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MONOFILAMENT AS A PROGNOSTIC TOOL OF PROTECTIVE SENSATION AFTER LASER THERAPY FOR DIABETIC NEUROPATHY

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ABSTRACT

The purpose of the study is to investigate the effect of high-energy MLS-laser therapy on sensation in patients with diabetic neuropathy, to compare the results of subjective touch sensation by the 10-g monofilament test with objective changes of ENG parameters of n. suralis, and to refine the reliability of the monofilament test as a means of detecting changes after treatment. **Materials and Methods:** 69 cases of patients with type 2 diabetes and lower limb sensory impairment detected by the 10-g monofilament test were followed in the study. Patients were divided into two groups: experimental-41 patients received high-energy laser therapy and control (placebo) group-28 patients with "sham" laser treatment. Electroneurography (ENG) of sensory fibers of peripheral nerves of lower limbs was performed to objectify the results of both groups. **Results:** In the experimental group, the percentage of patients with a sense of touch on all investigated sites at day 90 (left: 68.3%; right: 78%) was higher compared to that not only at day 21 (left: 56.1%; right: 63.4%) but also compared to baseline (left: 43.9%; right: 53.7%) for both lower limbs. Subjective improvement assessed by the 10-g monofilament test correlated with ENG parameters of n. suralis. **Conclusions:** MLS-laser treatment significantly improves lower limb sensation as assessed by the 10g monofilament test in patients with diabetic neuropathy. The Semmes-Weinstein monofilament test can be used not only to prove sensory disturbances but also to detect changes after therapy, including laser therapy.

Keywords: monofilament, sensation, MLS-laser, diabetic neuropathy

INTRODUCTION

Diabetic polyneuropathy (DPN) with loss of peripheral nervous system protective sensation is a major risk factor for one or more foot ulcerations followed by foot amputation [1]. The American Diabetes Association recommends that patients with type 1 diabetes for 5 or more years and all patients with type 2 diabetes are evaluated annually for DPN. Medical history and simple clinical tests are cited as the primary means. The most common early symptoms are caused by thin-fibre involvement and include pain and dysesthesia (unpleasant burning and tingling sensations). Involvement of the thick fibres can cause numbness and loss of protective sensation, which indicates the presence of distal sensorimotor polyneuropathy and is a risk factor for diabetic foot ulceration. The golden rule for determining the function of the thin fibers is a needle sense test and the temperature sense tested by a temperature discriminator. For the function of the thick fibers, the vibratory sensation test and the 10-g monofilament test are indicative. The 10-g monofilament test is indicative of protective sensation. These tests not only detect the presence of dysfunction but also predict future risk of complications [2]. Peripheral neuropathy is defined as the presence of at least one spot without sensation of touch on the left or right foot in the 10-g monofilament test [3]. The aim of this placebo-controlled study is to investigate the effect of high-energy MLS-laser therapy on sensation, as assessed by the 10-g monofilament test, in patients with diabetic lower limb neuropathy. To compare the results of subjective touch sensation in the monofilament test with objective changes of ENG parameters of n. suralis. To refine the reliability of the monofilament test as a means of proving sensory impairment and detecting changes after treatment.

MATERIALS AND METHODS

A total of 69 cases of patients with type 2 diabetes and diabetic neuropathy of the lower extremities were followed. Patients were randomly divided into two groups: an experimental (EG)- 41 patients

received high-energy laser radiation and a control (placebo) group (CG)- 28 patients received „sham“ laser treatment by directing the robotic device and light guide without releasing the beam.

The conduct of the study was approved by Decision №108/25.11.2021 of the Research Ethics Committee at MU-Varna.

A study of the sense of touch was performed using the Semmes-Weinstein monofilament. Both lower extremities are examined at three points: the tip of the thumb and the skin covering the head of the first and fifth metatarsal bones, plantarly. Scores are calculated using the "Monofilament Index". For each examined location in which the patient has sensation 1 point is added, in case of no sensation - 0, maximum score was 3 for each lower limb. The touch sensation test was performed three times: before the start of the treatment, after the end of the treatment course (on the 21st day) and on the 90th day after the start of the therapy. ENG of sensory fibers of peripheral nerves of lower limbs was performed to objectify the results. The study was performed under standard conditions, two times: before the start of the treatment and on the 90th day after the start of it. Sensory nerve action potential (SNAP) amplitude, conduction velocity (CV) and distal latency time (DLT) of n. suralis were measured.

We used an MLS laser, M6 of ASA Laser, Italy. It is a class IV NIR diode laser, distinguished by combining and synchronizing two emissions with different wavelengths - λ -808 nm in constant mode and λ -905 nm in pulsed mode. The treatment course was a total of 9 procedural days, three procedures per week for three weeks. The therapeutic methodology used was carried out in two stages. First, a scan of the foot (100-175 cm²) of both lower extremities was performed 20 cm away from the skin with an MLS fixed, robotic multi-diode device (remote technique). Then 7 areas on each lower extremity (fibular neck area, popliteal fossa, medial and lateral malleolus, mid-gluteal fold and two on the dorsum of the foot) were treated, each 3.14 cm² in area, with the MLS single-diode handheld applicator (contact methodology), with a total area of 21.98 cm². The frequency used in both stages is 1500 Hz, Int.100%, energy density:2.52 J/cm² in the remote method and 6.04 J/cm² in the contact method. Statistical methods used: Kolmogorov–Smirnov test, t-test, Mann-Whitney test, chi-square test, Wilcoxon signed rank test, ANOVA, Kruskal-Wallis. Differences were considered significant at alpha level<math>\lt;0.05.

RESULTS

Before treatment, there was no statistically significant difference between the experimental and control groups in terms of the age of diabetes and neuropathy, demographic and anthropometric indices, diabetes therapy administered, and glycated hemoglobin value. This also applies to the values of the lower limb sense of touch index bilaterally (left: $p=0.889$; right: $p=0.966$).

Control group: after the treatment (day 21) and on the 90th day of it, no change in the value of the parameter was observed with baseline parameters.

Experimental group: Left lower limb: after the treatment, there was a decrease in the percentage of patients with sensation at one of the study sites (2.4%), at the expense of an increase in those with sensation at two (41.5%) and three (56.1%) of the study sites. On the 90th day it showed a decrease in the percentage of patients with a monofilament index of 2 (29.3%), at the expense of an increase in those with a value of 3 (68.3%), compared to day 21 (fig.1).

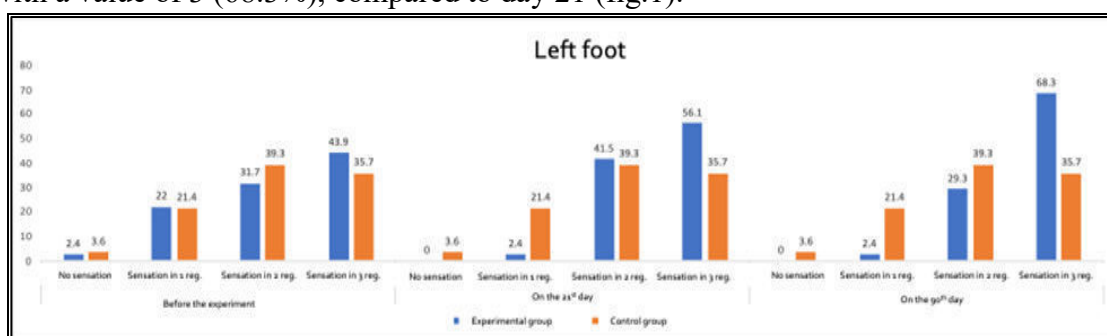


Fig.1 Change in the sense of touch in the left lower limb: baseline, day 21, day 90

Right lower limb: after the treatment, there was a decrease in the percentage of patients with a sense of touch at one of the study sites (2.4%), at the expense of an increase in those with a sense of touch at three of the study sites (63.4%), with no significant difference between groups ($p=0.217$). On the 90th day of treatment, there was a decrease in the percentage of patients with a monofilament index value of 1 (0%) and 2 (19.5%) and an increase in those with a value of 3 (78%) (fig.2).

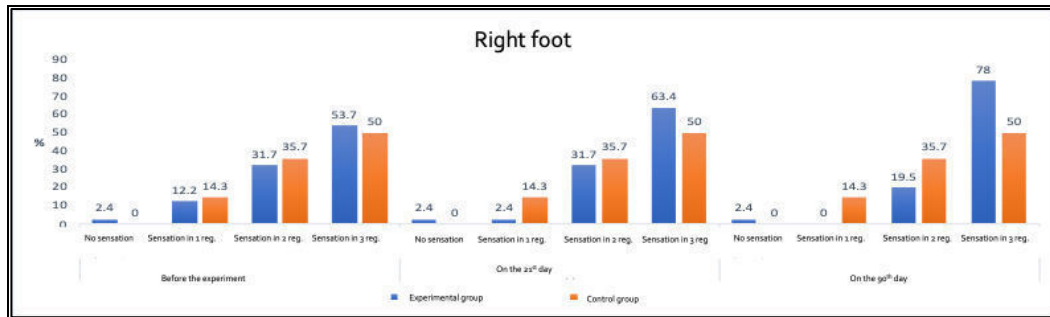


Fig.2 Change in the sense of touch in the right lower limb: baseline, day 21, day 90

The percentage of patients with a sense of touch in all investigated sites at day 90 (left: 68.3%; right: 78%) was higher compared to that not only at day 21 (left: 56.1%; right: 63.4%), but also compared to baseline (left: 43.9%; right: 53.7%) for both limbs. This resulted in a significant difference between the observed and comparison groups for both left ($p=0.006$) and right ($p=0.008$) lower limbs.

Before therapy, the groups were comparable on the mean values of ENG index, DLT, SNAP, and CV (Table 1) on both lower limb. On the 90th day after therapy, there was a significant statistical difference bilaterally in all three parameters (Table 1). In the EG, a greater number (and relative proportion) of patients moved to the lower values of DLT. No such change occurred in the CG. The EG showed an increase in SNAP amplitude bilaterally and the CG showed a decrease bilaterally. In the EG, an increase in mean CV, and in the CG a decrease in CV, was reported bilaterally.

Table 1. ENG data for n. suralis

		Before therapy	90th day after therapy	P
Distal latency		median (IQR)	median (IQR)	
n. suralis left	Experimental	3.0 (1.77)	2.8 (1.55)	0,001
	Control	3.0 (1.60)	3.7 (1.72)	<0,001
	p value	0,888	0,009	
n. suralis right	Experimental	3.1 (1.45)	2.7 (1.26)	0,003
	Control	3.1 (1.35)	3.8 (2.00)	<0,001
	p value	0,976	0,008	
SNAP				
n. suralis left	Experimental	2.6 (4.10)	3.8 (5.20)	<0,001
	Control	2.5 (4.55)	2.2 (4.23)	<0,001
	p value	0,98	0,046	
n. suralis right	Experimental	2.7 (2.85)	3.3 (4.84)	<0,001
	Control	2.4 (4.00)	2.0 (2.83)	<0,001
	p value	0,66	0,028	
CV				
n. suralis left	Experimental	42.9 (7.23)	46.8 (14.60)	<0,001
	Control	43.7 (12.38)	42.1 (10.48)	<0,001
	p value	0,497	0,012	
n. suralis right	Experimental	43.3 (8.03)	46.6 (12.50)	0,001
	Control	43.0 (8.94)	40.55 (8.73)	<0,001
	p value	0,579	0,019	

DISCUSSION

In some of the scientific publications related to the study of the effects of laser therapy on diabetic neuropathy, the 10g monofilament test is used solely as a diagnostic tool, proving the presence of neuropathy by a change in sensitivity [4; 5; 6]. There is a lack of studies investigating the change in surface sensation using the 10g monofilament test, both at the end of the therapy and for a period afterwards. From the presented results of the sense of touch index from our study, it is impressive that in the EG both at the end of treatment and on the 90th day from baseline, there was a significant change

in the percentage of patients with sensation at all sites studied for both lower limbs. In the CG after the treatment and on the 90th day of it no change in the value of the indicator was observed. ENG is an objective, quantitative method giving an assessment of peripheral nerve function. On the 90th day after therapy, the EG showed a shortening of the DLT compared to baseline by 6.7% on the left and 12.9% on the right. There was an increase in the amplitude of SNAP by 46.1% in the left and 22.2% in the right, and an increase in CV by 9% in the left and 7.6% in the right. There was no change in the control group in ENG parameters of n. suralis, which even showed some deterioration. The analysis showed that the statistically significant improvement in sensation based on the results for the sense of touch indicator correlated with the positive changes in the ENG indicators of the n. suralis, both at the end of the MLS-laser treatment and when reporting the results on the 90th day from the start of therapy. The positive results in the EG can be explained by the biostimulatory effect of the laser on the nervous system. Laser therapy induces Schwann cell proliferation, stimulates nerve metabolism, myelination and axon regeneration [7; 8; 9; 10]. Our results for the CV of n. suralis confirm those of Khamseh et al. obtained at the end of the 10-day course of MLS-MIX5 treatment. They reported a 4.4% increase in the left limb and 8.9% in the right limb [5]. A.A. Yamany and H.M. Sayed report a 32% increase in the rate of conduction of n suralis and a 23 % increase in SNAP amplitude in their laser therapy group. In their placebo group, they reported a 10% decrease in conduction velocity along the nerve and a 5.9% decrease in SNAP amplitude [11]. In addition to the positive end-of-treatment results observed by the other authors, our study demonstrates the long-term effect of high-energy, two-wavelength synchronized laser therapy.

CONCLUSION

MLS-laser treatment is associated with significantly improved lower limb sensation as assessed by the 10g monofilament test in patients with diabetic neuropathy. The subjective improvement was confirmed by a significant change in objective ENG scores of n. suralis. The Semmes-Weinstein monofilament test is an effective, inexpensive and easily applicable test. It can be used not only to demonstrate sensory disturbances, but also to detect changes after therapy, including laser therapy.

Abbreviations: MLS - Multiwave Locked System

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THE MARITIME PROFESSION AND THE PHYSICAL AND MENTAL HEALTH OF THE CREW: A STUDY OF ANTHROPOMETRICAL AND PSYCHOLOGICAL ALTERATIONS AFTER THE FIRST TRANSATLANTIC VOYAGE TO THE ANTARCTIC

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ABSTRACT

Numerous scientific studies show that major maritime accidents are often the result of human error, emphasizing the importance of the personality, physical fitness and psychological resilience of the seafarer. The purpose of this study is to assess the changes in the psychophysiological state of crew members who participated in the First Transatlantic Voyage to Antarctica on a Bulgarian scientific research ship with a military crew. Anthropometric, functional and psychological studies were conducted to provide a comprehensive assessment of each crew member's physiological and psychological state. Studies have been conducted before and after transatlantic voyages. The documented changes highlight the impact of extreme sea conditions on the physical and mental health of the crew.

INTRODUCTION

Ship crews are faced with several challenges that test the physique and psyche of every sailor. Combining the trials of marine life with an upcoming expedition to Antarctica puts an extremely strong and important emphasis on the factors influencing the health of marine professionals and their mental resilience. For the first time, a Bulgarian scientific research ship with a military crew provides logistics to the Bulgarian base on Livingston Island, Antarctica. The participants in this unique expedition are exposed to several extreme factors.

After the study of scientific publications examining various aspects of the maritime profession and the peculiarities of the life of scientists in Antarctica, the following groups of factors can be deduced: the natural environment (hydro-meteorological conditions), the habitability of the ship (vibrations, noise, fumes and the limited living conditions for rest, etc.) and the social environment (staying outside the family, lack of information, ability to move, etc.) (12).

MATERIALS AND METHODS

Considering all these specific requirements and the possible consequences for the physical and mental condition of the marine specialists participating in the expedition to Antarctica, a thorough study of the crew members of the scientific research ship "St. St. Cyril and Methodius" was conducted before departure and after return. The conducted study is part of a larger project aimed at researching maritime professionals, including divers, lifeguards at sea, ship specialists, etc. To date, 200 maritime professionals have been surveyed. In the article, we present the changes that occurred in the psychophysiological state of the crew members, as they can be commented on as a result of the specific requirements and extreme loads to which maritime professionals are subjected.

The main hypothesis of our research is that extreme meteorological and climatic conditions, as well as socio-psychological aspects of the maritime profession, have a significant impact on the physical and mental health of the crew, which is manifested in changes in the anthropometry, functional status and psychological endurance of seafarers before and after the transatlantic voyage to Antarctica.

The purpose of the conducted research is to determine the changes occurring in the body of marine specialists under the influence of extreme factors to take care of the health of each member of the crew. The subject of research is the changes that occurred in the physiological and psychological state of marine specialists, and crew members.

The research was carried out by a team including 4 researchers from the Medical University, VVMU and 7 young researchers from the Military Doctor department. They are carried out "in situ" on board

the ship in the real environment in which the research resides throughout the voyage. Research sessions are carried out immediately before departure and after returning from sailing.

Research methods used: Anthropometric studies take into account objective parameters of the human body, determining the ability of the organism to function in a given situation and to adapt to changing conditions (13).

Functional studies of the cardiovascular, respiratory and muscular systems determine their physiological range, which is directly related to the reaction to the dynamics of the professional load. Psychological studies of the ship's crew included: measuring the level of anxiety and depression with the Tsung Questionnaire. Faced with the challenges of the environment and the new way of life, both the body and the psyche must adapt successfully to guarantee the person's normal functioning in the new conditions.

During the review of scientific publications presenting studies of ship crews and participants in polar expeditions, it was found that, as a result of the impact of extreme factors, symptoms of restlessness, anxiety, sleep problems (1,2) and depressive symptoms (6) were observed. Therefore, to establish the changes occurring in the mental and emotional state of the participants in the transequatorial sailing, the level of anxiety and depression was investigated with Zung's questionnaires (Zung's SAS Self-Rating Anxiety Scale); Zung's Self-Rating Depression Scale(9).

RESULTS

1. Functional and anthropometric indicators

2. Psychological indicators

The results for individual indicators from the individual research sessions have been digitized and tabulated. The data were processed with SPSS 19. The following conclusions can be drawn from a comprehensive analysis of the obtained data:

When chest circumferences are measured – reduced values can be evaluated as reduced chest wall mobility. This tendency is shifted to the left of the table, i.e. towards older age. An exception is the case of increased weight, which explains the higher values. When measuring waist circumference, no significant trend was reported. Presence of a significant change in measured calf circumference. It is found that the circumference measured after returning is smaller. In the processing of the indicators with the program SPSS 19, Ulcoxon's test for the comparison of two dependent samples was found to be statistically significant in the comparison of the indicators when measuring the calf before departure and the indicators of its measurement after returning ($Z = -3.418$; $p < 0.001$). This can be discussed as a result of the reduced motor activity on board associated with the limited dimensions of the deck and other spaces. In everyday life, a person on land takes 5-10,000 or more steps. The size of the calf reflects the muscles for maintaining upright posture through the Achilles tendon during standing and walking.

Reporting of changes in the measurement of skin folds (caliperometry) of the body's upper and lower limbs. With the statistical data processing program using the Wilcoxon test, statistically significant differences were found when comparing the body skinfold measurements of the subjects before departure and the data obtained after their return ($Z = -2.877$; $p < 0.005$).

The studied % lipid content in body composition before departure and after return changed from -12.4 to +9.9. It was found to reduce the percentage of lipids in more than half of the cases.

No significant changes were observed during the performed functional tests.

Changes in the investigated levels of anxiety and depression measured before departure and after return are reported. By Wilcoxon statistical analysis, statistically significant differences in the level of depression were observed. The level of depression of the subjects measured before departure and compared with the results after their return from the expedition showed statistically significant differences ($Z = -2.260$; $p < 0.0027$). Statistically significant differences were observed in the level of anxiety in the subjects measured before departure and after return ($Z = -2.228$; $p < 0.0027$). The obtained results show dynamics in the mental state of the crew members. The effects of a 4-month long voyage, crossing 5 time zones and 5 more climate zones test the psyche of each crew member. The continuous

adaptation to the changes imposed by the environment, and the accumulated fatigue from the long voyage have an impact on mental health. The reported changes in the level of anxiety and depression were within the normal range, despite a slight increase in the values of the scales measured after return.

CONCLUSIONS

The conducted studies report changes in the measured physiological and psychological indicators. The dynamics in the values strongly depend on the individual characteristics of the person, his resources and attitudes to cope with prolonged extreme stress. The reported changes in the measured values for the various indicators are within the norm, which is an indicator of the good selection and training of the crew.

Discussion: The obtained results prove the importance of this first study and raise the question of the need to fully monitor the health status of ship crews participating in long voyages to care for the well-being of the crew and the successful performance of the assigned tasks. It follows the accumulation of a rich database of subsequent voyages. The presented model is in the process of being upgraded and improved.

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ESSENTIAL OILS AS A THERAPEUTIC APPROACH IN THE TREATMENT OF CHEMOSENSORY DISORDERS

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ABSTRACT

The senses of taste and smell play a vital role in conveying information about our surroundings. Sometimes loss of taste and smell is an early symptom of Parkinson's and Alzheimer's disease. The increasing number of patients with post-viral olfactory dysfunction (PVOD) following the COVID-19 pandemic has increased the general interest and concern about olfactory dysfunction. Olfactory dysfunction is perceived as a symptom affecting cognition, perception, emotional state and behavior that has a huge impact on the patient's quality of life. Common etiologies of anosmia and hyposmia include head trauma, acute or chronic rhinosinusitis, neurological changes secondary to SARS-CoV-2 infections, and neurodegenerative diseases. Currently, there are no established standard therapeutic methods for the treatment of PVOD. The antiviral effects of essential oils have been proven and are considered a natural antibiotic and have a unique set of benefits. They not only fight the bacteria and viruses that cause infections, but also provide care for both the microbiome and the overall health of the person. This makes them a preferred agent as a new therapeutic approach in the treatment of chemosensory disorders. **Aim** The aim of this article is to address the therapeutic antimicrobial approach in essential oil treatment of chemosensory disorders. **Materials and methods** Summarizing information from the world literature and sources regarding studies conducted on the use of essential oils as a therapeutic antimicrobial approach in the treatment of chemosensory disorders. **Results and conclusions:** Aromatherapy is a practice of complementary and alternative methods that involves the wide application of essential oils, including the prevention and treatment of respiratory diseases, improvement of mood and increased cognitive function.

Key words: therapeutic approach, essential oils, antimicrobial effects

INTRODUCTION

The common cold is the most common infectious disease in modern society and is caused by rhinoviruses, some coronaviruses, and others (*Haehner A et al., 2022; O'Byrne L et al., 2022*). It initially causes irritation in the nasopharynx, which quickly progresses to copious nasal discharge, stuffy nose, then a loss of smell that can last between 3 and 4 days, due to severe swelling and inflammation of the nasal mucosa. After applying unclogging drops, the sense of smell often returns for a short time, and after a relapse - it is almost always completely restored. The situation is different with the covid-19 infection. In most cases, the loss of smell occurs suddenly, in 36% it is accompanied by a loss of taste, and most importantly - at the time of its onset, there is almost always no increased nasal secretion (*Rebholz H et al., 2020*). The ongoing coronavirus disease 2019 (COVID-19) pandemic has drawn attention to PVOD, which affects > 50% of patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (*Tong JY et al., 2020*). In a meta-analysis of COVID-19 associated OD by *Hannum et al., (Hannum ME et al., 2020)* the investigators used a random-effects model and computed an overall prevalence estimate of 50.2% (95% CI, 38.9–61.5%) (*Helman SN et al., 2022*). Even if there is, it is lighter and incomparable to that of the common cold. The reasons for this have not yet been fully elucidated, and recent clinical studies have proposed various mechanisms for its occurrence - most often direct neurological damage to the olfactory epithelium, which occupies about 1.5% of the entire nasal mucosa (*Izquierdo-Dominguez A et al., 2020*). Sometimes loss of taste and smell is an early symptom of Parkinson's and Alzheimer's disease (*Haehner A et al., 2011; Zou*

YM et al., 2016; Torres-Pasillas G et al., 2023). Ample data have been collected on the potential capabilities of essential oils to potentiate antiviral effects and are considered a natural antibiotic, providing them with a unique set of benefits. They not only fight the bacteria and viruses that cause infections, but also provide care for both the microbiome and the overall health of the person. This makes them a preferred agent as a new therapeutic approach in the treatment of chemosensory disorders.

Aim The purpose of this article is to address the therapeutic antimicrobial approach in essential oil treatment of chemosensory disorders.

MATERIALS AND METHODS

Summary of information from the world literature and sources regarding research conducted on the use of essential oils as a therapeutic antimicrobial approach in the treatment of chemosensory disorders.

RESULTS

Currently, there are no established standard therapeutic methods for the treatment of post-viral olfactory dysfunction (PVOD) (*Koyama & Heinbockel T, 2022*), but the most commonly used method is a combination of essential oils, which is part of aromatherapy (*Gagnier JJ et al., 2013; Donelli D et al., 2023*). It was observed that patients with long-lasting COVID-19-related smell dysfunction improved after a 30-day olfactory training protocol including application of essential oils (*Donelli D et al., 2023*). The term “olfactory training” has been used based on the concept of training olfactory sensory neurons to relearn and distinguish olfactory stimuli. The essential oils used in olfactory training typically include rose, lemon, clove, and eucalyptus, which were selected based on the odor prism hypothesis proposed by Hans Henning in 1916 (*Koyama & Heinbockel T, 2022*). Aromatherapy is a practice of CAM (complementary and alternative methods) that involves the wide application of essential oils, including the prevention and treatment of respiratory diseases, improvement of mood and increased cognitive function. Antibiotic resistance is a complex and growing international public health problem with important consequences such as increased mortality and economic impact. CAM therapies also provide strategies and solutions that contribute to reducing the inappropriate use of antibiotics. A large number of essential oils are available on the Bulgarian market, with a different registration regime (medicinal products without a doctor's prescription, nutritional supplements, aromatherapy synergies, etc.). The richest blend of essential oils on the Bulgarian market is Carmolis® (*Menthol racemic, Thymi oil, Anisi oil, Cassiae oil, Caryophylli floris oil, Limonis oil, Lavandulae oil, Spicae oil, Citronellae oil, Salviae oil, Myristicae oil*). Carmolis® is an over-the-counter medicinal product that has a wide range of uses - oral drops, solution, solution for skin, solution for vapor inhalation and is used for stomach complaints, nervousness, travel disturbances, pain in the limbs. Another medicinal product is Tavipec® capsules. Contains lavender essential oil with a nourishing effect and adjuvant to antibiotic treatment for: acute and chronic bronchitis; bronchiectasis; cough in smokers; sinusitis. GeloMyrtol® soft capsules is a distillate of four different ELOM-080 plants (*eucalyptus, sweet orange, myrtle, lemon*). It exhibits mucolytic, secretomotor, secretolytic, antimicrobial, antioxidant, anti-inflammatory and antispasmodic effects. Roscalipt® capsules is a food supplement containing essential oils of rosemary (*Rosmarinus officinalis*) and eucalyptus (*Oleum Eucalyptus*) with a beneficial effect on lung function, the structure and functions of the liver and as an antioxidant. Medicines containing plant essential oils, as well as their individual components, used in the treatment of infectious diseases are well documented. This makes them suitable in the treatment of chemosensory disorders. However, choosing an appropriate safe oil and determining the most effective concentration should be taken into account to avoid any side effects during their use.

CONCLUSION

Currently, multiple publications have found an association between SARS-CoV-2 (COVID-19) infection and olfactory and/or gustatory dysfunction. These data suggest that there is a significant association between viral infection and olfactory or gustatory dysfunction and that this information

may aid in the early diagnosis of SARS-CoV-2 disease. Early diagnosis of olfactory disorders and the application of essential oil treatment methods can effectively stimulate the recovery of the sense of smell, improve the quality of life of patients and prevent complications.

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CONSUMPTION OF ALCOHOL-BASED HAND RUBS – 2018-2022 EPIDEMIOLOGICAL TRENDS AND EMPIRICAL LESSONS FROM BULGARIA

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ABSTRACT

Modern epidemiology studies various data trends to improve the IPC protocols and to prevent healthcare-associated infections (HAIs). This study **aims** to present the trends of alcohol-based disinfectants (ABD) consumption (used mainly for hand rubs) at a hospital level (University Hospital "St. Marina") and to compare it with data published in the scientific literature regarding pre-COVID, during-COVID and in the post-COVID period. The level of ABD consumption is a golden standard defined by the World Health Organisation (WHO), showing compliance of medical personnel to the good medical practice guidelines for hand hygiene.

Material and methods: single-center retrospective observational study of data from the hospital information system related to the consumption of ABD.

Results and comparative analysis: Data from the present study show that the total hospital use of ABD increased during the COVID-period (2020-2021) reaching 16.29 ml/patient-day (PD). However, during the post-COVID period, it returned to the levels from 2018 - 8.82 ml/PD.

Comparatively, our data shows that the amount of used ABD for the period at stake (2018-2022) corresponds to the results of a European study completed in 2012. Concretely, the use of ABD in the intensive care units of German hospitals increased to 129.4 ml/PD in 2018, and for non-risk wards to 28.8 ml/PD.

Conclusions: This is the first national study to provide open data with the idea of stimulating development and demonstrating the need for continuous personnel training on the quality of hand hygiene, as well as on compliance with the 5 hand hygiene steps by the WHO. There were good practices within the University Hospital "Saint Marina" in 2017-2018, when training was conducted on the topic "Techniques for hand hygiene with ABD". Lifelong education will improve personnel compliance and the incidence of HAIs.

Keywords: public health, consumption of alcohol disinfectants, hand hygiene, healthcare associated infections, Bulgaria, University Hospital "St. Marina"-Varna.

INTRODUCTION

In the context of infections prevention and control (IPC), modern epidemiology studies various data trends to improve the IPC protocols and to prevent healthcare-associated infections (HAIs). This study **aims** to present the trends of alcohol-based disinfectants (ABD) consumption (used mainly for hand rubs) at a hospital level (University Hospital "St. Marina") and to compare it with data published in the scientific literature regarding pre-COVID (2018-2019), during-COVID (2020-2021) and in the post-COVID (2022) periods of time. The level of ABD consumption is a golden standard defined by the World Health Organisation (WHO), showing compliance of medical personnel to the good medical practice guidelines for hand hygiene [1].

MATERIAL AND METHODS

Single-center retrospective observational study of data from the hospital information system related to the consumption of ABD mainly applied for hand rubs. Descriptive statistics are applied. A participatory approach is also applied, possible due to the professional positions of the researchers.

HAND HYGIENE AND HAIS – STANDARDS FOR PREVENTION AND CONTROL

Hand hygiene is one of the most cost-effective and efficient measures to prevent HAIs and the transmission of multidrug-resistant microorganisms [2; 3].

Rubbing hands with an ABD is a universal standard for hygienic disinfection. The 5 moments indicating mandatory hygienic disinfection are practical innovative elements of the strategy for successfully providing safe and quality medical care. Studies show that less than 40% of medical

personnel adhere to the rules of the 5 moments that are an indication of mandatory hygienic hand disinfection [4].

Research proved that the application of a single, easily implemented and affordable measure, such as the disinfection of the hands of medical personnel, can significantly reduce the levels of HAIs. A study conducted in 2020 at hospital settings found that increasing readiness to perform hand disinfection from 48% to 66% over a five-year period resulted in a reduction in the incidence of HAIs by more than 40% [5].

Measuring hygiene products consumption is an indirect method of assessing compliance with hand hygiene recommendations. Quantities of liquid soap, alcohol-based disinfectant and hygiene materials used by staff are measured to collaterally assess the level of IPC. The application of the method is easy, cost-effective time saving, and does not influence behaviors, therefore is objective. Certainly, there are weaknesses of this method the impossibility of assessing the quality of hand hygiene, whether all the rules for high-quality hygienic disinfection have been observed etc. However, it is worth doing it, focusing on the social and medical significance of hand hygiene [6].

ABD CONSUMPTION - RESULTS AND COMPARATIVE ANALYSIS:

University Hospital "St. Marina"-Varna is the largest university hospital in North-Eastern Bulgaria, which has 1290 beds and in addition 103 places for short-term care. The hospital is an attractive nationwide clinical centre due to its large capacity and high-tech equipment.

Maintaining adequate hand hygiene, including the use of ABD, is one of the key measures that University Hospital "St. Marina"-Varna implements in the fight against HAIs. Further, this was one of the crucial measures implemented during the COVID-pandemic. It has been proven to be one of the most reliable measures against the spread of HAIs.

This publication presents, in open access mode, summarized data from all clinics and departments, as well as day inpatients at the University Hospital "St. Marina"-Varna for the pre-COVID (2018-2019), during-COVID (2020-2021) and in the post-COVID (2022) time periods.

Data from the present study show that the total hospital use of ABD increased during the COVID-period (2020-2021) reaching 16.29 ml/patient-day (PD). However, during the post-COVID period, it returned to the levels from 2018 - 8.82 ml/PD [Fig. 1].

Comparatively, our data shows that the amount of used ABD for the period at stake (2018-2022) corresponds to the results of a European study completed in 2012. Concretely, the use of ABD in the intensive care units of German hospitals increased to 129.4 ml/PD in 2018, and for non-risk wards to 28.8 ml/PD [7].

The overall hospital consumption of ABD during the Covid-period (16.29 ml/PD) approximates results from a European spot study on the prevalence of HAIs and the antimicrobials consumption conducted in 805 European hospitals in the two-year period - 2011-2012, which showed a mean use with a value of 18, 7 ml/PD (interquartile range 10,3–30,6 ml/PD) [8].

The data presented here from the Hospital information system of "St. Marina"-Varna shows that the amount of ABD used for the period considered (2018-2022) corresponds to the results of a European study conducted between September 2011 and March 2012, covering 232 hospitals from 24 countries - median hospital use of 21 mL (interquartile range 9–37 mL/PD), 66 mL/PD (interquartile range 33–103 mL/PD) at the intensive care units (ICU) level, and 13 mL/PD (interquartile range 6–25 mL/PD) in the non-risk departments [9].

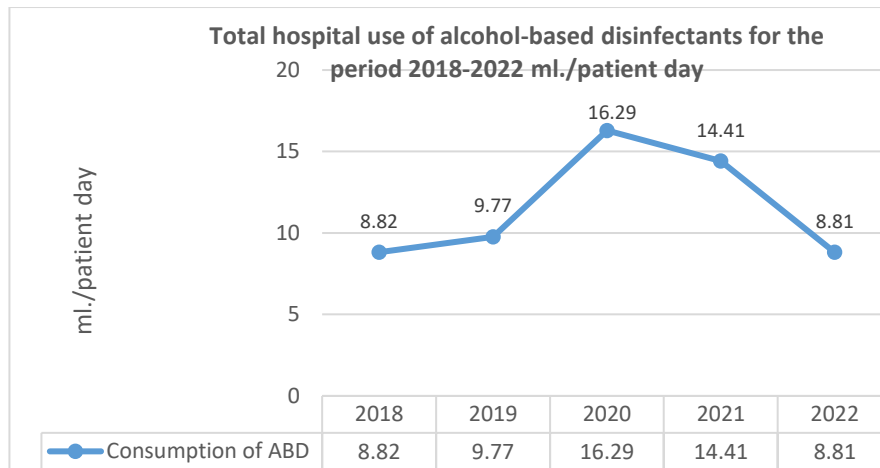


Fig. 1. Total hospital use of ABD for the period 2018-2022 ml./patient day Source: Hospital information system

Additionally, the use of ABD in the ICUs was studied based on the amount of ABD used and the beds/per day - Clinic of anaesthesiology and intensive treatment (CAIT), Pediatric clinic for intensive treatment (PCIT) and Clinic for intensive treatment and non-invasive ventilation (CITNV) [Fig. 2].

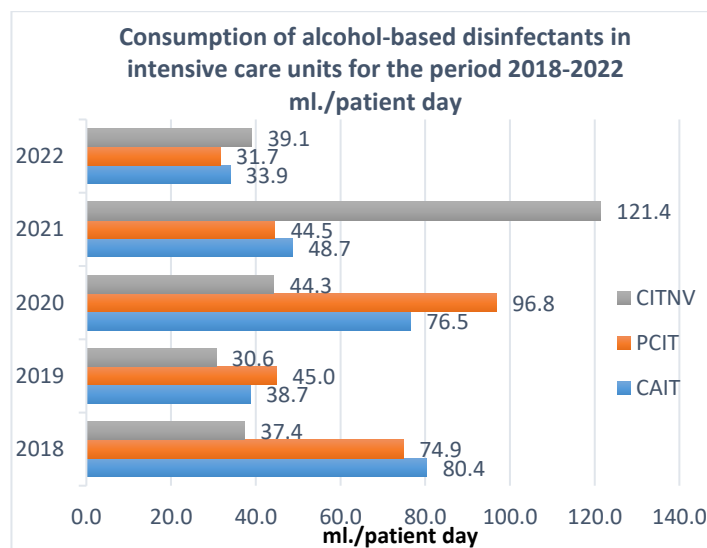


Fig. 2. Use of alcohol-based disinfectants in intensive care units from 2018 to 2022. Source: Hospital information system.

Abbreviations: Clinic of anaesthesiology and intensive treatment (CAIT), Pediatric clinic for intensive treatment (PCIT) и Clinic for intensive treatment and non-invasive ventilation (CITNV)

The amounts of ABD consumption in the intensive care clinics increased during the Covid-period, reaching 76.5 mL/PD for the CAIT, the PCIT - 96.8 mL/PD, and in the CITNV unit, the values increased threefold and reached 121 mL/PD in the year 2021. The 2018 results for the ABD consumption in the intensive clinics were significantly higher compared to the data in 2019, with values for the CAIT twice as high in 2018 (80.4 mL/PD) compared to the year 2019 (38.7 mL/PD). One of the explanation is that the 2018 increase in the amount of ABD consumption in the ICU was due to the trainings of the personnel on "Technique for hand hygiene with an alcohol-based disinfectant" during the pre-COVID period – from 2017 to 2018. The same trainings were held at the beginning of the COVID crisis 2020.

CONCLUSIONS

This is the first national study to provide open data with the idea of stimulating development and demonstrating the need for continuous personnel training on the quality of hand hygiene, as well as on compliance with the 5 hand hygiene steps by the WHO.

Successful global networks such as Health promoting hospitals [10] can stimulate every inpatient setting to be prepared for any kind of epidemic challenge. The good practices conducted within the University Hospital “Saint Marina” in 2017-2018, including training of the medical and health personnel on the topic "Techniques for hand hygiene with ABD" need to be multiplied at a national level. Lifelong education will improve personnel compliance and reduce the incidence of HAIs. The COVID crisis has proven that any training leads to increased hand hygiene compliance and when the danger is over, staff is gradually neglecting IPC measures. Importantly, standardized IPC measures are needed in every hospital against little-known or unknown biological threats.

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ONE HEALTH APPROACHES IN VETERINARY ORTHOPEDICS AND NEUROSURGERY – PERIOPERATIVE ALGORITHMS BASED ON HUMAN MEDICINE GUIDELINES

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ABSTRACT

The sustainable development of public health demands holistic approaches and the One Health (OH) movement offers such strategies. By utilizing principles based on OH and interdisciplinary expertise, the best practices and algorithms in human medicine can be applied to veterinary surgery.

The **aim** is to present the practical transfer of experience from human to veterinary medicine, with the goal of reducing surgical site infections (SSIs) in small animal veterinary surgery, specifically orthopaedics and neurosurgery.

Methods: A long-term pragmatic retrospective and prospective epidemiological study in veterinary surgery was followed by a literature review of successful human medicine practices in infection prevention and control (IPC). Proposals for care measures and practical recommendations were made to reduce postoperative complications.

Results: Standard monitoring systems are not present in veterinary surgery. Data and studies in veterinary medicine are scarce in the field of IPC. There is a lack of standardized good practices for the IPC associated with veterinary care.

Conclusions: Applying established procedures and practices from human to veterinary surgery presents a major opportunity and should form the basis for systematically incorporating OH approaches in public health and clinical practices. OH collaboration is needed to create high-quality algorithms acceptable and applicable to qualified veterinary teams to prevent SSIs in the context of the growing public health challenge of antimicrobial resistance.

Keywords: *Public Health, Infection Prevention and Control (IPC), One Health (OH), Surgical site infections (SSI), Antimicrobial resistance (AMR), Guidelines, Bulgaria*

INTRODUCTION

The sustainable development of public health demands holistic approaches and the One Health (OH) movement offers such strategies. By utilizing principles based on OH and interdisciplinary expertise, the best practices and algorithms in human medicine can be applied to veterinary surgery.

This report focuses on Surgical Site Infections (SSIs) in veterinary practice and explores ways to prevent them by studying and building upon existing Infection prevention and control (IPC) algorithms applied in human medicine. SSIs are complications in veterinary surgery with varying frequency, which occur within 30 days after a surgical intervention or within 90 days of an implant placement.

The aim of this report is to present the practical transfer of experience from human to veterinary medicine, with the goal of reducing SSIs in small animal veterinary surgery, specifically orthopaedics and neurosurgery. The following objectives have been formulated by the interdisciplinary team of experts to achieve the aim: 1) Short but substantial introduction to the philosophy of the One Health movement; 2) Review of the research on the subject - national and international data; 3) Analysis of the experience and measures to reduce SSIs; 4) Adaptation of IPC measures from human medicine in the veterinary surgery of animals – cats and dogs (orthopaedics and neurosurgery); 5) Identification of good practices and a summary of the training opportunities among veterinary surgeons in Bulgaria.

MATERIALS AND METHODS

A long-term pragmatic retrospective and prospective single-practice epidemiological study in veterinary surgery was followed by a literature review of successful human medicine practices in IPC. Pragmatic studies are conducted to evaluate the effectiveness of interventions under real-life routine

practice conditions, with the objective of producing results that have the potential for generalization and application in typical practice settings [1]. Therefore, proposals for potential guidelines and practical recommendations were formulated in order to mitigate postoperative complications.

RESULTS

The results of the study are presented in a threefold manner. Firstly, the One Health concept will be briefly introduced as it deserves recognition. The second part outlines the state of the art regarding IPC in veterinary surgery in Bulgaria and the study done by Dr Zlatinov and Dr Ivanov. Finally, guidelines are proposed based on the human medicine standards and experts' experience.

1. One Health philosophy and values – human and veterinary medicine hand in hand

The One Health concept is defined in various ways, but at its core is a public health mission that advocates closer cooperation and coordination between all spheres of life to protect the environment and the health of humans, animals and plants [2]. The ideas of OH are still not widely recognized and remain unfamiliar in Bulgaria. The first steps were taken at the Medical University of Varna in 2022 with a research project examining various dimensions of OH and disseminating OH ideas on a national scale [3]. This part of the report is a continuation of these ongoing efforts.

Nowadays, OH is a unifying holistic philosophy that enables integrative approaches to balancing and optimizing human, animal and plant health, combined with environmental preservation. The conceptualization of unified health has undergone evolutionary development from the beginning of the century to the present day [4, 5]. The transition from the progressive idea of "One Medicine" to the unifying movement of the XXI century - "One Health" is supported by all international organizations [6].

The Global Action Plan of the Quadripartite was published in October 2022 by four United Nations (UN) organizations - The Food and Agriculture Organization (FAO), The UN Environment Program (UNEP), The World Health Organization (WHO), The World Organization for Animal Health (WOAH). This report presented for the first time the holistic definition of One Health, proposed by the One Health High-Level Expert Panel (OHHLEP) [7]. "One Health is an integrated, unifying approach that aims to sustainably balance and optimize the health of people, animals, and ecosystems. It recognizes the health of humans, domestic and wild animals, plants, and the wider environment (including ecosystems) are closely linked and interdependent". The OH approach mobilizes multiple sectors, scientific fields and communities from different public health levels to collaborate in promoting well-being and addressing threats to health and ecosystems, while meeting the collective needs for clean water and air, affordable energy sources, proper agriculture and veterinary policies, sustainable IPC and stewardship regulations etc. The OHHLEP of the Quadripartite frames the following areas, in which The One Health approaches are essential, and they are as follows: 1) food and water safety; 2) IPC of the zoonoses; 3) environmental control; 4) AMR tackling "the silent epidemic". Particularly, the current analysis is focused on the second field – "IPC of the zoonoses", within a national context and is based on the empirical evidence from a single practice. The initial intent was to apply advancements from human medicine-to enhance IPC in veterinary orthopedics and neurosurgery services using the OH approaches (Figure 1).

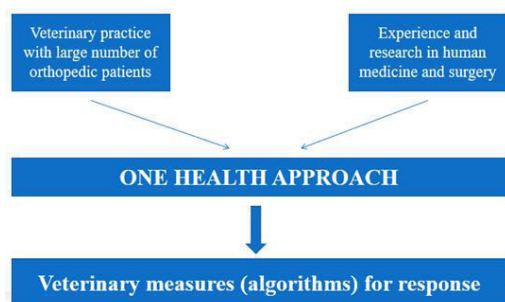


Figure 1: The One Health approach to manage IPC in veterinary practice - human and veterinary medicine hand in hand.

2. State of the art in IPC – evidence-based knowledge and professional experience in veterinary orthopaedics and neurosurgery

Nationally, there is scarce data regarding standardized measures or guidelines [8,9] for the IPC control of the infection related to veterinary medicine services (IRVMS), as well as for SSIs. There is no equivalent document in veterinary medicine comparable to the one available for human medicine - "Order No. 3, May 2013, for the approval of a medical standard for the prevention and control of nosocomial infections" [10]. The research in the field is lacking and there are knowledge gaps regarding relevant IPC measures in veterinary surgery. Implementation of perioperative care measures can significantly impact SSIs by reducing their incidence in the context of IRVMS [11].

Retrospective data analyses (single-practice study by Dr Zlatinov) showed a process of gradual and stable uphill trend regarding IRVMS and SSIs in the veterinary practice for a 10-year period. For the first five years, an average level of SSIs is maintained between 1 – 2 % of the surgical cases, and after this period a sharp increase is observed until the development of SSIs in about 5% of the cases. The statistics include only infections that appeared in a short post-operative period - up to 30 days after the surgical intervention and the analysis showed that: complications are observed almost entirely in dogs, very rarely in cats; the multidrug-resistant (MDR) isolates were mostly from samples from the surgical wash basin, the manual instrument handling area, the patient preparation area, and from other areas in the clinic; banal microflora was isolated from an orthopedic power tool, sterilized with dry paraformaldehyde tablets.

The following isolates were identified: MDR *Staphylococcus pseudointermedius* - 70%; *Enterobacter* spp., *Pseudomonas aeruginosa*, *Klebsiella* spp., *Proteus* spp.- 20%; and banal Gram-positive microorganisms in the remaining 10% of the cases.

The presence of endogenous strains of multiresistant microorganisms, often isolated from surfaces, equipment and medical devices from the clinic, was observed. In about 70% of SSI cases, it was *S. pseudointermedius*. At the peak of nosocomial infections, SSI levels exceeded 20% after orthopedic operations, which necessitates a temporary suspension of the activity of the orthopedic sector of the clinic. The high rate of complications requires consultation with a specialist and the search for adequate IPC (Dr D. Ivanov, who is a part of the authors team). As a result, the primary factors for SSIs increase were identified as follows: knowledge gaps regarding IPC and personal hygiene; low personnel compliance with the IPC measures; poor IPC practices; insufficient organisational structure regarding IPC; lack of screening tests for IPC check.

3. Beyond the state of the art in IPC in veterinary medicine – steps ahead

Building on the human medicine IPC guidelines and practices the following measures were proposed: regular training for personnel; spatial isolation of the surgical rooms in a new separate sector of the clinic after a significant technological reconstruction; optimising the use of disinfectants; minimizing the stay of patients in the clinic and adapting the antibiotic policy by conducting systematic studies of resistance to antibiotics of the isolates.

The effect on the incidence of SSIs was monitored for one year after the measures were introduced. The following results were observed: lowering trends in SSIs – among 1% of all clinical cases, 90% of isolates are identified as the multiresistant *S. pseudointermedius*. Two months after implementing the measures outlined in the report, MDR organisms have not been isolated from surface samples in critical areas of the clinic. A decrease has been observed in the rate of postoperative complications and in the use of antibiotics for SSI treatment.

Furthermore, a second practice has been built based on these recommendations. Currently, the veterinary practice primarily specializes in veterinary orthopedics and neurosurgery, emphasizing the need for high-quality IPC to minimize SSIs. At the beginning of clinical work organization, hygienic measures and algorithms regarding IPC are introduced in the clinic. The concept of the IPC team – comprising a veterinarian, IPC consultant and infectious disease epidemiologist – is to implement human medicine IPC standards with the potential to alleviate the burden of SSIs in veterinary practices.

Currently, the specific human medicine standards are supplemented with methodology guidelines of the Ministry of Health in Bulgaria, which introduce perioperative “care bundles”[12].

CONCLUSIONS

Applying established procedures and practices from human to veterinary surgery presents advantages and should form the basis for systematically incorporating OH approaches in public health and clinical practices. OH collaboration is needed to create high-quality algorithms acceptable and applicable to qualified veterinary teams and to prevent SSI in the context of the growing public health challenge of antimicrobial resistance. There is convincing empirical data that supports the development of standardized set of guidelines that can be followed in order to reduce IRVMS in veterinary practice. A pilot training workshop was conducted among leading veterinary surgical practices to introduce and discuss the proposed guidelines. The next steps will involve disseminating these guidelines, with this report serving as the initial phase of this process.

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A CLINICAL EFFECTIVENESS STUDY OF A PHYSICAL FACTORS COMPLEX IN CHILDREN WITH SLEEP-DISORDERED BREATHING SYNDROME (SDB) AND THE ASSOCIATED DAYTIME BEHAVIORAL SYMPTOMS

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ABSTRACT

SDB syndrome is a spectrum of obstructive disorders, the most severe of which is obstructive sleep apnea (OSA). It is associated with behavioral daytime symptoms such as mouth breathing, sleepiness, decreased attention, hyperactivity, learning and weight problems. The aim of our study was to investigate clinically and to evaluate the therapeutic effects of a complex of physical factors to influence the daily behavioral symptoms associated with SDB syndrome caused by adenotonsillar hypertrophy in children. **Materials and methods:** The study involved 76 children aged 3-10 years with tonsillar hypertrophy grade 3+, 4+ and several of the daily symptoms associated with the syndrome of disturbed nocturnal breathing (SDB). Clinical, physical, documentary, and statistical methods were used. The physiotherapy /PT/ program included: polarized, polychromatic, non-coherent, low-energy light /PPNL/ (Biopton - does not contain UVL) - 20 procedures; therapeutic ultrasound in the submandibular area. **Results:** a significant decrease in the mean values of the degree of tonsillar hypertrophy and the size of the nasopharyngeal tonsil immediately after treatment was observed / $p=0.0001$ /. During the first month, the physiotherapeutic effect is retained, and in the 3rd month it begins to decrease. The reduction in the extent of tonsillar hypertrophy correlated relatively strongly positively with a reduced incidence of sleepiness ($r=0.358$; $p=0.002$), and reduced attention ($t=6.400$; $p=0.0001$). A reduction in tonsillar hypertrophy ($p<0.05$) by month 3 and a reduction in nasopharyngeal tonsils after month 3 ($p<0.05$) were also observed, which correlated with a reduction in the incidence of sleepiness ($p=0.002$). The incidence of reduced attention decreased immediately after PT ($t=6.400$; $p=0.0001$), with no difference at month 3 ($t=-1.424$; $p=0.159$), as did the incidence of hyperactivity after therapy and at months 1 ($p=0.531$) and 3 ($p=0.159$). **Conclusion:** We have found correlations between the reduction of tonsillar hypertrophy and adenoid vegetations, and the influence of daytime behavioral symptoms associated with disturbed nocturnal breathing in children. The applied complex of physical factors has good therapeutic potential in this pathology. Research in this direction needs to be continued.

Keywords: disordered nocturnal breathing syndrome, adenotonsillar hypertrophy, daytime behavioral symptoms, physical factors

INTRODUCTION

SDB syndrome encompasses a spectrum of obstructive disorders, the most severe of which is obstructive sleep apnea (OSA). It is associated with nocturnal symptoms such as snoring, pauses in breathing, restless sleep, nightmares, enuresis nocturna. Daytime symptoms include mouth breathing, sleepiness, decreased attention, hyperactivity, learning problems, weight problems (8). Statistically, tonsillar hypertrophy ranks first as a reason for children and their parents to visit general practitioners and subsequently otolaryngologists. It is frequently associated with upper respiratory tract infections (tonsillopharyngitis) and the development of sleep-disordered breathing (SDB) syndrome, which determines the great interest of the medical community (7).

SOSA can be of central neurological origin (in < 5% of cases) or of obstructive origin (in > 95% of cases), affecting between 1% and 5% of children between two and eight years of age (6). Some authors

have found evidence of familial burden in adenotonsillar hypertrophy. (5) If the disease is left untreated, various cardiovascular, metabolic, and neurological comorbidities may occur. Serious behavioral problems may also occur in children.

The aim of the present clinical study was to evaluate the therapeutic effects of a complex of physical factors in influencing the daily behavioral symptoms associated with SDB syndrome caused by adenotonsillar hypertrophy in children.

MATERIAL AND METHODS

The study involved 76 children aged 3-10 years with tonsillar hypertrophy grade 3+, 4+ and with sleep-disordered breathing (SDB) syndrome with one or more of the daytime behavioral symptoms: daytime sleepiness, decreased attention, hyperactive behavior, who underwent physical therapy and rehabilitation at the St. Marina Diagnostical and Medical Center – Varna. All parents gave their written informed consent for their children to participate in this study.

The following methods were used: Clinical methods - anamnesis, method of assessing the size of the palatine tonsils; Documentary and Statistical Methods - questionnaire method, statistical processing of data; Physical Methods: preformed physical factors were applied to the children as follows: exposition to light 5 + 5 min. submandibular area in the tonsil area with polarized, polychromatic, non-coherent, low-energy light with the Bioptron device /does not contain ultraviolet rays /-for anti-inflammatory and biostimulating effect - 20 procedures and ultrasound therapy in the same area - 0,4 W/cm² - 4 + 4 min - for fibrolytic, anti-inflammatory and anti-edematous effect of the US - 10 treatments. The proposed FT program is safe and painless for children. The results were assessed at four time points: before, after treatment, at 1 and 3 months.

Criteria for Exclusion: Children with evidence of severe OSA indicated for immediate tonsillectomy; Children with acute purulent tonsillitis; Febrile condition; Children over 10 years of age; Children whose parents refuse PT treatment.

RESULTS

After the treatment, there was a significant decrease in the mean values of the degree of tonsillar hypertrophy. $p = 0.0001$. There was a significant reduction in the size of the palatine tonsils. On the first month the physiotherapeutic effect was retained, and on the 3rd month it began to deplete (Table 1)

Table 1. Changes in the mean values of the degree of tonsillar hypertrophy after PT

Indicators	Mean	SD	Mean Difference	SD	<i>t</i>	<i>p</i>
Tonsillar hypertrophy post PT	2,027	0,519	-0,040	0,257	-1,349	0,181
Tonsillar hypertrophy 1 month post PT	2,067	0,502				
Tonsillar hypertrophy 3 months post PT	2,253	0,548	-0,226	0,421	-4,657	0,0001

A positive effect of the implemented therapy was also observed in terms of adenoid vegetation. There was a statistically significant difference in the size of the nasopharyngeal tonsil before and immediately after PT ($t=4.682$; $p=0.0001$), as well as immediately after PT and three months after it ($t=-2.838$; $p=0.0006$). (Table 2).

Table 2. Changes in mean values of nasopharyngeal tonsil size after PT

Indicators	Mean	SD	Mean difference	SD	<i>t</i>	<i>p</i>
Nasopharyngeal tonsil after PT	1,280	0,508	-0,040	0,305	-1,136	0,260
Nasopharyngeal tonsil 1 month post PT	1,320	0,524				
Nasopharyngeal tonsil 3 months post PT	1,400	0,593	-0,120	0,366	-2,838	0,006

In the observed daily behavioral symptoms associated with SDB syndrome, we found that there was a reduction in the number of children with daytime sleepiness, but the difference was not statistically significant. / Table 3/

Table 3. Changes in the mean values of the frequency of sleepiness before and after PT

Indicators	Mean	SD	Mean difference	SD	<i>t</i>	p
Sleepiness before PT	0,447	0,551	0,140	0,390	3,235	0,002
Sleepiness post PT	0,307	0,464				
Sleepiness 1 month post PT	0,333	0,528	-0,026	0,367	-0,630	0,531
Sleepiness 3 months post PT	0,280	0,452	0,027	0,162	1,424	0,159

The reduction in the degree of tonsillar hypertrophy correlated relatively strongly positively with a reduction in the incidence of sleepiness ($r=0.358$; $p=0.002$). The mean values of the frequency of reduced attention immediately after PT were statistically significantly lower than those before PT ($t=6.400$; $p=0.0001$). After three months there was no statistically significant difference ($t=-1.424$; $p=0.159$), i.e. the effect of PT persisted. (Table 4)

Table 4. Changes of the frequency of reduced attention before and after PT

Indicators	Mean	SD	Mean difference	SD	<i>t</i>	p
Reduced attention before PT	1,197	0,731	0,490	0,663	6,400	0,0001
Reduced attention after PT	0,707	0,539				
Reduced attention 1 month post PT	0,707	0,539	0,000	0,232	1,000	0,0001
Reduced attention 3 months post PT	0,733	0,528	-0,026	0,162	-1,424	0,159

The mean values of the frequency of hyperactivity before PT differed statistically significantly from those after PT ($t = 3.670$; $p = 0.0001$). There was no statistically significant difference between the mean values of the frequency of hyperactivity immediately after PT on the one hand and one month, respectively, three months after it ($t=0.630$; $p=0.531$; resp. $t=1.424$; $p=0.159$), i.e. the effect of PT persisted. (Table5)

Table 5. Changes in mean values of frequency of hyperactivity before and after PT

Indicators	Mean	SD	Mean difference	SD	<i>t</i>	p
Hyperactivity before PT	1,118	0,783	0,251	0,563	3,670	0,0001
Hyperactivity after PT	0,867	0,644				
Hyperactivity 1 month post PT	0,840	0,658	0,027	0,367	0,630	0,531
Hyperactivity 3 months post PT	0,813	0,630	0,054	0,324	1,424	0,159

There was a moderately strong positive correlation between reduction in adenotonsillar hypertrophy and reduction in hyperactivity.

DISCUSSION

Untreated SDB syndrome can cause serious health problems in children. Due to the multifactorial genesis of the syndrome, no effective drug has yet been approved for its treatment in children. (1) The recommendations for surgical treatment in Good Medical Practice have been updated in 2019. (2) Physical factors are a good alternative and are also completely safe. This is the first study to investigate the effectiveness of a combination of polarized, polychromatic, noncoherent, low-energy light with the Bioptron device and ultrasound for the treatment of behavioral symptoms associated with SDB syndrome in children with adenotonsillar hypertrophy. Adenotonsillar hypertrophy is a common disorder in childhood that is associated with symptoms of SDB syndrome (7). In a study conducted by E. Soyulu et al, 2013 on children in the age group between three and five years, by routine

otorhinolaryngological examination (nasopharyngoscopy and tympanometry) they found that attention deficit hyperactivity disorder, anxiety and sleep disorders were diagnosed more frequently and with greater severity in the presence of adenotonsillar hypertrophy. In our study, we also observed an association between adenotonsillar hypertrophy and daytime behavioral symptoms. 75 of the children who participated in the study had one or more of the daily behavioral symptoms. Similar results to ours were obtained by C. R. Davies and J. J. Harrington (2016). After the physical therapy program, we found a statistically significant reduction in the size of the nasopharyngeal and palatal tonsils $p=0.0001$. Similar results to ours, but with insufficient statistical significance, were obtained in a study of 45 patients with sub obstructive adenotonsillar hypertrophy. Another randomized double-blind placebo-controlled clinical trial on the efficacy of halotherapy with aerosol or placebo for 10 treatments found that 44.4% of patients treated with aerosol had a reduction in the degree of adenoid and/or tonsillar hypertrophy by $\geq 25\%$ from baseline, compared with 22.22% of those treated with placebo ($p=0.204$) (4).

CONCLUSION

In our study, we confirmed the existence of reliable relationships between the reduction of tonsillar hypertrophy and adenoid vegetations, and the influence of daytime behavioral symptoms associated with disturbed nocturnal breathing in children. The applied complex of physical factors has good therapeutic possibilities in this pathology. Research in this direction needs to be continued.

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TUBEROSITY HEALING IN RSA: IT DOES MATTER. EARLY FUNCTIONAL RESULTS

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ABSTRACT

Fractures of the proximal humerus are one of the most common in clinical practice. With the aging of the population, their frequency increases, which leads to a proportional increase in the surgical intervention in the treatment of the polyfragmental types of these fractures. An established standard for them is shoulder arthroplasty, and its "inverted" variant - reverse shoulder arthroplasty. Although this type of prosthetics is characterized by relatively constant functional results, they strongly depend on the degree of consolidation of the tubercles to the prosthesis.

The purpose of the study is to analyze the relationship between the functional results (range of motion) and the degree of consolidation of the humeral tubercles to the implant. Comparison of radiographic data and clinical results showed a better functional outcome in patients with consolidated tubercles than those with migrated or unconsolidated ones.

The correct and stable fixation of the tubercles to the humeral stem is a prerequisite for a greater range of motion, resp. better functional outcome.

Keywords: RSA, tubercles, range of motion

INTRODUCTION

Fractures of the proximal humerus are characteristic of old age and affect in the majority of cases women with severe osteoporosis. Given the poor quality of the bone, these fractures are usually multifragmentary, with displacement and bone loss present [1].

Conservative treatment in these cases does not achieve the necessary goals regarding the range of motion of the limb. Operative treatment by means of open reposition and fixation with various implants is associated with a risk of non-union of the fracture, avascular necrosis of the fragments and penetration of the synthetic material into the joint. Shoulder arthroplasty is increasingly finding a solution to these problems in the treatment of comminuted fractures of the proximal humerus [2]

Reverse arthroplasty (RSA) is a biomechanical solution to the insufficient rotator cuff as a result of bone fragmentation or degenerative rupture of the same. The design of the prosthesis aims to improve the function of the deltoid muscle by medializing the center of rotation of the joint and distalizing the humerus. In this way, the humeral tubercles and the rotator cuff attached to them, which otherwise play a major role in the movement of the shoulder joint, are "isolated" [3].

Some authors do not recommend the reinsertion of the tubercles to the prosthesis, relying mainly on the function of the deltoid muscle and the positioning of the prosthesis. More and more series recommend the stable and precise attachment of the tubercle remnants in view of the greater range of motion, the stability of the prosthesis and the overall better functional result. Using different techniques to fix the tubercles, a rate of up to 85% consolidation is achieved [3,4]. Although precise tubercle fixation is present, the incidence of secondary displacement, migration, and nonunion remains high, predisposing to poor functional outcome. A prospective multicenter study demonstrated up to 50% tubercle nonunion in RSA. As a result, the authors reported reduced range of motion, low patient satisfaction, and inability to perform daily activities [5].

Current recommendations for the treatment of multifragmentary fractures of the proximal humerus with RSA require reinsertion of the tubercles [6]. This is a prerequisite for improved flexion and external rotation. Comparative analyzes between synthesized and excised tubercles demonstrate improved volumes of motion in favor of synthesized [6-8].

MATERIAL AND METHODS

The study was retrospective and included 34 patients with reverse shoulder arthroplasty (RSA) for a multifragment displaced fracture of the proximal humerus. The gender distribution is in favor of women - 32:2; the age range is 54-76 years. The follow-up period is 4 months. -24 m. Standard pre/post-operative radiographs were performed on all patients. In all patients, we performed preoperative CT to assess the fracture morphology and postoperative CT analysis of the position of the implants postoperatively, the degree of consolidation of the tubercles and their position. The final functional result was also analyzed - range of motion, pain and ability to perform daily activities. We have objectively divided the patients into 2 groups - 1) patients with consolidated and/or stably fixed tubercles; 2) patients with missing, resorbed or unfused and migrated tubercles (Fig. 1)

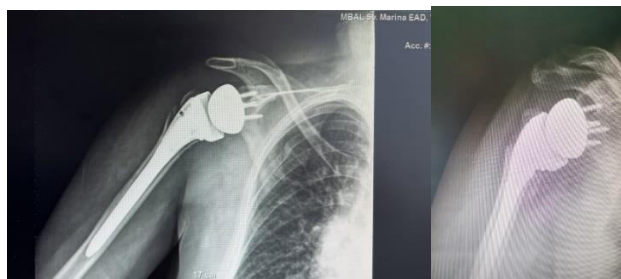


Fig. 1 Stably fixed tubercles (left) and migrated tubercles (right)

Functional outcomes were assessed using active range of motion: flexion, abduction, and external/internal rotation. Pain was also reported using a VAS scale. The reporting is done on the 1st, 6th and 12th of the month.

RESULTS

The results of the study are systematized in tabular form. Clinically, we report relatively stable indicators in the volume of movement in patients with stable and consolidated tubercles. Conversely, in patients with missing, lysed, or migrated tubercles, functional outcomes progressively worsened over the follow-up period.

evaluation	Tuberosity healed	Tuberosity migrated
Constant score	76	50
Forward flexion	115°	78°
Abduction	105°	70°
Int. rotation	L4-L5	-
Ext. rotation	12°	-



Fig. 2 Range of motion in tubercles consolidated to the prosthesis at the 6th postoperative month.

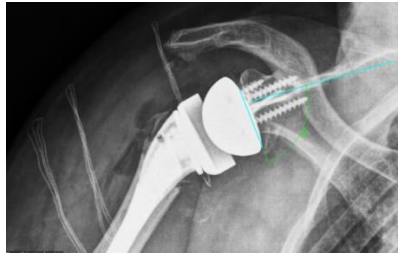


Fig. 3 The stable fixation of the tubercles with a correlation to the functional result



Fig. 4 Dynamics in the position of the tubercles. Postoperative first month (left) and 1 year postoperative (middle). It shows proximalization of the tubercles, correlating with unsatisfactory functional range of motion (right).

DISCUSSION

RSA arthroplasty for displaced polyfragmentary fractures of the proximal humerus is increasingly being used, and the age limit of the patients indicated for this tends to fall. This is due to the stable postoperative results in terms of pain, range of motion and quality of life. There is evidence of a significantly higher Constant Score in RSA compared with hemiarthroplasty. Several prospective studies have shown that non-union of the tubercles does not always lead to poor functional results, but depends on many other factors [9,10]. The classic concept of Grammont is medialization and distalization of the center of rotation, allowing the deltoid to perform the necessary movements with less effort [3]. In this situation, there is no need for consolidation of the tubercles. Recent studies, however, show that the union of the tubercles has a positive effect on the function of the rotator cuff, resp. increase in range of motion with an emphasis on rotation [9].

Our study reported a significant improvement in range of motion in patients with consolidated tubercles compared to those with unconsolidated or migrated tubercles: flexion 115° vs. 78; abduction 105° vs. 70°. A disadvantage that we report in our series is the significant reduction of rotation - external and internal in both groups. Logically, the worse results are with the second group, but in general the values achieved are far from those available in the literature, approaching only the results achieved by Valenti in several of his series - , 112° flexion, 97° abduction and 12.7° external rotation [11].

A review of 27 studies showed an advantage of consolidated tubercles over unfused tubercles in terms of functional outcome, particularly in terms of rotation. In addition, even minimal improvements in range of motion lead to improved daily activities [3]. Modern designs of the humeral stem are specifically aimed at stimulating consolidation of the tubercles and stable their fixation to the implant [10,12]. In our series, the differences are significant in abduction and flexion, while in rotation the values are close.

CONCLUSION

In summary, reverse arthroplasty presents with minimal complications and relatively consistent and predictable results. In our series, 2 cases of instability due to insufficiency of the subscapularis muscle and 1 case of infection were observed as significant complications.

As a limitation of our study, we consider the relatively small group of patients included in the study. Given the specificity of the procedure itself and the various social and geographic differences, we report our results as significant compared to studies with larger cohorts. In conclusion, our study shows an advantage of tuberosity consolidation over nonunion in terms of range of motion and satisfaction in patients with RSA.

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INTRODUCTION OF PRE-EXPOSURE PROPHYLAXIS (PREP) FOR HIV IN NORTH MACEDONIA: BRIEF REPORT ON THE DEMONSTRATION PROJECT TO DETERMINE FEASIBILITY AND ACCEPTABILITY OF PREP PROVISION AS PART OF STRENGTHENING SEXUAL HEALTH SERVICES

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ABSTRACT

Pre-exposure prophylaxis (PrEP) is the use of antiretroviral drugs to reduce the risk of acquiring HIV in HIV-negative individuals, especially in key populations. From February 2021, the implementation of a PrEP pilot project started in North Macedonia (NM), through which foundations will be provided for a better understanding how the health system could integrate PrEP as part of a comprehensive package of sexual health services and to encourage access to much-needed interventions to reverse the current rising trends in the incidence of sexually transmitted infections (STIs) in general.

Objective: To determine whether PrEP, as part of a comprehensive package of sexual health services, can serve as a tool for assessment, prevention and reduction of STI incidence in North Macedonia.

Materials and methods: The pilot project was designed as a prospective, unmasked cohort study. All participants were offered tenofovir disoproxil/emtricitabine as PrEP. At each visit, participants received risk reduction counseling and HIV and STI testing.

Results: Out of 84 initiated respondents (MSM 95.3%, TG 3.12%, SW 1.56%) with a mean age of 32.8 years, 1 new HIV infection (1.1%), 3 new hepatitis B infections (3.5%), 14 syphilis infections (16.6%) and 2 chlamydia infections (2.3%), were discovered.

Conclusion: PrEP as part of a comprehensive package of services for sexual health, can serve as an indicator of the state of STIs in NM and thereby enable mechanisms to control apparent concentrated epidemics.

INTRODUCTION

North Macedonia has a concentrated HIV epidemic in key populations, with new HIV infections on the rise, particularly in men who have sex with men (MSM) and transgender women (TWG) (1,2). PrEP should be offered as part of a comprehensive package of sexual and reproductive health (SRH) services.

AIM AND OBJECTIVE

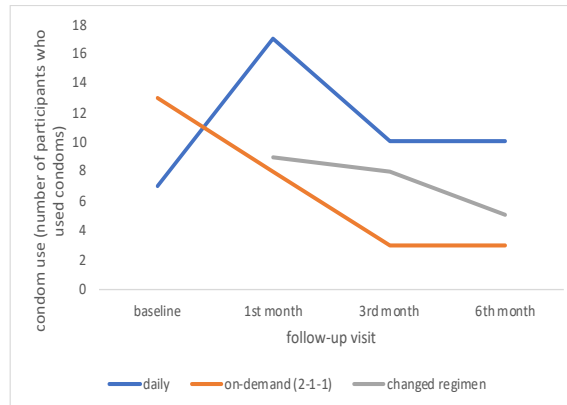
With this demonstration pilot project, we aimed to assess the feasibility and acceptability of offering PrEP in clinical and community-based settings in North Macedonia, with a primary focus of service provision to MSM and TG who are at increased risk for HIV infection and to evaluate the operating procedures for integrating PrEP within the healthcare system as part of a comprehensive package of sexual health services.

MATERIALS AND METHODS

The design is an open-label, single-arm treatment cohort. Participants in the demonstration project were coming from different cities in the country and had to give their written consent to enroll. A fixed-dose combination of tenofovir/emtricitabine (TDF/FTC) was offered to everyone as their PrEP regimen. The pilot sought to enroll individuals 18 years of age and who are at substantial risk for HIV acquisition. An initial consultation included confirmation of behavioral suitability, clinical evaluation and laboratory assessments. After initiation, follow-up appointments are scheduled at 1 month, month 3, month 6, month 9, month 12.

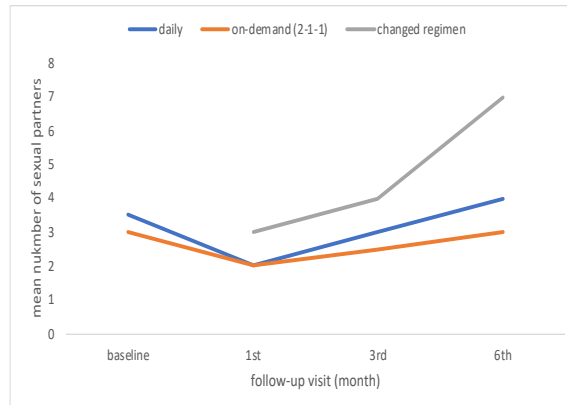
RESULTS

Between February and December 2021, 89 participants were enrolled: 83(93.3%) MSM, 4(4.5%) transgender women (TGW), 2(2.2%) cis-gender female sex workers (SWs). From the follow-up behavioral assessment we have discovered the following findings: Half of the PrEP users, 34 (53%) out of 64 respondents stated that they had used a condom (for at least one sexual intercourse) after starting PrEP (since the last visit).

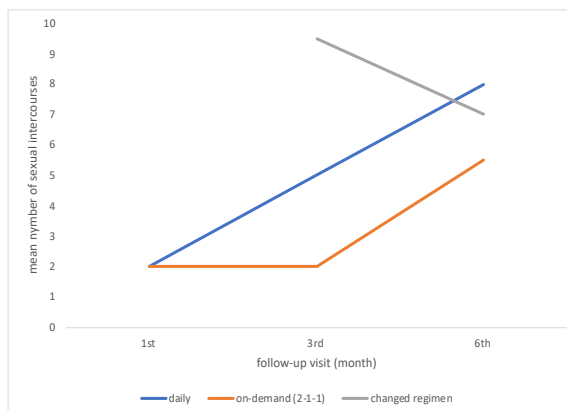


Graph. 1. Trend of condom use among the pilot participants

Interestingly, the condom use of participants who chose on demand regimen declined over time, where the condom use in participants who chose the daily dosing regimen peaked in the first month of using PrEP and then plateaued high for the remaining course of the pilot. Seven respondents stated that they had sexual intercourse with an HIV positive person. The highest number of sexual partners were registered in participants who changed the dosing regimen, with the tendency of increasing.



Graph. 2. Mean number of sexual partner over time



Graph. 5. Mean number of sexual intercourses over time

The mean number of sexual intercours constantly increased for the main two groups. Biological indicators of baseline laboratory findings were as follows: Only one of the respondents (1.12%) had a positive HIV test at the baseline screening, 3 respondents had hepatitis B positive result and 10 (17%) had a positive result for syphilis. At the follow up, none of the subjects in the study became infected with HIV during the period when they were using PrEP, no subjects in the study became infected with Hepatitis B or C during the period when they were using PrEP. Four new Syphilis infections were detected.

CONCLUSION

Provision of PrEP became available in North Macedonia through the PrEP pilot that was initiated in January 2021 within the SoS project. Prior to this time, there were no formal PrEP services in North Macedonia. A persistence rate of 75.2% can be considered satisfactory and demonstrates a high level of acceptability and feasibility for PrEP delivery within the healthcare system in North Macedonia. As participants show a sustained level of risk exposure, STIs monitoring within a PrEP delivery service can serve as an indicator of overall spread of STIs and thereby enable the adoption of strategies to prevent further circulation. Urgent measures must be taken considering the syphilis epidemic. Close collaboration between the community sector and the clinical setting is crucial for the success of the pilot and any future program.

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THERAPEUTIC BEHAVIOR AND OPTIMAL TIMING IN PRIMARY HEMIARTHROPLASTY FOLLOWING A FRACTURE OF THE FEMORAL NECK IN GERIATRIC PATIENTS

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ABSTRACT

Fracture of the femoral neck primarily occurs in geriatric patients, typically those aged 75-80 and constitutes 65% of all bone fractures and 90% of femoral fractures. Among this patient group, femoral neck fractures account for up to 25% of all musculoskeletal fractures. As age advances, there is an observed increase and doubling in the number of these fractures in each subsequent decade of life after the age of 50. The indication for primary hemiarthroplasty in geriatric patients at the Orthopedics Department of St. Anna Hospital, Varna, is determined according to the Garden classification.

Keywords: geriatric patients, primary hemiarthroplasty, fracture, femoral neck

INTRODUCTION

In 2011, Dhanwal [3] reported significant variations in the frequency of femoral neck fractures based on geographic and racially influenced differences in the incidence of these fractures. He found that this type of fracture is most commonly observed in Sweden, ranking second in frequency in Norway and Denmark, while being considerably rarer in Southern European countries.

Epidemiological studies highlight the correlation between the frequency of femoral neck fractures, age, gender, lifestyle, geographic latitude, and corresponding climatic conditions [1, 2]. European and American studies conducted in the age group over 75 years old indicate a gender ratio of approximately 2:1, with women being more frequently affected. The higher incidence in the female population is attributed to postmenopausal osteoporosis and their more slender skeletal structure.

According to J. M. Sikorski, R. Barrington, and colleagues, the mortality rate associated with femoral neck fractures within the first year following the trauma reaches up to 37% in patients over 80 years of age [4].

An important factor contributing to an increased risk of falls and fracture in the geriatric patient group is polymorbidity. The accompanying pathology adversely affects the course of treatment. The combination of fractures and accompanying diseases in this age group leads to challenges in selecting an appropriate treatment method [3, 7, 8].

OBJECTIVE

The aim of this study is to describe the therapeutic approach and optimal timing for primary hemiarthroplasty in cases of femoral neck fractures among geriatric patients.

MATERIALS AND METHODS

A clinical observation was conducted among 186 patients (74 males and 112 females) aged 80 and above, who had experienced a femoral neck fracture and were treated at the Orthopedics Department of St. Anna Hospital in Varna during the period from 2018 to 2020.

RESULTS

In the clinical group, 87% of patients reported a history of trauma. In 7% of cases, an accurate trauma history was not obtained due to accompanying dementia, and in the remaining 6%, fractures occurred without a clearly defined traumatic moment. These findings support the assertion made by A. Freeman and colleagues (1974) regarding the role of trauma in the pathogenesis of femoral neck fractures in geriatric patients [6].

Critical importance for the choice of the therapeutic approach is given to the severity of the fracture, as well as the degree of displacement of the fracture fragments. When developing the treatment strategy, we strictly adhere to the existing fracture classification according to Garden. Fractures classified as Garden IV present with complete displacement of fracture fragments. This limits the

possibility of reduction and creates significant instability caused by the comminution of the posterior cortex of the femoral neck. Justifiably, this type of fracture is eponymously referred to as an "unstable fracture." According to the Garden classification, our patients indicated for primary hemiarthroplasty were classified into types Garden III and IV (Table 1).

Table 1. Number of patients classified by Garden

Gender	Garden III	Garden IV
Male	46	22
Female	68	50

In these fractures, post-traumatic ischemia is a biological factor that disrupts the process of bone healing. According to W. Hood (1978) and F. Ficat (1980), the primary acute ischemia of the femoral head, caused by vascular damage during the trauma and leading to necrosis, categorizes these fractures as unfavorable for union [7]. Due to this reason, we assessed these fracture types, deeming osteosynthesis as a therapeutic approach for treatment, as uncertain and unjustified.

Some of the accompanying diseases in our studied clinical group involve metabolic disturbances in bone tissue, leading to a decrease in mechanical strength of the bone. A significant portion of our patients had paralysis affecting the lower extremity following a cerebral stroke. In cases where the fracture is on the intact weight-bearing limb, we regarded hemiarthroplasty of the hip joint as an absolute indication, considering the possibility of weight-bearing practically immediately postoperatively. Furthermore, other psychosomatic conditions inherent to advanced age may result in the impossibility of active cooperation from the patient, especially concerning prolonged protection of the hip joint. Patients who are unable to fully cooperate with the treatment, in our opinion, are indicated for primary hemiarthroplasty after an intracapsular fracture of the femoral neck, given the relatively simplified rehabilitation protocol.

The interval between the traumatic incident and the surgical intervention can significantly impact therapeutic outcomes. Among our patients with intracapsular fractures of the femoral neck, the timing for performing hip hemiarthroplasty was categorized into the following groups:

1. Within 3 days after the fracture: patients in good general health – 105 cases
2. Within 7 days after the fracture: Patients with polymorbidity requiring prolonged preoperative preparation or using indirect anticoagulants affecting the coagulation status - 55 cases.
3. After the first week following the fracture: Patients with polytrauma requiring extended preoperative preparation or patients seeking medical attention later - 26 cases.

In our opinion, operative treatment for geriatric patients following a femoral neck fracture should be conducted as soon as possible after the trauma, before the onset of hypostatic complications, aiming for their earliest possible involvement in rehabilitation protocols. The correct therapeutic approach to femoral neck fractures in geriatric patients could lead to rapid recovery and successful reintegration.

CONCLUSION

Hemiarthroplasty proves to be an effective treatment method for intracapsular fractures of the femoral neck in geriatric patients, offering the potential for restoring pre-fracture mobility.

The choice of therapeutic method for Garden III and IV fractures is justified by the unpredictable chances of fracture union due to ischemia of the femoral head, indicating primary hip arthroplasty in geriatric patients.

The therapeutic outcomes achieved with hip hemiarthroplasty after a femoral neck fracture have been the subject of numerous other studies and analyses similar to ours.

We find the therapeutic approach to hip hemiarthroplasty for femoral neck fractures in patients under 75 years old to be imprecise, or justified only with criteria not directly related to the fracture type.

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CORRELATION BETWEEN BIOCHEMICAL/VIROLOGICAL AND IMMUNOLOGICAL PARAMETERS IN CHRONIC HEPATITIS C

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ABSTRACT

Hepatitis C virus (HCV) infection remains a critical public health problem. Although the pathophysiology of HCV is not entirely understood, interleukin (IL)-17-producing CD4+ T cells, named T-helper 17 cells (Th17), consequently IL-23/IL-17 cytokines have been shown to play a significant role. The objective of these study was to determine correlation between biochemical parameters of liver injury and inflammatory/immune response (cytokines). 36 patients with CHC infection were recruited from the Clinic for Infectious and Tropical Diseases, University Clinical Center of Serbia (UCCS) from October 2018 to December 2019. Peripheral blood samples were collected and fine needle liver biopsy was done in all of the patients. All of the patients were done biochemical, virological analyses and measurement of plasma and liver tissue cytokines levels. Serum levels of AST and ALT displayed a strong positive correlation with serum IL-17A levels. Moderate negative association was found between serum IL-17A and the number of platelets and a positive moderate association between serum IL-23 and the number of platelets. The levels of AP were in moderate positive association with tissue levels of IL-6, IL-17A and IL-23. Serum IL-17A levels have shown negative moderate correlation with albumins as well as PT and positive moderate with bilirubin, also moderate positive association was found between AFP and tissue IL-17A levels.

Key words: chronic hepatitis C; biochemical parameters; inflammation; correlation

INTRODUCTION

Hepatitis C virus (HCV) infection remains a critical public health problem. Globally, an estimated 58 million people have chronic hepatitis C virus infection (CHC), with about 1.5 million new infections occurring per year. Approximately 290 000 people died from hepatitis C in 2019, mostly from cirrhosis and hepatocellular carcinoma [1]. The introduction of direct-acting antivirals (DAAs) enabled CHC to become curable, but disease progression may not be completely avoided, especially in patients with a high degree of fibrosis [2]. This is the reason for the continuous research of various factors, especially immunological ones in patients with CHC. Innate and adaptive immunity are closely linked to the prognosis of hepatitis C infectious (HCV) and the response to antiviral therapy. The immune response to HCV infection has a specific role in improvement of liver fibrogenesis. Multiple growth factors, inflammatory cytokines and chemokines may regulate the activation of hepatic stellate cells (HSCs) and their transformation to myofibroblasts [3]. Although the pathophysiology of HCV is not entirely understood, interleukin (IL)-17-producing CD4+ T cells, named T-helper 17 cells (Th17), and consequently IL-23/IL-17 cytokines have been shown to play a significant role. Rios et al.'s research [4] revealed that the only lymphocyte subset linked to advanced fibrosis was Th17. However, it is still unknown if Th17 can play both, a positive and a negative role. Recent studies investigate correlations between biochemical parameters and cytokine levels to assess the impact of the immune response on

liver damage. The objective of these study was to determine correlation between biochemical parameters of liver injury and inflammatory/immune response (cytokines).

MATERIALS AND METHODS

A total of 36 patients with CHC infection were recruited from the Clinic for Infectious and Tropical Diseases, University Clinical Center of Serbia (UCCS) from October 2018 to December 2019. Peripheral blood samples were collected and fine needle liver biopsy was done in all of the patients. All of the patients were done biochemical and virological analyses and measurement of plasma and liver tissue cytokines levels (IL-6, IL-10, IL-17A and IL-23). The diagnosis for the CHC patients was made using the European Association for the Study of the Liver (EASL) Clinical Practice Guidelines: Management of hepatitis C virus infection [5] and included anti-HCV antibodies during at least 6 months with positive real-time polymerase chain reaction (PCR) assays for quantifying HCV RNA and histological verification from liver tissue. Exclusion criteria were pregnancy, presence of decompensated cirrhosis, co-infection with human immunodeficiency virus (HIV) and co-infection with hepatitis A, B, or D virus for CHC group of patients, infection with HIV, hepatitis A, B, C or D for control group of patients, other chronic or acute liver disease (autoimmune/toxic), presence of any of an immunocompromised state, patients with HCC. Written informed consent was obtained from all of the patients. The study protocol was approved by the ethics committees of the Clinic for Infectious and Tropical Diseases, University Clinical Center of Serbia. The data obtained are presented as mean (\pm S.E.M.) or median (interquartile range). All statistical methods considered significant for the level of 0.05. Complete statistical analysis was performed in IBM SPSS ver. 26

RESULTS

The analysis of the association between cytokine levels and biochemical parameters was performed.

Table 1. Correlations between biochemical parameters and cytokine levels.

		S-IL6	S-IL10	S-IL17	S-IL23	T-IL6	T-IL10	T-IL17	T-IL23
PLT	Spearman's rho	.328	.281	-.459	.397	-.152	-.096	-.087	.159
	Sig. (2-tailed)	.076	.133	.011	.030	.423	.613	.647	.402
AST	Spearman's rho	.065	-.197	.707	.015	.377	.109	.345	.099
	Sig. (2-tailed)	.731	.297	.000	.938	.040	.567	.062	.604
ALT	Spearman's rho	.012	-.274	.657	-.021	.321	.080	.306	.095
	Sig. (2-tailed)	.948	.144	.000	.911	.083	.673	.101	.618
AP	Spearman's rho	.336	.013	.343	.288	.387	.327	.465	.480
	Sig. (2-tailed)	.070	.947	.063	.123	.035	.078	.010	.007
albumin	Spearman's rho	-.164	.356	-.596	-.070	-.181	-.095	-.077	.011
	Sig. (2-tailed)	.387	.053	.001	.713	.337	.616	.687	.952
bilirubin	Spearman's rho	-.031	-.078	.452	-.136	.353	.180	.253	.054
	Sig. (2-tailed)	.871	.681	.012	.474	.055	.342	.178	.776
PT	Spearman's rho	-.114	.271	-.371	-.074	-.035	.310	.035	.077
	Sig. (2-tailed)	.550	.147	.043	.699	.855	.095	.853	.688
AFP	Spearman's rho	-.199	-.127	.279	-.178	.230	.176	.406	.140
	Sig. (2-tailed)	.292	.503	.135	.347	.222	.353	.026	.461

PLT: platelets, AST: aspartate aminotransferase, ALT: alanine aminotransferase, AP: alkaline phosphatase; AFP: alpha fetoprotein; PT: prothrombin time; S: serum; T: tissue; IL: interleukin

Serum levels of AST and ALT displayed a strong positive correlation with serum IL-17A levels ($\rho = 0.707$, $p < 0.01$; $\rho = 0.657$, $p < 0.01$, respectively). We found a moderate negative association between serum IL-17A and the number of platelets ($\rho = -0.459$, $p < 0,05$) and a positive moderate association between serum IL-23 and the number of platelets ($\rho = 0.397$, $p < 0,05$). The levels of AP were in moderate positive association with tissue levels of IL-6, IL-17A and IL-23 ($\rho = 0.387$, $p < 0,05$; $\rho = 0.465$, $p < 0,05$, $\rho = 0.480$, $p < 0,05$ respectively). Serum IL-17A levels have shown negative moderate correlation with albumins ($\rho = -0.596$, $p < 0.01$) as well as PT ($\rho = -0.371$, $p < 0.05$) and positive moderate with bilirubin ($\rho = 0.452$, $p < 0.05$). We obtained moderate positive association between AFP and tissue IL-17A level ($\rho = 0.406$, $p < 0,05$). (Table 1). The other biochemical parameters have not shown significant correlations. The analysis of the association between cytokine levels and virological parameters was also performed. We found only the positive moderate correlation between HCV RNA PCR and tissue IL-17A levels ($\rho = 0.366$, $p < 0.05$), while we have not found association between cytokine levels and genotypes.

Table 2. Correlations between virological parameters and cytokine levels.

		S-IL6	S-IL10	S-IL17	S-IL23	T-IL6	T-IL10	T-IL17	T-IL23
HCV RNA PCR	Spearman's rho		.196	.132	.017	.078	.331	.235	.366*
	Sig. (2-tailed)	.647	.299	.488	.927	.681	.074	.211	.047
Genotyp	Spearman's rho	.043	.006	.126	.066	.166	-.220	.039	.048
	Sig. (2-tailed)	.820	.974	.506	.729	.381	.243	.836	.803

HCV: hepatitis C virus; RNA: ribonucleic acid; PCR: polymerase chain reaction S: serum; T: tissue; IL: interleukin

DISCUSSION

CHC is an infectious disease, caused by HCV infection. Previous studies have shown that patients with CHC have increased levels of IL-6, IL-17A and IL-23 in comparison with healthy group [6,7]. As one of the first laboratory abnormalities, CHC shows elevated transaminase levels as a result of liver damage. Numerous studies have shown that serum levels of ALT and AST are elevated in CHC patients in different stages of the disease [8,9]. In this study, levels of AST and ALT display a strong positive correlation with serum IL-17A levels, as well as moderate positive correlation between AP and tissue IL-6, IL-17 and IL-23 levels which can indicate that liver damage is caused by both, systemic and local proinflammation. Also, serum IL-17A levels shown negative moderate correlation with albumins, platelets number and PT as well as positive correlation with bilirubin. All of these biochemical parameters are reflection of synthetic liver function, which can be compromised by systemic proinflammation in CHC (hypoalbuminemia, hyperbilirubinemia and coagulation disorder). Elbanan et al. [10] described a positive correlation between serum IL-17 levels and transaminases as well as negative correlation between IL-17 and serum albumins, which is all in correlation with our results. We obtained positive correlation between tissue levels of IL-17 and AFP. Mostafa et al. [11] described higher levels of IL-17 and AFP in patients with hepatocellular carcinoma (HCC), so our results show the potential importance of these local proinflammations in the fibrogenesis of CHC, known to lead to carcinogenesis. Virological analyses shown positive correlation between serum levels of HCV RNK and tissue levels of IL-23. This result may lead to the conclusion that high viremia affects the pathophysiological mechanism of local inflammation and consequently liver damage.

CONCLUSIONS

Certain biochemical and virological parameters in CHC can be indicators of the degree of liver damage caused by systemic and local inflammation.

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CHALLENGES IN THE DIAGNOSIS OF LYME HEUROBORRELIOSIS

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ABSTRACT

Lyme borreliosis is a multisystem infectious disease caused by spirochete of the *Borrelia burgdorferi sensu lato complex*. The aim of the research was to determine characteristics in the clinical manifestations and standard parameters of blood and CSF in patients with possible LNB; to analysis of the results of Two-Tiered Testing for LD (*ELISA* and *Immunoblot* anti-Borrelia IgM/IgG); to determine the *ELISA* concentration of the chemokine *CXCL13* in the CSF of patients with possible LNB and its significance in the diagnosis of LNB and to examine the sensitivity of RT PCR in CSF and its significance in the diagnosis. The research was conducted as a prospective diagnostic study at the University Clinical Center of the Republic of Srpska in the period from October 2017 to October 2021. The examined group consists of patients who were hospitalized and treated due of suspicion of LNB. We analyzed the data of 141 patients who were hospitalized in UKC RS due to neuroinfection and in whom LNB was also considered as part of the differential diagnosis. Out of 141 patients, 51 of them met the conditions for participating in our study. In adult patients with LNB, dominates involvement of the peripheral nervous system. There are no significant deviations in hematological-biochemical analyzes. Pleocytosis may be present in the CSF even when there are no clinical symptoms of meningitis. Absence of pleocytosis in CSF is not a parameter that excludes LNB. The correlation between certain clinical manifestations of LNB and the presence of antibodies to certain specific antigens of *B.burgdorferi* in the *Immunoblot* test is low. The significance of determining the concentration of chemokine *CXCL13* in CSF as a marker in the diagnosis of LNB has not been proven, as well as for *RT PCR* in CSF. Additional prospective studies are needed for new reliable diagnostic tests.

Keywords: lyme neuroborreliosis, two-tier testing, chemokine CXCL13, Real-time PCR

INTRODUCTION

Lyme borreliosis is a multisystem infectious disease caused by spirochete of the *Borrelia burgdorferi sensu lato complex* and it is transmitted by *Ixodes* ticks [1,2,3,4,5]. In Europe, North America and parts of Asia, it is the most common vector-borne disease [2,5,6]. Lyme borreliosis with neurological manifestations is called lyme neuroborreliosis and it can be manifested at any point of early disseminated and late stage. There is no gold standard in the diagnosis of lyme neuroborreliosis (LNB) [7]. Diagnosis is usually made by recognizing the characteristic clinical signs and symptoms of the disease together with serological testing [8,9]. Diagnostic methods can be divided into indirect (*Enzyme-linked immunoassay (ELISA)* test, *Immunoblot* test) and direct (*Polymerase chain reaction (PCR)* and culture) [10]. Various studies have suggested that the detection of *CXCL13* in the cerebrospinal fluid (CSF) is a useful marker in the diagnosis of early LNB, even before a specific antibody response [4,11,12].

The aim of the research was to determine characteristics in the clinical manifestations and standard hematological and biochemical parameters of blood as well as parameters of cytochemical analysis CSF in patients with possible LNB; analysis of the results of Two-Tiered Testing for LD (*ELISA* anti-Borrelia IgM/IgG; *Immunoblot* anti-Borrelia IgM/IgG test); to determine the *ELISA* concentration of the chemokine *CXCL13* in the CSF of patients with possible LNB and its significance in the diagnosis of LNB and to examine the sensitivity of RT PCR in CSF in patients with possible LNB and its significance in the diagnosis of LNB.

METHODS

The research was conducted as a prospective diagnostic study at the University Clinical Center of the Republic of Srpska (UKC RS) in the period from October 2017 to October 2021. The examined group consists of patients who were hospitalized and treated in the UKC RS due of suspicion of LNB.

The inclusion criteria: Neurological manifestations that could correspond to the clinical manifestations of LNB; Performed lumbar puncture and cytochemical analysis of CSF; Diagnostic tests performed (*ELISA* anti-Borrelia IgM/IgG in serum and CSF, *Immunoblot* test anti-Borrelia IgM/IgG in serum, concentration of chemokine *CXCL13* in CSF and Real-time *PCR* in CSF and available other medical documentation: anamnestic data, clinical response to antibiotic therapy, hematological and biochemical blood parameters.

The exclusion criteria: No antibiotic therapy for Lyme disease before lumbar puncture; absence of clinical response to antibiotic therapy for LNB during hospitalization; diagnosis of another neurological disease and withdrawal of the patient from the study.

Data is presented with standard descriptive statistical methods in accordance with the type of data. The statistical significance of the examined differences was established for $p < 0.05$. Statistical analysis and graphical presentation of data was done with the help of the statistical software package SPSS 22 (IBM, 2013).

RESULTS

Initially, we analyzed the data of 141 patients who were hospitalized in UKC RS due to neuroinfection and in whom LNB was also considered as part of the differential diagnosis. Out of 141 patients, 51 of them met the conditions for participating in our study.

Out of 51 patients, 66.67% of them were female, 80.4% were over 40 years old. Only 31.37% had information about a previous tick bite. Most of them complained of a tingling sensation and weakness of the extremities, followed by headaches, ophthalmological problems and dizziness to a lesser extent. Disorders of consciousness, speech, facial nerve paresis, lower back pain and nervousness were less present. Most of them had symptoms for up to three months before being admitted to hospital.

The average values of the parameters of the blood count were within the reference values, with the exception of a slightly higher average value of monocytes in the differential blood count (13.86%). The average values of aspartate aminotransferase and alanine aminotransferase were within the reference values, and glycemia (6.07mmol/l) and C-reactive protein (5.87mg/L) were slightly above the upper limit.

Figures 1. and 2. show the number of cellular elements in CSF and the predominance of mononuclears.

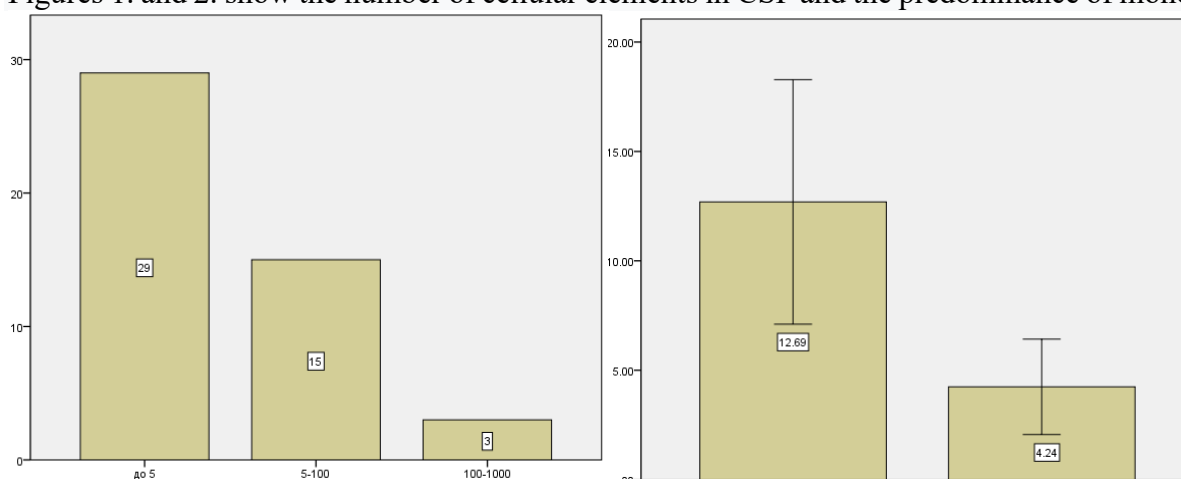


Figure 1.; 2. CSF grouped according to the number of cells and predominance of mononuclears

Elevated proteins in CSF had 19 (37.25%) of our patients and the range of elevated values were from 0.48 to 3.6 g/L. Nine subjects had slightly reduced glucosa in CSF.

Out of 51 of our patients, 13 (25.5%) had positive anti B.burgdorferi IgM antibodies in their serum by *ELISA* test and 39 (76.47%) had positive anti-B.burgdorferi IgG. Anti B.burgdorferi IgM *ELISA* test in CSF was positive in seven of our patients (13.7%) and 20 (39.2%) had positive anti B.burgdorferi IgG.

The result of the *Immunoblot* test anti B.burgdorferi IgM in the serum of our patients was borderline in four patients, positive in five of them, and there was no data for 18 of them. The result of the *Immunoblot* test anti-B.burgdorferi IgG in the serum of our patients was positive in 28 of them, and there were no data for 19 of them.

Figure 3. and 4. shows which antibodies to specific B.burgdorferi antigens were positive in our patients in whom the *Immunoblot* test of anti B.burgdorferi IgM/IgG in the serum was positive.

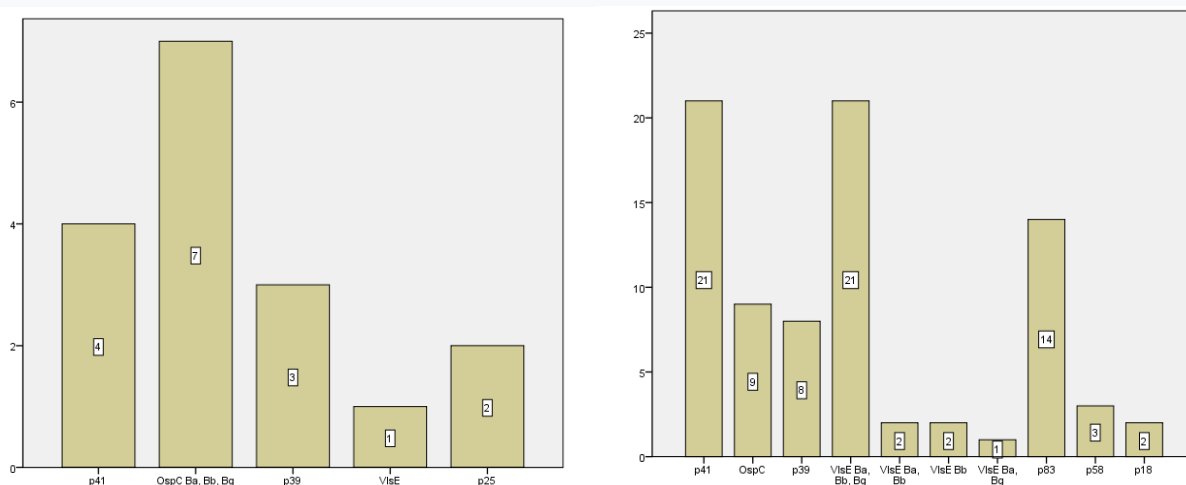


Figure 3.; 4. *Immunoblot* serum anti B.burgdorferi IgM/IgG positive antibodies to specific antigens of B.burgdorferi

By determining the concentration of the chemokine CXCL13 in CSF of our patients by *ELISA* test, 47 of them had normal values, three borderline values and only one had significantly elevated values.

By analyzing the correlation of the results of individual serological tests, a strong connection between the results of *ELISA* anti B.burgdorferi IgM in serum and in CSF can be observed ($\rho=0.802$, $p<0.001$). A strong relationship is also observed between *ELISA* anti B. burgdorferi IgG in serum and *Immunoblot* anti B.burgdorferi IgG ($\rho=0.787$, $p<0.001$).

The correlation coefficient between certain clinical manifestations and antibodies to certain specific antigens of B. burgdorferi is low and therefore these relationships are not significant for practical analysis. The results of the Real-time *PCR* method using a diagnostic set for the detection and quantification of B.burgdorferi sensu lato complex did not show the presence of bacterial DNA in any CSF sample.

DISCUSSION

The most common clinical manifestations of LNB in our patients are in accordance with the data from the literature^[4,13] as well as the values of hematological and biochemical blood parameters^[14,15,16,17]. Normal values of CSF analysis in patients with LNB is also described in the literature^[13]. The literature also states that the most common CSF abnormality is slightly elevated proteins together with lymphocytic pleocytosis^[13,14,18] and the glucose value in the CSF in patients with LNB is usually within the reference values^[19]. Positive results do not always mean a diagnosis of LNB, and negative results do not exclude it^[13,20,21]. The determination of the concentration of the chemokine CXCL13 in the CSF *ELISA* test was done in the Department of Microbiology of the UKC RS, the euroimmune test CXCL13 *ELISA* was used and the findings were mostly negative and did not help in the diagnosis as well as RT *PCR*. Also in the literature, patients with definite LNB have been reported to have negative CXCL13^[22,23]. CSF testing, including CXCL13, may be important for central nervous system

Lyme disease, but not for peripheral nervous system where *CXCL13* insensitivity has been detected in the cerebrospinal fluid. The concentration of *CXCL13* in the cerebrospinal fluid is generally normal in Lyme encephalopathy as well [23,24]. Other studies report that in early disseminated and late neurological manifestations of LNB, PCR in CSF is often negative and of limited value due to the small number of bacteria in these types of samples [86].

Conclusions In adult patients with LNB, involvement of the peripheral nervous system dominates compared to the central nervous system. Certain neurological symptoms, especially with information about a previous tick bite, should always prompt treatment in the direction of LNB. There are no significant deviations in basic hematological-biochemical analyzes. Pleocytosis may be present in the CSF even when there are no clinical symptoms of meningitis. Absence of pleocytosis in CSF is not a parameter that excludes LNB. Two-step serological diagnostic tests (*ELISA*, *Immunoblot*) are very important, but they should be interpreted with caution and in correlation with the clinical manifestation and other available tests. The correlation between certain clinical manifestations of LNB and the presence of antibodies to certain specific antigens of *B.burgdorferi* in the *Immunoblot* test is low and has no significance in establishing the diagnosis. The significance of determining the concentration of chemokine *CXCL13* in CSF as a marker in the diagnosis of LNB has not been proven. The sensitivity of *RT PCR* in CSF is very low and is not of great importance in diagnosis, so there is no reason to do it routinely. Additional prospective studies are needed for new reliable diagnostic tests in order to improve the diagnosis of LNB and distinguish active from inactive forms of LNB as well as from other diseases with similar clinical manifestations.

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WHITE BRINED CHEESE: RESIDENT MICROFLORA AND ASSOCIATED HEALTH BENEFITS

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ABSTRACT

Brined cheese is a cheese that is matured in brine in an airtight or semi-permeable container. This process gives the cheese good stability, inhibiting bacterial growth even in warmer climates. White brined cow's milk cheeses contain large amounts of probiotic bacteria, represented primarily by *Lactococcus lactis subsp. lactis* and *Lactobacillus casei*, as well as a symbiotic starter from bacteria *Lactobacillus delbrueckii subsp. bulgaricus* and *Streptococcus thermophilus*. Probiotics have varying mechanisms of action depending on species and are known to influence the host health in three main ways - by modulating the existing microbiota, communicating with the intestinal mucosa and/or by affecting functions that are not limited to the gastrointestinal tract, such as the immune system.

Keywords: white brined cheese, resident microflora, health benefits

INTRODUCTION

Fermented foods are gaining popularity due to health-promoting properties with high levels of nutrients, phytochemicals, bioactive compounds, and probiotic microorganisms. Cheese and more specifically white brine cheese is among the most researched and discussed functional foods. Milk products are rich in nutrients, supplying high-quality proteins, trace elements, vitamins and energy-rich fats.

Brined cheese, also sometimes referred to as pickled cheese for some varieties, is a cheese that is matured in brine in an airtight or semi-permeable container. This process gives the cheese good stability, inhibiting bacterial growth even in warmer climates. Brined cheeses may be soft or hard, varying in moisture content and in colour and flavour according to the type of milk used.

White brined cow milk cheeses contain large amounts of probiotic bacteria, represented primarily by *Lactococcus lactis subsp. lactis* and *Lactobacillus casei*, as well as a symbiotic starter from bacteria *Lactobacillus delbrueckii subsp. bulgaricus* and *Streptococcus thermophilus*. Probiotics are live microorganisms which have beneficial effects on the host when ingested in adequate amounts. Probiotic bacteria may stimulate immune effector functions in a strain-specific manner (Rask C at al., 2013).

AIM

To study the diversity of bacterial strains that normally reside in white brined cow milk cheese. As well as presenting the variety of starters that lead to obtaining various variations of this type of cheese.

MATERIALS AND METHODS

In our study, we used a documentary method to survey scientific publications, reports and current studies that, using biochemical and molecular-genetic techniques, present the bacterial set in white brine cheese.

RESULTS AND DISCUSSION

The microbial communities of the majority of the studied cheeses were dominated by lactic acid bacteria genera, like

- *Lactococcus* (10.3–77.1%)
- *Lactobacillus* (54-62%).

They are confirmed as facultative heterofermentative and 38% as obligate homofermentative. Of the facultative heterofermentatives, 20-24% were *Lactobacillus plantarum*, 20% were *Lactobacillus casei*, 11.5-18% were *Lactobacillus agilis*. Obligate homofermentatives were *Lactobacillus delbrueckii* (21%), *Lactobacillus helveticus* (14%), and *Lactobacillus salivarius* (3%) (Ehsani A et al., 2018; Kochetkova TV et al., 2023). *L. plantarum*, *L. casei* and *L. helveticus* were found in high enough levels (10^6 CFU/g).

Lactococci are coccoid Gram-positive, anaerobic bacteria which produce L(+)-lactic acid from lactose in spontaneously fermented raw milk which is left at ambient temperatures around 20–30°C for 10–20 h. They are commonly called ‘mesophilic lactic streptococci’ (Teuber M, 1995).

Lactobacillus is the largest genus within the group of lactic acid bacteria. The genus is split into three groups based on the carbohydrate fermentation pathways: (1) obligate homofermentative, (2) facultative heterofermentative, and (3) obligate heterofermentative lactobacilli. The two most obvious beneficial roles of lactobacilli are as starter cultures (to produce acid rapidly) and as probiotic cultures (De Angelis M & Gobbetti M, 2011).

Other bacterial species presented in white brined cheeses are:

- *Streptococcus* (13.9–93.9%),
- *Lactiplantibacillus* (13.4–30.6%)
- *Lentilactobacillus* (5.9–14.2%).

Streptococcus thermophilus formerly known as *Streptococcus salivarius subsp. thermophilus* is a gram-positive bacterium, and a fermentative facultative anaerobe, of the viridans group.

It is also classified as a lactic acid bacterium. *S. thermophilus* is found in fermented milk products and is generally used in the production of yogurt, alongside *Lactobacillus delbrueckii subsp. bulgaricus*. The two species are synergistic, and *S. thermophilus* probably provides *L. d. bulgaricus* with folic acid and formic acid, which it uses for purine synthesis (Siewwerts S et al., 2010).

Lactococcus, *Lactobacillus*, *Lactiplantibacillus* and *Lentilactobacillus* are members of family *Lactobacillaceae*. *Lactobacillaceae* are a diverse family of lactic acid bacteria found in the gut microbiota of humans and many animals. These bacteria are frequently used as probiotics. Probiotics have varying mechanisms of action depending on species and are known to influence the host health in three main ways: by modulating the existing microbiota, by communicating with the intestinal mucosa and/or by affecting functions that are not limited to the gastrointestinal tract, such as the immune system.

Lactobacillus has proven effects on the intestinal permeability and the immune system and may counteract translocation and inhibit the growth of harmful bacteria (Mangell P et al., 2006; Klarin B et al., 2008; Jones C et al., 2013; Rask C et al., 2013). *Lactobacillus plantarum* 299v (*Lp299v*) has been found to reduce recurrence of *Clostridium difficile*-associated disease. Enteral administration of the probiotic bacterium *Lp299v* to critically ill patients treated with antibiotics reduced colonisation with *C. difficile* (Klarin B et al., 2008). In a previous study, the investigators showed that a mixture of *Lactiplantibacillus plantarum* and *Lacticaseibacillus paracasei* had a dampening effect of peripheral immune response in children with ongoing celiac disease autoimmunity (Hakansson A et al., 2019). According to Rask C et al., 2013, intake of *Lactobacillus plantarum* strain 299v increased the expression of the activation marker CD25 on CD8(+) T cells and the memory cell marker CD45RO

on CD4(+) T cells, whereas intake of *L. paracasei* tended to expand the natural killer T cell population. The phagocytic activity of granulocytes was increased following intake of *L. plantarum* 299v, *L. plantarum* HEAL, *L. paracasei* or *L. fermentum*. The authors suggest that intake of probiotic bacteria may enhance the immune defence against, e.g. viral infections or tumours (Rask C et al., 2013).

Due to its unique fermentation process, *Lactococcus lactis* plays a key role in the manufacturing of dairy products. The superior biological activities of *L. lactis* in these functional foods include anti-inflammatory and immunomodulatory capabilities. *L. lactis* boosted growth performance, controlled amino acid profiles, intestinal immunology, and microbiota. Besides that, the administration of *L. lactis* increased the rate of infection clearance (Saleena LAK et al., 2023).

Health benefits associated with *S. thermophilus* include production of antioxidant compounds, risk alleviation for some types of cancer, anti-inflammatory effects, antimutagenic effects and stimulation of the gut immune system (Iyer R et al., 2010; Iyer R et al., 2010, Martinović A et al., 2020; Mizuno H et al., 2020).

CONCLUSIONS

Lactobacillus strains have proven anti-inflammatory properties by reducing pro-inflammatory responses to antigens. In conclusion, daily oral administration of *L. plantarum* and *L. paracasei* modulate the peripheral immune response, reduce colonisation with *C. difficile* and may enhance the immune defence against, e.g. viral infections or tumours. *Lactococcus lactis* and *S. thermophilus* also are associated with health benefits, as risk alleviation for some types of cancer, anti-inflammatory effects, antimutagenic effects and stimulation of the gut immune system.

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PATHOGENIC MICROFLORA IN WHITE BRINED CHEESE

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ABSTRACT

Cow milk white brined cheeses contain large amounts of probiotic bacteria, represented primarily by members of family Lactobacillaceae and *Streptococcus thermophilus*. However, it can be easily contaminated by food-borne microorganisms and pathogens from a variety of sources, including animal feces, soil, air, feed, water, equipment, animal skins, and humans. Thus, the spread of pathogens and microorganisms that deteriorate the microbiological composition of milk products and cheeses depends on many factors. The aim of the present study is to present and discuss results of scientific studies that present pathogenic bacterial species isolated from white brined cheeses. In our study, we used a documentary method to survey scientific publications, reports and current studies that present most isolated pathogenic bacterial strains from white brined cheeses and possible contamination sources. Due to its high nutritional value, cheese is an excellent medium for the growth of these pathogens. The main microbiological hazards of white brined cheese are associated with *Listeria monocytogenes*, *Escherichia coli* and *Staphylococcus aureus*.

Keywords: white brined cheese, pathogenic organisms, prevention, contamination

INTRODUCTION

While the consumption of foods is intended for delivering required nutrients, a new trend has been developed lately regarding the development of functional foods with additional properties contributing positively in health. Likewise, there is an increased demand and preference by the consumers lately to functional foods. There are many subcategories of functional foods such as prebiotic and probiotics. Probiotics are usually fermented food products containing at the final product probiotic microorganisms in adequate amounts.

Cow milk white brined cheeses contain large amounts of probiotic bacteria, represented primarily by members of family Lactobacillaceae and *Streptococcus thermophilus*. However, it can be easily contaminated by food-borne microorganisms and pathogens from a variety of sources, including animal feces, soil, air, feed, water, equipment, animal skins, and humans. Thus, the spread of pathogens and microorganisms that deteriorate the microbiological composition of milk products and cheeses depends on many factors.

AIM

The aim of the present study is to present and discuss results of scientific studies that present pathogenic bacterial species isolated from white brined cheeses.

MATERIALS AND METHODS

In our study, we used a documentary method to survey scientific publications, reports and current studies that present most isolated pathogenic bacterial strains from white brined cheeses and possible contamination sources.

RESULTS AND DISCUSSION

White-brined cheese is traditionally consumed either fresh or after ripening in a brined solution (5–20% NaCl) at room temperature (Ayyash and Shah, 2011). Although cheese is generally considered a safe food because of the physicochemical and antagonistic properties of lactic acid bacteria, part of foodborne outbreaks are related to contaminated cheese. White-brined cheese is a perishable food that can act as a medium for the rapid growth of foodborne pathogens (Al-Nabulsi AA et al., 2020). Foodborne illnesses related to cheese consumption have occurred in many countries. Due to its high nutritional value, cheese is an excellent medium for the growth of these pathogens. The transmission of bacterial pathogens during cheese-making, ripening, and storage can be attributed to direct contamination or cross-contamination events during processing, in retail and domestic environments (Kousta M et al., 2010; Tiwari U et al., 2014; Jordan K et al., 2018).

The main microbiological hazards of white brined cheese are associated with *Listeria monocytogenes*, *Escherichia coli* and *Staphylococcus aureus* (Bangieva DR, 2020) and *Salmonella spp.* (Napoleoni M et al., 2021).

Staphylococcal foodborne intoxication is among the common forms of bacterial food poisoning outbreaks (Dayan et al., 2016). This organism can grow in various foods (Gatadi et al., 2019) and moreover, any food, such as white-brined cheese, which requires considerable handling during preparation and is kept at warm temperatures or brined in low-salt solution after preparation, is also commonly implicated in staphylococcal food poisoning (Le Loir et al., 2003; Ahmed et al., 2019).

In 2020 Bangieva DR conducted a study in which microbiological and physicochemical methods were used to obtain a detailed picture of potential risk of foodborne illnesses linked to raw milk cheese consumption during the ripening process. The results indicate that in general, the hygienic quality of raw milk cheese was of unacceptable microbiological level. *S. aureus*, *E. coli* and *Listeria spp.* were found in cheese at levels that are of concern (Bangieva DR, 2020).

Talevski G, 2023 also published results that the microbiological quality of the raw milk was poor with an average bacterial count (1 680 000 CFU/ml) and somatic cell count (977 000 SCC/ml). The microbiological analysis of the white brined cheeses after 60 days of fermentation, showed an average of 40 700 CFU/g of aerobic mesophilic bacteria. Of the significant groups of microorganisms from a health point of view, the representatives of *Enterobacteriaceae* were the most represented in 70%, as well as *Escherichia coli* in 50% of the examined cheese samples. After two months of cheese ripening, the presence of coagulase positive staphylococci, *Salmonella spp.* and *Listeria monocytogenes* was not determined (Talevski G, 2023).

According to study of Hussein ND et al, 2023, *E. coli* and *S. aureus* were detected in 80% and 32% of the 50 white brined cheese samples, respectively. Notably, 80% and 32% of the samples exceeded the maximum permissible limit of *E. coli* and *S. aureus*, respectively. Additionally, they evaluated the antibiotic resistance profiles of the *E. coli* isolated from the cheese and found that a high percentage of the *E. coli* isolated from the cheeses showed resistance to clinically and agriculturally important antibiotics, while 75% isolates were classified as multidrug-resistant. These findings highlight serious food safety and antimicrobial resistance problems that require immediate interventions (Hussein ND et al, 2023).

Cheese-related *L. monocytogenes* outbreaks have had a relatively high fatality rate (15% to 30%), leading to increased public awareness of this infection (Lecuit M, 2007; Choi KH et al., 2016; Palacios A et al., 2022). A number of other diseases can be transmitted to humans through cheese. Microbes that can be transmitted lead to bovine tuberculosis, brucellosis, malaria, *Clostridium spp.* (Milva P&Focardi S, 2022), Campylobacter-related infections in consumers others (Nornberg et al., 2010; Bastam MM et al., 2021).

PREVENTION OF PATHOGENIC MICROORGANISMS CONTAMINATION

Aging for 60 days is believed to improve the antimicrobial properties of lactic acid bacteria. Lower levels of pathogenic bacteria, including *L. monocytogenes*, *E. coli O157: H7*, *Salmonella spp.* and *Campylobacter spp.* were found in cheese samples tested, supporting the hypothesis that 60-day maturation of raw milk cheese can improve microbiologically safe cheeses (Brooks JC et al., 2012). Eukaryotic microorganisms such as yeasts and molds can be common contaminants of cheeses and dairy products. In particular, these microorganisms can pose a serious health hazard due to their ability to produce mycotoxins.

The contribution of lactic acid bacteria on inhibiting the growth of foodborne pathogens was highlighted in presence of *E. coli* that evidenced a decrease to less than 1% after the addition of commercial starter cultures (Choi J et al., 2020; Nam JH et al., 2021). Lactic acid bacteria produce bacteriocins which are peptides with antimicrobial activity. Wide diversity of bacteria caught be bacteriocins-producers microbes.

Those produced by Gram-positive bacteria are classified into class I, containing heavily modified (lanthionine-containing) peptides called lantibiotics, and class II, containing non-modified peptides or peptides with minor modifications. Bacteriocins can be rapidly degraded by proteases in the gastrointestinal tract and thus they have no effects to human gut microbiota.

CONCLUSION

The principal organisms associated with food poisoning outbreaks caused by cheese are *Salmonella spp.*, *Staphylococcus aureus*, *Listeria monocytogenes* and enteropathogenic strains of *Escherichia coli*. Chees's aging for 60 days caught improve the antimicrobial properties of lactic acid bacteria and inhibiting the growth of foodborne pathogens.

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EPIDEMIOLOGICAL SURVEILLANCE OF HEALTHCARE-ASSOCIATED INFECTIONS IN SILISTRA REGION FOR A PERIOD 2017-2021

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ABSTRACT

The aim is to study status and trends of Healthcare-associated infections (HAIs) in the years before and after the Covid 19 pandemic from 2017 to 2021.

The data was collected from RHI- Silistra, National Center of Infectious and Parasitic Diseases (NCIPD) and Ministry of Health, National system for epidemiological surveillance of hospitals

Results and discussion: The study covers registration of patients in the three medical facilities (116,099 people) in the district and the registered total of 1003 HAIs in 792 patients.

There are data on the influence of the population structure and the workload of medical facilities on the occurrence of HAIs. According to these data the number of patients served in the district from 25400 (2017) and 25619 (2018) decreased after 2019 to 20265 (2020) and 20084 (2021). The relative share of transferred patients is at the expense of "MBAL-Silistra" AD (from 61.19% for 2017 and 62.34% for 2021).

The relative ratio of HAIs (based on the number of all admitted patients for the same period) has increased from 0.88% (2017) to 1.06% (2021). The leading pathogens causing HAIs are coagulase-negative staphylococci (CoNS) (28,21%), *Staphylococcus aureus* (20,54%) and *Enterococcus fecalis* (11,38%). **Conclusion:** The COVID 19 pandemic had impact on the HAI rates and pathogen profiles in district Silistra. The dominant nosocomial strains in all years have been coagulase-negative staphylococci (CoNS) with an average relative share of 28,21%. In the last year *Candida albicans* is in the second place on the list, mainly due to the incorrect or excessive use of antibiotics.

INTRODUCTION

Healthcare-associated infection (HAI) are a major public health challenge, which leads to a prolonged hospital stay, increased antimicrobial resistance, additional healthcare expenditures, as well as a high mortality [1,2,3,4]. In order to limit the spread of HAIs and antimicrobial resistance (AMR) in Bulgaria, there is a medical standard Ordinance No. 3 of the Ministry of Health. Medical teams work to reduce the incidence of nosocomial infections and limit the spread of antimicrobial resistance by following the principle of "do no harm". [5,6,7].

The aim is to study status and trends of Healthcare-associated infections (HAIs) in the years before and after the Covid 19 pandemic from 2017 to 2021.

MATERIALS AND METHODS

The retrospective analysis was carried out using the hospital register of HAIs for five- year period (2017- 2021 in the three medical facilities: Multiprofile hospital for active treatment – Dulovo, Multiprofile hospital for active treatment – Tutrakan and Multi profile hospital for active treatment – Silistra.

We used data from: RHI- Silistra, National Center of Infectious and Parasitic Diseases (NCIPD) and Ministry of Health, National system for epidemiological surveillance of hospitals. The data was analyzed with SPSS v. 20.0.using variance, comparative and correlation analysis. We accepted $p < 0.05$ as the level of significance.

RESULTS AND DISCUSSION

The analysis of data from the register in the medical facilities in the Silistra region shows that for the period 2017-2021, were diagnosed a total of 792 patients and 1 003 cases of HAIs were reported. The established average incidence is 0.86 per 1,000 patients. This shows that with longer hospitalization there are registered patients with more than one HAIs, on average 1.26 HAIs (Fig. 1).

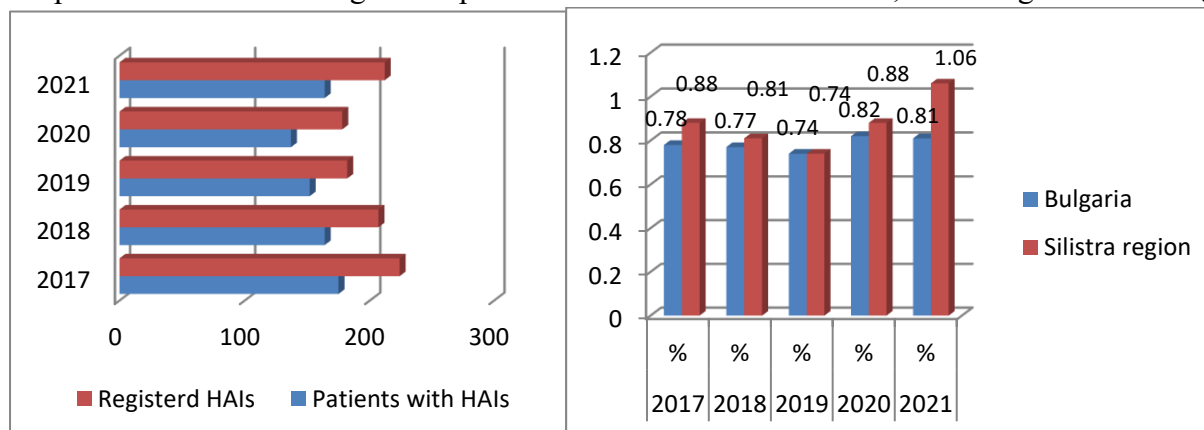


Fig.1 Number of registered healthcare-associated infections in Silistra region during 2017-2021

Fig. 2 Relative share of healthcare-associated infections in Bulgaria and in the Silistra region for 2017-2021

An increase in the relative share of HAIs from 0.88% (2017) to 1.06% (2021) was observed in district Silistra. This is more than the average level for Bulgaria of 0.78% (2017) to 0.81% (2021) (Fig.2). Multiprofile hospital for active treatment – Silistra. has the highest relative share of registered HAIs with an increase from 1.36% (2017) to 1.71% (2021). In contrast, in the other two hospitals, a decrease in the incidence of HAIs was observed: in Multiprofile hospital for active treatment – Tutrakan from 0.16% (2017) to 0.07% (2021) and in the Multiprofile hospital for active treatment – Dulovo, from 0.46% (2017) to 0.06% (2021). During 2020, there were no registered cases of HAIs in Multiprofile hospital for active treatment – Dulovo. A statistically significant difference was found between the three medical facilities and moderate dependence between Multiprofile hospital for active treatment – Tutrakan and Multiprofile hospital for active treatment – Dulovo, ($p < 0.05$).

The analysis of data from the register in the largest hospital in the district - MHAT – Silistra shows that for the period 2017-2021, were hospitalized 69 586 patients and 966 cases of HAIS were reported. The established average morbidity is 1,38 per 1,000 patients.

For the investigated period, the highest relative share of HAIs was registered in the Anesthesiology and intensive treatment department (AITD) from 13.46% (2017) to 18.23% (2021), and neonatology department from 7.26% (2017) to 10.82% (2021) followed by surgically separated where the indicators are twice as low, from 4.01% (2017) and 3.37% (2021). A significant difference in the morbidity of HAIs in the different wards in the hospital was found. The intensive care units are at the greatest risk for HAIs, which has been confirmed by other authors [6].

For the period 2017-2021, a total of (n=25 cases) healthcare associated infections were reported and 25 294 patients were hospitalized in MHAT – Tutrakan. The largest number of HAIs for period 2017-

2021 was registered in Anesthesiology and intensive treatment department (AITD) (n=8 cases) and in Gynecology (n=8). A pediatric ward has not reported any case.

In MHAT – Dulovo there is no intensive care unit. For the period from 2017 to 2021 were hospitalized 21 219 patients and 12 cases of HAIs were reported. The ward with the high risk for HAIs in the hospital is the Surgical ward where was reported 4 cases of HAIs.

The registered HAIs according to their localization in organs and systems are divided into 15 groups. Leading place in the structure of the HAIs during the period 2017-2021 are occupied by 7 groups: pneumonias associated with intubation (22.2%), *superficial surgical site infection* (19%), conjunctivitis (13.6%), Urinary tract infections (13.2%), Central venous catheter-related infections (4%), deep/organ-space surgical Site Infections (4%).

In etiological aspect, the recorded HAIs are represented by different microbial agents. Etiological diagnosis as the most accurate directs to correct therapy. Applied in time it affects the prognosis. The leading pathogens causing HAIs in Silistra region from 2017 to 2021 are Coagulase-negative *Staphylococci* (CoNS) (28.21%), *Staphylococcus aureus* (20.54%), *Enterdcocus faecalis* (11.38% *Enterobacter cloacae* (5.19%), *Candida albicans* (10.14%), *Escherichia coli* (8.66%), *Pseudomonas aeruginosa* (7.67%), *Acinetobacter baumannii* (6.13%), *Klebsiella pneumoniae* (1.48%) (Fig. 3).

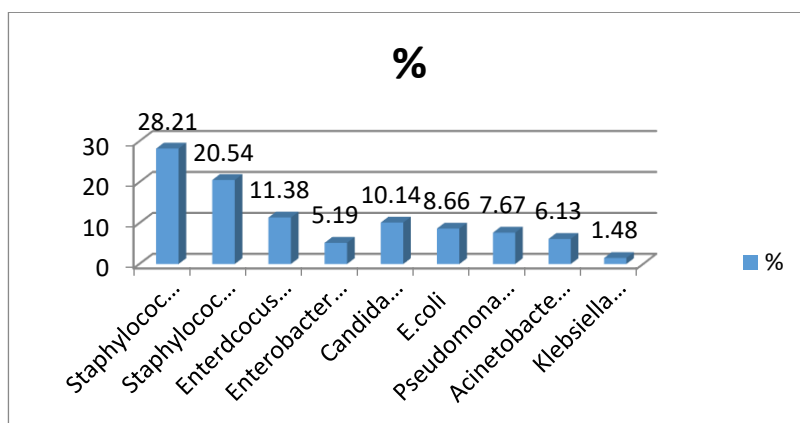


Fig. 3 Etiological structure of HAIs in Silistra region in period 2017-2021

While in other medical facilities in the Ruse region, *Acinetobacter baumannii* is the leader, 17.65% (2017-2021). *Klebsiella pneumoniae* 11.12% (2017), *Pseudomonas aeruginosa* 10.94% (2018), 14.45% (2020).

The correct reporting and recording of HAI cases depends on the quality of patient care, methods and means of collection, storage, transportation of samples, but also on the possibilities and volume of research in specialized microbiological laboratories, their number, apparatus, equipment, personnel [5,6,8,9].

During the research period, there were no unexamined patients in the Silistra region, which we have not encountered in other studies. Paunov and co-authors 2022 report the relative share of the unexamined from 10.59% in 2017 to 15.75% in 2021[7].

For the period 2017-2021, the percentage of the microbiologically unproven infections has decreased from 2% to 0%). As a matter of comparison in the Sliven region, the percentage of microbiologically unproven infection reached 22.44% in 2014, the unexamined cases accounted for a third of the cases - 32.29% in 2016 [10].

Gergova and co-authors (2018) report that only in 17-19% NI are etiologically clarified in MPHAT Sophia-Military medical academy.

CONCLUSION

1. The organization of epidemiological surveillance in the Silistra region corresponds to the state policy for the prevention of HAIs healthcare facilities.
2. An increase in the relative share of HAIs from 0.88% (2017) to 1.06% (2021) was observed in district Silistra. This is more than the average level for Bulgaria of 0.78% (2017) to 0.81% (2021).
3. The leading pathogens causing HAIs are coagulase-negative staphylococci (CoNS) (28,21%), *Staphylococcus aureus* (20,54%) and *Enterococcus faecalis* (11,38%).
4. There is an organization for a timely complete analysis of the epidemic surveillance of the HAIs and making adequate decisions to overcome the gaps

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ASSESSMENT OF PHYSICAL DEVELOPMENT INDICATORS, CHILD HEALTH STANDARD IN ORGANIZED COLLECTIVES SILISTRA REGION

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ABSTRACT

Monitoring the health status of children is the main task of the preventive activity in the organized collectives, the main criterion for the standard of health and priority of the health policy in Bulgaria.

Aim: To study the physical development of children in organized collectives in the Silistra region and their dispensary monitoring according to the International Classification of Diseases (ICD) for the year 2018-2021. **Materials:** Normative documents, reports, analyses, tests, data from preventive examinations and medical examinations, anthropometric measurements from 24 children's institutions in 132 groups with 12531 children attending the children's institution for 2018-2021.

Methods Methodology for conducting preventive examinations for children from 0 to 18 years, documentary, graphic, statistical. **Results:** Physical development, height and body mass index of 11,383 children in organized collectives in Silistra region are studied based on the individual assessment of anthropometric indicators in three groups: first group - norm, second group - extended norm, third - outside the norm (below the norm above the norm). The highest relative share has the first group of growth norm, 86.2% on average, and weight norm on average 83.31% for 2018-2021. We assess the physical capacity of 11,515 children as "Meeting the norms" for their age. The assessment of the state of health includes the dispensary and the registered anomalies during the preventive examinations. **Conclusions:** The indicator outside the norm for height is in favor of low height (below the norm) - from 66% (2018) to 67% (2021), and for weight above the norm - obesity from 62% for (2018) to 67.4% for (2021). Leading diseases for dispensation are vision disturbance, behavioral and emotional disorders., epilepsy, congenital abnormalities of the heart septum, chronic diseases of the tonsils and adenoid vegetations

INTRODUCTION

The pre-school age (3-7 years) is of great importance for the correct physical and mental development. In Bulgaria, the medical control of growth and development is performed via periodic prophylactic examinations of children and assessment of their physical performance. [1, 2,3]. Assessment of the physical development of children is based on morphological /anthropometric/ indicators. [4,5,6,7].

AIM

To study the physical development of children in organized childcare facilities in the Silistra region, Bulgaria.

MATERIALS AND METHODS

We analyzed reports from 24 childcare facilities in Silistra region (11 383 children). During the examinations, the standard methodology for conducting prophylactic screening in children from 0 to

18 years was used. The included indicators were height, weight, physical performance and dispensary monitoring according to the International Classification of Disease Diagnosis (ICD).

RESULTS AND DISCUSSIONS

Assessment of the body weight was performed for 94,2% of the children. Most of the studied children were in the group with normal weight – 85,5% (2018) to 82,0% (2021). The number of children with overweight exceeded two times the number of underweight children (Fig. 1).

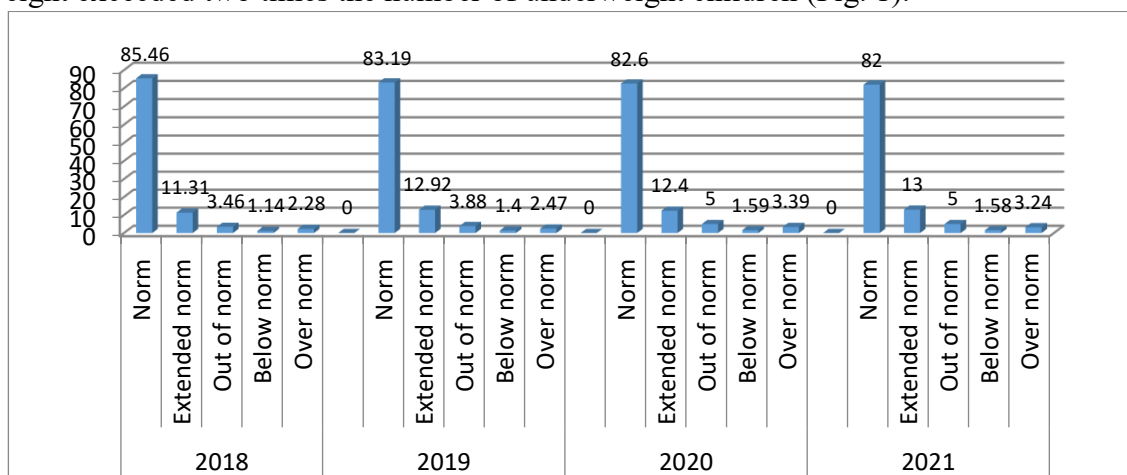


Figure 1. Groups of children according their weight Silistra, Bulgaria (2018-2021)

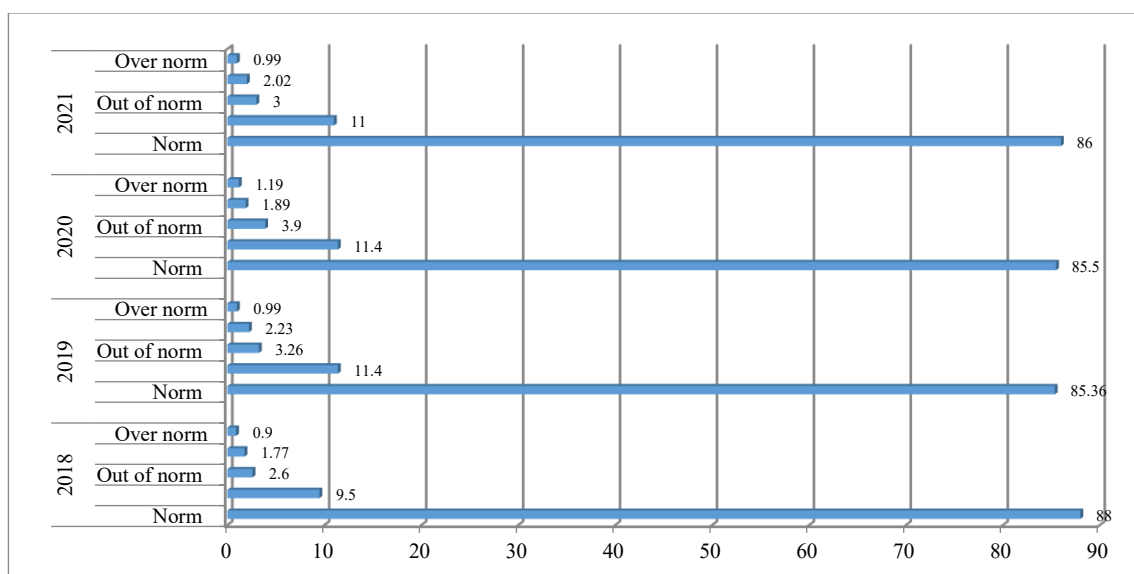


Fig. 2 Groups of children according their height Silistra, Bulgaria (2018-2021)

Most of the studied children were in the group with normal height – 88,0% (2018) to 86,0% (2021) (Fig. 2). Children below the norm for the height were more than the children over the norm. During the studied period, a total of 11 515 children were tested for physical performance. The majority (9982, 86,8%) succeeded to cover the norm. There was a sharp decrease in the proportion of the children with normal performance in 2019 (Tabl. 1).

Table 1. Physical performance of children Silistra, Bulgaria (2018-2021)

Year	2018	2018	2018	2018
Physical performance test (norm, %)	94,5	94,5	94,5	94,5

Table 2. Diagnoses of children subject to dispensary monitoring Silistra, Bulgaria (2018-2021)

Diagnosis	2018	2019	2020	2021	Total
Visual disturbance	1	1	1	1	4
Behavioral and emotional disorders	2	1	2	3	8
Epilepsiya	2		1	2	5
Congenital Heart Defects	1	1		6	8
Diabetes	1	1	1		3
Chronic tonsillitis and adenoid vegetations	4			4	8
Deafness		1	3		4
Acute and chronic pyelonephritis		1		2	3
Congenital hydrocephalus		1	2		3
Allergic rhinitis		2	2		4
Infantile cerebral palsy	5				5
Obesity	3				3
Autism	2				2
Asthma			2		2
Syndroma praeexcitationis			6		6
Mitral valve prolapse			1		1
Arthritis			1		1
Urethral atresia			1		1
Chronic bronchitis			6		6
Total	21	9	29	18	77

During the studied period, diseases subject to dispensary monitoring, were found in 77 children out of 11 383 (0,7%). Leading diseases were behavioral and emotional disorders, epilepsy, congenital heart defects, chronic tonsillitis, syndroma praeexcitationis, chronic bronchitis, etc (Tabl. 2).

CONCLUSIONS

Most of the children in Silistra region cover the norm for standard indicators of growth and development. The physical activity has to be popularized via organization of regular sport exercises, especially for overweight children.

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MEDICINES FOR NON-SMALL CELL LUNG CANCER (NSCLC) TARGETING EGFR EXON 20 INSERTION MUTATIONS – ACCELERATED APPROVALS GRANTED IN 2021 AND CURRENT STATUS AFTER CONFIRMATORY CLINICAL TRIALS IN 2023

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ABSTRACT

Lung cancer is the leading cause of cancer-related deaths worldwide in both men and women. The epidermal growth factor receptor gene exon 20 insertion (EGFR_{ex20ins}) mutations are an uncommon and heterogeneous group, resistant to conventional EGFR tyrosine kinase inhibitors (TKIs) and have been considered as an “undruggable target” for a long time. The aim of this scientific paper is to present the data from clinical trials, available in 2021 and confirmed the accelerated approvals for mobocertinib and amivantamab, including some pharmacokinetic and pharmacodynamic characteristics of both medications. We also present the data from PAPILLON study (NCT04538664) that met its primary endpoint with a statistically significant and clinically improvement in progression free survival (PFS) (as measured by BICR) in patients receiving amivantamab (Rybrevant).

In 2021, two medications amivantamab and mobocertinib received accelerated approval for treatment of advanced NSCLC with EGFR_{ex20ins} mutations. Both medications had shown promising results and similar efficacy in the early phase clinical trials. However, in 2023, after collection additional data for efficacy, the FDA and Takeda have decided to voluntarily withdraw Exkivity from the global market. Janssen Pharmaceutical submitted a supplemental Biologics License Application (sBLA) to the FDA seeking the expanded approval of Rybrevant in combination with chemotherapy.

Keywords: Non-small cell lung cancer (NSCLC), epidermal growth factor receptor gene exon 20 insertion mutations (EGFR_{ex20ins}) mutation, Amivantamab, Mobocertinib

INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths worldwide in both men and women. The epidermal growth factor receptor gene exon 20 insertion (EGFR_{ex20ins}) mutations are an uncommon and heterogeneous group, resistant to conventional EGFR tyrosine kinase inhibitors (TKIs) and have been considered as an “undruggable target” for a long time. A study reports that EGFR_{ex20ins} mutations are available in advanced non-small cell lung cancer (NSCLC) with a prevalence of 0.5% in overall NSCLC cases and 4.0% in EGFR-positive NSCLC. In 2021 U.S. Food and Drug Administration (FDA) approved two medications monoclonal antibodies - mobocertinib (Exkivity, Takeda) and amivantamab (Rybrevant, Janssen Pharmaceutical) for locally advanced/metastatic NSCLC with EGFR_{ex20ins} mutations. Then the both medications received accelerated approvals. Both mobocertinib and have different pharmacokinetic and pharmacodynamics characteristics, but amivantamab has more favorable safety profile - most common adverse drug reaction (ADR) are infusion-related reactions, while mobocertinib can cause QTc prolongation and has black box warning. In Aug 2023, Janssen Pharmaceutical submitted a supplemental Biologics License Application (sBLA) to the FDA seeking the expanded approval of Rybrevant in combination with chemotherapy for the first-line treatment of locally advanced or metastatic NSCLC with EGFR_{ex20ins} mutations. In Oct 2023 the FDA and Takeda have decided to voluntarily withdraw mobocertinib (Exkivity) from the global market. The pharmaceutical company, Takeda, has announced that the decision comes after a research study did not show the anticipated response.

AIM

To present the data from clinical trials, available in 2021 and confirmed the accelerated approvals for mobocertinib and amivantamab, including some pharmacokinetic and pharmacodynamic characteristics of both medications. We also present the data from PAPILLON study (NCT04538664) that met its primary endpoint with a statistically significant and clinically improvement in progression free survival (PFS) (as measured by BICR) in patients receiving amivantamab (Rybrevant). Following the announcement from Takeda for withdrawal of mobocertinib (Exkivity), we present the data from a phase 3 EXCLAIM-2 confirmatory trial (NCT04129502).

MATERIALS AND METHODS

Review of the regulatory information by the marketing authorization holders and the published data with results from the clinical trials.

RESULTS

Amivantamab is a fully-human immunoglobulin G1 bispecific antibody with immune cell-directing activity that targets EGFR mutations and mesenchymal-epidermal transition (MET) mutations and amplifications, while mobocertinib is an EGFR TKI. Both medications presented with positive results from clinical trials in 2021 and received accelerated approvals from FDA. The PAPILLON study (NCT04538664) met its primary endpoint and Janssen Pharmaceutical submitted a supplemental Biologics License Application (sBLA) to the FDA seeking the expanded approval of Rybrevant in combination with chemotherapy for the first-line treatment of locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations. However, the confirmatory trial for Mobocertinib did not meet the primary endpoint and the pharmaceutical company Takeda withdraw mobocertinib from the market.

In patients with NSCLC, the driver gene mutations, including the EGFR, have been extensively reported and EGFRex20ins are the third most frequent type of EGFR mutations, following exon 21 point mutations L858R and exon 19 deletions. The majority of patients with EGFRex20ins, in contrast to those with classical EGFR mutations, are highly resistant to current EGFR TKIs, classical chemotherapy, and immunotherapy, and their survival is quite unsatisfactory, which emphasizes the urgent need for alternative treatment approaches for this subset of patients.¹

In 2021 FDA gave accelerated approval to Janssen Pharmaceutical and Takeda for their monoclonal antibodies Amivantamab and Mobocertinib respectively, indicated for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFRex20ins mutation. The European Commission granted conditional marketing authorization of amivantamab in December 2021. Mobocertinib has not been approved by the EMA - the pharma company withdrew its application for a conditional marketing authorization in July 2022. Amivantamab (Rybrevant) was approved under accelerated approval based on overall response rate (ORR) and duration of response (DOR). Phase 1 study enrolled 81 patients, in CHRYSALIS (NCT02609776), a phase I trial, amivantamab-vmjw was associated with an overall response rate (ORR) of 40% (95% CI, 29–51) in the EGFR exon20ins NSCLC patient population (n = 81) after platinum-based chemotherapy. There were 3 complete responses (CRs) and 29 partial responses (PRs). The median duration of response (DOR) was 11.1 months (95% CI, 6.9—not reached; NR). The median progression-free survival (PFS) was 8.3 months (95% CI, 6.5–10.9), and overall survival (OS) was 22.8 months (95% CI, 14.6—NR).² (Table 1)

Table 1. Efficacy Results for CHRYSALIS Based on Kaplan-Meier estimates NE=Not Estimable, CI=confidence interval.³

	Prior Platinum-based Chemotherapy Treated (N=81)
Overall Response Rate (ORR) (95% CI)	40% (29%, 51%)
Complete response (CR)	3.7%
Partial response (PR)	36%
Duration of Response (DOR)	
Median, months (95% CI), months	11.1 (6.9, NE)
Patients with DOR ≥6 months	63%

The approval of mobocertinib (Exkivity) was based on data from Study AP32788–15-101 (NCT02716116). The overall response rate (ORR) in 114 patients whose disease had progressed on or after platinum-based chemotherapy was 28% (95% CI: 20%, 37%) with a median duration of response of 17.5 months (95% CI: 7.4, 20.3). Based on observed duration of response, a total of 59% of responders had a DOR \geq 6 months and 19% of responders had a DOR \geq 12 months. At the data-cutoff, the response was ongoing for 16 responders. The ORRs observed in the subgroups of patients who received prior anti-PD-(L)1 therapy (n=48) and those who did not receive prior anti-PD-(L)1 therapy (n=66) were 25% (95% CI: 14, 40) and 30% (95% CI: 20, 43), respectively.⁴ (Table 2)

Table 2. Efficacy Results in Study AP32788-15-101⁵ ^a Per BICR, CI = confidence interval ^b All responses were partial responses ^c Kaplan-Meier estimate using confirmed responses only ^d Based on observed duration of response

	EXKIVITY (n=114)
Overall Response Rate (ORR) ^a (95% CI)	28% (20, 37) ^b
Duration of Response (DOR)	
Median (months) ^c , (95% CI)	17.5 (7.4, 20.3)
Patients with DOR \geq 6 months ^d	59%
Investigator-assessed ORR (95% CI)	35% (26,45)
Median DOR (months) (63% of these patients had observed responses lasting longer than 6 months)	11.2

Matching-adjusted indirect comparison (MAIC) of mobocertinib versus amivantamab. There have been no prospective, randomized trials directly comparing the efficacy and safety of amivantamab and mobocertinib. Sai-Hong Ignatius Ou et al. presented results from MAIC of mobocertinib versus amivantamab at the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting (Abstract 9115). This MAIC study compared the ORR, DOR, progression free survival (PFR), and overall survival (OS). Researchers employed data from a phase I/II study (NCT02716116) of mobocertinib and compared it with data from a phase I trial (NCT02609776) of amivantamab. Differences in baseline characteristics adjusted for in the matching-adjusted indirect comparison study included but were not limited to age, race, sex, smoking status, prior lines of therapy, and time from advanced diagnosis. The OS with mobocertinib was 24.8 months, compared with 22.8 with amivantamab (hazard ratio [HR] = 0.95, 95% CI = 0.55–1.67). The PFS was similar between the groups as well, at 7.4 months with mobocertinib and 8.3 months with amivantamab (HR = 0.82, P = .417). The confirmed ORR per an independent review committee (IRC) was higher with amivantamab (40%) than with mobocertinib (30%), but this was not statistically significant (P = .230). For patients who responded to treatment, the DOR was numerically higher with mobocertinib (17.5 months) compared with amivantamab (11.1 months), according to the independent reviewers (HR = 0.56, P = .149).⁶

We compared the both medications from pharmacology prospective, focusing on adverse drug reactions (ADR) and drug-drug interactions. Despite being administered intravenously, amivantamab generally had a better safety profile in comparison with oral mobocertinib. Product labeling for mobocertinib includes a Boxed Warning for QTc prolongation and Torsades de Pointes.

Table 3. Pharmaceutical, pharmacokinetics and pharmacodynamics characteristics of amivantamab and mobocertinib. Warnings, safety and possible drug-drug interactions of amivantamab and mobocertinib as per marketing authorization holders ^{3,5}

	RYBREVANT (amivantamab-vmjw)	EXKIVITY (mobocertinib)
Pharmaceutical form, dosage and administration:	Injection: 350 mg/7 mL (50 mg/mL) solution in a single-dose vial for intravenous use. The recommended dosage is based on baseline body weight.	160 mg orally once daily, with or without food. Capsules 40 mg
Indications and usage:	RYBREVANT is a bispecific EGF receptor-directed and MET receptor directed antibody indicated for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFRex20ins mutations, as detected by an FDA-	EXKIVITY is a kinase inhibitor indicated for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFRex20ins mutations, as

	approved test, whose disease has progressed on or after platinum-based chemotherapy.	detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.
Warnings:	Infusion-Related Reactions (IRR) Interstitial Lung Disease (ILD)/Pneumonitis Dermatologic Adverse Reactions Ocular Toxicity; Embryo-Fetal Toxicity	BLACK BOX WARNING: QTc PROLONGATION AND TORSADES DE POINTES Interstitial Lung Disease (ILD)/Pneumonitis Cardiac Toxicity; Diarrhea; Embryo-Fetal Toxicity
Adverse drug reactions (ADR):	The most common ADR ($\geq 20\%$): rash, IRR, paronychia, musculoskeletal pain, dyspnea, nausea, fatigue, edema, stomatitis, cough, constipation, and vomiting. The most common Grade 3 or 4 laboratory abnormalities ($\geq 2\%$): decreased lymphocytes, decreased albumin, decreased phosphate, decreased potassium, increased alkaline phosphatase, increased glucose, increased gamma-glutamyl transferase, and decreased sodium.	The most common ADR ($>20\%$): diarrhea, rash, nausea, stomatitis, vomiting, decreased appetite, paronychia, fatigue, dry skin, and musculoskeletal pain. The most common ($\geq 2\%$) Grade 3 or 4 laboratory abnormalities: decreased lymphocytes, increased amylase, increased lipase, decreased potassium, decreased hemoglobin, increased creatinine, and decreased magnesium.
Mechanism of Action:	Amivantamab-vmjw is a bispecific antibody that binds to the extracellular domains of EGFR and MET. In in vitro and in vivo studies amivantamab-vmjw was able to disrupt EGFR and MET signaling functions through blocking ligand binding and, in exon 20 insertion mutation models, degradation of EGFR and MET. The presence of EGFR and MET on the surface of tumor cells also allows for targeting of these cells for destruction by immune effector cells, such as natural killer cells and macrophages, through antibody-dependent cellular cytotoxicity and trogocytosis mechanisms, respectively.	Mobocertinib is a kinase inhibitor of the epidermal growth factor receptor (EGFR) that irreversibly binds to and inhibits EGFR exon 20 insertion mutations at lower concentrations than wild type (WT) EGFR. Two pharmacologically-active metabolites (AP32960 and AP32914) with similar inhibitory profiles to mobocertinib have been identified in the plasma after oral administration of mobocertinib. In vitro, mobocertinib also inhibited the activity of other EGFR family members (HER2 and HER4) and one additional kinase (BLK).
Pharmacodynamics (PD):	The exposure-response relationship and time-course of PD response of amivantamab-vmjw have not been fully characterized	Mobocertinib exposure-response relationships and the time course of PD response are unknown. The largest mean increase in QTc was 23.0 msec (UCI: 25.5 msec) following administration of EXKIVITY 160 mg once daily. The increase in QTc interval was concentration-dependent.
Pharmacokinetics (PK):	Amivantamab-vmjw exposures increased proportionally over a dosage range from 350 to 1750 mg. Steady state achieved by the 9 th infusion. The accumulation ratio at steady state: 2.4. Distribution: Mean (\pm SD) volume of distribution 5.13 (\pm 1.78) L. Elimination: Mean (\pm SD) clearance 360 (\pm 144) mL/day. Terminal half-life 11.3 (\pm 4.53) days. Body Weight: Increases in body weight increased the VoD and clearance. Amivantamab-vmjw exposures are 30-40% lower in patients ≥ 80 kg compared to patients < 80 kg at the same dose. Exposures were comparable between patients who weighed < 80 kg and received 1050 mg dose and patients who weighed ≥ 80 kg and received 1400 mg dose.	After single- and multiple-dose administration, combined molar C _{max} and AUC _{0-24h} of Mobocertinib and its active metabolites, was dose-proportional over the dose range of 5 to 180 mg once daily. Absorption: Median time to peak concentration (T _{max}): 4 hours (1, 8 hours). Mean (%CV) absolute bioavailability is 37% (50%). Effect of Food No clinically meaningful differences in the combined molar AUC and C _{max} following administration of a high-fat meal or a low fat-meal. Distribution: Bound to human plasma proteins: 99% for mobocertinib and its metabolites. Mean (%CV) apparent volume of distribution (V _{ss} /F) 3,509 L (38%) at steady-state. Elimination Mean (%CV) plasma elimination half-life: 18 hours. Metabolism: primarily metabolized by CYP3A. Excretion: ~ 76% of the dose was recovered in feces and ~ 4% was recovered in urine.
Drug-Drug interactions :	No drug interaction studies have been performed. As an IgG1 monoclonal antibody, renal excretion and hepatic enzyme-mediated metabolism of intact amivantamab are unlikely to be major elimination routes. As such, variations in drug-metabolizing enzymes are not expected to affect the elimination. Due to the high affinity to a unique epitope on EGFR and MET, amivantamab is not anticipated to alter drug-metabolizing enzymes. Vaccines: Avoid the use of live or live-attenuated vaccines while taking amivantamab.	CYP3A Inhibitors: concomitant use with strong or moderate CYP3A inhibitors should be avoided. If concomitant use of a moderate CYP3A inhibitor is unavoidable, then the dose of EXKIVITY to be reduced. CYP3A Inducers: Concomitant use with strong or moderate CYP3A inducers to be avoided.

In August 2023 following the results from the Phase 3 PAPPILLON study (NCT04538664) Janssen Pharmaceutical submitted a supplemental Biologics License Application (sBLA) to the FDA seeking the expanded approval of Rybrevant in combination with chemotherapy for the first-line treatment of locally advanced or metastatic NSCLC with EGFRex20ins mutations. The Janssen Pharmaceutical announced new data, showing that first-line treatment with RYBREVANT® (-vmjw) in combination with chemotherapy (carboplatin-pemetrexed) resulted in a 60 percent reduction in the risk of disease progression or death (Hazard Ratio [HR]=0.395; 95 percent Confidence Interval [CI], 0.30–0.53; p

value $P < 0.0001$) in patients with previously untreated advanced or metastatic NSCLC with EGFRex20ins mutations, compared to chemotherapy alone. Overall, 308 patients were randomized (amivantamab-chemotherapy, 153; chemotherapy, 155). At median follow-up of 14.9 months, the median PFS was 11.4 months (95% CI, 9.8–13.7) for amivantamab-chemotherapy vs 6.7 months (95% CI, 5.6–7.3) for chemotherapy ([HR], 0.40; 95% CI, 0.30–0.53; $P < 0.001$). The 18-month PFS rate was 31% for amivantamab-chemotherapy vs 3% for chemotherapy. PFS benefit of amivantamab-chemotherapy was consistent across subgroups. ORR was 73% (95% CI, 65–80) for amivantamab-chemotherapy vs 47% (95% CI, 39–56) for chemotherapy (odds ratio, 2.97; 95% CI, 1.84–4.79; $P < 0.001$). Median PFS2 was not estimable for amivantamab-chemotherapy vs 17.2 months for chemotherapy (HR, 0.49; 95% CI, 0.32–0.76; $P = 0.001$). Interim OS analysis (33% maturity) showed a favorable trend for amivantamab-chemotherapy vs chemotherapy (HR, 0.67; 95% CI, 0.42–1.09; $P = 0.106$), despite 66%, of chemotherapy-randomized patients whose disease had progressed, receiving second-line amivantamab. The most common TEAEs ($\geq 40\%$) for amivantamab-chemotherapy were neutropenia, paronychia, rash, anemia, infusion-related reactions, and hypoalbuminemia; no new safety signals. Discontinuation of amivantamab due to treatment-related AEs was 7%.^{7,8}

In Oct 2023, the FDA and Takeda have announced plans working towards a voluntary withdrawal of mobocertinib (Exkivity) for EGFRex20ins mutation-positive locally advanced or metastatic NSCLC.⁹ Although no new safety concerns arise in the phase 3 EXCLAIM-2 trial (NCT04129502), the study's primary end point was not achieved. A total of 354 patients were randomized (mobocertinib 179; chemotherapy 175). Baseline characteristics were balanced between arms. This open-label, multicenter study (NCT04129502) randomized patients with untreated EGFR ex20ins and locally advanced/metastatic NSCLC to (1:1) mobocertinib 160 mg PO daily or pemetrexed 500 mg/m² plus cisplatin 75 mg/m²/carboplatin AUC 5 IV every 3 weeks for 4 cycles followed by maintenance pemetrexed. Response was assessed per RECIST v1.1. The primary endpoint was progression-free survival (PFS) assessed by blinded independent review committee (BIRC), with a planned interim analysis (IA) after 184 events. At IA (data cutoff April 4, 2023), BIRC-assessed median PFS was similar between arms (mobocertinib 9.59 months; chemotherapy 9.63 months), with BIRC PFS [HR]=1.038 and $P = 0.803$. The study met prespecified futility criteria (BIRC PFS HR > 1). BIRC confirmed objective response rates were (mobocertinib/chemotherapy) 32%/30%, confirmed disease control rates were 87%/80%, and median duration of response was 12 vs 8 months. Grade ≥ 3 adverse events (AEs) occurred in 62%/53% of pts. Discontinuations due to death (3%/1%) or AEs (10%/14%) were similar between arms. Delay in time to deterioration of lung cancer symptoms per EORTC QLQ-LC13 was noted with mobocertinib.¹⁰

CONCLUSION

In 2021, two medications amivantamab and mobocertinib received accelerated approval for treatment of advanced NSCLC with EGFRex20ins mutations. Both medications had shown promising results and similar efficacy in the early phase clinical trials. However, in 2023, after collection additional data for efficacy, the FDA and Takeda have decided to voluntarily withdraw Exkivity from the global market. Janssen Pharmaceutical submitted a supplemental Biologics License Application (sBLA) to the FDA seeking the expanded approval of Rybrevant in combination with chemotherapy.

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CONSERVATIVE TREATMENT OF ACUTE SOLITARY CAECAL DIVERTICULITIS

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ABSTRACT

The aim of this study is to assess the conservative treatment of acute solitary caecal diverticulitis. The antimicrobial therapy of caecal diverticulitis is reported as successful. The inflammatory process of the caecal diverticulum has been reduced and reverse regression of inflammatory signs was observed.

Keywords: caecal diverticul, treatment, pediatric surgery

INTRODUCTION

The diverticulum of the cecum is a rare, benign, generally asymptomatic lesion that manifests itself only following inflammatory or hemorrhagic complications. Most patients with inflammation of a solitary diverticulum of the cecum present with abdominal pain that is indistinguishable from acute appendicitis [1]. Cecal diverticulitis mimics prevalent acute appendicitis and is much more difficult to diagnose preoperatively. The therapy of this contentious condition includes conservative antibiotic treatment or aggressive resection. We describe a case of an 11-year-old female patient who presented with symptoms suggestive of appendicitis but were found at surgery to have an inflamed solitary diverticulum.

CASE REPORT

A rare case of an 11-year-old girl presenting with acute right, lower abdominal pain with solitary caecal diverticulum who was suspected preoperatively to have acute appendicitis is reported. The patient was urgently admitted to the department with complaints of abdominal pain and nausea since the previous day. The pain intensified and not affected by drugs. Physical examination revealed: in moderately damaged general condition. Afebrile, abdomen - at the level of the chest, moderately ballooned in the lower abdominal floor. Soft on palpation, painful in the lower right quadrant. Bloomberg sign positive with weakened peristalsis. The laboratory tests revealed an inflammatory constellation.

The ultrasound examination demonstrated a moderate amount of fluid in the abdomen and a round formation in the lower right quadrant with a diameter of about 20 mm suspicious for an ovarian cyst. After a collegium discussion by a pediatric surgeon, gynecologist, anesthesiologist and with data on peritoneal irritation, a decision was made for operative treatment.

A lower median laparotomy was performed. A high amount of serous exudate and a phlegmonously appendix were found. Revision revealed a diverticulum at the border between the cecum and c. ascendens (Fig. 1) and multiple enlarged lymph nodes in the given area. A typical appendectomy was performed. The abdominal cavity was flushed with an antiseptic solution. A tubular drain was placed in the pelvis. Postoperatively, due to the inflamed diverticulum and the existing mesenteric lymphadenitis, a strong antibiotic therapy was started which included Metronidazole, Cefuroxime and Gentamicin. After the second postoperative day, she was fed enterally. The abdominal drain was removed, and after normalization of the laboratory tests, she was discharged from the hospital on the 5th day.

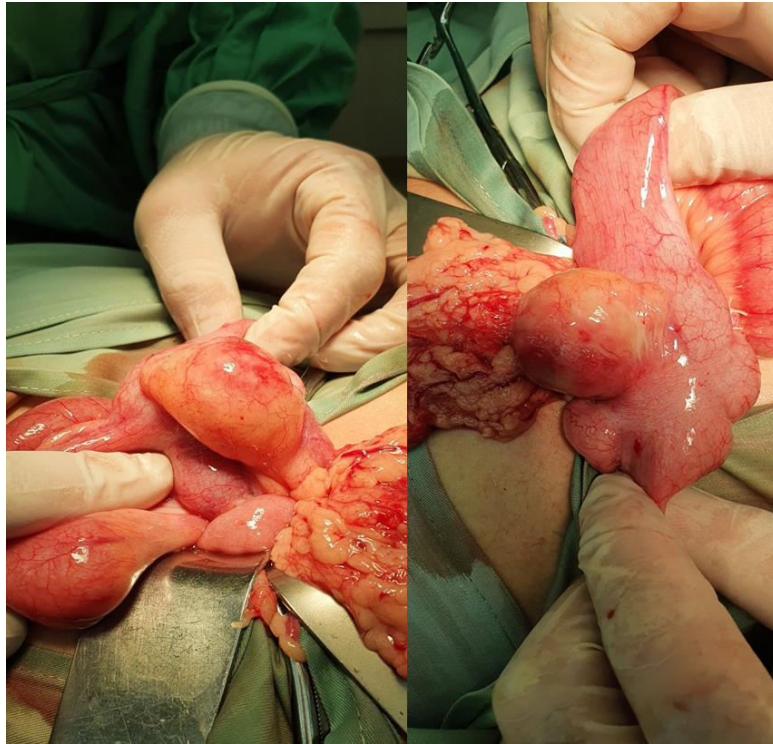


Figure 1. Intraoperative finding of solitary cecal diverticulum.

DISCUSSION

The cecum are infrequently involved in diverticulosis coli. The reported frequency is about 1 in 300 [2,3]. The cecal diverticula are usually solitary and are located in the area from 1 cm proximal to 2 cm distal to the ileocecal valve. Most of them arise from the anterior aspect of the cecum; therefore when inflamed they tend to perforate and cause acute, localized peritonitis. However, an acutely inflamed solitary cecal diverticulum is an uncommon cause of an acute abdomen [4]. Controversies exist regarding the optimal management in nonperforated cecal diverticulitis, ranging from conservative approach with intravenous antibiotics to surgical procedures such as diverticulectomy and right hemicolectomy [5].

CONCLUSION

In our case, we describe the conservative treatment of uncomplicated cecal diverticulitis diagnosed intraoperatively with the help of potent intravenous antibiotic therapy. However, most of the cases are treated surgically because of difficulty distinguishing it from an acute appendicitis.

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CLINICAL CASE OF A DOUBLE PYELOCALICEAL SYSTEM WITH A PARTIAL DUPLICATION OF THE URETER DIAGNOSED BECAUSE OF URETERAL CONCREMENTS AND SURGICAL INTERVENTION

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ABSTRACT

Malformations of the urinary system are common and account for about 3 percent of live births. These various malformations include ectopia, malrotation and other morphological variations such as number of kidneys, ureters etc. Binary ureter is one of them, which occurs in 1 in 125 cases or 0.8 percent of the unselected population with a female to male ratio of 1.6:1 or 62 percent of females. Clinical presentation of binary pyelocalyx is usually asymptomatic and is diagnosed accidentally. However, when symptoms occur (infection, reflux or obstruction), patients are likely to have complete and duplicated ureters. In some cases hydronephrosis can be severe enough to cause discomfort in the iliac region and overlapping symptomatology of various other diseases. The diagnosis is usually made during childhood or before birth, although it can be detected in adulthood. **The aim** of this study is to describe the diagnostic process, treatment and follow-up of a woman with a double pyelocaliceal system with partial duplication of the ureter diagnosed because of ureteral concrements and surgical intervention. **Methods** used in this report are analysis of available literature and medical records. **Conclusion:** The pathology described is rare for several reasons : most of these abnormalities are diagnosed in childhood, after a number of imaging studies and examinations, no diagnosis has been made for nearly 20 years, against the background of a dual calyx system and partial duplication of the ureter. It remains the question about the mechanism of how the two concrements are formed. Are their formation related to a different calyx system or not.

Keywords: female, dual pyelocalyx system , partial duplication of ureter

INTRODUCTION

Malformations of the urinary system are common and account for about 3 percent of live births. These various malformations include ectopia, malrotation and other morphological variations such as number of kidneys, ureters, etc. Binary ureter is one of them, which occurs in 1 in 125 cases or 0.8 percent of the unselected population with a female to male ratio of 1.6:1 or 62 percent of females. A double ureter can be unilateral or bilateral and sometimes it is complete or incomplete. Patients with this abnormality have an increased risk of urinary tract infections, pain, hydronephrosis and formation of concrements. Clinical presentation of a pyelocalyx duplex is usually asymptomatic and is diagnosed accidentally. However, when symptoms occur (infection, reflux or obstruction), patients are likely to have complete and duplicated ureters. Occasionally, hydronephrosis can be severe enough to cause discomfort in the iliac region and overlapping symptomatology of various other diseases [1].

The embryological duplication of the processes described above occurs when two separate ureteric buds arise from a single Wolffian duct. This fact explains the Weigert-Meyer rule, the future inferior pole of the ureter separates from the Wolffian duct earlier and thus migrates superiorly and laterally as the urogenital sinus grows. Duplication may vary. At one end of the spectrum, there is a duplication of the renal pelvis draining through one ureter. On the other end two separate collecting systems are draining independently into the bladder or ectopically [2]. The symptoms associated with a binary pyelocalyx may include pain, haematuria, dysuria and difficulty or abnormally frequent urination [3,4,5]. The diagnosis is usually made during childhood or before birth, although it can be detected in adulthood.

The used Imaging methods include renal ultrasonography, nuclear medicine, excretory urogram, computed tomography (CT) or nuclear magnetic resonance imaging. In adults, CT often visualizes and describes hydronephrosis, with greater prevalence in the upper pole portion [7].

AIM

The aim of this study is to describe the diagnostic process, treatment and follow-up of a woman with a double pyelocaliceal system with a partial duplication of the ureter diagnosed because of ureteral concrements and surgical intervention.

MATERIALS AND METHODS

Methods used in this report are analysis of available literature and medical records.

We present the case of a 33-year-old woman admitted for endoscopic removal of 2/1 cm and 3/1 cm ureteral concrements.

CASE REPORT

The woman was born from a first non-pathological pregnancy, with a normal delivery. No complaints related to the urinary system during childhood. Taken regularly for pediatric consultation and with regular vaccines. During early childhood suffered from a frequent tonsillitis of bacterial origin, treated symptomatically and with antibiotics.

The first urinary related complaints were at the age of 12 years, with symptoms of sacral pain unilaterally, dysuria and subfebrile temperature. The patient was treated with antibiotics after an examination and renal ultrasound by a nephrologist. The diagnosis was Acute pyelonephritis after an uroculture taken without isolation of bacterial causative organism.

One year later, she visited the emergency room of a GP service with complaints of severe right lower quadrant abdominal pain toward the iliac bone. After examination and some tests, she was referred to a pediatric abdominal surgeon. A diagnosis of acute appendicitis was rejected and she was treated symptomatically without a specific diagnosis.

At the age of 14 years, she looked for help in the emergency department of the hospital with severe unilateral pain on the right side of the sacrum, radiating to the leg. Consultations were made with a pediatric surgeon and urologist. No definitive diagnosis was made after ultrasonography of kidneys and other parenchymal organs. She was treated only symptomatically.

By the age of 22 with episodes of pain and complaints without a definitive diagnosis, with suspected unproven Chronic Pyelonephritis and renal concrements.

During pregnancy at 22 years in the 7th lunar month with low back pain and dysuria. Treated symptomatically and within a week symptoms resolved without requiring hospitalization.

In the following 11 years with repeated cystitis, specialist examinations, imaging and clinical laboratory tests without diagnosis. The condition responded to symptomatic treatment.

At the age of 33 years, she developed severe pain in the right sacral region radiating to the iliac bone and thigh, with subfebrile fever and dysuria. On the examination by a urologist and investigations, conservative therapy was ordered to treat grade I hydronephrosis- antispasmodics, antibiotic therapy, nonsteroidal anti-inflammatory drug and fluids.

After 10 days of treatment without success, she was hospitalized for extraction of 2 mid-ureteral concrements measuring 2/1 cm and 3/1 cm.

Both stones were removed during flexible ureteroscopy. Venous (excretory) urography shows the presence of a double calyx system and a double ureter, which flow into the upper third and continue as one. In both calyx systems there is hydronephrosis, which is a prerequisite for the formation of calculi and inflammatory processes. A Double J stent was not placed due to the diagnosed abnormality (Figure 1).

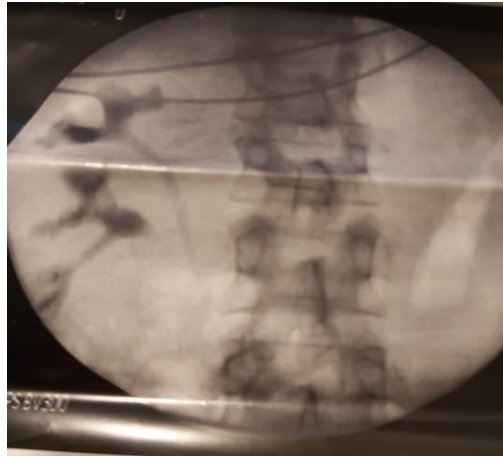


Fig. 1. Image of a dual pyelocalyx system with partial duplication of the ureter.

After surgery, the patient recovered without complications and was hospitalized after 3 days. Four months later the patient was complaining of a sudden need to urinate and inability to postpone. The need to urinate more frequently than usual and waking up at night to urinate. She was seen by the follow-up urologist and assigned a therapy, which was discontinued due to side effects a month later. Alternative treatment with non-invasive focused magnetic therapy was suggested. Ten treatments were done within 4 weeks, with the duration of one treatment: 30 min. After the treatments, the initial symptoms disappeared and there were no urinary complaints for the following two years. At the annual check-ups there were no changes in the kidneys and no complications were diagnosed in view of the abnormality. The patient follows a hygienic and diuretic regimen without taking medications related to the diagnosed abnormality.

CONCLUSION

The pathology described is rare for several reasons : such anomalies are diagnosed in childhood, after a number of imaging studies and examinations for nearly 20 years no diagnosis has been made, against the background of a double calyceal system and partial duplication of the ureter. It remains the question about the mechanism of how the two concrements are formed. Are their formation related to a different calyx system or not.

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ENHANCING THE QUALIFICATION OF MEDICAL LABORATORY TECHNICIANS IN THE MEDICAL COLLEGES IN BULGARIA: A PROPOSED MODEL

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ABSTRACT

The widespread use of technology in healthcare has greatly improved access to diagnostics and treatment for the population, leading to major implications for the quality of healthcare and services. This helps in monitoring morbidity and obtaining swift data on public health. Effectively managing this dynamic calls for the expertise of both skilled professionals and medical laboratory technicians on the interdisciplinary team. Health professionals must be able to adapt quickly to keep up with the constantly evolving dynamics. This is consistent with the higher number of students seeking to improve their skills in medical laboratory areas. Our study focuses on creating a framework for a Master's program designed to advance the skills of medical laboratory technicians who have completed a professional bachelor's degree at medical colleges in Bulgaria. Material and methods: a documentary approach to examine Master's programs open to professionals with a Professional Bachelor's degree was used. A Master's Program Model for medical laboratory technicians studying at the Medical Colleges in Bulgaria was created and assessed using a SWOT analysis to identify its strengths, weaknesses, opportunities, and threats.

Keywords: medical laboratory technicians, training, Master's program, qualification

AIM

This study aims to develop a Master's Program Model that will enhance the qualifications of medical laboratory technicians in the medical colleges in Bulgaria.

INTRODUCTION

The medical laboratory technician is a part of the diagnostic process, carrying out professional duties and following through with tasks assigned by a physician. The technicians collaborate with other healthcare experts, engaging in diverse tasks across various fields of medicine, both domestically and abroad. The medical laboratory technician has the professional training, knowledge, competencies and skills to work independently in the pre-analytical, analytical and post-analytical stages of laboratory tests. It requires critical thinking, adequate reactions, teamwork, creativity, etc. Continuous education and postgraduate courses are crucial in the rapidly changing field of laboratory medicine, driven by advancements in diagnostic methods and technologies, as suggested by recent studies.

MATERIALS AND METHODS

A documentary method was used to investigate Master's programs for which specialists with a professional Bachelor's degree may apply. A SWOT analysis was conducted to outline the strengths, weaknesses, opportunities and threats in establishing a new Master's programme for medical laboratory technicians studying at the medical colleges in Bulgaria.

RESULTS

Medical laboratory technicians perform various activities in specialised laboratories (clinical, microbiological, histological, parasitological, etc.). Research shows that the specifics of training and professional activities of medical laboratory technicians in our country and European Union countries are similar [1, 2]. Usually, specialists are employed in hospitals, outpatient facilities, or research laboratories with different profiles in the public and private sectors. The difference between medical laboratory graduates in Bulgaria and other European Union countries is the educational qualification. The prospect of establishing a Master's Programme Model has generated an interest among graduate medical laboratory technicians in Bulgaria. Enhancing their education presents career development opportunities in Bulgaria and abroad [3, 4]. A thorough SWOT analysis was conducted to anticipate

the advantages and potential drawbacks, as well as to identify opportunities and threats. According to the analysis, strengths and opportunities are proportional to threats and weaknesses. Creating a tailored Master's programme will address the demands of graduate students navigating a rapidly evolving technological and economic environment. The fast-paced nature of our society requires competent medical professionals who are fairly rewarded and have a strong sense of professional self-confidence [5].

SWOT analysis for establishing a Master's Program upgrading the training of medical laboratory technicians in the Medical Colleges in Bulgaria (Medical Laboratory Management Program).

Strengths

1. The establishment of a Master's degree program in the field of medical laboratory management will provide an opportunity for medical laboratory technicians to expand their knowledge in the field of medical laboratory management, laboratory information systems, healthcare, work with specialised medical equipment, etc. and to upgrade their qualification degree.
2. Personnel with acquired qualifications to meet the criteria for accreditation of medical institutions and European regulations.
3. The medical universities in the Republic of Bulgaria have academic staff, modern technical facilities and excellent infrastructure to provide training in the Master's program.
4. Involvement of students and doctoral students in research activities and projects.
5. Digitalisation of the learning process and the use of E-learning systems, including the application of anti-plagiarism software for coursework papers and Master's theses.

Weaknesses

1. Relatively low student and faculty mobility in EU countries due to differences in educational qualifications.
2. Need for intensive foreign language training – study of technical and medical English.
3. Introduction of new technical disciplines related to medical equipment.
4. Relatively low provision of the teaching process with textbooks and teaching aids due to the specificity of the taught disciplines.
5. Dynamics of software products.

Opportunities

1. Providing new advancement opportunities for medical laboratory technicians who have graduated from the medical colleges in Bulgaria.
2. Attracting students from EU and non-EU countries to participate in international mobility programs (Erasmus+).
3. Modernisation in healthcare, new medical devices, and the changing environment that requires specialised training of students with software products and knowledge of technical medical English.
4. Participation in national and international projects for best practices in the medical diagnostic field.

Threats

1. A decrease in the population of Bulgaria, hence, in the number of graduating medical laboratory technicians.
2. Continuous increase in the consumption of laboratory tests.
3. Inadequate remuneration in healthcare.
4. Stress, pandemics, busy schedules.

The Medical Laboratory Management specialty is multidisciplinary. It is open to all specialists with a professional Bachelor's degree in the speciality Medical Laboratory Technician graduates from the Medical Colleges in Bulgaria. The curriculum model has a minimum of 1035 academic learning hours (including the required core classes and two elective courses), with a minimum of 126 credits (including the required core classes, two elective courses and a state examination/thesis defence). The compulsory subjects are 19 and include: information systems in laboratory practice, medical diagnostic laboratory management, new diagnostic methods in microbiology, eHealth, fundamentals of healthcare management, training practice, healthcare project management, environment and nutrition,

introduction to programming, social medicine, terminology and communication in a foreign language, labour and administrative law, healthcare databases, technical safety in healthcare, infection control. The total credits for the compulsory courses are 105. Students will be required to complete 2 electives out of 4: introduction to Computer Programming, New Histological Practices, Modern Software in Clinical Laboratory Practice, and English with Medical Terminology. Each elective course provides the students with 2 credits. In addition to the required electives, 3 optional subjects are provided: history of medicine and public health, socially significant diseases, and communication skills. The optional courses also give 2 credits. The speciality requires four semesters of study and ends with either a state exam or thesis based on the student's grade point average (GPA) [6].

CONCLUSION

The laboratory profession must maintain a high level of professionalism to meet the constantly shifting requirements of the healthcare industry. Patients expect quality healthcare and services. All these changes are a prerequisite for a change in the training of medical laboratory technicians – establishing of postgraduate training, a change in the degree and a custom Master's program. The changes will raise the motivation of the students in the Medical Laboratory Technician speciality and the working medical laboratory technicians. They will enhance their proficiency in technology and new software products in the laboratory practice, empowering them to confidently seek new job opportunities – locally and internationally.

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PARENTS' ROLE IN FORMING HEALTHY HABITS IN CHILDREN UNDER 3 YEARS OF AGE

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ABSTRACT

The role of the parents is key in the upbringing of their children and in the formation of their healthy habits. **The aim** of the present study is to outline the role that parents have in building healthy habits in children under 3 years of age. **Materials and methods:** A direct anonymous survey was conducted among the parents of children of up to 3 years of age regarding the development of healthy habits. The survey covered 774 children (51.5%) who attended nursery centres in Varna in July 2020. The data were processed statistically, using a variation, comparative and correlation analyses.

Results: According to 69.8% of surveyed parents, both parents are involved in forming the child's healthy habits. A significant part of them (94.2%) share that they devote time to build healthy habits in their children on a daily basis. More than half of parents (55.4%) admit that they encounter difficulties with forming healthy habits, and in 86.3% of cases that is due to the child's resistance when learning the relevant habit. Parents report that they receive the main information regarding forming healthy habits in children from their GP, the internet and the nursery nurse. The majority of respondents (92%) believe that the family and the nursery play a major role in creating habits within the children. **Conclusion:** Parents are sufficiently informed regarding the healthy habits of a young child, but continue to encounter difficulties in their formation. The foundations of a healthy lifestyle are laid within the family environment but it is necessary to continue this process in the nursery. The parents' role remains key in the upbringing of their children and in the formation of their healthy habits.

Key words: parents, children, healthy habits, forming

INTRODUCTION

In Bulgaria, there are various practices for assisting young parents in raising and educating their children. Modern living arrangements require a large number of children to attend children's institutions from a very young age – nurseries [1]. The role of parents is key in the upbringing of their children and in the formation of healthy habits.

One of the main cornerstones of children's upbringing is the formation of their healthy habits [2]. Those habits are part of creating a positive attitude of the child towards a healthy lifestyle [3, 4]. The start of the process of creation of those healthy habits must be placed within the family [5]. The nursery nurse assists the parents in their efforts to instil positive healthy habits in their child [6, 7, 8, 9, 10, 11].

AIM

The purpose of this scientific communication is to outline the role of parents in building healthy habits in children up to 3 years of age.

MATERIALS AND METHODS

A direct anonymous survey was conducted among parents of children up to 3 years of age regarding the development of healthy habits. The survey covers 774 children (51.5%) who attended a nursery in Varna during July 2020. The data were processed statistically, using a variation, comparative and correlation analyses.

RESULTS AND DISCUSSION

We performed an analysis of parents of the children included in the survey, as a result of which the parents' main characteristics were outlined, as shown in the table below (Table 1).

Table 1. Parents' characteristics

Characteristics		No/%
age (years)	Mean \pm SD (range)	33.7 \pm 4.6 (23-45)
Sex	Male	73 / 9.4%
	Female	701 / 90.6%
Education	Primary and Secondary	133 / 17.2%
	Higher	641 / 82.8%
Employment	Unemployed	89 / 11.5%
	Employed	674 / 87.1%
	Studying	11 / 1.4%

Parents' characteristics show that young working parents with a higher education are predominant. According to 69.8% of the surveyed parents, both parents are involved in forming the child's healthy habits. At the same time, 1/4 (25.2%) respond that the child's upbringing is mainly taken care of by the mother (Fig. 1). This is because in early childhood the children are strongly attached to the mother in the family. The father is usually the working parent which is why they're often absent from home. The child spends more time with the mother and the responsibility falls on her to become more involved in creating the child's habits.

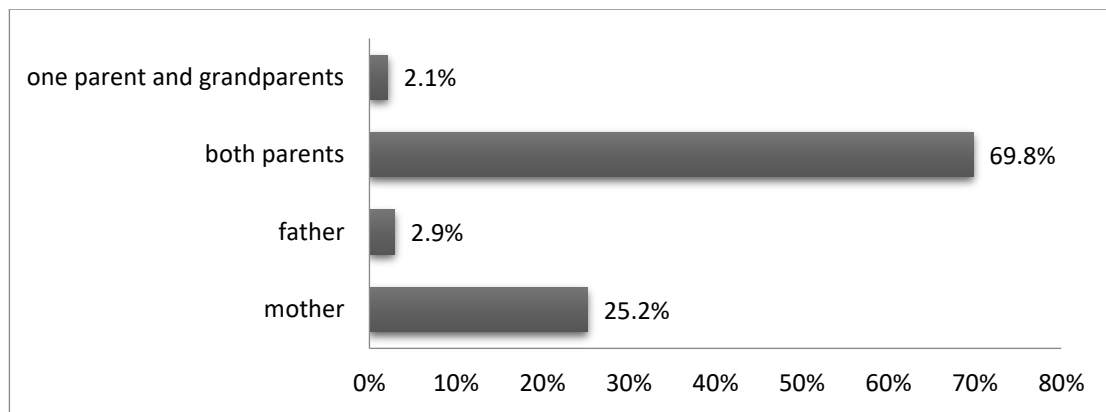


Fig. 1. Members of family who spend more time forming healthy habits in the child

A significant part of the parents (94.2%) shared that they devote time to build healthy habits during daily activities on a daily basis (Fig. 2). This is a positive trend, showing the family's assumption of responsibility of the child's upbringing and the parents' desire to raise a healthy and cultured generation.

More than half of the parents (55.4%) share that they encounter difficulties when forming healthy habits in their children, and in 86.3% of cases that is due to the resistance of the child when learning the relevant habit.

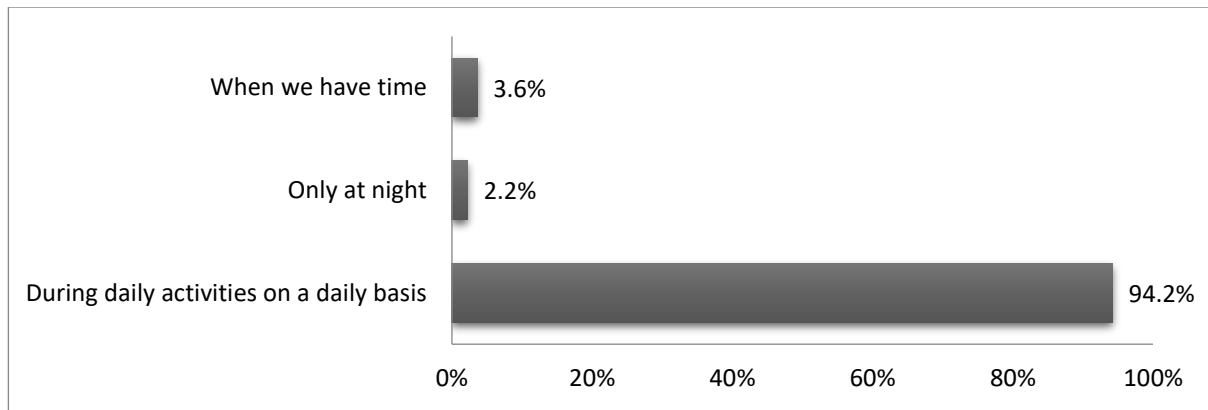


Fig. 2. Daily parent's commitment to form healthy habits in the child

Parents report that they receive the main information regarding building healthy habits in children from their GP (58.1%), the nursery nurse (35.0%) and the internet (41.5%) (Fig. 3). Parents trust and seek more information from the general practitioner, probably because their child has been under the GP's care since birth and they expect the GP to be most familiar with the child itself. A large percentage of the surveyed parents belong to a generation which grew up with the internet and is used to looking up all kinds of information online. This determines the placement of the internet in second place as a source of information for creating healthy habits. Furthermore, the internet offers much more diverse ways of presenting information – via movies, photographs, other people's experiences, etc. Nevertheless, for more than 1/3 of the surveyed parents, the nursery nurse is a reliable source of information who they trust when forming healthy habits in their children.

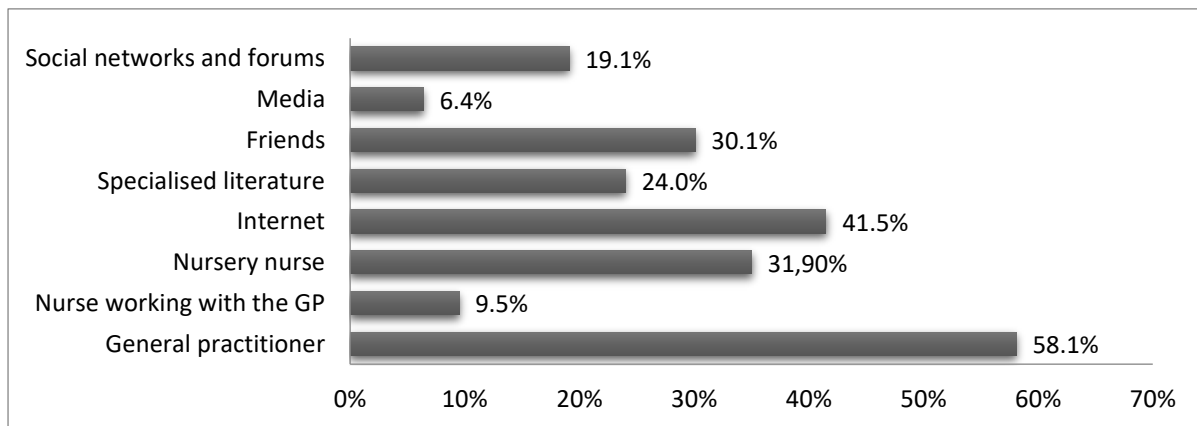


Fig. 3. Parents' information sources

The majority of respondents (92%) believe that the family and the nursery play a major role in creating habits in children, while 8.0% indicate it's only the family environment.

Approximately 1/4 of parents feel the need for additional information related to forming healthy habits in their children, and these are parents who have informed themselves from a single source only.

The awareness of parents regarding the types of healthy habits, the time and ways of their implementation within the young child is positively correlated with the number of sources of information they utilise.

CONCLUSION

The results of the study show that parents are sufficiently informed about the healthy habits of the young child, but continue to encounter difficulties in their formation. The foundations of a healthy lifestyle are laid in the family environment, but it is necessary to continue this process in the nursery with the assistance of the nurse.

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CAT SCRATCH DISEASE

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ABSTRACT

Approximately 24,000 people are infected with cat scratch disease (CSD) every year. CSD is caused by the bacteria *Bartonella henselae*, a gram-negative bacteria most often transmitted to humans through a bite or scratch from an infected cat or kitten. Although CSD is often a benign and self-limiting condition, it can affect any major organ system in the body, manifesting in different ways and sometimes leading to lifelong sequelae. It is a disease that is often overlooked in primary care because of the wide range of symptom presentation and relative rarity of serious complications. It is important for health care providers to recognize patients at risk for CSD, know what laboratory testing and treatments are available, and be aware of complications that may arise from this disease in the future.

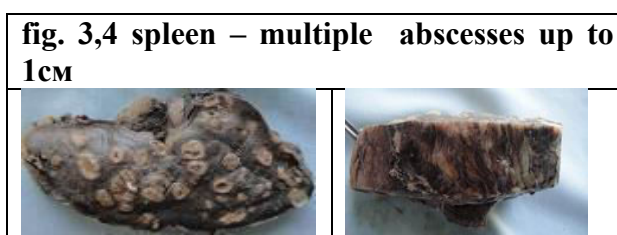
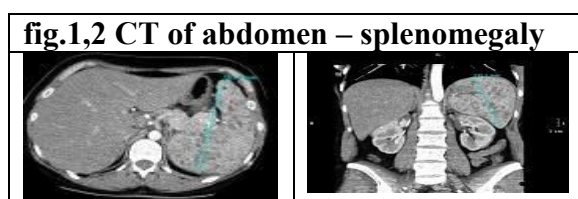
Keywords: *Bartonella henselae*, cat scratch disease, cat scratch fever

INTRODUCTION

Cat scratch disease (CSD) is a bacterial infection caused by the bacteria *Bartonella henselae*, a small, slow-growing, fastidious, intracellular, gram-negative bacillus that exists worldwide, transmitted to humans through a bite or scratch from an infected cat or kitten, dogs, foxes and even coyotes in USA.(9) Most patients have a history of a cat scratch or contact. Extension beyond the local site occurs in about 14% of patients, resulting in encephalitis, osteomyelitis, peritonitis, pneumonia, exanths, and hepatosplenomegaly.

CASE REPORT

A 34 – year female patient presented at the clinic with a three months history of weakness, sweating, fever to 38,5° C, heaviness, and pain in the left upper quadrant of the abdomen, weight loss about 30 kg. for a year and a half. There was a history of contact with cats but no bites or scratches. During the last year serological tests for leishmaniasis, tuberculosis, and hydatid disease are made. The results are negative. Laboratory tests included a white blood cell count $17,25 \times 10^9 / l$; Hb – 85gr/l.; Hct – 0,25; Platelet count- $452 \times 10^9 / l$. serological tests - Mycoplasma pneumoniae IgG – 0,71; Chlamidia trachomatis IgG – 0,27; Chlamidia trachomatis IgA – 0,50; Borrelia burgdorferi IgG – 0,50; Borrelia burgdorferi IgM – 0,49 reference values $N < 1$. CT scan was performed – hepatosplenomegaly liver 233/181mm., spleen 163mm. fig1. multiple focal hypoechoic lesions in the spleen fig.2 lymphadenopathy in the regions of the aorta, lower caval vein, mesentery vessels inguinal lymphadenopathy biggest sized 20mm.



The pathohistological finding presented various sized granulomas: the small ones with central necrosis and gigantic cell Langhans type; the big ones are presented with central necrosis with abscesses Recovery and therapy with Metronidazole 3x1fl. and Cefazolin 3x2 gr. for five days. Six months follow – up to the patient – without complaints. Serological tests repeated – antibodies against *Bartonella henselae* – IgG past medical history for feline disease.

DISCUSSION

Splenomegaly occurs in less than 10% of patients(9) and was first described by Inglis and Tonge in 1950. (2, 3) it has been associated withh erythema nodosum" and hepatomegaly (2,4,5,6,7,8,9,10) and

occurs most commonly in children younger than 15 years of age. (5,6,10,11) Approximately 24,000 people are infected each year in the United States with CSD(9). Only in two of the cases reported with hepatosplenomegaly there is lack of cat.

There are common signs in the past medical history and in the clinical symptoms in the literature case – reports described:

- presence of a pet – cat;
- scars from scratching or biting;
- lymphadenopathy of non-infectious process or malignancy;
- clinical presentation during two – three weeks;

According to Greenbaum et al. the CT – scan images are infrequent and usually the description is “some small defects”

B. henselae is difficult to isolate in human blood and tissue, although it is easy to isolate in the blood of cats. (12)

Although further studies are warranted, *B. henselae* has also been identified in Ixodes ticks from North America, Europe, and Asia.(13) *B. henselae* is most often transmitted from cats to humans via a scratch or bite through a break in the skin, but can also be transmitted to humans via a bite from an infected flea. Multiple outbreaks within a family have been documented; however, there is no documentation that *B. henselae* is transmitted from person to person. Although CSD is typically a self-limiting condition of usually 6 to 12 weeks duration, rare situational manifestations, including optic nerve involvement, which presents as optic neuritis or neuroretinitis, endocarditis inflammatory breast disease, encephalitis, and hematological manifestations such as thrombocytopenic purpura and hemolytic anemia are seen.(11,13) Ophthalmic manifestations of CSD are usually benign with an excellent prognosis for visual recovery. (13)

CONCLUSIONS

1. CSD is more frequent disease. The main cause for this is increase the number of pet and from the other side the new serological tests.
2. The atypical clinical symptoms, are associated with hematological or the nervous system. Involvement of the organs in the abdomen have been reported increasingly.
3. The exact diagnosis and successful treatment depend on the interdisciplinary collaboration between microbiologists, immunologists, surgeons and pathologists.

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GASTRIC ACTINOMYCOSIS - VERY RARE ABDOMINAL PATHOLOGY

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ABSTRACT

Actinomycosis is an indolent infection that usually presents a diagnostic challenge to the physician. Common sites of involvement include the cervicofacial, thoracic and abdominal regions. Abdominal actinomycosis although recognized for more than 150 years yet remains largely unknown for most of the clinicians. Its various clinical presentations are usually considered to present malignant process rather than infection.

Intramural gastric actinomycosis is extremely rare clinical entity and usually the original source of infection is unknown. The usual clinical presentations include low-grade fever, epi- or mesogastric pain, weight loss, and upper gastrointestinal haemorrhage. This chronic infection has a propensity to mimic malignancy.

We report a case of intramural gastric actinomycosis and review of cases of abdominal and gastric actinomycosis reported rarely in the literature. Reporting of such clinical case may help clinicians to increase the knowledge and awareness of this rare and curable disease.

Keywords: actinomycosis, gastric localization, gastrectomy

INTRODUCTION

Actinomycosis is an infectious disease caused by anaerobic, Gram-positive actinomycetes. Actinomycetes are a group of bacteria with high guanine-cytosine content found as a natural flora of the oral cavity. The four main clinical forms of Actinomycosis include cervicofacial (31-65%), abdominal/pelvic (20-36%), thoracic (15-30%) and cerebral form. Abdominal actinomycosis was first described in 1846 by W. Bradshaw/4/ (31 years before actinomyces were isolated). Gastric actinomycosis constitutes a rare, but treatable cause of gastric diseases.

CASE REPORT

A 65-year-old man was admitted in the Second Department of surgery with a 3–4-month history of epigastric discomfort and postprandial pain, nausea and rare vomiting, moderate weight loss (6-7 kg) and weakness. Physical examination revealed a moderate general condition, with a blood pressure 130/80, heart rate – 90/min. No fever or palpable lymph nodes. The only abnormal finding in abdominal examination was a palpable tumor formation with a diameter approximately 9-10 cm in the upper abdomen. Laboratory test results revealed: hemoglobin level – 106 g/l; white blood cells (WBC) – 16,33; platelet (PLT) – 431; blood glucose – 3,8; creatinine – 93; ASAT – 15,3; GGT – 110,1; total protein – 70,0 g/l; sodium - 142,0; potassium – 4,90. Ultrasound sonography was made – in left liver lobe a heterogeneous formation was found. A CT scan revealed a heterogenous tumor mass about 8/9 cm in diameter (fig. 1 a, b), coming from the lesser curvature of the stomach and a lesion in the liver – about 5 mm in right lobe.

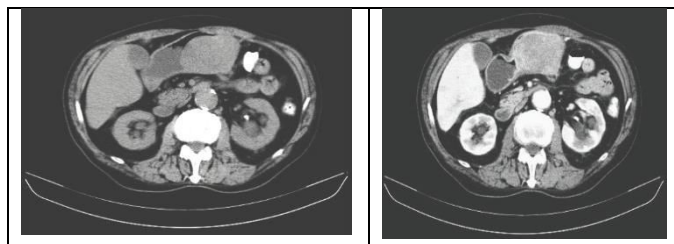


Fig. 1 a – CT scan – tumor mass of the stomach; **1 b** – contrast enhanced CT – diffuse heterogeneously enhancing mass-lesion in the stomach

An upper gastrointestinal tract endoscopy was made - a polypoid lesion showing approximately 5-6 cm protuberance into the gastric lumen, at the lesser gastric curvature with macroscopically normal mucosa above it. Biopsy specimens were negative for malignancy and showed nonspecific inflammatory reaction. An elective surgical intervention was performed with the presumption for gastric malignancy. During laparotomy a fixed tumor mass with dimensions 9/6 cm in the posterior stomach wall was found (Fig 2 a, b), no other abdominal abnormalities. A subtotal gastrectomy Roux-en-Y type was performed.

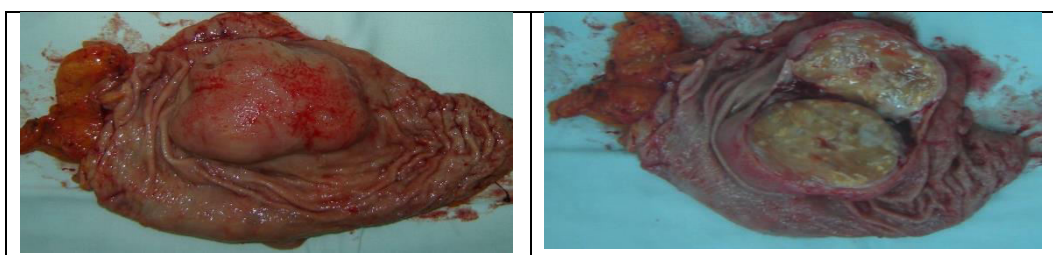


Fig. 2 a – Gross view of postoperative specimen; **2 b** – Cutting surface of the specimen (well defined tumor; intact mucosa)

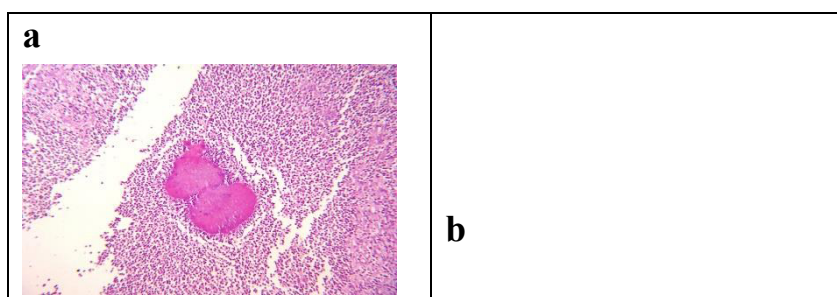


Fig. 3 a – cavity filled with leukocytes, and among them floating actinomycetes granule (Hemalaun eosin 10 x 10); **3 b** – actinomycetes granule (Hemalaun eosin 10 x 40)

One week treatment with antibiotics and parenteral proton pump inhibitor was administered after the operation. The patient was discharged with normal postoperative period and followed for a period of 6 months - in good health and free from symptoms, proceeding with antibiotic treatment. The pathohistological finding presented an inflammatory pseudo-tumor with chronic inflammatory cells, fibrous tissue. Gastric actinomycosis was diagnosed by the finding of characteristic “sulfur granules” (fig 3 a, b). All lymph nodes were negative for malignancy.

DISCUSSION

Actinomycosis has a worldwide distribution and is found with equal frequency in urban and rural dwellers. It is a rare chronic suppurative and granulomatous inflammation caused by anaerobic filamentous, Gram-positive bacteria of *Actinomyces* species. Actinomycosis was first diagnosed in a live patient by Ponfick in 1879 /4/, and was first isolated under anaerobic conditions in 1891. Berardi (1979) first reported the association between *Actinomyces israelii* and clinical abdominal actinomycosis /2/.

The predominant form in human disease is caused by *Actinomyces israelii*, with occasional cases caused by *A. naeslundii*, *odontolyticus*, *viscosus* or *meyeri* /6/. They are normal commensal inhabitants of the human GI tract and female genital tract. There seems to be a male-to-female ratio of between 1,5:1 and 3:1. The estimated population prevalence is one case per 40 -119 000 population /3/. Common sites of involvement include the cervicofacial, thoracic and abdominal regions. Factors that precipitate abdominal actinomycosis include previous abdominal surgery, bowel perforation, penetrating abdominal trauma and foreign bodies /6, 8, 9/. Gastric actinomycosis is extremely rare, possibly because the low gastric pH kills and inhibits the growth of the microorganisms. To date about 25 cases of gastric actinomycosis have been reported in the literature /6, 12/. The usual presenting clinical manifestations of gastric actinomycosis are low-grade fever, epigastric pain, nausea, vomiting, weight loss, fatigue and upper gastrointestinal bleeding /12/ CT findings usually demonstrate an infiltrative lesion with diffuse gastric wall thickening. The appearance suggests adenocarcinoma or lymphoma of the stomach /8,10/. They are commonly considered diagnostic of actinomyceal infection, but are present in only 50% of all cases /15/. Uncomplicated actinomycosis can be medically treated by antibiotics. A prolonged treatment course is required because of the poor penetration of antibiotics into the fibrotic tissue.

CONCLUSION

Abdominal and especially gastric actinomycosis still remains an uncommon clinical entity, that could mimic a wide variety of intraabdominal complaints, ranging from inflammatory diseases to malignant process. Diagnosis is difficult and no test allows definite diagnosis - less than 10% are diagnosed preoperatively. Although the findings are nonspecific actinomycosis should be included in the differential diagnosis when CT scans show an infiltrative mass with unusual aggressiveness and dense inhomogeneous contrast enhancement, especially in patients with leukocytosis, fever, or long-term use of intrauterine contraceptive devices. Surgical resection of the engaged region of the stomach followed by high dose long-term antibiotics assures definite treatment of the disease.

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IS THERE A CORRELATION BETWEEN THE NUMBER OF CLINICAL TRIALS OPENED FOR ENROLLMENT OF PATIENTS AND CERTAIN INDICATORS (HEALTH INDEXES) OF WHO?

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ABSTRACT

Introduction: The study evaluates the number of clinical trials opened for enrollment of patients and certain indicators (health indexes) of WHO. This set of measures is used to assess and monitor the health status of populations globally. These indicators cover a wide range of health-related dimensions and are essential for understanding health trends, making international comparisons, and informing health policy and planning.

WHO's annual World Health Statistics reports present the most recent health statistics for the WHO Member States and each edition supersedes the previous one. Publicly available information, extracted from *www.clinicaltrials.gov* showed that the total number of studies has significantly increased during the period 2014-2016. They have provided plenty of innovations in unison with important benefits to individuals, the medical community, and society as a whole.

Purpose: The aim of this study is to check if there is any correlation between the number of clinical trials and health indicators, proven to significantly increase the risk of chronic diseases. Obesity is a serious public health problem as it is steadily affecting the risk of developing chronic diseases such as type-2-diabetes, hypertension, coronary heart disease and certain cancers. Smoking also leads to illness and disability and harms nearly every organ in the body.

Materials/Methods: Two health indicators – obesity and smoking were statistically analyzed. It is supposed by article's researchers, that they have some importance on the clinical trial enrollment. The numbers were processed with Spearman's rho, and the read of the results does not show a correlation to be present for the period 2007-2016 based on official data extracted from Eurostat database.

Results: There is no correlation between the number of clinical trials opened for enrollment of patients and the certain health indexes which were investigated. This could lead to favorable conditions for trial conduct in the different countries of EEA.

Conclusions: Studying demographic factors is crucial for many reasons, as they provide valuable insights into the composition, characteristics, and dynamics of populations. This is considered to be crucial for the process of conducting clinical trials and the managers in it use demographic data to formulate and implement effective policies related to them. Understanding the healthcare, education, social welfare, and economic development helps in making informed decisions.

Keywords: clinical trials, smoking, obesity, correlation.

INTRODUCTION

The process of developing a new medicine is a complex and lengthy journey that involves several stages of research, testing, and regulatory approval. (1) The entire drug development process can take many years, often more than a decade, and there is a high risk of failure at each stage. (2) Additionally, collaboration between researchers, pharmaceutical companies, regulatory agencies, and healthcare professionals is crucial for the success of this complex process. (3) Clinical trials play a crucial role in the drug development process, serving as a systematic and rigorous method to evaluate the safety, efficacy, and overall benefits and risks of a new medicine before it can be approved for widespread use. (4) Only after receiving marketing authorization, the medicine can be promoted and advertised. (5)

The study evaluates the number of clinical trials opened for enrolment of patients and certain indicators (health indexes) of WHO. This set of measures is used to assess and monitor the health status of

populations globally. These indicators cover a wide range of health-related dimensions and are essential for understanding health trends, making international comparisons, and informing health policy and planning.

WHO's annual World Health Statistics reports present the most recent health statistics for the WHO Member States and each edition supersedes the previous one. (6) Publicly available information, extracted from www.clinicaltrials.gov (7) showed that the total number of studies has significantly increased during the period 2014-2016. (8)(9) They have provided plenty of innovations in unison with important benefits to individuals, the medical community, and society as a whole. (10)

AIM

The aim of this study is to check if there is any correlation between the number of clinical trials and health indicators, proven to significantly increase the risk of chronic diseases. Obesity is a serious public health problem as it is steadily affecting the risk of developing chronic diseases such as type-2-diabetes, hypertension, coronary heart disease and certain cancers. Smoking also leads to illness and disability and harms nearly every organ in the body.

MATERIALS AND METHODS

Health indexes for the period from 2007 to 2016 are extracted from the structured database of the World Health Organization. The information is compared to the generalized data of the number of ongoing clinical trials conducted in the countries of the EEA. Correlation link has been sought between certain demographic factors using Spearman rho (factor). This factor is used when the two variables are scaled, or one of the variables is scaled, and the other is quantitative. In this case, the quantitative value is transformed to scale. The Spearman's rank-order correlation is the nonparametric version of the Pearson product-moment correlation. Spearman's correlation coefficient, (ρ , also signified by r_s) measures the strength and direction of the association between two ranked variables.

R – correlation factor

p – the level of statistical importance (when $p < 0.05$ there is statistical importance, there is a relation between the investigated indicators).

N – the volume of the sample (in this case this is the number of countries, participating in the analysis, the number could be different because there is missing data for some countries)

RESULTS

The data about our study, for the number of ongoing clinical trials, which are open for enrollment, were collected from the internet website publicly available at www.clinicaltrials.gov database. It serves is a comprehensive online registry of privately and publicly funded clinical studies conducted around the world. It is maintained by the United States National Library of Medicine (NLM) at the National Institutes of Health (NIH). The primary purpose of ClinicalTrials.gov is to provide information to the public and healthcare professionals about the design and purpose of clinical trials, as well as their outcomes.

The overall growth in the number of clinical trials, which are conducted within the EEA countries during the period estimated period 2007-2016 shows that in the first half (from 2008 to 2012), there is a big upraise, calculated in percentage as 141,29% for 2011/2012. Compared to the second half of the period, it is a twice the value of the average rate for the years 2007-2016 – 67,15%. Since 2014, there has been a decline in the numbers, with the rate for 2015/2016 of half of the average being 34,99%. The data for the number of ongoing clinical trials (open for enrollment) has been extracted from www.clinicaltrials.gov database. On the table below the growth rate of clinical trials can be followed through the period.

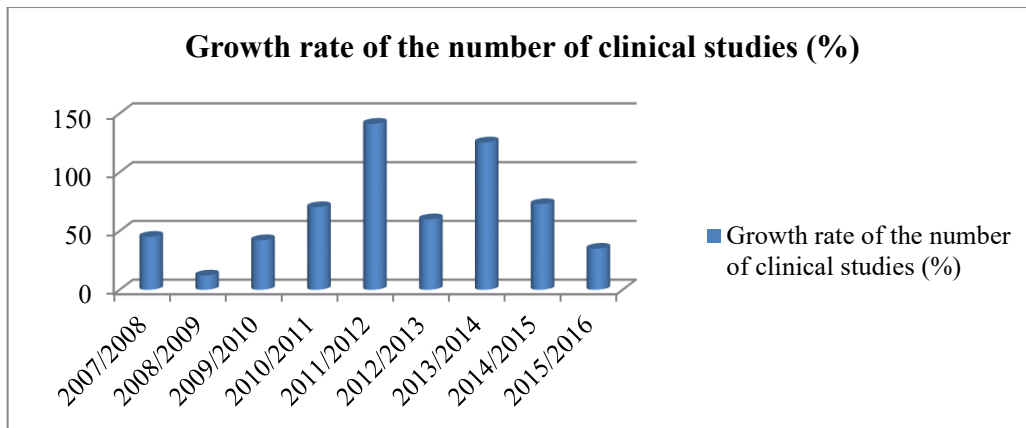


Figure 1. The growth rate in the number of clinical trials conducted by the industry for the period 2007- 2016 shown in percentage

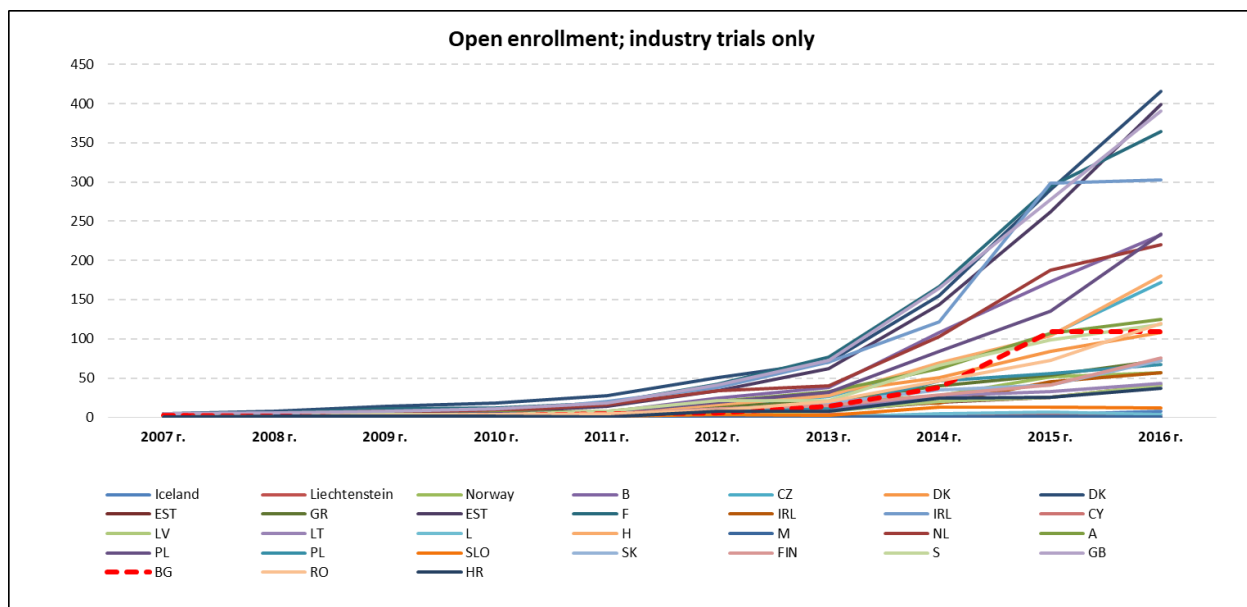


Figure 2. Total number of clinical trials in phase of enrollment for the period 2007-2016 for all countries in the EEA

According to data from last years, the obesity is becoming an epidemic across the world. According to data of the World Health Organization (WHO), in most of the European countries between 30 and 80% of the people 18 years old and older are overweight. Obesity is considered a metabolic disease with chronic character, result of complex relations between endogenic factors (genetic features, biological disbalance of hormones) and external environment. It is an etiological factor in the pathogenesis of chronic diseases like hypertension, dyslipidemia, atherosclerosis, insulin resistance, diabetes type 2, ischemic disease, breast cancer, prostatic cancer. For society as a whole, it has substantial direct and indirect costs that put a considerable strain on healthcare and social resources. Hypothesis: The increasing of the index value for Age-standardized prevalence of overweight (defined as BMI = 25 kg/m²) in people aged 18 years and over leads to a possibility for increase of the people suffering from cardiovascular chronic diseases, which could result in bigger patient population suitable for enrollment in clinical trials.

Result: The calculated correlation factor is not important, so a relation is not confirmed. During investigation of the Age-standardized prevalence of overweight (defined as BMI = 25 kg/m²) in people aged 18 years and over and the number of clinical studies in status of enrollment no official direct influence is confirmed. The study is strict for the period of 1007-2016 (from the moment when

Bulgaria became part of the European commission) and includes all countries from the European Economic Area.

Table 2. The correlation between clinical trials open for enrollment and Age-standardized prevalence of overweight (defined as BMI = 25 kg/m²) in people aged 18 years and over, WHO estimates (%) the countries of the EEA for the period 2007-2014

Number of studies in enrollment phase, led by the industry	Statistics	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Age-standardized prevalence of overweight (defined as BMI = 25 kg/m ²) in people aged 18 years and over, WHO estimates (%)	R	0,181	0,008	0,060	-0,044	-0,009	-0,057	-0,030	0,072	0,018	0,038
	p	0,337	0,968	0,755	0,818	0,963	0,763	0,876	0,707	0,927	0,844
	N	30	30	30	30	30	30	30	30	30	30

R- the calculated correlation factor between the number of clinical studies open for enrollment and factor of age-standardized prevalence of overweight in people aged 18 years old

p – factor showing statistical importance

N – countries data used for number of clinical trials open for enrollment and age standardized prevalence of overweight in people – varies through the years as no complete data was available for all countries in the EEA

Table 3. The correlation between clinical trials open for enrollment and Age-standardized prevalence of current tobacco smoking among people aged 15 years and over, WHO estimates (%) the countries of the EEA for the period 2007-2014

Number of studies in enrollment phase, led by the industry	Statistics	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Age-standardized prevalence of current tobacco smoking among people aged 15 years and over, WHO estimates (%)	R	0,035	-0,164	-0,153	0,071	-0,054	-0,037	-0,016	0,050	0,068	0,074
	p	0,860	0,404	0,438	0,721	0,784	0,851	0,936	0,801	0,732	0,710
	N	28	28	28	28	28	28	28	28	28	28

R- the calculated correlation factor between the number of clinical studies open for enrollment and Age-standardized prevalence of current tobacco smoking among people aged 15 years and over

p – factor showing statistical importance

N – countries data used for number of clinical trials open for enrollment and Age-standardized prevalence of current tobacco smoking among people aged 15 years and over – varies through the years as no complete data was available for all countries in the EEA

Hypothesis: The increasing of the index value for Age-standardized prevalence of current tobacco smoking among people aged 15 years and over leads to a possibility for increase of the people suffering from cardiovascular chronic diseases, which could result in bigger patient population suitable for enrollment in clinical trials.

Result: The calculated correlation factor is not important, so a relation is not confirmed. During investigation of the Age-standardized prevalence of current tobacco smoking among people aged 15 years and over and the number of clinical studies in status of enrollment no official direct influence is confirmed. The study is strict for the period of 1007-2016 (from the moment when Bulgaria became part of the European commission) and includes all countries from the European Economic Area.

DISCUSSION

Clinical trials are a cornerstone of evidence-based medicine, providing the scientific foundation for healthcare professionals to make informed decisions about the use of new medicines in patient care. The information generated from clinical trials is critical for regulatory agencies, healthcare providers, and patients to assess the benefits and risks of a new drug accurately.

The researched health factors could be easily extracted from the database of the World health organization portal. This public availability makes them suitable for any kind of research that could be done in advance, before starting a new clinical pregame for new medicine. This approach could facilitate the process of enrollment of patients in the clinical studies conducted by the industry, which could lead to shortening the timeframe from the point of creation of a new medicine to the time of registering it.

Particular variable, characteristic, or element can be studied, analyzed, or investigated in the context of an every clinical research project. Availability in this context implies that the necessary data or information related to that factor can be accessed, collected, and used by researchers for their studies.

CONCLUSION

Studying demographic factors is crucial for many reasons, as they provide valuable insights into the composition, characteristics, and dynamics of populations. This is considered to be crucial for the process of conducting clinical trials and the managers in it use demographic data to formulate and implement effective policies related to them. Understanding the healthcare, education, social welfare, and economic development helps in making informed decisions.

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UNVEILING CONNECTIONS: THE IMPACT OF VITAMIN D ON LANGUAGE DEVELOPMENT IN PEDIATRIC NEURODEVELOPMENTAL CONTEXTS

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ABSTRACT

Purpose: This literature review aims to investigate the impact of vitamin D on language development in pediatric neurodevelopmental contexts by analyzing a selection of articles published between 2012 and 2024. **Material/Methods:** The review includes studies with various designs, such as cross-sectional studies, prospective cohort studies, and randomized controlled trials. The populations studied encompass infants and children with and without autism spectrum disorders. Vitamin D levels were measured using blood samples, and language development was assessed using tools such as the Bayley Scales of Infant and Toddler Development and the Autism Treatment Evaluation Checklist. **Results:** The review found results suggesting that vitamin D status may play a role in language development, particularly during pregnancy and early childhood. Several studies indicated that higher vitamin D levels were associated with improved language outcomes, including vocabulary, grammar, and syntax. However, the outcomes were not consistent across all studies, with some finding no significant effect of vitamin D supplementation on language development. **Conclusions:** The review highlights the need for further research to determine the optimal vitamin D levels for language development and the potential benefits of vitamin D supplementation during pregnancy and early childhood. The findings have implications for clinical practice and public health policy, particularly in populations at risk of vitamin D deficiency.

Keywords: Vitamin D, Language Development, Neurodevelopment, Pediatrics, Pregnancy, Infants, Children, Autism Spectrum Disorder.

INTRODUCTION

Neurodevelopment refers to the complex process involving structural changes and functional maturation of neural circuits throughout life, shaping cognition, emotion, perception, learning, memory, attention, communication, social interaction, and executive functions. Among numerous environmental influences affecting brain growth and function, nutritional components like vitamin D have gained considerable interest due to their pleiotropic effects beyond bone metabolism [1]. Recent years have seen growing scientific exploration regarding the connection between vitamin D and neurodevelopmental processes, especially concerning language acquisition—one of the most critical aspects of human intellectual capacity. This literature review seeks to uncover current knowledge surrounding the influence of vitamin D on language development in pediatric neurodevelopmental settings. Specifically, we aimed to address two primary objectives: firstly, investigating whether variations in prenatal and postnatal vitamin D exposure correlate with differences in child language abilities; secondly, evaluating if interventions targeting vitamin D insufficiency could improve linguistic competency in vulnerable groups. To achieve our goals, we conducted extensive search in three prominent databases – PubMed, Scopus, and ScienceDirect – yielding relevant publications spanning from 2012 to 2024. Our focus centered on empirical studies employing sound experimental techniques, primarily comprising longitudinal observations, case-control comparisons, and

intervention strategies. Furthermore, given the scope of this paper, priority has been accorded to peer-reviewed journals reporting original research rather than reviews or commentaries. In sum, understanding how vitamin D impacts language development holds substantial promise towards informing preventative measures against suboptimal neurological functioning and improving therapeutics tailored specifically toward individuals suffering from impaired verbal capacities.

MATERIALS AND METHODS

The articles were identified through search in PubMed (n = 27), Scopus (n = 72), and ScienceDirect (n = 47). A total of 146 articles were identified, with 135 unique articles screened. After the screening and selection process, 13 articles were included in the final review. The screening and selection of studies for the final inclusion were carried out using Rayyan's Blind On option. The PICO descriptions for the narrative review are as follows: Population (P): Children with neurodevelopmental disorders, typically developing children. Intervention (I): Vitamin D supplementation, varying vitamin D levels. Comparison (C): Adequate vs. deficient vitamin D levels, placebo vs. active treatment. Outcome (O): Primary outcomes related to neurodevelopmental contexts and language development.

The included articles were a mix of study designs, including longitudinal cohort studies, retrospective surveys, retrospective reviews, randomized controlled trials, and case-control studies. The age range of the study samples varied from 6-8 months to 5 years. The interventions and exposures studied included vitamin D supplementation, varying vitamin D levels, and the effect of umbilical cord essential and toxic elements. The vitamin D measures included serum vitamin 25(OH)D levels in infants, maternal blood values of vitamin D during pregnancy, and serum 25-hydroxyvitamin D (25(OH)D) levels in children. The language and/or neurodevelopmental measures used in the studies encompassed a wide range of assessments, such as the Bayley Scale of Infant and Toddler Development, MacArthur Communicative Development Inventories, Peabody Picture Vocabulary Test—Revised, Kyoto Scale of Psychological Development 2001.

RESULTS

The studies included in this article demonstrated significant differences in language development between participants with vitamin D deficiency and those without. Tofail et al., 2019 found that vitamin-D-deficient children had significantly lower scores in activity and soothability subscales of temperament, understood a lesser number of words, and were less active during developmental assessments compared to group of children without vitamin D deficiency [2]. Some authors [3] reported that children of mothers with vitamin D deficiency (<30 nmol/L) scored significantly lower on cognitive and language scales in 1st trimester, and all language scales in 3rd trimester, compared to children of mothers with sufficient levels of vitamin D (>50 nmol/L). Other research group found a significant linear trend between quartiles of maternal vitamin D levels and language impairment at 5 and 10 years of age [4]. The risk of women with vitamin D insufficiency during pregnancy having a child with clinically significant language difficulties was increased close to twofold compared with women with vitamin D levels >70 nmol/L. Hart & All, 2015 reported that maternal vitamin D deficiency at 18 weeks gestation was significantly associated with reduced neurocognitive development in the offspring, including language impairment at ages 5 and 10 [5]. Guo et al., 2019 found that children with autism spectrum disorders (ASD) and vitamin D deficiencies had lower language scores compared to those without deficiencies [6] [7] [8]. These findings suggest an association between vitamin D deficiency and impaired language development in children.

DISCUSSION

The review of the studies on vitamin D and neurodevelopmental outcomes yielded several findings on association with language development [2] ; effect on neurodevelopmental skills [3]; language

impairment risk [4, 5]; vitamin D supplementation effects [9-13] observed substantial improvement in ASD rating scales in patients with higher final 25-(OH)D levels, indicating the potential efficacy of vitamin D supplementation in improving neurodevelopmental outcomes in children with autism spectrum disorders. The positive outcomes from the review provide valuable insights into the potential influence of vitamin D on language development and neurodevelopmental skills [12, 14], as well as the implications for maternal vitamin D status and supplementation in improving offspring's neurodevelopment.

Limitations of the narrative review on vitamin D and neurodevelopmental outcomes include the following: *Sample Size Discrepancies*: The studies exhibit variations in sample sizes, which may influence the generalizability of the findings. *Gender Disparities*: The gender distribution within the study populations was not always balanced, with some studies having a significantly higher proportion of male participants. This imbalance may introduce gender-related biases in the outcomes and limit the generalizability of the findings to both genders. *Retrospective Design*: Several studies employed a retrospective design, which can be susceptible to recall bias and limitations in establishing causal relationships. This design may restrict the strength of evidence compared to prospective or interventional studies. *Outcome Measures*: The diversity of neurodevelopmental outcome measures used across the studies, such as language assessments, cognitive scales, and behavioral inventories, makes it challenging to directly compare the results and draw overarching conclusions. Standardization of outcome measures could enhance the consistency and comparability of findings. *Vitamin D Assessment Timing*: Variability in the timing of vitamin D assessment, including prenatal, infancy, and childhood periods, may introduce complexities in interpreting the impact of vitamin D on neurodevelopmental outcomes. A standardized approach to vitamin D assessment timing could provide more cohesive insights. *Confounding Factors*: The potential influence of confounding variables, such as socioeconomic status, maternal education, and dietary habits, was not consistently addressed across all studies. Failing to account for these factors could introduce bias and limit the accuracy of the associations between vitamin D and neurodevelopmental outcomes. These limitations collectively suggest that while the studies offer valuable insights into the relationship between vitamin D and neurodevelopmental outcomes, caution should be exercised in generalizing the findings. Addressing these limitations through larger, well-controlled prospective studies with standardized measures and comprehensive consideration of confounding factors is essential to strengthen the evidence base.

CONCLUSIONS

Several practical implications and areas for further research regarding the relationship between vitamin D and neurodevelopmental outcomes are highlighted.

Implications for Practice. Healthcare providers should consider monitoring and addressing vitamin D levels in pregnant women and infants to potentially improve language development. There may be benefits from using vitamin/mineral supplements, including vitamin D, for individuals with autism spectrum disorders, especially in cognitive and language-related symptoms. Targeted interventions for pregnant women with low vitamin D levels may help reduce the risk of language impairment in their children.

Implications for Further Research. More longitudinal studies are needed to understand the causal link between vitamin D status and language development while considering factors such as socioeconomic status and maternal education. Research exploring the relationship between vitamin D supplementation and language development in children, especially those with neurodevelopmental disorders, could provide valuable insights for clinical practice. Future studies should conduct subgroup analyses based

on age, gender, and socioeconomic backgrounds to understand the varying effects of vitamin D on language development across diverse populations.

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THE BURDEN OF DEPRESSION ON THE LIVING WITH CHRONIC PAIN – A QUALITATIVE STUDY

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ABSTRACT

Chronic pain and depression have a negative impact on all areas of life, worsening the patient's functioning. **Purpose:** The aim of our study is to analyze the experiences arising from lifestyle changes of patients with chronic pain and the influence of depression. **Materials and methods:** A cohort comprising 120 individuals experiencing chronic pain underwent examination utilizing two approaches: 1) quantitative methods assessing emotional and sensory aspects (HAM-D-17, STAI, VAS), and 2) content analysis aimed at dissecting the experiences linked to lifestyle changes. **Results:** Out of the patients examined, 61 were identified as having a depressive episode, while 59 did not exhibit signs of depression. Among the non-depressed group, there were moderate levels of state and trait anxiety and mild pain intensity. Their experiences primarily revolved around coping with limitations imposed by their condition. Conversely, the depressed group showed moderate levels of depression severity and pain intensity, coupled with high levels of state and trait anxiety. Notably, their experiences were characterized by a reduction in social interactions, potentially heightening the risk of suicidal tendencies. **Conclusion:** Depression is a burden on the patient's lifestyle and daily functioning of individuals suffering from chronic pain. Therefore, addressing depression could serve as a focal point for effectively managing chronic pain.

Key words: chronic pain, depression, experiences, lifestyle, content-analysis.

INTRODUCTION

Chronic pain conditions have a negative impact on all areas of sufferers' lives, impairing their daily activities and functioning [1]. It has been found that pain suffering is influenced not so much by the physical aspects of pain, but by the emotional ones [2]. Depression and anxiety are emotional factors that affect the experience of chronic pain and have a role in the development of a depressive episode [3]. Depression stands out as the most extensively studied psychiatric comorbidity of chronic pain, given its significant impact on patients' quality of life and heightened risk of disability. [4]. The existing links between chronic pain and depression [5] led us to investigate the impact of this comorbidity on lifestyle changes in patients with persistent pain. The discourse surrounding this health issue is crucial, as its psycho-social ramifications extend beyond the individual and their family to impact society at large. [6]. The aim of our study is to analyze the specific experiences related to the change in lifestyle of patients with chronic pain and the influence of depression on their functioning.

MATERIALS AND METHODS

A study involving 120 hospitalized patients with chronic non-malignant pain of various origins was conducted. The study's design received approval from the Ethics of Scientific Research Committee at the Medical University of Varna, and all patients provided signed informed consent forms. Based on the presence or absence of a depressive episode, the sample was divided into two groups: a group without depression (n=59) and a group with depression (n=61). Two methods were employed to fulfill the objectives of the study. *Quantitative methods* were employed to assess the emotional and sensory dimensions of pain: 1) Hamilton Depression Rating Scale (HAM-D-17) for assessing severity of

depression; 2) Spielberger's State and Trait Anxiety Inventory (STAI) for assessing state and trait anxiety degree; and 3) Visual Analog Scale (VAS) to evaluate intensity of pain. *Content-analysis* was used as a qualitative method for analyzing the experiences related to the change of the patient's lifestyle. All participants were queried with the question "How has pain changed the way you live?" "The responses, transcribed verbatim by the researcher, underwent content analysis.

RESULTS

The mean age of the studied sample (n=120) was 51.90±11.94 years. The distribution by gender was uneven, with 81.7% (n=98) being women and 18.3% (n=22) being men. Based on the presence of clinical symptoms of depression, the sample was divided into two groups: 1) a group of 59 patients with chronic pain without depression and 2) a group of 61 patients with chronic pain with depression. The mean values of the studied indicators for the two groups and the presence of statistically significant differences are summarized in Table 1. The frequency distributions on the main scales were close to normal.

Table 1. Mean values of the studied indicators by group.

Indicator	Group without depression	Group with depression	Significant differences between groups (p < 0.05)
Depression severity	3,49±1,72	16,21±5,75	t = -25,976; p = ,000
Degree of state anxiety	36,27±8,77	50,23±13,89	t = -6,623; p = ,000
Degree of trait anxiety	40,17±7,85	54,69±11,74	t = -8,087; p = ,000
Pain intensity	3,8±1,91	5,82±2,73	t = -4,205; p = ,000

The most notable difference was observed in the severity (t-value) and significance (p-value) of depression, followed by state and trait anxiety, as well as pain intensity. The group with depression exhibited moderate levels of depression. State and trait anxiety levels were high among individuals with depression and moderate among those without depression. Pain intensity was moderate in the depression group and mild in the non-depression group. Content analysis was utilized to examine the responses of patients to the question "How has pain changed the way you live?" "The analysis aimed to find specific chronic pain experiences for the two groups. While chronic pain was a shared characteristic across the entire sample, the differing factor between the two groups was the presence of depression. Therefore, by conducting a comparative analysis of experiences between the two groups, it was possible to discern the specific chronic pain experiences for patients with depression. The documented experiences linked to lifestyle changes in both groups were categorized into six categories: "discontinuation of daily activities", "social isolation", "limitations in everyday life", "life dependent on pain control", "adopting a healthy lifestyle" and "no change in the lifestyle". The frequency rankings of these experiences are presented in Table 2.

The results of the comparative analysis revealed specific differences in experiences related to lifestyle changes between the two groups of chronic pain patients: 1) The most frequent themes in the group with depression were related to the cessation of daily activities (work, daily tasks, and usual activities), whereas in the group without depression, the predominant topics revolved around the limitations imposed by chronic pain on their lives. 2) The second most common themes among patients with depression were social isolation, whereas for those without depression, it was the absence of lifestyle changes. 3) Third in frequency were experiences of limitations imposed by pain for the group with depression, and discontinuation of some daily tasks for the group without depression. 4) Experiences

of dependency and pain management ranked next in frequency for the group with depression. 5) The adoption of a healthy lifestyle was ranked last and had an equal frequency in both groups. 6) A minimal number of chronic pain patients without depression shared experiences of social withdrawal and dependency on pain management. None of the depressed patients reported that their lives had remained unchanged.

Table 2. Content analysis of the answers to the question “How pain has changed the way you live?”

Patients with chronic pain and depression	Patients with chronic pain without depression
Discontinuation of daily activities 39 <i>I don't work (13); I'm not moving/lying (6); I don't go out (6); I stopped homework (1); I don't do it in everyday life (6); I can't take care of my child (2); Sedentary lifestyle (1); I have no desire to work (1); I have no desire for anything (1); I became lazy (1); I'm useless (2)</i>	Discontinuation of daily activities 10 <i>I don't work (3); I stopped sports (2); I don't physically exert myself (1); I'm not active (2); Sedentary lifestyle (1); I don't cope in everyday life (1)</i>
Social isolation 28 <i>Isolate myself (23); I don't have friends (3); I don't communicate (1); I don't share (1); I'm lonely (1)</i>	Social isolation 2 <i>Isolate myself (1); I'm closing (1)</i>
Limitations in everyday life 19 <i>I've restricted/slowed down movements (7); I restricted actions (2); I often rest (3); Hard to deal with in everyday life (6)</i>	Limitations in everyday life 27 <i>I limited my daily routine (5); I restricted my movements (11); I've reduced my activity (2); I've reduced the work (2); I'm guarding myself (3); I am cautious in everyday life (2); Rest more often (2)</i>
Life dependent on pain control 14 <i>Dependent on pain (2); Depend on my loved ones (3); I take into account the pain (5); I live in fear of pain (3); I live under the control of pain (1)</i>	Life dependent on pain control 4 <i>I take into account pain (1); Depend on my loved ones (3); My whole life has changed (1)</i>
Adopting a healthy lifestyle 1 <i>I changed my diet (1)</i>	Adopting a healthy lifestyle 1 <i>Healthy lifestyle (1)</i>
No change in the lifestyle 0	No change in the lifestyle 14

Discussion

Consistent with existing literature, our study's findings also highlight a higher prevalence of chronic pain among women [7]. Both male and female participants exhibited symptoms of anxiety, which are frequently associated with affective disorders. Patients experiencing chronic pain, particularly during depressive episodes, commonly report feelings of anxiety alongside other symptoms [8]. The interplay between depression, anxiety, and pain perception underscores the emotional factors shaping the experience of pain.

Qualitative research provides a unique insight into this subject by focusing on individual experiences of living with chronic pain [2]. Content analysis serves as a valuable tool in unraveling the essence of these experiences, providing a deeper understanding of this multifaceted issue [9]. In our analysis of responses concerning lifestyle changes resulting from chronic pain, we identified six distinct categories, each varying in frequency and specificity across the two study groups. Among non-depressed patients, the majority did not report significant lifestyle changes. However, a prevalent theme within this group was the experience of living with limitations imposed by chronic pain. This finding resonates with similar results from other qualitative studies, underscoring the detrimental

impact of pain avoidance behaviors and fear of pain on patients' daily lives [2]. Specific to the group with depression were the experiences of social isolation, while the experiences of discontinuation of daily activities and living in limitation were dominant. The meaning of life is intricately tied to an individual's pursuit of goals, satisfaction from achievements, establishment of close social connections, and contribution to both personal well-being and society. However, all these aspects are contingent upon one's physical and emotional health. For individuals living with chronic pain, the absence of a sense of purpose and fulfillment could potentially lead to suicidal thoughts [10]. Therefore, it is imperative to identify symptoms of depression and address specific experiences in managing chronic pain.

CONCLUSION

The combined impact of chronic pain and depression significantly affects various aspects of life, including physical functioning, emotional well-being, social interactions, and work capacity. Consequently, addressing depression emerges as a critical target for effectively managing chronic pain and improving overall quality of life.

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