport for people with hemophilia, and information about the professional's own sporting activities.
Results: Sixty-five questionnaires completed by doctors, nurses, and physiotherapists were returned from 26 hemophilia centres. Professionals either worked with children, adults, or both and clinical experience in hemophilia ranged from 6 months to 32 years. All professionals thought sport was beneficial and recommended it to their patients. The most common sports recommended were swimming, cycling, and racket sports, along with gym activities for adults. Most had the opinion that sporting activities should be carried out at least 3 times a week. Everyone agreed those sports with higher risk of injury, such as contact sports, should be avoided where possible, as the risks outweighed the benefits.
Conclusion: Despite variation in individual professional's views, the general consensus on sporting advice for those with hemophilia is very much in keeping with current published recommendations. Regular sport and exercise should continue to be promoted as part of hemophilia care, with the emphasis on treating each patient as an individual, considering their interests, abilities, and treatment options.

PO-WE-270
Patterns of Physical Activity in Australian Children with Hemophilia

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Background: The current widespread use of prophylaxis in developed countries has enabled greater participation in physical activity by people with hemophilia. However, there are no data on leisure-time physical activity and small-screen time in Australian children with hemophilia.
Methods: This prospective cohort study followed 105 Australian children with moderate and severe hemophilia A or B for one year. Each child's physical activity was assessed using two methods: a physical activity questionnaire (the Modifiable Activity Questionnaire for Adolescents—MAQ) administered via interview at baseline and a one week prospective activity diary completed at a randomly determined time during the course of the year.
Results: The MAQ demonstrated that the mean time spent in sport or leisure-time physical activity in the preceding year was 9.2 h week^{-1} (SD = 7.2). The average time spent in vigorous physical activity (>6 METS) was 4.9 h week^{-1} (SD = 4.2). The average small-screen time (defined as time watching television or videos, including time spent playing the computer or video games) was 2.0 h day^{-1} (SD = 1.3); and 71.4% of children performed vigorous exercise for more than 20 min on at least 3 days week^{-1}. However, only 22% of children met the current Australian government's physical activity guidelines for children and adolescents, and only 36% met the recommended guidelines for small-screen time (i.e. less than 2 h day^{-1}). Only 9.5% of children met the recommended guidelines for both. Results from the prospective activity diary (n = 66) indicate that, on average, children are inactive (including sleep) 86% of the day (20.6 h day^{-1}) and engage in vigorous physical activity 6.4% (1.6 h day^{-1}) of the day.
Conclusions: This study provides the first data regarding leisure-time physical activity in children with hemophilia living in Australia. The majority of Australian children with hemophilia are not meeting the current national physical-activity and small-screen time guidelines.

PO-WE-271
Quantifying the Challenge: Proposal for Evaluation of Musculoskeletal System in Swimmers with Hemophilia Undergoing Intensive Training

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Swimming is the ideal sport to practice for people with hemophilia (PWH) because it allows adequate maintenance of the musculoskeletal system. However, can it be practiced at high-demand levels without causing injuries that could limit the activities of daily life?
Objective: To determine the impact of the proposed swimming-program levels on the musculoskeletal system of people with hemophilia.
Methods: In addition to hematological follow-up, we evaluate each PWH who plans to swim 3,000 metres in open water in the Gulf of Mexico next June 2012. One year earlier, an initial visit was performed on 19 subjects, and we plan a second and a third evaluation at 5 months and 1 month before competition. An intensive training routine consisted of swimming 3 to 5 times week^{-1} in a swimming pool, starting with 1,500 m and progressing to 3,500–4,500 day^{-1}, in addition to some programed open-water practices; up to now they have carried out 1,500 m once, 2,600 m twice, 2,500 m once, and 5,000 m once. To determine the base level of each athlete and to establish their capacity for conducting training, we have used HJHS scale, complemented by an assessment on quadriceps isokinetic machines; ranges of motion was observed in functional values, muscle strength 4 + / 5 of Daniel's & Worthingtham Scale, and a proper relationship quadriceps/hamstring using isokinetic machines. At initial visit and after a 1,000 m open-water training, 9 patients were retired for medical reasons. Up to now, 2 more patients were retired by adherence failure. Currently 8 PWH, 5 severe, 2 moderate and 1 mild, continue their training. We expect to obtain encouraging results that can promote the practice of this discipline and establish the presence or absence of training injuries that could be associated with temporary disabilities on the musculoskeletal system.

41-VON WILLEBRAND DISEASE

FP-TU-04.3-1
A new class of mutations in the A3 region of von Willebrand factor inducing multiple functional defects in the protein

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Von Willebrand disease (VWD) is the most common inherited bleeding disorder and is caused by qualitative or quantitative defects in the plasma multimeric glycoprotein von Willebrand factor (VWF). VWF has two main roles in hemostasis: it promotes platelet adhesion to the injured vessel wall and it protects coagulation factor VIII from premature clearance. Three unrelated families were recruited in the French Reference Centre for von Willebrand disease with moderate bleeding symptoms associated with apparent quantitative VWF defect contrasting with a decreased collagen binding assay, an abnormal multimeric pattern, and an impaired response to desmopressin for two of them. Genetic analysis showed the presence of heterozygous mutations in the A3 domain and A3/D4 connecting segment of VWF, two never reported previously, L1696R and V1934G, and another, P1824H, described in a Spanish family. The mutations were reproduced by site-directed mutagenesis and mutant VWF was expressed in different expression systems, COS-7 cells, BHK cells, and in VWF-deficient mice through hydrodynamic injection. L1696R and P1824H were associated with very low expression levels both*in vitro* and *in vivo* with intracellular retention for P1824H. All three mutants displayed decreased binding to collagen types I and III but also decreased binding to platelet glycoproteins Ib and IIbIIIa. Multimerization was strongly impaired in L1696R and P1824H mutants. Co-transfections with wild-type VWF partially corrected these defects, but collagen binding remained abnormal and the *in vivo* thrombosis response was reduced, particularly for P1824H. The three mutations reported here are not purely collagen binding mutants but appear to induce multiple defects in VWF function, probably by affecting A3 domain conformation. In that regard, these specific patients should be diagnosed with type 2 VWD.

FP-TU-04.3-4
Generation and optimization of the self-administered bleeding assessment tool (Self-BAT)

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In order to standardize bleeding histories, several bleeding assessment tools (BATs) have been validated; all require time-consuming expert administration. Our goal was to develop a self-administered BAT. First, we converted the ISTH BAT into a pilot self-administered tool (Self-BAT) by ensuring a grade 4 reading level and lay language throughout. Then we obtained bleeding scores (BS) from both the expert-administered ISTH BAT and the Self-BAT (randomized order, 10 days apart) from adult controls and previously diagnosed type 1 VWD patients. The Self-BAT was optimized throughout the study based on focus-group feedback and intra-class correlation coefficient (ICC) data comparing the two BS. To date, 38 controls and 13 subjects with type 1 VWD have been enrolled. Bleeding scores (-1 to +4 scoring system for both) and laboratory results are shown in Table 1. The first version of the self-BAT was administered to a group of 23 controls. Based on the focus-group feedback, the Self-BAT was revised and then administered to an additional 15 controls. Analysis showed an overall ICC of 0.91 for the healthy controls reflecting excellent correlation. The optimized Self-BAT was then administered to 10 individuals with Type 1 VWD with an ICC of 0.76. The lower ICC reflected the tendency of affected subjects to remember more bleeding symptoms when prompted by an expert. One final revision was generated, which was then administered to 3 more type 1 VWD subjects. The ICC from this group improved significantly to 0.97. In conclusion, the Self-BAT generates bleeding scores with a high degree of correlation to expert-derived bleeding scores. Additional studies validating the use of the Self-BAT in the clinical assessment of patients are underway.

Table 1. Subject characteristics, lab values, and bleeding scores

	Normal Controls (n = 38)	Type 1 VWD's (n = 13)
Gender M/F	18/20	1/12
Age at study, median	38	37
Laboratory Values		
VWF:Ag (U mL^{-1}), mean (range)	1.10 (0.5–2.1)	0.56 (0.21–0.8)
VWF:RCo (U mL^{-1}), mean (range)	0.68 (0.44–1.22)	0.41 (0.21–0.63)
FVIII:C (U mL^{-1}), mean (range)	1.28 (0.85–1.71)	0.69 (0.47–0.81)
Blood group O (%)	15 (40)	10 (77)
Bleeding Score Results		
Mean BS (range) for Self BAT +SD	1.4 (-2 to 14) ± 3.2	11.6 (3 to 31) ± 6.4
Mean BS (range) for ISTH BAT +SD	0.8 (-3 to 12) ± 2.8	14.7 (1 to 20) ± 6.4

FP-TU-04.3-6
ADAMTS13 cleavage of recombinant human Willebrand factor in severe VWD patients

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Von Willebrand factor (VWF) is composed of a series of multimers with a molecular size ranging from 600 to 20,000 kDa. The ultra-high molecular weight (UHMW) portion of VWF multimers is more efficient in platelet interactions than the lower molecular weight portion, and as such it might have a thrombogenic potential under certain pathologic conditions. The concentration of UHMW multimers in healthy individuals' blood is low because the circulating specific metalloprotease ADAMTS13 rapidly cleaves UHMW VWF upon its release into the circulation. A recombinant VWF (rVWF) expressed in CHO cells has been developed as a new drug candidate for treating patients with VWF deficiency. Since this protein is not cleaved by ADAMTS13 during the expression phase, it has a high portion of UHMW multimers, similar to the human VWF stored in Weibel-Palade bodies of endothelial cells. *in vitro* experiments showed that when treated under mild denaturing conditions or under shear, rVWF was susceptible to ADAMTS13 of human or animal origin. Preclinical studies further revealed that intravenously applied UHMW-containing rVWF is rapidly processed by endogenous ADAMTS13 in various species. Here we show results from a recently completed Phase I clinical study, which clearly demonstrates that rVWF administered intravenously to severe VWD patients in a dose-range of 7.5 to 50 VWF:RCo IU kg^{-1} body weight is rapidly processed in the circulation. ADAMTS13-specific cleavage fragments appeared as soon as 15 min after application, as visualized by immunoblot analysis. The appearance of cleavage bands coincided with the decrease in multimer numbers, indicating that rVWF had been specifically cleaved by ADAMTS13 in the circulation. No thrombotic adverse events were seen during the study, underlying the suitability of the UHMW-containing rVWF for treating VWD patients.

PO-MO-228
Screening of von Willebrand disease in West Algeria

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Objectives: To determine reference ranges for the von Willebrand factor (VWF) in our laboratory, to use later for the interpretation of assay results; diagnose the Von Willebrand disease (VWD) in west Algeria.
Patients and Methods: Study conducted for six months in the west Algeria. 110 individus controls (61 women and 49 men, mean age of 26.4 years) had been tested and we analyzed 23 samples of patients. For each patient and individus controls tested was performed an activated partial thromboplastin time APTT, Prothrombin time, bleeding times, assay of factor VIIIc, assays of von Willebrand factor antigen VWF: Ag (STAGO), ristocetine cofactor VWF: RCo by visual method (SIEMENS), blood typing ABO and blood count. All hemostasis tests were performed with normal, pathological and standard controls (internal quality control). The type of Von Willebrand disease (VWD1, VWD2, VWD3) is determined by calculating the reports (VWF:Rco/VWF:Ag et FVIII:C/VWF:Ag). Results: reference ranges for the von Willebrand factor in our laboratory: VWF:Rco: 51%–127%; VWF:Ag: 61.5%–141.5%. We diagnose 23 patients with Von Willebrand diseases, 09 of the patients had VWD3, 08 had VWD1 and 06 had VWD2. The frequency of VWD3 was only 39%, of VWD1 35%, and of VWD2 26%. The frequency of consanguinity was 68% and 78% in VWD3.
Conclusion: In our series the frequency of VWD3 is higher than VWD1 and VWD2; Because the number of patients diagnosed is low, frequency of consanguinity and the diagnosis of VWD3 are easy than VWD2 and VWD1. It's so difficult for our laboratory to diagnose the VWD1 and VWD2 because is necessary to perform the specific test. We expected in the future to develop the diagnosis of VWD.

PO-MO-229
Treatment of von Willebrand disease patients undergoing surgical procedures or deliveries with a von Willebrand factor product devoid of FVIII: Results from five multicentre studies

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Given the rarity of severe von Willebrand disease (VWD), sample size given by pooling data from 4 prospective multicentre studies and 1 post-marketing study aimed at determining the best evaluation of the efficacy of WILFACTIN® in surgical procedures including childbirth. The study protocols provided two different regimens for an adequate level of circulating factor VIII (FVIII) before the procedure. For regular surgery, two infusions of von Willebrand factor (VWF) were administered: one at 12–24 h prior to procedure and one 0.5–1 h prior to the surgery. This allowed FVIII:C to increase naturally to a level sufficient for hemostasis (typically greater than 50% by 24 h). In an emergency, a single VWF infusion was administered 0.5–1 h prior to the surgery, immediately followed by a FVIII infusion. At total of 141 patients (81 type 2, 29 type 1,

27 type 3, and 4 unspecified), median age 34 years, underwent 215 procedures. Median basal level of VWF:RCo was 10%; 52 patients had FVIII:C<20%. These procedures included 54 dental cases, 45 gyneco-obstetrical (with 9 vaginal childbirths and 16 Caesarean deliveries), 37 orthopedic, 35 digestive, 28 general, and 6 procedures with other location. FVIII was co-administered with the first infusion of VWF in 34% of procedures. The mobilization of endogenous FVIII was the preferred regimen in 38%. Lastly, basal FVIII levels were judged as sufficient in the remaining procedures. For type 3, the median daily dose was 55 IU kg^{-1} for 6.0 days including post-surgical prophylaxis at home, while for type 1 and 2, the daily dose was 47 and 53 IU kg^{-1} respectively for 4 days. Efficacy was considered excellent/good for 143 of 144 (99.3%) evaluated procedures and moderate in one. There was a low incidence of the need for transfusion (7%) The overall tolerability was very good; neither VWF inhibitor nor thrombotic complications were reported. The results demonstrate that WILFACTIN® was efficacious and well-tolerated for surgical bleeding prophylaxis and delivery in VWD patients in which VWF replacement therapy is required.

PO-MO-230
Clinical use of a von Willebrand factor with a low FVIII content to control major bleeding episodes in von Willebrand disease patients: Results from prospective multicentre studies

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Bleeding symptoms are usually moderate to severe in von Willebrand disease (VWD) and high-molecular weight multimers of von Willebrand factor (VWF) are essential for normal platelet-dependent VWF function in the microvasculature. Replacement of VWF (even without concomitant administration of FVIII) leads to a corresponding increase in circulating FVIII through normal physiologic mechanisms. Data from 4 prospective studies were pooled and analyzed to assess the efficacy and safety of WILFACTIN® in patients experiencing major bleeding episodes, defined as events that required treatment in-hospital. Across all studies, there were a total of 88 episodes in 47 patients (5 type 1, 20 type 2, 21 type 3 and 1 unspecified). Median basal level of VWF:RCo was 6.0 IU dL^{-1} and 57.4% of patients had basal FVIII:C levels <20 IU dL^{-1}. Most episodes (55%) occurred in patients with type 2 VWD, while 39% occurred in type 3, and 6% occurred in type 1 VWD. The most commonly reported bleeding sites were gastrointestinal (43, 48.9%) and musculoskeletal (19, 21.6%). Due to the seriousness of hemorrhages, red blood cells transfusion was used in 42% of episodes and most of them involved gastrointestinal and nasopharynx tracts. A priming dose of FVIII concentrate was administered with the first infusion in 30 of 88 (34.1%) episodes. Overall, 75% of the episodes were treated with infusions <54.4 IU kg^{-1}. When stratified by injury site, the median infusion dosage and number of infusions was lower for gastrointestinal (40.8 IU kg^{-1}; 8 infusions) than for genitourinary (47.0 IU kg^{-1}; 12 infusions) or musculoskeletal (49.5 IU kg^{-1}; 10 infusions). Efficacy was rated as Good/Excellent in 82 cases (93.2%) and Moderate in 6 cases (6.8%). The overall safety was very good, including no report of inhibitors or thrombotic complications. Based on prospective studies conducted in a large cohort of patients, WILFACTIN® was shown to be effective and safe to control major bleeding episodes in VWD patients with various types of VWD.

PO-MO-231
Single-centre experience of the Gp1b latex immunoassay and ristocetin cofactor assay: A comparative study

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Background: Laboratory diagnosis of von Willebrand disease (VWD) is a renowned problem for clinicians. Latex immunoassays (VWF:Gp1b) have been developed to improve and possibly replace the traditional ristocetin co-factor assay (VWF:RCo) as a measure of von Willebrand factor (VWF) activity. Is this a cost effective tool that has a clear clinical benefit?
Objectives: To compare VWF:Gp1b with VWF:RCo. To establish how well these tests correlate and how they differ and if this has a bearing on clinical practice in a hemophilia centre.
Methods: Seventy-three patients' laboratory tests were reviewed and compared retrospectively. The aPTT, FVIII:C, VWF:Ag, VWF:Gp1b, and VWF:RCo were recorded. Ratios were calculated to diagnose type two patients. On the basis of these results, patients were divided into type 1, type 2, conflicting diagnosis, and uncertain diagnosis.
Results: VWF:Gp1b predicts higher activity levels for our group of patients, and this difference is statistically significant (P = <0.0001). The difference is also statistically significant when subdivided for type 2 (P = 0.0016) and conflicting diagnosis (P = 0.017) groups. At VWF:Ag >55 U dL^{-1}, VWF:Gp1b predicts a statistically significant higher activity (P = <0.0001). VWF:Gp1b and VWF:RCo conflict in diagnosis of 20 patients when ratios are calculated.
Conclusions: For the majority of patients, the two tests correlate well. However, the VWF:Gp1b predicts higher activity then the VWF:RCo. If this test is used before surgery to guide treatment doses, it may lead to under-treatment of patients with an increased risk of prolonged bleeding. The VWF:Gp1b predicts greater activity at VWF:Ag levels >55 U dL^{-1}. Over a quarter of our patients would have an alternative diagnosis if the VWF:Gp1b was used in isolation from their VWD subtype. The VWF:RCo has well-recognized problems, and it is important to consider its accuracy in our centre. Nonetheless, in times of financial pressures, it is important to use the most cost-effective and patient-centred investigations.

PO-MO-232
Surgery in VWD using different FVIII/VWF concentrates: A head-to-head comparative analysis

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In patients with von Willebrand disease (VWD), optimal dosing and monitoring of coagulation factor concentrates (CFC) during surgical procedures are unclear. Here, we present results from a prospective study on plasma-derived FVIII/VWF concentrates differing in ratio of FVIII and VWF (CFC-H: FVIII/RiCof ratio 2.4:1 and CFC-W: ratio 1:1) managing surgeries.
Methods: Forty surgeries were performed in 35 patients (minor procedures: 15, major: 25) who received either CFC-H (n = 20) or CFC-W (n = 20). Blood samples were collected pre- and post-surgery. The median doses of factor concentrates per kg BW were calculated, as well as correlations between doses applied and laboratory analyses.
Results: In total, 31 female patients (median age 57.4, range 17–79) and 4 male patients (median age 60.9, range 21–77) could be included comprising 30 patients with VWD type 1, 4 patients with type 2A, and one patient with type 3. Dosing was according the recommendations of the German federal medical council. The median loading dose (MLD) was 38 IU kg^{-1} for minor and 43 IU kg^{-1} for major surgeries. In patients receiving CFC-H MLD it was 41 IU kg^{-1}, in those receiving CFC-W MLD it was 34 IU kg^{-1} in minor surgery, and in major surgery 43 IU kg^{-1} and 42 IU kg^{-1}, respectively. In major surgery median maintenance dose (MMD) using CFC-H was 33 IU kg^{-1}, using CFC-W MMD it was 31 IU kg^{-1}. In minor surgery, MMD was 31 IU kg^{-1} using CFC-Hm, and 30 IU kg^{-1} using CFC-W. FVIII:C-, VWF-AG and RiCof analyses showed good correlations prior to surgery for both concentrates. After surgery there was no clear correlation between FVIII:C, VWF-AG, and RiCof using CFC-H, whereas these parameters correlated using CFC-W. No major bleed and no thrombosis occurred.
Conclusion: There are different VWF concentrates available today. However, there are clear differences between different products in monitoring surgical procedures depending on product properties. These have to be taken into account, when managing surgical patient.

PO-MO-233
Paraprotein specific binding for platelet receptor glycoprotein Ib as a cause of acquired von Willebrand syndrome in monoclonal gammopathies

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Objectives: The aims of this study were to determine the incidence of acquired von Willebrand syndrome (AVWS) in patients with monoclonal gammopathies (MG), to estimate the role of isolated paraprotein in decreasing ristocetin-induced platelet aggregation (RIPA), as well as to investigate the mechanism of paraprotein caused AVWS.
Methods: The study included 48 patients with MG in whom the plasma level of von Willebrand factor antigen (VWF:Ag) and RIPA were measured initially. Paraprotein was separated from the serum of six patients without RIPA. Platelet aggregation was measured in platelet rich plasma (PRP) from six healthy donors before and after addition of isolated paraprotein. Expression of platelet VWF receptor-glycoprotein (GP) Ib was determined by flow cytometry in PRP of healthy donors before and after addition of paraprotein using the monoclonal antibody CD42b and calculated as the percentage of CD42b positive cells, while mean fluorescence intensity (MFI) was used as the index of receptor expression. Identical tests were repeated with addition of immunoglobulins for intravenous use to PRP from these donors.
Results: Absence of RIPA was found for six patients with MG (12.5%) who had normal levels of VWF:Ag. Paraprotein isolated from serum of these patients significantly inhibited RIPA of healthy donors (P < 0.001). Expression of CD42b positive cells (P < 0.001) and MFI (P < 0.001) were significantly decreased after addition of paraprotein to PRP of healthy donors. In comparison, when human immunoglobulins were added to PRP of healthy donors, RIPA, expression of CD42b positive cells, and MFI were not significantly changed.
Conclusion: These investigations have demonstrated that paraprotein causes AvWS in patients with MG due to specific binding to the platelet VWF receptor GPIb. By this mechanism it disables the normal function of VWF.
Contribution to the practice: With comprehension of arising mechanism, AvWS needs to be considered in patients with MG and bleeding complication for adequate treatment.

PO-MO-234
Expression studies of von Willebrand factor missense mutations causing type 1 or type 2 von Willebrand disease (VWD)

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Background: Four novel candidate missense mutations affecting cysteine residues of the von Willebrand factor (VWF) were found in heterozygous state in four families with von Willebrand disease (VWD). Two of the mutations, C2085Y and C2327W, correlate with

VWD type 2A and the other two mutations, C2619Y and C2676F, correlate with VWD type 1. In this study, we aimed to assess the pathogenicity of these candidate missense mutations by expression studies.
Methods: The full-length wilde-type or mutant VWF cDNA of the four missense mutations was transiently expressed in HEK293T cells. Co-expression of the WT and mutant VWF mimicking the patient's heterozygous state was also performed. VWF antigen, ristocetin cofactor activity, and binding to collagen and GPIbα were measured. VWF multimer analysis was performed on secreted and intracellular VWF.
Results: Transfections of the mutation C2085Y showed no detectable secretion of recombinant VWF, and the mutants C2327W, C2619Y, and C2676Y showed a strongly reduced rVWF (10%, 18%, and 22% respectively). Co-transfections of the mutant and WT VWF resulted in marked reduction of secreted VWF, establishing the pathogenicity of these mutations in heterozygous state. The reduction of the ratio of VWF:RCo to VWF:Ag of WT/C2085Y and WT/C2327W implies a qualitative as well as a secretion defect of these two mutations. Multimer analysis of WT/C2085Y additionally showed a severe reduction of high molecular weight multimers.
Conclusion: The pathologic nature of all four identified candidate missense mutations was confirmed. An intracellular retention of mutants was shown for all four mutations, while an additional qualitative defect seems to be the pathologic mechanism for C2085Y and C2327W. Interestingly, this is the first description of mutations in D4 and C1 domains affecting the multimerization and thereby causing VWD type 2A. These data provide further evidence of the critical role of cysteine amino acids in VWF synthesis and expression.

PO-MO-235
Continued efficacy and safety of a new generation high purity, double virus inactivated VWF/FVIII concentrate in children with VWD following product switch

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A new-generation plasma-derived concentrate of von Willebrand factor (VWF) and factor VIII (FVIII) received marketing authorization for treatment of patients with von Willebrand disease (VWD) and hemophilia A in the United Kingdom in September 2009 (wilate®, Octapharma AG, Switzerland). Since March 2010, an ongoing observational study has been in progress at the Haemophilia Centre, Great Ormond Street Hospital for Children. We report 18 children (8 girls/10 boys) with VWD, ages ranging from 3 days old to 17.7 years, who were treated after switching to the new concentrate. The group comprised twelve children with type 1, one with type 2M Vincenza, three with type 3, and two with acquired VWD (both secondary to Wilms tumour). Sixteen received treatment for surgical procedures, 3 were treated on demand (including a new neonatal diagnosis of type 3VWD with a spontaneous catastrophic intrabdominal bleed), and 1 (with type 3 VWD) received prophylaxis following a recurrent ankle hemarthrosis. Surgical cases were treated for 1–3 days with an average daily dose of VWF:RCo between 30–80 IU kg^{-1} 1–2 times per day, dependant of VWF levels. For on-demand treatment, average dosages of 40–60 IU kg^{-1} were used. Hemostatic efficacy and tolerability of all treatments was excellent in all cases. Following the product switch, no adjustment of dosage or regimen was necessary. This update of data further confirms the efficacy, safety, and tolerability of a new plasma-derived concentrate of von Willebrand factor (VWF) and factor VIII (FVIII) (wilate®) in the maintenance of hemostasis in children with congenital and acquired VWD undergoing surgical procedures and gives further evidence of efficacy, safety, and tolerability in on-demand treatment and prophylaxis.

PO-MO-236
Age-related evaluation of clinical manifestation and treatment of von Willebrand disease evaluated in an open-label, prospective, non-interventional study (wilate®-set)

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Efficacy, tolerability, and dosing of a VWF/FVIII concentrate may differ in pediatric, adult, and elderly patients. It is therefore reasonable to collect and evaluate clinical data of patients from different age groups and to look into differences in treatment and reason for treatment with VWF/FVIII concentrate. A cohort of 120 patients suffering from all types of von Willebrand disease (VWD) from an on-going German post-marketing surveillance study was analyzed for age-related differences in treatment with a high-purity, double virus inactivated VWF/FVIII concentrate (wilate®).
Results: Thirteen children up to 12 years of age and 14 patients 65 years or older were treated for prophylaxis, hemorrhages, or perioperatively. Obvious deviations were found in general condition, bleeding locations, and types of surgeries for the elderly patients. Further, the data provide evidence of age-group-related differences regarding reason for administration (see table 1) and dosages administered. The efficacy and tolerability of wilate® treatment in children and the elderly was as high as in the total group.
Conclusion: Young or old age seems to have an impact on clinical requirements of VWD. However, larger cohorts are required to confirm these first findings of the non-interventional study 'wilate SET.'

Table 1. Number of patients having received injections for specified reason.

	Prophylaxis	Hemorrhage	Surgery	Others*
All patients	40 (33.3%)	35 (29.2%)	65 (54.1%)	31 (25.8%)
Age < 12 year	5 (38.5%)	5 (38.5%)	8 (61.5%)	5 (38.5%)
Age 13–64 year	28 (30.1%)	25 (26.9%)	48 (51.6%)	28 (30.1%)
Age ≥ 65 year	7 (50.0%)	5 (35.7%)	9 (64.3%)	1 (7.1%)

PO-MO-237
Clinical characteristics of patients with von Willebrand disease included in the Francecoag network

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The FranceCoag network (FCN) is a national registry of patients with hereditary bleeding disorders, including von Willebrand disease (VWD), which was implemented in 2003. The inclusion criteria for VWD are type 3, type 2 (VWF:RCo or VWF:CB/VWF:Ag<0.7 or FVIII:C/VWF:Ag<0.5 or RIPA positive at low-ristocetin concentration), and type 1 (VWF:Ag<30%). In November 2011, 1,319 patients were included, with a sex ratio (M/F) of 0.80 and a median follow-up of 1.8 years (range: 0.02–10.1). The median age at diagnosis is 12.9 years (range: 0–85.7) with a significant ($P = 0.013$) difference between boys 9.3 years (range: 0–80.6) and girls 15.3 years (range: 0–85.7). Twenty-three point four per cent of the patients were born before 1960, 30.3% between 1960–79, 30.9% between 1980–99, and 15.4% after 1999. The circumstances that aid in diagnosis include: family history in 45.9% of the cases, bleeding in 32.2%, and fortuitous diagnosis in 18.5%. The patients are HCV positive in 11.7%, HIV positive in 1.1%, and co-infected in 1%. During their follow-up, 12 patients had a life-threatening hemorrhage, including 3 of the central nervous system. At the last visit, 21.9% of patients had received VWF concentrate, 7.0% desmopressin, 1.5% both of them, 0.2% FVIII concentrates, and 69.4% no treatment. Eighteen deaths were declared, at a median age of 68.5 years (range: 25.4–88.7). Initial causes of deaths were cancer not linked to HIV/HCV ($n = 7$), hemorrhage not linked to HIV/HCV ($n = 3$), other causes ($n = 5$), and 3 unknown. Due to the complexity of diagnosis, the VWD national Reference Centre (RC) validates the types and subtypes of VWD by phenotypic and genotypic characterization of all patients. At that time, 283 FCN patients (21.4%) are included in the RC database. A later cross-referencing with the clinical data of FCN will refine the description of this large cohort.

PO-MO-238
A pregnant woman with von Willebrand disease (VWD) type 2b: Laboratory findings and peripartal bleeding management

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Background: Von Willebrand disease (VWD) type 2B is an autosomal-dominantly inherited bleeding disorder caused by activating mutations in the A1 domain, resulting in spontaneous VWF binding to platelet GP1b with subsequent proteolytic degradation. Only limited information is available on the peripartal management of pregnant women with type-2B VWD.
Case report: In a pregnant woman with severe thrombocytopenia (20–30 n L^{-1}) and spontaneous platelet agglutination on peripheral blood smear, previous testing for VWD type 2B had been inconclusive due to absent platelet aggregation at low concentrations of ristocetin. Electron microscopy had further revealed enlarged α-granules suggestive of concomitant platelet storage-pool disease. Consistently, ex-vivo stimulation of platelets with ADP or TRAP-6 resulted in only minimal CD62P expression, as analyzed by flow cytometry, while no CD62P was present on un-stimulated platelets. However, a very similar pattern was observed on platelets from the patient's father and brother, who also had low platelet counts and loss of larger VWF multimers, but no ultrastructural α-granule changes. Type-2B VWD was eventually diagnosed by genetic testing, revealing a previously described A1461D mutation in exon 28. Successful delivery of a healthy girl was achieved by VWF replacement (Willfact™) immediately before and 12 h after delivery in addition to intravenous antifibrinolytics, resulting in moderate blood loss with no need for red-cell or platelet transfusions. Postpartum, no abnormal bleeding occurred under continued treatment with tranexamic acid.
Discussion: This report further highlights the importance of genetic testing to the diagnosis of type-2B VWD, because the typical activity pattern may not be present in all patients. Our flow cytometry data confirm previous observations, according to which platelet agglutination in type-2B VWD is not associated with α-granule secretion, but instead suggest that binding of hyperactive VWF to platelets and/or megakaryocytes may induce a specific α-granule defect. Willfact™ was safe and effective for peripartal bleeding management in our patient.

PO-MO-239
Assessment of the burden of von Willebrand disease among patients receiving factor replacement therapy in a US commercial health plan population

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Introduction: The overall characteristics and service utilization patterns of von Willebrand Disease (VWD) patients who receive VWD/FVIII replacement therapy in the United States has not been extensively studied. This study compares the characteristics and service utilization of VWD patients who have received factor replacement therapy to a matched, non-VWD sample to assess the relative burden of VWD.

Methods: VWD patients were identified from the Thomson Reuters Marketscan® Database, which contains medical claims data from US commercial health plans. Patients were included if they had ICD-9 code 286.4 for VWD during the study period (1/1/2002 through 12/31/2010), at least 12 months of continuous health-plan enrollment post-VWD diagnosis, and at least 2 inpatient, emergency room, or outpatient visits at least 30 days apart, and received replacement therapy. A random sample of non-VWD patients was generated from the same database and matched 2 to 1 on age, gender, and length of enrollment. Patient characteristics, co-morbidities, and outpatient and inpatient resource utilization were compared.
Results: Of the 348 VWD patients included in the sample, the mean age was 28.6, and 58% were female. Compared to the matched patients (n = 696), VWD patients had significantly higher rates of chronic liver disease (7% v. 1%), pneumonia/influenza (14% vs. 10%), hepatitis C (8% vs. 0.3%), CVD (41% vs. 31%), and HIV (2% vs. 0.1%). VWD patients had a higher median number of outpatient visits (14.2 $year^{-1}$) compared to non-VWD patients (4.6 $year^{-1}$), and 31% of VWD patients had inpatient stays compared to 5% of non-VWD patients. Female VWD patients also had higher rates of hysterectomies (2.9% vs. 0.8%, P = 0.01).
Conclusions: Results suggest the burden on a health system of treating VWD patients who require factor replacement therapy may be significant. Further research is needed to understand the characteristics of VWD patients and the potential implications for treatment and service utilization.

PO-MO-240
Clinical diagnosis and laboratory screening in VWD pediatric patients of northwestern Mexico

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Introduction: Von Willebrand disease (VWD) is the most common inherited bleeding disorder affecting around 1% of the world population. The diagnosis approach is complex and must include bleeding history, clinical examination, and several biological laboratory tests. In Mexico there are a few studies on the VWD population, but the real incidence of VWD patients is unknown.
Objective: To determine the correlation between bleeding symptoms and laboratory screening to detect different types of VWD in the pediatric population from the northwestern part of Mexico.
Methods: After obtaining informed consent, a pediatrician conducted a clinical questionnaire of familial bleeding history and bleeding symptoms in children, who were subjected to a general physical examination and detection of bleeding symptoms. Plasma and DNA samples were obtained for laboratory testing: general clotting screening (BH, PT, aPTT, fibrinogen, Ivy BT); initial confirmatory testing (VWF:Ag, vWF:RCo, FVIII-I:C); final confirmatory testing (VWF multimers and molecular VWF gene analysis).
Results: We studied 25 pediatric patients from 22 independent families native to Jalisco, Colima, and Michoacán (11 girls, 14 boys), aged 3 to 16 years old. Twenty-one out of twenty-five (84%) had a familial bleeding history; 19/25 (76%) were referred for bleeding symptoms, and 6/25 (24%) after prolonged clotting times in pre-surgical testing. All patients but one has shown previous bleeding symptoms of variable importance. The main bleeding symptoms are petechiae and ecchymoses, epistaxis, bleeding tooth extractions, and hematomas. By the ratio values (<0.6 or >0.6) of VWF:Ag/WF:RCo and FVIII:C/vWF:Ag, we suggest a preliminary diagnosis of 10 patients with type 1 VWD, 6 type 2 VWD (2A, 2B or 2M), one type 2N VWD, and 8 patients with normal values. All patients will be further confirmed by multimer VWF analysis.
Conclusions: We found a good correlation between abundance and severity of bleeding symptoms in the patients and their initial confirmatory laboratory testing results (VWF:Ag; vWF:RCo; FVIII:C).
Project supported by the World Federation of Hemophilia through the Federación de Hemofilia de la República Mexicana and CSL-Behring of México.

PO-MO-241
PEGylated factor VIII provides prophylactic protection from mucosal bleeding in mice with von Willebrand disease (vWF/FVIII$^{-/-}$)

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Von Willebrand disease (VWD) is an inherited bleeding disorder caused by the deficiency or abnormal function of von Willebrand factor (VWF), an adhesive protein with pleiotropic functions in hemostasis and thrombosis. Since VWF is a specific carrier of factor VIII (FVIII) in plasma that protects FVIII from proteolytic degradation, the absence of VWF significantly reduces plasma FVIII levels. The disease severity of VWD is usually proportional to the degree of primary deficiency of VWF and secondary deficiency of FVIII. This manifests clinically in a mucocutaneous bleeding phenotype with characteristic symptoms, like epistaxis, oral cavity bleeding, and bleeding after dental extraction. In this study, we investigated whether a PEGylated FVIII molecule can provide protection from bleeding in VWF/FVIII$^{-/-}$ mice. In VWF/FVIII$^{-/-}$ mouse pharmacokinetic studies, PEGylated FVIII variants were observed to have significantly longer half-life than B-domain-deleted (BDD) FVIII (5.7–8.2 vs. 0.3 h). To evaluate whether a PEGylated FVIII provides prophylactic protection of mucosal bleeding in VWD, a novel mucosal bleeding mouse model was established and evaluated in vWF/FVIII$^{-/-}$ mice. In this model, a 3 mm incision in the mucosal layer was performed on the ventral side of the tongue to induce a bleeding injury. This selected location lacks large blood vessels, allows good standardization, and enables localization of the injury exclusively to the mucosal layer. Bleeding and re-bleeding time and blood loss were selected as endpoints. A comparison between different mouse strains showed a significantly prolonged bleeding and re-bleeding time (60%), as well as increased blood loss, in VWF/FVIII$^{-/-}$ mice compared with wild-type and FVIII$^{-/-}$ mice. Additionally, VWF$^{-/-}$ mice showed a mildly increased bleeding time and blood loss. PEGylated FVIII reduced mucosal bleeding, blood loss, and bleeding time in a dose-dependent manner. These results raise the possibility of using a PEGylated FVIII molecule to protect VWD patients from bleeding.
Conflicts of interest: All authors are employees of Bayer HealthCare LLC.

PO-MO-242
On-demand therapy after ITT failure in patient with von Willebrand disease type 3 and alloantibodies

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Introduction: Von Willebrand disease type 3 (VWD) is a rare bleeding disorder. The incidence is ranging from 1.1 to 1.5 million in European countries. VWD type 3 patients developing alloantibodies against VWF after the administration of multiple VWF/FVIII concentrates or transfusions constitute an incidence of 7.5–9.5%, and carriers of null mutations are especially afflicted. Data concerning the treatment of patients with alloantibodies against VWF are limited.
Case report: A 26 year old man with type 3 VWD developed alloantibodies against VWF:CB at the age of 9 during prophylaxis with VWF/FVIII concentrates. Treatment of recurrent bleeding episodes (epistaxis, soft tissue-, joint- and muscular-bleeding) with different VWF/FVIII concentrates had an insufficient effect. The half-life of VWF:CB, VWF:AG, and VWF:RCo after the administration of VWF/FVIII concentrates was very short and a high antibody titer against VWF:CB was documented (38 BE). ITT was started at the age of 20 using VWF/FVIII concentrates and immunesupressive therapy (steroids, mycophenolatmofetil, IVIG). During ITT, antibodies were not detected; nevertheless, half-life was still not normalized. After 3 years, ITT was stopped and we initiated prophylactic therapy followed by on-demand therapy with bypassing agent recombinant activated factor VII (rFVIIa). Severe bleeding episodes and side effects were not observed.
Conclusion: Treatment of patients with alloantibodies to VWF is difficult. Prospective studies focussing on the incidence, clinical and molecular parameters of alloantibodies against VWF, in patients with VWD type 3 are needed.

PO-MO-243
De novo mutation in von Willebrand disease type 2A

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Introduction: Von Willebrand disease is a bleeding disorder caused by inherited defects in the concentration, structure, or function of Von Willebrand factor. Type 2A is a qualitative variant with decreased platelet adhesion and a selective deficiency of high molecular weight VWF multimers. It accounts for approximately 10–15 percent of cases of VWD, and is usually transmitted as an autosomal dominant trait. Affected patients usually present with moderate to moderately severe bleeding.
Case: A girl of 7 months presented with hemorrhagic diathesis and coagulation tests suitable for VWD, and an abnormal multimer pattern: VWF:Ag 0.25 IE mL^{-1}, VWF:RiCo 0.05 IE mL^{-1}, showing lack of HMWM multimers. She was the first child of healthy parents. Neither parents had a history of bleeding problems, nor were bleeding problems in the families reported.
Methods: Genotyping was performed to confirm the diagnosis in the child. To determine the recurrence risk in a next pregnancy, DNA analysis was performed in both parents.
Results: DNA analysis of the child showed the following mutation: c.3814T > G p.C1272G heterozygous, which confirmed the diagnosis Von Willebrand disease type 2A (Sheffield database). Laboratory testing of the parents showed normal VWF:RiCo and antigen levels, normal patterns of multimers, and no mutation.
Conclusion: De novo mutations in Von Willebrand disease type 2A are very rare. The recurrence risk for a subsequent child is predicted to be less than 1%.

PO-MO-244
Detection of VWF gene Q793x mutation in type 3 von Wileberand disease patients

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Background and Objectives: Type 3 von Willebrand disease (VWD) is a relatively rare inherited disease characterized by severe clinical manifestations due to hemostatic abnormalities. Because of the autosomal recessive pattern of its inheritance, the disease is more frequent in regions with a high rate of consanguine marriages. We have previously demonstrated that despite various mutations throughout the gene, the Q793X mutation in exon 18 is more frequent in Iranian VWD patients. We have developed two assays to further investigate this mutation.
Materials and Methods: The Q793X mutation status was studied in 15 von Willebrand disease type 3 patients and 30 normal individuals by ARMS-PCR and real-time polymerase chain reaction (PCR) assays. Melting curve analysis was performed after each real-time PCR experiment. To confirm the assays results, all amplified gene fragments were sequenced.
Results: Three out of 15 patients were previously diagnosed as having Q793X mutation in homozygote status. This was further confirmed by the ARMS-PCR and real-time PCR assays. Interestingly, the mutation was also found in 2 other unrelated type 3 patients. Heterozygote status for the mutation was not detected in normal controls.

Conclusions: Both assays successfully detected Q793X mutation in the VWF gene, although each assay has its own advantages and drawbacks. It seems that the mutation is common in Iranian VWD patients; however, a large cohort of VWD patients is needed to further describe the frequency of the mutation in the Iranian population.

PO-MO-245
Colombia's experience with the last generation of von Willebrand/FVIII factor concentrate (wilate®)

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Introduction and objective: Colombian patients with von Willebrand disease (VWD) have experienced many limitations in diagnosis and treatment. The Hemolife program was introduced to provide better medical assistance. The objective is to present the program results and analyze the efficiency of wilate® in surgical procedures, long-term prophylaxis, and bleeding episodes in VWD patients.
Patients and methods: There are 17 patients on the program. 13 patients are on long-term prophylaxis, 3 patients are involved in 6 surgical procedures and 1 patient was treated for a gastrointestinal hemorrhage. Results:
The mean age of long-term prophylaxis patients is 24.4 years. The prophylactic average dose was 24.5 IU kg^{-1}, 5 patients 3 weekly doses, and 8 patients receive daily prophylaxis during menstruation. Follow-up time has an average 3.5 months. All patients on long-term prophylaxis have reduced hemorrhagic episodes. Clinical response to wilate® treatment is excellent in 92.3% of cases. Six surgical procedures were also evaluated. Three were major surgical procedures (initial mean dose of 36.9 IU kg^{-1} and mean maintenance dose of 28.7 IU kg^{-1} for 7 to 10 days) and 3 minor procedures (mean dose of 20.4 IU kg^{-1} for 2 to 6 days). In 100% of cases, the response to treatment has been considered excellent by patients and physicians. In addition, we have one patient who presented lower gastrointestinal bleeding who received a dose of 28.5 IU kg^{-1} day^{-1} for 3 days, with an excellent outcome: bleeding stopped within a few hours without adverse reactions.
Conclusion and contribution: In this group, wilate® treatment proved to be efficient in all surgical procedures. The 13 patients on long-term prophylaxis have a reduction in hemorrhagic episodes. The on-demand treatment for gastrointestinal hemorrhage was controlled, despite being a difficult bleeding to treat. It is important to improve the diagnosis of VWD and its proper classification in order to offer a more adequate treatment.

PO-MO-246
Exon 18 of the VWF gene is the second hotspot region in VWD patients from Southwest Iran

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Introduction: Von Willebrand disease (VWD) is a common bleeding disorder, resulting from defects in the glycoprotein VWF. The disease is sorted by deficiency (type1 and 3) and qualitative defects (type 2) of VWF (1). High heterogeneity besides the large size of the gene (178Kb) (2) makes the diagnosis of VWD very difficult and time consuming (3). In this regard, finding the regions with high-mutation frequency in each population facilitates diagnosis. A literature review reveals that some exons with high-mutation rate were selected (exons 28, 18, 45, 3). As we reported previously, exon 28 is the first hotspot of the gene, as almost all of our patients bear at least one mutation. We also found lots of novel genetic changes in exon 18, which are reported here for the first time.
Material and Methods: All mentioned exons were analyzed by PCR-direct sequencing. Results were examined by chromas 2.2 software for any mutations and SNPs.
Results: Sequencing results show different types of mutations in exon 18, including insertion and missense mutation (table 1). One novel SNP also find in intron 17–18, with the C to A change in homozygous manner in all patients.
Discussion: Exon 18 code the D' domain of the VWF that plays an important role in VWF-FVIII interaction. Mutations in this area can disrupt the VWF function and promote the disease. As previous report showed, single nucleotide deletions are common mutations in this exon, but in our study short insertions are prominent types of changes. This findings show the importance of future focusing on this exon in further studies to better understanding of the genetic changes of this area.

PO-MO-247
Prevalence of von Willebrand disease in Koreans

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Objective: Von Willebrand disease (VWD) is an inherited bleeding disorder that is caused by deficiency or dysfunction of von Willebrand factor (VWF). Although VWD is considered the most common congenital bleeding disorder, the prevalence varies from 0.1% to 2%. The purpose of this study was to determine the prevalence of VWD in southern Korea, Ulsan.
Method: Between March 2011 and September 2011 we prospectively investigated 256 patients referred to the surgery unit of our hospital and 756 healthy volunteers. Blood samples were collected for the determination of VWF:Ag, VWF:RCo, and FVIII. A standardized questionnaire was administered to evaluate hemorrhagic symptoms at the time of first examination, using a bleeding score ranging from 0 (no symptom) to 3 (hospitalization, replacement therapy, blood transfusion) The definition of VWD is either that levels of VWF:Ag and/or VWF:RCo are below 30 IU dL^{-1} or levels of VWE:Ag and/or VWF:RCo of 30–50 IU dL^{-1} with at least three hemorrhagic symptoms or a bleeding score of 3 in males and 5 in females.
Results: Forty-three subjects had levels of VWF:Ag and/or VWF:RCo below 30 IU dL^{-1}. Five subjects had levels of VWE:Ag and/or VWF:RCo of 30–50 IU dL^{-1} with at least three hemorrhagic symptoms or a bleeding score of 3 in males and 5 in females. In total, forty-eight subjects met the criteria for VWD, for a prevalence of 4.7%.

PO-MO-248
Management of delivery in eighteen women with type 2 von Willebrand disease: One centre's experience

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There is no doubt that type 3 von Willebrand disease (VWD) exposes pregnant women to a high risk of bleeding at the time of delivery and postpartum. The bleeding risk and the need for replacement therapy in women with type 2 VWD are not well established. We report our experience in the management of 29 consecutive deliveries (21 vaginal deliveries and 8 Caesarean sections) in 18 women with type 2 VWD. Fourteen women (22 deliveries) had basal ristocetin cofactor activity (VWF:RCo) <30 IU dL^{-1} including 6 (8 deliveries) with VWF;RCo <10 IU dL^{-1}, (none had type 2B), 4 women *(*7 deliveries*)* had type 2N with basal FVIII:C level < 30 IU dL^{-1}. At the end of pregnancy, complete correction of VWF:RCo (>50 IU dL^{-1}) was observed in only 5/22 cases. VWF:RCo level remained below 25 IU dL^{-1} in 8 cases. In the 2N VWD women, complete correction of FVIII:C level (>50 IU dL^{-1}) was observed in 2/7 cases. Regional analgesia was performed in 5 women (5 deliveries) with complete correction of the deficient factor. None of the women has been treated with von Willebrand factor (VWF) concentrate. In 11 cases, desmopressin has been infused, early after vaginal delivery (n = 7), or Caesarean section (n = 4) and repeated up to 36 h in 2 cases. No major adverse event occurred. Excessive bleeding was observed in 5 cases and was resolved by manual exploration of the uterine cavity, suture of a vaginal tear, and/or desmopression infusion. No women had to receive blood transfusion. In conclusion, our experience suggests that replacement should not be systematic in women with type 2 VWD (excluding type 2B VWD), even in the absence of correction of VWF:RCo and/or FVIII level at the time of delivery.

PO-MO-249
Changes in von Willebrand factor level and von Willebrand activity with age in type 1 von Willebrand disease

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In a normal population, studies indicate that von Willebrand factor level (VWF:Ag) and VWF activity (VWF:RCo) may increase by as much as 0.17 and 0.15 IU mL^{-1} per decade of increasing age, but the influence of age has not been evaluated in type 1 von Willebrand disease (VWD). In a retrospective cohort study, we reviewed the type 1 VWD database, which lists all type 1 patients seen at the Inherited Bleeding Disorders Clinic, Queen's University, Ontario, Canada, and identified 15 type 1 VWD patients over the age of 40 who had been followed for ≥10 years. The following information was extracted from the chart review: bleeding score using the condensed MCMDM1-VWD bleeding questionnaire, ABO blood group, baseline VWF multimer analysis, and all previously performed VWF:Ag, VWF:RCo, and factor VIII levels (FVIII:C). The patient group was made up of 10 females and 5 males, with 9 being blood group O, 2 blood group A, and 4 of unknown blood group. Twelve patients had VWF multimers performed, all of which were normal. Mean bleeding score was 10 (range 4–21, with an abnormal score being ≥4). Mean age at diagnosis was 37 (range 17–60 years), and duration of follow-up ranged from 10–26 years, with a mean of 14 years. Patients had between 2–10 time points of VWD testing data sets (mean of 5.7 time points). The mean VWF:Ag, VWF:RCo, and FVIII:C at time of diagnosis were 0.39 IU L^{-1}, 0.39 IU L^{-1}, and 0.70 IU L^{-1}. After a follow-up of 14 years, the mean VWF:Ag, VWF:RCo, and FVIII:C were 0.73 IU L^{-1}, 0.59 IU L^{-1}, and 0.86 IU L^{-1}. These values represent a statistically significant change as compared to the baseline (P = <0.001, 0.021, and 0.010 by paired samples t-test, respectively). Nine out of 15 (60%) patients had levels that increased into the normal range for VWF:Ag, VWF:RCo, and FVIII:C and no longer met the diagnostic criteria for type 1 VWD. In conclusion, patients with type 1 VWD experience age-related increases to VWF:Ag and VWF:RCo. As a result, the majority of mild to moderate type 1 VWD patients may self-correct with age and no longer meet the diagnostic criteria for VWD. Further studies are required to determine if the bleeding phenotype also resolves with the normalization of VWF:Ag and VWF:RCo levels.

PO-MO-250
Bleeding phenotype in children with moderate or severe von Willebrand disease: Iatrogenic bleeding is the presenting symptom in forty-two per cent of the index cases

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Introduction: Clinical expression of von Willebrand disease (VWD) in children may be different than in adults. Currently there is limited information available on the bleeding phenotype in children with VWD. Therefore we evaluated the occurrence of the type and severity of bleeding symptoms in a large cohort of children with VWD and compared it to adults with VWD.
Patients/methods: We included 140 children with type 1 (n = 70), 2 (n = 51) and 3 (n = 19) VWD (VWF levels $\leq$ 30 IU dL^{-1}) and 666 adults (≥16 years old) in a nationwide cross-sectional study (Willebrand in the Netherlands: WiN study). Bleeding severity was determined using the validated adult Tosetto bleeding score (BS) with supplementary pediatric-specific bleeding symptoms (umbilical stump bleeding, cephalohematoma, post-circumcision bleedings, post-venapuncture bleeding, macroscopic hematuria).
Results: Median age was 7 years in children and 45 years in adults. In children median BS was 5.5 (IQR 2–9), when pediatric-specific bleeding symptoms were included it was 6.0 (IQR 2–10). In adults the median BS was 11.0. Pediatric-specific bleeding symptoms were reported in 41 children (29%), occurring in 12 (17%) type 1 VWD, 17 (33%) type 2 VWD and 12 (63%) type 3 VWD patients (P < 0.001). Eight out of 31 index cases (26%) had a pediatric-specific bleeding symptom as presenting symptom. An iatrogenic bleeding was the presenting symptom in almost half of the index cases (n = 13 out of 31; 42%). The most frequent bleedings in children were cutaneous, minor wounds, tooth extraction, and menorrhagia. Compared to adults with VWD, children had significantly less bleeding from minor wounds, oral cavity, and gastro-intestinal tract, after surgery and tooth extraction, muscle hematoma, hemarthrosis, and menorrhagia (P < 0.05).
Conclusion: Pediatric-specific bleeding symptoms occur in a large proportion of children with VWD and iatrogenic bleeding is the presenting symptom in almost half the index case patients.

PO-MO-251
Venous thrombosis in von Willebrand disease occurs mainly after surgery

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Introduction: Von Willebrand disease (VWD) is caused by reduced levels or dysfunctional von Willebrand factor and is characterized by a bleeding tendency. It is well known that individuals with high von Willebrand factor levels have a higher risk for venous thrombo-embolism (VTE). We hypothesized that patients with VWD may be protected against VTE. Therefore, we investigated the prevalence of venous thrombosis in a large cohort of VWD patients.
Materials and Methods: We studied the clinical history of thrombosis in 666 adult patients (aged 16–85 years, median age 45 years) with VWD (von Willebrand factor levels <30%) in a nationwide cross-sectional study (Willebrand in the Netherlands study: WiN study). Clinical history of venous thrombosis was obtained from a questionnaire. Subsequently, past and current medical records were reviewed for all subjects to confirm the reported thrombotic events.
Results: Six of the 666 (0.9%; 95% CI 0.2–1.6%) adult VWD patients had a history of VTE. Four patients (0.6%; 95% CI 0–1.2%) suffered from pulmonary embolism, and 2 patients (0.3%; 95% CI 0-0.7%) had deep vein thrombosis. VTE only occurred in type 1 VWD patients (6 of 345), whereas no thrombosis occurred in type 2 and 3 patients. Remarkably, all patients with VTE had undergone a recent surgical procedure with perioperative hemostatic treatment. More specifically, patients were treated with FVIII/VWF concentrate (n = 1), desmopressin (n = 1), and solely tranexamic acid (n = 1). Strikingly, only 2 (of 6) patients received thrombosis prophylaxis for surgery. Several other thrombotic risk factors were also present in these patients, including immobility, malignancy, and oral conceptive use.
Conclusion: Venous thrombosis in VWD patients is rare and occurs mainly after surgery. Data confirm the necessity of thromboprophylaxis in these patients.

PO-MO-252
VWF gene expression analysis in a type3 von Willebrand disease family

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Background and Objectives: von Willebrand disease (VWD) is the most common inherited hemorrhagic abnormality. The disease is caused by defeciency of von Wilebrand factor (VWF), which is encoded by VWF gene. Type 3 VWD is the most severe form of the disease inherited as an autosomal recessive trait. Each molecular defect may result in a distinct outcome at mRNA. In the present study, the impact of 5941G/T mutation in VWF gene on mRNA expression was investigated in a VWD family.
Materials and Methods: Blood samples were obtained from a VWD patient and carriers of a family with E1981X alteration. To determine the VWF gene expression level, peripheral blood platletes were isolated and total RNA was extracted. Gene expression study was performed using TaqMan probe quantitative real-time polymerase chain reaction (PCR) assay on the platelet derived cDNA corresponding to patient and carriers.
Results: The patient in this family with nonsese mutation in exon 35 showed significantly lower levels of VWF mRNA compared to his hetrozygote parents and normal brother. The relative VWF gene expression normalized to GAPDH was 0.65 ± 0.22 and 0.012 ± 0.002 in the carriers and patient, respectively.
Conclusions and Discussion: Nonsense mediated decay (NMD) pathway prevents the synthesis of truncated protein. However, it has been shown that each mutation in the VWF gene has its particular impact on the gene expression. Here we showed that 5941G/T mutation in the VWF gene is subjected to NMD. This may dramaticaly decrease the truncated protein synthesis at the cellular level.

PO-MO-253
Molecular pathology of severe von Willebrand disease in Indian population

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Molecular diagnosis in von Willebrand disease (VWD) is a challenge for the laboratories involved for the following reasons: extremely large, that is, 9 kb coding sequence comprising of 52 exons, heterogeneous nature of mutations not restricted to a specific area of VWF gene, partial pseudogene copy (exons 23–34) requiring discrimination between VWF gene and pseudogene in PCR to amplify specifically the authentic VWF gene and the phenomenon of gene conversion due to recombination between the native VWF gene and the pseudogene. Using a combination of PCR-RFLP, conformation sensitive gel electrophoresis (CSGE), and DNA sequencing, we characterized mutations in 54 severe VWD patients from India. In 17 patients mutations were identified in the Arginine hot spots corresponding to 9 exons of VWF gene by PCR-RFLP technique. In the remaining 37 patients, mutations were identified either with an initial screening by CSGE involving 16 multiplex PCRs, followed by identification of the mutation by DNA sequencing, or by direct sequencing. Two common founder mutations were identified, i.e., P2063S in exon 36 of VWF gene found in 11 unrelated Indian patients belonging to Kachi Modh Ahmedabadi Ghanchi from Gujarat and R1779X detected in 5 unrelated patients from Uttar Pradesh belonging to the Gaderia community. In the remaining patients, we detected 8 nonsense mutations (3 novel), 14 missense (2 novel), 5 deletion (novel), 1 duplication of 48 bases (novel), and 2 gene conversion (length of gene conversion- 95 bases and 147 bases). Indian VWD patients thus exhibited a high heterogeneity in their mutation profile.

PO-MO-254
Polymorphic markers in VWF gene: Application in genetic diagnosis of affected families with VWD

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Genetic diagnosis in VWD by direct mutation detection is a complex and laborious procedure due to the large size of the VWF gene, high heterogeneity of mutations, and a large part of the gene showing 97% homology to a pseudogene in chromosome 22. Thus the indirect method of gene tracking using polymorphic markers within the VWF gene is the preferred method, which, when informative, is less expensive to offer genetic diagnosis to affected VWD families. The informativeness of six polymorphisms (N318K, T789A, R852Q, rs177702 C/T, rs 216312 A/G, intronic del TCT 13/83-85*. in VWF gene were analzsed in 100 VWD patients for their utility in genetic diagnosis of affected families by PCR-RFLP, CSGE and direct sequencing. The heterozygotic frequencies of N318K, T789A, R852Q, rs177702 C/T, rs 216312 A/G polymorphisms were found to be 11.4%, 8%, 5%, 4% and 7% respectively. The two polymorphisms i.e., T789A, Y795Y were found to be in strong linkage disequilibrium with rs36105228 GT/AC and rs216293 C/A with 8% heterozygosity. The Intronic deletion of 3 bases in intron 16 showed 4% heterozygosity among our patients. Besides intron 40 markers, these 4 markers can be successfully used in carrier and antenatal detection in Indian population. Additional markers identified in the present study will further add to the in formativeness to the existing intron 40 VNTR markers so as to offer diagnosis in majority of the families.

PO-MO-255
Detection of non-inhibitory binding antibodies to von Willebrand factor affecting the clearance of VWF:Ag in von Willebrand disease
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Von Willebrand disease (VWD) is an inherited rare bleeding disorder caused by a deficiency of von Willebrand factor (VWF). VWF facilitates platelet aggregation and stabilizes factor VIII (FVIII) in the circulation. Inhibitory antibodies to VWF have been reported in 10%–15% of type 3 VWD patients respetitively treated with pdVWF/FVIII concentrates. Clinical impact of non-inhibitory antibodies to VWF has not been previously reported. To investigate the immunogenicity of a novel recombinant human VWF (rhVWF), total binding and inhibitory anti-VWF antibodies were assessed in a Phase 1 study. Neutralizing antibodies to the key functional activities of VWF (VWF:RCo, VWF:CB, and VWF:FVIIIB) were measured using Bethesda-based assays (Nijmegen modification). To exclude false positive results, the detection limit for anti-VWF inhibitors was set to 1 BU mL^{-1} for all 3 assays. Samples were considered positive if they were at least 2 titer steps lower than the antibody titer detected in the screening assay. Three out of 39 subjects had a pre-existing high titer non-neutralizing binding antibody (all 1/1280) to VWF; 1 of these 3 was excluded from study due to the presence of an inhibitory antibody to VWF:CB (1.3 BU mL^{-1}) at screening, and the other 2 were treated with rVWF and/or pdVWF concentrate during the study. The high titer binding anti-VWF antibodies were associated with a significant decline in the VWF:Ag activity of either pdVWF or rVWF and consequential decreased activity of VWF:RCo, VWF:CB, and FVIII:C. One of the subjects had a reduced VWF:Ag IR of 1.1 IU dL^{-1}/(U VWF:RCo kg^{-1}) (mean 1.6 IU dL^{-1}/[U VWF:RCo kg^{-1}]) and a reduced VWF:Ag $t_{1/2}$ 2.4 h (mean $t_{1/2}$ 25.3 h) post infusion of rVWF (50 IU VWF:RCo kg^{-1}). None of the study subjects developed an inhibitory antibody to VWF or FVIII, and there was no impact on the subsequent treatment of bleeding episodes with commercial pdFVIII/VWF concentrates. The clinical relevance of non-neutralizing antibodies to VWF requires additional investigation.

PO-MO-256
Development of an automated VWF:RCo assay for measuring plasma samples with low activity
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The ristocetin cofactor (VWF:RCo) assay measures VWF's ability to agglutinate human platelets in the presence of ristocetin. An automated, CE-certified assay system, Dade Behring Coagulation System (BCS; Siemens, Marburg, Germany), is available for clinical purposes. The typical reference range using plasma standards is approximately 20 to 150% depending on the plasma lot used for the reference curve. A manual, semi-quantitative assay is available from Siemens for determining VWF:RCo values below 20%. Baxter developed a recombinant VWF (rVWF) and conducted a Phase I clinical dose escalation study in severe VWF-deficient patients to assess the pharmacokinetics at different doses starting with 2 IU kg^{-1} at the low end. A more accurate measurement below 20% was necessary for analysis of these samples. For this purpose we modified the automated method to expand the lower limit of detection below 10%, allowing the automatic testing of samples that otherwise could only have been measured by the manual method. The extension was achieved by increasing the plasma volume and changing the dilution media from NaCl to severe VWF-deficient plasma. Thus a reference curve could be constructed in the range of 25 to 8%. Both the standard and the low range were validated according to the International Conference on Harmonization (ICH) and FDA guidelines. Accuracy, repeatability, linearity, and intermediate precision were measured with a WHO plasma standard for VWF and with the rVWF both in a matrix of severe human VWF-deficient plasma, which mimics samples derived from the clinical study. All acceptance criteria were met for both ranges. VWF:RCo activity of samples at the low end of the standard and high end of the low range gave similar results, allowing the continuous accurate determination of the pharmacokinetics of rVWF during the Phase I clinical trial up to a concentration of 8%.

PO-MO-257
Analysis of the French cohort of sixty-five patients with type 2N von Willebrand disease identifies distinct molecular/clinical entities
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Type 2N von Willebrand disease (VWD) is defined by a markedly decreased binding of von Willebrand factor (VWF) to factor VIII (FVIII), recessively inherited. Sixty-five patients from 57 unrelated families were recruited in the French Reference Centre for VWD. Median age was 33.5 years old. (extreme: 6 to 83) and the F/M ratio was 1.7. Genetic analysis showed 8 distinct type 2N missense mutations of which 3 were novel. Patients were either homozygous for one 2N mutation or compound heterozygous (one 2N mutation associated with a null allele or another 2N mutation). Phenotypic analysis as a function of the genotype is summarized in the table.

Alleles	Nb of patients (%)	FVIII:C (IU dL^{-1}) (median; extreme values)	FVIII:C VWF^{-1}:Ag (median; extreme values)
R854Q/R854Q and R854Q/null or R854Q/2N*	56 (86%)	21 (4 – 47)	0.31 (0.12 – 0.60)
2N*/null	5 (8%)	4 (2 – 22)	0.12 (0.05 – 0.50)
R816W/R816W	4 (6%)	7 (2 – 7)	0.05 (0.01 – 0.08)
Total	65 (100%)	19 (2 – 47)	0.30 (0.01 – 0.60)

2N: 2N mutation distinct from R854Q*

Both FVIII:C level and FVIII:C/VWF:Ag ratio are more markedly decreased when VWD type 2N does not involve any R854Q allele (14% of cases). The clinical features correlated with biology. The features of R816W/R816W patients were childhood–onset disease (median age 3 years old), bleeding as the circumstance of diagnosis, hemarthroses and spontaneous life-threatening hemorrhages. In contrast, the patients carrying the R854Q mutation had an adulthood-onset disease (median age 25 years old), fortuitous circumstances of diagnosis (66% of patients), no joint bleeding but post-surgical hemorrhages when the diagnosis had not been performed (18% of cases). To be noted, menorrhagia was reported in 65% of women. The study of this large cohort underlines that type 2N VWD encompasses miscellaneous clinical entities that are closely related to the genotype.

PO-MO-258
French cohort of thirty-seven patients with type 3 von Willebrand disease: Molecular and clinical features
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Type 3 von Willebrand disease (VWD) defined by a virtually total defect in von Willebrand factor recessively inherited is the most severe form of the disease. Thirty-seven patients from 35 unrelated families were recruited in the French Reference Centre for VWD. Median age at inclusion was 29 years old (extreme: 1 to 62) and the F/M ratio was 1.8. Genetic analysis showed 34 distinct gene alterations (of which 20 were novel) including 2 complete gene deletion, 14 frameshift, 12 nonsense, 4 missense, and 2 splice site mutations. Nineteen patients were homozygous and 16 compound heterozygous. The median age at diagnosis was 14 months (extreme: birth to 29 years old). Circumstances of diagnosis were not documented (6 patients), familial antecedent (3 patients), or bleeding symptoms (28 patients): ecchymosis/hematoma (13), oral cavity bleeding/epistaxis (8), neonatal gastrointestinal bleeding (3), joint bleeding (1), post-circumcision bleeding (1), menarche (1), and post-partum hemorrhage (1). Half the patients of the cohort (17 patients) exhibited a life-threatening hemorrhage: oral cavity bleeding/epistaxis (5), hemoperitoneum (4), angiodysplasia (3), delivery hemorrhage (2), post-circumcision bleeding (1), hemothorax (1), and central nervous system bleeding (1). A focus on child-bearing age women (18 patients) showed menorrhagia (14) and hemorrhagic ovarian cysts complicated by hemoperitoneum (4). Only 8 patients of 18 became pregnant (13 pregnancies) and 11 pregnancies were complicated by an early fetal loss (3), a delivery hemorrhage (2), or a delayed post-partum hemorrhage (6). It is worth noting that 10 patients/18 (55%) never had children.
Three homozygous patients (8%) including 2 patients with a complete gene deletion, developed an alloantibody against VWF. In our cohort, secondary long-term prophylaxis (at least more than one year) was performed in 10 patients (27%). These data emphasize the severity of type 3 VWD, especially in women, and raise the question of a more aggressive prophylaxis.

PO-MO-259
Obstetric management in von Willebrand disease: Results of a retrospective study over a twenty-one-year period
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Pregnancy results in a progressive increase in factor VIII (FVIII) and von Willebrand factor (VWF), thus most of the women with von Willebrand disease (VWD) do not bleed during labour and delivery. We retrospectively describe the course and outcome of pregnancy in 76 women with various types of VWD (type 1: 40, type 2: 32, type 3: 4) over a 21-year period. One hundred and thirty-one pregnancies (70 in type 1, 54 in type 2, and 7 in type 3) were managed in our centre, between 1990 and 2011. Five pregnancies were complicated by vaginal hemorrhage occurring at the first trimester: 2 in

type 1 VWD (which did not require treatment) and 3 in type 3 (which required replacement therapy). Pregnancy was terminated by spontaneous vaginal delivery in 106/131 (67.8%) and Caesarean section for the remaining. Replacement therapy (WILFACTIN, LFB) was used in 48/106 (45%) of vaginal deliveries and in 16/25 (64%) of Caesarean sections. The mean dosage vWF:RCo was 56.8 IU kg^{-1} for an average of 6.2 days in cases of vaginal delivery and 10.3 days in cases of Caesarean section. The outcome was uneventful in 84% of cases. We reported 21 cases of bleeding (16%) in post-partum period: 10 (14.3%) in type 1, 8 (25%) in type 2, 3 (42.9%) in type 3, requiring additional infusions of VWF concentrate in 10 cases or administration of DDAVP in 2 cases. No neonatal complications were reported in any of the 133 babies. So, a multidisciplinary team of obstetrician, hematologist, anesthetist, and neonatologist and a monitoring of the hemostatic parameters during pregnancy are essential for an adequate management of these situations.

PO-MO-260

Coronary artery calcification score and carotid intima media thickness in patients with von Willebrand disease

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Introduction: Previous studies showed conflicting results on whether or not von Willebrand disease (VWD) is associated with a lower degree of atherosclerosis.
Objectives: To evaluate the presence and extent of subclinical atherosclerosis in patients with VWD.
Methods: Atherosclerosis was measured by coronary artery calcification score (CACS) and intima media thickness (IMT). CACS and IMT were compared to age- and sex-specific reference values and IMT also to matched controls. Cardiovascular risk profile was assessed.
Results: Twenty-seven patients with a median age of 49 years (range 32–74) were studied. Eight (31%) patients had a CACS > + 1 SD and five (19%) had an IMT >80th percentile. Median CACS was 33 (IQR 0–880) for men and 0 (IQR 0–1) for women. Mean carotid IMT was 0.68 mm (95% CI 0.69–0.79 mm) for men and 0.68 mm (95% CI 0.59–0.77 mm) for women. No differences in IMT were seen between VWD patients and controls. Patients with an increased CACS or IMT had a worse cardiovascular risk profile: they were older, were more frequently overweight, and had higher blood pressure and cholesterol. No relation was seen between severity of VWD and CACS or IMT.
Conclusion: the presence and extent of atherosclerosis in patients with VWD is comparable to age- and sex-specific reference values and controls and is independent of VWD severity. Our data do not confirm the alleged protection of VWD against atherosclerosis.
Contribution to practice: Although we have studied atherosclerosis and not events, these findings suggest that VWD patients should be monitored for traditional cardiovascular risk factors and receive counselling and preventive measures similar to the general population. Given the risk of myocardial ischemia, cardiovascular risk profile should be considered in older VWD patients before giving desmopressin.

42-WOMEN AND BLEEDING DISORDERS

S-MO-04.4-1
Identification and detection of carriers of hemophilia
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As patients with hemophilia live longer and integrate fully into society, the number of female carriers is likely to grow as the daughters of men with hemophilia are obligate carriers. It is important to draw up family trees and actively identify potential female carriers in the wider family. This should become an integral part of the routine review in a hemophilia clinic. The underlying genetic abnormality in an index case within the kindred should be identified. Direct genetic analysis should be used and RFLP analysis is no longer appropriate with the availability of modern technology. Testing should only be carried out in experienced laboratories, which should participate in external quality assurance schemes. It is important to offer genetic counselling before providing formal carrier testing. This should only be offered at an age when a girl is properly able to give consent and understand the issues raised. It is not appropriate on ethical grounds for such testing to be performed in very young children, although it is perfectly reasonable to check the factor level prior to surgery or other invasive procedures. This information alone will not establish whether the girl is a carrier or not. Follow-up counselling should be arranged if a positive result is obtained when the implications may be discussed in greater depth. Shared information on a national database can be very helpful in formulating advice in situations when a pregnant woman presents with a vague family history of hemophilia.

S-WE-01.2-4
Women's voices: Psychological perspective
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When a child is diagnosed with hemophilia, the family sinks into crisis. Whether there is a family history of the disorder or not, this diagnosis causes a psycho-emotional impact. The incidence of this impact on the mothers of children with hemophilia is increased for social and cultural reasons and by extreme male chauvinist attitudes as a consequence of which mothers are blamed for being carriers. When consulted, the psychologist sees clear evidence of notions connected with the crystal roof concept: the women's suspension or abandonment of their jobs or professional activities as an inhibition to go back to their social and everyday lives.
Objective: to work through this impact through various strategies in different programs and to assess the effect of these programs on women's quality of life.
Discussion: different programs were designed by the psychologist to deal with the impact of the disease: a) meeting with parents with a recently diagnosed child; b) reflection and debate workshops with mothers. During these programs, different tools were used. Topics were approached from a multidisciplinary perspective. Psychological interviews with the mothers were also taken into account. Surveys were conducted to evaluate the process.
Conclusions: a) meeting other women facilitates communication and reduces the level of anxiety; b) by discussing the situation they are facing, women are able to think about issues such as overprotective attitudes, self-esteem, and so forth that modify family dynamics, fostering a healthy environment.

S-MO-04.4-5
Women with inherited bleeding disorders: Reproductive choices
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Inherited bleeding disorders are life-long conditions that can present potentially debilitating musculoskeletal bleeding and life threatening intracranial hemorrhages. Despite advances in their treatments, they remain incurable and are commonly associated with significant long-term morbidity. Women with inherited bleeding disorders can pass on the gene defect to their offspring and, therefore, are at risk of having an affected child, depending on the inheritance pattern of the condition. The decision regarding reproduction is fundamentally complex and challenging and further complicated for these women due to their genetic risks. Developments in molecular genetics and technologies have created new opportunities and expanded the reproductive options for these women. In this presentation, reproductive choices of women and families with inherited bleeding disorders will be discussed. Current options for prenatal diagnosis will be explored, including the factors that influence the uptake of these options. Ongoing research in the field as well as future development will also be discussed.

S-MO-04.4-6
Management of pregnancy and delivery: What to expect when expecting
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It has been well established that part of the "physiological response" in pregnancy is a progressive elevation of factor VIII and VWF levels. However, in patients with von Willebrand disease, there is proportionately less elevation in the levels compared to those in the normal pregnant patient, which can lead to subsequent post-partum hemorrhage (PPH) up to 4 weeks post-partum. Ante-partum, the rise in the VWF level is typically >50%, so that if such patients need a dental extraction during pregnancy or other invasive procedure, desmopressin (DDAVP)
is not necessary if the VWF levels have "normalized." In those women whose levels have not exceeded 50%, there are, however, theoretical concerns for administering DDAVP pre-partum in terms of decreased placental flow, premature labour, and neonatal hyponatremia. But, in recent studies comprising a total of 70 patients, the use of DDAVP was not associated with any adverse events. Besides DDAVP, anti-fibrinolytic therapy is an option for control of PPH and can be considered prophylactically, especially in patients with VWF levels <50% at time of delivery. Management of active labour in preventing PPH should include aggressive utilization of uterotonics including oxytocin and additionally misoprostol per rectum, particularly in the non-DDAVP responsive Type 1 patient or in the Type 2 or 3 patients wherein replacement therapy with a VWF containing FVIII concentrate at the time of active labour followed by periodic dosing is in order. In all VWD patients regardless of subtype, weekly surveillance up to 4 weeks postpartum is also in order due to the sizable risk of delayed PPH.

S-MO-04.4-4
Preconception counseling: No one size fits all!
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Preconception counselling for women with bleeding disorders is extremely important. Often a woman's primary concern relates to the possible risk to the baby: what chance is there that the child will inherit the disorder, should she have prenatal testing to see if the child is affected, and if so, what are the risks of this? Prospective parents will have very different approaches to these issues influenced by cultural, religious, personal, or spiritual beliefs. No one size fits all! Most women don't focus so much on how the pregnancy and delivery might affect them personally. Many women with bleeding disorders have bleeding symptoms themselves. This is easy to understand in the case of the autosomal dominant (von Willebrand disease) or recessive disorders (factor XI, factor X deficiency etc.). However, increasingly it is being recognized that even so-called '*carriers*' of the hemophilia gene have excessive bleeding. In fact, for complex biological reasons, some '*symptomatic carriers*' of the hemophilia gene have such low levels of clotting factor that they manifest symptoms as severe as the males in their family. Pregnancy and childbirth can be a very dangerous time for some women especially if they are met by ill-informed medical professional who think that by definition 'a *carrier* cannot have symptoms.' Trying to convince these professionals that this is not the case can be one of the most frustrating things for women. Perhaps it would improve things if we stop using the words "carrier" or even 'symptomatic carrier' and instead describe **women who have the hemophilia gene** 'who bleed' or 'who do not bleed.' Whatever words we choose, what is vital is that women with bleeding disorders, symptomatic or not, are cared for by knowledgeable clinicians who understand the issues that women face, can guide them and their families through the complex decisions required, and can empathize with the difficult choices they face.

S-MO-04.4-2
Experiences of carriers of hemophilia: Established country perspective
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Despite advances in the treatment and management of hemophilia in the developed world, with the introduction of recombinant clotting factor concentrates and regular effective prophylaxis, carriers of hemophilia seeking information about reproductive choices still pose challenges to healthcare professionals within and outside of Specialist Treatment Centres. A carrier's own history, relating to the condition among affected members of her family, may strongly influence her feelings about having a son with hemophilia. This is particularly true, when considering subsequent pregnancies, for those who have lost close family members due to transfusion transmitted viruses, or for those who already have a son with hemophilia where there have been significant hemophilia-related problems. Family members may have strong opinions based upon their own experiences, which can prevent a carrier of hemophilia discussing her own choices within the extended family, where the first line of support is usually sought, leading women to feel isolated in their decision making or pressurized into complying with a family view that is not necessarily their own choice. Using examples from clinical practice, this presentation will explore the role of specialist professionals in supporting carriers of hemophilia before, during, and after pregnancies to ensure that care is optimized for the individual woman, and that accurate information and support is provided to enable them to feel comfortable and confident in making their own decisions.

S-WE-01.2-1
The voice of promise and comfort
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Commission Femmes De L'AFH, Sébastopol, France

During the French Hemophilia Society (AFH) National Congress in 2005, it was emphasized that 'hemophilia has an important impact on families, couples or siblings, with numerous consequences on life plans'. It is advisable to listen to 'women's useful and promising voice.' Since 2004, the AFH offers to link people together, to become less isolated, to implement mutual help and exchange coping strategies, because women have things to tell each other and that matters to them and everyone. They are women who are, often backstage and in various ways, close to people with hemophilia (PWH) and are concerned by hemophilia in their everyday life and/or for their future life (carriers). They share, from near and far, the life of PWH (mothers, of course, but also grandmothers, aunts, mothers-in-law, partners, widows, sisters, sisters-in-law, daughters, etc.) or are themselves concerned (carrier women, women with hemophilia or another bleeding disorder). 1) As a responsible member of the Women's Committee in France, I can tell you that: a) women's commitment alongside the PWH isn't always easy in their day-to-day life; b) some carrier women do feel guilty about transmitting hemophilia. We must

allow women to express how they feel about living with a person with hemophilia or themselves being a carrier, and that they may sometimes suffer too. A forum is needed so that they may tell their stories without feeling guilty or judged. The aim is to emphasize their need to be heard and recognized. 2) As a mother of twins with hemophilia, the greatest difficulty was to be recognized and accepted. We often had to prove that girls with hemophilia exist, though it is extremely rare, to medical staff as well as to other PWH from the NMO. It wasn't always easy to find the right balance between the desire to protect my daughters and help them become more independent. We are there so that everything we went through and everything we are expecting could become a gift for the younger generation. We hope women will get better preparation to be able to take charge of their future. We hope that during their lives, they will feel less guilty than we did.

S-MO-04.4-3
Experiences of carriers of hemophilia in developing countries
S. RAVANBOD
Iranian Comprehensive Hemophilia Care Centre, Tehran, Iran

The impact of hemophilia on families is significant. The impact depends on the availability and efficiency of care and treatment. It also depends on societal perceptions of genetic diseases and on the culture. In conservative societies, the hereditary nature of hemophilia particularly affects women who are carriers of this X-linked bleeding disorder. Social norms and practices have a huge influence on personal lives of these women. In patriarchal societies, women keep their carrier status a secret to avoid stigma. Hiding the disease within the family protects them from discrimination and harassment imposed by their in-laws. Over the past 21 years, as the mother of a child with severe hemophilia, aside from suffering menorrhagia, I have faced many of the negative and positive aspects of this genetic disorder in my own family. I have had the privilege to serve the hemophiia community in Iran in different roles, including providing educational materials, being a board member of the Iranian Hemophilia Society for three terms, and assisting in the establishment of the first Comprehensive Hemophilia Care Centre in Tehran. Moreover, I have been working in the molecular genetics laboratory for almost 10 years carrying out carrier and prenatal diagnosis for congenital bleeding disorders. I have witnessed firsthand the profound impact that carrier status can have upon various aspects of a women's life. The aim of this presentation is to discuss the impact of being a carrier in a developing country, and to make the audience understand the barriers that are rooted in socio-cultural factors. The presentation will help the audience realize that providing high-quality healthcare services requires an understanding of how people in different communities think and the way people interact and view life.

S-WE-01.2-2
Women's voices: Patient perspective
B. ZIEMELE
Latvia Hemophilia Society, Riga, Latvia

There are more than 243,000 people with bleeding disorders diagnosed around the world. Except for the numbers of those affected by hemophilia, women are equally diagnosed with bleeding disorders. Every person with hemophilia has a mother, who was most probably a gene carrier, and perhaps even symptomatic. It's only a couple of years since the world realized that women with bleeding disorders were actually being left out of the picture as far as attention to their bleeding issues. There are still many unanswered questions ahead, but young and passionate ladies around the world are willing and able to care about their future and ensure a better environment and everyday life. There are no universal guidelines to tackle everyday situations; usually one tries until they are successful. As a bleeder, I can suggest several tips on how to deal with small bleedings and to explain and cover blue marks. Although we live in the 21st century, it is still difficult to explain to people that you have a rare disease, that it is not contagious, and that you just have to live with it. If properly tackled, you can have a normal life like everyone else. One needs a reliable hematologist at hand who will engage and help when needed. One can use various tips from ladies around the world. Being active in your community is also a way to improve the overall situation. It is better to prepare than to tackle the consequences in almost every situation of your life—from leaving home for a few days to family planning and having babies. I believe being aware of the diagnosis, and knowing more than the average person about it, will help us live happy lives. Knowing that there are others just like you, doctors who can help, and even the chance to get treatment, will make our everyday lives less anxious and much safer.

FP-MO-01.1-5
Low factor VIII is associated with bleeding during early pregnancy
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Objective: The purpose of this pilot study was to compare the prevalence of hemostatic abnormalities in women with first and second trimester bleeding to the prevalence in women without bleeding. Methods:
After confirmation of a viable singleton pregnancy, women who were ≥18 years of age were enrolled at 12–14 weeks gestation. Exclusions included bleeding disorders or anticoagulation. PT, aPTT, fibrinogen, FV, FVIII, VWF:Ag, VWF:RCo, CBC, and ABO blood type were obtained on all subjects at enrollment. TT, FII, FVII, FIX, FX, and a FXIII screen were obtained on a subset of subjects. Clotting factor assays were repeated at 24–28 weeks gestation. Samples were processed on site and analyzed at the United States Centers for Disease Control and Prevention (CDC) Coagulation Laboratory. Results for subjects with and without bleeding were compared using Fisher exact test (Epi Info, CDC).
Results: Of the 125 subjects, 13 experienced vaginal bleeding prior to enrollment. Another 11 had first trimester bleeding after enrollment. Five continued to bleed in the 2nd trimester, including 1 who miscarried at 14 weeks gestation. Three subjects had new onset bleeding in the 2nd trimester. One miscarried at 21 weeks preceded by bleeding. One other miscarried at 17 weeks not preceded by bleeding. A total of 27 subjects bled in the first and second trimester. Twenty-four of the 27 subjects who bled (cases) and 89 of the 98 subjects who did not bleed (controls) had evaluable results. Five out of 24 cases compared with 3/89 controls had FVIII levels <60 IU dL^{-1} during pregnancy (relative risk = 4.94 [1.19, 20.61]). Two out of 5 cases and 1/3 controls with FVIII levels <60 IU dL^{-1} also had low VWF:RCo. Low levels of other clotting factors were not associated with first and second trimester bleeding.
Conclusions: During pregnancy, factor VIII levels <60 IU dL^{-1} are significantly associated with first and second trimester bleeding.

FP-MO-01.1-6
The Prevalence of Disorders of Hemostasis in Adolescent Girls with Menorrhagia
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Menorrhagia is a common menstrual pattern that characterizes the first years after menarche. Among the causes of abnormal uterine bleeding in adolescence, it is important to exclude underlying disorder of hemostasis, because epidemiological studies showed 5–20% prevalence of von Willebrand disease (VWD) and >20% prevalence of platelet dysfunction in adult women with unexplained menorrhagia. The study group included 110 adolescents with unexplained menorrhagia, median age of 14.4 years. All bleeding symptoms and used drugs were recorded. Standard evaluation included complete blood count, ABO group, prothrombin time, activated partial thromboplastin time, von Willebrand factor antigen, ristocetin cofactor, collagen binding assay, FVIII, FIX, FXI, bleeding time (BT) and platelet aggregation. Additional hemostatic studies included FII, FV, FVII, FX, FXIII, platelet membrane glycoproteins, and platelet activation markers. A laboratory abnormality was found in 42/110 (38.2%) subjects. Platelet aggregation was decreased in 20 (18.2%) patients, leading to diagnosis of inherited or acquired platelet dysfunction. VWD was diagnosed in 10/110 (9%) adolescents, mild deficiency of FVII in 6 (5.4%), FXI in 3 (2.7%), FV in 2 (1.8%), and FXII in 1 (0.9%). One hemophilia A carrier was also identified. BT was prolonged in 9/110 (8.2%) girls. A high proportion (38.2%) of adolescents with unexplained menorrhagia had an underlying disorder of hemostasis, platelet dysfunction and VWD being the most common disorders. The results highlight the importance of managing them in cooperation with both a gynecologist and a hematologist to ensure proper, timely diagnosis, so that appropriate treatments can be prescribed.

PO-MO-263
Pregnancy outcomes in women with, or carriers of, inherited bleeding disorders in a London obstetric unit with haemophilia comprehensive care centre
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Background: We audited pregnancy outcomes in women with inherited bleeding disorders (IBD) and carriers at a large London obstetric unit/hemophilia comprehensive care centre. We adhered to the guidelines for the management of IBD in pregnancy, produced by theUK Haemophilia Centre Doctors' Organization. From September 2008 until January 2012, there were 33 such pregnancies including von Willebrand (VWD) type 2 (7), Factor XI deficiency (6), hemophilia A carriers (5), VWD type 1 (4), hemophilia B carriers (3), factor VII deficiency (3), platelet disorders (3), and factor XIII deficiency carriers (2). All women were seen in a multidisciplinary antenatal clinic where individual birth plans were agreed upon. Twenty-one women had peri-delivery hemostatic treatment.
Maternal Outcomes: Primary postpartum hemorrhage (PPH) occurred in five women (15.2%), but none required blood transfusion. Four of these women had normal factor levels but had obstetric causes for hemorrhage (3 Caesarean sections, one had shoulder dystocia and a third degree perineal tear). One woman had hemostatic treatment before a Caesarean section but had a PPH from a complicated surgery. Secondary PPH occurred in one woman (3%).
Neonatal Outcomes: There was one spontaneous pre-term birth (3%) and four small-for-gestational-age babies (12%), but all had normal Apgar scores and did not require additional neonatal care. One baby was affected by shoulder dystocia. Six babies were diagnosed with IBD (18%) including three with VWD type 2, two with factor XI deficiency, and one with severe hemophilia A. One baby with type 2A VWD had cephalhematoma following a normal vaginal delivery.
Conclusion: With the exception of a secondary PPH and a cephalhematoma in a pregnancy with type 2A VWD, women with IBD who delivered at a unit with a hemophilia centre had similar outcomes as those with normal pregnancies. It is essential that pregnancies associated with IBD are managed via an expert multidisciplinary team approach.

PO-MO-264
Ovarian endometrioma in two women with Glanzmann's thrombasthenia
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Women with inherited bleeding disorders can present with a range of gynecological issues. We present two cases of ovarian endometriomas in women with Glanzmann's thrombasthenia (GT) and compare their management.

Case 1: A 21 year-old female (P0+0) with GT, presented with right iliac fossa pain, was found to have a right-sided ovarian cyst (8 × 8 × 8 cm) on ultrasound. A right ovarian cystectomy was performed with peri-operative transfusion of HLA matched platelets. Intra-operative bleeding was noted so the operation was converted from a laproscopic to open procedure. HLA matched platelets and rVIIa (90 mcg kg^{-1} × 2 doses) were also given. A 12 cm ovarian cyst was removed. Histology showed an endometrioma. She had an Implanon inserted with the addition of Cerazette. She is currently asymptomatic with minimal bleeding.
Case 2: A 38 year-old female (P0+0) with GT and anti-IIb/IIIa antibodies, presented with menorrhagia and iron deficiency anaemia. An MRI showed bilateral ovarian endometriomas and a left tubuo-ovarian complex measuring 3 × 5 × 3 cm. Ca 125 was normal. She had GNRH analogue (Zoldex) administered under the cover of HLA matched platelets and rVIIa with no bleeding complications. She opted for Implanon with HLA matched platelet and rVIIa cover. She bled post insertion and had to be admitted for further doses of HLA matched platelets and rVIIa. Since this time, she has had no PV bleeding and is not iron deficient.
Discussion: We present two cases of ovarian endometriomas in women with GT. For cysts >5 cm there is a risk of ovarian cyst accident (rupture, bleeding, or torsion). In these cases, cystectomy should be considered. GT is a severe bleeding disorders and surgery needs to be carefully considered and planned. A conservative approach is often favoured via hormonal manipulation to suppress bleeding and ovulation.

PO-MO-265
Coderouge 2012: First Canadian conference on bleeding disorders in women

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Over the past 10 years, the Canadian Hemophilia Society (CHS) has undertaken a variety of strategies to educate and raise awareness about bleeding disorders in women and promote access to comprehensive care. As of May 2011, there were 3,226 women with inherited bleeding disorders registered at Canadian hemophilia treatment centres (HTCs); 6 out of 25 HTCs have established multidisciplinary clinics for women. However, the majority of women with an underlying bleeding disorder remain undiagnosed. In 2011, the CHS developed a national program called *Coderouge: when women bleed too much*. The goal of this program, specifically targeted at healthcare providers and women, is to identify undiagnosed women with bleeding disorders and ensure that they have access to appropriate medical care. *Coderouge* awareness material for healthcare providers and women will be developed and spokespersons identified to assist with outreach efforts. A partnership with the Society of Obstetricians and Gynecologists of Canada (SOGC) has been established that will promote speakers at SOGC conferences, web-based education, and the development of clinical practice guidelines on the management of women with bleeding disorders. To launch this new initiative, the CHS is organizing *Coderouge 2012: The 1st Canadian Conference on Bleeding Disorders in Women*. On May 25, 2012, key healthcare providers, including HTC hematologists and nurses, gyneocologists, obstetricians, and family physicians as well as affected women will meet for a one-day conference exclusively dedicated to bleeding disorders in women. *Coderouge 2012* will feature topics including the management of bleeding disorders in women, quality of life, state-of-the-art research, and models for the establishment of multidisciplinary women's programs. It is hoped that as a result of the conference there will be an increase in the number of women registered in HTCs and the number of multidisciplinary programs for women with bleeding disorders in Canada.

PO-MO-266
Hemostatic changes during pregnancy in healthy women and in women with inherited bleeding disorders

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Introduction: The management of inherited bleeding disorders during pregnancy is challenging, in part, because there is a lack of information concerning the physiological changes of coagulation parameters during and after pregnancy. The purpose of this study is to assess prospectively the laboratory and clinical evolution of von Willebrand disease (VWD) and hemophilia in carriers during pregnancy and in the postpartum period, compared to control women.
Methods: Sixteen women with VWD (15 with type 1 and 1 with type 2), 5 hemophilia A carriers, and 17 women controls were recruited. FVIII:C and VWF antigen and activity levels were measured at 15–20, 28, and 32 weeks gestation, on admission and on days 1, 2, 4, 7, and 28 in the postpartum period. Baseline levels were taken from the chart at the time of diagnosis. Information on postpartum blood loss, oral contraceptive pill use, and breastfeeding was noted.
Results: Most patients had normal coagulation levels (≥0.5 IU mL^{-1}) by 20 weeks and some as early as 15 weeks. Levels were generally maximal by 28 weeks. Once the coagulation profile normalizes, it does not drop after. In postpartum, no decrease in factor levels was observed before day 4, and by day 7 more than 80% of patients still had normal values. No postpartum hemorrhages were reported. For controls, changes in VWF levels paralleled those in women with VWD. Most controls had a 1.5–2-fold increase in VWF levels by 28 weeks. In postpartum, most women did not return to baseline levels before day 28.
Conclusions: VWF profile in pregnant VWD patients follows a similar pattern to that of controls. Coagulation levels often normalize early in pregnancy and do not decline afterwards. Consequently, screening in early pregnancy is unlikely to be useful. In postpartum, levels generally return to baseline after day 7.

PO-MO-267
Viral infection status of 1036 women with inherited coagulation factor deficiencies within the Francecoag network

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The former cohort (1994-2002) of patients with hemophilia supported by the French health authorities was mainly designed to improve pharmacosurveillance, especially regarding transmission of infections. The cohort was extended in 2003 and included, by September 2011, 7,468 patients prospectively followed with all types of hemophilia and other inherited coagulation-factor deficiencies according to the inclusion criteria. We report here the status of the 1,036 (13.9%) female patients regarding hepatitis B (HBV), hepatitis C (HCV), and human immunodeficiency virus (HIV) infections. The cohort includes 720 women with VWD (type 1 with VWF:Ag<30%, type 2 with VWF:RCo or VWF:CB/VWF:Ag<0.7 or FVIII:C/VWF:Ag<0.5 or RIPA positive at low ristocetin concentration and type 3), 96 with FVIII <30%, 63 with FXI <20%, 59 with FVII <10%, 35 with FIX <30%, 21 with afibrinogenemia, 20 with FV <10%, 10 with FXIII <10%, 9 with FX <10% and 3 with FV+ FVIII <30%. Death occurred in 5 cases, but none related to a virus infection. The median follow-up in the study is 1.9 years (range:0.1–10). All women with FX, FXIII, and FV+FVIII deficiencies, 90.5% of those with afibrinogenemia, 75% of women with FV, 60% with FIX, 57.6% with FVII, 41.3% with FXI, and 38.5% with FVIII deficiencies received substitutive therapy at least once in their lifetime. According to the bleeding disorder, the proportion of women born after 1994, consequently not exposed to the risk of blood-borne virus infections varies from 11.1–40%. Forty-five patients are positive for HBV, 128 for HCV (including 29 co-infected with HBV), and 7 for HIV (including 6 co-infected with HCV and 2 also with HBV). Further detailed analysis of type and date of treatments will help to define more precisely the incidence of infections in exposed women and to compare the data to their male counterparts.

PO-MO-268
Almost all women with heavy menstrual bleeding experience menstrual pain

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Approximately 10–15% of women in Sweden suffer from heavy menstrual bleeding (HMB), that is, a menstrual blood loss exceeding 80 mL $month^{-1}$. It is well known that menstruation can cause pain. However, there is limited knowledge how women with HMB perceive menstrual pain. The aim was to estimate the occurrence and intensity of menstrual pain in women with HMB, and assess potential association between pain and amount of blood loss during menstruation. Sixty-four women with a median age of 35 (range 19–44) years, referred to the Karolinska University Hospital for HMB and hemostatic defects, were included. A Pictorial Blood Assessment Chart was used to measure the menstrual blood loss daily during menstruation and a Visual Analogue Scale (VAS) 0–100 mm (0 = no pain, 100 = worst possible pain) was used to measure pain intensity during the same days. Spearman's rank-order correlation coefficients were used to describe the association between amount of blood loss and VAS score. A coefficient between 0.10 and 0.29 was regarded as small, between 0.30 and 0.49 as medium, and between 0.50 and 1.00 as large. The median menstruation duration was 7 (range 3–17) days. Day 1, 51 (86%) women reported pain with a median VAS of 38 mm (range 0.1–97), day 2, 50 (83%) women scored 40 mm on VAS (median, range 0.4–97), and day 3, 43 (80%) women scored 33 mm on VAS (median, range 0.2–97). For day 4–13, pain intensity ranged between 0.7–79 mm on VAS. Correlation coefficients of medium size were found between pain intensity and amount of blood loss for menstruation day 1 and 3–7. The remaining days, the correlations were of large size. Results indicate a high prevalence of pain among women with HMB. Many experience intense pain over several days. Furthermore, a positive correlation was found between menstrual blood loss and pain intensity.

PO-MO-269
Current postpartum treatment strategies for von Willebrand disease may not adequately replace von Willebrand factor

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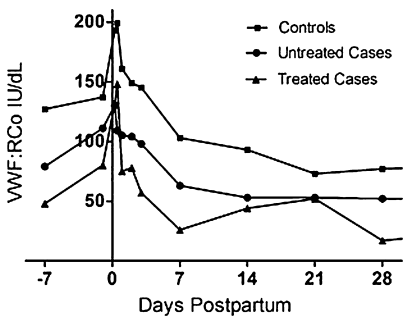
Objective: Von Willebrand factor (VWF) levels rise during pregnancy, peak at delivery, and fall postpartum (PP). The purpose of this study was to estimate when VWF levels return to baseline PP and make inferences about the appropriate duration of treatment for women with von Willebrand disease (VWD).
Methods: This was an observational study of VWF levels in women with VWD (cases) and without VWD (controls). Subjects were enrolled in the third trimester of pregnancy at 5 university medical centres. Controls were matched to cases on the basis of age and race. Providers were asked to avoid treating cases whose third trimester VWF levels were > 50 IU dL^{-1}. VWF:RCo, VWF:Ag, and FVIII were obtained at enrollment, on admission

to the hospital for childbirth, and at 4 hours, 12 hours, 24 hours, 48 hours, 72 hours, and at 7, 14, 21, 28, and 42 days PP. Specimens were processed within an hour of blood draw and analyzed centrally. Means were calculated for each assay at each time point. Three-way ANOVA was performed with a comparison of means for each pair using Student's test.
Results: Twenty-eight cases and 34 controls were enrolled. Twelve cases (6 type 1, 6 type 2) were treated. Treatment consisted of VWF concentrate in 10, desmopressin plus VWF concentrate in 1, and desmopressin in 1. Duration of treatment was 1–19 days. VWF levels fell rapidly after delivery, approached baseline 1 week PP, and reached baseline 3 weeks PP. VWF:RCo, VWF:Ag, and FVIII levels among cases paralleled those among controls, but were significantly lower at almost all time points. Levels were generally lowest among treated cases.



Conclusions: Current PP treatment strategies do not even raise VWF levels to those of women with milder, untreated VWD. Consequently, despite treatment, women with VWD may continue to be at risk of delayed postpartum hemorrhage.

PO-MO-270
Pregnancy Outcome of Women with Congenital Bleeding Disorders Managed by Multidisciplinary Team in an U.K. Hemophilia Comprehensive Care Centre Over Three-Year Period

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The outcome of pregnancies in women with known congenital bleeding disorders, managed by our multidisciplinary team over a 3 year period, were reviewed to identify any factors contributing to adverse outcome. Case notes of 55 pregnancies in 51 women were reviewed retrospectively; 25 pregnancies in 22 hemophilia A carriers, 18 pregnancies in 18 women with type 1 Von Willebrand Disease (VWD), 3 pregnancies in 2 women with type 2 VWD, 3 pregnancies in 3 women with factor XI (FXI) deficiency and a single pregnancy in a woman with Bernard Soulier Syndrome (BSS), dysfibrinogenemia, factor XIII (FXIII) deficiency, carrier of hemophilia B, carrier of FV, and carrier of FX deficiency. All pregnancies resulted in live births, with 50 vaginal deliveries and 2 planned Caesarean sections in severe hemophilia A carriers for maternal obstetric indications. Two women had a forceps delivery due to poor progression of labour associated with a severe post-partum hemorrhage (PPH) in one, a mother with BSS and a scalp hematoma in the male baby of the other, a carrier of severe hemophilia A. Forty-eight out of fifty vaginal deliveries were uncomplicated, including 17/19 deliveries in severe hemophilia A carriers. Of the 7 vaginal deliveries of males potentially affected by severe hemophilia, cord blood testing identified 5 affected individuals and no neonatal complications. The pregnancy of a women with FXIII deficiency was managed with 3 weekly factor XIII concentrate until 24 weeks and then 2 weekly to maintain trough factor XIII >10% and a bolus prior to vaginal delivery, which was uncomplicated. A woman with type 2 VWD experienced significant PPH following both her vaginal deliveries despite planned hemostatic support. In conclusion the majority of women had a normal vaginal delivery without excess complications, but safe management requires close observation during labour and liaison between obstetric and hematology teams.

PO-MO-271
Phenotypic Bleeding Penetrance in Female Carriers of Rare Inherited Coagulation Deficiency

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Objective: Phenotypic variability in carriers of rare inherited coagulation disorders (RICDs) has been observed. According to the X-inactivation (X lionization) phenomenon that caused a wide range of variability in biochemical and physiological status in females and also the effect of hormonal changes on coagulation factors, which has been presented in pregnancy or during oral contraception therapy. This study investigates the effect of heterozygous genotype in female carriers of RICDs on the penetrance of bleeding phenotype.
Methods: A cross-sectional study was performed among 66 females who were carriers of RICD, which had been confirmed by DNA study before 2010, and who were registered in Shiraz Hemophilia Society (SHS), Southern Iran. Data collection was done by a standard questionnaire containing items on personal characteristics, carrier detection test, medication usage, and history of bleeding. Also, 66 non-carrier women who had a first and or second degree relationship with known carriers has been studied as control group to reduce genomic and physiologic variety and other differences that can influence on clinical presentation.
Results: Mean ages of the carrier and control group were 17.9 ± 1.4 years and 19.9 ± 1 years, respectively. The most frequent diseases in the sample group were factor VII deficiency (24.2%), Glanzmann's thrombasthenia (16.7%), and factor X deficiency (13.6%). There were statistically significant relations between prevalence of bleeding phenotype including, subcutaneous hematoma (P value = 0.032), purporae (P value = 0.028), gingival bleeding (P value = 0.01), normal vaginal delivery, and Caesarean section bleeding (P value = 0.024) and hypermenorrhea (P value = 0.024) with heterozygosity of RICDs in females.
Conclusion: Findings show that female carriers of RICDs are in high risk area to present bleeding phenotype. So they should be informed about this risk to take care in operation and medication, especially during pregnancy and Caesarean section. However, further detailed studies at the phenotypic penetrance of mutant allele, with a larger sample size are recommended.

PO-MO-272
Frequency of Inherited Bleeding Disorders in Adolescent Girls with Menorrhagia

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Background: Menorrhagia is the most common bleeding symptom in women with inherited bleeding disorders (IBD). The reported incidence of IBD is between 5–20% in women with menorrhagia. However, the frequency of IBD in adolescent girls with menorrhagia is not well-known. Objective:
The purpose of this study was to determine the prevalence of IBD among female adolescents with menorrhagia.
Study Design: A bleeding questionnaire, annexed with a pictorial blood-loss assessment chart (PBAC), was delivered to 650 female university students staying at dormitories. Evaluation of PBAC revealed that 82 (21.8%) of the 376 responders had menorrhagia (>100 mL blood loss in a period). Subjects with menorrhagia were invited to hospital for gynecological examination and laboratory investigations that included a platelet count, prothrombin time, partial thromboplastin time, plasma levels of clotting factors, VWF:Ag and ristocetin cofactor activity, and PFA-100 analysis.
Results: The median age of 82 subjects was 19 (range 17–25) years. Of them, 10 (12.1%) were found to have an IBD. Von Willebrand disease (VWD) was the most common IBD detected in five, followed by platelet function disorders (PFD) in four, and factor XI deficiency in one subject. The prevalence for VWD, PFD, and FXI deficiency in adolescents with menorrhagia was 6.1%, 4.9%, and 1.2%, respectively. None of these cases had sought medical aid for menorrhagia. Conclusions:
Our results show that menorrhagia is a common problem in female adolescents. It is generally ignored, despite an IBD; mostly VWD and platelet function disorders are present in a significant proportion of cases. Identification of the underlying bleeding disorder is important for prevention of complications due to excessive menstrual bleedings, such as iron deficiency anemia, gynecological problems, and risks of childbirth.

PO-MO-273
The Prevalence of Underlying Bleeding Disorders in Patients with Unexplained and Explained Menorrhagia

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Introduction: Bleeding disorders have been recognized as an important etiologic and/or contributing factor in women with menorrhagia.
Objective: To assess the prevalence of bleeding disorders and symptoms in women with menorrhagia, with and without gynecological abnormalities.
Methods: We included 102 consecutive patients referred for menorrhagia, confirmed by a pictoral bleeding assessment chart score >100. Patients and controls (28 healthy volunteers without menorrhagia) had hemostatic testing in the first week after menstruation, and a bleeding history was taken. Patients underwent gynecological evaluation.
Results: Forty-six per cent of patients were anaemic, 61% had low ferritin. Twenty-six per cent of patients had endometrial polyps or submucosal uterine myoma, sufficient to explain menorrhagia. An underlying bleeding disorder was found in 29% vs. 11% (P = 0.04) of the patients vs. controls, and in 31% vs. 27% of the women with unexplained vs. explained menorrhagia (P = 0.75). We diagnosed 6 cases of von Willebrand disease (VWD), 4 cases of factor XI (FXI) deficiency, and one factor VII (FVII) deficiency. The only abnormalities found in controls were platelet aggregation defects (11% vs. 23% in patients). Patients had a significantly longer activated partial thromboplastin time (aPTT) compared to controls (26.5 vs. 25.0 sec; P = 0.001) caused by lower median levels of FXI (100 vs. 124 IU dL^{-1}; $P < 0.001$). Although non-menorrhagia bleeding symptoms were more prevalent in patients than in controls, additional bleeding symptoms did not predict for an underlying bleeding disorder in patients. Conclusion:
Bleeding disorders play an equally important role in the etiology of both unexplained and explained menorrhagia. A novel finding is the occurrence of low, but not deficient levels of factor XI.

PO-MO-274

Hemostatic Variations in Normal Women: The Role of Electronic Bleeding Questionnaire, Electronic Pictorial Chart, and a Global Hemostatic Assay in Predicting Mild Bleeding Disorders in Women

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Women with mild bleeding disorders (MBD) pose a diagnostic challenge, and menorrhagia, the most common presenting symptom, remains under-reported. We investigated novel approaches to predict MBD in seemingly normal women. We developed an electronic bleeding questionnaire (e-BQ), based on the condensed MCMDM-1questionnaire, using a web-based application stored on a local machine and security protected using data encryption accessed by a user-defined password. Additionally, the bleeding score (BS) was computed automatically within the application, and data were stored for future analysis and retrieval. We also developed an electronic Pictorial Blood Assessment Chart (e-PBAC) based on a widely accepted semi-objective method for assessment of menstrual blood loss, accessed via the Internet, where women enter their menstrual data daily from home. We recruited 50 normal females (ages 18–47). Three were excluded due to a family history of bleeding disorders. We assessed the hemostatic status of 47 females using thrombelastography (TEG), a global hemostatic assay, and whole blood aggregation in response to ADP, collagen, and ristocetin, together with a complete blood picture, with particular attention given to hemoglobin, hematocrit, and platelet count and size, along with PT and aPTT testing. The analysis showed 3 having an abnormal BS: 5–7 (normal =-1 – +4); further analysis of which revealed the diagnosis of VWD type 1. We also identified 11 with abnormal e-PBAC scores: 105–744 (normal=<100) who are currently under gynecological assessment. Two women were anemic, and one had small platelets. In addition, we report for the first time normal ranges for TEG parameters, platelet aggregation in females during proliferative phase of uterine cycle. We conclude that the electronic tools positively contributed to the process of data collection, helped identification of three females with MBD, and enhanced the correctness of menstrual data leading to proper identification of menorrhagia requiring gynecological investigation.

PO-MO-275

Hematological and Gynecological Assessment in Hemophilia Carriers

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Carriers with low factor levels may have an increased bleeding tendency. Overall, symptoms are mild; however, there is higher abnormal gynecological bleeding (menorrhagia, postpartum hemorrhage) and high risk of bleeding after trauma and surgery. This could have an important impact on health and quality of life. We have studied a cohort of 16 obligatory carrier patients (mother of two or more children with hemophilia or mother of a son with hemophilia and at least one other family member with hemophilia) and evaluated the hemorrhagic trend using the bleeding score (BS), analyzed diverse gynecologic parameters, and performed a general quality of life survey. Age (mean) was 43.7 years (22–60). The mean BS was 2.3; a higher bleeding trend was related with teeth extractions and bruises. Seven patients (44%) have a BS of more than 4. In women with fertile potential menorrhagia this was estimated using PBAC. The average score was 360. Ten out of eleven (91%) patients had scores above 100. Five patients (31%) had postpartum hemorrhage and 3 (18%) required hysterectomy due to menorrhagia. Half of the patients have dysmenorrhea, and none of them have consulted previously due to menorrhagia. No patients have received antifibrinolytics or factor replacement therapy due to menorrhagia. The average factor level was 60% (26%–134%). The average ferritin level in premenopausal women was 38 (18–72). Quality of life was assessed with a generic measure: none of the eight SF-36 scales was altered.

Conclusions: Carriers have a higher hemorrhagic trend. Gynecological bleeding has an impact over the carrier's life and most of our patients have menorrhagia and do not receive adequate assistance. Appropriate education and follow-up should be performed for this patients' group.

PO-MO-276

Successful in vitro fertilization (IVF) and pregnancy in Glanzmann's thrombasthenia under cover of recombinant factor VIIa

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A 35 year-old woman with Glanzmann's thrombasthenia (GT), with no further conservative treatment options for primary infertility, underwent in vitro fertilization (IVF). Ultrasound guided follicle aspiration was performed under cover of recombinant factor VIIa (rFVIIa). The patient became pregnant during the first treatment cycle. Pregnancy itself was uneventful. During pregnancy, the frequency of epistaxis increased significantly and could be treated successfully by local application of tranexamic acid and bipolar coagulation during one episode. In 38+1 weeks of gestation, primary Caesarian section was performed due to the elevated risk of peripartal bleeding again under cover of rFVIIa. Four HLA compatible platelet concentrates had been prepared as standby therapy. An apparently healthy child was delivered. Despite no evidence for increased intraoperative bleeding, post-operative hemoglobin concentration decreased to 6.7 g dL^{-1}, necessitating transfusion of 2 erythrocyte concentrates. Recombinant FVIIa was reduced successively and discontinued on day 10 after delivery. Under this regimen (including tranexamic acid 1000 mg tid p.o.), no further relevant bleeding complications occurred and lochia were even below average. The decision for rFVIIa over platelet transfusions was guided by the idea to prevent alloantibody formation against the GPIIb/IIIa complex. This case report demonstrates feasibility and safety of IVF in women with GT under specific treatment.

43-YOUTHS ISSUES

PO-WE-272
Importance of Youth Groups in a National Member Organization
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Introduction: Young PWH (people with hemophilia) are over-protected by their family and friends, and they face problems such as expensive or lack of available clotting factor concentrates (CFC), inadequate treatment facilities in many countries, lack of knowledge about CFCs, education, unemployment, counselling, and issues in marriage and sexual relations. These problems faced by young PWH in India guided the Hemophilia Federation, India, (HFI) to form a youth group.
Objectives: The main objective of the youth group was to develop a second line of leadership to carry forward the movement of HFI and to initiate self-sufficiency by providing education about the disorder.
Methodology: Around 80 young PWH were selected from HFI chapters with a structure of four youth leaders representing each region and a coordinator to organize regional and national camps. Leadership development and motivational workshops were integrated. A Youth Annual General Meeting was established where the constitution and manual of the youth group were adopted.
Challenges: Many youth were reluctant to join the movement due to time constraints, sense of futility, and discouragement from family members. Hence, sorting out their persoal lives became a priority rather than working for HFI. An agency to sponsor/fund the aforesaid events in methodology is required.
Conclusion: The youth group came into existence as it provided a solution o the problems related to education, jobs, marriage, sexual relations, and health-related guidance. This resulted in a strong bond among young PWH. Three years later, HFI now has a structured youth group. As a result, 25 of 71 HFI chapters have youth groups. Youth PWH are part of the executive committee in these chapters and one youth is in the Executive Committee of HFI.

PO-WE-273
Summer Camp for Hemophiliac Children in Serbia: Contribution to the Improvement of Hemophilia Care
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Introduction: Hemophiliac children and their families need education about the nature of the disease and treatment possibilities. Communication between the patients, physicians, and other medical staff is essential for optimal management.
Objective: To present our experience, activities, and results achieved over the course of eight summer camps and our contribution to the improvement of hemophilia care in Serbia.
Methods: Analysis of questionnaires, physiatric check-ups, and monitoring of children following the camp.
Results: Summer camps for hemophiliac children in Serbia have been organized once a year, as of 2004. Organizations involved include the Hemophilia Center, Blood Transfusion Institute of Serbia, Serbian Hemophiliacs Association, and pediatrician clinics from Belgrade, Novi Sad, and Nis. Camps have been attended by 57 school children (10–17 years) and 54 preschool children (2–6 years). Preschool children were accompanied by their mothers. Professional staff consisted of 7 members including medical doctors, the social worker, and other healthcare workers. Educational sessions about the nature of the disease, home treatment and self-injection of concentrate, physiatric check-ups, exercises and swimming, dental check-ups, psychological programs (group and individual sessions, questionnaires), and free activities (excursions, social games, painting) all took place. Camp participants were trained on home treatment and self-administration of concentrate, physical therapy and swimming, and dental care. Based on the questionnaire, the camp activities have increased the general knowledge of the disease and of the importance of excercise and swimming. Both children and parents were acquainted with the advantages of home treatment. Fifteen children and seven mothers were trained for the self-administration of concentrate.
Conclusion: Considering obtained results and the positive experiences of both the camp participants and professional staff, we shall continue to organize the camps in order to give every child with hemophilia the opportunity to participate in the camp activities at least once.

PO-WE-274
Understanding Health and Treatment Decision-Making among Youth with Hemophilia: A Qualitative Approach
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General Objective: To explore attitudes about health and living with hemophilia and to develop a conceptual understanding of treatment decision-making from the perspectives of young men (15–29 years) living with severe hemophilia A or B, recruited from three hemophilia treatment centres (HTCs) in Canada.
Specific Objectives: To understand the lived experience of hemophilia from a youth perspective; identify factors that affect young people's hemophilia management/treatment decisions and explore inter-relationships between factors; develop a conceptual model of treatment decision-making to assist healthcare providers with communication strategies to ensure optimal, individualized client care.
Methods: This qualitative study employed grounded-theory methodology using one-on-one interviews (n = 15). Data analysis was performed concurrently with data collection throughout this project. Emergent themes were identified collaboratively by the study team. Further analysis will use the constant comparative method (Strauss & Corbin 1998) to compare/contrast themes across interviews and develop theory pertaining to the study objectives that is grounded in the data. As the theory evolves, a literature review will be conducted to assist in the development of a conceptual model of the treatment decision-making process.
Contributions to Practice: The first generation of young people with hemophilia to have grown up using primary prophylaxis is transitioning from childhood to adolescence/early adulthood. A number of unanswered questions pertaining to primary prophylaxis persist: Can it be stopped and at what age? (Hay 2007; Richards et al. 2007; Van et al. 2005; Astermark 2003); Can and should doses be individualized? (WHO/WFH/ISTH 2002); What are the effects of stopping prophylaxis? (Fischer 2008; Su et al. 2007); and Why do some individuals discontinue or poorly comply with prophylaxis? By gaining an understanding of the lived experience of hemophilia from the perspective of young men, this study will shed light on these and other questions in this area.

PO-WE-275
Participation of Children in National Hemophilia Conferences
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The Irish Haemophilia Society provides support and education to members through three conferences each year. In 1998 the IHS introduced a children's program to allow parents to attend the sessions at the conferences. The program then developed as an opportunity to educate the children and assist them in developing a positive and proactive approach to living with their bleeding disorder. Starting with just 4 children, the program has now developed into four groups with an average of 52 children attending each conference. Each conference takes place over two days, during which the children participate in team-building exercises, workshops, and peer discussions. The children are divided into groups according to age as follows: 0–3 years, 4–8 years, 9–12 years, and 13–17 years. Specific programs are designed for each group to provide age appropriate information on their bleeding disorder delivered in an enjoyable format. This has included self-infusion workshops, puppet shows, movie-animation workshops, and podcasts. The activities are designed to encourage children to learn, build friendships, and get involved with the Society and the community. Many of the volunteer leaders have strong connections with hemophilia, and several have participated in and benefitted from the programs in the past. This involvement has allowed the society to create a mentoring program to help children adopt a positive attitude towards their bleeding disorder. With regular evaluations of all the programs, the content is consistently informative and appealing to the target groups.

PO-WE-276
Transition Questionnaire: From Pediatric to Adult Hemophilia Care
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For adolescents with hemophilia there are certain aspects which need focus. Studies have shown that compliance in adolescents with chronic disease is not always complete. It may be difficult to avoid the compliance problems of puberty in otherwise healthy boys with hemophilia, since psychological regression is a part of normal development. The importance of understanding this and yet encouraging our patients is an art. The importance of physical fitness cannot be stressed enough. Physical activity maintains normal body weight, which leads to a higher level of self-esteem, positive body image, and social adaption. The physical benefits of physical fitness are well known: muscle strength is optimized thus giving better support for joints, which leads to less spontaneous joint bleeds. We need to address these facts regularly and encourage our patients to keep as fit as possible. Physical fitness also broadens the choice of sport. To optimize care, the nurses at the adult department have introduced a transition questionnaire. The questionnaire has been in use since autumn 2010. We hope to gather valuable information regarding this group's self-esteem, level of physical activity, sports participation, eventual relationships/sexual issues as well as compliance. We plan to evaluate the results within 2 years.

PO-WE-277
A feasibility study of "managing hemophilia online": An Internet-based self-management and transitional care program for teens
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Adolescents with hemophilia (AWH) have heightened educational needs as they learn to manage their disease and become self-sufficient in preparation for transition to adult health care. There are no published reports of self-management programs for AWH. For

this reason, we have developed an innovative, interactive, Internet-based psycho-educational intervention to prepare AWH for transition to adult healthcare services. The site content and format is based on an in-depth needs assessment that included review of the literature, systematic website review, patient survey, and qualitative interviews with teens. Website usability was formally assessed in three iterative cycles, and changes were made to refine the prototype. Currently, a pilot randomized controlled study is underway to assess the feasibility of the online psycho-educational intervention (NCT01477437). In the feasibility study, participants (n = 50) from three tertiary care centres are being randomized to either the online self-management intervention or an attention control group. Feasibility will be assessed based on i) accrual and attrition rates, ii) compliance, iii) willingness to be randomized, and iv) satisfaction with the program. Choosing the correct outcome measures for the proposed RCT is a challenge, as few relevant adolescent-specific measures exist. The proposed primary outcome measure will be disease-specific knowledge gained. Secondary outcome measures will include i) quality of life (CHO-KLAT 2.0, Canadian Hemophilia Outcomes-Kids' Life Assessment Tool), ii) self-efficacy (Generalized Self-Efficacy-Sherer Scale), iii) self-management and transition readiness (Self-Management Skills Assessment Guide), and iv) program impact (HEI-Q-Health Information Impact Questionnaire). Estimates of treatment effects from the pilot data will determine the appropriate sample size for the prospective definitive randomized control trial.