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Course

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BLOOD AND BLOOD TRANSFUSION
Papers and abstracts

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INTENSIVE CARE, EMERGENCY MEDICINE,

BLOOD AND BLOOD TRANSFUSION

CONTENT

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WATER – ELECTROLYTE BALANCE

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ABSTRACT

Purpose of review

Maintenance of the balance between water and electrolyte composition of the body in a healthy people requires specific determinant homeostatic mechanisms.

Water constitutes 60% of the lean body mass and it is positioned in intracellular fluid (ICF) and extracellular fluid (ECF). The fluid inside blood cells and blood plasma is ECF. A constant osmotic equilibrium is maintained between the ICF and ECF, but their electrolyte composition differs. ECF contains sodium cations, while the ICF contains potassium cations stored in the muscles.

Water electrolytes balance is very important for general functioning of the body. Electrolytic abnormalities are caused by many factors and they may causewide variety of disorders.

Elaboration of Recent Findings

2% loss of the body mass, especially dehydration, could dysfunction water – electrolyte's balance. Only 0.5%-0.7% loss of the body mass could start balance disturbances. It is still unclear whether the response to small reductions in body mass reflects effectiveness of homeostatic mechanisms.

There are many reasons for electrolytes misbalance in the body, as well as genetic one. Scientists are investigating the genes responsible for hyper or hypo concentrations of the specific electrolytes. Hypomagnesaemia is associated to the disorders in magnesio-tropic proteins. Claudins 16 and 19 are the genes necessary for magnesium transport. Genetic hypomagnesaemia is caused by insufficient transport of magnesium in distal convoluted tubule. Muted magnesio-tropic protein is the main cause for magnesium loss, while the compensation in downstream tubule is impossible.

Summary

The water electrolyte balance in the body depends on the levels of electrolytes and the amount of water and their changes. Sodium, potassium, calcium, chloride, phosphate and magnesium are the electrolytes that play big role in water electrolyte balance in the body. We can measure the concentration of the ions in the laboratory, using ion selective electrodes technology.

The water – electrolytes balance depends on the amount of water that people take on daily bases and the amount of the daily lost excretions. Dehydration and over hydration are the margins of this balance.

Key Words: *balance, electrolyte, water*

INTRODUCTION

Water is the main constituent of the body which importance is as “milieu” responsible for the nutrients’ exchange. Maintenance of the balance between water and electrolyte composition of the body in healthy people requires specific determinant homeostatic mechanisms.

Water electrolytes balance is especially important for general functioning of the body. Electrolytic abnormalities are caused by many factors and they may cause wide variety of disorders.

Maintenance of water balance and electrolytes balance in the body depends on nephrons. Nephrons increase water excretion by diluting the urine and water conservation by concentrating the urine. They play the most important role for water and electrolyte balance in the body.

WaterRegulation

Individual amount of water in the body depends on the age, gender and the percentage of fat depot. It varies from 50 – 65% in adults, and from 70-90% in the newborns and infants. Water constitutes 60% of the lean body mass and it is positioned in intracellular fluid (ICF) and extracellular fluid (ECF). The fluid inside blood cells and blood plasma is ECF. A constant osmotic equilibrium is maintained between the ICF and ECF, but their electrolyte composition differs. ECF contains sodium cations, while the ICF contains potassium cations stored in the muscles. ECF are found in three compartments: in the vessels (intravasal water), in the interstitium (interstitial water) and transcellular water (water in the body’s cavities).

There are two control mechanisms of body water regulation. The first controlled mechanism of body water is antidiuretic hormone secretion, and the second regulation is the thirst.

Osmotic sensors induce the secretion of the antidiuretic hormone **(vasopressin)**. The mechanism of vasopressin is well known in the control of water permeability. Vasopressin’s secretion increases the permeability of the distal tubule, increasing the water reabsorption from the renal filtrate. The **perception of thirst** always motivates water intake in the body.

Disorders of vasopressin secretion result in disturbances of body fluids tonicity. Clinical manifestation is reduced plasma sodium concentration, in fact hyponatremia.

The water electrolytes balance depends on the amount of water that people take on daily bases and the amount of the daily lost excretions. Dehydration and over hydration are the margins of this balance. Medicines’ intake, vomiting, diarrhea, sweating, salivation, liver, or kidney disorders influence the water electrolyte balance in the body (1).

Water can be lost in insensible way, from the respiratory tract, as well as from gastrointestinal and in the urine tract. Water loss in the urine is regulated by antidiuretic hormone vasopressin.

The literature data showed that the loss of 2% of the body mass due to dehydration could disturb the function of water electrolytes balance. Some of them report that a loss of only 0.5%-0.7% of the body mass could start balance disturbances. It is still unclear whether the small reductions in body mass could reflects big disturbances in homeostatic mechanisms.

There is an observational study about participants exposed to a temperature of 30°C for three hours. Mood and cognition of the participants were monitored. The study indicates that dehydration starts with a loss of 0.66% of the body mass. (2)

Extracellular fluid osmolality is monitored by neurons in the hypothalamus that react on an increased osmolality. Increased osmolality drives increased water intake and stimulates vasopressin secretion from the posterior pituitary. Vasopressin secretion is extremely sensitiveto small changes in osmolality of the extracellular fluid.3-to 5-mosmol/kg H_2O increase in osmolality increase plasma vasopressin secretion to a level that produces maximal urinary concentration. Blood pressure and blood volume decreasing stimulates vasopressin secretion, too. Thermoregulation mechanism in the body is in alert status, to prevent hypothermia, caused by increased temperature in the body. Molecular mechanism involve integration between thermal and osmotic regulation of thirst, and vasopressin secretion, as well as high activity of the thermal and sensitive transient receptor potential vanilloid family of ion channels (TRPV).

Transient receptor potential vanilloid channels are integral membrane proteins. The TRPV superfamily of ion channels consists of 28 cation permeable channels, grouped into six subfamilies, based on sequence homology. (3)

ELECTROLYTES

Sodium, potassium, calcium, chloride, phosphate and magnesium are the electrolytes that play great role in water electrolyte balance.

The amount of the dissolved electrolytes in the body in plasma are responsible for Osmolality, osmolar pressure, the tonicity and the colloid osmolar pressure.

Osmolarity is defined as the number of particles per liter of fluid. Physiologic blood plasma osmolarity is approximately 286mOsmoles/L. Less than this is hypoosmotic, and greater is hyperosmotic.

Osmolarity is partially composed of proteins such as albumin in the serum. Another important osmotically active component to consider is glucose. Fluid will move towards hyperosmotic compartments and away from hypoosmotic compartments.

Osmolarity and osmolality are frequently confused and incorrectly interchanged. Osmolarity refers to the number of solute particles per 1 l of solvent, whereas osmolality is the number of solute particles in 1 kg of solvent. For dilute solutions, the difference between osmolarity and osmolality is insignificant.

Sodium

Normal range of blood sodium level is between 135 – 145 mEq/l.

Sodium disorders (hypo or hypernatremia) are common electrolyte disturbances in clinical medicine and practice. They are associated to increased rates of morbidity and mortality in intensive care unit.

Etiologies of **hyponatremia** are classified into four categories. The first is pseudohyponatremia, in which the sodium level is low due to hyperproteinemia, hyperlipidemia, or hyperglycemia. The other three categories include:

hypovolemic (fluid loss),

hypervolemic (fluid retention from heart failure, cirrhosis, or renal failure), and

euvolemic (inappropriate secretion of antidiuretic hormone).

Hypovolemic hyponatremia is managed by rehydration with isotonic saline. Hypervolemic hyponatremia is managed by addressing the underlying cause. Euvolemic hyponatremia is managed by restricting free water intake, addressing the underlying cause, and vasopressin receptor antagonists.

Patients with severe or acutely symptomatic hyponatremia have altered mental status or seizures and require urgent treatment. Patients with acute symptomatic exercise-induced hyponatremia, require urgent treatment – hypertonic saline administration with monitoring of sodium levels to avoid over rapid correction.

Hypernatremia occurs because of water loss or inadequate water intake. Management includes oral or intravenous hypotonic fluids (4).

Potassium

The normal plasma potassium level varies within a range of 3.5 – 5.0 mEq/L, although 2% of the total body potassium can be found in the extracellular fluid. Potassium homeostasis includes distribution of potassium between intra and extracellular fluids.

The control of the movement of potassium from intra to extracellular fluids is one of the ways to maintain body's potassium balance. For example, when potassium is lost through the renal system, the body pushes out cellular potassium into extracellular fluid in order to prevent the drop in plasma potassium level. Potassium intake, renal excretion and loss through the gastrointestinal tract plays important role in potassium homeostasis (5).

Potassium homeostasis is influenced by the activities of the sodium-potassium pump (Na-K-ATPase). The transport of sodium and potassium ions across the cell membrane depends on the activity of these enzymes, not on their concentration gradients.

The K+ balance in the body is very important, too. So, the body has developed numerous mechanisms to keep it in normal range. All the mechanisms involved are not well understood. For instance, **hypokalemia** can be treated by: reducing potassium losses, replenishing the potassium stores with oral or parenteral potassium chloride administration, evaluating toxicities and treating of diseases that lead to hypokalemia.

Hyperkalemia can be treated by balancing the body's potassium level. The point is to reduce the level of potassium in the blood, depending on the physiologic condition of the patient. Main goal of the treatment is to increase the reuptake of the potassium from the plasma into the cells (insulin with hypertonic glucose or 10% CaCl). Dialysis is the definitive treatment of

hyperkalemia. Intravenous calcium can be used for myocardium stabilization. Enzymes that are involved in the oxidative stress also affect potassium activities, like hem oxygenase-1. Understanding the interplay between potassium imbalance and oxidative stress will give more insight into the pathophysiology of many human diseases.

Calcium

The Ca++ balance in the body is also very important. Serum calcium concentrations are controlled within a range of 2-2.7 mmol/l. Only ionized calcium (40%) is physiologically active. 45% of the calcium is bound to albumin and 15% of the calcium is compound with the anions in citrate, bicarbonate, and phosphate forms. There is a relative increase in the ionized calcium component of the total serum calcium in acidosis. The calcium balance varies with the age. Children and young adults are usually in a slightly positive net calcium balance because of their growth. Beyond 25 – 35 years of age, when bones stop growing, the calcium balance tends to be neutral. Adults are in lite calcium negative balance (6).

Serum levels of ionized calcium are maintained in the normal range by the secretion of parathyroid hormone and by the calcitriol that is activeform of vitamin D. The mechanism of protection against calcium overload is the ability to increase renal excretion of calcium and reduce intestinal absorption of calcium. Patients with chronic kidney disease and patients with intestinal mall absorption, have no ability to maintain normal serum ionized calcium level. Generally, 15 – 25% of ingested calcium is absorbed.

There are two pathways of calcium intestine absorption: vitamin D dependent, and vitamin D independent pathway. Vitamin D independent mechanism prevails. Vitamin D dependent pathways are critical in calcium deficient states. If the ionized calcium level start to decrease, parathyroid hormone will increase bone restoration of the calcium into the circulation. Parathyroid hormone has an indirect effect to the kidneys. It increases the production of calcitriol by the kidney, which will increase the Trans cellular gastrointestinal absorption of calcium.

- There are 7 reasons for **hypocalcemia:**
- Decreased ionized serum calcium concentration,
- Decreased albumin corrected serum calcium concentration,
- Decreased gastrointestinal absorption or inability to mobilize calcium from bone,
- Massive tissue death (rhabdomyolysis) in trauma patients, lysis of a tumor'stissue, or severe pancreatitis,
- Excessive oral phosphate ingestion, phosphate toxins, or chronic kidney disease,
- Excessive deposition of calcium in bone inosteoblastic metastasis, in patients with prostate cancer, and
- Sepsis.

Phosphates

In the body of an adult, 500-800 g of phosphorus is found, arranged as 1% in lean tissue, 88% in skeleton and the rest in the cells. Plasma phosphorus exists in two forms, organic and inorganic, including phospholipids, ester phosphates, and inorganic phosphates. Inorganic phosphates are completely ionized, circulating primarily as HPO_4^{2-} or H_2PO_4 in a ratio of 4:1, at a plasma pH of 7.40.

Phosphate comes from food, grains, meats and food supplements (1g/day). Absorption takes place at a distal site of duodenum. There are two paths of absorption: calcium dependent and calcium independent. The most important is postprandial passive absorption of the phosphates.

In a cells 60-80% of phosphorus is absorbed by a diffusional process. Calciotropic hormone (vitamin D) has direct effect on its absorption, the active metabolites increases phosphorus absorption. Parathormone has minor effect on phosphorus absorption.

Renal phosphate reabsorption controls the serum concentration of phosphate. Renal phosphate threshold can be measured, but in the routine practice it is calculated by measurements of serum and urinary phosphorus and creatinine. The proximal tubule reabsorbs about 75% of filtered phosphate. The distal tubule segments reabsorbed only 5% of filtered urine.

Chloride

Chloride (96 – 106mEq/l) is the most abundant anion in the extracellular fluid. It is responsible for osmotic pressure and acid-base balance in the body. Cl ion is an oxidizing agent. Chloride is required for the production of gastric hydrochloric acid secreted from the parietal cells of the gastric mucosa in gastrointestinal tract. Mucosa also releases pepsinogen, which is activated by hydrochloric acid. Pepsinogen is the intrinsic factor needed for vitamin B_{12} absorption. Mucus protects the organ from being digested by the hydrochloric acid and proteases. Hydrochloric acid has bactericide effect in gastrointestinal tract (7).

Chloride acts as the exchange anion in the red blood cell for $HCO_{3,}$ (known as the chloride shift), allowing the transfer of CO_2 derived from the tissues back to the lungs (Groff and Gropper, 2000) (8).

Disturbances in chloride balance (dyschloremia) could be hypo and hyperchloremia. They are responsible for increased mortality in critically ill patients. Hyperchloremia produces hyperchloremic metabolic acidosis, increased hemodynamic instability. Hyperchloremia increases incidence of acute kidney injury.

The three main reasons for **hypochloremia** in critically ill patients are: active Cl loss through the gastrointestinal tract (vomiting, diarrhea), inadequate renal Cl reabsorption or dilution following infusion of hypotonic fluids. The additional reasons for hypochloremia are increased bicarbonate reabsorption in kidneys, chronic respiratory acidosis or hyperaldosteronism, high-volume bicarbonate infusion and excessive use of diuretics (furosemide).

Reasons for **hyperchloremia** are: bicarbonate loss through the gastrointestinal or renal tract (diarrhea), bicarbonate loss through the renal tract in renal tubular acidosis, a dilution due to volume loading with fluids with a low bicarbonate concentration, or high infusion of chloride-rich fluids. Plasma dilution may decrease bicarbonate levels, leading to increased Cl levels and acidosis.

Hypo and hyper chloremia affect renal, cardiovascular function, coagulation and have a major impact on clinical outcomes in critically ill patients (9).

Magnesium

Magnesium (1.5-2.5mEq/L) plays an important role in water electrolyte balance in the body. Magnesium introduced with vegetables is absorbed in the intestinal tract. Factors that improve its absorption include vitamin D, parathormone, growth hormone, thyroid hormones and the presence of sodium in the diet. Calcium, fats, phosphates and phytogenic acid can decrease intestinal absorption.

Magnesium absorption is dependent on two concomitant pathways in the small intestine and the kidneys: passive transport via claudins (Claudins 16 and 19 form), and active transport via the fine-tuning of magnesium absorption. The genes responsible for diseases associated to **hypomagnesaemia** produce mutation in magnesiotropic proteins (genetic hypomagnesaemia). The reason for insufficient magnesium transport in the distal tubule is mutated magnesiotropic protein. Magnesium loss cannot be compensated in downstream tubule segments (10).

Small changes in magnesium values are not clinically relevant. Clinically relevant values are between 0.5 mmol/L (1.0 mg/L) and 2.0 mmol/L (4.9mg/dL). Hypomagnesaemia is very frequent state, although the symptomatology (cramps, muscle spasms, paresthesia and arrhythmias) is very rare.

Calcium and magnesium are very important for neuromuscular functions, as well as for electrical activity of the myocardium and vascular tone. Magnesium is used in the treatment of ventricular arrhythmia associated to torsade de pointes. Intravenous or intramuscular magnesium sulfate is recommended for the prevention and the treatment of eclampsia.

On the other hand, **hypermagnesemia** (hypotension, nausea and vomiting) is a rare, but serious electrolytic disorder that can be fatal (11).

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MANAGEMENT OF ACUTE RENAL FAILURE

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ABSTRACT

In multiple clinical settings, Acute Kidney Injury (AKI) is a frequent condition. AKI increases the short and long-term mortality rate. Although the condition has become more widely recognized, yet there is still lack of definitions and increased number of studies has appeared examining AKI across many different clinical settings. Detailed medical history and physical examination are the key in determining the etiology of AKI and timeline of the progress. The fundamental principles in management of AKI are to treat the underlying cause, optimizing fluid balance and hemodynamics, correct electrolytes and eliminate or adjust the dose of nephrotoxic drugs. Therefore, optimizing hemodynamics and correction of volume depletion will minimize continuation of kidney injury and will improve recovery, preventing any chronic impairment of the kidney. However, there are no guidelines for improving hemodynamics and optimizing volume status for kidney protection. International guidelines for management of sepsis and septic shock recommend a goal-directed therapy (GDT). Acute Dialysis Quality Initiative has proposed a new fluid resuscitation strategy consisting of four phases: rescue, optimization, stabilization and de-escalation phases. Liberal fluid administration is allowed in the rescue phase; in the optimization phase, where the patient is hemodynamically stable, percutaneous fluid management is required with the aim to maintain hemodynamic stability; in the stabilization phase, when the patient is stable, equal or negative fluid balance is preferred; and in last de-escalation phase, all excessive fluid should be removed.

Key Words: *acute kidney injury, acute kidney injury management, acute renal failure.*

Introduction

Acute renal failure (ARF) or acute kidney injury (AKI) called nowadays, is a frequent condition in multiple clinical settings. AKI increases the short and long-term mortality rate. Although the condition has become more widely recognized, yet there is still lack of definitions and increased number of studies has appeared examining AKI across many different clinical settings.

AKI, presents sudden and frequently reversible reduction in the kidney function, when measured by glomerular filtration rate (GFR). AKI has 40-50% in-hospital mortality and more than 50% mortality in ICU (1).

The aim of this review was to fulfill the assignment for an academic course. In this article, we evaluated and updated the current practices for management of acute renal failure.

Methods

The primary literature search established heterogeneity and it did not allow qualitative systematic review or qualitative studies along the lines as proposed by Dixon (2). The method for theoretical qualitative meta-synthesis proposed by Sandelowski was not applicable as well (3). Due to the above mentioned reasons, a narrative review was undertaken.

All information used to write this paper were identified by key words searches of Medline, IBSS databases, Pubmed, CINAHL. Key words searched included “acute kidney injury”, “acute kidney injury management”, “acute renal failure”. Reference lists of primary articles found from initial search were also conducted. Personal and college libraries were searched for texts on researched subject.

Discussion

There is no definition of AKI; however, there are standard criteria used in clinical settings and in clinical trials. Among KDIGO (Kidney Disease: Improving Global Outcomes), RIFLE and AKIN (Acute Kidney Injury Network) criteria, KDIGO is currently the most frequently used one. KDIGO criteria include the presence of any of the following: Increase in serum creatinine level within 48 hours by 0.3 mg/dL (26.5micromoles/L) or more, Increase in baseline serum creatinine level for 1.5 times within a seven-days-period, Drop in urine output (UO) less than 0.5 ml/kg/h for at least 6 hours, Decrease in estimated GFR to <35mL/min/1.73 m^2 in patients <18 years of age (4).

Each patient with AKI should be initially assessed for: contributing reasons of the kidney injury, comorbidities, fluid status, therapeutic measures for prevention or reversion of kidney function worsening (5).

Pathophysiologically AKI is divided in three categories: pre-renal, renal and post-renal. Thus, the initial assessment of patients with AKI should differentiate the category of the injury (5, 6). Reduction in renal blood flow is the pathologic pathway of decreased GFR in any category of AKI. In pre-renal form, hypoperfusion is due to hypovolemia, hypotension or selective renal

vessels causes (stenosis, dissection). Intrinsic renal causes that affect tubule or glomeruli are the underlying mechanism for renal AKI. Pre-renal can be converted to renal if hypoperfusion is prolonged enough to cause renal cell damage. Post-renal AKI is mainly evoked by obstructive causes in bladder outlet. Unilateral obstruction may not lead to AKI due to normal working contralateral kidney, particularly if the obstruction is gradual as in the case of an existing tumor (7).

AKI pathogenesis is etiology driven. Endpoint in AKI is acute tubular cell necrosis that can be primarily due to direct toxin, or secondary due to ischemia. However, glomerulonephritis has other mechanism of injury; usually it is direct immune-mediated injury or immune complex deposition in the vessels. Detailed medical history and physical examination are key in determining the etiology of AKI and timeline of the progress (5.6).

The history of the urine output can be an indicator of AKI. For example: oliguria commonly indicates AKI, successive decrease in UO is seen in bladder outlet obstruction or due to urethral stricture, sudden anuria is usually due to acute vascular damage, glomerulonephritis or urinary tract obstruction (7). Performing detailed clinical examination including skin, eyes, ears and cardiovascular system may lead to a clue regarding the underlying cause of AKI.

Except of post-renal AKI, every cause of pre-renal and renal are overlapped. Pre-renal (hypoperfusion) and renal AKI usually coexist at the same time. We do not have a clinically valuable method for measuring renal blood flow (7). Recently, in clinical practice appeared certain methods for calculating the fluid balance such as calculating bioimpedance and ultrasound flow assessment through vena cava and left ventricular dimension (8). Every patient should be assessed individually for rehydration (9). The best way to determine the volume status is with fluid challenge. How much fluid we should give, remains an element of debate? (10) In addition, the choice of the safest fluid is the other addressed question. The safest way to provoke volume uptake and not to be afraid of the consequences of fluid overload is the leg rising test (LRT). LRT can add fluid in the vascular space reversibly without being afraid of the volume overload consequences (11). Studies show no favor among saline, albumen or balanced crystalloid solution treated patients, resulting in a similar mortality rate (9, 12, 13). On the contrary, synthetic colloids increase the risk of AKI (14). Currently, literature suggests treatment with balanced crystalloid of AKI patients in need of fluids (15). If UO is increased with the fluid challenge, is usually an indicator that AKI is pre-renal form. Additionally, clear differentiation should be made between volume responsive patient and volume responsive kidney. For example, a patent will have volume response with an increased cardiac output, but on the other hand, kidney is damaged and will not respond to fluid challenge. However, some patients with AKI may not respond to fluids, because there is loss in the third space leading to ineffectively restored vascular volume. Therefore, optimizing hemodynamics and correction of volume depletion will minimize continuation of kidney injury and will improve recovery, preventing any chronic impairment of the kidney (7). There are no guidelines for improving hemodynamics and optimizing volume status for kidney protection. However, international guidelines for management of sepsis and septic shock recommend a goal-directed therapy (GDT) with measurement of

central venous pressure, mixed central venous oxygen saturation, mean arterial pressure and UO (16). Maintenance of hemoglobin above 9 g/dL is recommended. One conclusion we can draw from this is that liberal fluid resuscitation as part of early GDT seems to be favorable in the first 6 hours. Hence, volume responsive AKI is for patients who improve UO with volume administration (17). Acute Dialysis Quality Initiative has proposed a new fluid resuscitation strategy of four phases: rescue, optimization, stabilization and de-escalation phases (18). Liberal fluid administration is allowed in the rescue phase; in the optimization phase, where the patient is hemodynamically stable, percutaneous fluid management is required with the aim to maintain hemodynamic stability; in the stabilization phase, when the patient is stable, equal or negative fluid balance is preferred; and in the last de-escalation phase, all excessive fluid should be removed (18).

Renal recovery from acute tubular necrosis lasts for very long period and sometimes it takes months for full recovery of renal function, but sometimes it may not recover completely. A very important step is to avoid usage of any nephrotoxic drugs, such as non-steroidal anti-inflammatory drugs, aminoglycoside antibiotics, angiotensin-converting enzyme, radiographic contrast agents. Another important step is renal drug dose adjustment (6, 7). In addition, an important measure is to limit the intake of potassium and phosphorus. Increased potassium has fatal consequences in AKI patients. Increased potassium is managed with the following approaches: diet restriction, dextrose iv with insulin, potassium binding resins (calcium and sodium), polystyrene sulfonates and calcium gluconate for stabilizing cardiac membrane and dialysis (1, 5, 6).

Dopamine at a renal dose (0.5 – 3 mcg/kg/min) for vasodilatation and increasing renal blood flow can increase UO, but it cannot change the mortality rate or improve AKI outcome (15, 19). Studies show that norepinephrine and vasopressin are preferred vasoactive drugs that increased blood pressure and improved renal perfusion in patients with AKI (20-22). Furthermore, inotropic drug levosimendan is a calcium sensitizer that causes vasodilatation and improves right ventricular function decreasing renal stasis. On the other hand, it dilates preglomerular arterioles increasing renal perfusion (23-25).

Dialysis is necessary for managing the complication of AKI, especially in patients prone to develop acid – base and electrolytes abnormalities such as increased potassium, uremic pericarditis and pulmonary edema. Some patients need diuretics in the oliguria phase for preventing fluid overload with pulmonary and cardiac complications. Furosemide acts in tubules with blocking of oxygen consuming sodium channels, and increases toxins washout with increased diuresis correcting fluid overload in AKI patients (26). Nevertheless, clinical studies failed to demonstrate that furosemide improves prognosis of AKI (27). Currently, medical evidence does not recommend the use of sodium bicarbonates for prevention and treatment of AKI (28, 29). The results for preventive effects of statins in AKI are controversial; hence, we cannot recommend the use of statins in AKI (30-34).

Many patients with AKI have benefit from continuous renal replacement therapy or continuous veno-venous hemofiltration (CVVH). It gives time for renal recovery (35). CVVH is very

effective continuous form of dialysis in hemodynamically unstable patients, but it is time limited measure for days or weeks. Due to the fact that patients with AKI sometimes need months to recover, therefore dialysis is required for support. At present, there is no ideal recommended time for initiation of CVVH in the literature (15).

Some specific form of AKI requires special treatment. For example, hepatorenal and cardio-renal syndrome need to be supported with vasoactive support and colloids with careful UO monitoring (5, 7). Some forms of glomerulonephritis require immunosuppressive therapy and sometimes plasma exchange. Plasma exchange is beneficial in hemolytic uremic syndrome as well. Patients with acute interstitial nephritis may recover instantly by using steroids. Surgical treatment is required in post-renal forms of AKI, such as prostatic hyperplasia, urethral calculi and nephrostomy for renal obstruction (6).

Many clinical trials on different drugs are trying to prove their efficacy in the treatment of AKI. Calcium channel blockers are shown to have natriuretic effect with vasodilatation on afferent arteriole (12). In a multicenter randomized controlled trial isradipine did not show benefits, and delayed graft rejection was found (36). Different effects are shown in trials of theophylline (phosphodiesterase inhibiting drug) for prevention of contrast nephropathy (37).

Prognostic factors for increased mortality in AKI patients are elderly, fluid balance, use of diuretics, the duration of illness, hypotension, inotropic support, oliguria, multiorgan failure (MOF), sepsis and poly-transfusion (6).

Commonly used biomarkers like plasma creatinine, serum and urine urea nitrogen, urine electrolytes and ultrasound, may not differentiate between patients without and with tubular injuries regardless of volume responsive AKI. Identification of such specific biomarkers of tubular injury may have important role in the therapeutic approach in AKI. Unnecessary therapy will be avoided in volume responsive patients, and on the other hand, specific pharmacological therapy can be initiated early in the volume unresponsive patients (1, 6).

In conclusion: Currently there is no definitive treatment; supportive care is the mainstay of management regardless of the etiology. In the management of AKI, the fundamentals are to treat the underlying cause, optimizing fluid balance and hemodynamics, correct electrolytes and eliminate or adjust the dose of nephrotoxic drugs.

Conflicts of Interest: None

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NUTRITIONAL THERAPY IN THE INTENSIVE CARE UNIT

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ABSTRACT

Meeting appropriate nutritional demands is a fundamental aspect of optimal patients' care. Optimizing nutrition delivery and preventing malnutrition can have a significant positive effect on clinical outcomes and costs of the care. Providing nutrition in critically ill patients has long been challenging issue, due to the difficulties in determining the nutrition requirements of the patients with heterogeneous characteristics, and selecting the timing and the route of administration. Different guidelines have been created by the experts in order to help clinicians to choose the appropriate nutritional therapy. Unfortunately these guidelines and recommendations sometimes are changed over the time according to the knowledge from the latest studies. This review aims to provide a comprehensive synthesis and interpretation of the so far known literature for nutritional therapy in ICU in order to assist clinicians in making practical decisions regarding nutrition management during the different stages of critical illness. As a conclusion from the literature, indirect calorimetry is the preferred method for assessing resting energy expenditure and the appropriate caloric and protein intake to counter energy and muscle loss. Enteral nutrition (EN) is recommended as a preferred route for early nutrition therapy in critically ill patients over parenteral nutrition (PN). Both European and American guidelines recommend hypocaloric nutrition in the first 48 hours, at 70 – 80% of calculated caloric needs in order to avoid overnutrition. From day three, the European guidelines recommend a more aggressive approach in which nutritional support can be increased to as much as 100% of the patient's requirements and supplemental parenteral nutrition can be provided if necessary.

Key Words: *artificial feeding, critically ill, enteral nutrition, guidelines, nutrition in ICU, nutrition support, parenteral nutrition.*

Introduction

To manage the nutritional requirements, it is fundamental in the optimal care for critically ill patients. Optimization of nutritional needs and prevention of malnutrition can have a positive effect on the clinical outcome in these patients. In recent years much interest has been paid to the role of nutrition therapy in critically ill patients, which resulted in an increased number of publications and updated international clinical guidelines in this area. However, the findings of the trials and conclusions of the international guidelines are conflicting: Enteral versus parenteral nutrition? When is the most adequate time to initiate nutrition therapy? Which is the optimal dose? Thus, their practical application is a challenge. The importance of the phase of the critical illness and individual characteristics of every patient is evident regarding nutritional interventions. The aim of this narrative review was to give summary and interpretation of literature related to nutrition of critically ill adults, and hence to help doctors to make practical, yet still evidence-based decisions concerning nutritional therapy during critical illness (1).

Material and Methods

In this review article, a comprehensive literature research was performed using PubMed and Google Scholar databases. The following key words or medical subject headings were used: "nutrition support", "artificial feeding", "enteral nutrition", "parenteral nutrition", "critically ill", "nutrition in ICU", "guidelines". The most relevant and recent literature, as well as current clinical guidelines were examined and summarized.

Definition

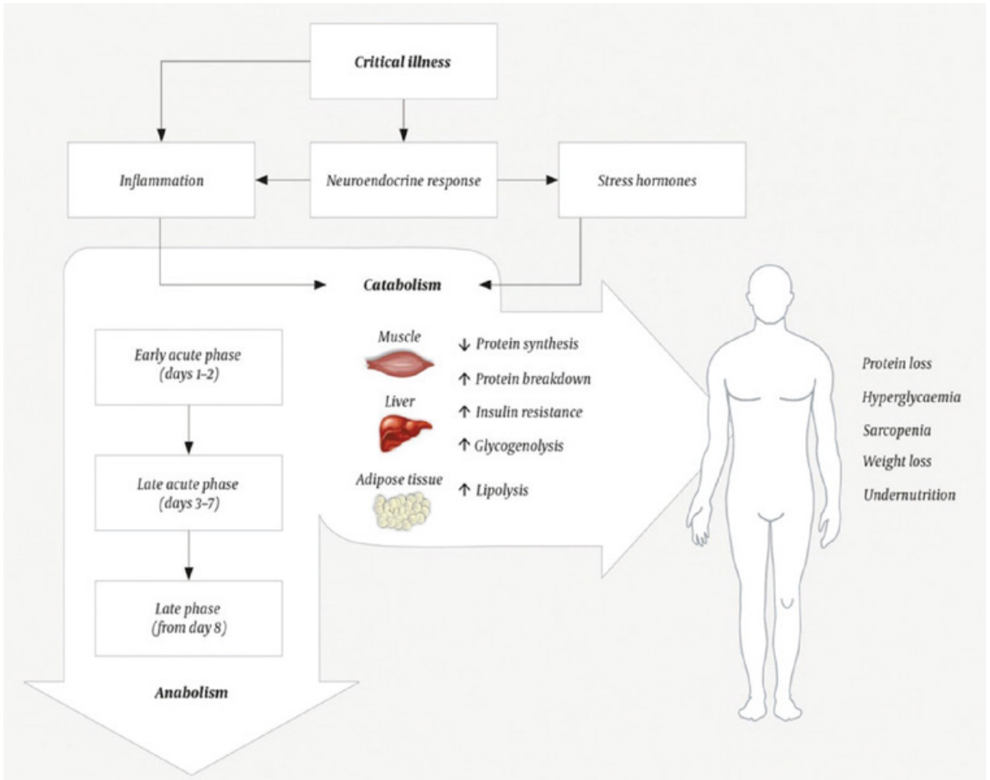
Nutrition, in technical terms, is defined as intake of nutrients, carbohydrates, fats, proteins, vitamins, electrolytes and water. Nutritional support is recognized as an essential therapy in maintenance of the body mass, immunological balance and reduction of metabolic disturbances. Undoubtedly, in medicine as in life, the phrase "One size does not fit all" or one medicine or dose is not to be given to every patient and at all times, raises the question why we would live under the illusion that we should give the same food or quantity of food at all times? (2).

Critical Breakdown of the Tissue: Shock /Catabolic State

Critical illness distinguishes itself with complex metabolic, hormonal and immunological changes. It is essential to understand the impact of these changes on nutrient metabolism in order to think about nutritional strategy (2, 3). In 1942, Cuthbertson described two different metabolic phases of acute illness – the 'ebb' or early shock phase followed by the 'flow' or catabolic phase (4). In brief, the 'ebb' phase is characterized by hemodynamic instability and hormonal changes (including insulin resistance). In this phase, delivery of nutrients to vital organs is a priority. This survival mechanism results in endogenous production of glucose, reduced energy expenditure compared to the level before the acute illness. The 'flow' phase occurs after the period

of hemodynamic stabilization and is characterized with an increased energy expenditure and catabolism. This phase also involves the breakdown of the tissue (including lean muscle tissue) in order to provide substrates to cover the immediate needs for the 'fight or flight' response. In this phase it is necessary to supplement the calories, especially proteins in order to avoid losing weight and minimizing the negative nitric balance (5). Recently, a third phase has been described, a phase where there is stress resolution by returning to anabolism and normal metabolic rate, and this phase has been named recovery. At this moment, there is no clinical marker that would signal when the patient shifts from one to another phase of the critical illness. According to the guidelines of ESPEN 2019, a new definition of the phases of the critical illness emerged: Acute Early Period – day 1-2, defined by metabolic instability and severe increase in catabolism (the ancient EBB phase), and Acute Late Period (ancient FLOW phase) – day 3-7, defined by a significant muscle wasting and a stabilization of the metabolic disturbances. The post-acute phase follows with improvement and rehabilitation or persistent inflammatory/ catabolic state and prolonged hospitalization (recovery phase) (6).

Figure 1. *Critical illness*



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Nutrition strategy

Having in mind the fact that the most dynamic phase is the acute one, the largest number of studies have examined different nutrition protocols in the acute critical illness. Traditionally, it was thought that aggressive nutrition strategy in the acute phase would result in a better clinical outcome. The results obtained in recent randomized controlled trials (RCTs) do not support the thesis about aggressive early nutrition; the explanation behind this may be in the fact that in this phase the energy needs are reduced and the endogenous production is preserved (5). Negative effects resulting from the aggressive nutrition in the early acute critical illness were shown in the EPaNIC multicenter trial. This trial showed shorter hospital stay, lower incidence of infectious complications, cholestasis and decreased duration of mechanical ventilation in the group with late initiation of parenteral nutrition and less aggressive nutrition in the early acute phase of critical illness (7).

Energy-dense versus routine enteral nutrition in the critically ill patients was studied by TARGET Investigators. They showed that the increased number of calories in the acute phase did not show a positive effect on survival, organic support, number of days spent in intensive care unit, as well as incidence of infectious complications. In general, the aggressive early calorie intake led to more often episodes of hyperglycemia and an increased need of insulin therapy (8). Other trials compared hypocaloric nutrition (low energy supply and adequate protein intake) and trophic nutrition (low energy supply and low protein intake) in the acute phase. They showed that hypocaloric nutrition has effect in preserving the intestinal epithelium, preserving immunologic function and limiting bacterial translocation, and it has no significant effect on mortality and morbidity of patients. This nutritional strategy has had a particularly positive effect in patients with acute respiratory distress syndrome (ARDS) and in patients with low risk of malnutrition (9).

Thus, the question is raised which energy target is to be reached in critically ill patients?

Energy Requirements

Determination of energy needs is one of the most significant challenges in critical illness. Overfeeding or underfeeding, as well as delayed achievement of energy target, are an accompanied phenomenon of critical illness (10). Both, underfeeding and overfeeding could be a cause of prolonged hospital stay, longer duration of mechanical ventilation, increased incidence of infections and mortality (11).

Energy requirements can be calculated in several ways, with empirical formulas, predictive equations or indirect calorimetry. If energy requirements are calculated with empiric formulas, NICE (National Institute for Health and Care Excellence) recommends nutrition support of 25 – 35 kcal kg−1 day−1 and ESPEN (European Society for Clinical Nutrition and Metabolism) recommends 20 – 25 kcal kg−1 day−1 in the initial phase of critical illness and 25 – 30 kcal kg−1 day−1 in the recovery/ anabolic phase. For determination of the energy requirements, there are more than 200 predictive equations that are based on age, gender, height, weight and severity of illness, but only few can be applied in critically ill patients. The most important of them are:

Harris-Benedict equation **(HBE)**, Ireton-Jones Energy Equations 2002 version **(IJEE)**, Schofield equation **(SE)**, Penn State University Equation 2003 a version **(PSU)** and Faisy Fagon Equation **(FE)**. These equations are burdened with many problems – accuracy varies significantly and it is due to heterogeneity of the pathology, stress factor, different body constitution and treatment. Studies have shown that the result of energy needs, calculated by the use of predictive equations, deviates from the real needs by 500 kcal or higher and that leads to overfeeding or underfeeding (12). Indirect calorimetry is a recommended method for precise determination of the energy expenditure by both ASPEN and ESPEN. The use of indirect calorimetry is limited due to the lack of equipment. Rest energy expenditure (REE) can be more easily calculated by the production of carbon dioxide (VCO2) using formula REE=8.2×VCO2. Although it is less accurate measurement than the indirect calorimetry, still it is more precise method than the use of predictive equations (13, 14). According to ESPEN, if indirect calorimetry is used for assessment of energy needs, isocaloric nutrition is progressively implemented after the first phase of acute illness. On the other hand, if predictive equations are used for the same assessment, hypocaloric nutrition is recommended. Both European and American guidelines recommend hypocaloric nutrition for the first 48 hours, at 70 – 80% of calculated caloric needs in order to avoid overnutrition. From day three, the European guidelines recommend more aggressive approach in which nutritional support can be increased to as much as 100% of the patient's requirements, and supplementary parenteral nutrition can be provided if necessary.

In general, when patients are admitted to the ICU, intensivists evaluate the nutritional risk. If patients have high nutritional risk, more than 80% of the energy target is administered within 48 – 72 hours of ICU admission. If patients have low nutritional risk, less than 18 kcal/kg/day might be an optimal calorie target ("defense" strategy). Then, after the patient's condition starts improving, the administered calorie dose might be increased ("offense" strategy).

Protein Needs

Critical illness is associated to proteolysis and muscle weakness that might reach up to 1 kg/daily. Recommendations for protein intake depend on the clinical condition of each patient. Weijs *et al*. showed that ICU patients with 1.2-1.5 g/kg/per day delivered protein, had reduced 28-days mortality. Nicolo showed an improvement in survival if patients received more than 80% of their protein target. In a retrospective study, Song *et al*. showed a significant improvement in ICU outcomes in ventilated critically ill patients receiving >90% of targeted protein intake. Patients with sarcopenia with a significant loss of muscle mass are at high risk of mortality, and high-protein nutrition can improve their outcome. The Nephro-Protect Trial showed that the administration of high doses of proteins improved the kidney function, without significant influence on the other clinical parameters (15, 16). According to the latest ESPEN 2019 recommendations, the best clinical results are achieved when protein components of 1.3 g/kg/ per day are given with progressive increase of the dose (6).

Carbohydrate Needs

During critical illness insulin resistance and hyperglycemia are common consequences of the stress response. In theory, carbohydrates can be excluded from the usage, but the functioning of the brain, erythrocytes, immunological cells, renal medulla and eye segments depend on carbohydrates supply. It is difficult to determine the exact optimal necessary quantity of carbohydrates. On one hand, there is a change in enteral delivery and change in intestinal absorption, but on the other hand, endogenous carbohydrate production is increased. Excessive glucose intake is associated to hyperglycemia, increased CO_2 production, emphasized lipogenesis, increased insulin needs, and changes in protein metabolism. According to recommendations, carbohydrate administration should not exceed 5 mg/kg/min (6).

Fat Needs

In critically ill patients absorption of fats is also impaired, and lipid metabolism is modified, along with the low level of triglycerides and high level of cholesterol in plasma (HDL). Excessive administration of fats might result in lipid overload, especially unsaturated lipids that can cause pulmonary function impairment and suppression of the immunologic system. According to the ESPEN guidelines intravenous lipid (including non-nutritional lipid sources) should not exceed 1.5 g lipids/kg/day and should be adapted to individual tolerance (6).

NICE guidelines also recommend inclusion of vitamins in every method of nutrition in critically ill patients. The substitution of thiamine and vitamin B is of special importance due to the possible pre-existing deficit, in order to avoid possible neurological complications. Electrolyte substitution is based on daily needs, clinical picture and serum values.

Nutrition can be peroral, enteral or parenteral. Although peroral nutrition, according to the generally accepted nutritional postulates, is the best type of nutrition, in ICU patients clinical nutrition mostly refers either to enteral or parenteral nutrition.

Enteral Nutrition

For a long period, the gastrointestinal tract has been considered to play a key role in the pathogenesis and progression of critical illness, thereby it was considered to be "a motor for systemic inflammation and organ dysfunction". Impairment in the homeostasis of the gastrointestinal tract epithelium can lead to an increased production of proinflammatory cytokines, dysfunction of gastrointestinal barrier and cellular apoptosis, which consequently lead to multiorgans' dysfunction. It is believed that short-term and long-term outcome in critical illness is ultimately dependent on a successful management of the nutritional support, especially if the enteral method is used. The key benefit of enteral nutrition is to maintain structural and functional integrity of the gastrointestinal tract, to attenuate the oxidative stress and inflammatory response and, on the other hand, to support humoral immune response, as well as to modulate the metabolism. Recent literature data confirm that even 20% of nutrition needs taken by enteral route are sufficient and

give positive results on gastrointestinal barrier. The current statistical data confirm application of enteral nutrition in 92% – 93% of patients in the modern intensive care units. It is indicated in patients with oral nutrition contraindication or inability to meet nutritional needs by oral nutrition, as well as in those with need for supportive nutrition due to reduced absorption (17). Patients who did not get oral nutrition for more than three days must be nutritionally supported by enteral nutrition (18).

Although enteral nutrition mostly includes naso gastric (NG), naso duodenal (ND) and naso jejunal (NJ) feeding, in some patients alternative feeding methods are performed where a tube is placed directly through the skin into the stomach or bowel, known as enterostomy feeding, which includes percutaneous endoscopic gastrostomy (PEG) and percutaneous endoscopic jejunostomy (PEJ). In cases of high-risk aspiration and intolerance to gastric nutrition, post-pyloric feeding is recommended because it is associated to a smaller rate of pneumonia. However, this method of nutrition requires expertise, it is considered as a less physiological option and has negative effects on gastrointestinal motility. Routine use of post-pyloric enteral nutrition is not justified.

Regarding the timing, early provision of EN within first 48 hours of ICU admission in patients who are mechanically ventilated is an established standard of care and supported by all clinical guidelines (6, 19). Studies showed that patients with early enteral nutrition, in the first 48 hours of ICU admission had less infections ($p<0.03$) than those with late enteral nutrition after 48 hours. When comparing the early enteral *versus* early parenteral nutrition, the importance of early enteral nutrition has also been emphasized. Reduction of infectious complications ($p=0.005$) in patients with applied early enteral nutrition has been confirmed, as well as a shorter stay in the intensive care unit ($p=0.01$) along with a shorter hospital stay ($p=0.002$). However, no difference between the groups has been found regarding the morbidity and mortality. McClave *et al*. in their study have shown the positive effect of enteral nutrition in general by reduction of morbidity from infections such as pneumonia, central venous infection, or abscess in the abdominal cavity. Other studies have confirmed a shorter hospital length of stay, as well as return of cognitive functions in trauma patients (20). However, there are always issues that raise dilemmas. Thus, the study conducted by Harvey *et al*. investigated the method of nutrition and its effect on the outcome in critically ill patients. Their randomized controlled study included 2388 patients and it did not find any significant difference in the mortality and infectious complications, neither in patients with parenteral nutrition nor in patients with enteral nutrition in the first 36 hours of admission. These results have opposed the paradigm that enteral nutrition is superior over parenteral one (21). All in all, the guidelines of the associations with regard to application of enteral or parenteral nutrition are the following:

ASPEN/SCCM (American Society for Parenteral and Enteral Nutrition/Society of Critical Care Medicine) guidelines suggest the "use of EN over PN in critically ill patients who require nutrition support therapy". Also, the Canadian Critical Care Practice Guidelines recommend similarly stating "when considering nutrition support for critically ill patients, we recommend the use of EN over PN in patients with an intact gastrointestinal tract." However, the inability to provide enteral nutrition early, may be a marker of the severity of illness which means that patients who can be fed enterally are less ill than those who cannot. In clinical practice there are various methods of feed administration **(Figure 2)** (22).

Figure 2. *Various methods of feed administration*

Bolus	Administers the feed solution over a 4-10 minute period, often via a syringe, several times a day; frequently in 150-200 ml each session
Intermittent gravity drip	Administers a set volume over 30-60 minutes several times a day, often by a given set only
Cyclic	Administers feed solutions during the night, in the daytime patients were allowed to eat normally
Continuous	Administers the full feed solution over a period of 8-24 hours, often using an enteral feeding pump set to a prescribed rate

Heterogenous results have been obtained in studies aimed to answer whether to apply bolus or continuous infusion of enteral nutrition, although feeding by bolus infusion might be alike the normal rhythm of feeding of healthy individual. In five small studies, the reduction of diarrhea duration was confirmed when continuous comparing and bolus infusion of enteral nutrition ($p=0.03$) was done (6). Other researchers found no difference between the two methods of nutrition regarding gastric residual volume, aspiration rate or pneumonia. According to Tavares *et al*. the continuous method reaches more rapidly the energy target. The ESPEN conclusion and recommendation is that continuous rather than bolus EN should be used (23).

Complication of Enteral Feeding

ICU patients often suffer from delayed or impaired gastric emptying, which results in an increased residual gastric volume. Regurgitation of stomach content may cause aspiration pneumonia and hence, enteral nutrition is often interrupted in patients with large quantities of residual gastric volume.

It is an ongoing debate whether the large quantity of residual gastric volume should be accepted. The gastric residual volume during enteral nutrition in ICU patients, in the REGANE trial showed that gastric residual volumes up to 500 ml could be safely tolerated (24). If the patient is intolerant of enteral feeding even at low doses, prokinetic drugs to increase intestinal mobility should be tried. Intravenous erythromycin is considered the first-choice treatment, with metoclopramide as an alternative or in combination.

Enteral Feeding in a State of Shock

What is to be done when the patient is in a condition of shock; which is the effect of enteral nutrition on gastrointestinal perfusion and splanchnic circulation; does it have to be administered?

Clinical trials conducted in a condition of cardiogenic shock have confirmed that if enteral nutrition is applied, then cardiac index is increased and blood flow through splanchnic circulation is increased, as well as absorptive capacity of gastrointestinal mucosa is preserved when vasopressin is administered. In spite of this, there is a concern about early enteral nutrition in patients who receive vasopressin due to eventual mesenteric ischemia and non-occlusive intestinal/ bowel necrosis. It has been noticed that the negative effect on gastrointestinal tract depends on administered vasopressors dosage. Still, the application of early enteral nutrition in patients with uncontrolled shock within the first 48 hours is rarely recommended.

Advantages and Disadvantages of Enteral Feeding

The use of enteral nutrition is considered to be more physiologic method of nutrition that enables numerous nutritional and non-nutritional benefits, such as preservation of both gastrointestinal integrity and gastrointestinal microbiological flora. Disadvantages of enteral nutrition are linked to potentially reduced nutritional supply, especially in the acute phase or in case of gastrointestinal dysfunction.

Of course, there are some limitations to the methods of feeding enteral. Absolute contraindications for using the enteral method include: ileus, multiple trauma associated to retroperitoneal hematoma, peritonitis, intestinal obstruction, gastric aspirate >500ml/6 h, active gastrointestinal hemorrhage, hemodynamic instability, uncontrolled hypoxemia and acidosis, intestinal ischemia, abdominal compartment syndrome, and high-output fistula without distal feeding access. Relative contraindications include diverticulum abscesses, early stages of small intestine syndrome, severe malabsorption, small intestinal fistulas, and the need for early nutrition support is not feasible for full feeding (25).

Enteral nutrition has **side effects** like any other invasive procedure. Complications of this nutritional method are divided into four categories, including mechanical effects (esophageal tracheal fistula, tube displacement and discharge, tube obstruction, food leak, and pulmonary aspiration), metabolic (such as hyperosmolaritis, hyperglycemia and hypoglycemia, electrolyte imbalance in blood, refeeding syndrome, hypercapnia and hypertonic depression), infections (sinusitis, otitis, pneumonia, necrotic peritonitis and enteritis), and digestive complications (diarrhea, constipation, vomiting, abdominal distension and hepatomegaly) (26).

Parenteral Nutrition

Parenteral nutrition is intake of all necessary energy and nutrition components in a form of solutions in the circulation (via peripheral or central venous route). According to statistical data parenteral nutrition is administered in 12%-71% of critically ill patients. The aim of parenteral nutrition is prevention or correction of nutritional deficit and malnutrition syndrome in cases of inadequate function of the gastrointestinal tract **(Figure 3)** (27).

Figure 3. *Indication for parenteral nutrition*

Parenteral Nutrition Indications
Inability to absorb enough digestive nutrition (large intestinal resection, short intestinal syndrome, enteritis caused by radiotherapy, severe diarrhea)
Complete or false intestinal obstruction, acute abdomen, or ileus and persistent digestive hemorrhage
Extreme catabolism when the digestive system is not usable for five to seven days
Failure to achieve enteral nutrition route
Disability to provide adequate food and fluids in the enteral method
Pancreatitis associated to jejunum intolerance
Trauma requiring frequent gastrointestinal surgical procedures

Even when enteral feeding is optimized and hypocaloric nutrition in the early acute phase is considered acceptable, enteral feeding is rarely sufficient to achieve desired nutritional targets. Studies have shown that only about 50% of calculated energy needs can be met with enteral feeding alone (6, 28). Depending on the spectrum and quantity of nutrients that are delivered in the organism, parenteral nutrition can **be partial (supplemental) or total**.

Supplemental parenteral nutrition is an additional method of treatment, which enables delivery of some substrates necessary for homeostasis maintenance by venous route. **Total** parenteral nutrition, on the other hand, is a method of nutritional therapy where all feedings or fluids are delivered by venous route.

Parenteral nutrition can be infused through a central or peripheral venous line. ***Peripheral venous*** access is suitable for application of nutrient mixture with lower osmolarity (<850 mOsmol/L) designed to supplement energy needs and to minimize negative energy balance. If total parenteral nutrition is required, then ***central access*** is recommended.

In cases of **SUPPLEMENTAL** parenteral nutrition, different attitudes regarding the timing of its administration have been proposed. The ESPEN 2009 guidelines recommend initiation of supplemental parenteral nutrition in the early phase of critical illness or within the first 48 hours of admission to the intensive care unit and reaching the energy targets at 72 hours. This is in contrast with ASPEN/SCCM guidelines that recommend administration of supplemental parenteral nutrition in patients with low and high nutrition risk, between the seventh and tenth day if patients are not able to intake >60% of energy and protein needs through enteral route. In other words, the recommendation of the American Associations is to start with parenteral nutrition in the late phase of critical illness. New European guidelines have changed and now recommend that parenteral nutrition should not be started in the early acute phase, but rather in the late acute phase between the third and seventh day in intensive care. The study of Casaer *et al*. compared the application of early and late parenteral nutrition and showed that early parenteral

nutrition was associated to increased morbidity, prolonged duration of mechanical ventilation, increased incidence of infections and longer hospital stay. This study was criticized in terms of patients' characteristics, calculation of energy needs with predictive equations and investigation protocol. However, it was assumed that reaching excessive calorie targets in the acute phase of critical illness might give negative results (29). Opposite to this study, another study (30) which included 1372 patients who got parenteral nutrition in the first 24 hours after admission in the intensive care unit, showed a significant reduction in ventilator days in these patients with early parenteral nutrition. Parenteral nutrition demonstrated positive results in undernourished patients who were to be operated on. In such cases, commencement of parenteral nutrition five to seven days prior to surgery is recommended, as well as its continuation in the postoperative period. However, in some patients **parenteral nutrition is contraindicated (Figure 4)** (27).

Figure 4. *Contraindications for administration of parenteral nutrition*

- adequate gastrointestinal tract function with access for enteral feeding	- severe hyperglycemia
- evidence that parenteral nutrition is unlikely to be required for more than 5 to 7 days	- severe electrolyte abnormalities on the planned day of initiation of parenteral nutrition
- intolerance of the intravenous fluid load required for parenteral nutrition	- any circumstance that may substantially increase the risk of intravenous-catheter placement

Parenteral nutrition sometimes is associated to onset **of complications (Figure 5)** (27).

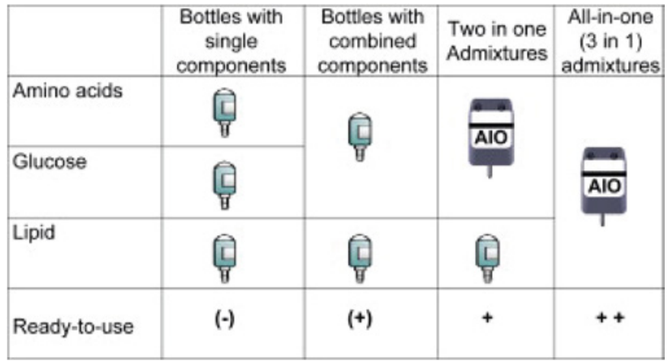
Figure 5. *Side effects after parenteral nutrition*

Mechanical complications	Low position of the central venous catheter: - pneumothorax - hemothorax - chylothorax - fluid in thorax - cardiac injury - cardiac arrhythmia Central venous catheter obstruction (partial or total) - air embolism - thrombosis - embolism
Metabolic complications	Hyperglycemia Hypoglycemia Hyperosmolarity Hyperlipidemia Hyperammonemia Electrolyte imbalance Deficiency in trace elements and vitamins Atrophy of intestinal villi
Septic complications	Infections of the catheter
Allergic complications	Lipids and proteins
Psychological complications	

Parenteral Solutions

Parenteral solutions are composed of carbohydrates (glucose), lipids and amino acids and can include electrolytes, vitamins and trace elements as required. They are defined by the relative composition of the macronutrients, osmolarity, pH and calorie content. These solutions can be administered using separate bottles, but are preferably administered using compounding or ready to mix bags.

Figure 6. *Systems for parenteral nutrition*



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The individual components (sterile infusions) are transferred into a single sterile plastic container, providing the user with a complex pharmaceutical formulation in the form of a single easy-to-use infusion system (31).

Solution of crystalline **amino acid** are used as a protein source during parenteral nutrition, and provide 4 kcal/gram of amino acid. These solutions always contain all essential amino acids, and the amount of non-essential varies depending on the admixture. A protein intake approximately 20% of total energy requirements is generally effective to limit nitrogen losses. Amino acids solutions are available from different manufacturers with different concentration from 3% to 20%.

Lipid emulsions are also an essential part of parenteral nutrition (6). Throughout the years, significant improvements have been made regarding lipid emulsion compositions. Soybean oils, which are based on long-chain triglycerides (LCTs) were the first used lipid emulsion compositions followed by medium-chain triglyceride (MCT)-based emulsions, olive oil (N-9) saturated lipid emulsions, and finally formulas containing fish oil. Current commercially available lipid emulsions contain different mixtures of oils and triglycerides (32). Lipid emulsions are available in concentrations of 10%, 20% and 30%. Use of lipids as an energy source can have important benefits. Oxidation of 1 g of intravenous fat obtains 9 kcal energy. They should cover 20-40% of energy requirements. In patients with hypertriglyceridemia lipid emulsions should not be started or should be temporarily interrupted (32).

Carbohydrates should cover 40-60% of total energy requirements during artificial nutrition. The most commonly used carbohydrate is glucose, while other carbohydrates (xilitol, sorbitol, levulose) are less used. The glucose solutions which are used for total parenteral nutrition have different concentrations, as listed in the table.

Figure 7. ***Glucose solutions of different concentrations, energy value and the level of osmolality.***

Concentration (ut/vol)	Energy kJ/l (kcal/l)	The level of osmolality (mosm/kg)
5%	796 190	278
10%	1591 380	555
20%	3182 760	1110
50%	7955 1900	2775
70%	11137 2660	3885

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The selection of glucose solutions depends on the estimated calorie needs and the total volume requirements. The oxidation of 1 g of glucose yields 4 kcal energy (33).

Over the last few decades, two-in-one (TIO) and all-in-one (AIO) admixture systems for parenteral nutrition have become available. Two-in-one PN infusate is a solution in which amino acids (20-25%) and glucose (75-80%) are combined in a single infusate together with electrolytes, vitamins and trace elements as requirement. All-in-one PN infusate is an emulsion in which amino acids (20-25%), glucose (55-60%) and lipid emulsion (20%) are combined in a single infusate with electrolytes, vitamins and trace elements as required (34).

The use of these systems prevents component manipulation, thus reducing the possibility of contamination and bloodstream infections.

Monitoring of the patients on parenteral nutrition is an imperative. The following parameters are to be monitored: metabolic status, regular glycemia control, daily follow-up of urea, creatinine, electrolytes, such as chlorides, phosphates, magnesium and bicarbonates and plasma triglycerides level. Monitoring of the generally-accepted nutrition markers like albumins and prealbumins in critically ill patients does not reflect the real nutritional status. Wound healing and general clinical condition of a critically ill patients are better marker of the nutritional status.

Conclusion

Optimized nutritional therapy in all critically ill patients is important in maintenance of the gastrointestinal tract function, maintenance of immunological defense, avoiding serious loss of muscle mass and function. This means that nutritional therapy is a key factor in promotion of short-term and long-term recovery. Indirect calorimetry is the most preferred method in the

assessment and determination of the target energy needs/ expenditure. Protein intake should be planned to reach 1.3 g/kg/day. The accent should be put on early enteral nutrition, and if it is impossible to be applied, parenteral nutrition should be initiated taking precautions to avoid overfeeding. Nutritional support should be applied on time, even before any individual nutrition deficit might happen, but it does not mean a routine and non-critical application of nutritional therapy in all hospitalized patients. However, in the newly emerged crisis with Covid-19, many new studies are necessary with an aim to discuss nutrition, which would enrich our knowledge about the metabolism of this disease and to adapt the strategy for nutritional support.

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FLUID AND ELECTROLYTE DISTURBANCE

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ABSTRACT

It is a fact that fluid and electrolyte disorders are one of the most frequent clinical problems in the departments of intensive care and emergency. The balance of the fluid and electrolyte keeps the homeostasis maintained in the body. In addition, it protects the functions of the cells, along with tissue perfusion and acid-base balance. In many diseases there are imbalances of electrolytes.

For the purpose of equilibrium of electrolytes in organisms, there is a number of regulating mechanisms. When disorders of these mechanisms arise, there may be some life-threatening conditions for the patient. There are some conditions which contribute to the disturbance in fluid and electrolyte homeostasis, such as: severe burns, brain damage, trauma, sepsis and so on. The findings of the studies suggest that these disorders exist among older people who have developed a higher degree of the disease.

The most important of the electrolyte contrast are hypo and hyper-states of sodium, potassium, calcium and magnesium.

The abnormalities which might occur in fluid and electrolyte in emergency states could cause fatal consequences. Intensive care should be practiced more as it is frequently impossible to observe the symptoms of critically ill patients and emergency states. The information that one can find in literature is occupied with electrolyte disorders and there is great amount of studies that observe patients with certain disorders or groups with certain risks. On the other hand, there are very few studies which observe the imbalance of fluid and electrolytes in patients with urgent states or critically ill. This work is focused on the general characteristics in critically ill patients as well as in patients with emergency states diagnosed with electrolyte disturbances. Finally, it will give crucial information to the medical literature.

Key Words: *emergency and critically ill patients, fluid and electrolyte disturbance.*

Introduction

It is crucial to understand the significance of the fluid and electrolyte balance in order to maintain homeostasis and to obtain treatment of various metabolic disorders. The most responsible organ that regulates this is the kidney. In addition to it, there are many more other mechanisms which are also included in this process, such as: aldosterone, hormonal activities of antidiuretic hormone and parathyroid hormone. They also help in the validity of the mechanism and they further excel it (1, 2).

Sometimes, there might be the reduced perfusion of the kidney because of hypovolemia or hypotension. If there is an inappropriate administration of fluid and electrolytes, it should be taken into consideration in the treatment.

It is really important to keep fluid and electrolyte in a good condition balance as it is important for the treatment of many critical conditions. Nevertheless, if some of the disturbances arise, one must immediately take care of it, i.e. observe it so that a regular treatment is obtained for the patient (3, 4).

The organ which is responsible for retention and excretion of fluid and electrolytes in individuals who do not have any health problems, is the kidney. However, the stress, hormonal interactions of different hormones do play key role in the regulation of the electrolyte and fluid balance in the organism.

It is easy to measure electrolyte balances when there are measurable biochemical parameters in the bloodstream.

Patients who suffer from fluid and electrolyte disturbances are demanding for anesthesiologists, as well as for urgent and intensive care.

The most frequent electrolyte disturbances are hyponatremia, hypernatremia, hypokalemia, hyperkalemia, hypophosphatemia, hypocalcemia and hypomagnesemia.

Dyspnea, fever and systemic deterioration are the most frequent symptoms in these patients. The most common symptoms and problems in patients with fluid and electrolyte disturbances are malignancies and the most common oncological diseases are lung and hematological malignancies.

The purpose of this work is to provide information on fluid and electrolyte disturbances that can frequently happen in critically ill patients and in emergency cases. In addition, it is preoccupied with the administration of fluid and electrolytes as well as medications related to disorders which arise due to them.

Fluid menagement

A necessary component of patient's care with hypovolemic shock or sepsis is volume resuscitation. Early goal-directed therapy, which has been suggested in the management of critically ill patients has been considered to improve the survival overall. It is used in the first phase of management in patients with severe sepsis or septic shock.

As opposed to the opinion of certain resuscitations of aggressive and liberal resuscitation, great number of people believe that the overload of fluid may be determined to critically ill patients. There has been paid no or very little attention to the consequences of fluid overload which results in respiratory failure, peripheral edema and increased cardiac demand.

What should be done and considered is the daily input and output of fluids along with the loss of it. In addition, it has been suggested to involve invasive monitoring of central venous pressure or pulmonary capillary wedge pressure.

Hyponatremia

As hypo and hypernatremia are related to increased mortality, sodium imbalances are really important in patients who are in need of intensive care, regardless their gender, age or diagnosis.

Conditions of disturbances in plasma sodium concentrations are great clinical problem for patients admitted to intensive care. Arif Kaori Balchi et al. in their study have proved that 65% of patients with emergency cases have natrium imbalance, but 60% of those had hyponatremia (5, 6).

Low plasma natrium represents a relative water excess in conjunction with impaired ability of the kidney to excrete electrolyte free water. The removal of water of the kidney needs urinary dilution. The removal of water by the kidney produces urinary dilution.

What is important about the management of hyponatremia, is the period of development of hyponatremia and its symptoms presented there. Plasma correction of sodium, especially in patients having seizures, should be acted upon without being late in symptomatic patients. It is important to begin with sodium chloride (with or without a loop diuretic) with 1-2 mL/kg/hr, so that sodium concentration is raised by 1-2mEq/L/hr. It is important to mention that the rapid correction is to be limited at the first management phase. Taking into consideration that the risk of osmotic demyelination may rise above the limit, the whole correction of Na+ need not to exceed 8-12mEq/L for 24 hours. The change in plasma Na+ is calculated with equations which were suggested by Adroue and Madias in the following way:

Change in plasma [Na+] = Infusate [Na+] – plasma [Na+] / Total body water + 1

Change in plasma [Na+] = Infusate [Na+] + infusate [K+] – plasma [Na+] / Total body water+1

It is significant to bear in mind that the proposed equations propose that the human body is a closed system not taking into consideration fluid and electrolyte gain or loss.

Euvolemic asymptomatic hyponatremia does not have to be urgently treated with therapy as the brain cells have adapted to hypoosmolality, which is indicated by the absence of symptoms. The first thing to do in treatment is to identify and remove reversible causes.

Hypovolemic hyponatremia is a consequence of water and solutes. Furthermore, there is greater level of loss of solutes. It was observed in a law-salt diet patients.

Hypervolemic hyponatremia is a condition that occurs when solute and water are kept in the body and when water is increased to greater level. All of this could sometimes be related to

heart, liver, or kidney dysfunctions. What helps in this situation is restriction of intake of water and sodium as well as administration of loop diuretics. As extracorporeal ultrafiltration was proved to improve congestion, lower diuretic requirements and correct hyponatremia, and it may be useful for patients with severe hyponatremia.

With the purpose of preventing the **osmotic demyelination** during the treatment of hyponatremia, the correction of plasma [Na+] needs to be less than 8-12mEq/L/day. Patients exposed to higher level of risk of developing osmotic demyelination are some of the following groups of patients: alcoholics, hypokalemic patients, malnourished patients, patients with previous hypoxic episodes, burn patients, or elderly women on thiazide diuretics. (8, 9)

Hypernatremia

It is a fact that the patients in the UCI are exposed to high risk of being diagnosed with ***hypernatremia***. There are some predisposing factors which include the administration of sodium bicarbonate solutions to correct metabolic acidosis; gastrointestinal fluid losses through nasogastric suction and lactulose administration, and water losses through fever, drainages, and open wounds (10, 11).

It is important to recognize symptoms, such as identification of the underlying defects of water metabolism, correction of volume disturbances and correction of hypertonicity, in order to detect and treat hypernatremia. Initial changes which occur as a result of this condition, involve altered mental status, such as restlessness, lethargy, irritability, somnolence and confusion. Some of the patients feel thirsty and they complain about it in case they are capable to communicate. Polyuric patients should be included in the process of evaluation of defects in urinary concentration because there has been some previous discovery that these disorders allow clinicians to replace urinary osmole excretion rate, which is helpful in differentiating water diuresis from solute diuresis (12).

The success of correction of hypernatremia is related to the rate of development and to the symptoms which appear. It is advised to replace half of the water deficit in the period of 12 to 24 hours. In addition, the deficit which remains may be corrected in the period of the following 48 hours. Nevertheless, the plasma rate decrease ought not to be more than 2mEq/L/hr.

Hypervolemic hypernatremia is a frequent condition and it is frequently iatrogenic, particularly for patients who receive large amount of saline or bicarbonate during their illness. Treatment of the condition of hypervolemic hypernatremia needs removal of excess sodium from the body. The source of sodium which is exogenous should be eliminated when it is not indicated clinically. In inducing negative sodium balance, loop diuretics with free water replacement may help a lot. When it comes to preservation, a rising plasma [Na+] should be considered as a counter effect to next administration of saline and should include treatment with hypotonic fluid via oral or parenteral route.

Correction of effective circulating volume deficit should be realized before the replacement of water deficit in treating patients with hypovolemic hypernatremia, especially in patients with hypotension and evident signs of hypovolemia. The cause of volume loss should be identified and corrected and isotonic sodium chloride should be given.

Hypokalemia

Some of the reasons for the occurrence of hypokalemia involve low dietary potassium intake, extrarenal potassium loss, shift into the intracellular compartment, and renal potassium loss. Medications which are often prescribed in this unit go hand in hand with hypokalemia. It is known that diuretics increase the loss of renal potassium in such way that they inhibit sodium reabsorption in the loop of Henle and in the distal nephron. In addition, amphotericin B is well known for its possibility to disrupt the function of the collecting dust, causing nephrogenic diabetes insipidus, renal potassium loss and distal renal tubular acidosis. Some of the non-reasonable anions such as some penicillin and aminoglycosides may lead to hypokalemia by means of the loss of obligatory potassium into urine (13, 14).

Signs and symptoms which suggest that there is a presence of this condition are neuromuscular, including paralysis, vomiting, weakness, nausea, respiratory muscle weakness, constipation, and rhabdomyolysis. The most serious complications associated to hypokalemia are cardiac arrhythmias, myocardial infarction, or heart failure. Electro cardio-graphic changes in patients with hypokalemia involve ST-segment depression, T-wave inversion T-wave flattening, and the occurrence of U waves.

What characterizes hypokalemia is confusion, aphasia and paresis. Even though the clinical signs and symptoms cannot be related to only one disorder of electrolyte imbalances, it is significant to see the physical aspects of hemodynamic changes of levels of electrolyte in blood.

Hyperkalemia

There are certain predisposing factors which might lead to this condition in critically ill patients, such as: renal failure, insulin deficiency and resistance, adrenal insufficiency, and burns, tissue damage from rhabdomyolysis, or trauma. Furthermore, there are many medications used in the ICU which can also lead to the occurrence of hyperkalemia. One of them is succinylcholine, which is a depolarizing muscle relaxant which is often used in the intensive care unit. Williams et al found out that potassium secretion from thrombocytes and leukocytes in severe thrombocytosis and leukocytosis could cause pseudo-hyperkalemia (15). The most frequent diagnosis are renal failures that might cause hyperkalemia. Some of the patients with hyperkalemia have spiked T-waves in ECG examinations. The interactions in more electrolytes have influence on ECG findings in these patients (14).

At the beginning, the therapeutic and diagnostic attempts should be preoccupied with exclusion of conditions related to hyperkalemia. The next thing to do is to evaluate urinary potassium excretion, which should be high if renal function is not compromised.

The plan for treatment of hyperkalemia is made with the urgency of patient's condition. The first thing to do in management in order to lower the effect of hyperkalemia is to use Intravenous

calcium gluconate. The next thing to do is to make the shift of potassium into intracellular compartment easier (10 IU of Insulin with 50 g Glucose, I.V. for 15 minutes). After acute management, there should be removal of body potassium in the use of therapy of hyperkalemia. For patients who have renal issues, dialysis is an effective treating method. Potassium excess sources should be sought and treated adequately.

Hypophosphatemia

Hypophosphatemia has been related to critical conditions such as Gram-negative sepsis and open-heart surgery (16, 17, 18). Critically ill patients have conditions that lead them to developing hypophosphatemia, including malnutrition and inadequate body phosphorus stores, acute respiratory alkalosis.

Plasma phosphorus concentrations in critically ill patients should be in normal range (2.5-4.5 mg/dL), considering the potential negative effects of hypophosphatemia. Asymptomatic to moderate hypophosphatemia (1-2.5 mg/dL) may be treated with oral phosphate supplementation in case the gastrointestinal tract is in good condition. Symptomatic or severe hypophosphatemia (<1.0mg/dL) need to be treated with I.V. phosphate solutions. For the patients who are on Continuous renal replacement therapy (CRRT), the first dosages ought to be higher, as the amount of phosphorus which is removed can be vast.

Hypocalcemia

One of the most common electrolyte abnormalities encountered in the ICU is hypocalcemia. When there are low total concentrations of calcium, it has been said that these influence a great number of critically ill patients (19). Hypocalcemia adds to the level of mortality in patients in the ICU. (20)

Calcium has many tasks in intracellular enzymatic pathways, and its role in cellular damage and cell death is not to be taken for granted [16]. The large number of oncological diagnoses has led to high frequencies of calcium balance disorders (14).

The most common reasons for hypocalcemia involve trauma, acute and chronic renal failure, sepsis, hypoparathyroidism, hypomagnesemia and other conditions. Hypocalcemic patients had more tachycardia, bradycardia and atrial fibrillation, while hypercalcemic patients had more atrioventricular block, spiked T-waves and ST segment changes (14).

It is a known fact that intravenous calcium should be administered as calcium gluconate or calcium chloride to improve acute symptomatic moderate (total serum calcium concentration 7.5-8.0 mg/dL) or severe (total serum calcium concentration < 7.5 mg/dL or ironized calcium concentration < 0.9 mmol/L) hypocalcemia. Calcium gluconate should be opted for routine calcium maintenance and supplementation. Utilization of calcium chloride should be limited to urgent and emergency situations, as it supplies with three times more elemental calcium than calcium gluconate.

Severe and symptomatic hypocalcemia must be managed shortly. At the beginning, 1000 mg of calcium chloride or 3 g of calcium gluconate may be administered over 10 minutes to overcome symptoms.

The condition of hypocalcemia is frequently accompanied by other electrolyte and disorders based on acid. In case hypocalcemia is not properly corrected by repeated administration of calcium, hypomagnesemia should be sought and corrected. Even though the exact mechanism of calcium-magnesium interaction is not known, it is believed that magnesium deficiency may have influence on the release or activity of parathyroid hormone. When metabolic acidosis occurs, hypocalcemia should be corrected before acidosis as the treatment lowers the level of ionized calcium, and that is why there might be problems such as tetany or cardiac arrest. Bicarbonate solution and calcium salt should be used in different intravenous lines to prevent the large number of calcium carbonate.

Hypomagnesemia

The condition of hypomagnesemia is often observed in ill patients who are in critical condition and its prevalence in this unit is said to be 50% (21). Severe hypomagnesemia can lead to certain changes, seizures, coma, and death. Hypomagnesemia is related to concomitant electrolyte disturbances.

Hypomagnesemia has a high prevalence rate, but its diagnosis may be intrigued by some factors. Firstly, it has nonspecific manifestations and is often taken for granted. Secondly, magnesium level is not examined regularly in blood test (22). Thirdly, patients may be hypomagnesemic although their serum magnesium level is normal. And lastly, magnesium deficiencies are generally covered by other electrolyte deficiencies.

The reasons for it may involve the extra gastrointestinal or renal losses, surgery, trauma, infection or sepsis, burns, transfusion of blood, products preserved with citrate, alcoholism, starvation or malnutrition and certain medications (e.g. diuretics, aminoglycosides, amphotericin B, cisplatin, digoxin, and cyclosporine), all these may be the cause for hypomagnesemia. Magnesium's fractional excretion is a helpful sign for differential diagnosis of hypomagnesemia (23). In patients who are critically ill and who are critical (plasma is [Mg2+] < 1 mg/dL), intravenous administration is preferred. Critical hypomagnesemia needs magnesium treatment with 32-64mEq (up to 1.5mEq/kg). Doses less than 6 g of magnesium sulfate are infused over 8-12 hours, and higher doses are given over 24 hours. Patients with renal impairment decreased dose should be prescribed in order to stop hypermagnesemia (24, 25).

Conclusion

It can be concluded that among the most common clinical problems encountered in intensive care and emergency states are fluid and electrolyte disorders. Some of these conditions may result in fatal consequences.

Symptoms are sometimes difficult to access and therefore the treatment may be difficult to be done in a successful manner.

Patients with emergency cases are frequently diagnosed with various oncological diseases. These malignancies can be high risk for electrolyte imbalances with electrolytes.

Knowledge about fluid and electrolyte homeostasis is required in order to provide optimal management and the underlying pathophysiology of the respective disorders. Last. but not the least, attention should be paid to the administration of fluid and medications which are related to fluid and electrolyte disturbances.

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CHEST INJURIES

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ABSTRACT

In the first four decades of life, traumatic injuries are the major cause for increased mortality rate in the population. Traumatic chest injuries, however remain part of multiple trauma injuries and account for 25% higher mortality risk in comparison to the cases where chest is intact. They usually never occur as single trauma injury. There are two types of traumatic chest injuries, blunt and penetrative, depending on the mechanism of action and clinical presentation. The aim of this presentation is to summarize the latest medical literature and the newest findings in relation to early diagnosis, surgical procedures and intensive care unit treatment of chest injuries. Multimodal approach with effectiveness in the treatment of these patients starting from the moment of injury until the full recovery in the intensive care unit is the key to success. Despite the potential high risk for poor outcome, the newest research papers show that only 10% of thoracic trauma patients results in a thoracotomy however, the most common treatment is the insertion of a thoracic drain, or no surgical intervention at all. Therefore, efficient diagnosis of the trauma combined with the collaboration of the anesthesiologist and thoracic surgeon results in more effective treatment, which furthermore has an effect on the mortality and morbidity rate in patients with thoracic injuries.

Key Words: *diagnosis, multidisciplinary approach, thoracotomy, traumatic injuries.*

Introduction

Chest injuries by the mechanism of occurrence are either blunt or penetrative and commonly are result of car accidents or falls from height. Triage of these patients can be tricky and challenging as many of them may not develop any symptoms of chest or pulmonary injuries on admission. However, it is not rear complications to occur 48 to 72 hours after the injury, and not rarely in such cases difficult breathingis accompanied with respiratory insufficiency (1). Battle et al.highlighted the risk factors associated to the development of complications in thoracic trauma patients in correlation to age, number of broken ribs, presence of chronic lung diseases, use of anticoagulants, and level of oxygen saturation (2). Recognizing the seriousness of the condition by knowing the risk factors for possible respiratory complications and admission in the ICU for further monitoring, is the key for better outcome. The prognosis of these patients worsen with the presence of other systemic injuries, such as injury of head and neck, abdominal injuries or bone fractures.

According to thetypes of tissue injured and the location of the injury, chest injuries may be divided in different classifications, but mostly accepted division is in relation to the layers of the thoracic cavity as 1. Injuries to the thoracic wall; 2. Injuries of the organs and blood vessels within the thoracic cavity; and 3. Injuries to the diaphragm.

Fractures to the ribs and sternum. The most common chest wall injuries are fractures to the ribs. They are result fromthe blunt trauma. The amount of broken ribs depends on the nature of the trauma and the age of the patient. The most common fractures happen from the 3rd to 9th rib while the fracture of the 1st rib is indicative for extremely heavy trauma with possible mediastinal, vascular, neurological trauma and lesions in extra thoracic tissue. This is due to the fact that the 1st rib is the shortest, strongest and the most protected due to the position behind the clavicle (3). If the last rib is fractured, abdominal trauma may be assumed. When ribs are fractured, patients usually experience symptoms of chest pain, especially pain during inspiration and/or when coughing, and they might have difficulty breathing. Diagnosis is achieved with a thoracic x-ray showing signs of fractures or complications associated tofractures (ex. pneumothorax, hemothorax). These patients are treated with analgesics, antibiotics and physical therapy. Simple fracture of the rib the most often heal on its own within 2-3 weeks, if no other complications are present.

Flail Chest is a rare traumatic injury that is characterized by fractures of at least three ribs in two or three places, with or without sternum fracture. This type of injuries occurs the most often in severe car accidents.

When these injuries are present, broken and injured segments can detach from the thoracic wall, causing paradoxical movement of the thorax and leading to complications, such as pneumothorax and hemothorax. Patients with flail injuries have paradoxical breathing which results in hypoventilation, hypoxia, hypercapnia and acidosis. Flail Chest injury is associated to high mortality and morbidity rates, more significantly in older aged patients and those with history of

lung contusions (4). 50% of cases require mechanical ventilation for 1-3 weeks after the chest wall has been stabilized. Some studies have shown that surgical fixation of the ribs may reduce the time spent on mechanical ventilation and days in the hospital (5,6).

Sternum fractures are the most often caused by car accidents where there has been an impact with the steering wheel or falls. 30% of patients with injured sternum also have fractured ribs, myocardial contusion or contusion of the lungs (7).

Lung contusions are serious injuries accompanied by fractured ribs resulting in worsened prognosis. During lung contusions capillary damage occurs and results in the accumulation of blood in the alveoli. This is leading to an inflammation response followed by realized cytokines and substantial lung edema. This leads to reduced gas exchange and respiratory insufficiencies. Complications associated to lung contusions include ARDS, but the most often pneumonia (8). During admission of traumatized patients, it is important to check the blood gas analyses, as they may give an indication for the severances of the injury, possible complications that may arise and whether mechanical ventilation is required. Chest X-ray and Computerized Tomography scan (CT-scan) are used for diagnosing of the condition. Lung infiltrates usually may prograde in the first 12 to 24 hours after the injury, so careful monitoring is needed. The treatment of lung contusions includes oxygen therapy, pain management, restricted fluid intake and mechanical ventilation in 25% of cases. It is notuncommon thesepatients, after survival and treatment, to have reduced function of the lungs which affects the quality of the life. **Traumatic Hemothorax** occurs when blood enters the interpleural space of the lungs. This may be caused by broken ribs, fractured vertebrae or laceration of the lungs. Hemothorax is associated to50-60% of the penetrative traumas, 60-70% of the blunt traumas and rarely associated by heart and blood vessel injuries. Large hemothorax may lead to hemorrhagic shock which is presented with tachycardia, low blood pressure, cold sweats, paleness and shortness of breath. Diagnosis is reached through a chest x-ray, ultrasound or CT scan. Treatment involves decompression of the interpleural space with the insertion of a pleural drain and correction of the volume deficit due to hemorrhagic shock. A thoracotomy may be done if the patient presents with a large hemothorax of more than 1500 mL of blood in interpleural space or if the patient continuously loses more than 200 mL of blood per hour.

A traumatic pneumothorax is caused by the presence of air in the interpleural spaceas the result of broken ribs, rupture of the airways or lung injury. It can be classified as open or closed, depending on whether a wound from the interpleural space to the outside environment exists or not. Patients presenting with pneumothorax experience chest pain, lack of sound during auscultation and/or hypoxia. Diagnosis is confirmed through radiological tests. Treatment is insertion of a pleural drain and the closing of the wound if necessary.

Tension Pneumothorax is the most common reversible cause of death in patients with chest trauma (9,10). Tension pneumothorax is a condition where the effect of one-way valve from the place of tissue rupture results in air being trapped inside and not being able to come out. This causes an increase in the interpleural pressure and further collapse of the lung, resulting in increased pressure on the mediastinal organs, decreased cardiac output and decreased venous return. Symptoms of a tension pneumothorax include respiratory distress, tachycardia, hypotension, a deviated trachea, distended veins on the neck and subcutaneous emphysema. Treatment is done through decompression by using a needle and inserting it into the 2nd intercostal space, in the midclavicular line, then inserting a pleural drain which location is confirmed by an x-ray.

Traumatic heart injuries. There are three types of traumatic heart injuries: contusion, rupture and tamponade. Myocardial contusion, is the most likely to occur in the right ventricle. Patients experience chest pain, dyspnea and shortness of breath. There are significant changes in the heart rhythm such as ventricular and atrial fibrillation and EKG changes of the ST segment and T wave. There are increased values for CPK and troponin enzyme markers. Massive heart contusion leads to cardiogenic shock. Therefore, attention has to be given to patients suspected to suffer myocardial contusion by admission in the intensive care unit and their continuous monitoring.

Rupture of the myocardium is almost always fatal. **Cardiac tamponade** is usually aresult of penetrative trauma. It is a condition that leads to heart failure due to the compression of the heart by the increase of fluid in the pericardial space. Diagnosis can be a challenge and consists of symptoms such as hypotension, impaired heart tones, jugular vein dilatation (Beck triad) and low voltage EKG changes (11). It is confirmed by echocardiography and treated with an urgent pericardiocentesis.

Traumatic rupture of the aorta. Aortic rupture due to thoracic trauma is the second leading cause of death and the most commonly occurs due to car accidents and 3 meter high falls. Aortic rupture is fatal for 90% of people at the site of injury, but if it is an incomplete rupture, patients are likely to present chest and back pain, dyspnea and cough, accompanied with left hemothorax and cardiac tamponade. The most affected site of injury is the proximal part of the descending aorta. Gold standard in diagnosis of aortic rupture is CT angiography.

Tracheobronchial injuries. The most commonly, 80% of tracheobronchial injuries occur about 2.5 cm from the carina. Clinical symptoms happen in relation to the size of the rupture. Thus, patients can manifest dyspnea, tachypnea, subcutaneous emphysema, hemoptysis, pneumothorax, and pneumomediastinum. Continuous loss of air after a thoracic drain is a sign of bronchial rupture that can be diagnosed with native radiography or CT scan. However, bronchoscopy is very important diagnostic method that should be performed in each suspected patient. Patients with tracheobronchial trauma need to be intubated and put on mechanical ventilation with the tube cuff located under the place of rupture.

Diaphragmatic rupture usually occurs as a result of blunt or penetrative trauma. Rupture due to blunt trauma accounts in 0.8 – 7% of patients, while penetrative trauma rupture occurs in 10 – 15% of patients (12).

Clinical signs related to this condition include chest pain, difficulties in breathing, haemodynamic instability, deviation of trachea and vomiting. Rupture of diaphragm is diagnosed with

native radiography, ultrasonography, CT scan and video assisted thoracoscopy (VATS). Surgery is the only available treatment.

Diagnosis of Chest Trauma

Multidisciplinary approach is the key to proper diagnosis and treatment of patients with chest's trauma. Good anamnestic evaluation, as well as proper clinical examination, gives the primary information about the mechanism and seriousness of the injury (13). Clinical examination is the first and the most important step that includes auscultation of chest, palpation of pulse, measurement of vital parameters, such as blood pressure, heart rate and blood saturation. Preoxygenation, airway management and mechanical ventilation follow the procedure. Primary evaluation is necessary in order to detect injuries that require urgent intervention, such as tension pneumothorax, open pneumothorax, rupture of the main airway, cardiac tamponade, massive pneumothorax, traumatic air embolism, fail chest. Native radiography and ultrasonography are very effective in the early detection of pleural effusion, heart injury or vascular ruptures. The interventions such as needle decompression, thoracic drainage or pericardiocentesis can usually be done simultaneously with the diagnosis. CT scan with contrast is obtained in cases when native radiography or ultrasonography are not sufficient (14). It points the location and gives more precise diagnosis of the injury.

Treatment of Chest Trauma

Following the diagnosis and assessment of the severity of the chest trauma, triage of patients is performed. Patients are admitted in the intensive care unit where special attention is paid to analgesia, as part of the traumatic shock treatment in general with appropriate use of fluids, oxygen support or mechanical ventilation, antibiotics and the need for thoracic drainage.

Analgesia

Chest trauma pain causes ventilation dysfunction leading to an increased incidence of complications such as atelectasis, respiratory failure, need for mechanical ventilation andpneumonia (15). Therefore, effective analgesia that allows taking deep breaths, coughing and expelling sputum, facilitates physical therapy and early removal from mechanical ventilation. Morphine titration is recommended for intense pain. In cases wherethere is no adequate morphine analgesia, the use of ketamine is recommended.

Systemic opioid analgesia with the use of fentanyl, remifentanil, and morphine is effective in the treatment of acute pain. In cases when pain persists for longer than 12 hours, regardless the received opioid treatment, locoregional analgesia is recommended. An epidural catheter is alsoa choice for pain treatment in complex and bilateral injuries, while paravertebral catheter placed under ultra sound is used in unilateral injuries. Studies suggest an advantage of epidural analgesia at the thoracic level over the systemic analgesia due to better efficiency and reduction

of the number of respiratory complications such as pneumonia, atelectasis (16). However, contraindications to epidural analgesia exist and they include coagulopathy, traumatic shock and hypovolemia, meaning that only about10% of patients with thoracic trauma can receive epidural analgesia. Effective method for analgesia in all patients with thoracic trauma is the intercostal block where local anesthetic is given as a single dose or continuous infiltration in the back of the intercostal space (17). Multimodal analgesia is the key for a successful treatment. It consists of combination of procedures and medications such as regional anesthesia, non-steroid anti-inflammatory drugs (NSAID), anxiolytics, gabapentin, ketamine.

Mechanical ventilation

Patients with chest trauma that have spontaneous respiration, but inadequate oxygenation with gas blood analysis of $pO2 < 60mmHg$ and $pCO2 > 60$ mmHg, are placed on mechanical ventilation. Mechanical ventilation in chest trauma patients should be protective with respiratory volume values of 6-8 ml/kg, plateau pressure < 30 cmH2O, PEEP > 5 cmH2O. In order to determine the PEEP value, the oxygen blood saturation SpO2 should not be lower than 92% when FiO2 is lower than 60%, maintaining hemodynamic stability at the same time.

Patients in shock condition, massive pneumothorax that has been drained, injury of head and neck and tetraplegia are placed on mechanical ventilation. In some cases of mild thoracic trauma, non-invasive mechanical ventilation (NIV) can be used in order to avoid intubation and mechanical ventilation. Those patients develop fewer complications and have shorter stay in the ICU compared to those on mechanical ventilation (18).

Antibiotics

The use and effectiveness of antibiotic prophylaxis in chest trauma patients and their ability to decrease the risk of infections is still a debate. The latest meta-analysis results conclude that antibiotics, used in chest blunt or penetrative trauma injuries where thoracic drainage is performed, decrease the risk of pneumonia and posttraumatic development of empyema (19).

In British thoracic Society guidelines it is strongly recommended the use of prophylactic antibiotic after insertion of thoracic drain despite low risk incidence of infectious complications (20).

Fluid management

One of the highlights in the treatment of chest trauma is the fluid management in order to compensate the fluid loss and circulatory volume. This enables adequate oxygen delivery and blood perfusion. Even though there is a negative fluid balance, the resuscitation is performed with a restrictive use of crystalloids by maintaining the blood pressure in a range between 60 – 70 mmHg until the regulation of the hemorrhage. This gives better results compared to fluid overload (21). Excessive intravenous fluids result in lung oedema which further worsens the ventilation and perfusion ratio and the overall result, due to the existing lung contusions in patients with thoracic

trauma. There is always a dilemma about the use of crystalloids or combination of crystalloids and colloids for a better outcome.

The amount of fluids is usually controlled by the value of blood pressure, lactate level and base deficit. Monitoring the dynamics of those parameters decreases the risk of excessive hydration and maintains proper fluid balance which further reduces the risk of complications.

Conclusion

There is a high incidence of morbidity and mortality in patients with thoracic trauma (22). Early recognition of the seriousness of the condition along with a proper diagnosis and urgent treatment is crucial for a good outcome. This can be managed with a multidisciplinary approach involving a team of anesthesiologists especially the ones in the intensive care department, surgeons, and radiologists. The use of the latest diagnostic techniques, as well as continuous education of the medical stuff about the early and aggressive medical treatment, is one of the important steps in the chain of saving patients after traumatic chest injury and decreasing the mortality and morbidity rate in these patients.

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DAMAGE CONTROL RESUSCITATION IN TRAUMA PATIENTS: NEW INSIGHTS FOR TREATMENT OF SEVERE BLEEDING

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SUMMARY

Damage control resuscitation (DCR) and damage control surgery (DCS) are two entities based on the identical resuscitative principles. DCS aims to manage life-threatening injuries temporary with early hemorrhage control, and to delay of the definitive repair after metabolic disorders and acidosis are resolved, while DCR aims to maintain hemostasis and to prevent trauma induced coagulopathy (TIC) in addition to standard resuscitation procedures. Focused critical care within the intensive care unit (ICU) for improvement of hemodynamic, electrolyte and metabolic status, as well as planned re-operation for definitive repair when physiology is normalized, is reasonable strategy. DCR is a goal directed strategy guided either by conventional coagulation tests or viscoelastic assays, and includes permissive hypotension with restrictive fluid resuscitation, balanced blood product-based resuscitation approach with 1:1:1 ratio in relation to plasma, red blood cells and platelets. Tranexamic acid (THA) should be administrated early in massive bleeding, even within the absence of clinically diagnosed hyperfibrinolysis. When hyperfibrinolysis is taken into account, fibrinogen and platelets should be administered to enable thrombin generation. Prothrombin complex concentrates could be the primary line therapy for thrombin deficiency when bleeding continuous despite fibrin and platelets (PLTs) supplementation. This DCR strategy relays on available resources.

Key Words: *damage control resuscitation, severe traumatic hemorrhage, trauma induced coagulopathy*.

Introduction

Severe bleeding is major cause of preventable death in trauma patients (1). Trauma registers serve as excellent resources to determine the predictors of outcome in trauma injured patients, but are still not present in every trauma or urgent center. However, data collected from them can give some projection of morbidity and mortality, which shows that 30-50% of all deaths occur within the first 4 hours after injury and are because of the acute blood loss and hemorrhagic shock (2). Furthermore, hemorrhage appears in 80% of all deaths within the first few hours at the patients with a higher injury severity score (ISS) (3). There is a disparity in mortality and disability worldwide, so in low-and middle-income countries there's higher mortality rate from injury due to the lack of the suitable equipment, organizational resources, or trained staff, also because of insufficient surgical care (4). Recent management principles in trauma bleeding in order to strengthen system of trauma care in countries at all economic levels are based on bleeding control bundle of care with guidelines for stopping hemorrhage as quickly as possible in order to prevent multiorgan failure and to reduce the mortality rate.

Purpose of review

This review aims to present current knowledge and clinical practice, as well as the latest insights into the DCR approach to trauma hemorrhagic patients. Therapeutic strategies based on damage control resuscitation principles are covered.

Elaboration of Recent Findings

There is not any magic measure that may assess the degree of bleeding in trauma patients. Mechanism of injury, physiological condition, laboratory data (base deficit and lactate levels), as well as injuries found on second investigation, are also useful for estimation of life-threatening hemorrhage. Bleeding from vessels with blood loss of 50% within 3 hours, and blood loss exceeding 150 ml/min in trauma, requires rapid control of the source of bleeding (5). It is essential to rapidly achieve surgical haemostasis with ligation of major vessels leading to the bleeding area, compression or electrocoagulation. Surgical haemostasis depends on operative visualization and control, and if it is nonsufficient may be fatal. Surgical bleeding presents 80% mortality within the operating theatre. Attempts to normalize blood pressure may result in increased blood loss and a greater risk of mortality. In cases of penetrating trauma, permissive hypotension may be a therapeutic option, provided surgical intervention is commenced rapidly. However, it is not recommended in cases of blunt trauma and is contraindicated in traumatic brain or spinal injury. There are bleedings in some situations where rather other therapeutic strategy than surgery has to be performed. These situations are area where surgical intervention has limited or no control of bleeding and where attempts of surgery can exacerbate traumatic hemorrhage and cause severe bleeding and coagulopathy. Risk of surgery with catastrophic consequences can appears in patient with fractures of pelvic ring or in bleeding as a result of coagulopathy. Surgery in these

conditions can cause further blood loss, physiological disorder and possibly death. Recently management of traumatic hemorrhage includes damage control resuscitation (DCR).

Damage Control Surgery and Damage Control Resuscitation

The concept of "damage control" in trauma patients with severe bleeding aims to restore the endpoints of resuscitation. DCS aims to manage life-threatening injuries temporary with early hemorrhage control and to delay of the definitive repair after metabolic disorders and acidosis are resolved, while DCR aims to achieve hemostasis and to prevent trauma induced coagulopathy (TIC) in addition to standard resuscitation procedures. Complete repair in trauma care with aggressive restoration of blood volume before surgery may increase mortality and morbidity. When the patient goes on immediately reparation of all injuries, he might survive at the first, but the likelihood of death from continued hemorrhage is extremely high. Defining situations during which traditional approach of hemorrhagic control may be fatal is of crucial importance. Not only abdominal (major vascular and visceral injuries) or thoracic trauma (massive blunt torso trauma and multiple torso penetrant injuries), indications for DCS are all scenarios in critical injured patients where lifesaving is achieved with staged surgery techniques (6). Bleeding in complex trauma situations along with critical factors (severe metabolic acidosis (pH < 7.30), hypothermia (T < 35°C), resuscitation and operative time duration > 90 minutes, coagulopathy as a signal of developing nonsurgical bleeding, massive transfusions with > 10 units PRBCs is high selected indication for initiating DCS. To reduce the physiological burden of a major intervention, interventional radiology could be choice. However, angiography with embolization remains debated and is performed only in selected cases during acute phase (7). Angiography with embolization would be high effective within the "golden hour", as it can be successful only in small number of patients who don't have reliable signs of arterial injuries. Complications range between 2-4% because this is an invasive technique (8, 9).

The concept of DCS takes into consideration the influence of the "lethal triad" (hypothermia, coagulopathy and acidosis) and systematic inflammatory and metabolic reactions following trauma. The aim is to restore endpoints of resuscitation (normothermia, serum lactate ≤ 2.5 mmol/L stable hemodynamics without inotropic support, no hypoxemia, no hypercapnia, normal coagulation, urinary output > 1 ml/kg BW/h) by early transfer from operating theatre to the ICU. Damage control sequences in surgery include three stages, first stage within the operating theatre with aim to produce survival at the patients which were supposed to die (control of hemorrhage, control of contamination, intraabdominal packing and temporary closing), second stage in ICU (warming, correct of coagulopathy, hemodynamic normalization, ventilator support and identification of the injuries) and third stage again within the operating theatre with removing the packing and definitive repair. This strategy may increase survival for 20-77% (10).

DCS combats the "lethal triad" of trauma providing permissive hypotension and restrictive fluid resuscitation furthermore as well as hemostatic resuscitation and balanced blood product

resuscitation. If the "lethal triad" is present, its unlikely that the surgical control is going to be successful.

Critical Bleeding

Critical bleeding may appear not only as a result of uncontrollable hemorrhage from surgical sites, but also as a result of coagulopathy thatis present early in trauma. TIC appears early after injury (11), one in all among 4 trauma patients have coagulopathy at admission (12), with prevalence of 5-42% per different coagulation tests (13). TIC is responsible for most of traumatic bleeding with catastrophic consequences (14). Pathomechanism of early TIC remains unclear. Recent studies suggest that dilution, consumption and impairment of coagulation factors are accompanied with early TIC, but the foremost activating factor is the endogenous coagulation disturbance in trauma itself. Complex combination of bleeding-induced shock, tissue injury-related thrombin-thrombomodulin-complex generation and activation of anticoagulant and fibrinolytic pathways may result in early TIC (15). TIC with hyperfibrinolysis (due to reduced fibrin utilization because of systemic hypoperfusion), play remarkable role in severe bleeding. The detection of hyperfibrinolysis is very important because it is usually undetected, undeclared or unexplored. Hyperfibrinolysis might be detected at the earliest with rotational thrombelastometry (ROTEM) and is related to higher mortality in severe trauma (16). Coagulopathy could even be present later due to the blood loss as a consequence of inadequate surgical haemostasis and increased fibrinolytic activity. Mechanism of this later "iatrogenic" coagulopathy is multifactorial including consumption and dilution of coagulation factors, adverse effects of massive transfusion and "lethal triade" (17).

Coagulopathy Monitoring

Routine detection of coagulation profile early in trauma (in the first half-hour to 1 hour), with repeated and combined prothrombin time (PTT) measurement, values of activated partial thromboplastin time (aPTT), fibrinogen and PLTs levels, is incredibly important as these factors are independent predictors for mortality (18). Although intensive control of coagulation tests from standard monitoring is imperative for better treatment, at massive bleeding, the results might not be sufficient. Coagulation tests are performed at 37°C and do not reflect coagulation status of patient in hypothermia. Bleeding because of coagulopathy might appear with normal aPTT if the cell phase of coagulation is impaired. Tests from standard monitoring monitor the initial phase of coagulation and presents only first 4% of thrombin generation. Therefore, it is possible that the standard coagulation profile seems normal, while the overall state of blood coagulation is abnormal. The failure of coagulation monitoring is resolved with viscoelastic methods that may be performed to help characterize coagulopathy and guide haemostatic therapy (Grade 1 C) (19, 20). Point of care tests, ROTEM and thromboelastography (TEG) provide monitoring in real time and individualized patient treatment with coagulation factors. TEG is a very sensitive tool

for detecting disorders within the enzymatic phases of coagulation in critically injured patients. However, viscoelastic tests have limitations: defects in primary hemostasis cannot be diagnosed, these tests cannot predict bleeding during or after surgery as they can give coagulation status within the moment, TEG might not distinguish between coagulopathy caused by dilution from thrombocytopenia and finally there is a lack of sensitivity to platelet dysfunction because to antiplatelet drugs (21).

Therapeutic Options for Traumatic Hemorrhage

Excessive bleeding increases the requirement for blood transfusion. Traditional treatment at traumatic hemorrhage involved aggressive restoration of blood volume, replacement with fluids (crystalloids and colloids) for maintaining circulatory volume and use of blood products before surgery. Massive blood transfusions modulate the immunologic response, due to the abnormalities of electrolytes, clotting factors, pH and temperature and may compromise coagulation in trauma patients.

Instead of aggressive crystalloid – based resuscitation, protocolled – used **blood derivates** improve morbidity and mortality in traumatic hemorrhage (22). There is still a debate regarding optimal ratio of blood products, however recently, it is confirmed that with 1:1:1 ratio in relation to plasma, RBCs and platelets (PLT), trauma mortality was reduced (23).

Early administration of **tranexamic acid** (THA), and substitution of fibrinogen deficiency are additional tools for DCR haemostatic resuscitation. THA as a primary haemostatic agent not only reduces perioperative bleeding, but is also used in the prevention of potentially massive bleeding. CRASH – 2 trial confirmed the benefit of early treatment with THA within 1 hour from injury (loading dose of 1 g followed by infusion of 1 g over 8 hours) in trauma patients with hemorrhage significantly decreasing death rate and requirement for blood transfusions (24). In terms of THA safety, no increased risk including thromboembolic events and renal failure are found in trauma (25). The pre-hospital Anti-fibrinolytics for traumatic Coagulopathy and Hemorrhage (PATCH) multi-centre randomized, placebo-controlled study currently recruiting participants aims to answer the question whether administration of THA in severely injured adults as soon as possible would improve their chances of survival as well as recovery after six months (26).

The role of **fibrinogen** in major trauma is not any longer underestimated. During massive bleeding, fibrinogen is the first factor that reaches critically low levels (< 1.0 g/L) before the PLTs and other coagulation factors. It is crucial to maintain the plasma fibrinogen level above 1.5 g/L in order to achieve effective clot formation (normal plasma fibrinogen concentration range from 1.8 to 4.3 g/L; median=2.3g/l). Decreased fibrinogen values are result of systemic hypoperfusion which is related to decreased fibrin utilization and hyperfibrinolysis. Fibrinogen level is independent predictor of mortality at patients with trauma hemorrhage (27). Evidence of fibrinogen use in trauma patients with bleeding is not yet as clear as it is with fresh frozen plasma or platelets transfusion. Although more randomized studies are needed to confirm the

role of fibrinogen in improving survival in trauma bleeding patients, recently studies has confirmed that fibrinogen administration can reduced requirement for allogenic blood products (28). Fibrinogen can be supplemented by the use of cryoprecipitate, fresh frozen plasma (FFP) and human purified fibrin concentrate. FFP contains relatively low Fibrinogen, it is not known exactly how much there is fibrinogen and the risk/benefit from the use of FFP has not yet been accurately estimated. Cryoprecipitate and fibrinogen concentrate are safer and more effective (due to the fibrinogen concentrations) options.

Fibrinogen supplementation may partially compensate for thrombocytopenia, but severe thrombocytopenia may impair thrombus formation even if the value of fibrinogen and thrombin production are normal.

Initially, the **PLT** count in trauma bleeding is not reduced and it was found to be less than 150.000/μL in 4% of trauma patients with ISS score = 5, and in 18% of patients with ISS score > 45. PLT count doesn't represent their function. The mechanism of PLT dysfunction continues to be unknown, but may involve "PLT exhaustion," where PLT become activated en masse and are refractory to stimulation for up to 24 hours afterward (13). Other potential reasons for PLT dysfunction in trauma could be complement activation or inflammation. Even a small impairment of PLT function can increase mortality in trauma bleeding. Moreover, PLT dysfunction is going to be the earliest and the most sensitive indicator of TIC. PLT therapy is usually recommended only if the patient continued to bleed after fibrinogen supplementation and has a clear deficiency of platelets less than 50×10^9 /L.

When bleeding persists despite fibrin supplementation and a sufficient number of PLTs, this might be due to insufficient thrombus formation. This insufficient thrombin production is an independent predictor of mortality. In this case, treatment is continued with a **prothrombin complex concentrate (PCC)** which can be the first line therapy for thrombin deficiency in major bleeding. There are insufficient reports on the utilization of PCC in massive bleeding, however, recently studies has confirmed that four-factor PCC together with FFP can improve outcome and reduce transfusion requirements in trauma bleeding patients (29). However, if viscoelastic tests that ought to determinate PCC administration are not available, the International Normalized Ratio (INR) could also be considered to possess limited value for emergency PCC treatment.

If there is no PCC, the choice is **Recombinant-Activated Factor VII (rFVIIa)**. rFVIIa is the last rescue option when the first-line treatment (control use of blood products) fails to manage bleeding. However, within the absence of monitoring of the full hemostasis, the administration of PCC and rFVIIa is unacceptable.

Therapeutic strategy for coagulopathy bleeding is based on the principle of goal directed resuscitation with individualized and targeted therapy and relays on available resources. Rational strategy for emergency haemostatic management in coagulopathic bleeding in trauma patients when ROTEM and TEG aren't available, includes therapy in three steps: I. stopping hyperfibrinolysis with 10-20 mg/kg/BW – THA; II. Enabling thrombin formation with 4-8 g human

fibrinogen concentrate and PLT and III. Improvement in thrombin generation with ≤ 20IU kg/ BW PCC (30).

Conclusion

DCR strategy for the treatment of severe bleeding in trauma patients, may contribute to their better outcome. Surgical techniques for hemorrhage control, not definitive repair and goal directed therapy for coagulopathy, are cornerstones for successful management in these patients.

Declaration of interest

None declared.

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SEPSIS AND SEPTIC SHOCK – REVIEW OF CURRENT APPROACHES FOR PREVENTION, DIAGNOSIS AND TREATMENT

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Introduction

Sepsis and septic shock are ones of the most urgent health emergencies that require immediate treatment. Early diagnosis and appropriate management in the early hours after the development of sepsis is very important. The speed of reaction optimizes treatment and improves the outcome in these patients.

The best management practices continue to evolve with continuous follow up of the evidence based recommendations. This paper represents the latest recommendations and guidelines for the treatment of sepsis and septic shock.

According to WHO resolution from May 2017, sepsis and septic shock are a global health priority (1). It is an emergency affecting almost 49.9 million cases around the world each year and half of them, 20 million, are among children. Almost 11 million people per year worldwide died, which accounted for 20% of all global deaths, as many as one in four. It is estimated that near 3 million children younger than five years of age died as result of sepsis. Average 85% of sepsis cases and deaths are among people in low-and middle-income countries (2).

The COVID-19 crisis has shown us even more that sepsis, infectious diseases and antimicrobial resistance represents Global Health Threats of the 21st Century (1). In 2 to 5% of the patients with COVID-19 and in 25 to 50 per cent of all hospitalized, the complications were developed such as sepsis and septic shock.

In 2001, a scientific body consisting of experts named as Surviving Sepsis Campaign (SSC) was formed by the International Sepsis Forum, Society of Critical Care Medicine SCCM) and European Society of Intensive Care Medicine (ESICM). This scientific body had main goal to develop evidence-based guidelines and recommendations for the resuscitation and management of patients with sepsis. The first publication of the guidelines was developed in 2004, where new definitions and clinical criteria were established in 2004: "Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-associated Organ Dysfunction" (3). They have been updated every four year to the latest 2016 version, where two separate expert units established evidence-based recommendations for children and adults. They represent initial treatment options with clinician's decisions remaining the final ones, and are the adequate option in a hospital and emergency wards. Some of them can be used in and out of hospital environment having in mind the availability of resources.

Definition and Guidelines

The definition of sepsis has changed over the time and experts will continue to make evolvement in line with the scientific improvements in sepsis understanding as complex multifactorial condition.

In 1991 the first definition of **Sepsis** was announced as a systemic inflammatory response syndrome (SIRS) with suspected or confirmed infection and 2 or more of the following criteria (4):

- Hypothermia < 36°C or hyperthermia > 38°C
- Tachycardia ≥ 90/minute
- Tachypnea > 20/minute, or arterial partial pressure of carbon dioxide < 32 mmHg
- Leucocytosis >12*10^9/l or leucopoenia <4*10^9/l.

Severe sepsis was worsening of sepsis associated with organ damage due to hypoperfusion and hypotension.

Septic shock was described as final deterioration with clinically manifested organ dysfunction and hypotension resistant to volume resuscitation requiring vasoconstriction agents.

Definitions were updated in 2001 (5) and in 2004, the Surviving Sepsis Campaign guidelines adopted the definitions and published the first model protocol for sepsis care used globally (6).

In United States sepsis was differently defined as present infection with minimum 2 SIRS criteria; severe sepsis as sepsis with organ dysfunction and serum lactate > 2 mmol/L); and septic shock as sepsis plus resistant hypotension requiring vasopressors, or hyperlactatemia ≥ 4 mmol /L (7).

In 2016, new definitions and criteria were issued by the Third International Consensus Definitions for Sepsis and Septic Shock – Sepsis-3 committee (8):

• ***Sepsis***

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction is characterized by increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more.

Patients with suspected infection, can be rapidly detected for sepsis with bedside clinical scoring system known as quick SOFA (qSOFA), if they have at least 2 of the following clinical criteria:

- ○ tachypnea ≥22/min,
- ○ impaired mental status, or
- ○ systolic blood pressure ≤ 100 mm Hg

• ***Septic shock***

According to this last definition from 2016, septic shock is marked by circulatory, cellular, and metabolic irregularities associated to a greater risk of mortality. Patients with septic shock require vasopressor agents to maintain a mean arterial pressure of at least 65 mm Hg Serum lactate level is greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia.

The term 'severe sepsis' was removed.

Sepsis Pathobiology

Previously sepsis was understood as infection with at least 2 of the 4 SIRS criteria explained only as inflammatory reaction. New meaning of sepsis incorporates both, pro-and anti-inflammatory reactions (9). Irregularities in coagulation system, have great impact on prognosis (10, 11). The new definition emphasizes the importance of determinants as age, underlying comorbidities, surgical and other injuries, medications, and source of infection (12, 13). The immune system disturbances play a major role in the pathophysiology of sepsis. Pathogen factor responsible for the infection will trigger the host immune response. Organ failures are the consequence of this dysregulated immune response (14).

Diagnosis and Risk Factors

Sepsis is described as a syndrome and can be diagnosed by a presence of clinical signs and symptoms in a patient with suspected infection.

Table 1. ***Short view on the definitions of sepsis***

Sepsis and septic shock

1992 Definitions of sepsis and septic shock

Sepsis

- Suspected or confirmed infections
- Two or more systemic inflammatory response syndrome criteria of:
- Temperature >38oC or <36oC
- Heart rate >90 beats per minute
- Respiratory rate > 20 breaths per minute or a PaCO2 < 32 mmHg or mechanical ventilation for an acute process
- White blood cell (WBC) count of >12 × 109/L or < 4 × 109/L, or > 10% immature neutrophils

Septic shock

Sepsis with hypotension, despite adequate fluid resuscitation, along with the presence of perfusion abnormalities that may include lactic acidosis, oliguria, or an acute alteration in mental state

2016 Consensus definitions of sepsis and septic shock (Sepsis-3)

Sepsis

- Suspected infection AND
- An acute change in SOFA score of ≥2 points consequent to infection

Septic shock

- Sepsis
- Hypotension requiring vasopressor therapy to maintain a mean arterial blood pressure of 65 mmHg or greater
- Serum lactate level greater than 2 mmol/L after adequate fluid resuscitation

New changes in defining the sepsis and septic shock help to track more quickly the patients with higher risk and those who needed treatment in intensive care unit (15).

Previously sepsis diagnosis required the presence of infection plus two or more systemic inflammatory response syndrome (SIRS) criteria and term 'severe sepsis' equals severe organ insufficiency (16).

In new definition from 2016, diagnosis of sepsis requires an infection with organ dysfunction manifesting acute change in SOFA score of two points or more.

Septic shock indicates circulatory failure with resistant hypotension requiring vasopressors. To maintain mean arterial pressure (MAP) 65 mmHg with serum lactate ≥ 2 mmol/L. Oliguria, altered mental status and delayed capillary refill are auxiliary clinical signs of tissue hypoperfusion (18). Hyperlactatemia is not a specific sign of sepsis, but can be very helpful in determining the severity of septic shock and is important part of many treatment protocols (19).

Table 2. *Sequential Organ Failure Assessment-SOFA score (17).*

	Score				
	0	1	2	3	4
Respiration: PaO_2/FiO_2 (torr)	> 400	≤ 400	≤ 300	≤ 200 with respiratory support	≤ 100 with respiratory support
Coagulation: platelets (G/L)	> 150	≤ 150	≤ 100	≤ 50	≤ 20
Liver: bilirubin (μmol/L)	< 20	20–32	33–101	102–204	> 204
Cardiovascular: hypotension	MAP ≥ 70 mmHg	MAP < 70 mmHg	Dopamine ≤ 5 or Dobutamine (any dose)[a]	Dopamine > 5 or Epinephrin or Norepinephrin ≤ 0.1[a]	Epinephrin or Norepinephrin > 0.1[a]
Central nervous system: Glasgow Coma Score	15	13–14	12-Oct	9-Jun	< 6
Renal: creatinine (microM) or urine output	< 110	110–170	171–299	300–440 < 500 mL/day	> 440 < 200 mL/day

[a] Adrenergic agents administered for at least 1 h (doses given are in μg/kg/min).

Following the statistics, pulmonary origin of sepsis is the main reason for admittance in intensive care unit for the patients coming from general and emergency departments, and abdominal origin is characteristic for operated patients (Table 2).

Table 3. *Common sites of infection and causative microorganisms*

Common infection sites	Common microorganisms
Pulmonary	Pneumococcus, staphylococcus, atypical infections, such as mycoplasma and legionella, viruses and Gram negatives
Abdominal	Gram negatives such as Escherichia coli, Klebsiella, anaerobic organisms, Enterococcus, Candida
Skin/soft tissue	Streptococcus, methicillin-sensitive Staphylococcus aureus, Gram negatives
Urinary	Gram-negative bacilli, Enterococcus
Intravascular catheters	MRSA, Coagulase negative staphylococcus, Gram negatives
Central nervous system	Neisseria, pneumococcus, Gram positives
Endocarditis	MSSA, coagulase negative staphylococcus

The Importance of Early Recognition and Early Treatment

Sepsis is a condition when time of action is very important. But the first step is how quick sepsis will be recognized. Immediate treatment, with fluid resuscitation and early administration of effective antibiotics are second important step (20, 21) proven with lot of clinical data and associated to less mortality.

Data from two observational studies confirmed the significance of early antibiotic administration in first golden hour (20). For each hour of delay, the relative risk of death from sepsis or septic shock may increase by 4 to 8% (21).

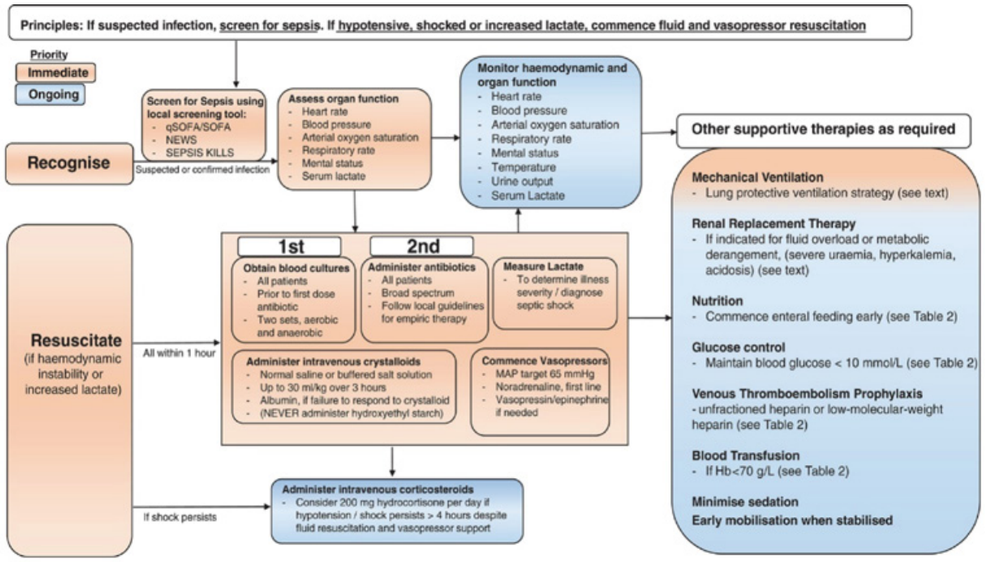
There are several screening tools helpful for recognizing the sepsis and septic shock and among them is a new quick screening tool known as quick SOFA score. This scoring system consists of three symptoms or clinical signs with assigned one point each:

- systolic blood pressure ≤100 mmHg,
- respiratory rate of ≥22 per minute,
- impaired mental status with GCS≤13.

This qSOFA scoring especially is helpful to identify patients with suspected sepsis placed in general hospital wards. Improved outcome is possible only when diagnosis and treatment of sepsis is fast without any delay, regardless of the used screening system.

Algorithm below presents screening and management in patients with sepsis and septic shock:

Figure. 1 *Flow diagram for the management of a patient with suspected sepsis*



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Management of patients with sepsis and septic shock

Hemodynamic management

The 2018 update of the Surviving Sepsis Campaign guidelines introduced the 'Hour-1 Bundle' which recommends treatment with intravenous fluids, measurement of serum lactate concentration as a marker of illness severity, administration of vasopressors, obtaining blood cultures and administering broad-spectrum antibiotics, all within the first hour (18).

In order to stabilize the hemodynamics, the primary treatment is fluid load with 30 ml/kg (cautiously in some patients) and vasopressor therapy needed to maintain a minimum of MAP of 65 mmHg.

Hypotension can be a sign of different pathological processes:

- Increased vascular permeability lead to hypovolemia and hypotension. Treatment is fluid resuscitation,
- Vasodilatation of venous and the arterial vessels treated with vasopressor agents,
- Sepsis-related myocardial dysfunction treated with positive inotropic agents.

Fluid overload (rate of 30 mL/kg over 3 hours) can be harmful in some patients especially in those with significant myocardial dysfunction. It is crucial to have into consideration all the patient related factors and treat cautiously,

Fluid resuscitation should start with crystalloid solution and sometimes albumin although there is no strong recommendation for doing this (23). Colloid solutions are not recommended because of possibility of acute kidney injury and death. Generally speaking, the minimum hemoglobin concentration below 70 g is a threshold for transfusion. Vasopressors should be initiated when MAP is below 65 mmHg.

The most commonly used vasopressor is Noradrenaline with or without Dobutamine. Adrenaline is associated to treatment-related lactic acidosis. Dopamine administration is currently under revision because its use is associated to significantly greater risk of cardiac arrhythmias. Phenylephrine in patients with septic shock results in higher in-hospital mortality (25). Vasopressin (26, 27), selepressin (28) and synthetic human angiotensin II (29), compared to noradrenaline are not superior. Levosimendan, is associated to some adverse effects.

Corticosteroids, Anti-inflammatory and Immune Stimulation

Corticosteroids act by immune modulation and cardiovascular modulation. The rationale for treating sepsis is the anti-inflammatory effects of corticosteroids.

Corticosteroid effects as hydrocortisone 200 mg per day were investigated in two separate clinical trials, ADRENAL and APROCCH.

Both studies in steroid group had findings of less blood transfusions, earlier release from intensive care unit, less time on mechanical ventilation and overall less mortality.

If fluid resuscitation and vasopressor therapy are sufficient enough to stabilize hemodynamics than it is not recommend to treat patients with corticosteroids. Intravenous hydrocortisone in dose of 200 mg per day is reserved only as final weapon in septic shock treatment protocols.

Renal Replacement Therapy (RRT)

Renal replacement therapy can be used for removing degradation metabolic products, fluid excess and other metabolic irregularities. It is interesting treatment for removing inflammatory mediators but currently there are no strong data that removing cytokines can improve outcomes for patients with septic shock (31, 32).

General intensive care management

- Mechanical ventilation with tidal volumes of 6 mL/kg.
- Plateau pressure of 30 cm H2O.
- A restrictive fluid administration.
- Prone position for 16 h each day.
- Extracorporeal membrane oxygenation (ECMO).
- Pharmacologic prophylaxis with unfractionated heparin or low-molecular-weight heparin.
- Non-pharmacological prophylaxis with anti-embolism stockings and passive and early mobilization.
- Recommend enteral nutrition within 48 h.
- Parenteral nutrition should be considered after one week of unsuccessful enteral nutrition.
- Blood glucose should be managed and blood glucose level is 6 to10mmol/L.
- Continuous or intermittent sedation should be minimized using short-acting sedatives including propofol and dexmedetomidine.
- Elevate bed head between 30 and 45º in mechanically ventilated patients.
- Active and early mobilization with patient participation.

Conclusion

Sepsis is a multifactorial syndrome, and its management is complex. It is an immense health issue seriously threating the global health having in mind that almost 11 million people die every year. Establishing a sound and trustworthy sepsis treatment protocol is being tremendous healthcare challenges,

Early recognition and rapid, appropriate treatment is crucial for saving millions of lives.

Revealing the whole pathological mechanism of sepsis and septic shock should be our future goal leading to improved evidence based guidelines and overall better outcome from sepsis and septic shock treatment.

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ANTIBIOTICS AND ANTIMICROBIAL RESISTANCE

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ABSTRACT

Man and the microbial world have had coexistence since the beginning of the world. But while some bacteria are able to establish a symbiotic balance with humans by providing a protective and stabilizing effect on the body, other bacteria attack and grow in human tissues causing disease.

An antibiotic is a type of antimicrobial substance active against bacteria and the most important agent for fighting bacterial infections. Antibiotics have been used since ancient times, but they caused a real revolution in the medicine in the 20th century. Proper classification and adequate understanding of how antibiotics work is especially important in the healthcare delivery process, and the use of antibiotics should always rely on the overall intended benefit, taking into account the adverse side effects.

On the other hand, the effectiveness and easy access to antibiotics have led to their overuse, and thus the emergence of resistance. Antimicrobial resistance is defined as the resistance of a microorganism to an antimicrobial drug that was once able to treat an infection with that microorganism. Resistance is a property of the microbe, not of a person or other organism infected with a microbe. Antimicrobial resistance is an ever-increasing public health problem worldwide. The low rate of detection of new antibiotics, together with the rapid spread of drug-resistant bacterial pathogens, is causing a global health crisis.

The rate of resistance to bacterial pathogens is growing rapidly in both intensive care units, despite advances in modern medicine and intensive care. Infections caused by these resistant pathogens are difficult to treat and are associated to increased morbidity, mortality and cost.

Hence, in this review we will consider the classification of antibiotics, their mechanism of action, with special emphasis on the mechanism of bacterial resistance.

Introduction

Antibiotics are used from very long time. Many civilizations have used the local application of moldy bread and many calls are arising from many ancient civilizations about its advantageous and promising effects. Antibiotics make a real revolution in medicine in the twentieth century. Sir Alexander Fleming, an English bacteriologist, in 1928 accidently discovered the first antibiotic named Penicillin after the fungus Penicillium notatum, while the first clinical trials and use in humans were reported in 1940 (1).

An antibiotic is a substance produced by one microorganism that selectively kills or inhibits the growth of another. It is very important in fight with bacterial infections and it is broadly used in the treatment of these infections.

Butantibiotics are not totally selective, fighting with bacteria they also fight and destroy some useful microorganisms that are in our systems and that we need. We should all be aware of this, take into account all the side effects before prescribing and taking antibiotics without real need.

On the other side, the productivity, the success, the effectiveness and the simple, easy access to antibiotics made the way to their overuse and some bacteria developed resistance against antibiotics. The World Health Organization (WHO) has classified antimicrobial resistance as a widespread “serious threat that is no longer a prediction for the future, it is happening right now in every region of the world and has the potential to affect anyone, of any age, in any country” (2). A human cannot be resistant to antibiotics, it is a possession of the bacteria, not the human infected.

Antimicrobial resistance (AMR) is an increasing medical problem in the world. The small amount of new antibiotic detection, together with the fast expansion of bacteria resistant to many drugs is becoming a huge health problem. Antimicrobial resistance is rising worldwide, especially in developing countries. The Centers for Disease Control and Prevention guesse that 2 million people only in the US will develop an AMR infection every year that will lead to 23,000 mortalities (3). Worldwide, prediction is that 10 million people per year will be dead as a result of AMR infectionsby 2050 (4). Currently, treatment options are limited and overused, so the search for new antibiotics is crucial.

The prevention of the uncontrollable use of antibiotics plays the largest role in the decline of AMR. And the prevention includes prescribing or consuming antibiotics only when needed. Some antibiotics with narrow spectrum are better to use than broad spectrum antibiotics whenever it is possible, because they can lead to lesser resistance and smaller amounts of side-effects.

The aim of this paper is to review the classification of antibiotics, their mechanism of action, brief spectrum of activity and the mechanism of bacterial resistance.

CLASSIFICATION OF ANTIBIOTICS

There are many ways of classifying antibiotics. The most common classifications are based on their molecular or chemical structures, their type of action and spectrum of activity (5).

The first classification is based on chemical or molecular structures, whereby antibiotics are divided into: Beta-lactams, Macrolides, Tetracyclines, Quinolones, Aminoglycosides, Sulphonamides, Glycopeptides and Oxazolidinones. Antibiotics that belong in the same group are in general with comparable form of efficacy, allergic reactions and adverse effects.

According to the mode of the action, antibiotics are divided into two groups: bactericidal that kill bacteria and bacteriostatic antibiotics that limit the growth of bacteria. These two groups can interfere between themselves, so exact distinction is not possible.

The third classification is according to the spectrum: broad spectrum antibiotics, that are used for infections where specific microbe is undetermined and narrow spectrum antibiotics that can be more successful in some type of infections when the type of microbe is familiar.

In this review we will look at antibiotics in terms of their structure.

Beta-lactam Antibiotics

Beta-lactam antibiotics are very wide group, with same structural characteristic – the beta-lactam ring. They are the most frequently prescribed antibiotics. This group of antibiotics include: Penicillins, Cephalosporins, Carbapenems, Monobactams andBeta-lactamase inhibitors.

The mechanism of action of the beta-lactam antibiotics is the inactivation of the cell wall synthesis, by disabling the enzymes in the cell wall tissue, known as penicillin binding proteins.

The main mechanism of resistance of this type of antibiotics is the production of enzymes that split penicillins, cephalosporins, or two of them (penicillinases, cephalosporins, beta-lactamases). Some changes in the enzymes can also be a reason for resistance (6).

Penicillins

Penicillin is a group of antibiotics, derived originally from common moulds known as penicilinium moulds. It is the first discovered antibiotic and penicillins are probably the most secure antibiotics. Based on the range of bacteria against which they are active, penicillins can be classified into the following categories:

- Penicillin G is highly active against the most gram-positive cocci, gram-positive rods, gram-negative cocci and anaerobes. Some bacteria that belong to these classes developed resistance to penicillin.
- Antistaphylococcal penicillins (nafcillin, oxacillin, cloxacillin and dicloxacillin). These groups are used for treatment of penicillinase-producing staphylococci.
- Broad-spectrum penicillinsare well known for the treatment of gram-negative bacteria. These agents have been stratified into: the second generation (ampicillin, amoxicillin and related agents), the third generation (carbenicillin and ticarcillin) and the fourth generation (piperacillin).

Cephalosporins

Cephalosporins cover extensive assortment of organisms, and in general, are good accepted and tolerated, and simple for administration and processing. They are the most frequently prescribed and administered antibiotics; more precisely, they make up one third of all prescribed and administered antibiotics by the National Health Scheme in the United Kingdom (7).

In clinical practice, cephalosporins are grouped into five "generations" based upon their spectrum of activity and each new generation has wider activity against aerobic gram negatives.

- The first-generation parenteral cephalosporins cover the most gram-positive cocci (staphylococci/streptococci), but not enterococci, oxacillin-resistant staphylococci, and penicillin-resistant pneumococci. They also cover *Escherichia coli*, *Proteus mirabilis* and *Klebsiella pneumoniae*.
- The second generation cephalosporins are divided into two groups. The first subgroup covers *Haemophilus influenzae* and *Moraxella catarrhalis, while the second* subgroup are the cephamycins, which cover many strains of *Bacteroides*.
- The third-generation parenteral cephalosporins are with smaller activity for gram-positive cocci, but are highly active against Enterobacteriaceae, *Neisseria*, and *H. influenzae*. Ceftazidime also cover *Pseudomonas aeruginosa*.
- The fourth-generation parenteral cephalosporins have parallel activity as the third generation cephalosporins, but covering also *P. aeruginosa*.
- The fifth-generation parenteral cephalosporin ceftaroline has activity against methicillin-resistant staphylococci, penicillin-resistant pneumococci, and enteric gram-negative rods.

Carbapenems

Carbapenems have extremely wide spectrum of antimicrobial activity. Nowadays, these agents are among the most powerful antibiotics, and they are administered when patients with infections are severely ill or suspected of having resistant bacteria, so they are often called "antibiotics of the last resort". They cover a big list of gram-negative organisms, together with the ones that produce beta-lactamases, many anaerobes, involving *B.fragilis*, and finally gram-positive organisms. Imipenem, meronem, ertapenem and doripenem are representatives of carbapenems.

Unfortunately, bacterial pathogens resistant to this class of antibiotic-saving have been reported. Bacterial resistance to carbapenems is increasing globally and is rapidly becoming an international interest (8).

Monobactams

Aztreonamhas single Betalactam ring, it has very good cover for a gram-negative bacteria, with Neisseria, Haemophilus Sp, intermediate on *P. aeruginosa*, but very poor activity against gram-positive organisms or anaerobes.

Beta-lactamase inhibitors

Clavulanate, sulbactam, tazobactam, avibactam, vaborbactam and relebactam are beta-lactamase inhibitors. In general, they have small antimicrobial action, however they obstruct the activity of many plasmid-mediated beta-lactamases. Mixture of these agents with ampicillin, amoxicillin, piperacillin, ceftolozane, orceftazidime results in antibiotics with an intensified spectrum of action that cover many bacteria containing plasmid-mediated beta-lactamases. The addition of avibactam to ceftazidime, vaborbactam to meropenem, and relebactam to imipenem opened a new era for fighting bacteria that are producing carbapenemases.

Fluoroquinolones

Fluoroquinolones are bactericidal antibiotics that have very favorable pharmacokinetic belongings, like big volume of distribution and very wide antibacterial spectrum.

Fluoroquinolones are inhibitors of DNA synthesis, binding to the A sub-unit of DNA gyrase and preventing supercoiling of DNA.

Their spectrum of activity is very broad, they covergram-positive, gram-negative, anaerobes, mycobacteria and many common respiratory pathogens.

Representatives of fluoroquinolones are:

- Ciprofloxacin that covers gram-negative bacilli, including *P. aeruginosa;*
- Levofloxacin that hasbigger activity against gram-positive bacteria, while less action against *P. aeruginosa;*
- Moxifloxacin covers gram-positive organisms and few anaerobes, but is very effective against mycobacteria;
- Delafloxacin is the most recent fluoroquinolone. It also covers anaerobes, but it is the first quinolone that covers methicillin-resistant *Staphylococcus aureus* (MRSA). However, clinical practice with delafloxacin is very partial.

Bacterial resistance to fluoroquinolones is becoming international problem and it is chromosomally encoded.

Aminoglicosides

The aminoglycoside group of antibioticsinvolves a lot of different agents: gentamycin, tobramycin, amikacin, plazomycin, streptomycin, neomycin and paromomycin, all of them available for medical use. But gentamicin, tobramycin, and amikacin are used the most commonly.

Aminoglycosides bind to the aminoacyl site of the 30S ribosomal subunit (it is a complex of 16S ribosomal RNA and 19 proteins), inhibiting the translocation of peptidyl-tRNA and also causing misreading of mRNA, leaving the bacterium unable to synthesize proteins vital to its growth.

This group of antibiotics is mainly used for the treatment of severe infections caused by aerobic gram-negative bacillis (9). Also, not so often they can be used in for the management of some gram-positive infections.

Resistance to aminoglicosides is rare. It is usually a result of inactivation of the drug by enzymes produced by bacteria or throughout an efflux system that reduces the accumulation of aminoglycosides.

Glycopeptides

Vancomycin, teicoplanin, telavancin, dalbavancin, oritavancin belong to this group of antibiotics, although vancomycin is its most popular representative.

Glycopeptides inhibit peptidoglycan synthesis, compromising the subsequent enzymatic steps in the synthesis of cell wall.

Vancomycin is used for treatment of patients with suspected or proven invasive gram-positive infections, including MRSA. It is antibiotic for which there is the biggest medically proven understanding for treatment of infections produced by MRSA (10).

Individualization of the dosing regimen of vancomycin and frequent reassessment are needed to optimize drug efficacy, minimize toxicity and minimize appearance of resistance.

Variety of genes are responsible for the resistance to vancomycin. The end result is the replacement of peptidoglycan precursors, to which vancomycin binds with significantly lower affinity (11).

Lincosamides

Lincosamides are class of antibiotics that include clindamycin and lincomycin. Their mechanism of action is mainly to bind to the 50 S ribosomal subunit of the bacterial ribosome and to inhibit protein synthesis. Some other different antibiotics like macrolides have the same mechanism of action and can compete in binding to the ribosomal subunit.

Clindamycin is a representative of this group and it is used in the therapy of anaerobic, streptococcal and staphylococcal infections.

There are few mechanisms of bacterial resistance to clindamycin, involving drug inactivation, drug efflux or adjustment of the target. Resistance has been conferred by both plasmid-and chromosomally mediated mechanisms.

Macrolides

Macrolides are a class of natural products; they have a broad spectrum of antibiotic activity and are usually used in patients with penicillin allergy (12).

Their mechanism of action is: they bind tightly to the 50S subunit of bacterial ribosomes, preventing exit of the newly synthesized peptide and hence blocking bacterial protein production.

Azitromycin and clarithromycin are macrolide antibiotics, products of the erythromycin. They also have wider spectrum of activity than erythromycin and they cover some gram-positive and gram-negative bacteria, some mycobacteria and atypical pneumonia pathogens (13).

There are two main mechanisms of developed macrolide resistance: methylases change the binding site on the bacterial ribosomal RNA, that present high level of macrolide resistance and active efflux pumps for macrolides that present low to medium level of macrolide resistance.

Oxazolidinones

Linezolid is a bacteriostatic, synthetic oxazolidinone antibiotic used in vancomycin-resistant enterococci (VRE) infections.

It is protein synthesis inhibitor that binds to the 50S ribosome, preventing peptide bond formation and thus the addition of new amino acids (14).

Linezolid is mainly used parenterally, although it can be used also orally.

Early data on linezolid were obtained in setting up sympathetic use programs. One report describing its sympathetic use in nearly 500 patients with various VRE infections, reported a cure in 81 percent of the cases (15).

Resistance to linezolid is usually a product of mutations or possessions of other organisms.

Tedizolidis a newer drug in the same class as linezolid; data on its efficacy for treatment of MRSA bacteremia are limited.

Polymyxins

Polymyxins are the independent class of antibiotics; various combinations are involved. Nevertheless, only polymyxin B and polymyxin E (colistin) are used in medical practice.

Polymyxins bind to the 50S subunit of the ribosome preventing association to the 30S subunit. They also inhibit protein synthesis by preventing formation of the first peptide bond.

Polymyxin B and colistin have narrow antibacterial spectrum, they are primarily used for infections due to multidrug-resistant organisms, such as carbapenem-resistant Enterobacteriaceae, Pseudomonas aeruginosa and Acinetobacter spp. They are also used for treatment of cystic fibrosis in aerosolized form. (16)

Acquired resistance to polymyxins is rare, but increasing worldwide, especially among carbapenem-resistant gram-negative bacilli. The mechanisms of polymyxin resistance remain the subject of ongoing researches, although a common mechanism appears to be modification of the lipid A component of lipopolysaccharide.

Sulfonamides

Sulphonamides are reportedly, the first group of antibiotics used in therapeutic medicine, and they still play very important role in medicine. They cover both gram-positive and gram-negative bacteria, but are the most frequently used for urinary tract infections.

Sulfonamides are inhibitors of folic acid synthesis (bacteria cannot use preformed folic acid). Theyalso inhibit bacterial growth by preventing the synthesis of tetrahydrofolate, which consequently inhibits DNA synthesis. (17)

Trimethroprim-sulfamethoxazole (TMP-SMX) is also known as co-trimoxazole and is a combination of two antimicrobial agents (one sulfonamide) that act synergistically against a wide variety of aerobic gram-positive and gram-negative bacteria and some protozoa.

Tetracyclines

Tetracyclines are class of antibiotics with wide spectrum.

The first tetracycline was chlortetracycline, revealed in 1948. Since then until nowadays, many other tetracyclines have been discovered. Doxycycline and minocycline are used the most often. The next studies and explorations in the field of tetracyclines ran into the discovery of the glycylcyclines. Tigecycline was the first of this new class of agents and exhibits broad-spectrum antibacterial activity similar to the tetracyclines (18). Newer agents approved in 2018 include eravacycline, sarecycline and omadacycline.

Tetracyclines interact with the 30 S subunit of the bacterial ribosome and prevent binding by tRNA molecules blocking protein synthesis.

The tetracyclines are active against some aerobic gram-positive and gram-negative bacteria, atypicals and spirochaetes.

Resistance to tetracyclines develops with prevention of the gathering of the antibiotic in the cell withreducing influx or expanding efflux. Usually there is a cross resistance inside all tetracyclines, if there is resistance to one drug, there is resistance to all of them.

Conclusion

The continuous detection, development and introduction of antibiotics in our health care system have helped significantly in our fight against infectious diseases caused by bacteria. However, the persistent appearance of bacteria resistant to virtually all known antibiotics is a matter of serious concern, so the search for new and more effective antibiotics continues undiminished. Adequate characterization and understanding of the exact function of antibiotics is of utmost importance to the protection of the health care delivery system.

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MAJOR OBSTETRIC HEMORRHAGE

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Major obstetric hemorrhage (MOH) is one of the leading causes of maternal morbidity and mortality in the obstetric practice. Life-threatening hemorrhage occurs in around one in every 1000 deliveries with significant differences between developed countries and third world countries. It is reported that massive obstetric hemorrhage in Africa and Asia is responsible for 30% of maternal deaths while in the UK and the US it is accountable for 3.4% and 11.4% respectably (1, 2,3). In 2015, MOH is reported in 8.7 million cases which led to 83,000 deaths (4).

There is no universal statement on the unique definition of massive obstetric hemorrhage. However, according to the most institutions, it is defined as a blood loss of more than 1500 ml or a fall in hemoglobin levels under than 4 g/dl. Also, blood loss greater than 3000 ml in less than 3 hours (50% of blood volume) or blood loss of 150 ml/minute in 20 minutes (>50% of blood volume) or the need for transfusing more than 4 units of blood during pregnancy, child birth or in the postpartum period may represent MOH.

Major obstetric hemorrhage owns typical features and differs from surgical hemorrhage in non-pregnant population. Several factors are responsible for such a phenomenon:

Early diagnosis of hypovolemia is impaired; the physiological changes associated to pregnancy (cardiac changes by term is increased in stroke volume by 30%, heart rate by 10-15 b/min and cardiac output by 50%, peripheral vascular resistance decreased) may mask the early signs of shock like tachycardia and increased systemic vascular resistance; hemodynamic collapse occurs only when almost 40-45% of circulating volume is lost. All these factors may lead to delay in recognition of blood loss and initiation of life-saving treatment (16, 17);

Difficulty in exact blood loss estimation. The ability to estimate blood loss in parturient is compromised due to the mixing of blood with amniotic fluid or concealment of blood in the uterus, peritoneal cavity or retroperitoneal space;

High placental blood flow. The utero-placental unit in the third trimester has a potential source of rapid and life treating bleeding, because it receives 12% of the cardiac output at term pregnancy (i.e. 700 ml/min);

Inability to recognize the risk factors: special care and attention is needed to identify the risk factors responsible for hemorrhage in the obstetric period (11). Ultrasonography helps in diagnosing the cause of hemorrhage and may help also to confirm the presence of concealed hemorrhage in asymptomatic patient.

THE CAUSES FOR OBSTETRIC HEMORRHAGE: depending on the time of the pregnancy and onset time, MOH can be classified into three types: antepartum, intrapartum and postpartum.

The most common factors for **ante and intra partum causes** of hemorrhage are: placenta praevia, both placenta accrete and pancreta, placental abruption, uterine rupture and trauma. Placenta accrete (pancreta) are abnormal implantations of the placenta with partial or complete infiltration in the myometrium of the uterus; placenta previa is also an abnormal implantation of the placenta low in the uterus and over the uterine cervix. Placental abruption is abnormal separation of the placental lining from the uterus. Maternal hypertension, preeclampsia, trauma, advanced age, history of previous abruption, multiparity, elderly primigravida and previous uterine surgery are all risk factors for developing a placental abruption or placenta previa. Uterine rupture is regarded as being a life threatening emergency with a very high morbidity and mortality rate although it is regarded as a very rare cause of APH (7).

Post-partum hemorrhage (PPH) is the most commonly ascribed as forms of **4 T's** – tone (utery atony), trauma, tissue (retention), thrombin (coagulopathy), Table1.

Table 1. *Risk factors for PPH.*

Classification	Risk factors
Tone (utery atony)	Multiple pregnancy Previous PPH Obesity (BMI>35) Large baby (>4kg) Prolonged Labor (>12hrs) / prolonged 2nd stage Advanced maternal age (>40 years, primiparous) Retained placenta Asian ethnicity Placenta Praevia
Tissue	Retained placenta Placenta accreta, increta and percreta (high mortality: associated to previous caesarean section)
Trauma	Delivery by caesarean section (emergency>elective) Operative vaginal delivery Mediolateral episiotomy Large baby (>4kg)
Thrombin	APH (placental abruption) Pre-eclampsia Sepsis
Other	Pre-existing coagulation problems, thrombocytopaenia, women taking anticoagulants

UTERINE ATONY is the most common cause of PPH with prevalence of over 70% of cases. Genital tissue trauma can be associated to operative cesarean delivery, episiotomy and delivery of a neonate of >4kg.

The causes of COAGULATION PROBLEMS may be preexisting, as congenital disorders or they can be acquired. The most usual ante-natal bleeding disorders seen in pregnancy involve von Willebrand disease and other coagulation factor deficiencies; inherited disorders in platelet number and/ or their function. Acquired coagulopathy in the post-partum period can be due to DIC that evolves in patients after massive abruptions, amniotic fluid embolism and can also be associated to prolonged carriage of a dead fetus (Table 2).

Table 2. *The most frequently causes of DIC related to obstetrics:*

Causes of DIC related to obstetrics:
Intrauterine death (>2 weeks previously)
Amniotic fluid embolus
Sepsis
Pre-eclampsia
Placental abruption
Retained products of conception
Induced abortion
Excessive bleeding
Acute fatty liver

Dilutional coagulopathy after bleeding can occur due to hemodilution from the replaced blood (80%) with large volume of fluids replacement that do not contain adequate coagulation factors, making patients prone to develop DIC. Hypothermia and acidosis can worsen the situation. The use of anticoagulants (LMWH) during pregnancy can also be associated to PPH. APH and PPH can present as vaginal or can be concealed, so a high clinical suspicion should always be aroused in patients with existing potential risk factors for these conditions.

MANAGEMENT OF MAJOR OBSTETRIC HEMORRHAGE: Basically, one of the main problems in obstetric hemorrhage is to try to differentiate between bleeding caused by tissue and vascular injury and bleeding due to a concurrent impairment of coagulation. Regardless of the primary cause of hemorrhage, inevitably all will result in coagulopathy if early treatment is not successful (8). Management of MOH is focused toward 1. maternal resuscitation and 2. treatment of the cause of the hemorrhage.

1. Maternal resuscitation

In a massive hemorrhage or patient in clinical shock, parturient need active resuscitation. Maternal resuscitation should be done with the aim of volume replacement and improving the oxygen carrying capability (9, 10). Irrespective of the degree of hypovolemic shock, fluid therapy is the best guided by continual assessment of maternal vital signs, hemoglobin, acid base balance and urine output. Signs suggestive of hypovolemia in APH patients should be monitored carefully, but practitioners should be aware that the extent of bleeding is almost always underestimated in obstetric patients (Table 3).

Table 3. *Typical signs in hypovolemic in non-pregnant populations.*

Assessment of intravascular depletion: signs suggestive of hypovolemia
a. Hypotension
b. Heart rate > 120 beats/minute
c. Urine output < 0.5 ml/kg/minute
d. Capillary refill time < 5 seconds

** Early signs of hypovolemic may be impaired in obstetric patients.*

Following factors need to be addressed as the **first step of maternal resuscitation** in MOH (Table 4):

Table 4. *First step measures for MOH.*

Protocol for resuscitation in massive hemorrhage
Assess airway
Assess breathing
Evaluate circulation
Oxygen by mask: 10-15 liters/minute
Intravenous access – 14 G cannula x 2, central venous cannulation in. CVK in collapsed pts
Left tilt position
Keep the mother warm using appropriate available measures
Until blood is available, infuse up to 3.5 liters of crystalloid (RL 2 liters, avoid hypertonic solutions) and/or colloid (1-1.5 liters) as rapidly as possible
The fluid should be adequately WARMED.
Special blood filters should NOT be used as they slow the rate of infusion.

Special care should be given not to infuse cold fluids in order to prevent hypothermia and coagulopathy. Hypothermia and acidosis significantly impair coagulation. For those reasons, all i.v .fluids should be warmed and the patient's temperature must be maintained if necessary by active warming.

Once 3.5 l of warmed crystalloid (2500ml) and/or colloid (1000ml) have been infused, further resuscitation should continue with blood. Blood transfusion should always be initiated as early as possible in MOH. When cross matched blood is not available, uncrossed group specific blood or 'O' – negative blood should be given. It is very important to remember that hemorrhage results in the loss of not only red blood cells, but also blood components and platelets. There is recent data from military institutions that aggressive replacement of coagulation products may improve outcome. Once four units of packed red blood cells (RBCs) have been transfused, consideration should be given to the replacement of other blood components (1:1 ratio of RBC to FFP) (18). Transfusion of RBCs alone increases the oxygen carrying capacity of blood, but will not correct an underlying coagulopathy.

The best way to guide transfusion procedure is based on regular full blood count and coagulation's studies, however in a major hemorrhage, waiting for coagulation results from the laboratory must not delay transfusion of coagulation factors. Treatment goals transfusion used by the UK military provide useful guidelines for patients with MOH. The following may serve as a guide to the main hematological goals in the management of massive blood loss (Table 5).

Table 5. *Guide to use of blood products in MOH.*

UK military
Hb > 8g.dl-1 If less, transfuse RBCs
INR < 1.5 If prolonged, transfuse Fresh Frozen Plasma (FFP)
Platelets > 50 × 10^9/l-1 if less, transfuse platelets
Fibrinogen > 1.5 gl-1 if less, transfuse cryoprecipitate 1unit/5 kg

Suspicion of disseminated intravascular coagulation should prompt earlier administration of platelets and cryoprecipitate.

Monitoring treatment of MOH: Rapid administration of large quantities of stored blood components in MOH will result in a profound metabolic disturbance. The severity of this metabolic disturbance is unpredictable, but must be anticipated and managed to prevent avoidable morbidity and mortality. Close monitoring is essential to guide therapy and minimize the potential complications of massive transfusion. Pathology monitoring may be via the laboratory or through the use of Point of Care Testing (POCT).

The two most important biochemical disturbances complicating massive transfusion are hyperkalemia and hypocalcaemia. Maintenance of normal calcium concentrations during hemorrhage helps prevent coagulopathy also. Ten milliliters of 10% calcium chloride per 4 units packed red cells or blood are part of the routine management of hemorrhage by the military.

Fresh frozen plasma should be given in a ratio to 1:1 to blood and early transfusion of platelets should be considered (11). With the recommendations in the British Committee for Standards in Hematology guidelines, fresh frozen plasma is usually given empirically without waiting for the coagulation screening in patients in which we consider to have coagulation alteration (placental abruption, amniotic fluid embolism, dead fetus) or in phase of extended bleeding (18). Treatment with 1 liter of FFP and 10 units of cryoprecipitate (2 packs) can be given, while awaiting coagulation studies (17). The goal is to maintain thrombin and fibrinogen generation while replacing factors of coagulation as early as possible (12). Giving unnecessary plasma and platelets should be discouraged in order to reduce the risk of transfusion-related acute lung injury. Point of care coagulation tests may aid decision-making and reduce unnecessary transfusions.

Fibrinogen is essential for coagulation and is a vital component in the coagulation pathway. It is massively consumed during major obstetric hemorrhage and levels rapidly decrease early in the hemorrhage. During pregnancy, fibrinogen levels increase and women should be considered severely hypofibrinogenemic and transfused fibrinogen if levels fall below 1.5 g/l. It is recommended to give fibrinogen rich products (FFP; cryoprecipitate, fibrinogen concentrate) with the aim to keep fibrinogen levels above 2 gr/L. Low fibrinogen levels <2gr/L is predictor for major obstetric hemorrhage. The other advantage of giving cryoprecipitate and fibrinogen concentrate is that they don't cause volume overload or haemodilution (12).

Prothrombin complex concentrate **(PCC)** is a derivate from the cryoprecipitate supernatant from large plasma pools, from which antithrombin and factor XI are removed. 2 variants exist – 3 factor PCC (factor II, IX, X) and 4 factors PCC (factor II, VII, IX, X). Before the era of recombinant factors it has been used as a treatment for hemophilia. Now, its clinical use is mainly as replacement therapy in emergency settings. Several studies have shown that PCC can reduce the need for transfusion in patients with major hemorrhage (20). It can be administered prophylactically in patients with coagulopathy (prolonged PT/INR) or can be administered in patients with postoperative bleeding with a normal coagulation profile (off label indication).

Despite the limited evidence for its use, *activated factor VIIa* can be used as a treatment option for the coagulopathy caused by a MOH, but only if the patient has adequate concentrations of fibrin-more than 1 g/l and platelets-more than 20×109/l. Using activated factor VIIa, raises a major concern about the risk of thrombosis (13). According the Green-top Guideline No. 56, recombinant factor VII should only be used if coagulopathy cannot be corrected by massive blood component replacement as it causes poorer outcome in women with AFE (16).

Tranexemic acid **(TA)** is an antifibrinolytic and is recommended by the WHO to be used in MOH, independently of the cause. The WOMAN trial revealed that TA should be started in the first 3 hours after PPH in a dose of 1 gr, repeating the dose in the next 30 minutes if the bleeding doesn't cease. Prolonging its initial use reduces its effect, with no effect if given 3 hours after onset (14, 15).

Patients in which we have clinical suspicion for major bleeding should be promptly treated based on preemptive knowledge. Throughout the treatment Hb, hct and coagulation profile should be repeatedly screened, but time should not be wasted to wait for laboratory results. If available TEG and ROTEM can be used to guide the treatment of the coagulopathy.

The main therapeutic goal management of massive blood loss are summarized in Table 6.

Table 6. *Treatment targets for massive transfusion.*

Physiology	***Hematology***	***Biochemistry***
Systolic Blood pressure of 90 mmHg	Hemoglobin>8 g/l	Ionized Ca2+ >1.0 mmol/
Urine output of at least 0.5 ml/kg/hr	Hematocrit> 3%	Lactate < 2 mmol/l l
Core Temp > 36 C	Platelet count >75 × 109 /l	Base Deficit 3%
	Fibrinogen > 1.5 g/l	K+ < 5.0 mmol/l
	PT and APTT < 1.5 x mean control	Core Temp > 36 C
	pH >7.3	

***** *From a guideline from the British Committee for Standards in Hematology.*

2. Treatment of the causes of the hemorrhage.

Pharmacological treatment options include uterotonic drugs. These drugs treat and prevent uterine atony as the main cause of PPH and can control and prevent the development of a MOH. Various uterotonic drugs are used, all of which should be used with caution:

Oxytocin is the first line treatment for uterine atony, but it should be used with care in patients with decreased vascular volume because it can precipitate tachycardia and hypotension. It reduces the risk of PPH by 60% (7). It causes vascular muscle relaxation which can cause hypotension with a reflex tachycardia. This may occur particularly if it is given as a bolus dosage, so this bolus should not exceed 5 units i.v., which may be repeated and should always be given slowly. This is commonly followed by an infusion at 10 unitsh−1.

Ergometrin is recommended as a second-line uterotonic. It can be given i.v., but the risk of severe adverse reactions is increased. It can worsen hypertension and is contra-indicated in hypertensive conditions and preeclampsia as it may provoke prolonged severe hypertension. The recommendation usage is i.m. (500μg) or slow i.v. (250 – 500 μg) only in a life-threatening emergency.

Carboprost -methyl prostaglandin F2-a is used when other uterotonic drugs fail to cease PPH due to uterine atony. It is contraindicated in patients with asthma due its ability to cause bronchospasm. It can also cause nausea and vomiting.

Misoprost – prostaglandin F1 is also when other uterotinic drugs fail to control the bleeding. It can cause transient increase in temperature and shivering.

Surgical management may be needed to manage MOH. This includes removing of the residual placenta, intra-uterine balloon tamponade, uterine and hypogastric artery ligation or uterine suture and abdominal hysterectomy (HTA). The decision to perform a HTA should be considered in patients in which previous medical procedures are not successful and the patient continues to bleed and becomes hemodynamic unstable. The focus of resuscitation in these patients should be preservation of their lives rather than preservation of theirs uterus.

CONCLUSION

Obstetric hemorrhage is frequently underestimated, so identification of risk factors and early recognition of MOH is priority for successful outcome. The role of anesthesiologists is crucial, but the management of hemorrhage should be multidisciplinary with precise plan of action. All obstetric units should have a protocol for the management of hemorrhage and immediate access to O-Rhesus negative blood. Call for senior help is important. Early transfusion of blood and blood components reduced the incidence and severity of coagulopathy and other complications. If hypofibrinogenemia is identified during PPH, fibrinogen substitution may be an important early intervention. Mandatory testing of coagulation is recommended to allow rational use of products.

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HAEMOSTASIS AND HAEMORRHAGE

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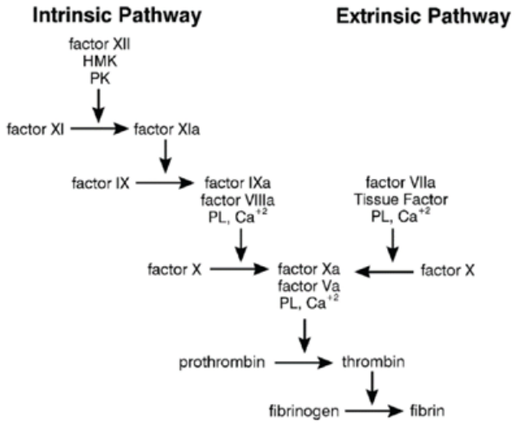
1. Haemostasis

Normal haemostasis practically incorporates interaction of two processes that are traditionally known as primary and secondary haemostasis. The final outcome of these complex and interdependent processes, is the formation of solid haemostatic (fibrin) cloth and stop of further bleeding. Simultaneously with the activation of the haemostatic cascade, the natural control mechanisms in the form of fibrinolytic system and antifibrinolytic cascade processes, are being activated as well. The end result of the complex haemostatic cascade reactions is the control of the ongoing haemorrhage, but also at the same time, prevention of excessive intravascular coagulation and prevention of uncontrolled fibrinolysis. The complete resolution of the formed cloth and re-establishment of the adequate blood circulation represents the final stage of haemostasis.

The primary haemostasis represents the initial response of the system upon the injury of blood vessel wall, and incorporates interaction of the nearby present platelets (Plt) with the endothelium of injured wall of the blood vessel. The first response of the blood vessel is local vasoconstriction as an attempt to limit the blood loss. Although the nerve reflexes play some role, it is accepted that local vasoconstriction response primarily is the result of the local myogenic spasm (1). Depending on the severity of the injury of the vessel wall, this reflex vasoconstriction can last from few minutes to several hours. The second component of the primary haemostasis is the formation of the initial platelet thrombus. Platelet primarily adhere to the collagen in the vessel wall that is being exposed after the endothelium injury. The next step in the cascade process is the activation and subsequently aggregation of the surrounding Plt to the site of injury. The formation of the platelet thrombus (initial cloth) usually takes from 3-7 minutes.

Secondary haemostasis incorporates the sequence of processes that ends with the formation of fibrin cloth. The coagulation factors (CF) are activated either through the intrinsic or the extrinsic pathway of the activation of coagulation cascade. According to the traditional understanding of the coagulation, the two pathways merge together into common pathway. The end result of this phase of coagulation, is the conversion of circulating fibrinogen into active fibrin. This process is usually completed in 3-10 minutes.

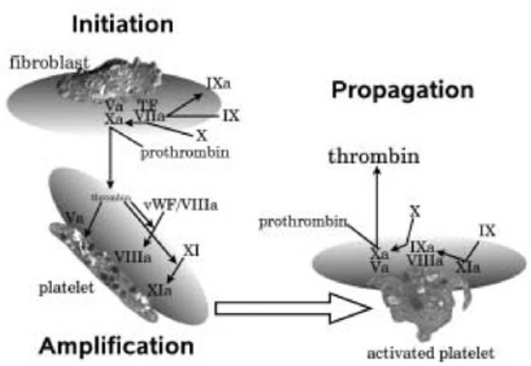
Figure 1. *The cascade model of coagulation (From Hoffman et al. [2])*



The final stage of coagulation is contraction of the components of the formed fibrin cloth (platelet thrombus, fibrin and trapped Erythrocytes (Er)) and formation of solid haemostatic cloth, also known as final cloth. In normal circumstances this final phase is finished within one hour. Platelets (Plt) are playing vital role in the haemostatic process. The initial adhesion of Plt to the sub endothelial collagen fibbers, is followed by the activation phase, which triggers the degranulation of the α granules and dense granules of the surrounding Plt.(3) Many active substances that are being released during the process, have the effect of expression of until then, inactive receptors on the Plt surface. This enzymatic activity will rapidly increase the adhesion and aggregation properties of the surrounding Plt. Alongside with their role in the primary haemostasis, Plt also acts as catalysts in the cascade activation processes between different CF, promoting the conversion of prothrombin into active thrombin. Plt also have influence on the final retraction of the haemostatic cloth (3).

Besides the traditional understanding of the coagulation cascade some authors recently are increasingly accepting the novel cell-based model of coagulation (2).

Figure 2. *The cell-based model of coagulation (From Hoffman et al. [2])*



2. Tests of Coagulation

Bleeding Time

Bleeding time is evaluating the effects of the primary haemostasis, which is referring to the initial interaction of Plt with the blood vessel wall and the formation of the Plt thrombus. The predictive value of this test is considered to be relatively low and the test shouldn't be performed if the Plt count is $<100 \times 10^9$/L. (4) Also the results of this test shouldn't be taken into consideration during clinical decision making, if the patient was taking aspirin in the previous 7-10 days or NSAID's in the period of 1-4 days (5). The bleeding time can have abnormal values in isolated acquired or inherited disorders of the Plt function and in other minimal disorders of the coagulation process. Accordingly, this test is not recommended as secure predictor of surgical bleeding and shouldn't be routinely performed pre operatively (3, 5).

Activated Partial Thromboplastin Time – APTT

APTT reflects the activity of the CF that are participating in the intrinsic and common pathways of the activation of coagulation cascade. Prolonged APTT is the most commonly considered to be, the result of: deficit of circulating CF, excess of CF inhibitor or the influence of heparin (5). This test is less sensitive, as compared to Prothrombin time (PT), on the effects of warfarin, as well as the effects that the liver disease and vitamin K deficiency have on haemostasis. The greatest clinical applicability of APTT is in the following areas: monitoring of the therapy with heparin (but it doesn't have great diagnostic value when the patient is on therapy with LMWH – clexane), detection of CF deficiency, detection of lupus inhibitor, CF inhibitors and their antibodies (4, 5).

Prothrombin Time – PT and International Normalized Ratio – INR

PT reflects the activity of the extrinsic and common pathway of the activation of coagulation cascade. This test is performed by the addition of thromboplastin to the patient's plasma, which then activates the tissue activating factor. Compared to APTT, PT is significantly more sensitive in detection of coagulation defects caused by the effects of oral anticoagulant therapy, and less sensitive to the effects of therapy with heparin (5, 6). In clinical practice, PT is the most commonly used as a monitoring tool in the follow up and control of oral anticoagulant therapy. For the purpose of standardized approach in the treatment of this group of patients, another test in the form of the International normalized ratio (INR) was introduced. The INR value provides the clinicians with the reproducible and standardized result in accordance to the local reagents and the methodology of work in the different laboratories (4). PT is also used for the detection of vitamin K deficiency, as well as follow up and treatment of the patients with hepatocellular diseases. On the other hand, PT has only limited value in establishing diagnosis in patients with hereditary disturbances of coagulation (5).

Thrombin Time – TT

TT is performed by the addition of thrombin in the patient's blood sample and is the most commonly used to assess the process of conversion of fibrinogen to fibrin. It is considered that TT can solely detect the abnormalities of the fibrinogen and fibrin formation (4,6). In everyday clinical practice, the main uses of this test are: detection of heparin in the sample of patient's blood (especially if the patient has prolonged APTT), as a complementary test in establishing the diagnosis of Disseminated Intravascular Coagulation (DIC), detection of low levels of fibrinogen and detection of rare inherited anomalies of fibrinogen and dysfibrinogenemia (4,7).

3. Bleeding and Massive Transfusion

After major trauma and especially in polytraumatized patients that have sustained injuries on multiple tissues and organs, one of the main complications is uncontrolled massive haemorrhage and haemorrhagic shock. Although less frequent in the operation theatre (OT), massive bleedings is also one of the most alarming emergencies, both during elective or urgent surgical procedures. The sub sequential massive transfusion of blood and blood components (MT), although inevitable part of treatment protocol, can also be cause of complications and further deterioration of patients clinical condition. The most common definition of MT is the transfusion of an approximately one circulating volume of blood during the period of 24 hours (8). In this population of patients in which MT was inevitable therapeutic intervention, we can expect that a certain form of coagulopathy will develop in relatively high percentage (9), The literature shows that abnormal values of both PT and APTT can be measured after the transfusion of 12 units of packed red blood cells (PRBC's), while reduced Plt count can be seen after the transfusion of 20 PRBC's (8, 9).

3.1 Pathophysiology of Coagulopathy in MT

The first therapeutic intervention during massive bleeding is the introduction of the wide bore intravenous (i.v.) cannula and administration of high volume of fluids (crystalloids and colloids if needed). In the early phases of the reanimation of these patients, it is also necessary to take active measures to control the body temperature and to warm up the shocked patient. It is recommended to start the warming process of the bleeding patients as soon as possible (10,11). This is of course much more difficult to achieve in traumatized patients outside the hospital, than during major surgery in the OT. When the initial i.v. substitution of the lost circulating volume of blood with fluids is not enough, and when the bleeding cannot be immediately controlled, the next step is the transfusion of PRBC's, Plt, and accordingly to the latest recommendations, early administration of fibrinogen and CF (12). The experiences shows that during elective surgery, rapid haemodilution which is the result of administration of large volumes of crystalloids over a short period of time, can result in significant changes in the haemostatic balance of the patient. In the clinical perspective, the consequences will be presented in some form of clinical coagulopathy and either further bleeding or excessive intravascular coagulation (11, 13). These changes can be detected and followed by using thromboelastometry (TEG/ROTEM) (14). The shift in the balance of the complex coagulation system, is suggesting increased generation of thrombin and hypercoagulable state, even in the absence of continuous active bleeding. On the other hand during infusion of high volume of colloids (especially high molecular starch – HES), we can often detect abnormal Plt function. In general, we can summarize that, administration of high volumes of i.v. fluids during a short period of time (especially colloids), will result in significant haemodilution and reduction in the CF concentration.

The evidence from the literature shows that, a group of patients where active measures to maintain normal body temperature (normothermia) were undertaken during the whole perioperative period, had significantly less blood loss compared to other patients. It is accepted that by avoiding excessive hypothermia, we can help in preserving both the normal haemostatic processes, as well as their control mechanisms (10). The main negative effect of hypothermia (core body temperature <35°C) is the slowing down of the initiation and activation phase of the coagulation cascade, which is consequently disturbing the balance of the coagulation system. The science data also confirms that hypothermia can also have negative effects, such as: decreased enzymatic activation of the Plt, slowing down of the synthesis of CF in the liver and increased fibrinolysis (11). This is the reason why the results of multiple research studies are showing that patients who were acidotic and hypothermic for certain period of time, either during major trauma or in the perioperative period, had significantly larger bleeding, despite timely substitution of blood components, PRBC's, Plt and fresh frozen plasma (FFP) (10, 11, 13).

Frequent control of the haemoglobin level (Hb) and timely correction of anemia in the actively bleeding and shocked patient, have great contribution in the preservation of normal haemostatic function. According to the currently available data, there are two scientific explanations regarding the level of Hb during the reanimation process of the patient in hemorrhagic shock that are incorporated in the latest recommendations. Erythrocytes (Er) are playing important role in the control of biochemical responses of activated Plt at the site of injury of the blood vessel wall. (11) This is confirmation of the hypothesis about multi cellular nature of initial phase of coagulation and the formation of initial Plt cloth. Er contain adenosine diphosphate (ADP) that plays important role in the process of activation of Plt. (9, 10). At the same time Er are also indirectly involved in the activation of the surrounding circulating Plt by activation of platelet cyclooxygenase and production of thromboxane A_2. The second mechanism, through which Er are influencing the haemostatic potential of the patient, is their rheological effect on the rest of circulating components of the blood. In normal circumstances, the Er flow is highest near the center of blood vessel and they have natural tendency to push out the circulating pool of Plt, towards the wall of the blood vessel. In this setting, Plt normally flow near the endothelium layer, the place where they usually exert their action. It is accepted that in this way, Er are acting in indirect fashion by creating ideal conditions for interaction between Plt and damaged endothelium

and thus promoting the initial haemostatic response to injury. During active bleeding on the other hand, the circulating pool of Er is decreasing, which causes unopposed Plt to start circulating near the center of the blood vessel. In this setting, as Plt in the absence of force that is pushing them outwards, starts circulating away from the endothelium, they are at the same time losing their haemostatic potential (11, 13). Considering the effect that Er are having in maintaining the potential and balance of the haemostatic system of the blood, the latest recommendations suggest that the level of Hb must be frequently checked and maintained >8gr/dl during the acute phase of the resuscitation process of the patient that is actively bleeding (12).

3.2 Level of Platelets (Plt)

During the acute phase of resuscitation of massively bleeding patient, it is mandatory to regularly check: the level of Plt, the level of fibrinogen and the activity of CF. It is accepted that during MT, the deficit in the level of fibrinogen is the first anomaly that develops in the course of the development of coagulopathy (8). Consequently, the current recommendations are suggesting that in the early stages of resuscitation, the level of fibrinogen must be measured, and the deficit must be substituted as soon as it is diagnosed (4). The first line of choice for the substitution of fibrinogen, is the use of fibrinogen concentrate, and if not available cryoprecipitate. Due to small and relatively variable concentration of fibrinogen, the use of FFP is not recommended for rapid substitution (4, 12). One of the main consequences of MT is the decrease of the level of Plt. The first reason for the drop in the Plt count, is the consumption of the circulating pool of Plt at the place of injury of the blood vessel wall. The second reason is rapid haemodilution that develops early in the resuscitation process, mainly because of rapid administration of crystalloids, as well as transfusion of Er and FPP that are relatively poor with Plt.

One of the key emphasis in the latest recommendations is the importance of correct anamnesis of pharmacological history of the bleeding patient (where it is possible) or heteroanamnesis from the patient relatives (4). We should insist on receiving correct information about the patients' therapy with anticoagulant drugs that are influencing different stages of the coagulation process. Acutely bleeding patients, which were on therapy with drugs that are reducing the Plt's ability for activation and aggregation, will inevitably need Plt transfusion, even if the Plt count is normal. According to the recommendations, in the patients with ongoing bleeding, absolutely critical level of Plt is 50×10^9/l(4). The literature review shows that the drop of Plt count below this critical level, will compromise the normal haemostatic potential of the blood (3, 9). This is the reason why the recommendations suggest that the trigger value for Plt transfusion in bleeding patient, should be 75×10^9/l (4,12). This practice enables safe margin for the clinicians in the treatment protocol, which guarantees that Plt count will not drop below the critical level of 50×10^9/l at all stages of the resuscitation. In the population of bleeding patients that has suffered brain trauma or has been polytraumatized, it is recommended to keep higher trigger value of Plt, 100×10^9/l (4,12).

We should always keep in mind that depending on the cause of bleeding, there are some key differences in the treatment of the different populations of massively bleeding patients. Unlike during massive bleeding associated to major trauma, in the patients that are bleeding during operations and invasive procedures, the pathogenesis of coagulopathy is different. In the operation theatre (OT) during major operations (especially during elective surgery), regardless of the extensity of the procedure, the trauma to the tissues and organs is easier to be controlled and is more limited to the operation site, as compared to the traumatized patients. Also even in the situation of unexpected massive blood loss, in the OT there are ideal conditions, for timely intervention with administrations of adequate volume of crystalloids and/ or colloids. In these patients, if needed, transfusion of Er and other blood components, can be started significantly sooner, than in traumatized patients outside the hospital. This gives the clinicians opportunity to establish normovolemia in a timelier manner, and also to engage rapid substitution of the decreasing levels of Hb, Plt, fibrinogen and CF. We should never underestimate, the great significance that maintaining the normal body temperature and correction of acidosis has on the normal haemostatic potential of the patient. All this taken into consideration, we can conclude that, acquired coagulopathy that is developing during massive bleeding and MT in the OT, is mainly associated to the secondary deficit of fibrinogen and decreased activity and/ or low levels of CF (7, 8).

4. Treatment of the Coagulopathy associated to MT

Numerous attempts have been made over the years, for the discovery of the ideal way to monitor the changes of complex coagulation system during major trauma and surgery. Unfortunately, according to the current evidence, we don't have a single, reliable and fast diagnostic test, that will enable clinicians with continuous monitoring of dynamic changes in the coagulation profile during hemorrhagic shock in the critical ill patients. Currently available tests attempt to measure the potential of coagulation by quantifying certain segments of the haemostatic cascade. Regarding the traditional tests of haemostasis, current recommendations suggest that, in the bleeding patient when the measured level of fibrinogen is normal, only marked elevations in the values of APTT and PT (1.5-1.8 times above control/ standard values) can be considered significant in the clinical decision making process (4). This population of patients can be considered at high risk of developing clinically significant coagulopathy.

In the latest literature reviews, the current knowledge in this field puts a great emphasis on the implementation of "the point of care" principle in the algorithms for treatment of acquired coagulopathy (4, 12, 13). This implies the inclusion of diagnostic tools such as TEG/ ROTEM, which are examining the quality of different segments of haemostasis and fibrinolysis, by using the thromboelastographic principle. By measuring the viscoelastic properties of the patient's blood, TEG/ ROTEM within a short time interval (5-10 minutes), are capable of producing real-time image about the in vivo ability for the formation of firm haemostatic cloth and his subsequent

lysis (14, 15). On this way the clinicians are provided with a quick estimate of the action of both coagulation regulatory mechanisms and anticoagulation pathways. The most importantly, this practice offers a reliable and reproducible data that can help in prompt decision making.

The golden rule during the prevention and treatment of the coagulopathy associated to massive bleeding and MT, is rapid intervention specifically directed towards the deficit of the elements of coagulation. This is so called **"deficit-directed" principle** in the resuscitation of these patients (10, 11). The clinical decision whether to administer Plt and when, depends on the measured Plt count, tests of coagulation, but also on the clinical evaluation of the patient's clinical condition. The recommendations suggest that administration of Plt is allowed only for correction of clinically manifested coagulopathy that is clearly associated to low Plt count and/ or decreased functional ability of the circulating pool of Plt (4, 12).

We should always keep in mind that during massive bleeding and MT, the first negative change that is affecting the balance of the coagulation system, is the decrease in the circulating level of fibrinogen (7, 8, 10). Current knowledge suggests that during major bleeding, the alteration of the level of fibrinogen is happening before the decrease in the level of Plt and CF, all of which are promoting the development of the coagulopathy associated to MT. This is why the level of fibrinogen must be measured early in the resuscitation process, especially if we know that a low concentration of fibrinogen will impair the final phase of coagulation and the formation of solid haemostatic cloth. Regular measurement of the fibrinogen level will give us chance to timely correct the decrease in the fibrinogen concentration in the acutely bleeding patient. In a patient where we are suspecting the development of acquired coagulopathy, the measured concentration of fibrinogen <1.5-2.0 gr/l must be considered as hypofibrinogenaemia (4). This patient caries a significant risk of further bleeding. According to the current recommendations, the first line of choice is the administration of fibrinogen concentrate in the initial dose of 25-50 mg/kg. Only when fibrinogen concentrate is not available, the recommendations suggest the use of cryoprecipitate in the dose of 4-6 ml/kg (4). FFP according to the current clinical evidence, is not recommended as a secure source of fibrinogen, mostly because of a small and variable concentration of fibrinogen. Cryoprecipitate on the other hand, is considered to have a relatively constant concentration of: fibrinogen, CF VIII, CF XIII and vonWillebrand factor. However, during the administration of Cryoprecipitate, we need to be aware that there are individual variations in the content, and also of the danger (although minimal) of transmission of infectious agents.

When the patient has significantly prolonged values of APTT and PT (>1.5/ normal values), and no other coagulation abnormality can be detected, we can conclude that the patient has a deficiency of CF in the circulation or their low activity. If the patient also has normal level of fibrinogen, these results should trigger the substitution of CF. There are specific tests of coagulation that are measuring the concentration of specific CF in the patient's blood sample. Still we need to know that these tests are not available in every laboratory, and even if they are available, it takes several hours for the results to be ready. When a patient is confirmed to have deficit of CF, we need to start the substitution process. The recommended way is the administration of fabric CF preparations. Preparations that contain single CF are the most commonly used for treatment of patients that have inherited CF deficiency. Currently on the market there are also preparations that are containing several CF. Good example of these preparations is Prothrombin Complex Concentrate (PCC). These formulations are containing all the vitamin K dependent CF, as well as Protein C and Protein S, that play active role in the anticoagulation regulation processes. Special attention should be paid to the bleeding patients (during operation or trauma) that are on therapy with some of the oral anticoagulants. These drugs have the pharmacological action to antagonize vitamin K dependent synthesis of CF in the liver, and are decreasing the activity if CF in the patient's blood. Before surgery or other invasive procedure, it is recommended that these patients receive i.v. dose of vitamin K and also substitution of CF deficiency by administration of PCC preparation (11). This preparations are recommended as a first line of choice for CF substitution, mainly because they have a relatively constant and balanced concentration of CF in the final solution. This is making the whole resuscitation process much more controllable in comparison to FFP (2, 9). Also they have superior security profile in the field of possible transmission of infectious agent to the recipient's blood. Only when PCC preparations are not available, substitution can be done by administration of adequate volumes of FFP (4, 12). However regarding the clinical use of FFP, we need to emphasize this facts: 1) concentration of CF in one unit of FFP is small and variable and also highly dependent on the characteristics of every single donor; 2) large volume of FFP is needed to achieve satisfactory concentration of CF in the recipient's circulation. This practice brings significant danger of volume overload and rapid haemodilution; 3) administration of FFP caries significant risk of transmission of infectious agents; 4) probably the most dangerous complication is the development of acute immune reaction in the recipient, caused by the presence in the FFP, of active immune elements from the donor. This can lead to potentially fatal complications, such as acute lung injury ALI/ TRALI (4, 11).

Excessive fibrinolysis and premature decomposition of the already formed haemostatic cloth, playsignificant role in the development of acquired coagulopathy that accompanies major bleeding and MT. The main clinical manifestation in this setting will be prolonged and persistent bleeding, even when the deficiency of other elements of coagulation has been corrected. This is the reason why administration of tranexamic acid must be included as mandatory part of the treatment protocols for hemorrhagic shock (8, 12). Currently in clinical practice, tranexamic acid is the most commonly used for the treatment of the ongoing bleeding in OT after major trauma and for prevention of major bleeding during surgery and other invasive procedures (4, 12). In the current data from the literature, there is a strong suggestion that tranexamic acid, if administered early and in an adequate dose (20-25 mg/kg), will have positive role in the limitation of further bleeding and the development of acquired coagulopathy (4).

Alongside with the standard therapeutic methods in the treatment of acquired coagulopathy, there are some very important additional interventions that can significantly improve the final

outcome. Lately a number of so called **"additional factors"** in the development of acquired coagulopathy have been identified. Data from many research studies are showing that if clinicians fail to correct these conditions in a timely manner, it can promote further misbalance of the coagulation system (8, 9). This is the reason why the latest recommendations are strongly suggesting: early treatment of the hypothermia, correction of clinical acidosis and correction of hypocalcaemia (4, 12). It is recommended that in traumatized patient with massive bleeding, and especially in the OT, active measures to worm up the patients must be undertaken as soon as possible (12). The available data are clearly showing that, the group of patients where normal body temperature was successfully preserved during resuscitation process, had significantly lower blood loos and decreased need for transfusion of blood components (10, 11). It is also recommended that during active bleeding, we need to perform strict control of the patient's acid-base balance and timely correct the clinical acidosis (3). Despite the fact that the correction of the Ph value alone, cannot control the developing coagulopathy, still this intervention will surely help in the easier recovery of the coagulation system.

The treatment algorithm during MT, must also incorporate regular measurements of the level of calcium. Hypocalcaemia that can frequently be seen in these patients, must be promptly corrected with adequate i.v. calcium infusion (4). The preservation of normocalcaemia is very important for normal functioning of coagulation mechanisms, especially because calcium plays a vital role as a cofactor in the activation of certain CF in the coagulation cascade. The evidence from the literature is suggesting that during acute bleeding and MT, until the complete cessation of bleeding, the level of calcium needs to be maintained above 0.9 mmol/l (4, 12). This will help in preservation of the normal balance of haemostasis in critically ill patient.

At the end we can conclude that acquired coagulopathy is relatively frequent complication of massive bleeding and MT. The clinicians need to be aware of the fact that patients that develop this complication, will have higher rate of prolonged bleeding and higher possibility of potentially lethal complications during the resuscitation process. This is the reason why it is mandatory that current recommendations from this field must be incorporated in the local treatment protocols for acute bleeding during major trauma or during surgery.

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BURNOUT, JOB DEMANDS, AND MUSCULOSKELETAL PAIN IN ANAESTHESIA HEALTH PROFESSIONALS

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ABSTRACT

The **aim** of this study was to determine the frequency of burnout and musculoskeletal pain, and to assess their association to job demands in anesthesia health professionals (HPs).

Methods. Cross-sectional study analyzed 79 anesthesia HPs (29 physicians, 50 nurses), aged 40.2±10.8 years, and 81% being females. Burnout and job demands were assessed by Maslach Burnout Inventory and Hospital Experience Scale, respectively. We used Symptoms Survey for Work-Related Musculoskeletal Disorders for the evaluation of musculoskeletal pain.

Results. Burnout was registered in 23 participants (29.1%), and 82.3% of HPs had musculoskeletal pain in at the least one area of the body that lasted more than two days in the last year. Musculoskeletal pain in at the least one area of the body was significantly more frequent in HPs with burnout (95.7% *vs*. 76.8%) (χ^2=3.98, *p=0.046)* (OR=6.65, 95%CI 0.82-54.2). Organizational (3.3±0.6 *vs*. 2.9±0.8) *(t=2.24*, *p=0.028)* and cognitive (3.1±0.8 *vs*. 2.6±0.8) *(t=2.46*, *p=0.016)* job demands were significantly higher in burnt out anesthesia HPs. There was significant association between burnout and neck (χ^2=8.62, *p=0.003)* (OR=7.88, 95%CI 1.68-36.88), forearm (χ^2=4.81, *p=0.028)* (OR=4.91, 95%CI 1.07-22.62), upper back (χ^2=10.39, *p=0.001)* (OR=6.33, 95%CI 1.91-21.05), and foot (χ^2=5.05, *p=0.025)* (OR=3.13, 95%CI 1.13-8.62) pain.

Conclusion. We detected high frequency of burnout and musculoskeletal pain in anesthesia HPs. Adequate management of jobs' demands is necessary for prevention of burnout and musculoskeletal pain in these HPs.

Key Words: *burnout, job demands, musculoskeletal, anesthesia, health professionals.*

ANALYSIS OF BODY COMPOSITION AND EATING BEHAVIOR IN FEMALE STUDENTS

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ABSTRACT

The knowledge about indicators of health status, such as body composition and eating behavior, is important especially in transitional period of life, such as beginning of college education.

The aim of this study was to examine the body composition status and eating behavior in young female population.

Material and Methods: 135 (one hundred and thirty five) female students of first year at Medical Faculty in Skopje participated in this study, with mean age 18.78 ±0.72 years. The body mass was analyzed with bioelectrical impedance analyzer. In Body 720, and skeletal muscle mass (SMM), body fat percent (BF%, waist to hip ratio (W/H), body mass index (BMI) were obtained. The eating behavior was evaluated with weight related eating questionnaire (WREQ), four subscales were determined: routine restraint (RR), compensatory restraint (CR), susceptibility for external cue (SEC) and emotional eating (EmE). **Results:** Obtained anthropological data were as follows: average height=165.25±5.68 cm; weight=62.01±12.18kg; SMM=23.17 ± 4.4; BMI=22.81; BF%=29.5 ±8.82; W/H ratio = 0.87 ± 0.06. WREQ results showed RR=6.04 ±3.17; CR=6.82 ±3.5; SEC=11.63 ±5.13; EmE=11.13±5.03.

Conclusions: Obesity diagnose parameters in young female students showed high body fat percent and normal BMI and WH ratio values. Parameters of eating behavior were significantly high which could indicate disturbance in eating patterns.

ELASTOGRAPHY FOR NONINVASIVE LIVER FIBROSIS EVALUATION IN CHRONIC LIVER DISEASES

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ABSTRACT

Recent studies introduced Shear-Wave elastography (SWE) as a noninvasive method for diagnosis and grading liver fibrosis in patients with chronic liver diseases (CLD). It is useful for evaluation of fibrosis progression and surveillance in CLD and for assessment of the treatment response. The goal of this study was to present our preliminary experience with SWE in CLD and to identify patients with no or mild fibrosis and those with severe fibrosis or cirrhosis.

Material and Methods

Liver stiffness was measured by SWE and the results are presented in kilopascals (kPa). The measurements are obtained from the liver lobes trough the intercostal space. The median value in kPa of ten liver stiffness measurements in different locations was considered as the representative. METAVIR scoring system was used to assess the extent of fibrosis. Fibrosis stage represents the amount of fibrosis and range from F0 trough F4. The study included 50 patients with CLD.

Results

SWE was performed in 50 patients with chronic liver disease, including 29 with chronic hepatitis (12 HCV, 14 HBV and 3 autoimmune hepatitis), 11 with steatosis/ steatohepatitis and 10 with cirrhosis. Diagnosis was established by clinical, laboratory, radiological and/ or histopathological examinations. Out of 29 patients with chronic hepatitis, SWE measurements revealed mild fibrosis (F0-F1) in 12 (41,4%) patients; significant fibrosis (F≥2) in 8 (27,6%) patients; and advanced fibrosis/ cirrhosis (F≥3, F=4) in 9 (31%) patients. 11 (91,7%) out of 12 hepatitis C patients showed significant and advanced fibrosis more frequently than 4 (28,6%) out of 14 hepatitis B patients. Three patients with autoimmune hepatitis showed mild fibrosis. SWE findings of 11 patients with steatosis/ steatohepatitis showed mild fibrosis (F0-F1) in 6 (54,5%) patients and significant fibrosis (F≥2) in 5 (45,5%) patients. Increased liver stiffness in patients with steatosis/steatohepatitisa is related to disease progression to fibrosis and inflammation that increases share wave velocity and results in reduced elasticity. SWE in 10 patients with clinical findings corresponding to liver cirrhosis revealed mild fibrosis in 3 (30%) and increased fibrosis stage in 7 (70%) patients.

Conclusion

Share wave elastography is a useful, noninvasive screening method for identifying patients with fibrosis and estimation of the tissue stiffness and fibrosis progression in CLD. These finding are important for adequate management of chronic liver disease. The limitation of the technique is measurement of difficulties in cases of obesity and presence of ascites.

Key Words: *Share wave elastography, chronic liver disease, liver fibrosis*

ILEOCAECAL TUBERCULOSIS MIMICKING CROHN DISEASE: A CASE REPORT

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ABSTRACT

Introduction:

Ileocecal region and transverse colon are the most common locations of intestinal tuberculosis (TBC) which is not as common as pulmonary, and very often can be misdiagnosed. Frequently, the clinical features and macroscopic lesions can be difficult to distinguish from Crohn's disease.

Case Presentation:

A 24-years-old male was presented with 4 years history of chronic diarrhoea, and several vomiting attacks, conservatively resolved. Colonoscopy disclosed a 4-5 cm long stricture distally of hepatic flexure, and complete stenosis of the right colon. Biopsy specimen revealed features of ulcerative colitis which was the reason for steroid treatment. Five months later, he underwent right hemicolectomy, due to intestinal obstruction; histopathology displayed Crohn's Disease. Imuran was introduced, but two weeks later he developed pulmonary disease, with fever, dry cough and concomitant vomiting. Under suspicion of bronchopneumonia, he was admitted to pulmonary ward. Since next three days his general condition was deteriorating, he was transferred to surgical unit. Surgery revealed fibro-purulent peritonitis with skip lesions of small bowel. Surgical biopsy showed lesions typical for intestinal TBC. In the meantime sputum culture on Lowenstein-Jensen medium confirmed the diagnosis of pulmonary TBC. Quadruple anti-TBC therapy was started immediately after surgery. A year later, pulmonary finding presented sequels of TBC, and MRI enterography unveiled regular signal from the intestinal wall.

Discussion / Conclusion:

A case of misdiagnosed intestinal TBC, which was treated as Crohn's Disease, became a life-threatening condition. We can conclude that possibility of TBC must be kept on mind especially when clinical improvement is missing or general condition is worsening, after due time of introducing the immunosuppressant therapy.

Key Words: *Crohn's Disease, intestinal tuberculosis, therapy.*

SUCCESSFUL OUTCOME OF PREGNANCY IN THE SETTING OF LIVER CIRRHOSIS – TWO CASES REPORT

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ABSTRACT

Pregnancy is not common event in patients with cirrhosis. Morbidity and mortality in pregnant woman with cirrhosis are higher than that of the general pregnant population. Gastrointestinal hemorrhage in liver cirrhosis is serious manifestation and may place the fetus at risk. Two patients with liver cirrhosis and gastrointestinal hemorrhage during pregnancy are reported.

CASE 1 - 26 years old woman in the 32nd week of gestation was admitted to our hospital due to upper gastrointestinal bleeding. Liver cirrhosis of cryptogenic origin was revealed when she was 23 years old and splenectomy was performed because of splenomegaly and severe hypersplenism. At the admission upper endoscopy revealed bleeding gastric ulcer, portal gastropathy and esophageal varices grade 2. Endoscopic hemostasis with clips was done. A hemoglobin level failed to 6 gr and five units of blood were required. The patient's condition was stabilized and the pregnancy was maintained satisfactory in the next 6 weeks, when 2500 gr infant was delivered by cesarean section. Two days after partum the patient developed massive variceal bleeding followed by hemoglobin level of 53 g/L. In the same time, the patient showed signs of hepatic decompensation (low albumin level, ascites, pleural effusion). Band ligation of varices was done and the bleeding stopped. Additional treatment consisted of octreotide infusion, albumin infusion, diuretics and therapeutic paracentesis. Both mother and infant were discharged on day 18.

CASE 2 - 23 years old pregnant woman in 12th week of gestation was admitted in emergency due to massive haematemesis. Urgent gastroscopy revealed large esophageal and fundus varices with active bleeding and the Sengstaken tube was placed during 72 hours. Additional investigations have found cirrhotic liver, dilated portal vein, splenomegaly, ascites, thrombocytopenia, low albumin level and HCV RNA infection g.1. After 4 weeks, the patient had new onset of variceal bleeding, when band ligation was performed (No 6). In 20th week of gestation new episode of bleeding occurred, which has been stopped by continuous octreotide infusion. The Cesarean section was performed and healthy girl was delivered. Follow-up in the last 3 years has shown stable condition of the mother, eradication of varices by subsequent band ligation. Consequently antiviral therapy with sofosbuvir/ ledipasvir has been administrated with HCV RNA elimination. The baby was HCV RNA negative.

Conclusion: During the pregnancy in cirrhosis there is a high risk of life-threatening complications as variceal bleeding and hepatic decompensation. Appropriate management of these events and careful monitoring can lead to successful pregnancy outcome.

Key Words: *Variceal bleeding, Liver cirrhosis, Pregnancy.*

SEVERE WORSENING OF AUTOIMMUNE LIVER DISEASE WITH GOOD OUTCOME

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ABSTRACT

Introduction: Autoimmune liver disease encompasses autoimmune hepatitis, primary biliary cholangitis and primary sclerosing cholangitis. IgG-4 associated cholangitis can also be included in this group as a separate entity. These conditions remain a diagnostic challenge, due to their resemblance in clinical course and laboratory findings, to the multitude of other etiologies of liver injury.

Case Report: We present a case of recurrent severe hepatitis in a 43-years-old female patient. Disease course was marked by initial onset followed by nearly four years of remission, and a second more aggressive flare. Initial findings pointed to SLE as the underlying cause, however formal criteria were not fulfilled and the findings were not reproduced. Extensive testing for infectious, genetic, systemic and autoimmune disease was performed with the aim of ascertaining the underlying pathologic process. An autoimmune etiology was deemed the most feasible, due to detection of antinuclear antibodies with a titer of 1:1160 and anti dsDNA. The treatment with corticosteroids, UDCA and plasmapheresis yielded an excellent clinical outcome.

Discussion: The exact disease process remains elusive despite extensive testing. The possibility of a toxic precipitant cannot be excluded with absolute certainty. The clinical course, serology, histopathology and response to treatment suggest an underlying autoimmune disease.

Conclusion: Findings provide the strongest support for AIH, or an overlap syndrome. Formal diagnostic criteria can only be fulfilled with evaluation of additional panel of autoantibodies, as LKM1, anti-SLA, pANCA and anti-gp210. Nevertheless, the treatment approach yielded an excellent outcome and would have remained largely unaltered, as the aforementioned testing for autoantibodies have been available.

Key Words: *Autoantibodies, Autoimmune, Hepatitis.*

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Dag Stat. Mackinnon A. Available from: http//www.mhri.cdu.au/biostats.Accessed May 5th 2006.

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I _____ (THE FIRST AUTHOR FULL NAME) declare Conflict of interest or declare non Conflict of interest.

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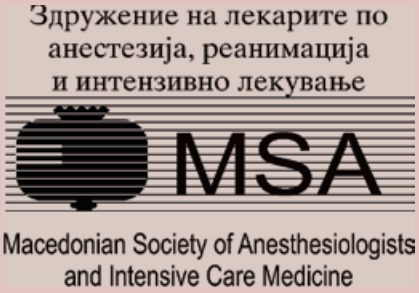
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