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COMPARISON OF THREE SEVERITY SCORING MODELS FOR MORTALITY PREDICTION OF COMMUNITY-ACQUIRED PNEUMONIA

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ABSTRACT
Introduction: Community-acquired pneumonia (CAP) is among the leading cause of morbidity and mortality worldwide. Several scoring models have been developed to accurately asses a disease severity and early to predict the outcome, however an optimal prognostic tool still is not clearly defined. The aim of this study was to compare three commonly used scores in patients with CAP, in order to determine the best tool that will early identify those with increased risk for mortality. **Methods:** The study included 129 patients aged ≥18 years with CAP hospitalized at the intensive care unit (ICU) at the University Clinic for Infectious Diseases in Skopje, during a 3-year period. Demographic, clinical and biochemical parameters were recorded and three scores were calculated at admission: SOFA (Sequential Organ Failure Assessment Score), SAPS II (Simplified Acute Physiology Score) and APACHE II (Acute Physiology and Chronic Health Evaluation II). Primary outcome was 30-day in-hospital mortality. Receiver Operating Curve (ROC) analysis was performed and areas under the curve (AUC) were compared to evaluate mortality prediction capacities of the scores. **Results**: The mean age of the patients was 61 year, predominantly were males (66,7%), most (79,1%) had co-morbid condition and Charlson Comorbidity index was significantly increased in non-survivors. An overall mortality was 43.4%. All severity scores had higher values in patients who died, that was statistically significant with the outcome. The AUC values of the scores were 0,749 for SOFA, 0.749 for SAPS II and 0.714 for APACHE II, showing similar prediction ability. **Conclusion**. Commonly used severity scoring models accurately identified patients with CAP that had an increased risk for poor outcome, but none of them showed to be superior over the others in ability to predict the mortality.

Key words: community-acquired pneumonia, severity scores, mortality

INTRODUCTION
Community-acquired pneumonia is one of the most common, potentially fatal infectious disease and one of the leading cause for hospitalization, health care costs and death worldwide. Approximately 20 % cases are admitted to hospital and 8-36 % require treatment in ICU due to disease severity [1,2]. An accurate assessment of disease severity and early prediction of poor outcome is of crucial importance for successful management [3,4]. Therefore, several severity scoring models were developed to guide the clinical decision on the site of care upon the diagnosis and to assess the prognosis of community acquired pneumonia. Frequently used mortality prediction tools in ICU are SAPS II (Simplified Acute Physiology Score) [5], SOFA (Sequential Organ Failure Assessment score) [6], APACHE II (Acute Physiology and Chronic Health Evaluation II) [7] and MPM (Mortality Prediction Model) [8].
The aim of this study was to compare three commonly used severity scoring models in patients with community-acquired pneumonia, in order to define the best tool that will early identify those with increased risk for lethal outcome.

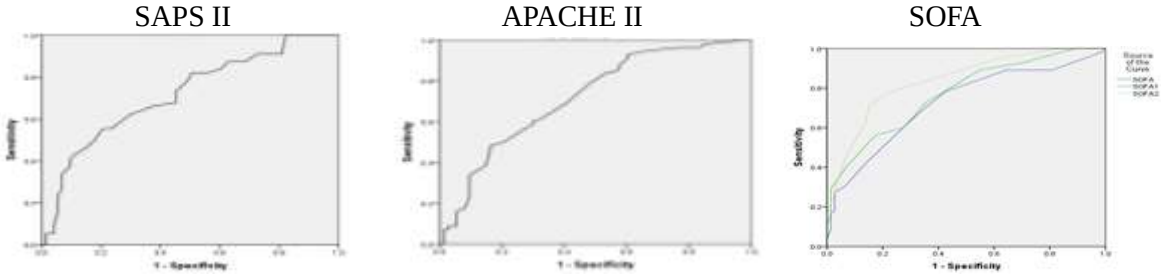
MATERIAL AND METHODS
The study included 129 patients aged ≥18 years with CAP consecutively admitted at the ICU of University Clinic for Infectious Diseases in Skopje, North Macedonia. It was observational and group comparison study that took place from January 2017 to December 2019. Pneumonia was

defined in accordance with IDSA/ATS guidelines. Outcome was defined as survival or death during the 30 days of hospital treatment. Patients were divided into two groups according to the outcome: survivors and non-survivors. In all, demographic, clinical and biochemical parameters were recorded. Charlson Comorbidity Index was calculated to predict the 10-year survival. Three mortality prediction scores were calculated in the first 24 hours of admission: SOFA, SAPS II and APACHE II. All laboratory tests were performed by standard methods in the biochemical laboratory at the hospital. Patients received standard treatment in accordance with the national guideline for pneumonia. Statistical analysis was performed with SPSS 23.0 software. Multivariate analysis using stepwise logistic regression was conducted for all variables that were found to have a P value ≤0.1 on univariate analysis. To assess the predictive values a ROC analysis was performed and AUCs were calculated for each score. $P<0.05$ was considered as significant.

RESULTS

A total of 129 patients were enrolled in the study. The mean age was 61.07 ± 16.36 years and 66.7% were males. The overall 30-day mortality rate was 43.4 %. Most (79.1%) had one or more comorbid condition and Charlson Comorbidity Index was higher in non-survivors that showed significant association with the outcome. The baseline characteristics, clinical findings and biochemical parameters are presented in Table 1. The mean values of analyzed severity scoring models are shown in Table 2. All significantly differ between the groups, i.e. the deceased patients had higher values of every score. Results from ROC analysis are presented on Figure 1 and Table 3, showing that all scores had similar values of AUC (0,749 for SOFA and SAPS II, 0,714 for APACHE II) presenting that they all have strong ability to predict the mortality in patients with CAP.

Figure 1. ROC curves and areas under the curve of analyzed severity indexes



DISCUSSION

The key finding of our study was that the tested scores adequately identified the patients who had high risk for poor outcome, they all have similar predictive capacity, but none of them showed to be superior over the others in mortality prediction. A overall mortality of 43,4% is high but still within the range of published data [9,10]. Charlson comorbidity index, was higher in non-survivors and was associated with the poor outcome, that corresponds with other studies [11]. SAPS II, SOFA, and APACHE II proved to have a significant association with the mortality and were identified as independent outcome predictors. ROC analysis found similar values of AUC as follows: 0.749 for SAPS II and for SOFA and 0.714 for APACHE II. This finding corresponds with the literature data that confirm the similarity between these models in their ability to predict the mortality [12,13,14].

Table 1. Demographic, clinical and biochemical characteristics of study population

Parameter	All n=129	Survivors n=73	Non-survivors n=56	*P-value*
Age (years)	61.07±16.36	60.47±15.36	61.86± 7.70	0.634

Male Female	86 (66.7) 43 (33.3)	53 (72.6) 20 (27.4)	33 (58.9) 23 (41.1)	0.132
Charlson Comorbidity Index	3.49±2.85	3.01±2.21	4.11±3.43	**0.030**
Body temperature	37.7 ± 0.94	37.80 ± 0.94	37.57 ± 0.95	0.170
Heart Rate	109.15 ± 22.93	106.01 ± 21.63	113.23± 24.18	0.771
Respiratory Rate	31.74 ± 8.69	31.71 ± 9.60	31.77 ± 7.41	0.971
Mean Arterial Pressure	84.19 ± 21.78	89.31 ± 21.41	77.51±20.59	**0.002**
Leucocyte count, $x10^9$/L	13.88 ± 11.71	14.00 ± 12.67	13.73 ±10.45	0.891
Haemoglobin, g/L	124.83 ± 23.68	128.23 ± 23.24	120.39 ± 23.73	0.063
Platelets, $x10^9$/L	223.50 ± 125.80	244.84 ±140.06	195.68 ± 98.79	**0.021**
Serum glucose, mmol/L	9.68 ± 4.95	9.17 ± 4.16	10.35 ± 5.79	0.188
Blood urea, mmol/L	11.96 ± 8.61	10.99 ± 8.22	13.23 ± 9.01	0.143
Alanin-aminotransferase, U/L	61.74 ± 72.61	65.93 ± 76.75	56.39 ± 67.27	0.471
Asparat-aminotransferase, U/L	73.18 ± 95.14	76.20 ± 103.73	69.31 ± 83.69	0.693
C-reactive protein, mg/L	222.67 ± 161.48	234.71 ± 166.59	206.69 ± 154.49	0.335
pH	7.38 ± 0.12	7.41 ± 0.98	7.36 ± 0.13	**0.035**
pO_2, kPa	58.80 ± 16.37	58.97 ± 13.88	58.59 ± 19.14	0.892
Lactates, mmol/L	2.72 ± 2.41	2.22 ± 1.30	3.34 ± 3.21	**0.010**
Oxygen saturation (%)	86.59 ± 9.36	88.36 ± 7.37	84.41 ± 11.03	**0.018**

Table 2. Severity scoring models in study population, stratified by the outcome

Score	All n=129	Survivors n=73	Non-survivors n=56	*P-value*
SAPS II	27.48 ± 21.89	20.69 ± 18.93	36.33 ± 22.47	**<0.001**
SOFA	5.90 ± 3.37	4.70 ± 2.44	7.46 ± 3.78	**<0.001**
APACHE II	34.12 ± 19.72	28.08 ± 18.16	41.99 ± 19.02	**<0.001**

Table 3. Areas under the curves for analysed severity indexes

				95% Confidence Interval	
Severity index	**Area**	**Std. Error**	**Asymptotic Sig.**	Lower Bound	Upper Bound
APACHE II	**.714**	.055	.001	.607	.821
SOFA	**.749**	.055	.000	.642	.857
SAPS II	**.749**	.053	.000	.645	.853

CONCLUSION

The results of this study showed that SOFA, SAPS II and APACHE II scores can accurately identify patients with pneumonia that have an increased risk for lethal outcome, all have strong mortality prediction ability, but none of them demonstrated an advantage over the others.

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PLACENTAL INFRACTIONS - FROM PATHOLOGICAL FINDINGS TO THE CLINICAL SIGNIFICANCE: A CASE REPORT

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ABSTRACT
Purpose: This case report and literature review refers to a case of postnatally diagnosed multiple typical placental infarcts in a patient with preeclampsia, fetal retardation and successful pregnancy outcome. **Case:** A case of 22-year-old patient in 37 + 6 gestational weeks with hypertonia and intrauterine growth restriction (IUGR), who delivered a baby with weight 2300gr in University Hospital "Maichin dom", Sofia, Bulgaria . After delivering the placenta we noticed that there are large fibrin depositions in the placenta and segments, suspectful for placental infarctions, which the pathohistological examination confirmed. **Conclusion:** Similar cases are very rare and a few have been published. Placental infarctions are a major risk factor for pre-eclampsia, premature birth, spontaneous abortions, intrauterine retardation and fetal death.

Key words: placenta, preeclampsia, fibrin depositions, placental infarction, intrauterine growth restriction

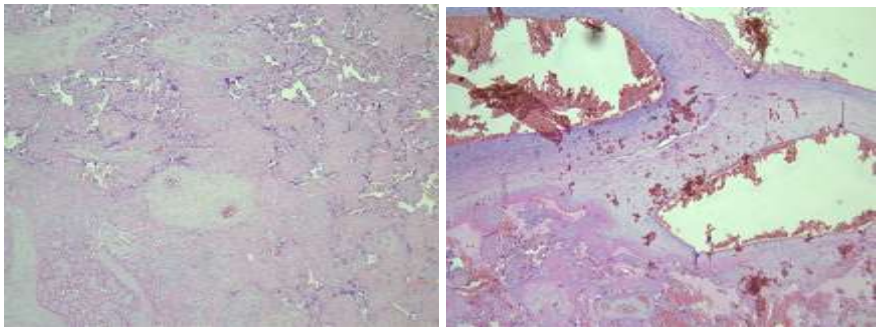
INTRODUCTION
The placenta is the most important temporary organ in the human body responsible for oxygenation, nutrition and fetal wellbeing. The abnormal remodeling of the uterine spiral arteries is considered to be the key feature in the pathogenesis of preeclampsia. Preeclampsia (PE) is a condition, which affects around 7% of pregnant women. It is characterized by hypertension and proteinuria with onset after 20 weeks of gestation. Common pathological features in PE include small placentas with decidual arteriopathy, infarctions of the placenta, abruption and intervillous thromboses. Ultrasound examination of the placenta is important part of the diagnosis, because it has specific changes, including thickness or thinning of the placenta, cystic areas, infarction of the placenta or placental hematoma. Disruption in the blood flow to the placenta is usually the main cause of abnormal fibrin deposition and infarction of the placenta, which can lead to IUGR, placental abruption and stillbirth. Our publication represents a case of placental infarction with abnormal fibrin depositions in the placenta.
The lesion termed "placental infarction hematoma" is associated with fetal death and adverse perinatal outcomes - first described by Bendon [1, 2]. The placenta undergoes physiological changes during pregnancy, which are described as placental aging. During pregnancy, the normal placenta increases in size reaching at term an average of 22 cm in diameter, a thickness of 2,5 cm and a weight of 500 grams and it`s echogenisity - we can visualize small hyperechoic masses, which are most likely composed of calcium depositions in the placenta. The amount of this depositions determines the ultrasound Grading (According to Grannum classification). [3] During the first and second trimester of pregnancy this depositions are in small amount, and during the third trimester the level increases. [4] Other factors, like for example smoking, could have as an result higher grade of the placenta before reaching the third trimester. Sonographically we can also visualize small white fibrin deposits around 1-2 cm. This depositions are a normal finding in 20% of term pregnancies, but in some cases the deposition could be a pathological process, which could reach more than 25% of the placental surface and is associated with the risk of late spontaneous abortion, fetal retardation, stillbirth and premature birth.

CLINICAL CASE

A 22-year-old patient in 37 + 6 gestational weeks, who was hospitalized in University Hospital "Maichin dom", Sofia, Bulgaria because of hypertonia during pregnancy. The current pregnancy is the third in a row, spontaneously occurring, with hospitalization at 23 gestational weeks, due to edema of the limbs and established RR values up to 140/100 mmHg without prescribed therapy. Upon admission to the hospital with elevated blood pressure values and ultrasound data for intrauterine retardation of the fetus - corresponding to 34 + 3 gestational weeks. The previous two pregnancies ended with intrauterine death in 20 gestational weeks and a voluntary termination of pregnancy. In addition to the arterial hypertension, the patient reported beta thalassemia, but no data and documentation has been found. From the blood count, there are no deviations from the norm - Leu - 12.6 G\L; Hb – 116 g/L; PLT – 143 G\L ; Total protein and albumin - normal; Protein in 24-hour diuresis - normal. The patient gave birth to a female fetus with a weight of 2300 g by vacuum extraction, because of fetal asphyxia and during the management of the placental period due to retention of the placenta; manual extraction of the placenta with subsequent instrumental revision of the uterine cavity was required. Numerous areas with ischemia and the presence of large fibrin deposits with a diameter of about 2-3 cm were found on the surface of the placenta (Fig. 1).

Figure 1: Macroscopic appearance: placenta with multiple, different in size /between 2-5 sm/, well delineated, polygonal white-tan yellow lesions, firmer than the surrounding parenchyma.

Figure 2: Histopathology: A - well demarcated field, clearly demarcated from the surrounding parenchyma showing ischemic necrosis with complete loss of nuclear staining; collapse of the intervillous space; at the periphery - signs or early villous necrosis;
B – Venous ectasia and intramural fibrin deposition showing marked dilatation of stem villous veins relative to adjacent arteries (lower right).



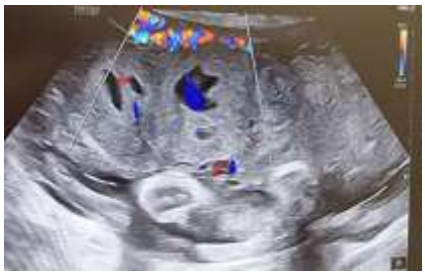
Histological examination of the placenta confirmed the presence of extensive anemic infarcts, acute blood stasis and fresh hemorrhage around the basal plate of the placenta. This case illustrates very well, how placental insufficiency and infarction lead to complications during delivery- intrapartal fetal asphyxia, retained placenta, and with successful outcome. (Fig.2-A, B).

The mother and the baby were discharged from the hospital on the 5th day without any short-term complications.

DISCUSSION

Cases of placental infarctions are very rare, reports in the literature are isolated, and the diagnosis is most often made postnatally, as in our case. No evidence of placental infarcts was present in our case antenatally. Antenatal diagnosis is based on specific sonographic findings as presented below. Sonographic images of the placenta in preeclampsia are very typical and can be suspected antenatally and proven postnatally based on the following: intraplacental anechogenic areas with a specific hyperechogenic rim. (The so-called "Jelly placenta" described by Prof. R. Romero).

Figure 3: Ultrasound examination presents a hypoechoic region with thick hyperechoic rim and as well circumscribed mixed\hyperechoic pattern mass.



Superb Micro-vascular Imaging (SMI) is a technique for imaging blood flow that visualizes low-velocity flow in small vessels, which also minimize motion artifacts and can significantly and compared to traditional blood flow imaging methods such as color Doppler. This technique allows infarct area to be easily measured by measuring the area surrounded by small blood vessels [4, 5].

Placental infarction is common in pregnant women with gestational hypertension, chronic nephritis, primary hypertension, and diabetes. It refers to a localized area of ischemic villous necrosis due to the interruption of the maternal blood flow into the intervillous space due to spasm, stenosis, or occlusion of the decidual spiral artery caused by the systemic or localized maternal vascular disease. [6] Fetal vascular malperfusion (FVM) can lead to vascular stasis, which promotes fetal vascular thrombosis. [7, 8, 9] Fibrin depositions in the placenta can be divided in different three groups: Subchorionic, perivillous and infarction of the maternal floor. Subchorionic fibrin depositions are caused by blood stasis in the subchorionic region. [10] Usually they are seen as white or yellow hard plaques on the fetal surface. Perivillous fibrin deposition is caused by stasis of maternal blood flow around individual villi results in fibrin deposition and may result in reduced villus oxygenation. Within certain limits these are visible as small yellow-white placental nodules and are considered normal. Maternal Floor Infarction is extreme variant of perivillous fibrinoid deposition is a dense fibrinoid layer in the basal lamina of the placenta and is mistakenly called an infarct. The lesion has a thick, white, hard surface that obstructs normal maternal blood flow into the intervillous space. Their etiopathogenesis is not well defined, but some cases are associated with autoimmune diseases of the mother such as lupus [11,12]. According to the pathologists placental parenchymal lesion comprised of villi that have undergone ischemic necrosis due to focally reduced placental (maternal) blood flow [13]. Histologically fibrinoids are glossy and acid staining. They can be divided in two histological types: fibrin-type and matrix-type. Fibrin-type fibrinoid is mostly composed of fibrin together with other molecules derived from blood clotting or degenerative processes. Matrix-t1pe fibrinoid is a secretory product of invasive extravillous trophoblast cells [14]. Our pathohistological findings correspond with the cases presented in the literature.

CONCLUSIONS

The placental hypovascularisation and hypoperfusion are associated with placental insufficiency - the condition specific for hypertension in pregnancy, pre-eclampsia and other pregnancy related conditions. The main cause of this pathology is disruption of uterine blood flow, which leads placental hypoperfusion, oclusion and spasm of uterine spiral arteries, which can cause placental infarction. The manifestation of these changes is the fetal distress.

This pathophysiologycal condition is rare and difficult to predict antenatally, but we have to keep it in mind, when we have a patient with signs of hypertension, PE, IUGR and history of fetal demise with a previous pregnancy.

The case illustrates very well a placental infarction with positive pregnancy outcome.

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EPIDEMIOLOGY OF INTESTINAL INFECTIONS IN SILISTRA REGION, BULGARIA FOR THE PERIOD 2019-2023

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ABSTRACT

Intestinal infectious diseases are a major epidemiological group in terms of significance for pathology in people in Bulgaria and the world.

Aim: In the present study, we aimed to analyze the main epidemiological characteristics of intestinal infections without the group of viral hepatitis in Silistra region.

Materials and methods: Data from performed epidemiological studies, analyses, microbiological and immunological studies of the Regional Health Inspection (RHI) Silistra. Scientific Center for Infectious and Parasitic Diseases (NCZPB) Sofia, as well as data from the national information system on infectious disease in the Republic of Bulgaria. Epidemiological, statistical, documentary, graphic and comparative methods were used to analyze and present the information database. **Results:** Intestinal infections ranked second by a wide margin in the years before and after the pandemic. In 2019, the incidence of intestinal infections in the Silistra region was 49% and was above the national average of 29.27%, in the rest of the period it was significantly below the national average. **Conclusion:** In the Silistra district, a large difference in the incidence of intestinal infections was observed in the years before and after the pandemic. In 2019, the incidence of intestinal infections in the Silistra region was 49% and was above the national average of 29.27%, in the rest of the period it was significantly below the national average Etiologically undetermined enterocolitis occupies the highest share in the group of intestinal infections (70%). During the study period, salmonellosis and shigellosis were sporadic in the Silistra region. Systematic work is established on the timely diagnosis and registration of 6 types of infectious intestinal infections: unspecified enterocolitis, dysentery (shigellosis), salmonellosis, colienteritis (escherichiosis), rotavirus infection, campylobacteriosis from the total of 20 with acute viral hepatitis.

Key words: intestinal infections, features, dysentery, salmonellosis, colienteriti,

INTRODUCTION

Intestinal infectious diseases are a major epidemiological group of significance for human pathology in Bulgaria and the world. They are caused by various agents- bacteria and viruses that usually spread by faecal–oral route [1, 2]. Epidemiological surveillance in Bulgaria includes 20 intestinal infections, including viral hepatitis.

AIM The purpose of this study is to describe the incidence of intestinal diseases infections without the group of viral hepatitis in in Silistra region for the period 2019-2023.

MATERIALS AND METHODS

Data from performed epidemiological studies, analyses, microbiological and immunological studies of the Regional Health Inspection (RHI) Silistra. Scientific Center for Infectious and Parasitic Diseases (NCZPB) Sofia, as well as data from the national information system on

infectious disease in the Republic of Bulgaria. Epidemiological, statistical, documentary, graphic and comparative methods were used to analyze and present the information database.

RESULTS AND DISCUSSION

In the Silistra region, there was a large difference in the incidence of intestinal infections in the years before and after the pandemic. The relative share of intestinal infections in Silistra region was 49% for 2019 and was above the national average of 29.27%, in the remaining period it was significantly below the national average (Fig. 1).

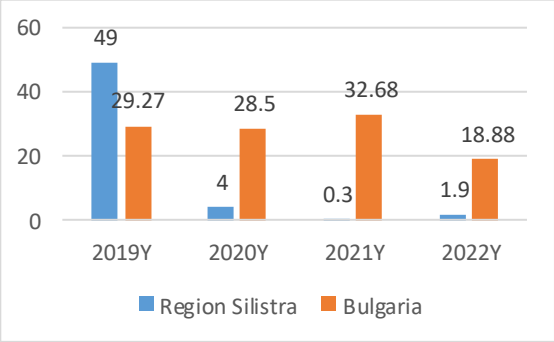

Fig. 1 Incidence Rate of Enteric Infections in Silistra and Bulgaria for 2019-2023

Fig. 2 Incidence of etiologically unchecked cases of enterocolitis in Silistra and Bulgaria for 2019-2023

Etiologically unchecked cases of enterocolitis have the highest share in the group of intestinal infections (70%) (Fig. 2). The highest average annual incidence of reported Campylobacter infections refered to 0-4 age group (90.2 per 100 000), followed by 1-4 age group (178.16 per 100 000). In the Silistra region the cases of shigellosis are sporadic (Fig. 3) and the main reason for the spread is the poor hygiene and low health culture of the Roma population, predominant in the municipality of Kaynardzha. The social polarity of society and the presence of groups with low standard and health habits brings out Shigella flexneri as an etiological factor.

The incidence of salmonellosis in the Silistra region throughout the period is below the average for Bulgaria, and in 2023 it is 2%000, i.e. four times below that of the country 8.51%000/2023 (Fig. 4) Leading etiological species among the etiologically proven causative agents of diseases with diarrheal syndrome are S. enteritidis and S. tiphimurium.

During the study period, salmonellosis and shigellosis were sporadic, which confirms the improvement of the sanitary and hygienic condition of the cold chain, the thermal processing of food products and the control of public catering [3, 4].

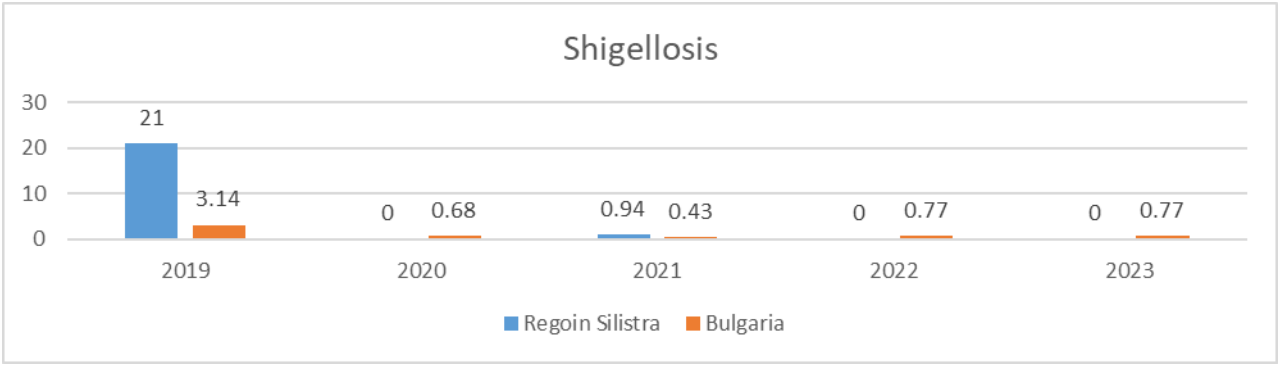

Fig. 3 Incidence of shigellosis in Silistra and Bulgaria for 2019-2023

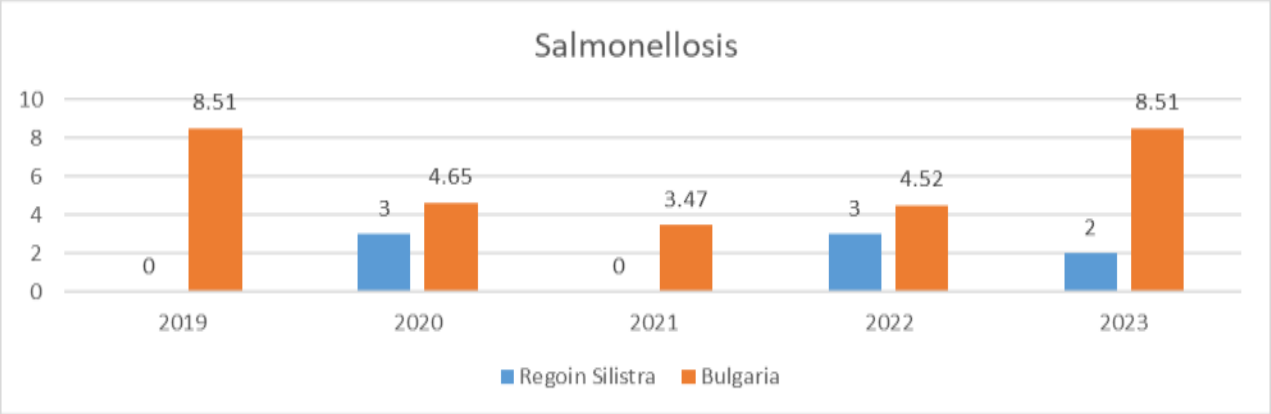

Fig. 4 Incidence of salmonellosis in Silistra and Bulgaria for 2019-2023

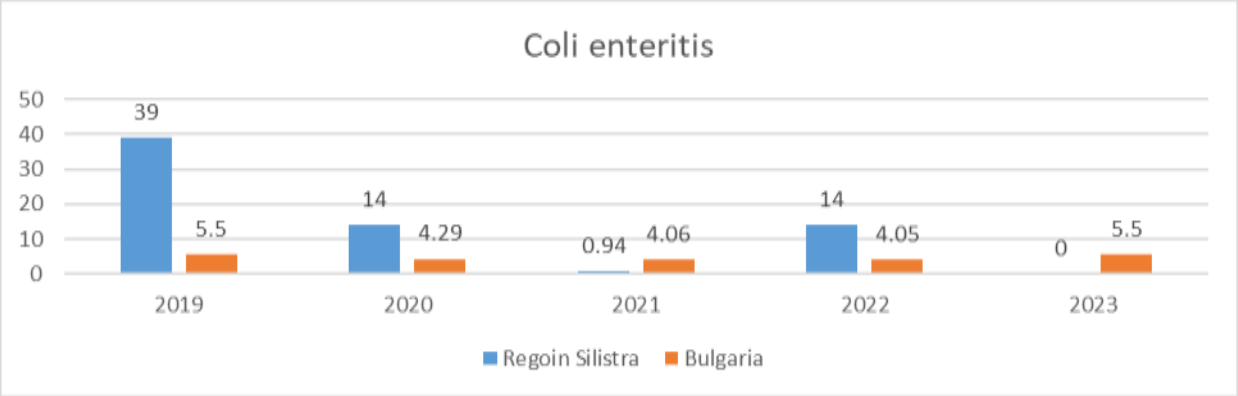

Fig. 5 Incidence of E coli enteritis in Silistra and Bulgaria for 2019-2023

The incidence of E coli enteritis in Silistra district (Fig. 5) is 39%000/2019, 14%000/2020, 2022 and is above the average, for the country from 4.05%000 to 5.5%000 for the entire period. The distribution by age groups outlines the highest morbidity in children from zero to 5 years.

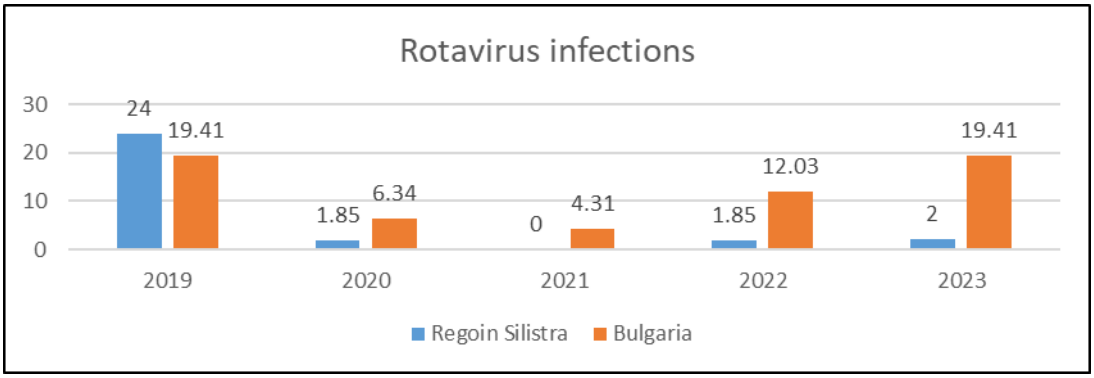

Fig. 6 Incidence of Rotavirus infection in Silistra and Bulgaria for 2019-2023
In 2019, the Silistra region was in third place in the incidence of rotavirus gastroenteritis (24/100 thousand) with the national average of 19.41%000. In 2020, in Silistra, the morbidity rate was 1.85%000, compared to the national average of 6.34%000 (Fig. 6).

CONCLUSION
In the Silistra region, there was a large difference in the incidence of intestinal infections in the years before and after the pandemic.

The relative share of intestinal infections in Silistra region was 49% for 2019 and was above the national average of 29.27%, in the remaining period it was significantly below the national average.
During the study period, salmonellosis and shigellosis were sporadic in the Silistra region.
Etiologically unchecked cases of enterocolitis have the highest share in the group of intestinal infections (70%).
Systematic work on the timely diagnosis and registration of 6 types of infectious intestinal infections is established: unchecked enterocolitis, dysentery (shigellosis), salmonellosis, colienteritis (escherichiosis), rotavirus infection, campylobacteriosis from the total of 20 with acute viral hepatitis.

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PHARMACOLOGICAL MANAGEMENT OF INFANTILE HEMANGIOMAS: THE ROLE OF PROPRANOLOL – A REVIEW

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ABSTRACT
Propranolol ((2RS)-1-(naphthalen-1-yloxy)-3-(propan-2-ylamine)propan-2-ol hydrochloride) is a first-generation β-blocker, initially introduced by the British scientist Sir James Black. Its primary indication is the treatment of hypertension. However, it is also prescribed for conditions such as angina pectoris, atrial fibrillation, myocardial infarction, migraine, essential tremor, hypertrophic subaortic stenosis, and pheochromocytoma. Notably, new indications for this drug continue to emerge, including its use in treating proliferating infantile hemangiomas.
Infantile hemangiomas are among the most common benign vascular tumors in infants, affecting 4–10% of newborns. The purpose of this review is to examine the treatment methods for infantile hemangiomas. In most cases, the standard approach involves active observation due to the natural course of the condition. However, cases with complications may require immediate treatment. The primary treatment modalities include systemic and topical medications, with β-blockers—particularly propranolol—being the most commonly used. In certain instances, combined therapy may be recommended, involving surgical intervention following the reduction in size of the hemangioma.

Keywords: β-blocker, propranolol, infantile hemangioma

INTRODUCTION

Infantile hemangiomas (IH) are the most common benign vascular tumors in infancy (Kowalska et al, 2021). The diagnosis and treatment of IH present a complex and challenging task. The main challenge lies in the accurate assessment and management by a multidisciplinary team, including neonatologists, pediatricians, pediatric cardiologists, dermatologists, and pediatric surgeons. Unlike other tumors, IHs have the unique ability to involute after a phase of proliferation, often leading primary care providers to assume they will resolve spontaneously without intervention or significant consequences (Darrow et al, 2015). Therapeutic strategies should be tailored to the individual, considering factors such as the size, morphology, and location of the lesion, as well as the potential for complications.. Numerous classifications of hemangiomas exist, based on factors such as shape, size, and location. The most widely accepted classification of vascular anomalies is that adopted by the International Society for the Study of Vascular Anomalies (ISSVA). It divides vascular anomalies into two main categories: vascular malformations and vascular tumors. Vascular malformations are structural defects that are present at birth, including venous, lymphatic, capillary, and arteriovenous malformations, as well as mixed forms. These are generally congenital and grow proportionally with the individual. Vascular tumors are abnormal growths of blood vessels. Examples include benign tumors like infantile hemangiomas, which are common in infants and typically grow before gradually shrinking, and congenital hemangiomas such as rapidly involuting (RICH) or non-involuting (NICH) types. Other examples are locally aggressive tumors like kaposiform hemangioendothelioma (KHE) and malignant tumors like angiosarcoma (https://www.issva.org).
Infantile hemangiomas are recognized as the most common benign vascular tumors, affecting up to 4–5% of children (Kanada et al, 2012; Kilcline &Frieden, 2008). Other studies report an

incidence of IHs in 1% to 3% of newborns (Pratt, 1953; Jacobs &Walton, 1976). The prevalence of IH is higher in females, with the female-to-male ratio varying between 3:1 and 5:1, or more recently reported to range from 1.4:1 to 3:1 (Hoornweg et al, 2012; Haggstrom et al, 2008).

AIM

The aim of this article is to provide an overview of current approaches in the diagnosis and treatment of infantile hemangiomas (IHs), with a focus on the role of β-blockers, specifically propranolol, in the management of these benign vascular tumors. The article examines various therapeutic strategies, including both conservative and surgical methods, emphasizing the importance of an individualized approach based on lesion characteristics and the presence of complications. Additionally, it highlights the safety and efficacy of propranolol in treating IH, offering new perspectives for treatment and minimizing side effects in affected patients.

RESULTS

The treatment of infantile hemangiomas (IHs) may include both conservative medical therapy and surgical interventions. Conservative treatment can be administered either locally or systemically. The first observation of hemangioma regression occurred following the application of corticosteroids in patients with hemangioendothelioma and thrombocytopenia during the 1950s and 1960s (Katz & Askin, 1968).

In 1967, Zarem and Edgerton treated seven children with prednisolone tablets to reduce hemangioma lesions. All seven patients responded positively, showing significant breakdown of the hemangiomas and regression of the lesions post-treatment (Zarem & Edgerton, 1967). Following this success, the authors reported the safety and efficacy of intralesional corticosteroid application for the treatment of IHs (Mazzola, 1978; Chantharatanapiboon, 2008).

In 2008, Léauté-Labrèze et al. accidentally discovered the therapeutic effects of propranolol for IHs, finding its safety profile to be acceptable. They reported their experience treating thirty-two infants with severe IHs while investigating propranolol's use in IHs treatment. The dosing regimen followed was 2 to 3 mg/kg per day, administered two or three times daily (Léauté-Labrèze et al, 2008; Sans et al, 2009).

Propranolol has since been extensively used for the management of complicated and significant cases of IHs. Although the exact mechanism of action is not fully understood, propranolol is believed to work through several mechanisms, including vasoconstriction, inhibition of angiogenesis and nitric oxide (NO), and regulation of the renin-angiotensin system. Some studies recommend a treatment duration of 3 to 12 months to achieve full regression of the tumor (Starkey & Shahidullah, 2011; Léauté-Labrèze et al, 2015).

McMahon et al. reported significant results in the treatment of superficial hemangiomas with timolol maleate (McMahon, 2012).

Although propranolol is considered a safe drug, it has been associated with adverse events such as cardiogenic shock, sinus bradycardia, hypotension, heart failure, bronchial asthma, and bronchospasm. There is also evidence suggesting a risk of hypoglycemia and even unconsciousness (Bakalli, 2019). Therefore, it is crucial for parents to adhere strictly to the prescribed treatment regimen.

DISCUSSION

The role of propranolol in treating infantile hemangiomas represents a major breakthrough in pediatric dermatology. While the natural history of IHs involves spontaneous regression in many cases, complications such as ulceration, bleeding, and functional impairment often necessitate pharmacological intervention (Graaf et al, 2016). Propranolol’s mechanism of action, which involves inhibiting angiogenesis and inducing vasoconstriction, is believed to contribute significantly to its therapeutic effect. Nevertheless, treatment must be individualized, considering the size, location, and complexity of the hemangioma. Furthermore, while propranolol is

generally well-tolerated, careful monitoring for side effects is essential, especially in infants with underlying health conditions (Mansouri et al, 2014).

Given the potential for both spontaneous regression and the need for therapeutic intervention in complicated cases, the treatment approach should always be tailored to the individual. For most patients, a course of propranolol may be the most appropriate choice. However, when a hemangioma causes severe functional or cosmetic issues, or does not respond to pharmacological treatment, surgical intervention might be necessary. This combined approach enhances the chances of a positive outcome with minimal long-term side effects.

CONCLUSION

The primary approach for managing infantile hemangiomas (IHs) is active observation due to their natural course of regression. However, in cases with complications, immediate intervention may be necessary. The mainstay of treatment includes systemic and topical medications, with β-blockers, particularly propranolol, being the most commonly used. In certain instances, a combined therapeutic approach may be recommended, which could involve surgical treatment following a reduction in the size of the hemangioma.

Given the potential for both spontaneous regression and the risk of complications, it is essential to tailor treatment based on the individual characteristics of each case, including lesion size, location, and the presence of associated complications. Ongoing research into the mechanisms of propranolol and other therapeutic options continues to enhance the management of IH, offering hope for improved outcomes and fewer side effects in the future.

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MICROBIOLOGICAL STUDIES AND THEIR DIAGNOSTIC VALUE FOR HEALTHCARE-ASSOCIATED INFECTIONS IN THE COMPLEX ONCOLOGICAL CENTER – RUSE, BULGARIA DURING 2020-2022

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ABSTRACT

Introduction: Healthcare-associated infections can occur in different care units and can affect both patients and healthcare professionals. Bacteria represent the most common cause of nosocomial infections and, due to the excessive and irrational use of antibiotics, resistant organisms have appeared [1]. Therefore, rapid identification of the specific etiological agent and the selection of an adequate therapeutic approach are necessary. **The aim** of the work is to analyze the most frequently isolated microorganisms from clinical materials taken from patients suspected of nosocomial infection in the Complex Oncological Centre- Ruse for 2020-2022. **Materials and methods**: The data was collected from medical documentation for microbiological investigations; reports and analysis from the microbiological laboratory "Biosana-yug" in Ruse, which serves the Complex Oncological Centre- Ruse. **Methods:** statistical, epidemiological analysis. **Results:** During the period January 2019-June 2020, a total of 1822 clinical materials from patients suspected of VBI were examined in the "Biosana-yug" - Ruse laboratory, at the Complex Oncological Centre- Ruse with the number of wound secretions -765 and blood cultures -673 exceeding from 6 to 8 times those of the other samples received. Total positive samples were 19% (n=346). The relative share of positive samples is the highest in surgical drains - up to 80.76%, urine culture- 59.64%, coproculture - 43.33%.
Conclusion: Predominance of Gram-positive bacteria (66.99%) over Gram-negative bacteria (26,82%). Fungi with medical importance of genus Candida compose 5,77 percent from the isolated pathogens. This is an indirect indicator of the effectiveness of the applied hygiene measures during the COVID-19 pandemic.A major role in the epidemiology program's efforts to minimize nosocomial infections in the Complex Oncological Centre- Ruse plays laboratory "Biosana-yug" in Ruse. Through the rapid and consistent identification of isolated pathogens, it serves as an early warning center for infection problems.
Key words: healthcare-associated infections, bacteria detection etiology

INTRODUCTION

Healthcare-associated infections can occur in different care units and can affect both patients and healthcare professionals. Bacteria represent the most common cause of nosocomial infections and, due to the excessive and irrational use of antibiotics, resistant organisms have appeared [1]. Therefore, rapid identification of the specific etiological agent and the selection of an adequate therapeutic approach are necessary. The aim of the work is to analyze the most frequently isolated microorganisms from clinical materials taken from patients suspected of nosocomial infection in the Complex Oncological Centre- Ruse for 2020-2022.

MATERIALS AND METHODS

The data was collected from medical documentation for microbiological investigations; reports and analysis from the microbiological laboratory "Biosana-yug" in Ruse, which serves the Complex Oncological Centre- Ruse.

Epidemiological analysis, statistical and graphic methods are used.

RESULTS AND DISCUSSION

During the period January 2019-June 2020, a total of 1822 clinical materials from patients suspected of Healthcare-associated infections were examined in the "Biosana-yug" Ruse laboratory, at the the Complex Oncological Centre- Ruse with the number of wound secretions - 765 and blood cultures -673 exceeding from 6 to 8 times those of the other samples received.

Total positive samples were 19% (n=346).

The relative share of positive samples is the highest in surgical drains - up to 80.76%, urine culture- 59.64%, copro culture - 43.33%, tip of cannula - 35.46%, bile - 35.29%. abscess - 30.75%, nasal and throat samples-100% have no statistical reliability, because they are from single materials ($p<0.05$).

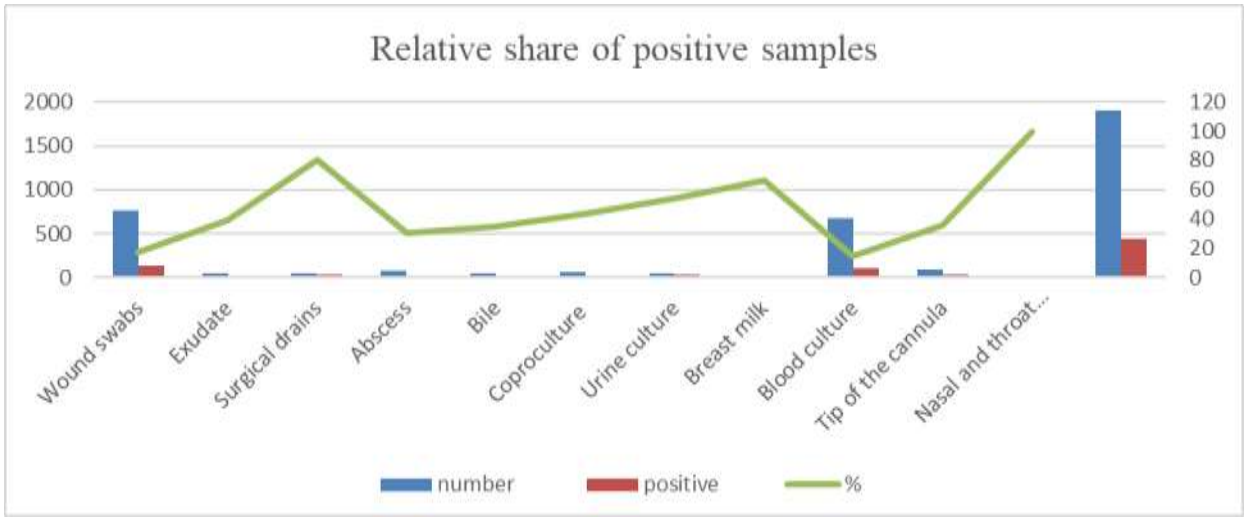

Fig. 1 Relative share of positive samples

From Gram positive microorganisms the leading pathogens causing HAIs in Complex oncological center - Ruse from 2020 to 2022 are *Staphylococcus aureus* (36.7%), *S.epidermidis* (8,09%) and *S.agalactiae* (5,78%). From Gram negative microorganisms are *Klebsiella spp.* (7,51%), *E.coli* (6,07%) and *Proteus vulgaris* (3,46%). *Clostridium difficile* and *Candida glabrata* have the same share (3,46%).

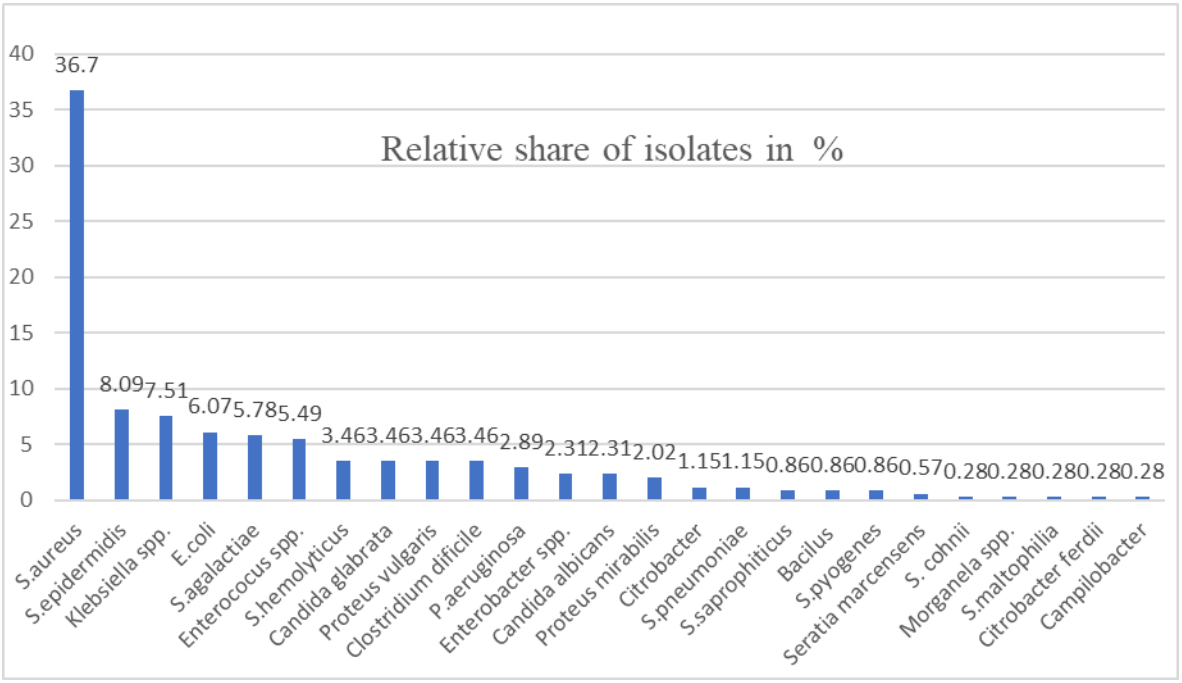

Fig. 2 Relative share of isolates in %

Antibiotic pressure led to the increased detection of fungi and *Clostridium difficile* in HAIs clinical samples, as noted by other authors [2, 3, 4].

CONCLUSION

The retrospective study made it possible to analyze the etiological structure of infections of patients in the Complex Oncology Center - Ruse in 2020-2022.

Predominance of Gram-positive bacteria (66.99%) over Gram-negative bacteria (26,82%). Fungi with medical importance of genus Candida compose 5,77 percent from the isolated pathogens. This is an indirect indicator of the effectiveness of the applied hygiene measures during the COVID-19 pandemic.

A major role in the epidemiology program's efforts to minimize nosocomial infections in the Complex Oncological Centre- Ruse plays laboratory "Biosana-yug" in Ruse. Through the rapid and consistent identification of isolated pathogens, it serves as an early warning center for infection problems.

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SPECTROSCOPIC AND MICROBIOLOGICAL STABILITY ANALYSIS OF 45-YEAR-EXPIRED NIVALIN AMPOULES

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ABSTRACT
Galantamine, an alkaloid derived from plants of the *Amaryllidaceae* family, acts as a reversible inhibitor of acetylcholinesterase and a ligand for nicotinic acetylcholine receptors. This study investigates the stability of Nivalin ampoules (Galantamine hydrobromide) manufactured in 1979, using spectroscopic analyses (UV-VIS and IR), pharmacopoeial reactions, and microbiological assays after 45 years of storage. UV-VIS spectroscopy identified characteristic absorption at 288 nm, with minor irregularities suggesting degradation products. IR spectroscopy confirmed structural consistency with minor deviations in fingerprint regions. Chemical tests verified the intact bromide salt form, and sterility testing showed no microbial growth. Despite 45 years of storage, the ampoules maintained active galantamine and sterility, highlighting the potential extended stability of certain pharmaceutical products under controlled conditions.
Keywords: Nivalin, Galanthamine, expired drugs, stability, microbiological stability

INTRODUCTION
Galantamine is an alkaloid that is extracted from plant sources - bulbs and flowers of Galanthus nivalis, Galanthus caucasicus, Galanthus woronowii and other members of the Amaryllidaceae family, such as Narcissus, Leucojum aestivum and Lycoris, including Lycoris radiate (Heinrich, 2010). It has a heterotetracyclic structure with three chiral centers and belongs to the group of benzazepine alkaloids (Figure 1).

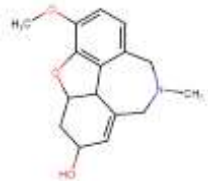

Fig 1. Chemical structure of Galntahmine; **Fig 2.** Image of Nivalin ampoule produced in 1979.

The Bulgarian connection with galantamine is the name of Dimitar Paskov, who extracted the alkaloid from a tuber of the marsh snowdrop that grows in Bulgaria (Paskov, 1959). The pharmacological activity of galantamine hydrobromide is expressed in competitive and reversible inhibition of the enzyme acetylcholinesterase, which leads to an increase in the concentration of acetylcholine and enhances its action. In addition, it is a ligand for nicotinic acetylcholine receptors, which can increase the presynaptic release of acetylcholine and activate postsynaptic receptors (Lilienfeld, 2002).

The expiration date of a medicine indicates the specific date after which that medicine cannot be considered safe for use. This date is usually marked on the packaging. After opening, the potency of most medicines, with the exception of specific medicines such as nitroglycerin, insulin,

epinephrine and tetracycline, remains at least 70-80% of their original potency for a period of 1 to 2 years after the expiration date, provided that they are stored under appropriate conditions. The rate of degradation of medicines is not the same for all products, as different active ingredients degrade to different degrees and at different rates. The chemical composition of a medicine can changes over time, especially if it has been stored incorrectly. Factors such as heat, light and moisture can significantly accelerate the degradation of active ingredients, leading to reduced effectiveness. This poses a particularly serious risk for life-saving medicines, where reduced potency can have serious consequences.

Every pharmaceutical product should be accompanied by a package insert with comprehensive information about its indications, potential adverse reactions, possible drug interactions, and expiration date. Since 1979, the Food and Drug Administration (FDA) has required all pharmaceutical manufacturers to include an expiration date on their products. However, some expired drugs may retain their potency (Gikonyo et al, 2019).

Current research shows that many drugs maintain up to 90% of their effectiveness for at least five years after expiration, and in some cases longer, when stored under optimal conditions. Many drugs retain a significant portion of their potency even a decade after their expiration date. However, potential problems can arise as a result of contamination, which can lead to increased levels of microbial activity or the formation of toxic breakdown products (Arioua & Shaw, 2023). In Bulgaria, the conditions and procedure for the destruction, processing or use for other purposes of expired medicinal products are regulated by REGULATION No. 4 of May 16, 2018, issued by the Minister of Health, and promulgated in the State Gazette, issue 43 of May 25, 2018 (Naredba 4, 2018).

It describes in detail the conditions under which such medicines are handed over and destroyed, who has the right to carry out this activity and who are the authorities that control the process. Expired medicines fall under the "hazardous waste" category and as such must be collected at places designated for this activity by the relevant municipality. If they are incorrectly disposed of in public containers, in the sewer or in nature, they pose a serious environmental hazard. Improper isposal of expired medicines can lead to contamination of groundwater, which stores almost a third of the world's total freshwater reserves (EEA, 2023; Toneva& Dimitrova, 2023; Toneva& Dimitrova, 2023). Their destruction is carried out by specialized companies in incinerators. Campaigns for the handover of expired medicines to mobile collection points are often organized, with the last such initiative dating back to October 2024. The aim of this study is to investigate the stability of expired Nivalin ampoules through spectroscopic analysis, analytical reactions, and to assess their microbiological stability after 45 years of storage.

MATERIALS AND METHODS

UV-VIS and IR spectroscopic analyses were performed, and pharmacopoeial analytical reactions were applied to confirm the presence of Nivalin. The microbiological stability of the ampoules after 45 years of storage was assessed through blood agar inoculation. The methodology is part of the standards for sterility control of pharmaceutical products.

RESULTS

UV-VIS Spectroscopy

UV-VIS spectroscopy (ultraviolet and visible spectroscopy) is a powerful analytical tool used to study molecular compounds by measuring their light absorption in the ultraviolet (UV) and visible (VIS) spectra. This methodology is primarily used to identify compounds, determine concentrations, and investigate the chemical and physical properties of substances. The maximum peak for the compound is observed at 288 nm, which is seen in both samples (Figure 3a). The irregular lines in the spectrum of the expired drug may be due to the presence of degradation products, which result in inelastic transitions between different molecular orbitals (e.g., from $\sigma \rightarrow \sigma^*$ or $\pi \rightarrow \pi^*$ transitions), leading to light absorption in the UV or visible spectrum. Additionally, molecules with significant electron interactions, as well as those

containing complex functional groups (such as aromatic rings or heteroatoms), may exhibit uneven absorption, appearing as wrinkled lines instead of well-defined peaks. This assumption is supported by the spectrum of the standard, where all peaks are clearly defined.

IR Spectroscopy

Infrared spectroscopy is a powerful method for determining the chemical structure of compounds, with each chemical group absorbing light at specific frequencies in the infrared radiation range (approximately 4000 to 400 cm^{-1}). Both spectra reveal vibrational bands due to the presence of OH groups and a relatively broad valence band for CH bonds in the range of 3050 to 2800 cm^{-1}. In the region of double bonds, two absorption bands are observed at approximately 1600 cm^{-1}. The strong band in the fingerprint region at 1430 cm^{-1} is again attributed to CH. The two spectra are identical except for some poorly defined bands in the spectrum of the expired drug, which are most likely due to the presence of degradation products (Figure 3b).

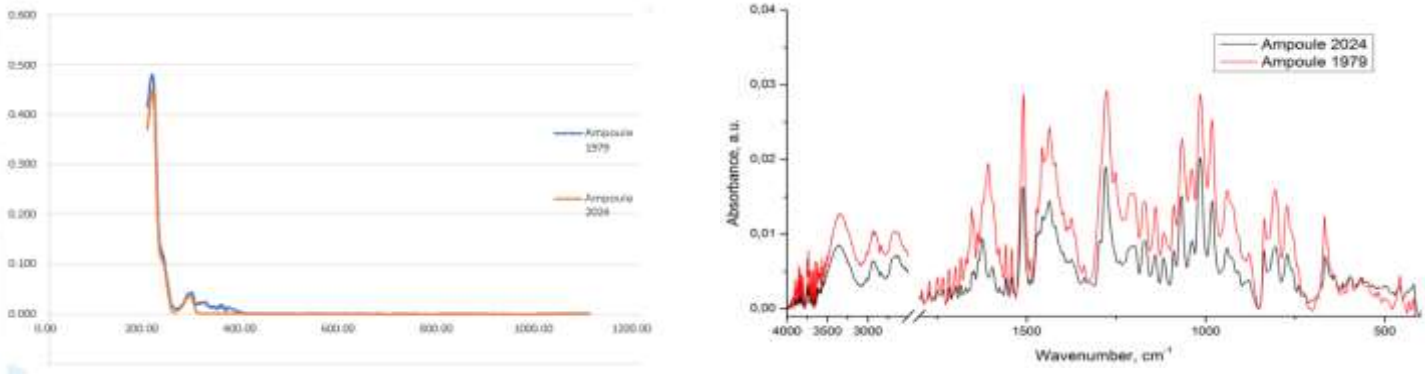

Figure 3. a) UV-VIS spectrum of a Nivalin ampoule with expired expiration date compared to the standard (2024 ampoule); b) IR spectrum of a Nivalin ampoule with expired expiration date compared to the standard (2024 ampoule).

Pharmacopoeial Reactions

The formation of colored compounds is evidence of the successful course of the pharmacopoeial reactions as follows: when interacting with ammonium molybdate in concentrated sulfuric acid, the characteristic blue-green coloration appears. It was successfully confirmed that Galantamine is in the form of a bromide salt. A yellowish precipitate, poorly soluble in ammonia solution, forms when silver nitrate solution is added.

Microbiological Evaluation

The microbiological test was negative. No microbial growth was observed, providing evidence of sterility in the examined ampoules with expired expiration dates (Figure 4).

Figure 4. Microbiological evaluation of an expired Nivalin ampoule

CONCLUSION

The applied methods for analysis and identification of Nivalin ampoules confirm the presence of the active substance and their microbiological stability despite the long storage period of 45 years.

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METHODS OF PHYSICAL THERAPY FOR LOCAL TRANSDERMAL APPLICATION OF DRUGS FOR THE TREATMENT OF DISEASES OF THE MUSCULOSKELETAL SYSTEM-REVIEW

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ABSTRACT

The development of medical macromolecules is attracting great interest in research and the pharmaceutical industry. The growing interest is probably due to the minimal side effects, high specificity and endogenous affinity for the target tissue or cell. **Purpose:** The aim of this review was to examine the selected literature in order to recognise the therapeutic use of Iontophoresis (IP) and phonophoresis (PP) and their mode of action. **Material/Methods:** We selected dozens of studies describing meta-analyses, reviews and systematic reviews, free full-text only. **Results:** There is no definitive statistically significant benefit of IP and PP compared to placebo or other physical therapy modalities. **Conclusions:** There is a need to develop and research a dosage form containing natural products suitable for topical application with the aim of transdermal deposition using physical therapy methods.

Keywords: iontophoresis, phonophoresis, diseases of the musculoskeletal system, transdermal application, drugs

INTRODUCTION

Non-invasive transdermal delivery by IP and PP is an alternative route of administration for local and systemic delivery of biological macromolecular drugs. IP is a method for local drug delivery using an electric field. Ultrasound (US) is used to improve percutaneous absorption of drugs.

MATERIALS AND METHODS

The aim of this review was to examine the selected literature to identify the therapeutic use of IP and PP and their mode of action in musculoskeletal disorders. We identified English-language studies from 2014 to 2024 by searching MEDLINE and the Physiotherapy Evidence Database (PEDro) using the terms IP and PP. Methodological quality was assessed using the Physiotherapy Evidence Database (PEDro).

RESULTS

Table 1. Reviewed Articles for Iontophoresis

Article	Participants	Inclusion Criteria	Measurement	Results	PEDro Score
Sims [1]	systematic review	lateral epicondylitis	pain, function, and main complaint on Likert scale, VAS, PFFQ, MGS, DASH	inconclusive short-term benefit in pain relief after IP corticosteroids.	N/A
Sayegh [2]	systematic review	lateral epicondylitis	PRTEE, DASH; PFFI, EuroQoL (EQ)-5D and pain-free grip strength	no superiority of corticosteroid IP over placebo.	N/A
Fathy [3]	22 industrial workers	chronic tennis elbow	VAS, OES and by a handgrip dynamometer	both IP dexamethasone and Cyriax exercises were successful as treatment, without priority between them both	5/10
Baktir [4]	20 patients	lateral epicondylosis	VAS, pressure algometer, PRTEE, and grip strength dynamometer	IP had better effects for pain, function, and grip strength compared to PP	6/10
García [5]	88 patients	impingement syndrome	DASH, Constant-Murley score, and SF-36 scale	The combination of PP diclofenac and an exercise program (EP) is better than IP with diclofenac and EP or EP alone.	7/10
Simpson [6]	systematic review	rotator cuff tendinopathy	pain and function	No evidence of superiority of acetic acid IP treatment compared with placebo.	N/A
Reda [7]	30 patients	carpal tunnel syndrome	sensory nerve conduction velocity of median nerve and a pain	statistically significant differences in favor of shock wave treatment over IP with dexamethasone and lidocaine.	6/10
Osmanoglua [8]	72 patients	carpal tunnel syndrome	VAS, BSSS, BFCS, grip strength, and electrophysiological examination	Extracorporeal Shock Wave Therapy appears to be more effective than Corticosteroid IP.	5/10
Martin-Vega [9]	Systematic review and meta-analysis	carpal tunnel syndrome	sensory and motor nerve conduction velocity, pain intensity, handgrip strength, or pinch strength	IP with Corticosteroid was not superior to other interventions.	N/A
Abdelhalim NM [10]	45 patients	plantar psoriasis	(6MWD) test	IP methotrexate is effective in improving functional impairment in lifestyle, increasing functional capacity, and reducing pain	5/10
Eker [11]	37 patients	knee osteoarthritis and Baker's cyst	NRS, WOMAC and US	clinical and functional improvement with dexamethasone IP.	7/10

Table 2. Reviewed Articles for Phonophoresis

Article	Participants	Inclusion Criteria	Measurement	Results	PEDro Score
Durmus [12]	41 patients	chronic neck pain	VAS, NDI, BDI, and PSQI	treatment with capsaicin PP and exercise was superior to placebo, capsaicin PP and exercise, and exercises.	5/10
Dorji [13]	systematic review	nonspecific neck pain	GRADE, QoE	PP with capsaicin plus exercise is superior to PP diclofenac plus exercise and exercise alone.	N/A
Bayram [14]	66 patients	impingement syndrome	VAS, QuickDASH, NHP	significant improvement with continuous and pulsed mode PP	9/10
Okan [15]	60 patients	lateral epicondylitis	VAS, PRTEE and QuickDASH	Significant improvements in four groups - US, mucopolysaccharide polysulfate PP, ketoprofen PP and exercise combinations	4/10
Karaman [16]	45 patients	carpal tunnel syndrome	electrophysiologically, clinically, and US	PP with ketoprofen and low-level laser therapy did not provide additional effects to exercise therapy	5/10
Nakhostin-Roohi [17]	93 female athletes	anterior knee pain	WOMAC	PP with virgin olive oil is as effective as piroxicam gel	5/10
Boonhong [18]	61 patients	osteoarthritis of the knee	VAS and WOMAC	US combined with TENS, and PP piroxicam were effective without significant differences between them	9/10
Haghighat [19]	51 patients	knee osteoarthritis	NPRS and Kellgren-Lawrence grades	no superiority between PP with aloe vera gel, unmedicated US, and sham US with aloe vera gel.	8/10
Akhalkatsi [20]	29 patients	knee contractures caused by arthrofibrosis.	knee flexion contractures	superiority of combined use of static progressive stretching and hydrocortisone PP over standard exercise	4/10
Joshi [21]	52 patients	knee osteoarthritis	VAS, goniometry, WOMAC, SEBT	no clinically significant difference between PP plant extract gel and US alone in addition to an exercise program	4/10

DISCUSSION

The clinical results (quality of life, spontaneous and provoked pain and range of motion in the affected joints) did not show a definite statistically significant benefit of IP and PP compared to placebo or other physical therapy modalities.

CONCLUSIONS

The conclusions from the literature review are that there is a need to develop and research a dosage form containing natural products suitable for topical application with the aim of transdermal deposition using physical therapy methods. Future long-term studies would offer the possibility of local anaesthesia and suppression of inflammation in patients with musculoskeletal disorders without the characteristic undesirable side effects.

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LONG TERM REHABILITATION RESULTS IN PATIENTS WITH ORTHOPEDIC IMPLANTS OF THE UPPER AND LOWER EXTREMITIES

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ABSTRACT

In the last 5 decades, with the improvement of surgical treatment, patients with orthopedic implants need long-term rehabilitation. A major problem of early rehabilitation is that many physiotherapy modalities are unsuitable for patients with metal implants due to contraindications.

Purpose: The aim of the present study is to analyze and compare the effects of application of physical therapy modalities in patients with orthopedic implants of upper and lower extremity.

Material/Methods: The contingent of the study were 240 patients with orthopedic implants who meet the inclusion criteria. We used four methods to track the signs at five different periods for patients. Patients were divided initially into groups according to the anatomical area where the implant was placed and the joint contracture. Patients from each group were randomly assigned to one of two treatment groups - kinesitherapy and Multiwave Locked System (MLS) laser treatment or kinesitherapy and deep oscillation treatment. **Results:** Patients in the eight treatment groups have both short-term and long-term improvement of functional status and level of pain questionnaires, centimeters at the four moments for each research joint, goniometry of each research joint and spontaneous pain in the VAS. The comparative analysis between the two therapeutic programs did not report a statistically significant difference in one of the methods. **Conclusions:** When it comes to public health, Deep Oscillation and MLS laser therapy can significantly impact treating symptoms in patients with orthopedic implants in their upper and lower limbs. This can lead to a shorter period of forced rest and help prevent complications from operative treatment. It is recommended that longer-term results be followed to establish the statistically significant superiority of one of the complex therapies we applied.

Keywords: orthopedic implants, kinesitherapy, Deep Oscillation Therapy, Multiwave Locked System laser

INTRODUCTION

Extremity fractures are socially significant diseases due to treatment costs and disability [1]. Thanks to the development of orthopedic surgery as well as drug prophylaxis, the treatment of patients with limb fractures requires long-term rehabilitation. Several protocols are known for early rehabilitation with kinesitherapy, but postoperative complications can compromise the patient's recovery. One major issue with physiotherapy is that many physical treatments are unsuitable for patients with metal implants due to contraindications [2]. Recently, MLS laser [3] and deep oscillation treatment [4] have been developed as an alternative approach. These methods are widely used to reduce fibrosis, joint contractures, and swelling and to prevent potential wound complications [5].

The aim of the present study is to analyze and compare the effects of application of physical therapy modalities in patients with orthopedic implants of upper and lower extremity.

MATERIALS AND METHODS

This prospective, randomized, parallel study was conducted with permission from the Research Ethics Committee at Varna Medical University.

To guarantee the conclusions drawn from the results, a preventive examination was carried out for the presence of a therapeutic emission of the laser device before and after conducting the experiment.
The contingent of the study were 240 patients aged 20 to 80 years with orthopedic implants who meet the inclusion criteria.
All enrolled patients were randomly assigned to treatment groups using an online generated randomization sequence.
Methods that were used for tracking the signs are: questionnaires - Shoulder Pain and Disability Index (SPADI) [6], The Mayo Elbow Performance Score (MEPS) [7], Knee Injury and Osteoarthritis Outcome Score (KOOS) [8], The Foot and Ankle Disability Index (FADI) [9], centimeter and goniometry evaluation, pain according to Visual Analogue Scale (VAS) [10], at five different periods for patients of the eight subgroups.
Statistical methods were used to process the data and analyze the results.
Patients were divided initially into groups according to the anatomical area where the implant was placed and the joint contracture - shoulder (group A), elbow (group B), knee (group C), and ankle (group D). Patients from each group were randomly assigned to one of two treatment subgroups - kinesitherapy and MLS laser treatment (subgroups A1, B1, C1 and D1) or kinesitherapy and deep oscillation treatment (subgroups A2, B2, C2 and D2).
All patients were assessed at five different time points: T0 - at baseline before starting treatment, T1 - after completing the therapeutic course of early rehabilitation, T2 - after completing the therapeutic course of rehabilitation up to one month, T3 - after completing the the therapeutic course of rehabilitation up to three months and T4 - at the sixth month after the start of treatment.

RESULTS

Pairwise comparison showed that there was a statistically significant difference of time effect ($p<0.000$) between all pairs in subgroup A1 and A2 - Flexion, Abduction, Internal rotation (F0) and SPADI; subgroup B1 - Spontaneous VAS pain, MEPS; subgroup B2 - Spontaneous VAS pain; subgroups C1 and C2 - KOOS Symptoms; subgroups D1 and D2 – Dorsiflexion.
Pairwise comparison showed that there was a statistically significant difference of time effect ($p<0.000$) between all pairs and no statistically significant difference between T0-T1 in subgroup C1 Flexion ($p<1.000$), subgroup D1 ($p<0.168$) and D2 ($p<0.179$) - Ankle circumference difference; between T0-T1 ($p<1,000$) and T3-T4 ($p<1,132$) in subgroup C2 Changes in the ROM – extension.
The pairwise comparison showed that there was a statistically significant difference in the effect of time ($p<0.000$) between all pairs and no statistically significant difference between T1-T2 in subgroup A1 ($p<1.000$) and A2 ($p<1.000$) - External rotation (F0); subgroup C1 - Knee circumference difference ($p<0.854$), Changes in the ROM - extension ($p<1.000$), Flexion ($p<1.000$), subgroup C2 - Knee circumference difference ($p<0.509$), Spontaneous VAS pain ($p<1.000$), KOOS Pain ($p<0.696$), KOOS ADL ($p<1,000$), KOOS QOL ($p<1,000$. The pairwise comparison showed that there was a statistically significant difference in the effect of time ($p<0.000$) between all pairs and no statistically significant difference between T2-T3 in subgroup A1 ($p<1.000$) and A2 ($p<1.000$) - Spontaneous VAS pain ($p<1,000$); subgroup C1 - Spontaneous VAS pain ($p<1,000$), KOOS Pain, ($p<0,809$), KOOS ADL ($p<1,000$), KOOS QOL ($p<1,000$).
Pairwise comparison showed that there was a statistically significant difference of time effect ($p<0.000$) between all pairs and no statistically significant difference between T3-T4 in subgroup B1 - Flexion ($p<1,000$), Extension ($p<0.101$), Pronation ($p<1.000$), Supination ($p<0.498$); subgroup B2 - Flexion ($p<1,000$), Extension (°) ($p<0,101$), Pronation ($p<1,000$), Supination ($p<0,498$), MEPS ($p<0,344$); subgroup D1 - Plantar Flexion ($p<0.563$), Spontaneous VAS pain ($p<0.089$), FADY ($p<0.117$); subgroup D2 - Plantar Flexion ($p<0.789$), Spontaneous VAS pain ($p<0.098$), FADY ($p<0.158$).

After the injury of the elbow joint before treatment (T0) the measured indicators are not reliable. After the operation, the elbow joint is in a relaxed position up to 90°. A reduction in geometry reports an improvement and reduction in stiffness.
No statistically significant difference was found in the between-group analysis of the treatment effects of the two therapeutic methods in all measures (Table 1).

Table 1. Group Statistics

			T0		T1		T2		T3		T4
Sig. (2-tailed)	A1-A2	Flexion (°)	0,351	0,351	0,407	0,407	0,584	0,584	0,22	0,22	0,699
		Abduction (°)	0,4	0,4	0,55	0,55	0,509	0,509	0,663	0,663	0,54
		External Rotation (F0) (°)	0,731	0,731	0,694	0,694	0,878	0,878	0,959	0,959	0,748
		Internal Rotation (F0) (°)	0,493	0,493	0,568	0,568	0,581	0,581	0,545	0,545	0,787
		VAS mm	0,839	0,839	0,611	0,611	0,813	0,813	0,777	0,777	0,786
		SPADI (%)	0,764	0,764	0,805	0,805	0,842	0,842	0,691	0,691	0,478
	B1-B2	Flexion (°)			0,461	0,461	1	1	0,61	0,61	0,915
		Extension (°)			0	0	1	1	0,717	0,717	0,799
		Pronation (°)			0,728	0,728	0,902	0,902	0,621	0,621	0,621
		Supination (°)			0,012	0,013	0,013	0,013	0,519	0,519	0,317
		VAS mm			0,966	0,966	0,651	0,651	0,571	0,571	1
		MEPS			1	1	0,259	0,259	0,138	0,138	0,184
	C1-C2	circumference difference mm	0,405	0,405	0,147	0,147	0,083	0,083	0,321	0,322	0,371
		Flexion (°)	-0,033	-0,033	-0,333	-0,333	1	1	0,333	0,333	0,5
		Extension (°)	-0,733	-0,733	-0,333	-0,333	0,5	0,5	0,4	0,4	0,367
		VAS mm	0,653	0,653	0,599	0,599	0,756	0,756	0,782	0,782	0,779
		KOOS Pain	0,965	0,965	0,83	0,83	0,977	0,977	0,988	0,988	0,691
		KOOS Symptomes	0,98	0,98	1	1	1	1	1	1	1
		KOOS ADL	0,931	0,931	0,823	0,823	0,967	0,967	0,917	0,917	0,816
		KOOS QOL	0,627	0,627	0,603	0,603	0,553	0,553	0,99	0,99	0,965
	D1-D2	circumference difference mm	0,924	0,924	0,697	0,697	0,678	0,678	0,294	0,294	0,387
		Dorsiflexion (°)	0,595	0,595	0,656	0,656	0,863	0,863	0,651	0,651	0,638
		Plantar Flexion (°)	0,401	0,401	0,672	0,672	1	1	1	1	1
		VAS mm	0,674	0,674	0,819	0,819	0,889	0,889	1	1	1
		FADY (%)	0,123	0,123	0,093	0,093	0,881	0,881	0,82	0,82	0,724

DISCUSSION

When it comes to public health, Deep Oscillation and MLS laser therapy can significantly impact treating symptoms in patients with orthopedic implants in their upper and lower limbs. This can lead to a shorter period of forced rest and help prevent complications from operative treatment. It is recommended that longer-term results be followed to establish the statistically significant superiority of one of the complex therapies we applied.

CONCLUSIONS

Patients in the eight treatment subgroups have both short-term and long-term improvement of functional status and level of pain questionnaires, centimeters at the four moments for each research joint, goniometry of each research joint and spontaneous pain in the VAS. The comparative analysis between the two therapeutic programs did not report a statistically significant difference in one of the methods.

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RESEARCH OF BASIC PHYSIOLOGICAL INDICATORS OF THE RESPIRATORY SYSTEM AND ANTHROPOMETRIC INDICES IN MARINE PROFESSIONALS

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ABSTRACT
Respiratory system functionality, closely tied to physical fitness, is critical for sustaining aerobic metabolism and ensuring the efficiency and safety of maritime activities. Recognizing this, a collaborative effort by MU-Varna, the Bulgarian Red Cross, and the Naval Academy aims to develop a model for functional assessment of respiratory and musculoskeletal systems in maritime professionals. This study focuses on spirometric analysis to evaluate lung function and its correlation with anthropometric indices among maritime trainees. The findings are expected to inform tailored training programs, enhancing personal safety and operational efficiency in maritime professions. This research underscores the importance of respiratory fitness as a determinant of seafarers' health and performance, offering valuable insights for mitigating risks in the marine industry.

Keywords: Maritime safety; Respiratory function; Spirometric analysis; Physical fitness; Occupational health

INTRODUCTION
The maritime profession is accompanied by a number of hazards that are risky to the health and life of maritime professionals (1, 2). Water traumatism is a problem that cannot be definitively solved and requires strict regulation of any maritime activity. Marine professionals play a key role in ensuring safety at work in the aquatic environment (3, 8). According to data of D. Stavrev (2020), the human factor is the cause of about 80% of all incidents at sea.
Therefore, one of the important conditions for reducing accidents when working in a marine environment is that all persons professionally engaged in maritime activities, as well as trainees for maritime professionals, are fully healthy – in good physical shape and in good mental health. High physical exertion and neuro-mental tension, chronic fatigue, negative environmental factors, a number of harmful habits, such as smoking, alcohol use, psychotropic agents, obesity and others, hide potential risks of accidents occurring when working in a marine environment (2, 3). It is a fact that in an aquatic environment changes occur in the course of a number of physiological processes - biomechanical problems associated with movements, changes in the mechanisms of thermoregulation and energy consumption, in the activity of the cardiovascular system, nervous system, breathing (2, 3). These changes are particularly pronounced in extreme situations, where maritime professionals expend significantly more muscular strength and energy. The aqueous environment exerts strong mechanical pressure on the chest, increasing the resistance to breathing, which counteracts the expansion and ventilation of the lungs. This negatively affects the indicators of gas exchange, on which the normal functioning of other organs and systems depends. Therefore, although not directly, for assessing the physical fitness of marine professionals, the indicators of pulmonary ventilation, characterizing respiratory function and ensuring sustainable aerobic metabolism for the whole organism, are particularly important. In this respect, from the above-mentioned literature data (1, 2, 3), it is necessary to consider that better functionalities of the respiratory system, associated with better physical training and training of seafarers, are a leading factor in increasing the efficiency of their activity and at the same time improving their personal safety.
In view of this, a team from MU-Varna, the Bulgarian Red Cross and the Naval Academy started working on the development of a model for functional assessment of the respiratory system and musculoskeletal system in marine professionals to improve their personal safety and increase the efficiency of their maritime activities. The aim of this study, as part of the developed model, is to

measure and analyze new spirometric data characterizing lung function and related anthropometric indices in persons studying the maritime profession.

MATERIALS AND METHODS

A total of 54 persons whose occupation is related to the marine environment took part in the survey (Table 1). Participants are divided into two comparable groups: 28 (51.9%) water rescue trainees in the BRC system and 26 (48.1%) cadets from the Naval Academy.

Table 1. Main groups and distribution of participants by number, gender and age.

Total number of participants (n=54)	**Water Rescue Trainees - Bulgarian Red Cross**	**Cadets from the Naval Academy**
Men n (%)	24 (44.4%)	17 (31.5%)
Women n (%)	4 (7.4%)	9 (16.7%)
Average age (year) ± SD	21.25±7.65	20.19±1.02
Total number in group n (%)	28 (51.9%)	26 (48.1%)

Distribution by gender (Table. 1) shows that in both groups the number of men is higher compared to women. Of the group of water rescuers, 24 (44.4%) were men and 4 (7.4%) were women. Of the Naval Academy cadets, 17 (31.5%) were men and 9 (16.7%) were women. The average age of all participants was 20.74±5.53 years. In the water rescue group, however, the age range varies widely, from 17 to 47 years old, and Naval Academy cadets range in age from 19 to 22 years old. All participants in the study were non-smokers.

The examination of the indicators of pulmonary ventilation was carried out using a spirometry method (4, 5, 7). For this purpose, a modern spirometer of the MIR 010 series under the trade name Spirolab was used, which also has the function of a pulse oximeter. The apparatus is capable of measuring and recording more than 30 airflow indicators and the flow/volume curve is displayed on the display in real time. For the correct interpretation of the results, the apparatus compares the measured values with the so-called predictive values, which are calculated on the basis of pre-entered anthropometric data for each participant. The assessment of the spirometric test is always carried out according to the best result. In order for the test to be carried out properly, participants must be completely healthy, rested and fully cooperate with the test. During the study, each of them used an individual disposable nozzle. Of the spirometric parameters recorded in this study, three were analysed – forced expiratory volume per 1 s (FEV_1), forced vital capacity (FVC) and their percentage ratio FEV_1/FVC (Tiffno index).All subjects are enrolled in the study voluntarily, for which they have previously stated their written consent. All participants were informed for the nature, risks and expected benefits of the study.

RESULTS

The results of the study are presented in Tables 2 to 6.

In the table. 2 are presented the anthropometric indicators - average height (cm) and weight (kg), as well as the range of their fluctuations in men and women from the two groups studied.

Table 3 shows the average values and their standard deviation of spirometric indicators - FVC, FEV_1, FEV_1/FVC% (Tifno index) in water rescue students at the Bulgarian Red Cross and cadets from the Naval Academy.

Correlation analysis data is presented in Tables 4, 5 and 6. From the ones presented in the table. 4 results show that there is a statistically significant, although weak, correlation between FVC and growth in the group of water rescue students ($r=0.536$, $p=0.03$), but for Naval Academy cadets the correlation is not statistically reliable ($p>0.05$).

Table 2. Anthropometric indicators - average height and weight in men and women of the group of water rescuers and the roughness of naval cadets.

Indicator	**Water Rescue Trainees - Bulgarian Red Cross**		**Cadets from the Naval Academy**	
	Men	**Women**	**Men**	**Women**

	Average value	SD (±)	Average value	SD (±)	Average value	SD (±)	Average value	SD (±)
Height (cm)	180.08	6.87	167.50	13.67	179.88	5.97	167.00	5.81
Weight (kg)	78.08	10.12	61.00	13.04	77.41	9.74	56.89	5.80

Table 3. Spirometric indices – FVC, FEV_1 and FEV_1/FVC(%) in the water rescue students of the Bulgarian Red Cross and the cadets of the Naval Academy.

Study groups	FVC (L)			FEV_1 (L)			FEV_1/FVC(%) the Tiffno Index		
	Average	It's Min.	It's Max.	Average	It's Min.	It's Max.	Average	It's Min.	It's Max.
Water Rescue Trainees	4.89	2.94	7.84	4.27	2.82	6.15	88.71	71.30	100.0
Cadets from the Naval Academy	4.34	3.15	5.77	4.08	2.73	5.43	94.55	65.80	100.0

Table 4. Correlation relationship between FVC with anthropometric stature and weight in water rescuers and naval cadets.

Group	Correlation factor / Statistical significance	FVC	Growth	Weight
Water Rescue Trainees - Bulgarian Red Cross (n=28)	Pearson Correlation (r)		0.536	0.476
	p-value		0.03	0.01
Cadets from the Naval Academy (n=26)	Pearson Correlation (r)	**FVC**	0.321	0.629
	p-value		0.110	0.001

Moderate correlation between FVC and weight (Table. 4) was found in water rescuers group (r=0.476, p=0.01), and in naval cadets the correlation was significant (r=0.629, p<0.001).

Statistically significant correlation (r=0.683, p<0.001) is also reported between FEV_1 and the growth of water rescuers (table. 5), but for naval cadets the correlation has no statistical reliability **(**r=0.271, p=0.180).

Table 5. Correlation between FEV_1 and anthropometric indicators of height and weight in water rescuers from the Bulgarian Red Cross and naval cadets.

Group	Correlation factor / Statistical significance	FEV_1	Growth	Weight
Water Rescue Trainees - Bulgarian Red Cross (n=28)	Pearson Correlation (r)		0.683	0.593
	p-value		0.001	0.001
Cadets from the Naval Academy (n=26)	Pearson Correlation (r)	**FEV_1**	0.271	0.540
	p-value		0.180	0.004

For water rescuers, the correlation between FEV_1 and weight was also statistically significant (r=0.593, p<0.001) (Table 1,5) and is significant **(**r=0.540, p=0.004) for Naval Academy cadets.

The data from the correlation analysis show no significant correlations between FEV_1/FVC (%) (Tifnoindex) and the studied anthropometric indices - height and weight in both water rescue students and naval cadets (Table 6).

Table 6. Correlation relationship between FEV_1/FVC(%) and anthropometric growth and weight in water rescuers and naval cadets.

Group	Correlation factor / Statistical significance	FEV_1/FVC (%)	Growth	Weight
Water Rescue Trainees - Bulgarian Red Cross (n=28)	Pearson Correlation (r)		0.057	0.015
	p-value		0.773	0.940
Naval Academy Cadets (n=26)	Pearson Correlation (r)	**FEV_1/FVC (%)**	-0.109	-0.179
	p-value		0.597	0.381

DISCUSSION

From the ones presented in the table. 2 data show that anthropometric indicators - height and weight have higher values in the group of water rescuers - men and women compared to men and women from the group of cadets of the Naval Academy. It is also noteworthy that the variations in height and weight of the students in water rescue are greater compared to the cadets from the Naval Academy. This can be associated with the observed differences in age range between the participants from the two groups - for the water rescue group the age range is wider and ranges from 17 to 47 years, and for the cadets from the Naval Academy - from 19 to 22 years. To the extent that it is known from the literature that the spirometric indicators characterizing respiratory function depend on anthropometric data, age and sex of the subjects studied (6, 7), it is possible to assume that the measured higher values of anthropometric indices in the group of water rescuers are a prerequisite for better respiratory system functionalities - better pulmonary ventilation and more efficient gas exchange. From the ones presented in the table. 3 spirometric data shows that according to anthropometric indicators, FVC has a higher average value in the group of water rescuers compared to naval cadets. The measured average value of the cadets from the Naval Academy is 88.7% of that of the water rescuers. When looking for a correlation between FVC and anthropometric indicators - height and weight in participants from both groups (table. 4) there is a statistically significant, although weak, correlation between FVC and growth only in water rescue students ($r=0.536$, $p=0.03$). The correlation between FVC and weight was moderate in the water rescue group ($r=0.476$, $p=0.01$), and in naval cadets the correlation was significant ($r=0.629$, $p<0.001$).Corresponding to anthropometric data, the measured mean value of FEV_1 (Table. 3) is higher and shows greater variations also in the group of water rescuers compared to naval cadets. For Naval cadets, the average value of FEV_1 is 95.6% of that of water rescuers. Correlation between FEV_1 and anthropometric indices – height and weight (Table 5), is statistically significant ($p<0.001$) for water rescuers and is significant between FEV_1 and weight ($p=0.004$) for Naval Academy cadets.

Percentage ratio FEV_1/FVC (Tiffenau index) (Table. 3) is within the normal range (5.6), reaching very high values, up to a maximum of 100% for participants in both groups. However, when comparing between groups (table. 3) the data show that the average value of this indicator is higher for naval cadets compared to water rescuers, and no significant correlations between this indicator and the anthropometric indices - height and weight of the participants from the two groups are reported from the correlation analysis made. In our opinion, the high results of the Tiffno index in both groups tested show on the one hand the very good physical development of all subjects, which is a prerequisite for high efficiency of pulmonary ventilation and respiratory function in general. On the other hand, the higher values of the Tiffno index in naval cadets tend to be seen as a result of the better training and systematic physical training of cadets during their training at the Naval Academy. This results in a better development of the respiratory muscles carrying out the respiratory movements and may explain the differences found in this indicator between the cadets from Naval Academy and the water rescuers from Bulgarian Red Cross.

CONCLUSIONS

1. Based on the results of the correlation analysis, we can confirm the existence of a causal relationship between the measured spirometric indices – FVC and FEV_1 and the anthropometric data (height and weight) in the participants of both groups.
2. The results presented showed that all participants had normal spirometric tests.
3. According to the obtained anthropometric data, the values of FVC and FEV_1 are higher for water rescue trainees compared to Naval Academy cadets.
4. The higher average values of spirometric indices – FVC and FEV_1 in the water rescue group can be taken as an expression of higher functional capacity of the respiratory system – greater pulmonary ventilation and more efficient gas exchange.
5. The reported higher values of the Tiffno index, as a percentage ratio between FEV_1 and FVC, in naval cadets are, in our opinion, a result of the better training and systematic physical training

of cadets during their training at the Naval Academy. This is a prerequisite for better development of the respiratory musculature performing the respiratory movements and explains the higher results achieved in the spirometric test.

6. As far as it is assumed that respiratory function, albeit indirectly, is important for the physical fitness of seafarers (1, 2, 3), the generally high results of spirometric testing in all study participants are a prerequisite for improving their personal safety and for increasing the efficiency of their maritime activities.

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STEWARDSHIP OF ANTIBIOTICS IN CRITICALLY ILL PATIENTS

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ABSTRACT
Introduction: poses a critical challenge in Intensive Care Units (ICUs), exacerbated by the overuse of broad-spectrum antibiotics in managing sepsis and other infections in critically ill patients. The aims of this study are to explore the principles and practices of antibiotic stewardship programs (ASPs) in ICU settings to mitigate the emergence of multidrug-resistant (MDR) pathogens. **Material and methodology:** We made research in PubMed, Cochrane Library and Medline with words: Antimicrobial resistance (AMR) AND Intensive Care Units (ICUs). A systematic approach to implementing early and appropriate antibiotic therapy, followed by de-escalation based on culture and sensitivity results, is emphasized. **Results:** In PubMed with words: Antimicrobial resistance (AMR), during last 10 years, are published 8587 papers. With words: Antimicrobial resistance (AMR) AND Intensive Care Units (ICUs) we found only 32 papers. **Conclusions:** The study highlights the benefits of ASPs, including reduced MDR pathogen risk, minimized drug toxicity, and preservation of antibiotic efficacy. Challenges in resource-limited settings, such as low- and middle-income countries (LMICs), are discussed, underscoring the need for global collaboration in combating AMR. The findings advocate for interdisciplinary ASP frameworks that integrate evidence-based practices to improve patient outcomes and sustain healthcare systems worldwide. By addressing AMR through robust stewardship efforts, this study underscores the ethical and clinical imperatives to preserve antibiotics for future generations.

Kye words: stewardship, antibiotic, Intensive Care Units, Antimicrobial resistance

Sepsis is a major issue in the Intensive Care Units (ICUs) and carries a high mortality risk. Its incidence and prevalence have increased globally over the last years and still continues to be one of the leading causes of patient admissions to ICUs (1–3). The primary focus for intensive care specialist is to identify common sepsis sites, likely pathogen(s) associated with specific organ infections, and to recommend optimal antimicrobial strategies. In ICUs, infections such as pneumonia, sepsis, intravascular line infections, and intra-abdominal infections are prevalent, and prompt administration of antibiotics can be life-saving (4–6). So both effective and timely antimicrobial therapy is crucial for improving patient outcomes in critically ill patients (7). But in realty the situation is rather complex. These patients are at high risk of infections due to weakened immune systems, invasive procedures, and prolonged hospital stays. The need for antibiotics in this population is undeniable; however, inappropriate use of antibiotics in these patients poses risks, including drug toxicity, disruption of the gut microbiome, and which is the most important they can lead to the emergence of multidrug-resistant (MDR) pathogens (1,3,5,6).

Selecting the right antibiotic and administering it at the right time are crucial. The concept of "early and appropriate" antibiotic therapy is critical in managing infections in sepsis and critically ill patients. Several studies have shown that delayed or inadequate antibiotic therapy is associated with increased mortality, especially in patients with sepsis and septic shock (8,9). While immediate, empiric broad-spectrum antibiotic therapy is life-saving for patients with

severe sepsis or septic shock, in now days is a growing concern about the overuse of these antibiotics, which can contribute to antimicrobial resistance. Use of broad-spectrum antibiotics in the ICU is often necessary due to the severity of infections and the need for rapid intervention, but on the other hands antibiotic resistance is a growing global health threat, significantly affecting patients admitted to ICUs. Thus, a balanced approach involving rapid initiation of broad-spectrum antibiotics, followed by de-escalation and guided antimicrobial stewardship, is advocated. Broad-Spectrum Antibiotics like carbapenems or piperacillin-tazobactam are commonly used to cover a wide range of Gram-positive, Gram-negative, and anaerobic bacteria, but their overuse contributes to the emergence of MDR pathogens. This is a significant challenge in ICUs, as infections with MDR pathogens are harder to treat and are associated with worse outcomes (6-8).

Another point is de-escalation and Antimicrobial Stewardship in ICU. De-escalation involves narrowing the spectrum of antibiotic therapy based on culture and sensitivity results. The benefits of de-escalations are reducing of the risk of MDR pathogens, minimizing drug toxicity, and helping preserve the efficacy of existing antibiotics.

Antimicrobial resistance (AMR) is an urgent global health crisis, recognised by the World Health Organization (WHO) as one of the top ten threats to humanity. AMR is estimated to have caused 1.3 million deaths worldwide in 2019, with low- and middle-income countries (LMICs) bearing the brunt of this burden. These regions face significant challenges, including insufficient surveillance systems and limited resources to address community-acquired infections, which exacerbate the problem (8).

For these reasons hospital antibiotic stewardship programs (ASPs) have emerged as a vital strategy in combating AMR by optimising the use of antibiotics to improve patient outcomes while curbing the development of resistance. ASPs are designed to promote the principle of administering “the right antibiotic to the right patient, at the right time, in the right dose, and through the right route.” By implementing evidence-based prescribing practices, they aim to minimise the misuse of antibiotics, which is a primary driver of AMR. This approach is particularly important in high-risk settings such as ICUs, where the use of parenteral and broad-spectrum antibiotics is prevalent. In these environments, ASPs play a crucial role in reducing the emergence of MDR pathogens by limiting unnecessary antibiotic exposure (1,3,5-8).

The Core Elements of Hospital Antibiotic Stewardship Programs, as outlined by organisations such as the CDC, provide a structured framework for effective implementation. These elements emphasise leadership commitment, accountability, access to drug expertise, actionable interventions, monitoring of antibiotic use, transparent reporting, and ongoing education. Hospitals that integrate these components into their practices have demonstrated improved prescribing patterns, reduced rates of healthcare-associated infections, and lower resistance rates. Furthermore, ASPs encourage interdisciplinary collaboration among clinicians, pharmacists, microbiologists, and infection prevention specialists, fostering a holistic approach to tackling AMR (7,9,10).

However, the global nature of AMR demands coordinated and equitable action. High-income countries have made significant strides in implementing ASPs, supported by robust healthcare systems and dedicated funding. Conversely, LMICs often lack the necessary infrastructure and resources to establish these programs effectively. Addressing this disparity is essential, as the disproportionate impact of AMR on vulnerable populations in LMICs threatens global progress. International efforts must focus on capacity building, funding, and the establishment of adaptable stewardship frameworks to bridge this gap. Beyond their clinical impact, ASPs represent a moral obligation. Antibiotics are a finite resource, and their overuse jeopardises their efficacy for future generations. Stewardship programs embody the ethical responsibility to use these life-saving treatments judiciously, ensuring their availability for those who need them most. By preserving the effectiveness of existing antibiotics, ASPs safeguard public health and reduce the economic burden associated with resistant infections (6,7).

In conclusion, hospital ASPs are indispensable in the fight against AMR. They optimise patient care, mitigate the spread of resistance, and promote a culture of evidence-based medicine. While challenges persist, particularly in resource-limited settings, the global implementation of stewardship programs is a critical step toward sustainable healthcare. By uniting healthcare systems worldwide in this effort, we can ensure the continued efficacy of antibiotics, protecting both current and future generations from the escalating threat of AMR.

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ECHOCARDIOGRAPHIC EVALUATION OF INFECTIVE ENDOCARDITIS - OUR EXPERIENCES

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ABSTRACT
Infective endocarditis (IE) is an infection of the lining of the heart ventricles and valves, caused by bacteria, fungi, or other infectious agents [1].The diagnosis and treatment of IE is challenging, therefore careful physical examination, detailed medical history and echocardiography are essential[8]. Our objectives are to describe the incidence, clinical characteristics, microbiological profile and in-hospital outcome of infective endocarditis, as well as to obtain early diagnosis and timely treatment of patients by introducing echocardiography for the very first time at the Clinic for Infectious Diseases and Febrile Conditions in Skopje [2]. A prospective study was conducted on 15 patients admitted with prolonged febrile illness to the Clinic, in a period of nine months. All patients were selected in accordance with the Duke criteria and underwent detailed history taking, clinical examination, blood culture and echocardiography [7]. Blood cultures were positive in 8 patients (61,5%). Staphylococci were the prevalent microorganisms (62,5%)[1][6]. IE should be considered in every patient with prolonged febrile illness. Echocardiography is crucial to be conducted in all patients suspected or confirmed IE [2].

Keywords: Infective endocarditis, blood culture, vegetation, TTE, imaging techniques

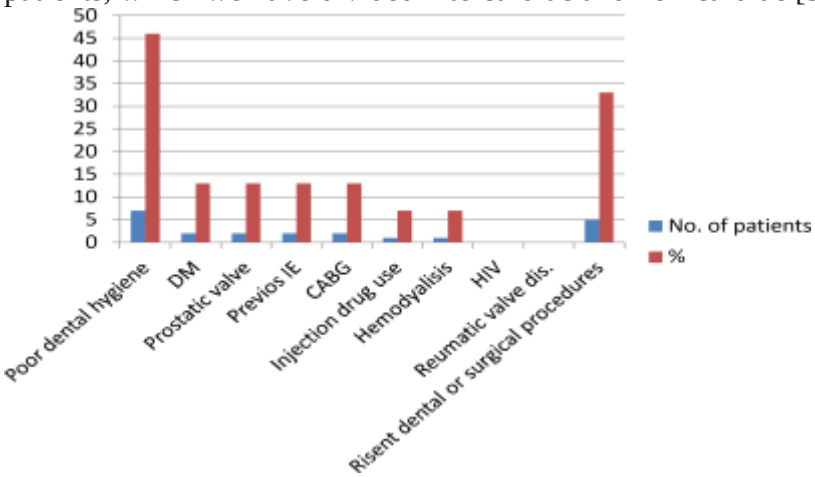
INTRODUCTION
Endocarditis is a life-threatening infection of the lining of the heart ventricles and valves, caused by bacteria, fungi, or other infectious agents [1]. Its clinical presentation is highly variable, depending on whether it presents acutely, sub acutely, or chronically. Without early identification and treatment, a myriad of intracardiac and far-reaching extracardiac complications may develop [9][10].

MATERIALS AND METHODS
A prospective study was conducted on 15 patients admitted with prolonged febrile illness to the Clinic for Infectious Diseases and Febrile Conditions in Skopje in a period of nine months. All patients were selected in accordance with the Duke criteria for the diagnosis of IE [7].

RESULTS
In-hospital events included the following: heart failure in 4 patients (30,7%), systemic embolization in 3 patients (23%), and renal failure in 3 patients (23%)[10]. The most common localization of the vegetation was on the mitral valve in 46,7%, with mild type of regurgitation in 53.3% of patients. Native valve endocarditis was diagnosed in 86.7% of the patients, whereas in the rest IE was diagnosed as a consequence of the presence of a prosthetic valve and indwelling cardiac device [9].

DISCUSSION
This study investigated the importance of echocardiographic evaluation of patients presenting with febrile condition or suspected for infective endocarditis [2].We improved our diagnostic capacities and patient management and care by introducing echocardiography for patients presenting with prolonged febrile illness, especially when cardiac involvement is suspected.

Different world studies confirmed the staphylococci group as the most prevalent microorganisms as well as left-sided endocarditis, as more prevalent [4][6].We have successfully integrated echocardiography into diagnostic protocol for prolonged febrile illness in our Clinic for both diagnosis and follow up. Although the study was conducted in a small cohort, our findings are in line with the Duke criteria, who have demonstrated an overall sensitivity of 80% for diagnosis of IE**,** all of whom additionally underwent detailed history taking, clinical examination, laboratory and microbiological tests, blood culture, echocardiography and CT[7][8]. The largest number of patients or 73.3%, had an acute onset with high degree of fever. In 53% of patients fatigue was registered as the most pronounced sub-acute symptom on admission. Laboratory exams and biomarkers typically yield non-specific results. Several risk factors were present in the studied patients, which we have divided into cardiac and non-cardiac [9] (Graph 1).



Graph 1. Most common risk factors

In the study, we did confirm that most common pathogens were *Staphylococci*, MSSA and MRSA, which were detected in 50% of patients**,** and then *St. mutans, Salmonela enteritidis gr. D* and *Ent. galinarum* were isolated as causative agents in 7%, and *E. coli ESBL* positive and negative in one of examined patients [1][4][7]. In all patients included in the study, the definite diagnosis of IE was established by the presence of 2 major criteria, or 1 major criterion and at least 3 minor criteria [7]. Imaging technique that we utilize for diagnosis of IE was TTE as key imaging technique, performed in all of the examined patients [2]. CT scan, MRI were conducted in order to access local IE complication (abscesses, pseudoaneurysms, and fistulae) as well as IE related distant lessons (systemic complications, including septic emboli, detection of neurological complications), and to identify the original source of bacteraemia [8][3][10]. Only 4 patients remained without complications, the remaining 73% of patients developed more than one complication simultaneously. The most common complications during the hospital stay included heart rhythm disturbances and heart failure in 27%, renal failure and systematic embolization in 20% of patients [3][10]. Two of the patients developed splenic abscess and spondylodiscitis, and in 20% of them, sepsis occurred as a complication of the diagnosed IE. Our findings in this cohort study are correlated with different studies an indicates a more frequent localization of vegetations on the mitral valve and need for surgical intervention indicated in 46,7% of the patients with mild type of regurgitation in 53,3%[5][9] (Table 1)

Table 1. Results obtained from the performed TTE

Description	***N = 15***	***%***
Prosthetic valve endocraditis	2/15	13,3%
Native valve endocarditis	13/15	86,7%
Localization of vegetation		
Aortic valve	6/15	40%
Mitral valve	7/15	46,6%
Tricuspid valve	1/15	6,7%
Aortic and mitral valve	1/15	6,7%

Type of regurgitation		
Milde	8/15	53,3%
Severe	7/15	46,7%
Surgery required	7/15	46,7%
Underwent surgery patients	5/7	71,4%
Refused operative treatment	1/7	14,3%
Deceased patient	1/7	14,3%
Conservatively treatment	8/15	53,3%

In 7 patients, surgical treatment was indicated, 5 of them were transferred to the cardiac surgery department, and after the surgery, they were discharged from the hospital in a clinically stable condition and one patient refused surgical treatment [5][9]. In the remaining 53.3%, conservative treatment with appropriate antimicrobial therapy was continued [5]. The percentage of surviving patients is 93,3% and one patient deceased during hospital treatment developing heart failure and septic shock, resulting in a low in-hospital mortality rate of 6,7% [6].

CONCLUSION

Infective endocarditis, should be considered in every patient with prolonged febrile illness, since it encompasses increased in-hospital events with a high mortality rate. Echocardiography is crucial in all patients with suspected or confirmed IE. Careful evaluation, including the introduction of echocardiography as an imaging technique at our Clinic assisted the process of timely diagnosis of patients with prolonged febrile condition and guide management, limiting mortality and morbidity. A multidisciplinary team is essential for a successful delivery of integrated care. The introduction of echocardiography also contributed to an earlier and more accurate diagnosis of the primary disease and its complications, as well as uniform antibiotic treatment and optimized timing for surgical intervention.

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UNICOMPARTMENTAL KNEE ARTHROPLASTY - CURRENT CONCEPTS AND RESULTS

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ABSTRACT
Unicompartment knee replacement is less invasive procedure, indicated por partial knee arthritis. Most common indications include medial cartilage wear and aseptic necrosis of the medial femoral condyle. **Diagnosis:** Imaging diagnostics and clinical examination, including X-Ray and MRI imaging are performed in such patients. Clinical tests to confirm disease symptoms of partial knee involvement should be done in all patients. **Materials and Methods**: We present 151 cases in 5 years follow up. 149 of them on the medial side of the knee, 2 - on lateral. Ages varies between 35 and 80. Gender distribution 88 F and 73 M. Midvastus approach was performed in all 149 cases. In 2 cases was used lateral parapatellar approach. 109 of patients suffer from medial arthrosis and 41 - avascular necrosis. Implants are mobile bearing 9 and fixed bearing 142. For the results evaluation was used Oxford knee score(OKS) and knee society score (KSS)- performed before surgery and 6 months after UKA. **Results**: OKS show average 21,5 points before surgery increasing to 45 after unicondylar knee replacement. KSS shows 60-70 points before and 90-100 after surgery. **Complications:** Two male patients complained about severe pain in the knee. One of them was mobile bearing, one fixed bearing. Both of them was revised to total knee at 9 month after first surgery. **Conclusion:** Unicompartment knee replacement surgery improve knee function and pain without sacrificing the whole knee, preserving its own proprioception and ligament stability.

Key words: unicondylar knee replacement, indications, surgical technique

INTRODUCTION
Unicondylar, or partial knee replacement is an alternative joint replacement for patients whose knee arthritis involves one compartment of knee joint. In a large percentage of cases, this involves damage to the medial compartment of the joint and varus deformity. Normally, arthritic process of the knee starts with medial compartment and with time altered biomechanics and local pathological processes lead to progression of the disease to other parts of the knee joint [1]. Unicondylar arthroplasty makes it possible to treat only the affected part of the joint, preserving primarily the intra-articular ligamentous structures, biomechanics and proprioception of the knee. Minimally invasive techniques and modern instrumentation allow the surgical intervention to be performed predictably and the results to be superior to those of total knee arthroplasty [2].
Problem with the survivorship of unicondylar knee implants is from key importance, especially in middle age and active patients group. Nevertheless there are some studies, showing early failure due to aseptic loosening of unicondylar knees, most authors show excellent mid term and long term results with this surgery [3]. We have to mention very important issue regarding longevity of the implant – with unicondylar knee most of the patients are able to achieve more active lifestyle, including contact sports, facts affecting implant survival rate.

INDICATIONS AND CONTRAINDICATIOS
There has been an evolution in the indications for this surgical intervention in recent decades towards expanding the group of patients suitable for unilateral knee replacement. Oxford group extended the old indication of Kozinn&Scott regarding the range of motion, degree of deformity, affection of patellofemoral joint and age limitations. Indications for unicondylar knee replacement on imaging methods are shown on figure 1.

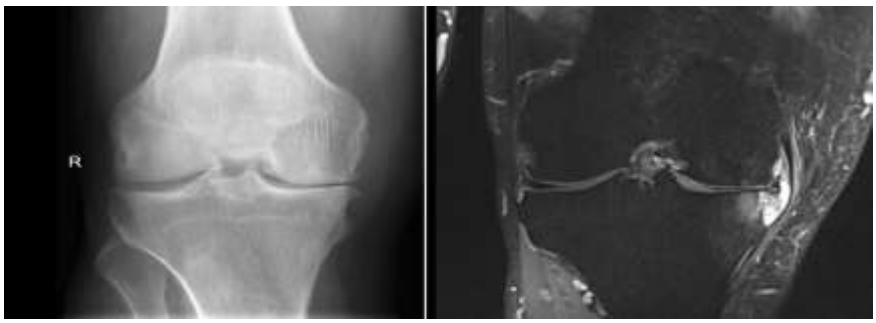

Fig. 1. Indications for unicondylar knee arthroplasty – medial arthritis presented on X-ray (left) and MRI imaging (right)

Imaging methods can provide sufficient information about the involvement of the knee compartments by the arthritic process, but clinical examination and patient history are of primary importance in patients who undergo unicondylar arthroplasty. Clinical assessment of patellofemoral pain is important and, if present, total knee arthroplasty should be discussed as treatment method.

SURGICAL TECHNIQUE FOR UNICONDYLAR KNEE ARTHROPLASTY

Unicondylar knee arthroplasty is a true resurfacing procedure. It is a minimally invasive procedure with short operative time and limited tissue trauma, compared to total knee arthroplasty [4].

A standart incision between 8 and 10 cm placed medially or laterally from the center of patella. For medial disease we perform midvastus approach, for lateral disease – lateral parapatellar approach. In almost all cases without contraindications we use pneumatic tourniquet during surgical procedure to ensure better visibility and superior cementing technique.

The starting bone resection in unicondylar arthroplasty is proximal tibial resection. An extramedullary guide is used for this purpose. It is important to observe some important points: the osteotomy should be neutral with respect to the varus/valgus angle, the depth of resection should be minimal (about 2-4 mm) and an anterior-posterior slope (slope) of about 5 degrees or more should be performed depending on the natural slope of the patient's tibia. The vertical tibial resection should be placed as laterally as possible and should be medial to the insertion of the anterior cruciate ligament.

For distal femoral resection the measured resection technique is used. Proximal tibial cut is used as a reference for the level and degree of femoral resection. The sizing of the femoral and tibial components should be done so, that no medio-lateral impingement as well as conflict with the medial facet of the patella and the soft tissue structures around the knee should happen. Because the articulation of the femur and tibia is based on the round-on-flat principle, the size of the tibia can be independently chosen with no relation to the size of the femur.

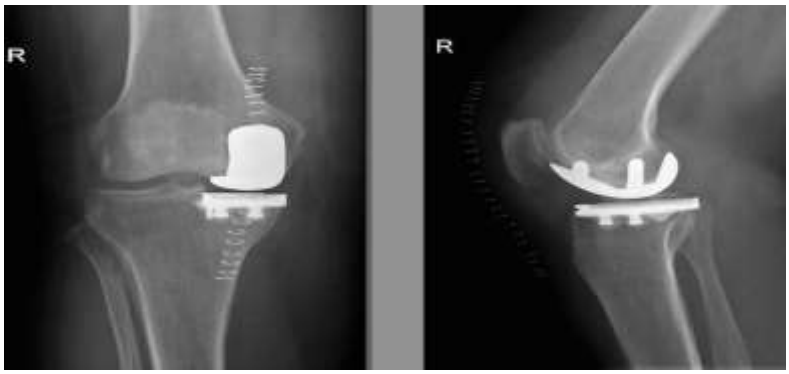

Fig. 2. Postoperative X-ray after unicondylar knee arthroplasty

MATERIALS AND METHODS

In our series we present 151 cases in 5 years follow up. 149 of them on the medial side of the knee, 2 - on lateral. Ages varies between 35 and 80. Gender distribution is 88 female and 73 male patients. Midvastus approach was performed in all 149 cases. In 2 cases was used lateral parapatellar approach for indication lateral unicompartmental arthroplasty. 109 of patients suffer from medial arthrosis and 41 - avascular necrosis. Implants are mobile bearing 9 and fixed bearing 142. For the results evaluation was used Oxford knee score (OKS) and Knee Society Score (KSS) performed before surgery and 6 months after UKA.

RESULTS

OKS show average 21,5 points before surgery increasing to 45 after unicondylar knee replacement. KSS shows 60-70 points before and 90-100 after surgery. **Complications:** Two male patients complained about severe pain in the knee. One of them was with mobile bearing unicondylar knee implant, one with fixed bearing implant. Both of them was revised to total knee at 9 month after first surgery.

POSTOPERATIVE MANAGEMENT AFTER UNICONDYLAR KNEE ARTHROPLASTY

Tissue trauma, duration of surgery, blood loss and pain syndrome after unicondylar arthroplasty are significantly less than after total arthroplasty. This enables patients who have undergone unicondylar knee replacement to begin weight bearing, passive and active motion and joint recovery in the early postoperative period. Full weight bearing is stimulated as early as possible in the day 1 after surgery. Preserved biomechanics and proprioception of the knee joint allows for full recovery of knee function postoperatively, including active exercise and sports [5].

CONCLUSION

Unicondylar arthroplasty is an excellent surgical option for the treatment of advanced stages of unicompartmental knee arthritis. Minimal surgical trauma, contemporary implants and a improved and reproducible surgical technique are reasons for an excellent postoperative outcome [7]. We believe that, although with minimal tissue and bone trauma, unicompartmental knee arthroplasty is a challenge not for the surgeon allone, but also for the rehabilitation team and for the patient as well [8]. A precisely performed surgical technique followed by adequately organized physiotherapy are important tools for an optimal surgical outcome [9]. Expanding indications in the last decades for unicondylar knee arthroplasty for young patients and patients with higher body mass index (BMI) can ensure better knee function in huge group of patients, undergoing knee arthroplasty surgery.

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IMPORTED FURUNCULAR MYIASIS IN THE REPUBLIC OF NORTH MACEDONIA - A THREE CASE STUDY

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ABSTRACT

Introduction: Furuncular myiasis is a parasite disease most commonly found in tropical regions. It is the most widespread clinical manifestation of myiasis that occurs when larvae of various species of flies penetrate the skin and cause cutaneous lesions. **Objective:** To present cases of imported furuncular myiasis acquired during a stay in Africa. As far as we know, these are the first cases reported in the Republic of North Macedonia. **Case report:** We present a group of three patients with myiasis acquired during a journey to Tanzania. The symptoms occurred three days after being bitten by hairy flies, and manifested with sporadic papular lesions accompanied by pain and itching. They contacted our hospital 6 days after being bitten. During examination of all three patients, on the bitten spot, several papulonodular, indurated, separated lesions, with centrally positioned eschar, localized on the upper, lower extremities and glutes were noted. On the sixth day of symptom appearance, the patients had sensations of subcutaneous movements in skin lesions, dropping out of the eschar and a beginning of larvae coming out from the nodular changes. All cutaneous changes were treated by a plastic surgeon by extirpation of larvae from them. Favorable clinical course followed, with a complete regression of the local findings. Larvae have been forwarded to the Microbiology and Parasitology Institute with myiasis confirmation. **Conclusion:** In patients with cutaneous papulonodular changes returning from tropical regions it is necessary to include myiasis in differential diagnostic consideration.

Key words: Africa, cutaneous lesions, larva, fly, imported disease.

INTRODUCTION

Human myiasis is a neglected disease caused by parasitic infestation of the skin, cavities, and other body parts by larvae (maggots) of a wide variety of dipteran flies [1]. Myiasis has a global sporadic distribution. However, it is more frequently reported from people visiting tropical areas in Africa [2,3,4,5]. Numerous types of myiasis could occur in humans. Depending on the affected body parts it can be classified as cutaneous, nasopharyngeal, intestinal, and urogenital myiasis [6]. Cutaneous myiasis is the most common form of human myiasis which occurs after the penetration of dipteran larvae into the skin [7]. Furuncular, migratory, and wound myiasis are the three clinical forms of cutaneous myiasis [8]. However, furuncular myiasis is the major type that usually manifested with papular and nodular skin lesions. Cordylobia anthropophaga in Africa and Dermatobia hominis in North America are the primary fly species identified for the distribution of furuncular myiasis [5].

We present a mini series of imported furuncular myiasis on three patients who were on a vacation in Tanzania.

CASE PRESENTATION

On the 29thof January 2024, three female patients (daughter, mother and mother-in-law), on the age of 12, 35 and 58 years came for a medical examination at the University Clinic of Infectious Diseases – Skopje (Figure1). Prior to that on the same day they were examined by a dermatologist and redirected to the clinic. Their symptoms occurred three days before their check

up with the appearance of sporadic papular lesions accompanied by pain and itching. Their epidemiology questionnaire consists of a journey to Tanzania- Zanzibar for a vacation which lasted for ten days from 16.01.2024 to 26.01.2024. Three days before symptom appearance, in their hotel room, they were bitten by big hairy flies on the same spots where the skin changes appeared. During examination, on all the three patients, on the bitten spot were noted multiple papulonodular, indurated, separated lesions,with a diameter of 1-2 cm, with centrally positioned eschar. The skin lesions total of five on patient 1 (the 12year old) where localized as two on the upper left arm (Picture 1.), two on the glutes and one on the lower right arm. On the day of the bites the patient presented with vomiting, diarrhea and temperature of 38°C lasting for one day. Patient 2 (the 35year old) presented with two papulonodular, indurated, separated lesions, with centrally positioned eschar, one located on the lower left leg and the other on the lower right leg. No general symptoms where noted. Patient 3 (the 58year old) presented with two lesions with the identical characteristics as the two other patients. One of them was located on the lower left leg and the other one on the lower right leg. No general symptoms where noted. On all patients' biochemical analysis and serological tests for Leishmania were made, and no abnormalities where noted. Therapy was not given and they were rescheduled for another check-up after 4 days.

On the 2nd of February, after six days of symptom appearance, the patients came for another check-up. They all had sensations of subcutaneous movements in the skin lesions, dropping out of the eschar and a beginning of larvae coming out from the nodular changes (Picture 2). Antibiotic treatment with amoxicillin/clavulanic acid for five days was ordinated to all patients alongside a tetanus prophylaxis for patients 2 and 3. All patients were forwarded to a plastic surgeon where all cutaneous changes were treated and extirpation of larvae (Picture 3.) was made on all of them. The larvae were examined by a microbiologist at the Institute of Microbiology -Skopje where myiasis was confirmed. Favorable clinical course followed for all patients, with a complete regression of the local findings, without any complications.

Figure 1. Timeline of events:

23.01.24 (Bites by flies) — **26.01.24 (First symptoms appearance)** — **29.01.24 (Paopular/nodular lesions, First hospital check up)** — **02.02.24 (Larval extirpation)**

Picture 1. Skin lesions six days after bite in patient no. 1

Picture 2. Skin lesions nine days after bite in patient no. 1
Picture 3. Larva from skin lesions

DISCUSION

Here, we present a mini-series of the first cases of imported furuncular myiasis in the Republic of North Macedonia. They are close relatives and had identical exposure to hairy flies while they acquired the disease during their stay in Tanzania- Zanzibar.

Sporadic cases with imported furuncular myasis are described in different countries in the world [5, 9], including the Republic of Serbia [10], as a neighboring country. Additionally, a lot of the cases were imported from different countries of Africa [2,3,4,5] including Tanzania [11].

Based on the characteristics of the skin lesions and the fact that the disease was acquired in Africa, our opinion is that myasis in our patients was caused by Cordylobia anthropophaga. In the present study all patients were deployed in urban/semi-urban setting of an endemic geographic area of East Africa. All patients in this study reported skin papulonodular lesions with a diameter of 1-2cm and symptoms of pruritus, pain and movement, similar to other report [3]. The average duration from the moment they were bitten to symptom onset was three days, and the penetration in the dermis was nine days matching with other similar cases where the shortest period of penetration to the dermis was 2 days and the longest was 7 days [12]. The only difference between our and other studies was the lesion distribution. In our study the most common sites involved were the gluteus and extremities compared with the other case studies where the most common sites were the abdomen and chest [2]. We suppose that the lesion distribution happened in this manner because in our patients those areas of the body were covered by clothes.

Our patients were treated by previous recommendations with antibiotics. On the other hand, tetanus prophylaxis was given to those patients previously inadequately vaccinated [12]. In the literature there is a discrepancy of the therapeutic approach in the post extirpation phase of the larvae, considering that some medical practitioners do not use tetanus prophylaxis [13] and other medical practitioners do not use antibiotic treatment [14].

Prevention for myiasis in travelers should include avoiding contact with flies and prevent bites by wearing long-sleeved clothing, using insecticides, drying clothes in bright sunlight and ironing them in order to destroy occult eggs laid in clothing [15].

CONCLUSION

The increased tourism to tropical countries enhances the risk of acquiring imported cutaneous myiasis, so it should be considered in differential diagnostics in patients with skin lesion that have recently travelled to tropical regions.

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RECURRENT CLOSTRIDIOIDES DIFFICILE COLITIS – CASE REPORT

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ABSTRACT
Recurrent Clostridium difficile infection (rCDI) is usually defined as the reappearance of enteral symptoms 2-8 weeks after resolution of the initial episode with an appropriate therapy. Recurrence occurs in approximately 25% of patients within the first 30 days of the treatment. A 62-year-old female was initially hospitalized at our hospital within the intensive care unit (ICU) due to acute encephalitis and bilateral bronchopneumonia. Her comorbidities were diabetes mellitus and hypertension. She was treated with a combination of parenteral beta-lactam antibiotics for 35 days, acyclovir, probiotics, gastric suppression, and other supportive therapies. On the 18th hospital day, she developed diarrhea with liquid mucous green stools, prompting stool cultures and a C.difficile toxins test, which were negative and her condition stabilized spontaneously. A week later, she experienced a recurrence of enteral symptoms when stool cultures showed C.difficile positivity, but negative toxin tests. A colonoscopy was performed, revealing pseudomembranous pancolitis. Treatment continued with intravenous metronidazole and oral vancomycin for two weeks, alongside probiotics. This led to gradual improvement and normalization of stool consistency. Control cultures were C.difficile negative, and she was discharged after 49 days. Three weeks later, she complained of persistent watery stools and malaise, thus she was readmitted. New stool cultures confirmed C.difficile positivity with negative toxin tests. A repeat colonoscopy showed significant regression of pseudomembranous colitis and biopsy results indicated chronic nonspecific colitis. She was treated with probiotics, intravenous metronidazole for a week, and oral vancomycin. On first follow-up visit after three weeks, she returned asymptomatic with normal stools, and was advised to continue oral vancomycin, rifaximin, and probiotics. A second follow-up visit two weeks later confirmed normal stool characteristics. Prolonged use of antibiotics, extended hospital stays, advanced age, severe preexisting illness are significant risk factors for recurrent CDI. Prolonged oral vancomycin therapy has shown high efficacy in treatment of this serious condition.

Keywords: C.difficile, antibiotics, colitis, recurrence.

INTRODUCTION
Clostridioides difficile infection (CDI) is of great significance in hospitals worldwide and represents the most common cause of infectious diarrhea among hospitalized patients. It is a significant contributor to high morbidity and mortality, particularly among older adults. CDI is the leading cause of antibiotic-associated diarrhea [1]. Recurrent CDI (rCDI) is defined as the reappearance of symptoms 2–8 weeks after completing treatment, following symptom resolution with appropriate therapy. Approximately 25% of cases occur within the first 30 days aftertreatment cessation, less commonly, up to 2 months post-treatment. rCDI may be due to a relapse of the initial strain or reinfection with a new strain [2]. Risk factors include antibiotic use, advanced age, gastric acid suppression, hypervirulent strains, severe underlying illness and/or renal impairment, prior CDI history, severity of the previous CDI episode, prolonged hospital stay, and lack of adaptive immune responses to bacterial toxins A and B [3]. Diagnosis of CDI is based on history, physical examination, presence of risk factors, and fecal laboratory tests (EIA for *C. difficile* GDH antigen, EIA for toxins A and B, cell culture cytotoxicity assay, selective anaerobic culture, and nucleic acid amplification test). Adjunctive diagnostic tools include abdominal and pelvic imaging (contrast-enhanced CT) and lower gastrointestinal

endoscopy [4]. Treatment for rCDI depends on the recurrence. For the first recurrence in non-severe cases, oral metronidazole, vancomycin, or fidaxomicin are recommended, and for severe cases, oral vancomycin or fidaxomicin. Recommendations for second episode are a tapered/pulsed vancomycin or oral fidaxomicin and for the third or subsequent recurrences recommendations include fecal microbiota transplant (FMT) or oral fidaxomicin. Supportive care, such as correcting fluid and electrolyte imbalances, is crucial. Other therapeutic options include alternative antibiotics (rifaximin, nitazoxanide, teicoplanin), probiotics, intravenous immunoglobulin, monoclonal antibodies (actoxumab-bezlotoxumab), and anion-binding resins (tolevamer) [4]. However, despite modern diagnostic and therapeutic options, CDI remains a significant medical challenge.

We present a rare case of a patient with active C.difficile colitis on colonoscopy, despite multiple negative stool antigen and toxin tests, and then its reccurence.

CASE DESCRIPTION

A **62-year-old female patient** was initially hospitalized at our hospital within ICU department due to **acute encephalitis and bilateral bronchopneumonia** in a critical general condition. Her medical history included**insulin-dependent diabetes mellitus** and **arterial hypertension**.

First Hospitalization: The patient was admitted from September 23rd, 2022, to November 10th, 2022 (49 days). During this period, treatment included 35 days of parenteral beta-lactams(ceftriaxone 8 days than carbapenem 27 days), 21 days of acyclovir, pantoprazole, probiotic and other supportive therapy. Clinical Course:

- Day 18: The patient developed four episodes of liquid, green, mucous stools.
  - Laboratory results: Leu 11.5 × 10⁹/L, Neut 84%, Lymph 9%, Mono 7%, CRP 44 mg/L, sCreatinine 81 µmol/L.
  - Microbiology: Stool culture for Salmonella, Shigella, Campylobacter, Yersinia and for *C.difficile*as well as immunochromatographic test for toxins A/B were negative.
  - Symptomatic therapy led to spontaneous resolution within a few days.
- Day 32: Recurrence of four liquid, green, mucous stools.
  - Laboratory results**:** Leu 11.7 × 10⁹/L, Neut 92%, CRP 55 mg/L, sCreatinine 48 µmol/L.
  - Microbiology:Stool culture was negative; culture for *C. difficile* positive; test for toxin A/B was negative.
- Symptomatic therapy was initiated, but symptoms persisted, and the condition worsened.
- Day 35: Colonoscopy revealed pseudomembranous pancolitis (figure 1 and figure 2).

Beta-lactam antibiotics were discontinued, and the patient was started on intravenous metronidazole and oral vancomycin for 14 days. This resulted in gradual resolution of diarrhea, with normalization of stool frequency and consistency.

- Follow-up stool cultures were negative, and the patient was discharged.

Second Hospitalization:The patient was readmitted three weeks later, from December 2 to December 15, 2022 (11 days), with a 10-day history of watery, mucous diarrhea. The patient had been on nitrofurantoin for two weeks prior to admission for a urinary tract infection.

Initial Workup:

- Laboratory results: Leu 12.2 × 10⁹/L, Neut 64%, Lymph 19%, Mono 13%, CRP 42 mg/L, sCreatinine 29 μmol/L.
- Microbiology:Stool culture negative; *C. difficile* culture positive; toxin A/B test negative.

Clinical Course:

On December 9, 2022 (Day 7), colonoscopy showed significant regression of pseudomembranous lesions, limited to the cecum and rectum. Biopsy confirmed chronic non-specific inflammation. The patient was treated with:

- Intravenous metronidazole (500 mg three times daily for 7 days).
- Oral vancomycin in a tapered regimen: 125 mg four times daily for 10 days, 125 mg twice daily for 7 days, 125 mg once daily for 7 days, 125 mg every third day for 14 days.The initial portion of therapy was administered during hospitalization, with the remaining doses completed at home under guidance.

Follow-Up:

At the first follow-up, three weeks after the discharge, the patient reported no symptoms, with normal stool. Oral vancomycin tapering and rifaximin (200 mg three times daily for 14 days) were recommended, along with probiotics. At the second follow-up two weeks later, the patient remained asymptomatic, with normal stool characteristics.

DISCUSSION

CDI is one of the most commonly recognized healthcare-associated infections worldwide [1]. The disease spectrum ranges from non-severe to fulminant infection and death, where non-severe disease is characterized by watery diarrhea with three or more loose stools per day [4]. There are three different severity criteria for CDI based on SHEA/IDSA, ACG and hospital specific guidelines. They are: mild-moderate disease, severe disease and severe complicated [4]. Our patient met the criteria for mild-moderate disease. There is no single rapid test to diagnose CDI and diagnosis usually requires a multi-step diagnostic approach [5]. The current management for the diagnosis and treatment of CDI starts with clinical suspicion. Patients typically present with acute onset of diarrhea with more than 3 stools in a 24-hour period, fever, abdominal pain and leukocytosis, in the setting of recent antibiotic use and/or hospitalization [5]. Stool samples should be collected and sent for stool GDH antigen testing and for EIA toxin A and B testing. If testing is negative for either, then a nucleic acid amplification testing (NAAT) is done to confirm the diagnosis [4]. In our case, NAAT was not available. The EIA tests were negative all the time, however the clinical suspicion was still high and the decision was made for a diagnostic colonoscopy which ultimately revealed pseudomembranous colitis. Pseudomembranes are only found in 13% of patients who have CDI and are typically suggestive of severe infection [5]. Once she was started on appropriate antibiotics for CDI, her symptoms improved. The fact that our patient got better after the treatment further confirms that C.difficile was the culprit of her pseudomembranes. The exact mechanism for why patients can have multiple negative stool testing for CDI but still have endoscopic evidence of active C.difficile-mediated pseudomembranous colitis remains a conundrum and more research is needed for it to be elucidated.

CONCLUSIONS

The prolonged use of broad-spectrum antibiotics, prior and extended hospitalization, advanced age, severity of pre-existing conditions, and comorbidities are among the most significant risk factors for the development of recurrent *Clostridioides difficile* infection (rCDI) in hospitalized patients. A prolonged oral vancomycin regimen demonstrates high efficacy in the treatment of recurrent CDI. Although pseudomembranes in the colon are non-specific, they are most commonly associated with *C. difficile* colitis especially in the appropriate clinical setting where there is a high index of suspicion. In rare instances patients can have multiple false negative tests for *C. difficile* due to unclear reasons. Thus, it is necessary to consider the use of direct

visualization of the colon by endoscopy in such cases, to facilitate accurate diagnosis and to implement prompt and appropriate treatment.

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DISTINCTIVE FEATURES OF EATING HABITS AND DIETS AMONG CHILDREN AGED 6–12 YEARS AND DEVELOPMENT OF DENTAL CARIES IN THIS TARGET GROUP

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ABSTRACT
Aim: The study aims to explore the dietary habits and nutrition of children aged 6–12 years concerning the development of dental caries. **Materials and methods:** The study included 277 children, consisting of 158 boys and 119 girls. The food intake data from children's food diaries over a 3-day period were analysed. The dental status of children was evaluated employing the WHO D1MF(T+t). **Results:** The prevalence of carious lesions was much higher in children who consumed carbohydrates and so-called "junk foods" in comparison to those who preferred eating fruits and vegetables, with a recognised and reliable difference between the two groups (χ^2 =8.8 $p<0.01$). There was statistical reliability regarding the dental caries in children who had snacks between the main meals compared to those who did not have intermediate meals (χ^2 =10.9 $p<0.001$). A reliable relationship was revealed when comparing the development of carious lesions between the group that missed a meal for the day and the one that did not (χ^2 =53.1 $p<0.001$). The reliability of the results was shown in children who preferred going to fast food restaurants as opposed to children who occasionally visited such places (χ^2 =24.4 $p<0.001$). **Conclusion:** The results of the study indicate that the adolescents have unhealthy eating habits. The active involvement of parents, teachers, and dental professionals is essential for the promotion of oral health and the development of rational eating patterns.

Keywords: Food diary, dental caries, eating habits, children

INTRODUCTION
Childhood is crucial to cultivating healthy eating habits [1]. Promoting healthy eating and adherence to a balanced diet is essential for children's overall and oral health. [2]. Adopting poor dietary habits during childhood can significantly increase the likelihood of future caries development. Such behaviours, particularly when coupled with improper dental care, may result in gingival and periodontal diseases. [3]. **Aim:** The aim of the study is to analyse the eating habits and diets of children aged 6–12 years related with the onset of dental caries.

MATERIALS AND METHODS
The study comprised 277 children, including 158 boys and 119 girls. The children and their parents were given instructions to record the types of food consumed on an hourly basis in a food diary over a period of three days. The dental status of the children involved in the study was evaluated using the D1MF(T+t), applied by WHO.

RESULTS
Various eating patterns play a crucial role in the etiology of carious lesions among the children in the study.

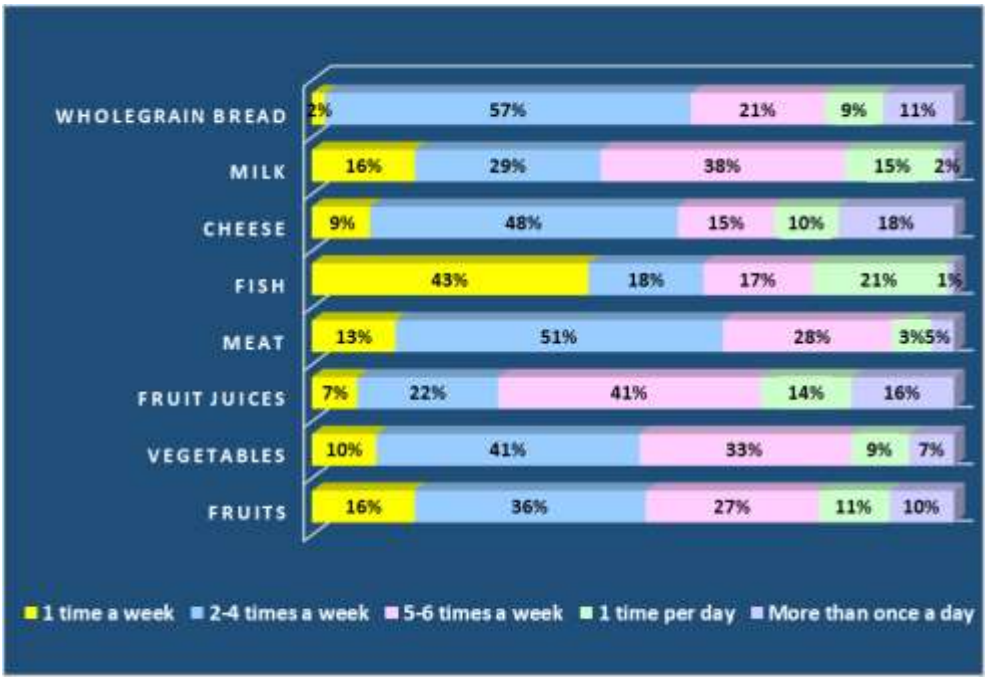

Diagram № 1. Consumption of staple foods among children

Diagram № 1 illustrates that children's dietary regimens rarely include milk and dairy products, fruits, and vegetables; instead, they prefer meat and, to a lesser extent, fish, along with whole grain bread. The data presented in **Diagram № 2** indicates that children have a preference for carbohydrate foods, including white bread, pasta, carbonated and sweetened drinks, chocolate, and confectionery. Their consumption varies from once a week to more than once a day. This fact also explains the high intensity of dental caries in most children.

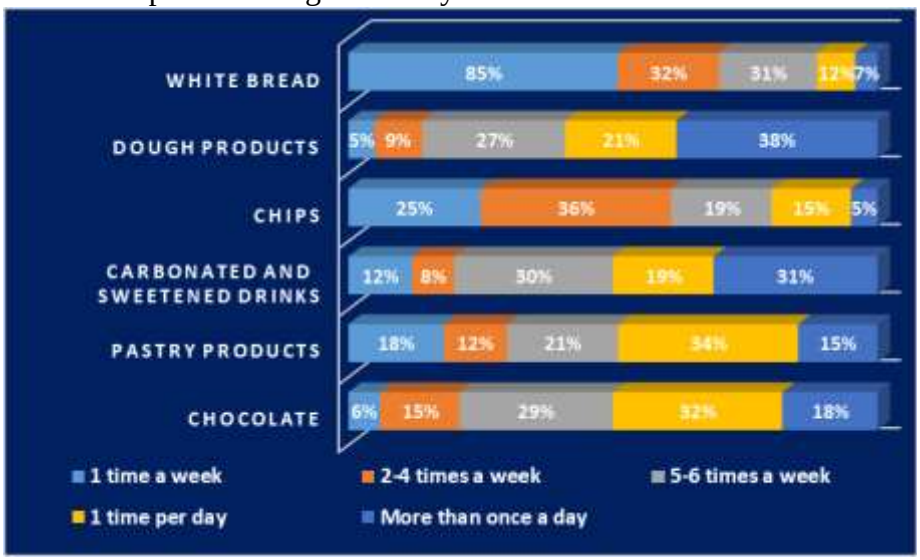

Diagram № 2. Consumption of carbohydrate foods among children

Variables	DıMFT				χ^2 p
	With caries	Without caries	With caries Total	Without caries Total	
Type of eating habits					
With a predominance of fruits and vegetables	10%	3%	92%	8%	χ^2 =8.8 p<0.001
With a predominance of carbohydrate foods and junk foods	82%	5%			
Skipping meals					
Yes	29%	10%	84%	16%	χ^2 =53.1 p<0.001
No	55%	6%			
Frequency of meals in restaurants for fast food					
Every week	64%	5%	92%	8%	χ^2 =24.4 p<0.001
Once a month	19%	2%			
From time to time	9%	1%			
Eating between meals					χ^2 =10.9 p<0.001
Yes	87%	1%	87%	13%	
No	0%	12%			

Table 1. Eating habits and dental caries among children

The results shown in **Table 1** suggest that children who consume carbohydrates and "junk food" have a tendency to develop a higher proportion of carious lesions compared to children who mostly eat fruits and vegetables. The difference between the two groups is statistically significant (χ^2 =8.8 p<0.01). Statistical reliability (χ^2 =10.9 p<0.001) is also proven among children who consume intermediate meals between the main ones. In a comparison between children who skip intermediate meals and those who eat snacks, including carbonated beverages and confectionery (such as candies, bars of chocolate, salted sticks, crackers, and croissants), a higher incidence of caries was seen in the latter group. In addition, a reliable correlation was identified when comparing the results of carious lesions in children who skipped meals during the day with those who did not (χ^2 = 53.1 p<0.001). The reliability of the results was further demonstrated in children who often frequented fast-food restaurants (χ^2 = 24.4 p<0.001), in contrast to children who visited such facilities only occasionally.

DISCUSSION

Beginning at a young age, it is essential to inculcate in children the values of healthy eating and maintaining a diet that is well-balanced for a variety of reasons [1, 4]. Giving them the appropriate vitamins and minerals through their diet will enable them to grow and develop to their maximum potential. A healthy eating will supply children with energy and motivation, increasing their capacity to learn. Adopting beneficial behaviours in infancy will facilitate better choices in adulthood [5, 6,7]. Consistent consumption of sugar-laden foods ultimately results in obesity, dental problems, and psychological disorders [8].

CONCLUSION

According to the results obtained, the children who were examined have unhealthy eating habits. Active promotion of oral health and the formation of appropriate eating habits requires the committed involvement of parents, teachers, and dental professionals. Certain foods are inappropriate on children's everyday menus and should be avoided. These include all consumables containing sugar: carbonated beverages, prepackaged juices, confections, candies, waffles, chips, etc.

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CORRELATION BETWEEN THE EATING HABITS AND SEVERITY OF DENTAL CARIES AMONG CHILDREN AGED 6 TO 12 YEARS

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ABSTRACT
Aim: This study aims to evaluate the relationship between eating habits and the severity of dental caries in children aged 6 to 12 years, taking into account their various nutritional status. **Materials and methods:** The study encompasses a total of 277 children, comprising 158 boys and 119 girls. The severity of dental caries in children has been evaluated through the D1MF(T+t) index. An analysis has been conducted on the relationship between eating habits and the severity of dental caries, employing the Spearman correlation coefficient. **Results:** A strong adverse correlation was identified between D1MF(T+t) and the consumption of sugar and confectionery (rho =-0.36, p<0.001). A positive, although modest, association was determined between D1MF(T+t) and the consumption of chips and crackers (rho=0.18, p=0.019*). Negative correlations were reported between D1MF(T+t) and the consumption of jam, honey, and both fresh and sour milk. No relationship has been found between D1MF(T+t) and the consumption of cereals, fruits, vegetables, pasta, and junk food (p>0.05). A strong positive correlation was established between D1MF(T+t) and the consumption of fizzy and sweetened drinks (rho =0,34, p<0,001). **Conclusion:** The significant correlation between the severity of dental caries and the frequency of consumption regarding various food products among studied children necessitates revisions in their eating habits to enhance their oral health.

Keywords: Eating habits, children, dental caries

INTRODUCTION
The formation of children's eating habits must begin at an early age, since the initial seven years of a child's life are crucial; during this time, parents, teachers, and dentists have the most impact on the eating behavior of children [1]. During this period, it is essential to provide children with healthy foods that lack sugar and to educate them on proper oral hygiene practices, as both diet and oral hygiene play crucial roles among the risk factors associated with the development of dental caries [1, 2, 3]. In the absence of tailored preventative measures to halt the progression of caries, the condition will persist, necessitating the use of contemporary techniques that remove decayed tissue and reduce pain during treatment, particularly in paediatric cases [4]. **Aim:** The aim of the study is to evaluate the relationship between eating habits and the severity of dental caries in children aged 6 to 12 years who have diverse nutritional status.

MATERIALS AND METHODS
The study comprised 277 participants, including 158 boys and 119 girls. The D1MF(T+t) index has been applied to evaluate the severity of dental caries among children. The relationship between eating habits and the severity of dental caries has been examined employing Spearman's correlation coefficient, with values ranging from -1.00 to +1.00. A correlation value of +1.00 indicates a perfect positive correlation, whereas a value of -1.00 suggests a perfect negative correlation.

RESULTS

Table № 1. illustrates the correlation between the severity of dental caries and the nutritional status of the studied girls.

Table № 1. Correlation between D1MF(T+t) and the nutritional status of girls

Nutritional status of girls	**n**	**Mean D1MF(T+t)**	**RHO**
Underweight	20	5.5	0.811
Normal weight	59	8.8	
Overweight	23	6.0	
Obesity	17	11.9	
Total	119		

***Spearman's RHO correlation test: p<0.05= significant**

As established by the Spearman's RHO correlation test, the correlation between D1MF(T+t) and the nutritional status of girls has shown a p-value of 0.810, which indicates that there is a strong relationship between the two variables.

Table 2 provides the correlation between the severity of dental caries and the nutritional status of the studied boys. The results obtained after applying the Spearman's RHO correlation test have suggested a moderate correlation between D1MF(T+t) and the nutritional status of the boys within the experimental group.

Table 2. Correlation between D1MF(T+t) and the nutritional status of boys

Nutritional status of boys	**n**	**Mean D1MF(T+t)**	**RHO**
Underweight	18	6,6	0.318
Normal weight	80	7.83	
Overweight	18	8.17	
Obesity	42	10.50	
Total	158		

***Spearman's RHO correlation test: p<0.05= significant**

Table 3 illustrates the correlation results between the severity of dental caries, represented by the D1MF(T+t) index, and the frequency of dietary intake of various foods and beverages among the studied children. A significant negative connection has been determined between D_1MF(T+t) and the consumption of sugar and confections (rho=-0.36, p<0,001). A positive but weak correlation exists between D_1MF(T+t) and the consumption of chips and crackers (rho=0.18, 0.019*). Researchers reported negative correlations between D_1MF(T+t) and the consumption of jam, honey, and milk, including both fresh and soured. No correlation was identified between D_1MF(T+t) and the consumption of cereals, fruits, vegetables, pasta, junk food (p>0.05). A very strong positive association has been established between D_1MF(T+t) and the consumption of fizzy and sweetened drinks (rho=0,34, p<0,001).

Table 3. Correlation between D1MF(T+t) and the frequency of food consumption

Eating habits	≤ 2 times a week		3-6 times a week		1-6 times a week		Spearman's correlation coefficient (Rho)		K-W test
	D1M(T+t)	rho	D1M(T+t)	rho	D1M(T+t)	rho	rho	p-value	p-value
Cereals, of which white bread, Dobrudzha, whole grain, rye rye-wheat	2.52±4.5	0	4.55±6.36	0.9	3.28±4.02	0,2	0.08	0.317	0.5142
Pasta and macaroni products	4.48±2.8	4	4.27±2.65	4	4.81±3.55	3	-0.08	0.285	0.5628
Sugar, chocolate and pastry products	3.07±3.12	2	4.09±2.69	4	5.63±3.29	5	**-0.36**	**<0.001***	**<0.001***
Junk food	4.08±3.27	4	4.74±3.22	4	4.79±2.89	5	0.13	0.1046	0.2675
Chips, crackers	3.4±3.03	4	4.23±2.91	4	6.34±3.96	7	0.18	**0.019***	**0.0339***
Jam, honey	2.69±3.64	1	4.53±3.62	1	5.73±3.55	5	**-0.22**	0.0527	0.1501
Milk (fresh and sour)	4.49±3.19	4	2.63±3.88	5	3.49±3.33	3	**-0.12**	**0.119***	**0.0171***
Dairy products, of which cheese and cottage cheese	4.57±2.8	4	2.98±3.69	4	3.89±3.48	3	**-0.15**	0.0527	0.1501
Fruits	3.98±2.27	2.5	3.67±1.56	0	3.44±3.92	2	0.04	0.5761	0.0548
Vegetables	1.85±3.05	0	3.77±2.23	2	3.87±2.78	3	0.03	0.7132	0.9166
100% fruit juice	3.35±2.98	2.5	3.48±4.38	10	4.26±3.17	4	0.06	0.4074	**0.0484***
Fizzy drinks	2.06±3.18	0	5.35±2.67	4	5.06±5.67	4	0.34	**<0.001***	**<0.001***
Sweetened drinks	2.26±2.77	2	6.04±2.83	4	4.78±3.29	4	0.34	**<0.001***	**<0.001***

DISCUSSION

Diet has a substantial impact on the nutritional status of children. It plays a vital role in the development and maintenance of oral health, making it possible for children to enjoy the benefits of diverse and nutritious food [5, 6]. The education and motivation are meant to help children understand the impact of food and nutrition on their oral and overall health, as well as establish a healthy, balanced, and rational eating routine [7,8]. It is worth the effort to explain to the child the importance of eating nutritious foods every day that are beneficial for growth and health. [9] Furthermore, it is crucial to clarify that while some "treat" foods may be enjoyable, their potential negative impact on health makes them inappropriate for daily consumption [10].

CONCLUSION

Motivating and promoting oral health are crucial factors in helping children change their unhealthy eating habits. Their diet will be balanced and appropriate when they are encouraged and taught to eat foods that are good for their dental health.

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COMMUNITY-ACQUIRED PNEUMONIA WITH PLEURAL EMPYEMA AND THROMBOSIS OF RIGHT POPLITEAL ARTERY AS COMPLICATIONS: CASE REPORT

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ABSTRACT

Purpose: To present a patient with community-acquired pneumonia with empyema and right superficial femoral and right popliteal artery thrombosis as rare complications.

Case report: We present 63-year-old female with fever and shortness of breath, seven days prior hospitalization. On admission the patient was febrile, tachydyspnoic with low oxygen blood saturation. On physical exam weakened breathing in the basal parts and crackles in the upper parts of the right lung were noted. After 48 hours, pain appeared in the right lower limb and pulsation of the right popliteal and right dorsalis pedis artery were absent. Laboratory and microbiological analyzes, ultrasound guided diagnostic thoracentesis, chest X-ray and chest CT scan, doppler ultrasound and CT angiography of blood vessels of the lower extremities, were performed. Empyema of the pleura and thrombosis of the right popliteal artery were diagnosed. In addition to the conservative treatment, the patient underwent surgical treatment.

Conclusion: Complications in patient with community-acquired pneumonia and empyema related to coagulation disorders are very common, but artery thrombosis of the lower extremities is the most rarely reported thrombotic complication. Severe infections complicated by thrombotic events required a rapid, integrated and multidisciplinary management approach.

Key words: Community-acquired pneumonia, empyema, peripheral artery thrombosis.

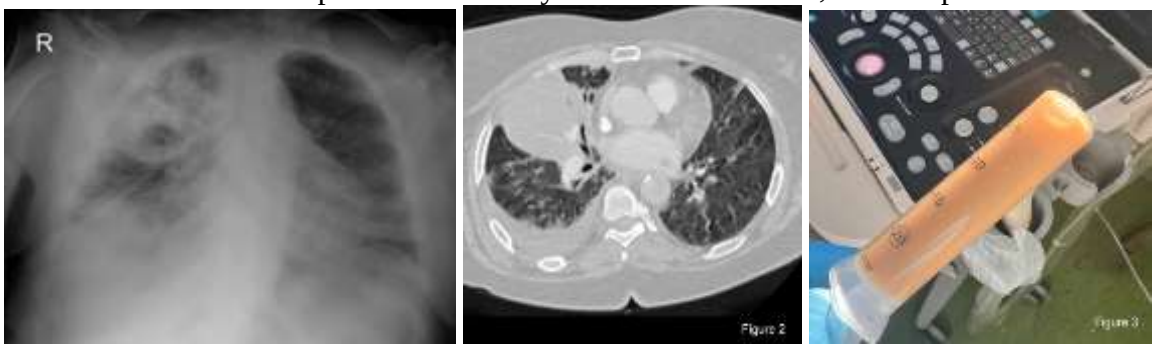
INTRODUCTION

Pneumonia is an acute inflammation of the lung parenchyma, the most severe form of acute respiratory infections. [1] It is the fourth leading cause of death worldwide with an average mortality rate of 7% in community-acquired pneumonia and 29% in severe community-acquired pneumonia. Severe community-acquired pneumonia is defined as pneumonia that requires supportive therapy in intensive care units, because of multiorgan impairment. Pleural effusion and pleural empyema are very common complications of pneumonia. About 20% of patients with bacterial pneumonia also have pleural effusion. [2] Respiratory tract infections are associated with an increased risk of arterial and venous thrombosis, myocardial infarction and stroke, especially in smokers, older patients and patients with a history of previous cardiovascular disease. Systemic abnormalities in the coagulation process are not only observed in cases of sepsis, but also in pneumonia. [3]

CASE PRESENTATION

A 63-year-old female smoker, without history of pass illness, was admitted to the hospital with symptoms of fever and shortness of breath, seven days prior hospitalization. On admission the patient was with high fever, BP 185/85mmHg, tachydyspnoic with 89% oxygen blood saturation. On physical exam was noted weakened breathing in the basal parts and crackles in the upper

parts of the right lung. A deviation in the initial laboratory analyzes were noted in: WBC 61.4 $x10^9$/l (3.5-10.0 $x10^9$/l), Neutrophil count 55.9 $x10^9$/l (1.2-8.0 $x10^9$/l), C-Reactive Protein 353.8 mg/l (>10 mg/l), Sodium 128 mmol/l (136-145 mmol/l), Alanine Aminotransferase 96 U/L (10-63 U/L), Aspartate Aminotransferase 250 U/L (5-37 U/L), Lactate Dehydrogenase 362 U/L (81-234 U/L), Blood Urea Nitrogen 38.2 mmol/l (2.8-7.2 mmol/l), Creatinine 234 mmol/l (49-115 μmol/l), D-Dimers 8393 ngr/ml (0-500 ngr/ml). A chest X-ray showed a slight pulmonary transparency in the right lung due to massive consolidation. (Figure 1) On CT angiography of the thorax, consolidation of the entire parenchyma in the upper lobe and pleural effusion of the right lung was noted. Descending thoracic aorta with calcifications as well as eccentric soft plaques. Abdominal aorta, iliac arteries with atherosclerotic plaques without repercussion of the flow lumen. (Figure 2) The patient was placed on oxygen support with a flow rate of 6 l/min, crystalloid infusion solutions, antibiotic therapy with Ceftriaxone and Azithromycin, anticoagulant therapy with Nadroparine Calcium 5700IU Anti-Xa/0.6ml x2. Forty-eight hours after admission, patient reported new episode of shortness of breath as well as severe pain in the right lower limb. Physical examination revealed a drop in blood oxygen saturation with an increase need for oxygen flow 10 l/min, inaudible breathing in the basal parts of the right lung, and absent popliteal and dorsalis pedis artery pulsation of the right leg. Ultrasound guided diagnostic thoracentesis was performed and 25 ml of pus was evacuated for microbiological investigations. (Figure 3) Microbiological analyses of sputum, and pleural puncture were negative. Doppler and CT angiography of peripheral blood vessels were performed and thrombosis of the right popliteal artery was diagnosed. (Figure 4) The patient was transferred to the surgical department, where was performed thoracic tube drainage and thromboembolectomy according to Fogarty method. After surgical interventions, conservative treatment was continued with Vancomycin, Imipenem and Nadroparine Calcium 5700IU Anti-Xa/0.6ml x2, as well as other supportive therapy in duration of two weeks. Control CT angiography of peripheral blood vessels was with normal blood flow of the arteries along the entire length. On the control CT chest was noted zone of post-inflammatory band-like adhesions, without pleural effusion.



DISCUSSION

After lung infections especially bacterial pneumonia, the accumulation of fluid in the pleura progresses to parapneumonic effusion. Some clinical characteristic like long length of fever, chest tightness, lymphocytosis, high level of C-reactive protein, low serum albumin and low sodium levels should arouse suspicion for development of empyema. [4] Risk factors like old age, poor dental hygiene or recent dental procedure, smoking, malnutrition, immunosuppression, diabetes mellitus, respiratory and cardiovascular diseases are associated with development of complicated parapneumonic effusion or empyema. [5] The most common microbiologic organisms causing empyema include Streptococcus species, Staphylococcus aureus, and a variety of gram-negative organisms and anaerobes. Anaerobic infection is common in empyema but can be challenging to identify in cultures. [6] The therapeutic approach to empyema should include empirical antimicrobial therapy and surgical plans. There is no common approach that would be suitable for all patients. If the empyema is in the exudative phase, thoracentesis may be utilized as a therapeutic measure as well as a diagnostic one. Antibiotic dosages are modified by the cultures' sensitivity. If antibiotic medication was started before specimen cultures were

acquired, up to 50% of the cultures would be negative. If the fluid is thick or extremely purulent, thoracostomy with chest tube drainage is necessary. [7] Fibrinolytic drugs can be administered through a chest tube to dissolve fibrin loculations, with varying degrees of efficacy. Some findings suggests that intrapleural fibrinolysis can shorten the period of hospitalization. [8] The inflammatory response during a severe infection activates the procoagulative phases and inhibits the inhibitory phases in the blood coagulation process. The pathogenetic mechanism of thrombus formation in severe infection may be due to the direct action of pathogens or as a result of the inflammatory response. [9] A systematic review that include studies with total numer of 63,834 patients, which assesse the incidence of vascular complications in patients with community-acquired pneumnia, showed that acute coronary artery disease such as myocard infarction and stroke may occur in about 1-11% of patients, in the early phase of acute infections. Pulmonary thromboembolism and deep vein thrombosis are less clinically characterized in patients in the acute phase of infection. [10] In another large prospective cohort study including 3921 patients with community-acquired pneumonia, 8% of subjects had one or more acute cardiovascular manifestations during hospitalization. Old age, hypoalbuminemia, cardiac and renal chronic diseases, multilobar and pneumococcal pneumonia have been reported as factors associated with these events. [11] The occurrence of arterial thrombosis of the lower extremities in this context has been reported less frequently. A large number of studies have been published about arterial thrombosis of the lower extremities associated with Covid pneumonia, one study associated with Chlamydia psittaci pneumonia and three studies associated with Mycoplasma pneumonia. [12,13]

CONCLUSION

Complications in patient with community-acquired pneumonia and empyema related to coagulation disorders are very common, but artery thrombosis of the lower extremities is the most rarely reported thrombotic complication. Severe infections complicated by thrombotic events required a rapid, integrated and multidisciplinary management approach.

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HIV PRE-EXPOSURE PROPHYLAXIS AS A TOOL AGAINST THE SILENT SYPHILIS EPIDEMIC IN NORTH MACEDONIA

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ABSTRACT
Introduction: Syphilis and other sexually transmitted infections (STIs) in North Macedonia among key populations pose a significant public health challenge. The number of reported cases has increased in recent years, possibly due to improved access to healthcare and more effective screening practices. **Objectives:** To explore the potential of Pre-Exposure Prophylaxis, traditionally used for HIV prevention, as a strategic tool in detecting syphilis as well as to demonstrate the importance of PrEP services in the early detection of other sexually transmitted infections (STIs). **Materials and methods:** PrEP services in North Macedonia began as a pilot project designed to evaluate the effectiveness of PrEP in preventing HIV and other STIs, including syphilis. All participants were provided with Emtricitabine/Tenofovir Disoproxil Fumarate according to guidelines. During their initial visit, participants underwent serological antibody testing for *Treponema pallidum*. Further testing was conducted based on the initial antibody results, including the Treponema pallidum hemagglutination assay (TPHA) and rapid plasma reagin (RPR). This approach aimed to enhance early detection and treatment of STIs, with a particular focus on syphilis. **Results:** Out of 147 PrEP users, 19 individuals or 12.9% contracted syphilis. These 19 cases represent 18.5% of the total 103 detected syphilis cases over the last four years. This data suggests that a significant proportion of asymptomatic syphilis cases are detected among PrEP users, indicating that PrEP services may contribute to better screening and early detection of syphilis. **Conclusion:** Through regular medical check-ups required for PrEP users a potentially suspected increase in syphilis incidence rates was found. This means that PrEP has a serious impact on early detection and reducing the transmission rate of syphilis.

Keywords: PrEP, HIV, Syphilis, STIs, screening

INTRODUCTION
In North Macedonia, HIV and other sexually transmitted infections (STIs) are predominantly concentrated among key populations, notably men who have sex with men (MSM). In the past screening practices for STIs have faced challenges due to limited interest and lack of financial support. The number of reported cases has increased in recent years, possibly due to improved access to healthcare and more effective screening practices. PrEP as a screening and prevention tool was started in 2021 and became a significant tool for controlling HIV spreading, also in the detection of other STIs such as syphilis especially in asymptomatic cases.

OBJECTIVES
The study aims to understand the usefulness of PrEP as a tool in detecting other STIs such as syphilis. This explores how Pre-Exposure Prophylaxis (PrEP), used for HIV prevention, can also help detect syphilis and other STIs early. The initiative underscores the importance of integrating PrEP services into broader STI prevention and detection efforts.

MATERIALS AND METHODS

The PrEP pilot project in North Macedonia was structured as a prospective, unmasked cohort study aimed at evaluating the efficacy of PrEP in preventing not only HIV but also other STIs, with a particular focus on syphilis. Participants received Emtricitabine/Tenofovir Disoproxil Fumarate (FTC/TDF) following established PrEP guidelines.

During their initial visit despite HIV, hepatitis B virus (HBV), and hepatitis C virus (HCV), participants underwent serological antibody testing for *Treponema pallidum*, the bacterium responsible for syphilis. If initial serology was positive (T.Pallidum IgM), further testing was conducted using the Treponema pallidum hemagglutination assay (TPHA) and rapid plasma reagin (RPR) tests to confirm active infection and determine the disease stage. This structured testing approach was intended to improve early detection and prompt treatment of STIs among participants, strengthening PrEP's potential as a comprehensive preventive tool against a broader spectrum of sexually transmitted infections.

RESULTS

From February 2021 to October 2024, 147 individuals accessed the PrEP service in North Macedonia. At their initial visit, behavioral suitability was assessed, and clinical evaluation with laboratory testing was performed for HIV, Hepatitis B virus, Hepatitis C virus, and *Treponema pallidum*. Follow-up evaluations were conducted one month later and then every three months for those adhering to proper PrEP use.

Notably, 19 individuals, all of them men, (12.9%) were diagnosed with syphilis during their first visit (14 of them), or follow-ups (5 of them). Asymptomatic all of them. (Figure1)

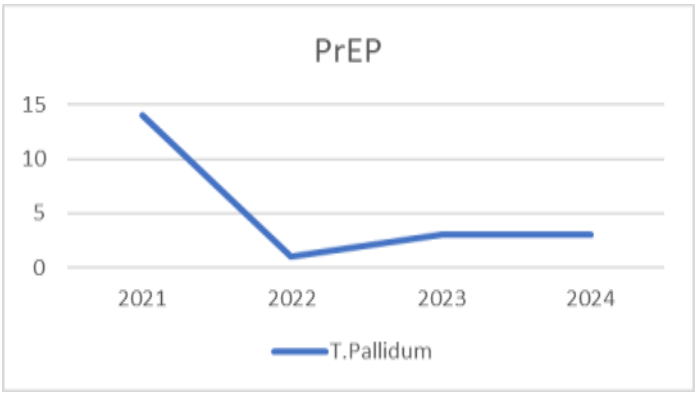

Figure 1: Positive serology of Syphilis through four years with PrEP service

During the same period (2021-2024), 84 syphilis cases were detected in the ambulance at the University Clinic for Infectious Diseases in Skopje. These 19 cases account for 18.5% of the 103 syphilis cases detected in the country during this period (Figure 2). Four cases of hepatitis B infection were also detected through the PrEP program.

This data underscores the important role that PrEP services play in addressing not only HIV prevention but also the detection and management of other sexually transmitted infections (STIs).

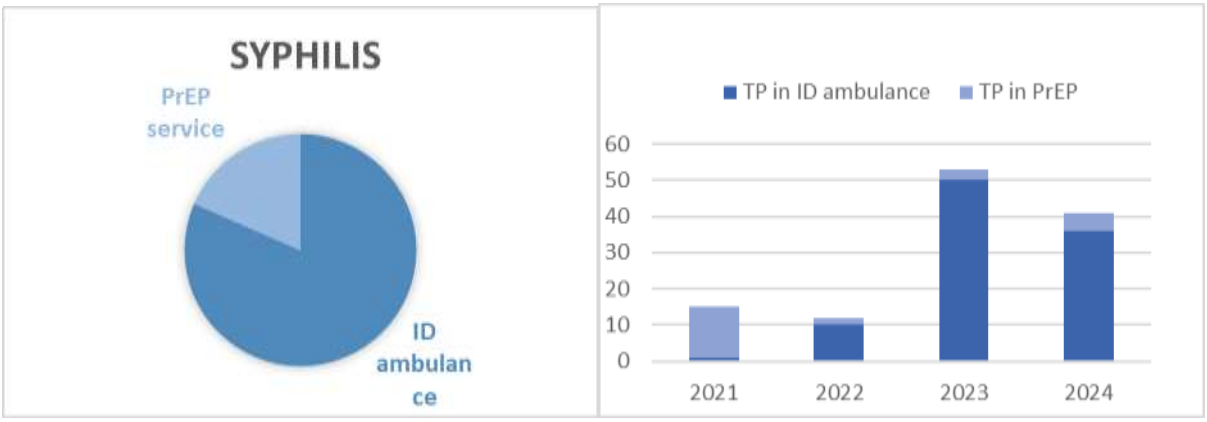

Figure 2: Proportion of positive tests for Syphilis between ID ambulance and PrEP service

DISCUSSION

Syphilis is a sexually transmitted infection (STI) caused by the bacteria Treponema pallidum. It is a worldwide spread infection, highly prevalent among males who have sex with males (MSM), and infects an average of 11.8% of MSM in reporting countries in 2019 according to the World Health Organization.[1,2] Syphilis and other STIs in the Republic of North Macedonia are on the rise, as shown by reports from the Institut for Public Health. In 2023, 60 cases of syphilis were reported, despite only 30 individual cases documented for the period between 2014 and 2021. Compared to 2022, the number of cases surged by 2.7 times.[3]

In one study in Melbourne, researchers retrieved medical information collected at the Sexual Health Centre between February 2016 and March 2019. During the study period, 572 MSM attended the PrEP clinic. The rate of syphilis screening among men attending the PrEP clinic was high—96%. It was even higher among men who participated at the STI clinic between scheduled PrEP appointments—99%. [4]

Another study reported that quarterly STI screening would diagnose 18,250 more STIs than screening six months over 10 years of follow-up in more than 36,000 men who have sex with men (MSM), although this effort would not be cost-effective.[5]

PrEP programs require regular medical check-ups, typically every three months, to monitor users' health and adherence. These visits are ideal opportunities for routine STI screening, including syphilis. Testing for syphilis during PrEP follow-ups ensures timely detection and treatment of the infection. It aims to diagnose STIs early, provide targeted therapy, and break chains of transmission. However, there is a debate on the frequency of screening, considering the need to optimize healthcare resources and concerns about increasing antibiotic resistance. [6]

CONCLUSION

Many cases of syphilis remain undiagnosed in the general population due to the absence of symptoms or limited access to regular testing. However, integrating routine STI screening into PrEP services ensures that infections like syphilis can be detected earlier, often during the asymptomatic phase. Early detection helps initiate timely treatment for affected individuals and reduces the risk of further transmission within the community.

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OUR EXPERIENCES IN THE SURGICAL APPROACH TO THE TREATMENT OF LUNG CANCER

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ABSTRACT
It is considered that 2,200,000 new patients with lung cancer are detected annually in the world (Globcan 2020), i.e. 1,135 in the Republic of North Macedonia (Globcan 2020), of which only 59 patients were surgically treated at the thoracic and vascular surgery clinic in 2022, which is 85% of the total surgically treated in the Republic of North Macedonia. The use of oncological drugs before surgical treatment can contribute to the application of surgery in cases where it was not possible, as well as reduce the tumor so that a less extensive surgical procedure can be applied. At the Thoracic and Vascular Surgery Clinic, of 59 patients surgically treated for lung cancer, 49 (83%) were treated with open anterolateral thoracotomy, and lobectomy with lymphadenectomy was most commonly performed in 41 (49.5%). Early diagnosis of lung cancer, using computed tomography screening, would allow the use of less aggressive approaches, such as videothoracoscopic surgery, robot-assisted surgery, and the use of less extensive lung resections such as segmentectomies with lymphadenectomy.

Key words: lung cancer, surgery, lobectomy with lymphadenectomy

INTRODUCTION
The extensiveness of the disease (clinically advanced stage), histological structure (small cell carcinoma), limited respiratory reserves, limited cardiac reserves, deterioration of the general condition makes lung resection impossible. That is why only 10% of newly diagnosed patients with lung malignancy undergo surgical intervention with lung resection. [1, 2] The use of neoadjuvant oncology therapy in a certain percentage increases the chance of lung resection. Of course, perhaps the introduction of a screening program with computed tomography enables the detection of lung cancer in the earliest stage of the disease, which significantly increases the percentage of lung resections. [2]
The aim of this paper is to determine the optimal approach in the surgical treatment of lung cancer through the analysis of operative material of patients operated on at the University Clinic for Thoracic and Vascular Surgery in 2022, analysis of surgical approach, type of lung resection and analysis of pathohistological findings.

MATERIAL AND METHODS
In 2022, 59 patients with proven lung cancer were surgically treated at the Thoracic and Vascular Surgery Clinic. The study did not include patients in whom lung malignancy was not proven, as well as patients in whom the surgical intervention was for diagnosing changes. Descriptive parameters (gender, age), pathohistological findings, TNM descriptors, preoperative application of neoadjuvant therapy, disease stage resulting from TNM descriptors, surgical approach, type of lung resection and removed part of the lung were analyzed.

RESULTS

At the Clinic for Thoracic and Vascular Surgery in 2022, 59 patients were operated on for lung cancer. Of them, 44 (74.6%) were men, and 15 (25.4%) were women. The age of the patients was from 40 to 79 years, with an average age of 64.22 years. Distribution of type of lung cancer according to sex of patients were presented to **Table 1**.

Table 1. Distribution of type of lung cancer according to sex of patients

Patohistology	**Male**	**Female**	**Total**
Squamos-cell	27 (45,8%)	5 (8,5%)	32 (54,2%)
Adeno-carcinoma	11 (18,6%)	8 (13,6%)	19 (32,2%)
SCLC	0	1 (1,7%)	1(1,7%)
Another	6 (10.2%)	1 (1,7%)	7 (11,9%)
Total	44 (74,6%)	15 (25,4%)	59 (100%)

Table 2. Distribution of patients presented to type of surgical approach and type of lung resection according to TNM stage

	STAGE						
TYPE	I	IIA	IIB	IIIA	IIIB	IV	T
Torakotomy	9	10	8	16	4	2	49
VATS	2	3	1	3	1	0	10
Total	11	13	9	19	5	2	59
Wedge	1	1	0	0	1	0	3
Lobectomy	9	11	7	14	2	2	45
Bilobectomy	0	1	0	2	0	0	3
Pulmectomy	0	0	2	2	2	0	6
other	1	0	0	1	0	0	2
Total	11	13	9	19	5	2	59

In terms of tumor size, the most common tumor was in T2 stage (3-5 cm), 24 (40.7%), followed by T3 with 14 (23.7%). Involvement of intrathoracic lymph nodes is in 17 (28.8%). Unfortunately, the most common disease stage is IIIA, represented by 19 (32,20%), followed by IIA, represented by 13 patients (22%). However, it should be noted that in 37 patients (62.7%) neoadjuvant therapy (chemotherapy) was given before surgery in order to reduce the tumor and the stage of the disease. **Table 2** present the results of the representation of type of operation and type of lung resection depending on the representation of TNM stage. It was the treatment of an advanced stage of disease that was the reason for an open approach (anterior small thoracotomy) which was applied in 49 (83%) patients, and videothoracoscopic resection in 10. In terms of lung resection, lobectomy with lymphadenectomy was most often used, in 45 (76,27 %), followed by pneumenectomy with lymphadenectomy in 6 (10.2%), followed by bilobectomy, wedge excision and another type of resection in 3 (5) %) for each type.

DISCUSSION

The procedure that entered the standard protocols of the treatment of lung malignancy is the introduction of lobectomy with lymphadenectomy. This was followed by the use of segmentectomy with limphadenectomy in the treatment of lung malignancy, first described by Jensink 1973. [3] The results of Ginsberg 1995 indicated that the results of using lobectomy were better than using sublobar (segmentectomy) resections in terms of survival and that in I stage, so lobectomy remains the standard procedure. [4] Saji 2022 published the results of the Japanese Society of Oncologists of surgical treatment of peripheral lung malignancy in the earliest stage of the disease, comparing segmentectomy with lobar resection of the lung and the results were identical in both groups, indicating that segmentectomy may become the method of choice in the treatment of peripherally located early lung malignancy. [5] The development of surgical treatment does not end here, namely by giving specially colored tumor-specific markers (OTL

38), so minimally invasive precision surgery is performed, removing the tumor in a healthy state by removing a minimal amount of healthy lung parenchyma. [6] The extent of surgical resection will primarily depend on the size of the tumor, histological structure, involvement of one or more lobes of the lung parenchyma, involvement of surrounding structures, etc. In the 90s of the 20th century, intensive work was done to introduce videothoracoscopy in thoracic surgery, so Rovario 1992 described videothoracoscopic anatomical lobectomy for the first time. [7] Of course, this required progress in anesthesiology techniques (one-lung ventilation), progress in videothoracoscopic cameras and their resolution, progress in the construction of specialized videothoracoscopic instruments, etc. Already in 2006, videothoracoscopic lung resections have been introduced in all guidelines in the treatment of lung malignancy. In 2011, Diego Gonzales first performed a videothoracoscopic lobectomy through a single 3-4 cm opening (uniportal), and in the same year, Chen performed a lobectomy on a non-intubated patient. [8] The latest innovation in the surgical treatment of lung malignancy is the application of robot-assisted thoracoscopic surgery, where in 2012 Cao performed the first robot-assisted videothoracoscopic surgery. [9] Advanced stage of the disease, which was present in the largest number of patients (IIIA -27.11%), the fact that 2/3 of the patients were in an advanced stage, which necessitated the use of neoadjuvant therapy, clearly indicates that for radical surgery it is necessary to an open thoracotomy was performed. The reception of a double-lumen tube (ventilation of one lung) and staplers allows the application of a small anterolateral thoracotomy with anatomic lung resection, in 49 (83%). In our material, radical lobectomy with lymphadenectomy was most often applied (45 patients – 76,27%). In the surgical treatment of lung malignancy, the application of videothoracoscopic radical anatomical lung resections, especially in advanced stages, is recommended to be performed in centers with extensive experience in videothoracoscopic approaches.

CONCLUSION

Introduction of screening in the risk population will allow early detection of lung malignancy, in the earliest stage, and this will allow the application of videothoracoscopic or robot-assisted lung resection in a much higher percentage.

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METHICILLIN-SENSITIVE STAPHYLOCOCCUS AUREUS BACTEREMIA AND MENINGITIS ASSOCIATED WITH SPINAL AND PSOAS MUSCLE ABSCESS – CASE REPORT

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ABSTRACT

Methicillin-sensitive Staphylococcus aureus (MSSA) can cause a range of severe infections, including bacteremia and meningitis. While MSSA-related bacteremia and meningitis are serious on their own, they can also be associated with complex complications such as intraspinal and psoas abscesses. We report a case of a 72-year-old male with symptoms including lower back pain, leg weakness, malaise, fever and headache. Initial laboratory results showed leucocythosis, hyponatriemia and elevated CRP, while cerebrospinal fluid analysis indicated significant pleocytosis and neutrophilia. After admission, three blood cultures were obtained, all of which isolated *MSSA.* During hospitalization, a CT scan of the thorax and MR of the spine were performed, revealing bilateral pleural effusion, L5-S1 intraspinal abscess, and an abscess in the ileopsoas muscle. After 6 weeks of antibiotic therapy, a follow-up MRI was performed, which showed regression of the abscesses.

This case underscores the severe complications of *Staphylococcus aureus* infection, including meningitis, sepsis and abscesses. Effective management relies on prompt diagnosis, comprehensive evaluation, and targeted antibiotic therapy. The patient's positive outcome highlights the importance of early recognition and tailored treatment in complex infections.

Keywords: S.aureus, meningitis, bacteriemia, abscess

INTRODUCTION

Methicillin-sensitive *Staphylococcus aureus* (MSSA) is a major pathogen responsible for a range of infections, from mild skin conditions to life-threatening diseases. MSSA can cause severe systemic infections, including bacteremia, endocarditis, osteomyelitis, pneumonia, and meningitis. The ability of *S. aureus* to form biofilms, its resistance to host immune defenses, and the production of various toxins contribute to its pathogenicity and the severity of infections [1, 2].

One of the most serious complications of MSSA infections is **bacteremia**, which can lead to sepsis and affect multiple organs. **Meningitis** caused by MSSA is relatively rare but can occur, particularly in patients with underlying conditions such as immunosuppression, trauma, or concurrent infections. Delayed diagnosis and treatment can lead to severe neurological sequelae and high mortality rates [3]. In addition to meningitis, MSSA infections can lead to the development of **abscesses** in various anatomical locations. Spinal cord **abscesses** and **psoas muscle abscess** are particularly concerning, as they can cause significant morbidity and long-term disability if not diagnosed and treated promptly. The symptoms include back pain, neurologic deficits, fever and systemic signs of infection. These abscesses often require prolonged antibiotic therapy for optimal treatment outcomes.

The outcome of MSSA-related infections depends on timely and accurate diagnosis, which involves a combination of clinical evaluation, microbiological cultures, and imaging studies. Antibiotic therapy should be tailored based on susceptibility patterns. Early recognition and intervention are crucial for preventing severe complications such as sepsis, organ dysfunction, and neurological impairment.

CASE DESCRIPTION

A 72-years old patient presented at our clinic with symptoms that began four days before admission. These included lower back pain, malaise, pain and weakness in both legs and gait disturbance. One day before admission, he also experienced fever and chills. After initial evaluations by a neurosurgeon, abdominal surgeon, and gastroenterologist, the patient was referred to an infectious disease specialist due to suspected infectious etiology. The patient had no significant past medical history or underlying health conditions. On arrival, the patient was afebrile (36.9^0C), alert and oriented with stable vital signs: heart rate of 89/min, blood pressure of 130/60mmHg, respiratory rate of 16/min and oxygen saturation of 96% on ambient air. The physical examination revealed bilateral crepitations on pulmonary auscultation. Neurological evaluation demonstrated tremor and weakness in the lower limbs, along with positive meningeal signs. Initial laboratory investigations showed elevated white blood cells (WBC) with domination of neutrophils (Neut), hyponatremia and elevated C reactive protein levels (CRP). (Table 1). Initial cerebrospinal fluid analysis revealed pleocytosis with neutrophilia, elevated lactate and protein level concentration (Table 2).

Table 1. Initial patient laboratory data

Parameters	Level	Reference Range
Hb	121	120-180 g/L
RBC	4.17	4.3-5.8 x 10^{12}/L
WBC	21.7	4.0-.10.0 x 10^9/L
Platelets	163	150-400 x 10^9/L
Hct	0.35	0.40-0.54 L/L
Neut	0.90	0.40-0.70 %
Lym	0.02	0.21-0.25 %
BUN	8.5	1.7-8.3 mmol/L
Creatinine	50	62-133 µmol/L
Glycemia	17.4	4.1-6.3mmol/L
AST	83	10-47 U/L
ALT	103	10-52 U/L
Serum Na^+	128	134-145 mmol/L
CRP	233	0-10 mg/L

Table 2. Initial CSF analysis

Parameters	Result	Reference Range
Appearance	Yellow	Clear
Pandy	+	-
WBC count	8704/µL	<5cells/µL
Neutrophils	90%	<2%
Protein	38.1g/L	0.15-0.45g/L
Lactate	14.5mmol/L	<2.8mmol/L
Glucose	1.9mmol/L	>2.5mmol/L
Parameters	**Result**	**Reference Range**
Appearance	Yellow	Clear
Pandy	+	-
WBC count	8704/µL	<5cells/µL
Neutrophils	90%	<2%
Protein	38.1g/L	0.15-0.45g/L
Lactate	14.5mmol/L	<2.8mmol/L
Glucose	1.9mmol/L	>2.5mmol/L

The CSF culture, incubated for 48 hours, yielded growth of MSSA. Additionally, three blood cultures obtained on admission were positive for MSSA, supporting the diagnosis of a systemic bacterial infection.

Initial treatment included a third-generation cephalosporin (ceftriaxone, 2 g intravenously every 12 hours) and a glycopeptide antibiotic (vancomycin, 1 g intravenously every 8 hours). Adjunctive therapy consisted of corticosteroids (dexamethasone 0.15mg/kg/day intravenously every 6 hours), antiedematous treatment with mannitol, and anticoagulant therapy with low-molecular-weigh heparin, symptomatic and supportive measures. Antihypertensive therapy with angiotensin-converting enzyme and calcium channel blockers was initiated after elevated blood pressure was noted. Additionally, treatment with rapid-acting insulin was provided based on blood glycose levels.

On the 7th day of hospitalization, a CT scan of the thorax and lumbar spine revealed bilateral pleural effusion and suspected spinal cord and psoas muscle abscesses.

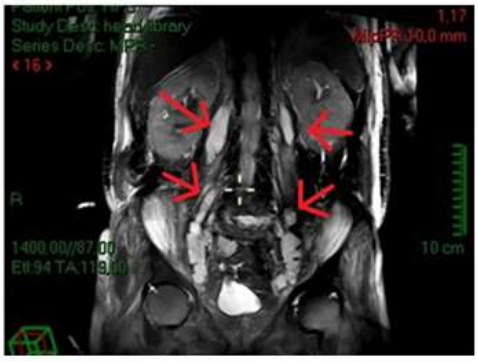
Antibiotic therapy was subsequently adjusted to a carbapenem (meropenem, 2 g intravenously every 8 hours). Furthermore, albumin supplementation and diuretics were introduced. A diagnostic pleural puncture was performed, and microbiological analysis of the pleural fluid was negative. Histopathological findings classified the effusion as Group I, consistent with non-specific inflammation. After two weeks of treatment, a magnetic resonance imaging (MRI) scan was performed, confirming the diagnosis of an epidural abscess extending from L2 to C3 (Figure 1) and psoas muscle abscesses spanning their entire length (Figure 2). The MRI findings were reviewed in consultation with neurosurgeon, who determined that there was no indication for surgical intervention at this time. The recommendation was to proceed with conservative management, including continuation of the current antibiotic therapy. A subsequent lumbar puncture revealed pleocytosis with a white cell count of 89 cells/μL, neutrophil predominance (70%), a lactate level of 5.2 mmol/L, protein concentration of 3.67 g/L, and glycorrachia of 2.7 mmol/L. Blood cultures (three consecutive sets) were obtained during this period and were negative.

Over the final four weeks of hospitalization, the patient demonstrated significant clinical improvement. He remained afebrile, with stable vital signs, normal vesicular breath sounds, and no reports of pain. Additionally, the patient regained full ability to perform both passive and active movements. The clinical improvement was followed by the normalization of inflammatory markers (leucocytes: 5.7 x 10^9/L, CRP decreased to 7 mg/L) and normal CSF findings.

To confirm the therapeutic response, a control MRI was performed at the end of six weeks of treatment. This scan demonstrated significant regression of both the spinal cord and psoas muscle abscesses, with no evidence of new abscess formation or spinal involvement. With stable vital signs, resolved inflammation, and full independent mobility, the patient was discharged from hospital.

Figure 1. MRI demonstrating spinal epidural abscess

Figure 2. The red arrows indicated bilateral psoas abscess



DISCUSSION

Bacteremia and meningitis caused by MSSA, particularly when associated with spinal cord and psoas muscle abscesses, represent severe and life-threatening infections, especially in immunocompromised populations such as the elderly. These infections pose significant diagnostic and therapeutic challenges due to aggressive nature of the pathogen. Early recognition and initiation of appropriate antimicrobial therapy are critical for improving clinical outcomes. [4]. Delays in diagnosis can result in rapid progression of the disease, leading to significant neurological deficits, systemic complications, and increased mortality risk. Comprehensive imaging and microbiological evaluations are essential for accurate diagnosis and to guide targeted therapeutic interventions. Elderly patients, who often present with atypical symptoms and multiple comorbidities, required a high index of suspicion to identify MSSA-related infections promptly [5]. Multidisciplinary approaches, involving infectious disease specialists, neurosurgeons, radiologists, physical therapist, nurses and family support are crucial for effective management. [6]

CONCLUSION

This case underscores the critical importance of early detection and aggressive treatment strategies in managing MSSA bacteremia and meningitis with associated abscess formations. Enhancing awareness and clinical vigilance in at-risk populations can significantly reduce the adverse outcomes associated with these formidable infections.

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ACUTE-ON-CHRONIC LIVER FAILURE IN A PATIENT WITH HEPATITIS B VIRUS INFECTION

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ABSTRACT
Acute-on-chronic liver failure (ACLF), also referred to as acutely decompensated cirrhosis, is a clinical condition characterized by sudden hepatic decompensation in patients with pre-existing chronic liver dysfunction, often accompanied by extrahepatic organ failure and increased mortality in some cases [1–4]. Hepatitis B is one of the leading causes of chronic liver disease worldwide,[5,6] and patients with chronic hepatitis B are at high risk of developing ACLF under certain conditions.[6] The Republic of North Macedonia is classified as a country with an intermediate prevalence of chronic HBsAg carriage, with approximately 2–5% of the population being chronic HBsAg carriers [5]. Despite the vaccination program initiated in 2004, acute hepatitis B viral infection remains relatively common in North Macedonia[5]. Here, we present the case of a female patient with ACLF resulting from acute viral hepatitis B in the context of pre-existing metabolic-associated steatohepatitis (MASH).

Key words: Hepatitis B, ACLF, cirrhosis, MASH

INTRODUCTION
Acute-on-chronic liver failure (ACLF) is a severe form of acutely decompensated cirrhosis, associated with a 28-day mortality rate of 20% or higher (compared to 5% or less among patients with acutely decompensated cirrhosis without ACLF)[2]. ACLF is characterized by the functional failure of one or more of six major organ systems (liver, kidney, brain, coagulation, circulation, and respiration) and systemic inflammation, often triggered by acute precipitants (intrahepatic, extrahepatic, or both)[2,3]. There is a an East-West divide in the underlying chronic liver conditions and the causes of acute precipitating events in ACLF patients [1,2]. According to the Asia-Pacific Association for the Study of Liver (APASL), patients with chronic liver disease not amounting to cirrhosis, such as chronic hepatitis B or metabolic-associated steatohepatitis (MASH), can also present with ACLF after an acute insult [2]. APASL defines ACLF as an acute hepatic insult manifesting as jaundice and coagulopathy, complicated within four weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease[1,2]. In contrast, the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) include only patients with established cirrhosis as the underlying chronic liver disease in ACLF[1,2]. The Chinese Group on the Study of Severe Hepatitis B (COSSH) proposed a definition of ACLF specific to hepatitis B virus (HBV)-related chronic liver disease, which closely aligns with the European definition [2]. ACLF represents a complex interplay between hepatic insults and systemic inflammation, leading to significant morbidity and challenging therapeutic decisions. Various factors can trigger ACLF, including hepatic causes such as alcohol-related liver injury, drug-induced liver damage, viral hepatitis (A, B, C, D, E), hypoxic injury, and liver surgeries like TIPS (transjugular intrahepatic portosystemic shunt) placement. Extrahepatic triggers commonly include bacterial infections and major surgical procedures. Approximately 40–50% of patients with ACLF are identified as having an unrecognized precipitating event [4]. The connection between hepatitis B and ACLF is significant, as hepatitis B is one of the leading causes of chronic liver disease globally.[4] Patients with chronic hepatitis B, particularly those with cirrhosis, are at high risk of developing ACLF under certain conditions[3,6]. MASH, or metabolic-associated steatohepatitis, refers to the progression of non-alcoholic fatty liver disease

(NAFLD) to non-alcoholic steatohepatitis (NASH).[7,8] MASH is characterized by fatty liver disease accompanied by liver inflammation, driven by metabolic factors such as obesity, insulin resistance, and type 2 diabetes, with individuals over 40 years of age being at increased risk [7,8].

Here, we report the case of a female patient who developed ACLF as a result of acute viral hepatitis B, compounded by preexisting MASH.

CASE PRESENTATION

A 61-year-old female, a nonalcoholic with type 2 diabetes and hypertension, presented with a two-week history of nausea, vomiting, abdominal pain, and jaundice. She was admitted to the University Clinic for Infectious Diseases and Febrile Conditions in Skopje, a tertiary referral hospital. Laboratory tests revealed slightly elevated bilirubin and significantly elevated aminotransferase levels: Bilirubin 35 μmol/L (ref. 0–20 μmol/L), conjugated bilirubin 29 μmol/L (ref. 0–5 μmol/L), alanine aminotransferase (ALT) 482 U/L (ref. 10–52 U/L), aspartate aminotransferase (AST) 354 U/L (ref. 10–47 U/L), alkaline phosphatase (ALP) 164 U/L (ref. 38–126 U/L), gamma-glutamyl transferase (GGT) 199 U/L (ref. 8–78 U/L). Alpha-fetoprotein (AFP) levels were normal. Coagulation parameters, including thrombin time (TT), prothrombin time (PT), and activated partial thromboplastin time (aPTT), were within normal limits. Serological tests for viral hepatitis were positive for HBsAg, immunoglobulin M antibody to hepatitis B core antigen (anti-HBc M), and Hepatitis B e Ag (HBeAg). Test for hepatitis A (HAV), hepatitis C (HCV), and human immunodeficiency virus (HIV) were negative. Testing for hepatitis D virus (HDV) and hepatitis E virus (HEV) was unavailable. Autoimmune hepatitis (AIH) was excluded. HBV DNA PCR testing, performed in-house using the Abbott RealTime HBV assay (LLD 10 IU/mL), revealed an HBV DNA level of 4,000,000 IU/mL. Abdominal ultrasonography performed during the first week of hospitalization revealed liver steatosis. Patients' serum lipid levels were slightly elevated triglycerides 2.62 mmol/L (ref. ≤2 mmol/L), LDL cholesterol 3.8 mmol/L (ref. 2.2–3.7 mmol/L). The patient was started on antiviral therapy with nucleos(t)ide analogs (NUC) with Lamivudine, along with hepatoprotective therapy and ursodeoxycholic acid. By the third week of hospitalization, the patient developed hepatic decompensation, including ascites, worsening hyperbilirubinemia (262 μmol/L), inversion of aminotransferase levels (AST 655 U/L, ALT 448 U/L), hypoalbuminemia (28 g/L), prolonged aPTT (38.4 s; ref. 27.9–37.7 s) and elevated AFP (14.52 ng/mL; ref. 1.09–8.04 ng/mL). A CT scan showed a cirrhotic liver, splenomegaly, and peritoneal fluid in the perihepatic, subhepatic spaces, and lesser pelvis. Therapy was adjusted to include an aldosterone receptor antagonist, and five doses of human albumin were administered. By the fifth week of treatment, the patient showed significant improvement, including resolution of ascites, reduction in bilirubin levels (81 μmol/L), decreased aminotransferase levels (ALT 285 U/L, AST 230 U/L) and normalization of serum albumin. Upper GI endoscopy was performed revealing nonspecific duodenitis. The patient was discharged with compensated liver function and continued on antiviral therapy. At six months, seroconversion was observed with negative HBsAg and the appearance of anti-HBs antibodies. HBV DNA PCR showed <10 IU/mL. A FibroScan® revealed fibrosis stage F4 (39.4 kPa). At the nine-month follow-up, the patient remained well. Serology confirmed persistent negative HBsAg and positive anti-HBs antibodies. Aminotransferase levels and AFP were normal. A follow-up FibroScan® indicated fibrosis stage F4 (16 kPa). HBV DNA PCR testing was repeated, with results pending.

DISCUSSION

ACLF is distinct from decompensated cirrhosis due to its acute precipitating event and potential reversibility. Over a period of six months, with resolution of the acute event, our patient achieved complete recovery. According to MASH criteria, our patient had type 2 diabetes, hypertension, was over 40 years old with ultrasonographic evidence of steatohepatitis. In MASH, the liver is often in a state of chronic inflammation, making it susceptible to exacerbation of the inflammatory response by acute events, such as infections. [8] In this case, acute hepatitis B

virus infection triggered ACLF. Similar to our case are the findings in the study of Sun J.L. et al. [9] where hepatitis B virus is a trigger factor for developing ACLF. The choice of Lamivudine for antiviral therapy was made due to the patients' financial constraints, as it is the only NUC analog covered by the national health insurance fund in the Republic of North Macedonia.[5] In contrast, Tenofovir, which is considered a first-line therapy, is not subsidized and requires out-of-pocket payment by the patient. [5] The initiation of antiviral therapy reduced HBV DNA levels, alleviating the viral burden on the already compromised liver and providing it with a greater opportunity for recovery [9]. Anti-viral therapy is required for long-term prognosis and NUCs have been reported to improve the transplant-free survival rate in ACLF patients. [9] Similar findings were reported in the study by Li H. et al. [10], where 274 patients (55.1%) with ACLF triggered by hepatitis B infection showed improved outcomes following the introduction of causal therapy with NUCs compared to those who received no therapy. In our patient, antiviral therapy will continue until a definitive functional cure is confirmed, defined as sustained HBsAg loss on two separate occasions, at least six months apart, along with undetectable HBV DNA. However, the possibility of seroreversion under certain conditions remains an open question. Liver transplantation is often a life-saving procedure for ACLF patients, but it is challenging to perform in our setting. In the Republic of North Macedonia, liver transplantation is only performed using deceased donors, as living donor liver transplantation is not available. These procedures present significant challenges, including timing, organ allocation, and post-transplant outcomes as pointed out in the study of Belli S.L et al. [11]. In this case, the patient benefitted from vigilant management, timely initiation of antiviral therapy, robust supportive treatment, and her relatively good overall condition, all of which contributed significantly to the positive outcome.

CONCLUSION

Although ACLF is associated with high mortality, this case underscores the importance of promptly initiating specific therapy for the precipitating event, alongside supportive treatment, as both can be crucial for successful patient recovery. The disease course and improvement depend on the nature of the acute event and the stage of the underlying chronic liver disease. Our case highlights that even asymptomatic chronic liver diseases, such as MASH, carry a risk of developing ACLF when an acute precipitating event occurs, such as acute hepatitis B. In our patient, we achieved seroconversion marked by the loss of HBsAg and the presence of anti-HBs antibodies. However, the HBV DNA level, while below the lower limit of detection (LLD), remained quantifiable. Consequently, it is essential to continue antiviral therapy until HBV DNA levels are undetectable on two separate occasions to ensure a functional cure. Ongoing advancements in diagnostic techniques, treatment strategies, and transplant protocols will be pivotal in improving survival rates and quality of life for patients facing this complex clinical scenario. In conclusion, ACLF remains a challenging and potentially life-threatening condition that requires a comprehensive and multidisciplinary approach to care.

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ACUTE BACTERIAL MENINGITIS-CHALLENGES AND CONCLUSIONS

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ABSTRACT
Acute bacterial meningitis is an urgent condition characterized by significant morbidity and mortality. In the last decades, epidemiology of the most common etiologic agents as well as the age limit has changed significantly, with dominant involvement of the adult population and population at risk. Streptococcus pneumoniae remains the most common bacteria causing bacterial meningitis. The aim of this study is to observe the changes in the prevalence of etiologic agents and their dominance, the most commonly affected age groups, as well as comorbidities and complications in patients with acute bacterial meningitis treated at the University Clinic for Infectious Diseases in Skopje, R.N. Macedonia. In the last seven-year period, 194 patients with acute bacterial meningitis were treated. The etiologic agent in cerebrospinal fluid was confirmed in 94 (48.45%) patients, with the predominance of S. pneumoniae in 74 (78.72%). L. monocytogenes with 10 (10.63%) and N. meningitides with 6 (6.38%) were less represented. Male sex is dominant with 111 (57.21%) and older age groups as well. More than half of the patients, from the study, belonged to the at risk population with the highest percentage of them presenting with more than two comorbidities, as well as complications. In our study group, 41 (21.13%) of the patients died. Because of the substantial mortality and morbidity, it remains an urgent need to optimally deploy existing vaccines worldwide and develop new prevention strategies and treatment options.

Keywords: acute bacterial meningitis, S. Pneumoniae

INTRODUCTION
Acute bacterial meningitis (ABM) is above all and most importantly an urgent condition characterized by significant morbidity and mortality [1] According to statistical data of World Health Organization 2.5 million people are affected annualy, with 318 000 of them being deaths.[2,3] Despite the huge progress in diagnostic methods and treatment as well as implementation of national immunization programs, ABM is still a burdening infectious disease worldwide. It is one of the 10 most common causes of death, from infection. [4]
In the last three decades, epidemiology of ABM have changed significantly. Streptococcus pneumoniae (SP) remains the most common etiologic agent. H. Influenzae (HI) and N. Meningitides (NM) record a significant decline. It is primarily because of the introduction of new vaccines, the most common causing microorganisams developing ressistance to antibiotics, as well as the introduction of newer more modern treatments. [5,6]
To begin with the first studies in 1950 up until 1977, when the Nationwide surveillance system was established by WHO, we notice that the most dominant causes of ABM were HI, NM, SP, in more than 80% of cases. In 1990 the picture changes with the introduction of the vaccine against HIb, with it being replaced by SP as the most dominant cause. With that, the incidence of ABM in children significantly decreased. [2,5] Two important decisions, as well, for the involvement of the vacccines for SP and NM contribute to the decreasment of the incidence of bacterial meningitis as a whole.[7,8]

Diagnosis of bacterial meningitis is impossible without cerebrospinal fluid analysis. New diagnostic procedures like the polymerase chain reaction (PCR) enabled more efficient etiologic agent detection. Antibiotic treatment is empirical and it is based on the age of the patient and regional rate of antibiotics susceptibility of the most common agents. [4,9,10]

MATERIAL AND METHODS

The study was retrospective, clinical and carried out in the University Clinic for Infectious Diseases and Febrile conditions, Skopje, R.N. Macedonia. We analyzed 194 patients with ABM. On admission the following characteristics were observed: demographic features, confirmed etiologic agents and presented comorbidities and complications. Etiologic agents in cerebrospinal liquor (CSF) were confirmed by CSF culture and multiplex polymerase chain reaction (PCR). The data was statistically processed in the SPSS program for Windows 13,0. with suitable statistical methods. The value of $p<0,05$ was taken as significant, and the value of $p<0,01$, as highly significant.

RESULTS

We observe the data and statistics from our clinic beggining in 1975 up until 2024. In the analyzed period, we had treated around 2000 patients. Regarding the involvment of etiologic agents, several time periods were analyzed. First from 1975 to 2006 when 1371 patients were analyzed , with the dominance of: NM 48.3%, HI 21,5%, and SP 17.2%, second analysed period, from 2007 to 2012 with 201 patients when dominant confirmed etiologic agents were: SP 61.01%, NM 13.56%, and HI 13.56%, third from 2012 to 2016 with 212 patients analysed and dominance of: SP 43.1%, NM 23.5%, and L. monocytogenes(LM) 21.6%. Fourth and last analysed period from 2017 to 2024 we observed 194 patients and the dominant etiologic agents were: SP 78.7%, LM 10.6%, NM 6.4%. From this data we can notice that the trend of involvement is changed in the three most common causes of acute bacterial meningitis: NM, HI and SP, with the dominant representation of SP in the last three analyzed periods and its steady trend of growth of 17.2 to 78.7%. In the opposite, with NM we noticed a dramatic lowering trend of involvement of 48,3 to 6,4%b, and same with HI, from 21.5 to 2.1%.

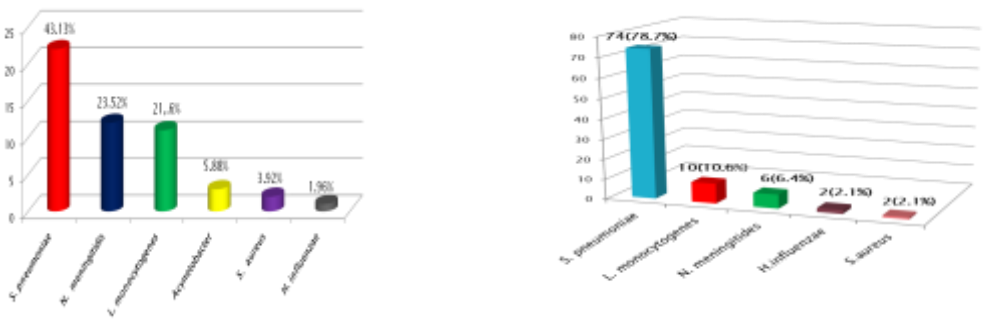
Table 1. Demographic characteristic of patients

Variable	N total (194)	%	P
Male	111	57.21	0.896
Female	83	42.79	
≥50 years	115	59.27	<0,01
≤50 years	79	40.7	
comorbidities	144	74.22	
≥ 2 comorbidities	100	69.4	<0,01
≤ 2 comorbidities	44	30.5	
complication	132	66.39	<0,01

$p<0,05$ significant, $p<0,01$ highly significant

The percentage of confirmed etiologic agents in acute bacterial meningitis in our patients increased dramatically with the introduction of the PCR method in 2016. When we analyzed and compared two consecutive periods, one from 2012 – 2016 and the other one from 2017-2024, we noticed dramatic increase in the percentage of confirmed etiologic agents in CSF, from 24% in the first analysed period (2012-2016), to nearly 50% in the second period (2017-2024), $p<0,01$. SP was dominant confirmed ethilogic agent. [Fig. 1]

Figure 1. Confirmed etiological agents in two different periods 2012-2016 and 2017-2024



In the last analyzed, seven- year period from January 2017 to October 2024, 194 patients with ABM were treated. The etiologic agent in CSF was confirmed in 94 (48.45%) patients, with the predominance of SP in 74 (78.72%). LM with 10 (10.63%) and NM with 6 (6.38%) were less represented. Demographic characteristic, comorbidities, and complications of our patients are shown in Table 1. [Table 1]

DISCUSION

The most dominant cause of ABM in adult population is SP. NM and HI are more rarely mentioned. LM mostly causes meningitis in immunocompromised individuals and patients above 65 years. [11] In the last three decades with the intorduction of the HIb and NM vaccines, as well as the pneumococcal vaccine implementation the etiology and epidemiology of acute bacterial meningitis has significantly changed. Hib which was a leading cause of ABM in the early childhood period, after the vaccine involvement is nearly eradicated, but however, it is still present in the adult population and immunocompromised population. This is present in R. N. Macedonia as well from 2005. [2,10]

A big role in the decreasement of cases of meningitis, mostly in children and teenagers, plays the implementation of the meningococcal vaccine in 90s. The implementation of the pneumococcal vaccine in the regular vaccination calendar at the beginging of the new era lowered the meningitis occurrence in children as well, however SP remains the leading cause for ABM in adult population especially after 50 years of age and population at risk. All of the above resulted in a dramatic reduction of the incidence of bacterial meningitis in children, and currently the majority of patients are adults. [4,5,10]

Etiologic agent confirmation in bacterial meningitis is the key for treatment. Newer diagnostic technologies like PCR, dramatically increased the percentage of conformied etiologic agents in CSF and acompanied for a timely etiologic treatment. However it has to be outlined that cerebrospinal fluid culture remains to be the gold standard for etiologic diagnosis in ABM. [9,10] When we analised our patients with bacterial meningitis in two periods one from 2012 to 2016 and the other one from 2017 to 2024 we noticed increasing in percentage of confirmed etiological agents of bacterial meningitis from 24 to nearly 50 ($p<0.01$), and we confirmed the sovereignty of the PCR method as a confirmatory technique for identification of ethulogic agents. Most studies confirmed high sensitivity and specificity of these method in etiological diagnosis of ABM. [10]

ABM is a condition in which in spite of timely diagnosis and treatment many complications occur. Most commonly reffered complications are systemic such as sepsis and pneumonia as well as neurologic such as subdural empyema, brain abscesses and cerebritis, hydrocephalus and many other neurologic outbursts. In our stady the most common complications were sepsis and bronchopneumonia. We also had patients with subdural empyema, cerebral abscesses and hydrocephalus. More than 70 percentage of our patients had more than one comorbidities and severe clinical course. The mortality rate in bacterial meningitis even after prompt treatment implementation remains high, especially in older age population and patients with underlying comorbidities. [6,7,10]

CONCLUSION

New technologies such as the multiplex PCR method, allow us to have higher percentage of confirmed ethiologic agents of bacterial meningitis. Vaccination introduce us in the new era of dominance of new ethiologic agents and should be recommended not only in children but in adults as well, particulary the ones that have a history or predisposition for meningitis. In the years coming, we will confront older patients with less typical clinical picture and many serious

complications. Even though the treatment of bacterial meningitis primarily affects infectious diseases experts, the new era makes it a multidisciplinary disease.

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WOUND COMPLICATION AFTER VENASEAL CLOSURE OF INCOMPETENT PERFORATOR VEINS

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ABSTRACT

Chronic Venous Insufficiency (CVI) and venous ulceration is a common health problem causing significant patient morbidity. Apart from the chronic physical and psychological disability caused to the individual, it also results in an enormous economic burden to the health care administration. Global prevalence rates of CVI are variable but may be as high as 40% among females and 17% among males [1]. The new minimally-invasive techniques for treating CVI are steadily acquiring dominance, due to their simplicity, efficiency and low complication rate.[2] Venaseal closure procedure is a relatively new technique that involves intravenous glue application via catheter for creating permanent seal in the vein.[3] Its simplicity and efficiency nas made it a very attractive choice for the treating physicians, as well as the patients. [3, 4] However, multiple studies have reported few different types of adverse reactions cause by the adhesive n-butyl cyano-acrylate (NBCA) [6-8]. We are presenting the case of a 44-year-old male with severe postprocedural granulomatous reaction after Venaseal closure of bilateral crural perforator veins, leading to a necessary surgical intervention for removal of the material and prolonged wound treatment.

INTRODUCTION

Superficial venous incompetence (SVI) is the most common cause of lower extremity superficial venous reflux and varicose veins; while incompetent perforator veins (PVs) are the most common cause of recurrent varicose veins after treatment, often unrecognized. Perforator vein insufficiency can result in pain, skin changes, and skin ulcers, and often merits intervention. Minimally invasive treatments have replaced traditional surgical treatments for incompetent perforator veins. One of those treatments, which is increasingly gaining popularity due to its simplicity, short procedural time, avoidance of tumescent anesthesia and high efficiency is the Venaseal closure procedure. It involves transcatheter intravenous glue application via punction of the target vein, which polymerizes in a matter of seconds, leading to a permanent firm intraluminal seal formation. Since there is no thermal reaction, there is no risk of thermal skin or nerve injury. The malleable catheters of different sizes allow for application into any target vein, including perforator veins, and the very short polymerization time significantly reduces the risk of DVT. Presented in this manner, it appears as a procedure of choice for treating perforator veins. Nevertheless, there is a foreign material involved that creates a permanent fixture in the vein, which can be felt under the skin, deformed or broken into fragments in mobiles areas, such as the knee, as well as provoke a hypersensitivity reaction as a foreign body in certain individuals.

Case description

Forty-four-year-old male patient, presenting with bilateral skin and subcutaneous tissue inflammation with severe erythema, edema, induration and ulcerations of the skin on both calves with purulent exudate, was admitted in our surgical department. The patient was referred by his

treating physician, who performed the Venaseal procedure in this patient of the PVs bilaterally, 2 months priorly and noted the gradual skin changes in the following weeks. (view Figure 1-3)

The laboratory findings were Hemoglobin 146g/l, RBC 5.7T/l, WBC 11.8 G/l, CRP 56 mg/dl. Blood glucose 7.2mmol/l, TC 5.2 mmol/l, LDL 4.1 mmol/l, HDL 1.1 mmol/l. The patient had amnestic data of insulin tolerance, without clinically confirmed diabetes. The ultrasound of the lower extremities revealed subcutaneous edema of the calves, hyperdense formations in the medial perforator veins of the calves, consistent with the Venaseal adhesive, surrounded by hypoechogenic zones with heterogenic center and hyperdense lining, consistent with abscess formations in the subcutaneous and dermal tissue. The deep fascia and underlying muscles seemed intact. The distal portion of the GSV bilaterally was found thrombotic, non-compressible, with no flow. The diagnose of distal superficial thrombophlebitis with cellulitis was confirmed and surgical excision, debridement and drainage, was indicated. The excised material was sent for pathohistological examination. The findings were of a foreign body- type reaction. (view Figure 4, 5)

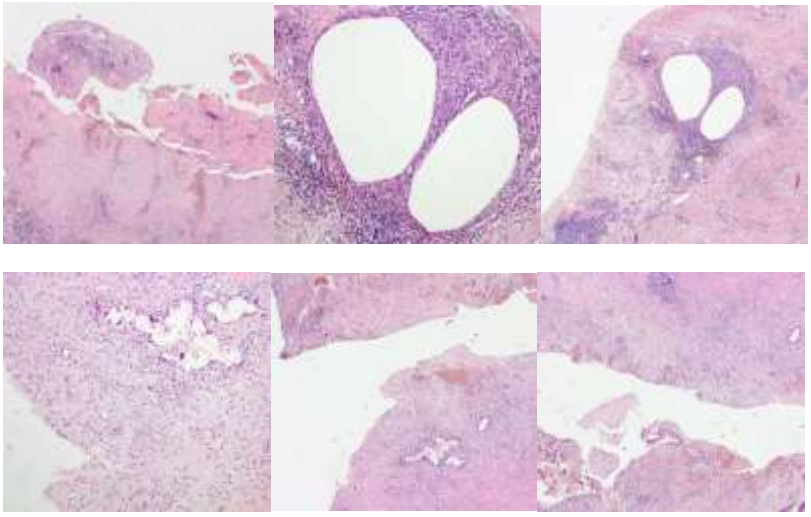

Figure 1

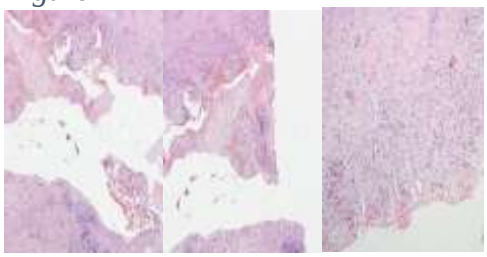

Figure 2

Figures 4 and 5 tissue cuts showing foreign body inflammatory reaction

The patient was discharged the

next day, with oral wide-spectrum antibiotic for 10 days. The subcutaneous drains were removed after 7 days. Regular wound dressing was performed ambulatory each 3 days, until complete healing.

DISCUSSION

While Venaseal closure of perforating veins is technically simple and effective solution for permanent closure of incompetent PVs, with a very low risk of DVT, there is still to be considered the fact of the foreign-body effect of the undegradable adhesive, as well as the reaction of hypersensitivity against its compounds. We have performed this procedure ourselves in our center, so far without undesirable outcomes, but we acknowledge the real possibility of such adverse effects, with the serious consequences for the patients, both from medical and financial aspect. All of the available adhesives on the medical market, are so far non-biodegradable, remaining very long time, if not a lifetime, as a foreign material in the body. T. Further-more, in the mobile areas of the body, such as the popliteal area and around the ankle, the firm permanent subcutaneous fixture created by the glue, has a real possibility of breakage and fragmentation that could lead to puncture damage to the surrounding tissue at movement. There is also the question if this procedure is suitable for diabetic patients, where we have the advantage of avoiding thermal tissue damage, which is a real benefit in these patients, but with the possibility of implanting a bacterium under a firm seal of adhesive in these immunocompromised patients.

CONCLUSION

Venaseal closure procedure for incompetent superficial veins is one of the modern minimally invasive treatments, delivering well known advantages as a procedure. However, we believe that further evidence on its midterm-long term safety is needed, provided by large scale randomized trials, before it can be adopted as procedure of choice for the general patient population.

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IN PATIENTS WITH CHRONIC HEPATITIS C VIRUS INFECTION IN THE REPUBLIC OF NORTH MACEDONIA

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ABSTRACT

Background/Purpose: Chronic hepatitis C (CHC) infection remains a significant global health challenge, affecting approximately 71 million people worldwide. Until recently, the standard of care for chronic hepatitis C involved a combination of pegylated interferon and ribavirin (PEG-IFN/RBV). However, the advent of direct-acting antiviral (DAA) agents has revolutionized the management of CHC, making it the first ever curable viral infection. **Aim:** To retrospectively analyze the efficacy of PEG-IFN/RBV combination therapy versus DAA regimens in patients with CHC in the Republic of North Macedonia. **Material/Methods:** This single-center retrospective study included 686 patients with CHC: 404 (58.9%) received PEG-IFN/RBV, and 282 (41.1%) received DAAs, including combinations of paritaprevir/ritonavir, ombitasvir, sofosbuvir, ledipasvir, velpatasvir, glecaprevir, pibrentasvir, elbasvir, grazoprevir with or without ribavirin. **Results:** The mean age of PEG-IFN/RBV patients was 34.4 ± 9.69 years, with a sustained virologic response (SVR) rate of 75.5%. Therapy was discontinued in 72 (18%) due to serious adverse effects. Among DAA-treated patients, the mean age was 47.17 ± 13.78 years, with an SVR rate of 97.3%. Adverse effects were minimal, and therapy was discontinued in 13 (4.6%) patients due to pregnancy, patient choice, or incomplete data due to COVID-19. The Pearson Chi-Square test for treatment outcomes (DAAs vs. PEG-IFN/RBV) showed a statistically significant difference in favor of DAAs therapy ($p < 0.001$). **Conclusion:** DAAs are highly effective and well-tolerated, offering significantly improved outcomes compared to PEG-IFN/RBV.

Keywords: chronic hepatitis C, pegylated interferon, ribavirin, direct acting antivirals

INTRODUCTION

Chronic hepatitis C virus (HCV) infection remains a global health issue, affecting over 71 million people worldwide, [1-3] with 80-85% of cases progressing to chronic disease. This progression increases the risk of cirrhosis and hepatocellular carcinoma (HCC). [4] In 2016, the World Health Organization (WHO) initiated a global health strategy aiming to eliminate viral hepatitis as a public health threat by 2030. Goals include reducing HCV incidence and prevalence by 90%, treating 80% of eligible patients, and reducing HCV-related mortality by 65%.[5] Sustained virologic response (SVR), the absence of detectable HCV RNA 12–24 weeks post-treatment, remains the primary indicator of treatment success.[6] Initially, pegylated interferon (PEG-IFN) and ribavirin (RBV) were standard HCV therapies but were limited by significant adverse effects.[7,8]The development of direct-acting antitivirals (DAAs), has revolutionized HCV treatment. DAAs The advent of direct-acting antivirals (DAAs) revolutionized treatment, achieving SVR rates exceeding 90% with improved tolerability. [1-3,5,9,10] In North Macedonia, chronic hepatitis C (CHC) prevalence is estimated at 1%. This study evaluates the efficacy of PEG-IFN/RBV and DAA regimens in CHC patients in North Macedonia.

MATERIAL AND METHODS

This retrospective, single-center study analyzed 686 CHC patients treated at the University Clinic for Infectious Diseases in North Macedonia. HCV antibody detection and RNA quantification were performed using Abbott Architect systems. Genotyping and liver fibrosis

assessments (via FibroScan or biopsy) were conducted prior to treatment. Patient data included demographics, comorbidities, previous treatments for HCV infection, and laboratory results. From 2003 to 2015, patients received PEG-IFN and weight-based RBV (24 weeks for genotypes 2 and 3; 48 weeks for genotypes 1 and 4). Since 2015, DAA regimens, guided by European Association for the Study of the Liver (EASL) recommendations, have been utilized. The primary endpoint was SVR 12/24 weeks post-treatment defined as negative HCV RNA for both patients' groups.

Statistical Analysis: Quantitative variables are expressed as mean and standard deviation and were compared using the Student's t-test. Qualitative variables are expressed as percentages and were compared using the Chi-square test. Differences were considered significant when $p < 0.05$. SPSS version 23 (Chicago, IL, USA) was used for all calculations.

RESULTS

Of 686 patients, 404 (58.9%) received PEG-IFN/RBV therapy. The patient genotypes consisted of 179 (44.3%) with genotype 1, 206 (51%) with genotype 3, 12 (2.9%) with genotype 4, 6 (1.5%) with genotype 2, and 1 (0.2%) patient with a co-infection of genotypes 1 and 2. The mean age was 34.4 ± 9.7 years. SVR24 was achieved in 305 patients (75.5%), with therapeutic failure in 99 (24.5%) and treatment discontinuation in 72 (18%) due to serious adverse events (SAEs). Younger patients were more likely to achieve SVR (mean age 33.1 ± 9.2 vs. 36.2 ± 10.1 years, $p = 0.02$). In the DAA group (282 patients), 250 (88.6%) were genotyped, 153 (61.2%) had genotype 1, 46 (18.4%) had genotype 3, 48 (19.2%) had genotype 4, 2 (0.8%) had genotype 2, and 1 (0.4%) had a co-infection of genotypes 1 and 3. Regimens included sofosbuvir/velpatasvir (28.7%), sofosbuvir/ledipasvir (17.7%), and 3D combinations (37.9%), 23 (8.1%) with elbasvir/grazoprevir, 13 (4.6%) with sofosbuvir/daclatasvir, and 8 (2.3%) with the glecaprevir/pibrentasvir combination. Mean age was 47.2 ± 13.8 years. SVR12/24 was achieved in 249 patients (97.3%), with therapeutic failure in 7 (2.8%) and discontinuation in 13 (4.6%), primarily for non-medical reasons. No significant age-related differences in SVR were observed in the DAA group ($p = 0.07$). When comparing outcomes, DAAs had significantly higher SVR rates than PEG-IFN/RBV ($p < 0.001$).

DISCUSSION

This study provides valuable insights into the treatment outcomes of patients with chronic hepatitis C (CHC) over a two-decade period. A total of 686 patients were treated using two distinct therapeutic approaches: pegylated interferon and ribavirin (PEG-IFN/RBV) and direct-acting antivirals (DAAs). The findings reveal significant differences in efficacy, safety, and tolerability between these treatment modalities. Of the 404 patients treated with PEG-IFN/RBV, the sustained virologic response at 24 weeks (SVR24) was 75.5%, indicating a satisfactory cure rate. This SVR in our patient cohort treated with PEG-IFN/RBV was higher than reported in other studies. [10,11] Previous studies have shown that among genotype 1 or 4 patients with a rapid virologic response (RVR), the likelihood of SVR is approximately 80%-90% when treated for 48 weeks. [12,13] Conversely, patients with genotype 2 or 3 are more susceptible to PEG-IFN/RBV treatment, with more than 80% achieving SVR in a 24-week treatment course. [14,15] However, more recent studies have identified genotype 3 as a difficult-to-treat genotype. [16] The higher SVR observed in our cohort could be attributed to better treatment adherence compared to other studies. Therapeutic failure occurred in 24.5% of patients, while 18% discontinued therapy due to serious adverse events (SAEs). A significant association was observed between younger age and a higher likelihood of achieving SVR, with younger patients demonstrating better outcomes. Interestingly, this finding diverges from previous studies, which suggest that older age is a factor associated with reduced responsiveness to PEG-IFN/RBV therapy in our study. [17,18] Conversely, among the 282 patients treated with DAAs, the overall SVR rate was 97.3%, with therapeutic failure observed in only 2.8% of cases. These findings align closely with those of other studies. [1-3,19,20] Importantly, the tolerability of DAAs in our

cohort was markedly superior to that of PEG-IFN/RBV, as no serious side effects required therapy disruption or modification. This finding about the safety of DAAs in our cohort is consistent with the one found in the literature. [1-3,21] Therapy discontinuation occurred in only 4.6% of cases, primarily due to non-medical reasons such as pregnancy, loss to follow-up, or voluntary withdrawal. DAA therapy demonstrated consistent efficacy across age groups, with no statistically significant difference in SVR rates between younger and older patients. This indicates that DAAs are highly effective regardless of patient age, further supporting their role as the preferred treatment option for CHC. When comparing the two treatment modalities, patients treated with DAAs had a significantly higher likelihood of achieving SVR than those treated with PEG-IFN/RBV. This finding underscores the superiority of DAAs in terms of efficacy and safety. The study has several limitations, including its retrospective design and the potential loss of follow-up data, particularly during the COVID-19 pandemic. Additionally, the high cost of DAA therapy remains a significant barrier to universal access despite its clear clinical advantages.

CONCLUSION

This study underscores the transformative impact of DAAs on CHC management. While PEG-IFN/RBV played a crucial historical role, DAAs now set the standard for CHC treatment. Addressing access barriers to DAAs and ensuring comprehensive follow-up are essential to achieving global HCV elimination goals. Cost-effectiveness studies should evaluate DAAs' potential to reduce complications, hospitalizations, and mortality. In conclusion, DAAs represent a milestone in CHC management, offering unprecedented efficacy and safety.

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INFECTIONS IN CANCER PATIENTS RECEIVING RADIOTHERAPY

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ABSTRACT

This review explores the relationship between radiotherapy and infection risk in patients with cancer and examines the mechanisms of immune suppression, types of infections, risk factors, and prevention strategies. Radiotherapy induces immunosuppression by reducing lymphocyte populations, damaging skin and mucosal barriers, and increasing susceptibility to bacterial, fungal, and viral infections. Risk factors include radiation area, treatment volume, nutritional status, smoking habits, and pre-existing conditions. Concurrent chemoradiotherapy also increases the risk of infection. Prevention strategies included prophylactic antimicrobials, maintenance of oral hygiene, and nutritional support. Effective management of infection risk during radiotherapy requires a multifaceted approach, including vigilant monitoring, prophylactic measures, and prompt treatment. As cancer treatments evolve with the integration of immunotherapy and targeted therapies, ongoing research is necessary to develop tailored infection prevention and management strategies to ensure optimal patient outcomes, while minimizing complications.

INTRODUCTION

Radiotherapy, crucial in cancer treatment, adversely affects the immune system and natural barriers. This review explores the complex relationship between radiotherapy and infection risk, highlighting immunosuppression and damage to skin and mucosal barriers, which increase infection susceptibility and potentially impact treatment efficacy. Risk factors include radiation area, dose, irradiated volume, and patient-specific factors. The review covers radiotherapy's effects on the immune system, natural barriers, common infections, and current prevention and management strategies. It addresses bacterial, fungal, and viral pathogens, focusing on conditions like skin cellulitis, pneumonia, urinary tract infections, and opportunistic infections. Additionally, it discusses integrating immunotherapy and targeted therapies and their impact on infection risk, emphasizing preventive measures and a multidisciplinary approach to patient care.

REVIEW RESULTS

1. Common causes of infections during radiotherapy

1. Immune suppression

Radiotherapy induces both immunosuppressive and immunostimulatory effects, which influence the efficacy of cancer treatment. It primarily reduces lymphocyte populations, leading to lymphopenia due to direct cytotoxic effects and alteration of the bone marrow microenvironment. Lymphocyte radiosensitivity varies among subpopulations, with B cells being more sensitive than T cells and NK cells showing the highest resistance. Neutrophils are also affected by radiotherapy and play a significant role in cancer immune response. Advanced techniques such as IMRT and VMAT aim to minimize bone marrow exposure, reduce hematologic toxicity, and preserve immune function [1]. However, the effects of radiotherapy on neutrophils are complex and dose dependent. Radiotherapy can also reprogram neutrophils and induce functional changes. The balance between promoting antitumor immunity and inducing immunosuppression is influenced by factors such as radiation dose, fractionation, and treatment timing [2]

2. Damage to Skin and Mucosa

Mucositis is a common complication of radiotherapy and is characterized by direct DNA damage in epithelial cells, leading to cell death and generation of reactive oxygen species (ROS). This

triggers inflammation, weakening the mucosal barrier and forming painful ulcers. Tissue repair attempts occur during healing, but persistent inflammation may delay recovery and increase infection risk [3]. Radiation-induced dermatitis affects up to 95% of radiotherapy patients, ranging from mild erythema to severe ulceration. High doses can cause moist desquamation and skin necrosis, increasing infection risk. Effective management, including barrier creams and moisturizers, is crucial for mitigating skin reactions and maintaining skin integrity [4].

3. Concurrent chemoradiotherapy

The combination of radiotherapy and chemotherapy enhances efficacy but increases infection risk due to immunosuppression. Radiotherapy causes localized skin damage, while chemotherapy induces systemic immunosuppression with higher febrile neutropenia risk in patients receiving both treatments. These effects lead to increased skin and systemic infections. [5].

4. Devices (Catheters and Ports)

Procedures that compromise the natural barriers between internal and external environments increase the risk of infection by allowing microorganism entry. Proper aseptic practices are crucial for mitigating these risks, preventing contamination, and protecting patients and healthcare workers from pathogens [6].

2. Types of Infections During Radiotherapy

Patients undergoing radiotherapy face increased infection risks due to immunosuppression and damage to the skin and mucosal barriers. Common infections include bacterial, fungal, and viral types. Bacterial infections such as cellulitis and abscesses are prevalent, especially in irradiated areas. Thoracic radiation patients are at a higher risk of pneumonia, particularly those with pre-existing lung conditions or immunocompromised patients. Pelvic radiation can lead to urinary tract infections due to bladder irritation. Fungal infections, mainly Candida species, are significant in head and neck radiation patients due to mucosal damage. Viral infections, particularly reactivation of Herpes Simplex Virus and Herpes Zoster, are notable due to radiation's immunosuppressive effects [7]

3. Risk Factors for Infections

The risk factors for infections during radiotherapy are multifaceted and can significantly impact patient outcomes. These factors included the area of radiation, dose and irradiated volume, nutritional status, and pre-existing conditions. The anatomical area that receives radiation plays a crucial role in determining the type of infection that may arise. For instance, pelvic radiation is associated with a higher incidence of urinary tract infections (UTIs) owing to its direct impact on the bladder and surrounding tissues. Thoracic radiation can lead to pneumonia, particularly in patients with pre-existing lung conditions or in immunocompromised patients. Head and neck (HN) radiation patients are at increased risk for aspiration pneumonia due to impaired swallowing. Higher doses of radiation and larger treatment volumes are directly correlated with increased immunosuppression. Nutritional status is critical for immune function, with malnourished patients showing weaker immune responses. Pre-existing conditions, such as diabetes, chronic lung diseases, or ongoing infections, further increase the risk of developing infections during radiotherapy [8]

4. Prevention and management

Prevention and management of infections associated with radiotherapy are critical for ensuring patient safety and treatment efficacy. Prophylactic measures in severely immunosuppressed patients may include antibiotic or antifungal medications to reduce the risk of infection. Patients undergoing head and neck radiation are particularly susceptible to candidiasis, due to compromised mucosal barriers and reduced salivary flow. Prophylactic antifungal therapy can be beneficial in preventing invasive fungal infections, especially in neutropenic patients [10]. Antiviral prophylaxis against Herpes Simplex Virus (HSV) and Varicella-Zoster Virus (VZV) may be necessary in immunocompromised individuals, as reactivation of these viruses is common in patients undergoing chemotherapy and radiotherapy [11].

Proper skin care during radiotherapy, involving patient education on gentle cleansing and regular moisturizing, is essential for maintaining skin integrity and reducing infection risk [11]. Dental evaluation prior to radiotherapy, especially for head and neck treatments, coupled with diligent oral hygiene including alcohol-free mouth rinses, is crucial for preventing radiation-induced oral complications such as candidiasis [12].

The use of granulocyte colony-stimulating factor (G-CSF) can help patients undergoing combined chemotherapy and radiotherapy by stimulating neutrophil production. Additionally, tailored nutritional support is crucial for preventing malnutrition-related susceptibility to infections [15].

Prompt treatment with early use of antibiotics, antivirals, or antifungals upon the first signs of infection can significantly reduce the risk of severe complications [13].

5. What are the next and "New" treatment strategies in oncology?

The future landscape of cancer treatment is evolving with the integration of targeted therapy, immunotherapy, and their combination with radiotherapy. Immune checkpoint inhibitors, enhance antitumor responses, but can lead to immune-related adverse events (IrAEs). Corticosteroids, while effective in treating irAEs, can compromise the immune response and increase opportunistic infection risk [14].

CONCLUSION

Infections are still a significant concern for patients with cancer undergoing treatment, affecting treatment efficacy and patient outcomes. Healthcare providers must implement a multifaceted approach including regular monitoring, prevention strategies, early detection, and aggressive treatment protocols. Coordinated efforts from a multidisciplinary team are crucial for comprehensive care and optimal prognosis. As innovative therapies such as immune checkpoint inhibitors and targeted therapies have become more prevalent, ongoing research and clinical vigilance are necessary to develop effective strategies for infection prevention and management.

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CLINICAL AND LABORATORY MONITORING OF THE EFFECT OF ALBENDAZOLE THERAPY IN DIFFERENT FORMS OF TOXOCARIASIS

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ABSTRACT: Toxocariasis is a zoonotic parasitosis. The **purpose** of the study is to monitor the effect of Albendazole therapy by analysing clinical and laboratory indicators before, during and after its administration. **Material/Methods:** The subjects of the study were 34 children and 38 adults, with confirmed toxocara infection. Clinical symptoms and changes in laboratory parameters were monitored before and after treatment with Albendazole, supplemented with antihistamines. **Results:** The clinical forms in children and adults were stratified based on disease's symptoms. Etiological treatment reduced the clinical signs and improved laboratory parameters within the first month after its application. The addition of antihistamine therapy is essential to avoid the exacerbation of symptoms. Control tests after 6 months exhibit a noticeable decline in Toxocara antibodies in ELISA. **Conclusion:** Albendazole is an effective treatment for the various clinical forms of confirmed toxocariasis, and the monitoring of the symptomology and laboratory findings confirms its role as a first-choice therapy.

Keywords: Albendazole, anthelmintic treatment, ELISA, toxocariasis, Western blot

INTRODUCTION

Toxocariasis is a worldwide distributed zoonosis that is still insufficiently researched [1]. Human toxocariasis is caused by the larvae of nematodes–*Toxocara canis* and *T. cati*. Currently, toxocariasis is classified into four clinical forms.Visceral toxocariasis (VLM), Common or covert (CT), ocular toxocariasis (OT) and neurotoxocariasis (NT) [2,3,4]. Due to the self-limiting nature of the CT, the necessity for treatment of this tissue helminthiasis remains a subject of debate. [5]. The administration of systemic etiological therapy is required in VLM, OT and NT. Albendazole is considered one of the appropriate choices for the treatment. Other recommended medications include mebendazole, thiabendazole, diethylcarbamazine and ivermectine but none are registered for use in the Republic of Bulgaria at the time of our research. Albendazole is administered orally at a daily dose of 10-15 mg/kg b.w. divided into 2 doses (BID), taken with fatty food to increase its bioavailability. Courses of therapy with varying duration, ranging from 5 to 14 days, are recommended [5].
The purpose of the study was to monitor the effect of Albendazole therapy by analysing clinical and laboratory indicators before, during and after its administration in patients with confirmed toxocariasis.

MATERIALS AND METHODS:

The subjects of this research were Toxocara IgG seropositive patients, part of a widespread epidemiological study to establish the seroprevalence in Northeastern Bulgaria [6]. The diagnosis was confirmed, by two-step testing for the specific Toxocara IgG antibodies [3]. The patients were screened via a commercial enzyme-linked immunosorbent assay (ELISA) kit - Ridascreen–Biopharm. The positive and borderline sera were verified with Western blot (LD BIO). The patients with positive result on both tests were treated with Albendazole and invited to participate in the current study. From 130 confirmed cases 72 (55,4%) patients consented and were monitored on the first and sixth month after the etiological therapy. The duration of the Albendazole treatment (10 mg/kg body weigh) was tailored to each case considering, age and clinical manifestation. Additional antihistamine therapy (in standard doses) was prescribed from

the first day of the etiological treatment. The clinical symptoms were recorded and several laboratory parameters (CBC, differential count, and total IgE) were examined before, during and one and six months after the treatment completion.
The data was collected in comprehensive tables and analysed with the Analysis ToolPak of Excel 365. The results were stratified by age and clinical form, and reported as fractions.

ETHICAL APPROVAL: The design and protocol of the study were endorsed by the Commission for Ethics of Research of Medical University Varna (Protocol No.81/28.02.2019).

RESULTS

Seventy-two patients accepted to actively participate in this study and were monitored before, during and on the first and sixth month after the etiological therapy. Thirty-four (47,2%) were children up to 18 years and 38 (53,8%) were adults aging between 19 to 88 years.
Based on accepted criteria of Pawlowski [2] the 34 seropositive children were classified in all four clinical forms. VLM was determined in 22 (64.7%) patients. In 20 the infection was accompanied by iron deficiency anaemia, respiratory disorders, enlarged lymph nodes, anorexia, geophagia and increased irritability. In two children, asthma and atopy were diagnosed. NT was established in one girl with epilepsy, and one boy with chorioretinitis was diagnosed with OT. CT was confirmed in ten children (29.4%), with eosinophilia < 10% and the total IgE <150 IU/ml. Five of those had a history of dermatitis and five – with allergies.
Upon the start of therapy CBC, differential blood count and total IgE were evaluated. All children had increased eosinophils ranging from 7 to 34%, with 23 (67.6%) registering values above 10%. In all, except for the girl with epilepsy, elevated total IgE was observed. In 18 (52.9%) the levels exceeded 200 IU/ml. In 21 (61.76%) anaemia and leucocytosis (13-18.10^9/l) were registered. Etiological therapy with Albendazole was prescribed to all, with a daily dose of 10 mg/ kg body weight, BID, with food. Due to the enhanced reaction of the immune system and possibility for future migration, the treatment is insufficient decided on a 14-day course of therapy. On the third day during the treatment, the number of eosinophils increased in all. In two children whose parents neglected the simultaneous antiallergic treatment, the clinical signs exacerbated with urticarial rash, malaise and fever. Those symptoms quickly subsided after inclusion of standard doses of antihistamines.
The control tests at the first month after treatment showed normal eosinophils levels 33 (97.1%) of the patients. Only in the case with OLM, the elevated eosinophils persisted. Return of Hb values near the reference limit was discovered in all 21 (61.8%) children with initial anaemia. In all, the leukocytes reached the standard range. Enlarged lymph nodes (in five children) and abdominal discomfort (in four) were the most common remaining symptoms.
At the 6th month after the treatment, the levels of the specific *Toxocara* IgG (ELISA) decreased in all patients, and all monitored laboratory parameters returned to healthy ranges in 30 (88.2%). The exception was the child with OT, in whom the eosinophilia persisted. In 3 children with concomitant onco-hematological diagnosis deviations in the blood parameters were registered, but those could be attributed to the lack of remission in their primary condition. Progressive resolution of the clinical symptoms was observed in all children, with lymphadenopathy persisting the longest.
Based on the same diagnostic criteria [2,3], only tree clinical forms were detected in the 38 seropositive adults that participated in the study. VLM was diagnosed in 17 individuals (44.7%), based on the presence of systemic allergy, respiratory or digestive symptoms and a total IgE levels over 100 IU/ml. NT was established in five adults (13.2%) with epilepsy and/or cognitive disorders. Sixteen (42.1%) of the adults were classified as having CT due to the non-specific general symptoms - malaise, headache, sleep and behavioural disturbances, rashes and itching or remain asymptomatic. In sync with the literature no OT was registered in adults [1,2,3].
The initial examination before treatment revealed mild eosinophilia of 7-10% in 12 (31.6%) adults accompanied by unspecified respiratory allergy. In 20 (52.6%), the total IgE was elevated

above 100 IU/ml. Sixteen of those showed various manifestations of systemic allergy, respiratory or digestive symptoms, with dermatitis being the major symptom in three. One patient had a diagnosis for epilepsy. No other deviations in the laboratory findings were recorded in the adults with confirmed *Toxocara* infection. In all individuals with VLM and NT, we appointed a treatment course of Albendazole for 14 days. A shorter course of 7 days was advised for the patients with CT, with supplemental therapy with antiallergic.

Similarly, to the therapeutic response in children, an increase in blood eosinophils was observed in all adults during the first days of the treatment course. Three patients with VLM who have not taken antihistamines described exacerbation or re-emergence of the allergic symptoms. The laboratory findings on the 1-st month after treatment showed decline of the eosinophilia and IgE to normal levels in the majority of the tested adults. Only in seven cases (18.4%) with long-term history of systemic allergy, the total IgE levels remained above 100 IU/ml at that point, but with reduced values compared to the initial numbers.

At the 6th month, in 37 (97.4 %) of the adults, the positive indices in ELISA Toxocara IgG decreased and the monitored laboratory parameters returned to normal.

In all participating adults, progressive resolution of the clinical symptoms was observed within 2-3-4 months, terminating their long-term history of allergic manifestations of the respiratory tract, skin, and digestive tract.

DISCUSSION

Toxocara infection in humans is still one of the unfamiliar and unrecognisable parasitosis. Studies show substantial seroprevalence rates in Bulgaria (> 18%) Europe (~14%) and the rest of the world [1,6]. There is need for increased awareness among the medics about the diversity of the clinical symptoms and the laboratory findings in the diseased p. This will ensure timely etiological testing and confirmation of the diagnosis with the two tests approach Comprehensive anamnesis, thorough physical, laboratory and imaging examinations are essential to confirm the clinical form. Albendazole is one of the most effective anthelmintic agents with specific effect against nematode infections. The results of our prolong follow up confirms its efficacy against *Toxocara* infection. Both children and adults showed improvement of the clinical findings and laboratory parameters and full recovery was observed in most at the 6-th month.We can recommend two-week courses of therapy with Albendazole to be appointed in all cases of VLM, OT and NT. Shorter therapies can be effective in adults with asymptomatic CT, but close monitoring of the laboratory indicators is required.

CONCLUSION

Our study supports the use of Albendazole (10 mg/kg body weight, BID) as a first-choice therapy for human toxocariasis. The methodical elicitation of the medical condition is essential for the individual assessment of the clinical form and quantification of the treatment duration in children and adults. Another issue that supports the need for observation is the immune reaction against the dying nematode larvae in the tissues. This unavoidable complication should be anticipated, and patients need to be informed in advance for its possibility. Furthermore, the described reactions require mandatory inclusion of antihistamine medications from the first day of the etiological therapy.

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HAEMOPHILUS INFLUENZAE MENINGITIS IN A ADULT: A RARE ETIOLOGY OF MENINGITIS – CASE REPORT

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ABSTRACT
Haemophilus influenzae is a gram-negative bacterium that commonly causes meningitis in children, rarely in adults, particularly in immunocompetent individuals. Most adult cases occur in those with predisposing conditions such as chronic diseases and immunosuppression. We describe a case of meningitis caused by *Haemophilus influenzae* in an immunocompetent 66-year-old male. The patient received treatment with ceftriaxone and he was discharged in good clinical condition, with no neurological deficits. *Haemophilus influenzae* meningitis in adults underscores the importance of considering this rare pathogen in the differential diagnosis of bacterial meningitis.

Keywords: *Haemophilus influenzae*, meningitis, lumbar puncture

INTRODUCTION
Haemophilus influenzae is a gram-negative bacterium that can cause a wide range of localized and invasive infections in humans, such as epiglottitis, pneumonia, septicemia, and meningitis.[1] Historically *H. influenzae* used to be the most common cause of bacterial meningitis, and primarily a disease of infants and young children.[2,3] With the introduction of the *H. influenzae type B (Hib)* vaccine in the late 1980s, the incidence of Hib-related diseases significantly declined, especially in pediatric populations. However, invasive *H. influenzae* infections in adults, particularly meningitis, remain rare and often occur in individuals with predisposing factors such as immunosuppression, recent head trauma, or cerebrospinal fluid leaks.[4] Patients ≥ 65 years of age with invasive *H. influenzae* disease have higher case-fatality ratios than children. [5] Up to 20% of patients who survive Hib-meningitis have long-term neurological sequelae, such as hearing loss. [6]
In this case report, we present an unusual case of *H. influenzae* meningitis in an adult male with hypertension but no other apparent risk factors. We discuss the clinical presentation, diagnostic process, and successful management of the case, underlighting the importance of early recognition and the role of polymerase chain reaction (PCR) in confirming the diagnosis. This case underscores the need for vigilance in identifying rare etiologies of meningitis and demonstrates the critical impact of timely intervention on patient outcomes.

CASE REPORT
A 66-year-old male with poorly controlled hypertension presented to the emergency department with a 2-day history of headache followed by fever and vomiting. The patient's family reported that his symptoms had worsened rapidly over the past 24 hours, leading to difficult speaking and decreased responsiveness. He had no history of Hib vaccination and no known immunosuppressive therapy.
After a neurological examination that revealed positive meningeal signs, and a CT scan, which excluded acute neurological disorder a suspection for meningitis was set. Further testings for definitive diagnosis and infection identification followed.

On a day of admission in our clinic, he had a high fever (39ºC) and he was confused, disoriented, with positive meningeal signs. His vital signs included blood pressure of 154/90mmHg, respiratory rate of 17 breaths/min, and pulse rate of 109 beats/min. The remainder of the systemic examination was unremarkable.

Results of the initial laboratory studies were as follows results: leucocytosis 14,9 $\times 10^9$/L (ref.ranges 4.0 – 10.0 $\times 10^9$/L) with a domination of polymorphonuclear leucocytes, erythrocyte sedimentation rate 90 mm/h, and C-reactive protein 131 mg/L (ref.ranges 0 – 10 mg/L), the rest of his serum biochemistry values were normal.

A lumbar puncture was performed, and cerebrospinal fluid (CSF) analysis revealed: pleocytosis of 7594 cells/mm3 (90% polymorphonuclear), elevated protein level (14.30 g/L), and low CSF glucose level (1.0 mmol/L) at glycemia 7.3mmol/L (Table 1). Because an initial diagnosis of bacterial meningitis was made, the patient was immediately started on empiric intravenous antibiotics, including ceftriaxone and vancomycin. *Haemophilus influenzae* was detected from cerebrospinal fluid by molecular method (PCR) and the culture was negative thus vancomycin was discontinued, and monotherapy with ceftriaxone continued for a total of 14 days. Dexamethasone was also administered for 4 days. The patient responded well to treatment, the fever resolved, and he gradually regained full orientation. A second and third lumbar puncture were performed on the 3th and 14th hospital day and the cerebrospinal fluid findings improved significantly. The patient was discharged in good clinical condition, with no neurological deficits and normal cerebrospinal fluid results. (Table 1)

Data/Indicators	Day 1	Day 3	Day 14
CSF	Cloudy	Cloudy	Clear
Pandy	+	+	-
Leucocytes/mm³	7594	406	15
Polymorphonuclear %	90	80	-
Protein g/L	14,3	2.85	0,50
Glycose mmol/L	1.0	2.5	2.3
Lactate mmol/L	13.62	5.03	2.17
Culture	Negative	Negative	Negative
PCR CSF	H.influenzae	-	-

At a follow up visit one month later, the patient remained symptom free, with no evidence of long-term cognitive impairment or relapse of infection.

DISCUSSION

Haemophilus influenzae type B (Hib) was once a leading cause of bacterial meningitis in children prior to the widespread adoption of Hib vaccination. However, its incidence in adults remains rare, accounting for only a small fraction of bacterial meningitis cases. This case is particularly noteworthy as it occurred in an otherwise immunocompetent adult with hypertension, a condition not typically associated with increased susceptibility to *H. influenzae* infections.

Adult-onset *H. influenzae* meningitis often presents similarly to other bacterial meningitis etiologies, with symptoms including headache, fever, neck stiffness, and altered mental status. [7] The overlap in clinical presentation underscores the need for comprehensive diagnostic evaluation. While Gram stain and cultures are traditional diagnostic tools, they may fail to identify the pathogen, as seen in this case. Molecular diagnostics, particularly PCR, have proven indispensable in such scenarios due to their speed, high sensitivity and specificity.[8]

Treatment of *H. influenzae* meningitis involves prompt administration of third-generation cephalosporins, such as ceftriaxone or cefotaxime. [9]. In this case, the patient responded well to 14 days of intravenous ceftriaxone, with no residual neurological deficits.

This case emphasizes several critical points: the utility of PCR in identifying rare pathogens when conventional methods fail, the importance of early empiric antibiotic therapy in bacterial meningitis, and the role of vigilant clinical monitoring and management of comorbidities. Continued surveillance and research into adult cases of *H. influenzae* meningitis are necessary to better understand risk factors, optimal diagnostic strategies, and treatment protocols for this uncommon but potentially life-threatening condition.

CONCLUSION

Haemophilus influenzae meningitis in adults underscores the importance of considering this rare pathogen in the differential diagnosis of bacterial meningitis. Early diagnosis and prompt initiation of appropriate antibiotic therapy remains essential for successful outcome. PCR was essential in diagnosing this case, underscoring the value of molecular diagnostics in identifying pathogens when traditional methods are inconclusive. Hib vaccination should be considered in adults with risk factors to prevent such rare but serious infections.

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VARICELLA ZOSTER VIRUS AND MENINGITIS IN IMMUNOCOMPETENT PATIENT- CASE REPORT

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ABSTRACT

Varicella zoster virus reactivation, also known as herpes zoster is common in older adults and immunocompromised individuals and often causes a painful, vesicular rash limited to a dermatomal distribution. On occasion, it can lead to various neurological complications as well. Meningitis caused by varicella zoster virus infection is uncommon in immunocompetent patients. We report the case of a 49-year-old male patient that presented with a one-week history of persistent headache that did not resolve with analgesics. He was previously healthy and immunocompetent, with a history of chickenpox in childhood. The CSF PCR analysis revealed a VZV infection causing acute aseptic meningitis with no shingles rash eruption on physical examination. Intravenous treatment with Acyclovir was started and following a three-week treatment course, the patient was discharged in good general condition with normal CSF results.

Keywords: Aseptic meningitis, Varicella Zoster Virus, Acyclovir, Immunocompetent

INTRODUCTION

Varicella zoster virus, a member of the Herpesviridae family, is a DNA virus. When a person comes into contract with VZV, the individual initially develops varicella. After this acute episode, the virus remains latent in the cranial nerves, dorsal roots and autonomic ganglions. In most cases the virus stays dormant for decades until the host's VZV-specific immunity declines, allowing the virus to reactivate spontaneously. This results in shingles (herpes zoster) and is typically characterized by pain and a rash in a dermatomal distribution.[1]. This reactivation can also result in specific neurological complications: Ramsay Hunt syndrome, encephalitis, peripheral motor neuropathy, myelitis, Guillain Barré syndrome, stroke with VZV vasculopathy and isolated clinical meningitis. [2,3]. VZV meningitis was first described in the 1980s in immunocompetent patients and it is considered the third leading cause of viral meningitis today (after Enteroviruses and Herpes simplex virus type 2). Advances in PCR techniques in the 1990s enabled to detect viral DNA in the cerebrospinal fluid of patients with shingles and neurological signs. [4]. VZV encephalitis is known to be associated with high mortality risk and significant neurological sequelae despite treatment with Acyclovir.

However, this type of encephalitis predominantly occurs in immunocompromised patients. In contrast, VZV acute isolated meningitis appears to show a favourable course and treatment outcome. Traditionally VZV meningitis has been treated with IV Acyclovir in accordance with the *Infectious Diseases Society of America* (*IDSA)* treatment guidelines.[5]

We report a case of a reactivation of VZV infection leading to acute aseptic meningitis with no rash present in a previously healthy immunocompetent 49-year-old male.

Case Presentation

A 49-year-old male patient without significant medical history, was hospitalized at the University Clinic for Infectious Diseases due to one-week history of persistent, diffuse headache that did not resolve with analgesics, accompanied by nausea, vomiting and photophobia. The patient was initially hospitalized at the Clinic of Neurology for two days, where a CTM scan and CT

angiography of the cerebral vessels were performed, both showing normal results. Laboratory and biochemical tests were normal with no inflammatory markers. An infectious disease specialist was consulted. During the clinical examination, the patient was found to be febrile, conscious, communicative, oriented, with positive meningeal signs. A lumbar puncture was performed, revealing cerebrospinal fluid findings including pleocytosis of 285 cells/μL, lymphocytic predominance of 92%, lactate levels of 2.02 mmol/L, protein levels of 0.8 g/L, and glucose levels of 2.7 mmol/L. PCR testing of the cerebrospinal fluid identified the Varicella Zoster Virus. Intravenous treatment with Acyclovir was started at a dose of 15mg/kg every eight hours. On the second day of hospitalization, the patient developped diplopia. An ophthalmological examination and MRI of the head were performed, which revealed increased intracranial pressure. Anti-edema therapy together with Acetazolamide 250 mg were added to the treatment regimen.The patient remained afebrile, hemodynamically stable, with preserved consciousness throughout the hospitalization. No skin changes were observed, and laboratory and biochemical analyses were normal. Microbiological and serological tests for other infections were negative. In the second week, there was a gradual regression of meningeal symptoms, improvement in vision and overall clinical improvement. After a three-week treatment course, the patient was discharged in good general condition with normal lumbar puncture results and a normal control MRI of the head. The patient was followed up after discharge and was doing well with complete resolution of symptoms.

	First lumbal puncture (26.05.24)	II lumbal puncture (08.06.24)	III lumbal puncture (15.06.24)
Pleocytosis	285cells/μL	85cells/μL	10cells/μL
Ne	8%	10%	/
Ly	92%	90%	/
Alb	0,81g/l	0,56 g/l	0,50 g/l
Lac	2,02 mmol/L	2,07 mmol/l	2 mmol/l
Glu	2.7 mmol/L	3,6 mmol/l	3,2 mmol/l
PCR (csf)	VZV	/	/

DISCUSSION

Several studies conducted in patients with herpes zoster have demonstrated that subclinical meningeal irritation can occur in 40–50% of cases, but a careful review of the literature showed that VZV-related neurologic disease can occur in absence of the classic herpes zoster exanthema, even in immunocompetent patients. [6] This may confirm the ability of the latent virus in the spinal ganglia to travel directly to the central nervous system without the classical skin involvement. [7]. Our case demonstrates the same phenomenon, but with increased intracranial pressure as a predominant clinical feature. The mechanism behind this increase remains poorly understood. Further explanation suggested by Lo et al. is the post-infectious allergic response to the causative virus and diffuse brain swelling. [8]. Some cases have been reported in the literature of reactivation of VZV with direct invasion of cranial nerves in otherwise immunocompetent patients. In particular, one case exhibited involvement of CN VI with increased intracranial pressure and bilateral papillary edema. [9] . Our case points out the unusual course of the disease, in absence of neuralgia and exanthema. Even more, there were no potential risk factors or conditions causing immunosuppression in the patient. The patient underwent a series of investigations, including testing for the human immunodeficiency virus (HIV), which was negative. In our case, treatment was carried out with intravenous Acyclovir at a dose of 15 mg/kg, for a duration of three weeks, considering the complexity of the case, the appearance of diplopia and the MRI findings of the head. [10]

CONCLUSION

Our case highlights that even in relatively low-risk patients, physicians must maintain a high level of clinical suspicion for the complications of VZV reactivation. This case demonstrates that VZV may be considered in cases of aseptic meningitis in immunocompetent individuals, even without exanthema, and it may increase the intracranial pressure, leading to symptoms, and causing reversible neurological deficit. A timely recognition and initiation of specific treatment with Acyclovir significantly contributes to the positive outcome of the disease and reduces the risk of complications associated with the infection.

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ROLE OF POLYMORPHONUCLEAR NEUTROPHIL LEUCOCYTE COUNT IN JOINT ASPIRATE FOR DIGANOSTICS OF PJI

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ABSTRACT
Low-gradre periprosthetic joint infection (PJI) continues to be diagnostic issue in constantly increasing nuber of arthroplasties worlwide. Preoperative diagnosis of PJI is critical for optimal treatment and functional results. Determination of polymorphonuclear neutrophil leukocyte count in synovial fluid is currently used as an independent criteria for the diagnosis of PJI. **The purpose** of this report is to present the relationship between increased polymorphonuclear neutrophil leucocyte (PMN) count and PJI. **Material and methods:** We examined 19 patients with suspected clinical and uncertain radiological signs for PJI. The study was conducted at the Department of Orthopedics and Traumatology, University Hospital "St. Marina", Varna. We analyze polymorphonuclear neutrophil leukocyte count in synovial fluid in suspected infected arthroplasties, in degenerative arthritis and patients with rheumatoid arthritis (RA) as a control group. **Results:** there is significant relationship between increased neutrophil leukocyte count and PJI, thus this parameter should be used as a sensitive marker for PJI

Keywords: periprosthetic joint infection, neutrophil leukocyte

INTRODUCTION
The rate of periprosthetic joint infection (PJI) after total hip arthroplasty (THA) and total knee arthroplasty (TKA) ranges from 0.2 to 2.5% after primary and up to 10% after revision arthroplasties [1]. Increased life expectancy is factor which leads to elevation of complications overall. Nevertheless, periprosthetic joint infection (PJI) continues to be burden, leading to unsatisfactory results, multiple surgeries with prolonged treatment and healthcare expenses. Many patients continue to have complains despite the lack of radiological signs for major complication as implant malposition or loosening. Presence of low-grade pathogen is difficult to diagnose, especially in outpatient conditions. The diagnosis of PJI is standartly made by screening for elevated serum inflammation markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), and additionally with the aspiration of the joint and analysis of the synovial fluid [2]. Determination of increased polymorphonuclear neutrophil leukocyte count in synovial fluid is used as additional criteria for suspected PJI.The aggregation of a bacterial biofilm matrix, composed of polysaccharides, is considered to play an major role in false negative results of culture as well as antibiotic resistance in these patients [3]. Number of synovial fluid biomarkers have also been used in the diagnosis of PJI , including C-reactive protein (CRP) of the joint aspirate, alpha-defensin (AD), and synovial fluid leukocyte count [4,5], and are used as 2018 International Consensus Meeting (ICM) criteria for hip and knee PJI [6]. Despite the fact that, the use of these markers is invasive and carries the potential for introducing infection into the joint, leucocyte percentage is considered reliable paramether. Sometimes, fluid obtained from joint aspiration is insufficient to conduct a comprehensive analysis of biomarkers, but multiple studies shows, that 2 ml of fluid is enough for extracting results [8].

MATERIAL AND METHODS
The study was performed from 04.2023 to 10.2024. All patients (19 pts) who had chronic symptoms (more than 4weeks after the index procedure and having symptoms more than 3 weeks) were enrolled- blunt pain, discomfort and slightly elevated CRP. Patients with radiological evidence of septic loosening or fistula were excluded from the study.

Joint aspirates were sent for microbiological culture, cell count analysis (including PMN count and PMN% analysis), Saline joint infusion was not used in any patients in this study. Synovial fluid samples were collected in ethylenediaminetetraacetic acid-coated tubes and had been transported to the laboratory and stored at room temperature. The specimens were analyzed immediately.
There has been created control group with same number of patients (19 pts) having degenerative arthritis with elective joint replacement to be done. Ten of these patients had history of inflammatory rheumatoid arthritis. Procedure was performed the same manner as investigated group. Additionally, which is part of the department revision arthroplasty protocol, sonication and tissue culture samples were done.

RESULTS

In THR group mean cell count was 14,700 cells / μL(8,000-17,200) , TKR group – mean cell count was 16,700 cells / μL(9,800-24,900) and in RSA - 8350 cells / μL. Average PMN % was 81.9 % in THR group, 87,4 % in TKR group and 76,8% in RSA group. Only 21,5 % from all patients had positive tissue culture sample, but all patients had positive sonication sample.
In control groups the distribution of these parameters was: THR group (hip arthritis) PMN cell count - 54 cells / μL(15-126) , PMN %- 23,5 % and TKR group (knee arthritis) PMN cell count - 68 cells / μL(55-80) , PMN % 34.2 %. All tissue culture samples were without bacterial growth.

DISCUSSION

Diagnosing PJI is complex procedure-clinical evaluation, imaging and laboratory testing- blood and joint aspirate which, according to American Academy of Orthopaedic Surgeons is increasing its importance. There are still not clear consensus regarding standard approach for diagnosis and treatment of PJI [6,8]. There is debate about accuracy and sensitivity of PMN count (%) in synovial fluid, because of multiple tests availability for diagnosing it. Recent literature studies revealed that synovial markers, such as PMN%, are a more accurate indicator of PJI, even in patients who have active inflamatory non-bacterial arthritis [9]. In our study, we noticed that patients with RA had slightly elevated PMN cell count and percentage, but still far away from the results of suspected PJI patients. Karlidag present data from large study, that absolute synovial PMN count is cheap, easy to perform, readily available, and reliable adjunct tool for detecting chronic PJI [10]. In his study, significant number of infected arthroplasties shows absolute synovial PMN count of over 1,415 cells/m, which is considered as reliable value. Moreover, synovial PMN % showed higher specificity (93.6%) than AD (Alfa-defensin) in detecting hip PJI. The AD is an antimicrobial peptide released from activated neutrophil cells. According to Deirmengian, AD is inferior to absolute synovial PMN count and PMN% in detecting chronic PJI [11].
Applying NLR (neutrophil leucocyte ratio) as a diagnostic tool for PJI has a number of advantages [12]. The NLR is a cheap and available measure obtained joint aspirate, that can be used not only in hospital conditions, but even in outpatient clinical practice. More importantly, this tool may allow early detection of PJI. The importance of early diagnosis of PJI is very beneficial in terms of therapeutic options for the patient
and increase success rates of implant retention procedures as DAIR , compared to the “gold standard “- two stage revision [13]. According to many studies, early surgical intervention is reducing bacterial resistance due to formation of biofilm [14].
In a consensus meeting, the baseline of PMN in the aspirate for acute periprosthetic infection (within 4 weeks after implantation or onset of symptoms) was set at 10,000 cells/μL, because different publications stated threshold values from 8,900 cells/ μL to 13,000 cells/ μL [15,16]. Additionally, the cut-off values was determined to be 89% in several studies [15] and 79.5% in another study, The International Consensus Group meeting fixed the borderline at 90% PMN in

the aspirate. Our results are slightly lower than this borderline, but with additional tissue culture samples and sonication, we think that are enough sensitive for diagnosing PJI.

LIMITATIONS

Our study has several limitations. The investigated group and control group are small .We didn't include parameters as blood samples (WBS,ESR,CRP) and other diagnostic tools as Musculoskeletal Infection Society (MSIS) recommends. This is done on purpose, so we focus only in studied parameter- PMN count and percentage, as independent value.

CONCLUSION

In conclusion, the results of the our study present, that synovial fluid PMN levels are subject to considerable variation, but consistently higher in patient with suspected PJI. PMN% showed a significantly higher percentage in PJI and a significantly lower chance of false positive results, especially with additional sonication performed.Thus, our findings emphasize the importance of PMN count and % for PJI diagnosis. New diagnostic tools, such as PCR and next-generation sequencing of synovial fluid, are gaining popularity and significance. Expenses and need of significant laboratory equipment for those tools, makes simple PMN count even more valuable in diagnosing PJI

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A REVIEW OF STRATEGIES FOR COMBATING ANTIMICROBIAL RESISTANCE: INNOVATIONS, FUNDING, AND NEW THERAPEUTIC APPROACHES

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ABSTRACT
The introduction of antimicrobial agents into clinical practice has been one of the greatest milestones in medical history, transforming the treatment of infectious diseases. However, antimicrobial resistance (AMR) has emerged as a global health threat, undermining the effectiveness of current antibiotics and other antimicrobial agents, and leading to the rise of infections that are difficult to treat. This review explores strategies to combat AMR, focusing on innovations in antimicrobial agent development, alternative therapeutic approaches, and funding mechanisms supporting AMR research. Key strategies discussed include the discovery of new antibiotics, particularly through the exploitation of natural products, antimicrobial peptides (AMPs), bacteriocins, phage therapy, and probiotics. The review also highlights significant global funding programs, such as Horizon 2020 and GARDP, which support the development of new antimicrobial agents and alternative therapies. Despite the promise of these new approaches, challenges remain in their commercialization, implementation, and long-term efficacy. The article emphasizes the need for continued global collaboration, appropriate use of antimicrobial agents, and the integration of new therapies with prevention and infection control measures. The effort to combat AMR requires a holistic, multi-disciplinary approach to ensure the sustainable effectiveness of antimicrobial therapies in the future.

Keywords: AMR, phytotherapy, natural compounds, bacteriocins, antimicrobial peptide

INTRODUCTION
The introduction of antimicrobial agents into clinical practice is one of the greatest achievements in medicine. These compounds include antibiotics, antivirals, antifungals, and antiprotozoal drugs. Most are active substances of synthetic or natural origin that inhibit the growth or kill various microorganisms (bacteria, viruses, fungi, and parasites). They are used in daily medical practice and are essential for preventing and treating infections in humans and animals (health.ec.europa.eu, 2017). Antimicrobial drugs have undeniably revolutionized the treatment of infectious diseases and have saved countless lives (Murugaiyan et al., 2022). The average human lifespan has increased by 23 years since the introduction of the first antibiotic in 1910. With the success in treating infectious diseases, opportunities for various modern medical procedures, including surgical interventions, cancer treatments, organ transplantation, and more, have expanded (Hutchings et al., 2019).
Antimicrobial resistance (AMR) represents a global health challenge threatening the effectiveness of existing antibiotics and leading to an increasing risk of uncontrollable infections. Despite advances in medicine and pharmacology, AMR remains a significant issue as pathogenic microorganisms develop resistance to antibiotics and other antimicrobial agents (Abushaheen et al., 2020). These organisms can cause hard-to-treat infections, leading to increased mortality and significant economic losses (Read &Woods, 2014; Khameneh et al., 2016). Despite various

efforts to combat AMR, including the development of new drugs and alternative therapies, a definitive solution to the problem is still lacking.

MATERIALS AND METHODS

The aim of this study is to analyze the main strategies for combating AMR, including innovative approaches in the development of antimicrobial agents and the role of various alternative therapies. For this purpose, a comprehensive review of scientific articles indexed in databases such as PubMed, Scopus, ResearchGate, and Web of Science was conducted. Additionally, reports from global health organizations such as the WHO and data on funding initiatives supporting research on new antimicrobial agents and infection control approaches were analyzed. The research methodology encompasses the analysis of current scientific publications and organizational reports related to AMR, as well as a detailed review of financial initiatives and programs that promote advancements in this field.

RESULTS

Development of New Antimicrobial Agents

One of the main priorities in the fight against AMR is the discovery of new antibiotics. Despite progress in synthetic chemistry, most efforts focus on extracting natural products with antimicrobial properties. Research on antimicrobial peptides, bacteriocins, phage therapy, and probiotics shows significant potential for future applications. Antimicrobial peptides (AMPs) are small molecules that play a crucial role in the host's innate immunity (Wang et al., 2019) against a broad range of microorganisms, including bacteria, fungi, parasites, and viruses (Mohammed et al., 2017; Kang et al., 2017; Lei et al., 2019). In the AMR database, 3791 antimicrobial peptides from six kingdoms were reported in 2021, including 431 from bacteria, 4 from archaea, 7 from protozoa, 6 from fungi, 824 from plants, and 2519 from animals (DRAMP; Kang et al., 2019). Besides antibacterial activity, AMPs have been found to possess various biological functions such as immune regulation, angiogenesis, wound healing, and antitumor activity (Zhang & Gallo, 2016; Roudi et al., 2017; Pfalzgraff et al., 2018; Mookherjee et al., 2020). The differences in the composition of the cellular membrane between pathogens and host cells are believed to be the basis of AMP's target specificity (Zhang et al., 2021). Phage therapy relies on using naturally occurring phages to infect and lyse bacteria at the site of infection. Biotechnological advancements further expand the possibilities of potential phage therapeutics, including new strategies using bioengineered phages and purified phage lytic proteins (Lin et al., 2017).

Financial Incentives for Scientific Research

Multiple global initiatives and funding programs such as the EU's Horizon 2020, the AMR Accelerator, and the Global Antibiotic Research and Development Partnership (GARDP) support efforts to combat AMR. These programs focus on creating new antimicrobial drugs, as well as developing alternative therapeutic approaches and combined strategies. The Global Antibiotic Research and Development Partnership (GARDP) represents a collaborative effort between the WHO and the Drugs for Neglected Diseases Initiative to promote research through public-private partnerships. The ultimate goal is to develop and introduce five new drugs by 2025 that are effective against the most dangerous drug-resistant bacteria, as identified by the WHO (WHO, 2017).

The process from molecule discovery to its market release as a drug is highly complex and typically spans up to 15 years. ENABLE is a platform dedicated to the discovery of antimicrobial drugs targeting Gram-negative bacteria, which are among the most difficult to treat. It provides investments in specialized expertise and the development of networks, including those in the private sector and academia, necessary for drug discovery and preclinical development. The platform's goal is to advance at least one product to clinical trials. As of 2019, ENABLE had five compounds under development, selected from over 100 initial participants who expressed interest, significantly exceeding the original target (op.europa.eu, 2019).

Alternative Therapeutic Approaches

There are many alternatives to traditional antibiotics with significant potential for treating resistant infections. These include antimicrobial peptides, bacteriocins, and probiotics, which possess unique mechanisms of action different from those of traditional antibiotics. Thus, they could offer new ways to overcome microbial resistance. Bacteriocins exhibit antibacterial activity and a specific mechanism of resistance to strains closely related to the producing bacteria (Dobson et al., 2012; Yang et al., 2014). This resistance is typically associated with a specific protein encoded in the bacterial genome (bacteriocin operon) (Mokoena, 2017; Hols et al., 2019). Almost all bacteriocins are small cationic molecules with hydrophobic or amphiphilic characteristics that exhibit limited to broad inhibitory activity against closely related and unrelated species (Eijsink et al., 2002; Arqués et al., 2015).

Natural Compounds and Phytotherapy

Natural products, particularly those with antimicrobial properties such as extracts from medicinal plants and essential oils, are becoming increasingly valuable in the fight against AMR. Many plants and their active ingredients exhibit high antimicrobial activity and can be used as part of combined therapeutic strategies. The World Health Organization (WHO) encourages the use of medicinal plants as adjunctive therapy in the absence of conventional treatment. The focus is on researching bioactive compounds, their chemical composition, and the pharmacological potential of various plant species to synthesize compounds with lower toxicity than existing molecules (Boccolini & Boccolini, 2020).

DISCUSSION

Antimicrobial resistance is a complex issue that requires a comprehensive approach for resolution. Research on new antimicrobial agents, especially natural products and new biotechnological therapies, is at the heart of efforts to overcome resistance. While progress in the discovery of new drugs is evident, there are still many barriers to the commercialization and implementation of new therapies in clinical practice. Even with the availability of new developments, issues related to the proper use of antimicrobial agents and the need for global collaboration remain critical factors for successfully tackling AMR.

Alternative therapies such as phage therapy, antimicrobial peptides, and probiotics show promising results but also require further research to determine their long-term effectiveness and safety. It is important to recognize that solving the AMR problem will require combining new antimicrobial agents with prevention and infection control approaches, including improving hygiene practices and reducing the overuse of antibiotics in both medical and agricultural sectors.

CONCLUSION

Despite significant progress in the development of new antimicrobial agents and alternative therapies, the fight against AMR remains a global issue that requires the united efforts of health, scientific, and governmental institutions. Innovative approaches such as natural products, new molecules, and biotechnological strategies offer new prospects for the treatment of resistant infections. To achieve long-term success, strengthening efforts to prevent AMR and establishing sustainable global partnerships for research and funding in this critical field are essential.

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GRAVITY X-RAY FOR EVALUATION OF SUPINATION EXTERNAL ROTATION TYPE ANKLE FRACTURES

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ABSTRACT
Introduction: Ankle fractures are one of the most common musculoskeletal injuries [1]. Their classification is essential for the choice of treatment and prognosis for the recovery period. Differentiating the individual subtypes of supination external rotation (SER) fractures remains a challenge. **The Purpose:** Gravitational radiography plays an essential role in separating SER II from SER IV, and the aim of this work is to demonstrate its effectiveness.
Materials and methods: For a period of 4 years (09.2020 – 09.2024), 172 gravity X-rays were performed for SER fractures. 37 of them were treated operatively. **Results and Discussion:** In 130 patients there was no increase of the medial clear space (MCS) above 5 mm. In the remaining 42 cases, the MCS was more than 5 mm. An increase in the MCS is a sign of damage to the deltoid ligament. This is an unstable situation and requires surgical treatment. **Conclusion:** Gravity X-ray has a high informative value in differentiating SER II from SER IV.

Keywords: Ankle fractures, Supination external rotation, Medial clear space, Gravity X-Ray

INTRODUCTION
Supination external rotation (SER) ankle fractures constitute approximately 85% of all ankle fracture cases, making them the most prevalent type [2]. This high incidence underscores, the importance of accurately diagnosing and classifying SER fractures to ensure appropriate treatment and management, as variations in the condition of associated structures like the deltoid ligament can significantly influence patient outcomes. The sequence of injury in SER fractures progresses as follows: it begins with the rupture of the anterior tibiofibular ligament (SER I), followed by an oblique fracture of the fibula (SER II), then either a rupture of the posterior tibiofibular ligament or an avulsion of the posterior malleolus (SER III), culminating in a transverse fracture of the medial malleolus or rupture of the deltoid ligament (SER IV). The deltoid ligament serves as the primary stabilizer of the ankle joint; its rupture, particularly when accompanied by a fracture, creates an unstable condition within the ankle's structural integrity, necessitating careful assessment for optimal management. [4]. The treatment of these fractures is determined by the stability of the ankle joint, assuming that SER I and SER II fractures are stable, without disruption of the ankle ring, while SER III and SER IV are unstable and are indicated for surgical treatment [3]. When performing standard X-ray in cases where the deltoid ligament is damaged (SER IV), it cannot be differentiated from (SER II), as the diagnostic algorithm for these fractures includes gravity X-ray, MRI or arthroscopy.
Each method has its advantages and disadvantages, but the aim of this work is to demonstrate the effectiveness of gravity X-ray as a highly specific method for rapid, effective, painless and efficient classification of the individual subtypes of SER ankle fractures.

MATERIALS AND METHODS
Over a four-year period, from September 2020 to September 2024, gravity X-rays were conducted on 172 patients aged 18 to 70 who presented with an isolated oblique fracture of the fibula classified as SER type at an emergency center. These patients were informed about the necessity of undergoing a specific X-ray examination, facilitating a focused investigation into the relationship between their injuries and the condition of the deltoid ligament, a critical stabilizer in ankle joint integrity. In this specific positioning for the gravity X-ray, the patient is placed in a lateral decubitus position, ensuring that the fractured malleolus faces downward. The X-ray

beam is then directed at an angle of 10 to 15 degrees of internal rotation to effectively capture the mortise view, providing clear visualization of the ankle joint and any associated injuries, particularly crucial for assessing the stability of the fibular fracture and the condition of the surrounding ligaments.

Fig. 1. Positioning of the ankle for gravity X-ray

In this radiograph, the MCS and superior tibiotalar space (STS) are measured and in cases where the MCS is less than 5mm or the difference betwenn MCS and STS is less than 2mm it is considered SER II and the patient is referred for conservative treatment. In cases where the MCS is over 5mm or the differences between MCS and SCS is more than 2mm surgical treatment is performed due to the presence of an unstable fracture type SER IV (fig. 2). The results obtained are compared with those of the intraoperative finding.

Fig. 2. Significant increasing in MCS over 7mm. SER IV type

RESULTS

Among the 172 patients studied with isolated oblique fibular fractures, 130 exhibited no increase in medial clear space (MCS) above 5 mm or a difference greater than 2 mm with the STS, while 43 patients did show significant increases in these measurements. Importantly, all 37 of the patients who required surgical intervention were found to have deltoid ligament ruptures, emphasizing the critical role of MCS assessment in identifying potential ligamentous injuries associated with these fractures (fig. 3). This correlation emphasizes the need for a comprehensive evaluation of MCS to accurately guide treatment and management decisions

Fig. 3. Deltoid ligament rupture. Operative finding.

DISCUSSION

The condition of the deltoid ligament plays a crucial role in determining the treatment for SER fractures. The degree of change in the MCS in deltoid ligament injury varies in different literature sources [6]. In general, a MCS of 4 mm or more, with this value at least 1 mm greater than the STS, appears to represent a deltoid ligament tear [7]. In our study, we define a significant increase in MCS of 5 mm or more, with a difference of 2 mm from the STS, as a robust indicator of deltoid ligament rupture, aiming to minimize unnecessary surgical interventions.

Magnetic resonance imaging is an imaging study with the ability to differentiate SER types, but it is associated with increased time consumption and cost, making it not always appropriate. Arthroscopic evaluation is another option but it is very invasive for diagnostic tool.

CONCLUSION

This study highlights the significance of gravitational radiography in distinguishing between SER II and SER IV ankle fracture subtypes, which is crucial for determining appropriate treatment and anticipating recovery. Over a four-year period, 172 gravity X-rays were conducted on patients with SER fractures, revealing that an increase in MCS correlates with deltoid ligament damage, necessitating surgical intervention. The findings suggest that gravity X-ray is an effective diagnostic tool in the clinical evaluation of ankle fractures, particularly in assessing the stability of SER fractures.

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BOTULISM - A CLINICAL EPIDEMIOLOGICAL CHALLENGE

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ABSTRACT

Botulism can arise from the consumption of contaminated food, injuries, or medical and cosmetic procedures. Due to its nonspecific symptoms and frequent omissions in epidemiological histories, diagnosing botulism remains a significant challenge. **Aim** The present study aims to analyze the prevalence of botulism in Europe during 2023, with a particular focus on cases associated with intragastric injections of botulinum toxin, and to investigate the risks associated with its improper use in medical and aesthetic practices. Additionally, the study underscores the necessity of enhanced regulation and awareness regarding the use of botulinum toxin. **Methods and Materials:** Data on the prevalence of botulism were gathered from the European Centre for Disease Prevention and Control (ECDC) and the national health services of the affected countries. A bibliographic search was conducted in the PubMed, Scopus, and EMBASE databases. **Results:** In 2023, 87 cases of botulism associated with intragastric injections of botulinum toxin for weight loss were reported within the European Union and the European Economic Area. Germany reported 30 cases, Austria and France each reported one, Switzerland reported two, and Turkey reported 53 cases. In Bulgaria, three cases were recorded, one of which was treated at the University Hospital "Saint Marina" in Varna. **Conclusions:** Strict control over the use of botulinum toxin and increased awareness among medical professionals and the public are essential to prevent new cases of the disease, particularly those related to iatrogenic interventions.

Keywords: botulism, toxin, iatrogenic

INTRODUCTION

Botulism is a rare, neuroparalytic, and potentially fatal disease that affects individuals across all age groups. It is caused by the neurotoxin produced by the bacterium *Clostridium botulinum*. This toxin ranks among the most potent poisons known to science, leading to severe muscle paralysis and, in some cases, death. Botulism may result from the ingestion of contaminated food, wounds, or medical and cosmetic procedures. Due to its nonspecific symptoms and frequent omissions in epidemiological history, diagnosing botulism remains a considerable challenge. While botulinum toxin is generally regarded as safe, its widespread use and continuously expanding indications raise concerns about its safety profile. BTX-A is a potent, long-acting inhibitor of both striated and smooth muscle contractions. Hypothetically, BTX-A inhibits acetylcholine-mediated peristalsis, which is primarily responsible for gastric motility. This inhibition can lead to delayed gastric emptying, early satiety, and subsequent weight loss. [1] There are two additional forms of botulism that do not occur naturally: inhalation botulism and iatrogenic botulism, which arises following the administration of botulinum neurotoxins (BoNTs) for therapeutic or cosmetic purposes. Due to the small doses of BoNT typically injected, iatrogenic botulism (IB) is usually observed as isolated cases, often involving localized effects on nerves or muscles near the injection site with mild to moderate symptoms. These cases may result from accidental overdoses or the use of contaminated or non-standard products. [2]
Overweight and obesity increase the risk of metabolic complications, hypertension, cardiovascular disease, and cancer.[1] Long-term weight reduction can mitigate many of these health issues; however, current interventions—including dietary modifications, exercise, behavioral therapies, and pharmacological treatments—achieve only short-term, modest weight loss for most patients. In the search for innovative treatments, intragastric injection of botulinum toxin A (BoNT-A) has been explored for obesity management due to its potential to delay gastric

emptying and induce early satiety, ultimately reducing caloric intake and promoting weight loss. Studies have demonstrated that intragastric BoNT-A injections can be effective in inducing weight loss for up to six months post-application. [3] To date, no research has assessed the effects of intragastric BoNT-A injection beyond six months or its potential impact following bariatric surgery. It has been suggested that preoperative intragastric BoNT-A use might enhance weight loss prior to bariatric procedures and sustain its effects afterward. [4] While BoNT-A has been established as a safe treatment, long-term efficacy remains inconsistent across various indications due to its relatively short duration of action.

Aim: To analyze the prevalence of botulism in Europe during 2023, with a particular focus on cases associated with intragastric injections of botulinum toxin, and to investigate the risks associated with its improper use in medical and aesthetic practices.

MATERIALS AND METHODS

Data on the prevalence of botulism collected from the ECDC, from affected countries national health centers and University hospital “St. Marina”. A bibliographic search was conducted in the PubMed, Scopus, and EMBASE databases.

RESULTS

Between 2012 and 2021, an average of 94 human botulism cases per year were reported in European Union (EU) countries. By the end of March 2023, the World Health Organization (WHO) reported an iatrogenic botulism outbreak involving 87 patients following bariatric procedures at two hospitals in Istanbul and Izmir, Turkey. According to the European Centre for Disease Prevention and Control (ECDC) under International Health Regulations (IHR), associated IB cases were also reported in Germany, Austria, France, Switzerland, and Turkey. [5] The majority of affected patients were middle-aged adults, predominantly women, with several cases requiring intensive care due to severe deterioration. As of March 24, 2023, Turkey reported 53 confirmed IB cases between February 28 and March 8, with 31 hospitalizations. These cases were linked to intragastric BoNT-A injections performed in hospital X (50 cases) and hospital Z (3 cases). Investigations revealed that the BoNT product involved was approved for import but was used off-label, with evidence of high-dose applications and potential contamination. [6] By April 3, 2023, Germany had reported 34 botulism cases, including 9 confirmed and 21 probable cases. Switzerland reported two probable cases, and Austria and France each reported one probable case. Thirty-one patients reported receiving intragastric botulinum neurotoxin injections (IBNI) before developing botulism. Three patients claimed to have contracted foodborne botulism in Istanbul without undergoing stomach injections of BoNT; however, their names appeared on the list of individuals treated with IBNI in Germany, as provided by Turkish authorities.

A total of 32 cases were treated at a private hospital (Hospital X) in Istanbul, Turkey. One patient was treated in Istanbul at an unidentified hospital, while another underwent IBNI at a private hospital in Izmir (Hospital Y). Of the reported cases, nine were men and 25 were women, aged 20–52 years (median age: 36.5). Most patients (27 out of 30) were either Turkish nationals or of Turkish descent. Notably, 22 out of 23 individuals who received IBNI after February 18 developed botulism. [7]

The Turkish Medicines and Medical Devices Agency investigated the material and concluded that a genuine product was found, albeit used off-label. The ECDC and WHO/Europe, with participants from Turkey, several EU countries, and Switzerland, announced the outbreak in the Weekly Communicable Disease Threats Report compiled by ECDC and in RKI's weekly "Epidemiologisches Bulletin" [7].

In Germany, patients with IBNI from the lists provided by Turkish authorities were contacted and advised to seek medical attention if they exhibited symptoms typical of botulism. Concurrently, additional undiagnosed patients were encouraged to seek medical care through tweets in both German and Turkish on March 10 and 23, 2023.

In Bulgaria, eight cases of botulism have been registered since the beginning of 2023, three of which are linked to the "stomach Botox" epidemic in Turkey as of April 2023. One case involved hospitalization at University Hospital Saint Marina in Varna with quadriparesis and intestinal tract paresis. Due to pronounced neurological symptoms, the patient was referred to the neurology department. A history of prior treatment in Turkey emerged, followed by discussions with Turkish physicians, who reported similar issues among numerous patients. Due to the lack of botulinum antitoxin, treatment was conducted with Nivalin, and the patient recovered.

Among medications containing BoNT, BoNT/A1 preparations are most commonly used due to their several-month half-life . Even though all products contain BoNT/A1 as the active ingredient, not all companies have licensed their products for the treatment of specific conditions. Additionally, the composition of products regarding the presence of BoNT complex proteins and excipients varies by brand and manufacturer. The units are not interchangeable, and each product is administered using a brand-specific dosing regimen [8].

In the current outbreak, Turkish authorities suspect that both the use of high-dose injections, which cause continuous vomiting leading to subsequent electrolyte imbalances, and the use of illicit generic drugs with non-standardized dosages and recommendations are the primary causes of the crisis.

Turkish clinical protocol guidelines for obesity and metabolic surgery highlight inconsistent and contradictory evidence in the literature regarding the use of BoNT/A injections for weight-loss procedures. The Turkish Society for Bariatric and Metabolic Surgery emphasizes that intragastric BoNT/A injections should only be applied as part of clinical trials or research studies approved by relevant research ethics committees. However, the Turkish Ministry of Health noted that the use of botulinum toxin as an approach to bariatric surgery is still practiced in many private clinics across the country.

In response to the issue, the Turkish Society for Clinical Microbiology and Infectious Diseases underscored the importance of increasing botulinum antitoxin stocks in Turkish hospitals to maintain national capacity for the treatment of botulism cases [9, 10].

A similar outbreak of iatrogenic botulism was reported in Egypt in June–July 2017. Nine patients developed botulism after intramuscular injections of a newly imported high-concentration unlicensed BoNT-A preparation. The patients were hospitalized 5–10 days after the BoNT-A injections.

These cases highlight the risks of BoNT/A injections when not applied within evidence-based medical practices. There is a need for international guidelines to define indications and safe dosing regimens, particularly in the context of medical tourism.

CONCLUSION

The routine and emerging indications for the use of BoNT-A are increasing, and as a result, cases of iatrogenic botulism will become more frequent. Physicians should remain vigilant for iatrogenic botulism in post-treatment follow-ups after BoNT-A administration and in the differential diagnosis of neurological disorders presenting with similar findings. [11]. Intragastric botulinum toxin injections may be beneficial and safe in obesity treatment, but better-designed, placebo-controlled, long-term studies with adequate sample sizes are needed.

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THE ROLE OF METHYLENE BLUE IN ENHANCING SURGICAL OUTCOMES FOR SACROCOCCYGEAL PILONIDAL DISEASE

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ABSTRACT

Sacrococcygeal pilonidal disease (SPD) is a common condition primarily affecting young men after puberty, characterized by the formation of cysts or abscesses in the intergluteal cleft. This condition leads to significant discomfort, pain, and decreased quality of life, with the potential for recurrent infections. Various risk factors have been identified, including male gender, young age, obesity, hirsutism, deep natal cleft, poor hygiene, and professions involving prolonged sitting. Despite advancements in treatment, SPD remains a challenge due to the complexity of visualizing sinus tracts and ensuring complete excision of the pathological tissue, which can often result in recurrences. Methylene blue dye has gained attention as an effective tool for identifying sinus openings and marking affected tissues during surgery. The present study reviews the use of methylene blue for excising pathological tissue and its role in reducing recurrence rates and postoperative complications. The article presents clinical experience and outcomes, including healing times, recurrence rates, and post-surgical pain management. Results indicate that methylene blue improves surgical navigation, thus contributing to more precise excision. However, it highlights the need for further studies to validate its long-term effectiveness and explore potential complications associated with its use.

INTRODUCTION

Sacrococcygeal pilonidal disease (SPD), also known as "hair nest" (from Latin pilus – hair, nidus – nest), is a common condition affecting approximately 26 per 100,000 people annually (Brown et al., 2012). It is most frequently diagnosed in young men post-puberty and rarely presents in childhood or later in life. The disease causes significant discomfort, including pain, infections, and a reduced quality of life, often limiting the individual's ability to work or perform daily tasks effectively (Harries et al., 2019). The primary risk factors include male sex, young age, obesity, hirsutism, deep natal cleft, poor hygiene, and certain occupations or sports associated with prolonged sitting (Harlak et al., 2010). Historically, the first description of this disease was made by Mayo in 1833. In 1847, Anderson presented a method for treating infection in the intergluteal region in his article titled "Removed Hairs from Ulcer." Since then, the lesion has been known by various terms, including pilonidal cyst, pilonidal sinus, pilonidal disease, pilonidal fistula, and supracoccygeal cyst or fistula (Mayo et al., 1833; Hap et al., 2017). SPD has been considered a congenital disease based on the presence of epithelial channels and hypotheses regarding residual embryonic structures. However, more recent studies support the acquired nature of the disease, emphasizing the role of mechanical factors, hair, and local inflammatory processes (Gage, 1935; Bookman, 1924; Lannelongue, 1882; da Silva, 2000; Harlak, 2010). Factors such as friction, pressure, and hair penetration into the skin are key to the development of SPD. Among the main risk factors for SPD are male sex and young age, with the disease being more common in men after puberty. Anthropometric characteristics such as a deep natal cleft and hirsutism (excessive hair growth) also increase the risk. Occupational and daily habits, such as

prolonged sitting (e.g., for drivers) or professions requiring physical contact with hair (e.g., hairdressers), also play a role. Additionally, poor personal hygiene, obesity, and excessive sweating can contribute to the development of the disease. Studies on the role of obesity suggest that it increases the risk of SPD, but there is still a lack of sufficient prospective studies to confirm all potential risk factors (Hull & Wu, 2002; Cubukçu et al., 2000; Mentes et al., 2006). The treatment of sacrococcygeal pilonidal disease (SPD) is challenging due to the difficulties in visualizing the sinus channels, especially in anatomically complex areas such as the perineum, where preserving healthy tissue is crucial (Strevinas et al., 2013). Incomplete removal of the channels often leads to recurrences (Durgut, 2018). One of the most effective methods for identifying the sinuses is the injection of methylene blue (MB), which significantly reduces the long-term recurrence risk (from 30% to 16%) (Doll et al., 2013). However, the liquid form of MB can create difficulties by contaminating gloves, instruments, and surrounding tissues in the event of channel perforation (Dietrich et al., 2008; Strevinas et al., 2013). Various surgical approaches for treating SPD have been employed, including the Karydakis and Limberg flap, marsupialization, and complete excision with MB, but there is no established standard method (Karydakis, 1973; Limberg, 1966; Bunch, 1946; Bascom & Bascom, 2007; Harris & Holloway, 2012).

The aim of this study is to evaluate the effectiveness of methylene blue in improving the quality of tissue excision in patients with sacrococcygeal pilonidal disease. This study highlights the importance of methylene blue for identifying sinus tracts and reducing the risk of recurrence, as well as aiding in the precise removal of pathological tissue. Additionally, it examines the impact of methylene blue on postoperative healing, recurrence rates, and complication frequency. Despite its promising results, the study emphasizes the need for further research to confirm its long-term benefits and potential complications, ensuring more comprehensive understanding and optimal use in clinical practice.

MATERIALS AND METHODS

In this review, we examined databases such as Scopus and Web of Science using keywords such as "pilonidal sinus," "pilonidal abscess," and "wound healing." The presented results include our clinical experience and observations regarding wound healing rates, time to complete recovery, recurrence rates, postoperative complications, time to return to work or education, and assessment of postoperative pain.

RESULTS

In the description of surgical techniques, the use of methylene blue for visualizing fistulas in pilonidal sinus disease is particularly noteworthy. Cyst removal requires careful resection of all areas with inflamed tissue, not just those colored by the dye.(Fig.1a) Although methylene blue facilitates operative navigation, the procedure must remain radical, and any resected tissue should be carefully examined.(Fig. 1b) In our practice, we use methylene blue to identify the openings of the cyst with a probe before making the skin incision. This helps us determine the extent of resection and the shape of the wound. (Fig. 2a; Fig. 2b) For optimal visibility, the patient's buttocks are fixed to the surgical table. The resection is performed along the midline to the sacral fascia, removing both the dyed and visibly inflamed tissues.

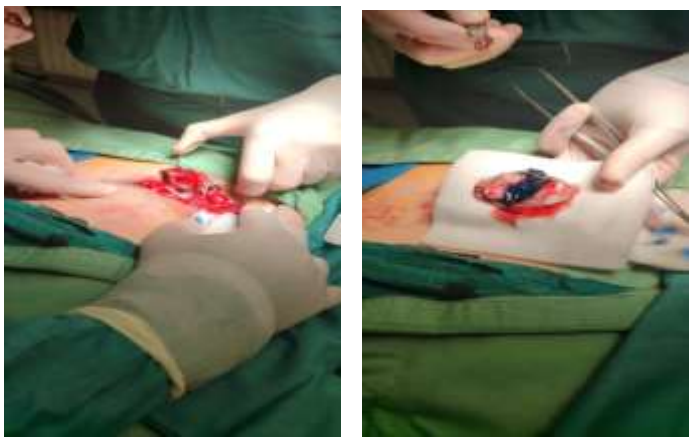

Figure 1. a) Radical resection of cyst; b) Postoperative examination of the cyst fistulas

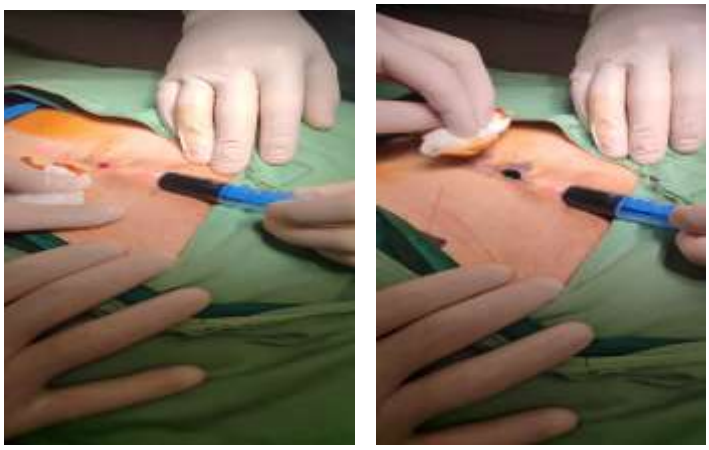

Figure 2.a) Preoperative application of methylene blue; b) Leaking of methylene blue from the opposite fistulous opening

Regarding the healing process, we employ two methods. One is to leave the wound open for secondary healing through granulation. The other method involves primary closure of the operative wound. In this method, the subcutaneous tissue is mobilized, and to ensure optimal hemostasis, an electric knife is used. Sutures are placed so that they include the skin, subcutaneous tissue, and the sacral fascia, while tension at the intergluteal cleft is minimized through appropriate fixation. Additionally, spaces are left between the sutures to allow for drainage of exudate. Typically, a drain is placed in the wound, and the dressing is secured with sutures. The dressing and drain are removed after 1-2 days, and patients are usually discharged on the second day.

Until complete recovery, patients attend regular follow-up visits, and good hygiene of the operated area is recommended. In the presence of fluid, it is drained, and if the wound ruptures, it is left to granulate. After healing, laser hair removal is recommended to prevent recurrence. Various surgical techniques and postoperative care methods, such as negative pressure therapy (VAC), have been used in different clinical cases. However, no established strategy ensures both a low risk of recurrence and high patient comfort. The most suitable approach is one that the surgeon is well-versed in, the patient accepts, and which has proven to yield good results. If the chosen method leads to frequent complications or recurrences, alternative treatment methods should be considered.

CONCLUSION

In conclusion, methylene blue serves as a valuable adjunct in the surgical management of sacrococcygeal pilonidal disease, particularly in enhancing the quality of tissue excision and reducing recurrence rates. The study affirms the efficacy of this method in improving surgical precision, although it also stresses the necessity for further research to assess its long-term

benefits and identify potential complications. Given the complexities involved in treating SPD, a personalized approach tailored to the patient's condition and needs remains crucial. Ultimately, methylene blue may serve as an essential tool in optimizing the outcomes of pilonidal disease surgeries, though further evidence is required to establish its definitive role in clinical practice.

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