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SELF-ASSESSMENT OF PHARMACISTS REGARDING THE PRACTICE OF DISPENSING ANTIBIOTICS IN PUBLIC PHARMACIES

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MELISA PHARMACY, MAJUR, ŠABAC, SERBIA

Summary:Introduction: Approximately at the end of one century after the discovery of penicillin, the world is facing the development of bacterial resistance to antibiotics. The focus of our work is the pharmacist, as one of the key actors in the chain of antibiotic dispensing. Through research, we aimed to determine the level of knowledge among employees in pharmacies in the city and municipality of Šabac in the Republic of Serbia about antibiotics, antimicrobial resistance, the legal framework regulating the area of antibiotic dispensing, as important factors for self-assessment in the practice of antibiotic dispensing in public pharmacies. **Objectives:** (1) to examine the knowledge of pharmacy employees about antibiotics, antimicrobial resistance (AMR), and the legal framework regulating the area of antibiotic dispensing; (2) to investigate the practice of antibiotic dispensing in public pharmacies; (3) to assess differences in the practice of antibiotic dispensing based on gender of the respondents, pharmacy location, and level of education. **Methodology:** A cross-sectional study was conducted using a purposefully created questionnaire consisting of 33 questions, through which respondents self-assessed their knowledge related to antibiotics and the practice of antibiotic dispensing in the last six months. Health workers of all levels of pharmacy education employed in almost all pharmacies in the territory of the city of Šabac (including city and rural pharmacies) participated in the study. Data were collected from March to August 2022. **Results:** The total number of respondents in the study was 229, with the majority being female. Regarding formal education, the majority of respondents were graduate pharmacists (59%), followed by higher pharmacy technicians (3.5%) and pharmacy technicians (37.6%). When it comes to viral infections, 95.2% of respondents knew that antibiotics are ineffective in such cases; while 72.6% of respondents believe that acute sore throat should not be treated with antibiotics. As much as 99.6% of respondents confirmed the statement that inappropriate use of antibiotics contributes to the increase in antibiotic resistance. Also, 96.5% of respondents confirmed that dispensing antibiotics without a prescription leads to the development of antibiotic resistance. A total of 90.8% of respondents are aware that pharmacists can be penalized in accordance with existing legal regulations if they dispense antibiotics without a prescription. In practice, dispensing antibiotics without a prescription is still present in certain situations. Although this phenomenon is not common based on survey responses ("I always prescribe without a prescription at the patient's request") for the surveyed locations of infections, it occurs in a small number of cases, from 1.4% to 4.0%. However, based on the response "I sometimes prescribe without a prescription at the patient's request," it occurs more frequently in certain clinical conditions and complaints: most commonly urinary tract infections in 52% of cases, infected wounds - 42.4%, acute sore throats in 29.8%, and diarrhea - 15.7%, and least commonly for common colds and coughs in 9.2%. At the patient's request, the majority of respondents - 79.9% never dispense antibiotics without a prescription, but still globally 20.1% of respondents sometimes dispense antibiotics without a prescription or doctor's report. **Conclusion:** Based on the results of the sample of 229 pharmacist and pharmacy technician respondents, it is concluded that dispensing antibiotics without a prescription is still present in practice in certain situations. Although this phenomenon is not common from responses: "I always prescribe without a prescription at the patient's request" for surveyed locations of infections (1.4% to 4.0%), and sometimes for certain conditions and complaints, most commonly for common colds and coughs at 9.2% and most commonly for urinary tract infections - 52%, At the patient's request, 79.9% of respondents never dispense antibiotics without a prescription, but still globally 20.1% of respondents sometimes dispense antibiotics without a prescription or doctor's report. Antimicrobial resistance is a systemic issue that undoubtedly requires teamwork of all stakeholders in society where the role of pharmacists and pharmacy technicians is one of the most significant.

Keywords: antibiotics, antibiotic resistance, pharmacists, antibiotic dispensing in public pharmacies.

INTRODUCTION

Antibiotics are becoming increasingly ineffective as drug resistance spreads globally, leading to more severe infections and increased mortality. Considering that several decades have passed since the beginning of mass antibiotic use, the development of bacterial resistance to antibiotics is an expected process of evolution in terms of bacterial genetic adaptations to environmental conditions. With the understanding that the number of bacteria doubles every 20 minutes, it becomes clear how significant the possibilities for resistance development are. Bacterial resistance to antibiotics today poses one of the greatest threats to global health [1]. While resistance to antibiotics occurs naturally, irrational antibiotic use accelerates this process, resulting in increased mortality, prolonged hospital stays, and higher medical costs. According to antibiotic consumption data, the Republic of Serbia ranks high among European countries, while a high level of resistance is observed in all tested bacterial species in our country, similar to countries in Southern and Eastern Europe [2]. Mass antibiotic use has led to a significant problem of antimicrobial resistance (AMR) over time. AMR was initially addressed by the development of new classes of antimicrobial agents and chemical modification of existing ones. However, the development of new antimicrobial drugs has not kept pace with the ability of microbes to develop resistance. As a result, AMR is now a global public health challenge and an escalating threat to infectious disease control worldwide. AMR results in prolonged illness, increased risk of infection spread, increased morbidity, and higher mortality rates, with associated increases in financial and societal costs [3].

At the global level, the World Health Organization (WHO) as the coordinating body for global public health, recognizing the problem of irrational use of antibiotics and their increasing inefficacy, has initiated specific actions among United Nations member countries on this issue. At the World Health Assembly meeting in 2015 dedicated to the development and implementation of multisectoral national action plans, member countries committed to a framework presented in the Global Action Plan (GAP) on antimicrobial resistance (AMR) in 2015. This plan was later endorsed by the United Nations Food and Agriculture Organization (FAO) and the World Organisation for Animal Health (OIE) [4]. Immediately after the adoption of GAP to address AMR, the International Pharmaceutical Federation (FIP) released a document in 2015 titled "Fighting Antimicrobial Resistance: The Contribution of Pharmacists." This informative document outlined various activities involving pharmacists aimed at preventing AMR and slowing down its progression. The reason for creating such a document lies in the unique position of pharmacists in healthcare systems, making them the most accessible healthcare professionals and thus indispensable in addressing the issue of AMR. FIP continues its efforts to combat AMR in line with action plans extending up to 2030 [5].In accordance with initiatives by the United Nations, the World Health Organization, the European Centre for Disease Prevention and Control, the International Pharmaceutical Federation, and other relevant international health institutions, since November 2015, the Ministry of Health of the Republic of Serbia has joined global efforts to combat antimicrobial resistance and promote rational antibiotic use. The Ministry of Health formed a Working Group to develop a national guide for good clinical practice in rational antibiotic use to create a comprehensive, evidence-based, and practical guide. The national guide for good clinical practice aims to motivate healthcare workers to incorporate evidence-based recommendations into their daily practice, thus contributing to improving the quality and safety of patient care in the healthcare system of the Republic of Serbia [6]. Shortly thereafter, on February 7, 2019, the Government of the Republic of Serbia issued a Regulation on the National Program for Controlling Antibiotic Resistance [7]. Over the past few years, the state has implemented various organized measures, primarily involving the education of healthcare professionals, media campaigns to raise awareness about the importance of rational antibiotic use and the threat of antimicrobial resistance among healthcare workers and the general population, strengthening the capacity of microbiological laboratories, and developing strategic documents, among others. However, assessing the effects of all these measures remains challenging [8].

Pharmacists' awareness of antimicrobial resistance (AMR) issues and rational antibiotic use is annually emphasized during the World Antimicrobial Awareness Week, which is part of a global campaign aimed at increasing awareness and understanding of AMR. This week is observed from November 18th to 24th and encourages best practices in the public and urges all key stakeholders to take action to reduce the further emergence and spread of AMR [9]. This day is also marked in our country, notably on November 18th, as the European Antibiotic Awareness Day, with a similar goal of drawing attention of professionals and the public to the threat posed to public health by bacterial resistance to antimicrobial

drugs and increasing awareness of the need for rational antibiotic use. All these measures have significantly raised awareness among pharmacists in recent years.

Ultimately, it's worth noting that important factors influencing pharmacists' self-assessment in antibiotic dispensing practices include individual levels of pharmacist knowledge, inspection supervision, lack of time to dedicate to each patient individually, profit motives, "incentivizing" rewards, knowledge of legal regulations, personal attributes, and others.

OBJECTIVES

The specialist work from which this text originated set three specific objectives that the conducted research needed to address:

1. Investigate general knowledge about antibiotics, antimicrobial resistance (AMR), and legal frameworks among healthcare workers employed in pharmacies (pharmacists and pharmacy technicians).
2. Examine the practice of dispensing antibiotics in specific situations (such as viral infections, sore throat, colds, urinary tract infections, infected wounds, and other conditions) in public pharmacies (both state-owned and private).
3. Evaluate differences in the practice of dispensing antibiotics based on the gender of the respondents, the location of the pharmacy, and the level of education.

As a general goal, the work aimed to empirically present the self-assessment of pharmacists regarding the practice of dispensing antibiotics in public pharmacies.

THE METHODOLOGY

The study was conducted as a cross-sectional study using a purpose-designed questionnaire through which respondents self-assessed their knowledge related to antibiotics and their practices in dispensing antibiotics over the past six months. The research involved healthcare workers of all levels of pharmacy education (pharmacists, pharmacy masters, graduates, technicians) employed in almost all pharmacies in the city of Šabac (including both urban and rural pharmacies). Additionally, participants attending the XV Professional Conference "Marketing in Pharmacy," held in Šabac on March 19, 2022, under the theme "New Knowledge, Skills, and Competencies of Healthcare Workers - Challenges in the 21st Century," organized by the Pharmacy Institution "Melissa" and the drugstore "Lin" from Šabac, were also included in the study. Data were collected from March to August 2022.

The collected data were analyzed using the statistical program SPSS, employing descriptive analysis (frequencies, mean values, and standard deviations). To assess the existence of statistically significant differences in the prevalence of certain socio-demographic characteristics and knowledge indicators, the Pearson Chi-square test (χ^2) was utilized. Mean values and dispersion parameters proven to originate from populations with normal distribution were presented as mean values ± standard deviations.

The questionnaire was created for the purposes of this specialist work, mostly through modification of the questionnaire used in Ana Balać's specialist work [10]. An expert panel consisting of four experts (two pharmacy masters with over 20 years of experience in pharmacy practice, and two university professors experienced in pharmaceutical practice research) additionally adapted the questionnaire based on changes in practice that occurred between the previous research and the current study, particularly regarding antibiotic dispensing in the Republic of Serbia. Furthermore, limitations identified in previous research, the National Guide for Good Clinical Practice for Rational Antibiotic Use, and the original research by Shukry Zawahir et al. served as references for creating the initial version of the questionnaire based on Ana Balać's research.

The questionnaire used in the study consisted of three sections:

Section 1: Knowledge related to antibiotics;

Section 2: Practices in dispensing antibiotics over the past six months;

Section 3: Socio-demographic data.

RESULTS

During the research, a total of 400 questionnaires were distributed to respondents. As the completion of the questionnaires was based on a voluntary principle, out of the total number of distributed questionnaires, 258 were completed, with 29 not fully filled out. Therefore, the total number

of respondents who completed the questionnaire in a qualitatively satisfactory manner for use in the research was 229, or 88.76% of the total number of completed questionnaires. Looking at the gender structure of the questionnaires used in the study, 200 respondents were female (87.3%). In terms of formal education, the majority of respondents were individuals with a completed pharmacy faculty degree – pharmacists (59%), followed by higher pharmacy technicians (3.5%) and pharmacy technicians (37.6%). The research showed that the minimum number of pharmacists per pharmacy was one, while the maximum was six. More than half of the pharmacies had two employed graduated pharmacists (57%). Almost all pharmacists in pharmacies had a license to practice (98.6%), with only 3 respondents indicating that not all pharmacists in their pharmacies were licensed. The average age of the respondents was 40.1 years, and the average years of work experience were 14.4 years. Most respondents worked in city pharmacies (47.6%), followed by pharmacies in smaller towns (39.2%), while the smallest number worked in rural pharmacies (13.2%).

Results related to knowledge about antibiotics:

Respondents answered 33 questions from the questionnaire, and the results of the survey show that only 37.1% of respondents know that antibiotics are substances that can kill or inhibit the growth of bacteria, while 63.9% believe that antibiotics act not only on bacteria but also on other microorganisms (fungi, viruses, and parasites). When it comes to viral infections, 95.2% of respondents know that antibiotics are ineffective in that case; 98.7% of respondents are sure that common colds and coughs should not be treated with antibiotics, while 72.6% of respondents believe that acute sore throat should not be treated with antibiotics. The vast majority of respondents correctly answered that bacterial infections are treated with antibiotics (96.9%), while 97.4% of respondents are aware that antibiotics will be less effective in the future if used frequently.

Antibiotic resistance is a significant and widespread problem worldwide, with the majority of respondents (96.5%) agreeing with this statement. Regarding the assertion that the voluntary use of antibiotics is one of the causes of resistance, 98.7% of respondents confirmed this.

More than 90% of respondents answered affirmatively to the following questions:

- Inappropriate use of antibiotics contributes to the increase in antibiotic resistance (99.6%).
- Issuing antibiotics without a prescription will lead to the development of antibiotic resistance (96.5%).
- One of the causes of antibiotic resistance is that patients do not adhere to prescribed antibiotic regimens (94.3%).

Regarding the statement that one of the causes of resistance is discontinuation of antibiotic use before completing the therapeutic regimen, 86.5% of respondents confirmed this, while 50.2% of respondents also confirmed that the use of antibiotics at a dose higher than prescribed is one of the causes of resistance.

A very small number of respondents (11.8%) responded that there are antibiotics in Serbia that can be dispensed without a prescription, but the majority are aware of regulations stating that pharmacists in Serbia cannot legally dispense antibiotics (95.6%), and that pharmacists can be punished if they dispense antibiotics without a prescription (90.8%).

The overall knowledge score ranged from 18 to 31, meaning that none of the respondents had a maximum score of 33. The average knowledge score for the total sample was 26.26 ± 2.92.

Results related to the practice of antibiotic dispensing in the last six months

Responses to questions regarding the dispensing of antibiotics without a prescription are as follows:

- Upon patient request, 79.9% of respondents NEVER dispense antibiotics without a prescription.
- For adult patients with symptoms of viral infection, 97.8% of respondents NEVER dispense antibiotics without a prescription.
- For children with symptoms of viral infection, 99.1% of respondents NEVER dispense antibiotics without a prescription.
- For adult patients with mild symptoms caused by bacterial infection, 82.1% of respondents NEVER dispense antibiotics without a prescription.
- For children with symptoms of bacterial infection, 86.9% of respondents NEVER dispense antibiotics without a prescription.
- If they know the patient, 69.9% of respondents NEVER dispense antibiotics without a prescription.

Whether respondents require prescriptions from doctors to be original or photocopied is shown in the following table (Table 1).

Table 1 - Distribution of responses regarding whether prescriptions from doctors should be original or photocopied

Issuing antibiotics prescribed on a doctor's report (e.g., specialists from a hospital institution)	**number of respondents**	**percentage of respondents**
original prescription	150	65,5%
photocopied prescription	34	15%

Responses to the question of whether antibiotics were dispensed without a prescription for specific conditions in the past month are presented in Table 2. Although this occurrence is rare based on the response "I always (100%) prescribe without a prescription at the patient's request," for the examined infection localizations, it was rare for the urinary tract - ranging from 1.3% to 4.0% for common cold and cough or diarrhea. However, based on survey responses: "I sometimes dispense antibiotics without a prescription (in a range of 25-75% of cases) for certain conditions i.e. infection localizations, this happens (most often in urinary tract infections - 52.0%, infected wounds - 42.4%, acute throat inflammation 29.8%, and diarrhea - 15.7%, and least often in common cold and cough - 9.2%. Despite the fact that the highest number - 79.9% of respondents never dispense antibiotics without a prescription at the patient's request, still 20.1% of respondents sometimes dispense antibiotics without a prescription or doctor's report.

Table 2 - Distribution of responses to questions about whether respondents dispensed antibiotics without a prescription during the past month for the specified conditions, symptoms, or localization of potential infection

Conditions/Symptoms	**NEVER0%**	**25%**	**50%**	**75%**	**ALWAYS 100%**	**I DON'T KNOW**
Acute sore throat	70,2 %	18%	6,1%	3,9%		1,8%
Common cold and cough	90,8%	5,7%	1,3%	4%	4%	1,3%
Infected wound	57,6%	21%	10,9%	5,7%	2,2%	2,6%
Urinary tract infections	48%	28,4%	17%	3,5%	1,3%	1,7%
Diarrhea	81,7%	13,5%	2,2%		4%	2,2%

Results regarding the practice of antibiotic dispensing concerning participants' gender, pharmacy location, and educational level

To address one of the objectives of this study, which pertains to assessing differences in antibiotic dispensing practices based on participants' gender, pharmacy location, and educational level, we analyzed the data obtained from the study precisely based on these socio-demographic characteristics (Table 3).

Table 3 - Responses regarding gender, educational level, and pharmacy location

Statement	Gender	Education level	Pharmacy location
	X^2 (Df); p value		
"I dispense antibiotics without a prescription if the patient requests it."	0,391(2); p=0,822	1,852(4); p=0,763	6,701(4); p=0,153
"I dispense antibiotics without a prescription to adult patients with mild symptoms due to viral infections."	**8,276(2); p=0,016**	2,513(4); p=0,642	2,907(4); p=0,574
"I dispense antibiotics without a prescription to children with symptoms of viral infection."	0,293(1); p=0,589	1,405(2); p=0,495	2,223(2); p=0,329
"I dispense antibiotics without a prescription to children with symptoms of bacterial infection."	0,415(2); p=0,813	2,755(4); p=0,600	7,772(4); p=0,100
"I dispense antibiotics without a prescription if I know the patient and upon their request."	0,352(2); p=0,838	1,663(4); p=0,797	**11,608(4); p=0,021**
"I dispense antibiotics without a prescription to adult patients with mild symptoms caused by bacterial infections."	0,293(2); p=0,864	3,525(4); p=0,474	7,188(4); p=0,126
"When dispensing antibiotics prescribed once, I return the prescription/order/form with a facsimile of the doctor's signature to the patient."	3,015(2); p=0,221	4,130(4); p=0,389	5,110(4); p=0,276
"When dispensing antibiotics on a paper prescription/order/form, I record the issuance on the paper prescription/order/form by affixing my signature, date, and the number of boxes dispensed."	2,047(2); p=0,359	8,166(4); p=0,086	6,467(4); p=0,167
"When dispensing antibiotics prescribed on a physician's report (specialist from a hospital institution), I document what was dispensed on the report and authenticate that record with a stamp."	1,068(2); p=0,586	**10,028(4); p=0,040**	2,469(4); p=0,650
"When dispensing antibiotics prescribed on a physician's report (e.g., specialist from a hospital institution), I request that the report be original."	2,452(2); p=0,293	0,296(4); p=0,990	1,762(4); p=0,779
"When dispensing antibiotics prescribed on a physician's report (e.g., specialist from a hospital institution), I request that the report be photocopied."	0,584(2); p=0,747	6,572(4); p=0,160	3,086(4); p=0,544
"When dispensing antibiotics on a paper prescription/order/form, I document the dispensing (with my signature, date, and the number of boxes dispensed) and stamp the pharmacy's seal on the paper prescription/order/form."	4,757(2); p=0,093	2,298(4); p=0,681	5,851(4); p=0,211
"I make photocopies of the reports/prescriptions/orders for which antibiotics are prescribed but not retained, and I keep copies in the pharmacy."	0,652(2); p=0,722	3,671(4); p=0,452	2,576(4); p=0,631

The results we obtained show that in terms of gender, there is a statistically significant difference in responses only for the statement "I issue antibiotics without prescription to adult patients with mild symptoms due to viral infections." 6.9% of male respondents answered "sometimes," while only 0.5% of female respondents did so. A statistically significant difference in education level is observed for the statement "When issuing antibiotics prescribed by a hospital specialist, I document what was issued on the report and stamp that record with a seal." The response "always" was given by the majority of pharmacists (83.7%), followed by higher pharmacy technicians (75%), and then pharmacy technicians (68.6%). Although only licensed pharmacists are legally allowed to dispense prescription drugs, it is evident in practice that pharmacy technicians also dispense drugs because a high percentage of them responded positively to this question. Every pharmacy must have a responsible pharmacist present, and only in their presence can a pharmacy technician dispense medication. Personal connections with patients, the so-called "patient-oriented care" concerning the location of the pharmacy, is represented by the statement "I issue antibiotics without prescription if I know the patient, upon their request," and it is the only one that statistically differs in responses. Employees in pharmacies in smaller locations predominantly responded with "never" (79.8%).

DISCUSSION

If this study from Sri Lanka from 2016/17 is compared with our research from 2022, several important observations can be made. Firstly, the study from Sri Lanka had a national character, considering that the survey was conducted across all provinces of the country, while our research focused on one (micro)region (the city of Šabac and its surroundings). Furthermore, antibiotics are still dispensed without a prescription in both countries, despite legislative frameworks prohibiting it; the knowledge of pharmacy staff on the topic of antibiotics, AMR, and antibiotic dispensing practices is significantly better in the Republic of Serbia; knowledge about antibiotics is one of the reasons that significantly influences the reduction of antibiotic dispensing without a prescription, therefore, further education and raising awareness about these issues in both countries are recommended; the level of formal education of employees in the Republic of Serbia is higher than that of their colleagues in Sri Lanka; personal acquaintance with patients in both countries is a major reason for dispensing antibiotics without a prescription; the profit motive is extremely significant in both countries. Finally, awareness of AMR and its harmful impact on the entire population cannot be left as a problem only for pharmacy employees and patients. The significance of this issue is such that it requires the activation of the entire society, from the governments of all countries (including Sri Lanka and the Republic of Serbia), which will incorporate this topic into public health policies, to a broad action by media professionals to spread awareness about these issues, revising educational programs, improving educational plans for personnel being trained for pharmaceutical activities, and other measures.

Regarding the Republic of Serbia, Ana Balać, a specialist at the Faculty of Pharmacy, University of Belgrade, defended her specialist paper titled "The Use of Antibiotics: Beliefs, Knowledge, and Experiences of Pharmacists and Pharmacy Technicians" in 2020. For her paper, she conducted research on the use of antibiotics, which covered the knowledge and experiences of pharmacists and pharmacy technicians on this topic. Comparing her research with ours, which has a time difference of three years, we conclude that respondents possess relatively good knowledge about antibiotics and AMR. Both studies aimed to raise awareness among pharmacists and pharmacy technicians about their role in antibiotic dispensing and the fight against AMR [10].

The most important factors related to the practice of dispensing antibiotics in this study are the level of education, personal knowledge, experience, keeping up with developments in pharmaceutical activities, personal connections with patients, and the so-called "patient satisfaction." What could not be precisely examined through this questionnaire is the well-known tendency for profit and the approval (or encouragement) of certain practices by pharmacy owners. Along with these phenomena, there is invariably weak inspection supervision of the legal regulations defining this area.

CONCLUSION

Self-assessment of pharmacists regarding the practice of dispensing antibiotics in public pharmacies in the city and municipality of Šabac in the Republic of Serbia was examined through responses to 33 self-assessment questions from the completed questionnaire. The results of the study

show that regarding viral infections, 95.2% of respondents know that antibiotics are ineffective in such cases; 98.7% of respondents are confident that common colds and coughs should not be treated with antibiotics, while 72.6% of respondents believe that acute throat pain should not be treated with antibiotics. However, there is a lower level of knowledge about the mechanism of action of antibiotics. Only 37.1% of respondents know that antibiotics are substances that can kill bacteria (bactericidal antibiotics) or prevent the growth of bacteria (bacteriostatic). Respondents have shown a fairly good level of knowledge about antibiotics and antimicrobial resistance (AMR) and legal frameworks.

However, despite the good level of theoretical knowledge and relatively good legal framework, based on the results from the sample of 229 pharmacists and pharmacy technicians, we conclude that the practice of dispensing antibiotics without a prescription still persists in certain situations. Although this phenomenon is not common based on the survey response "I always prescribe without a prescription at the patient's request" for the examined localizations of infections, it occurs in a small number of cases (1.4% to 4.0%). However, based on the response "I sometimes prescribe without a prescription at the patient's request," it happens more often in certain clinical conditions and complaints: most commonly urinary tract infections in 52% of cases, infected wounds in 42.4%, acute throat inflammation in 29.8%, and diarrhea in 15.7%, and least commonly in common colds and coughs in 9.2%. At the patient's request, the majority of respondents - 79.9% never dispense antibiotics without a prescription, but globally, 20.1% of respondents sometimes dispense antibiotics without a prescription or doctor's report. The most important factors related to the practice of dispensing antibiotics in this study are the level of education, personal knowledge, experience, keeping up with developments in pharmaceutical activities, personal connections with patients, and the so-called "patient satisfaction." Specific "circumstances" that must be taken into account are also of exceptional importance, as the statement "I prescribe antibiotics without a prescription if I know the patient, at his request..." is the only one that statistically differs in responses. Employees in pharmacies in smaller towns mostly indicated "never" (79.8%). The significance of higher education is shown in the response to the question "When dispensing antibiotics prescribed on a doctor's report, I record what was issued on the report and stamp the record," statistically significantly more pharmacists (83.7%; p=0.040) do it always, while pharmacy technicians do it sometimes (68.6%). Like all problems, the issue of antimicrobial resistance (AMR) is a systemic one, which undoubtedly requires teamwork of all stakeholders in a society where the role of pharmacists and pharmacy technicians is one of the most significant.

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METEORISM AND ABDOMINAL DISTENSION

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Summary: Meteorism or bloating in the abdomen and abdominal distension are among the most common digestive issues that patients experience at both primary and secondary care levels. Up to 10-30% of the general population experiences bloating problems. Symptoms are even more prevalent in patients with functional gastrointestinal disorders. Bloating is often associated with a feeling of increased pressure in the abdomen and the release of gas from the intestines. A healthy individual can tolerate up to 500 ml of air in the gastrointestinal tract without major symptoms, but in patients with irritable bowel syndrome, symptoms can be triggered by even minimal increases in gas volume in the gastrointestinal tract. The composition of intestinal gases partly explains their origin: nitrogen (N2) is usually from swallowed air; hydrogen (H2) is produced by bacterial fermentation of carbohydrates; carbon dioxide (CO2) is produced by bacterial fermentation of carbohydrates, fats, and proteins; methane (CH4) is produced during anaerobic bacterial metabolism. When there is an imbalance between gas production and expulsion in the digestive system, it manifests as a feeling of bloating with or without visible abdominal distension. When defining functional disorders related to bloating, it is crucial to exclude possible organic causes of symptoms. Bloating and abdominal distension occasionally occur even in healthy individuals as a result of normal digestion (especially after meals rich in fats and fermentable sugars). The characteristic of "physiological" bloating and distension is that they occur shortly after meals, are short-lived, and disappear after urination or passing gas. Initially, bloating and abdominal distension were only understood as consequences of excessive air in the intestines. Today, we know that the pathophysiology of both conditions is much more complex and the result of different mechanisms. In addition to increased gas production, which accumulates in the intestines along with fluid, altered intestinal microbiota and functionally altered enteric nervous system, which cause visceral hyperalgesia and motility disorders, also have a significant impact. The epidemiological dimension and numerous causes, including malignancies, indicate the need for this type of diagnostic approach in patients with bloating. Diagnosis can involve many tests, including invasive ones, which may pose a certain risk to the patient and a financial burden on the healthcare system. Therefore, a step-by-step approach and a targeted approach are necessary when managing each individual case. The purpose of this study is to present the treatment approach for patients with bloating and to draw attention to the most common medical conditions that may cause increased gas in the gastrointestinal tract.
Keywords: meteorism, bloating, gastrointestinal tract, diagnostics

INTRODUCTION

The primary characteristic of meteorism is the accumulation of gases in the gastrointestinal (GI) tract, which causes a feeling of bloating and abdominal distension. Meteorism and abdominal distension are among the most common digestive issues that patients experience at both primary and secondary care levels. Meteorism is a very common symptom occurring in people of all ages, equally prevalent in all races, and can be present in both babies and older individuals. Approximately 15-23% of Asians and 15-30% of Americans suffer from bloating [1,2]. In Slovenia, about 10-30% of the general population have bloating problems [3].

This issue was highlighted in the past by the Persian physician Avicenna in his Canon of Medicine. Avicenna used keywords such as bloating and gases, attributing the causes of bloating to dietary factors, inappropriate lifestyle, gastrointestinal, and other reasons. Furthermore, Avicenna classified the causes based on the location of origin, dividing them into the upper part of the abdomen (stomach) and the intestinal part of the abdomen. He also listed 38 medicinal plants used as remedies. Modern scientific data support most of the causes of bloating mentioned in Avicenna's Canon [4].

Symptoms of meteorism are even more prevalent in patients with functional gastrointestinal disorders [5]. Meteorism is almost invariably associated with symptoms such as bloating, distension, and the passage of gas from the intestines. The causes of meteorism are usually benign, such as overeating, swallowing air during meals, or excessive fermentation in the intestinal microbiota. More concerning causes may include bowel obstruction, kidney stones, functional disorders related to overeating, bacterial overgrowth, inflammatory bowel diseases, food intolerance, allergies, blunt trauma to solid abdominal organs, peritonitis, and idiopathic causes.

When defining functional disorders related to bloating, it is crucial to exclude possible organic causes of symptoms, including malignancies.

Diagnosis can involve many tests, including invasive ones, which may pose a certain risk to the patient and a financial burden on the healthcare system. Therefore, a step-by-step approach and targeted treatment approach are necessary [3].

Meteorism and abdominal distension - definition of terms:

Meteorism, bloating, and distension are different terms used to describe the same condition: increased gas in the digestive tract. Meteorism is the medical term for this condition, while bloating and distension are more common terms in everyday language. Bloating refers to a feeling of tightness or fullness in the abdomen, while distension refers to a visible increase in abdominal girth. Flatulence is another medical term that refers to the passage of gas from the anus.

In a healthy individual, the gastrointestinal tract usually contains 100 to 200 ml of gas, which is physiological and reflects the dynamic process of gas formation during digestion. Gases can enter the gastrointestinal tract during feeding (aerophagia), arise from the breakdown of substances and bacterial fermentation. They are eliminated during defecation, through the diffusion of gases from the intestines into the systemic circulation, and some gases are necessary for the metabolism of the intestinal microbiota. In addition to causing discomfort, intestinal gases can be associated with more serious symptoms. In the intestinal microbiota, bacteria such as Bacteroides, Ruminococcus, Roseburia, Clostridium, Eubacterium, Desulfovibrio, and Methanobrevibacter are among the most common microbes responsible for the formation of intestinal gases. More than 99% of intestinal gas consists of hydrogen, carbon dioxide, and methane, while less than 1% consists of other odorous compounds. Food groups associated with intestinal gases include legumes, vegetables, fruits, cereals, and for some individuals, dairy products. This food is rich in indigestible carbohydrates such as oligosaccharides of the raffinose family, fructans, polyols, and for sensitive individuals, lactose. These carbohydrates are fermented by colonic bacteria, producing gases directly or through cross-fermentation [8].

The composition of intestinal gases partly explains their origin: nitrogen (N2) is usually from swallowed air; hydrogen (H2) is produced by bacterial fermentation of carbohydrates; carbon dioxide (CO2) is produced by bacterial fermentation of carbohydrates, fats, and proteins; methane (CH4) is produced during anaerobic bacterial metabolism. When there is an imbalance between gas production and expulsion in the digestive system, it manifests as a feeling of bloating with or without visible abdominal distension. A healthy individual can tolerate up to 500 ml of air in the gastrointestinal tract without major symptoms, but in patients with irritable bowel syndrome, symptoms can be triggered by even minimal increases in gas volume in the gastrointestinal tract [6,7].

Meteorism (bloating) is a symptom that patients describe as a feeling of increased pressure in the abdominal cavity. Simultaneously, abdominal distension may accompany it, wherein we find an objectively increased volume of the abdomen; however, abdominal distension can also occur as an independent sign [8,9]. Bloating and abdominal distension occasionally occur even in healthy individuals as a result of normal digestion (especially after meals rich in fats and fermentable sugars). The characteristic of "physiological" bloating and distension is that they occur shortly after meals, are short-lived, and disappear after urination or passing gas. Initially, bloating and abdominal distension were only understood as consequences of excessive air in the intestines. Today, we know that the pathophysiology of both conditions is much more complex and the result of different mechanisms. In addition to increased gas production, which accumulates in the intestines along with fluid, altered intestinal microbiota and functionally altered enteric nervous system, which cause visceral hyperalgesia and motility disorders [9,10].

The pathophysiology of functional gastrointestinal disorders with meteorism and abdominal distension is multifactorial and not fully understood. Several underlying mechanisms have been proposed that may coexist in individual patients:

1. **Intraluminal content of the gut** (increased gas and fluid volume)
2. **Visceral hypersensitivity**
3. **Abdominal-diaphragmatic dysenergia** (Instead of the relaxation of the diaphragm and contraction of the abdominal walls, food intake leads to relaxation of the abdominal walls, and the diaphragm moves lower and closer to the abdomen. This leads to increased pressure in the abdominal cavity, which can lead to meteorism, pain, and in some cases, constipation. ADD is often seen together with pelvic floor muscle disinhibition.)
4. **Constipation**
5. **Obesity**
6. **Dysbiosis** (leading to chronic inflammation, which then leads to sensory and motor dysfunction)
7. **Psychogenic comorbidities** (anxiety and depression) [1,3]

These factors can interact and contribute to the development and persistence of symptoms associated with meteorism and abdominal distension.

Approach to patients with meteorism:

The etiology of meteorism and abdominal distension is highly diverse, categorized into organic and functional causes. Diagnosis is often demanding, prolonged, and costly.

Understanding the most common pathological conditions is essential for the rational treatment of patients with meteorism. Patients can be spared from many unpleasant and potentially risky examinations, and prompt symptom improvement can be achieved through proper disease recognition and treatment. When organic causes are ruled out, particular attention must be paid to alarm symptoms. (Alarm symptoms are indicators of possible organic diseases, and it is necessary for a gastroenterologist to examine the patient as soon as they are noticed. These symptoms include: sudden onset anemia due to bleeding from the digestive tract, significant unintended weight loss, persistent vomiting, difficulty swallowing, and the presence of a palpable mass in the abdomen.) The presence of these signs with bloating should prompt us to quickly perform endoscopic and imaging diagnostics to rule out potential significant organic diseases. Otherwise, endoscopic and imaging diagnostics often provide little information when diagnosing the causes of functional meteorism [7,10,11g.

Patient dietary habits are important in history taking. Consuming large individual meals and fast eating can cause postprandial bloating. Such patients are advised to eat smaller meals several times a day. Additionally, certain foods can cause excessive bloating: onions, legumes, coffee, carbonated beverages, or fruit sugars [11]. In particular, these latter mentioned foods produce a lot of gas during breakdown, which is the cause of the problem. This knowledge formed the basis for the very popular "FODMAP" diet today. The FODMAP diet is a dietary approach used to alleviate symptoms of irritable bowel syndrome (IBS), which include pain, bloating, diarrhea, and constipation. FODMAP is an acronym for fermentable oligosaccharides, disaccharides, monosaccharides, and polyols, which are types of carbohydrates that some people cannot digest well. The FODMAP diet reduces the intake of these substances and can help reduce inflammation and gas production in the intestines. The FODMAP diet is conducted in three phases: elimination, reintroduction, and adaptation. In the first phase, all high-FODMAP foods are eliminated, in the second phase, they are gradually reintroduced one by one to determine which foods cause symptoms, and in the third phase, the diet is adjusted based on individual tolerance. The effectiveness of a diet avoiding fermentable oligo-, di-, monosaccharides and polyols has been demonstrated in randomized studies in patients with irritable bowel syndrome [12,13]. Dietary history is also important for identifying possible diseases resulting from the harmful effects of food on the gastrointestinal system. Among them, lactose intolerance is the most common [14]. If problems occur after consuming gluten in the diet, celiac disease diagnosis is necessary [15]. Exocrine pancreatic insufficiency in older individuals is not so rare [16].

Bloating can also result from certain medications, and it is one of the side effects of metformin, while opioid analgesics can cause both bloating and constipation simultaneously [11]. In the case of constipation, there is disrupted stool and gas expulsion, which then accumulate in the digestive tract. Up

to 80% of patients report bloating symptoms when they have constipation. In most patients, bloating symptoms will disappear after resolving constipation [17]. When further defining the causes of bloating, the timing of the onset of symptoms can be helpful. If discomfort occurs shortly after eating, the cause of bloating is usually in the upper gastrointestinal tract – "gastric bloating." However, if a patient reports bloating long after eating, the cause is usually lower in the digestive tract - "intestinal bloating."

In summary: When "gastric" meteorism is present, we usually think of disorders of gastric emptying, gastroparesis, functional dyspepsia, GERD, or biliary gastritis. In this case, the most commonly used diagnostic tools are gastroscopy or X-ray imaging of the upper GI tract. If it is "intestinal" meteorism, we suspect intolerance to food ingredients, small intestinal bacterial overgrowth (SIBO), celiac disease and gluten sensitivity, malabsorption syndrome, bowel malignancy, intestinal infections, bowel ischemia (abdominal angina), exocrine pancreatic insufficiency, or functional bowel diseases. Diagnostic procedures include serological tests for celiac disease, hydrogen breath test, imaging and endoscopic diagnostics, and if necessary, anorectal manometry. A simplified algorithm for the initial treatment of meteorism is summarized in Figure 1 [3].

Figure 1. Simplified procedure for the initial treatment of a patient with flatulence

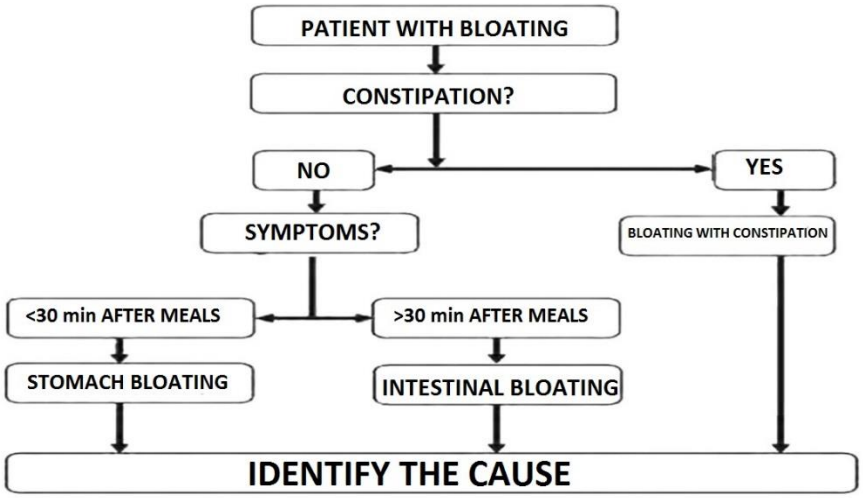

Table 1 shows some of the previously mentioned etiologically most common conditions and common diagnostic procedures [3].

Table 1. Common etiology and some of the diagnostic tests for flatulence

"STOMACH" BLOATING	• Stomach emptying disorders • Gastroparesis • Functional dyspepsia • GERD (Gastroesophageal Reflux Disease) • Biliary gastritis	• Gastroscopy • Gastric motility tests • Systemic diseases – diabetes, scleroderma...
"INTESTINAL" BLOATING	• Food ingredient intolerance • Small intestinal bacterial overgrowth (SIBO) • Celiac disease and gluten sensitivity • Malabsorption syndrome • Intestinal malignancies • Intestinal infections • Intestinal ischemia (abdominal angina) • Exocrine pancreatic insufficiency • Functional bowel diseases	• Serology for celiac disease • Hydrogen breath test • Imaging and endoscopic diagnostics • Anorectal manometry

Certain more significant conditions that cause bloating

Among the more common causes of bloating are diseases due to altered absorption of nutrients and food intolerances. The most common causes of malabsorption can often be ruled out without invasive interventions, even at the primary healthcare level. In recent years, gluten-related diseases have become significant gastrointestinal tract disorders. We must consider them, among other reasons, because of their epidemiological dimensions. According to some estimates, celiac disease, non-celiac gluten sensitivity, and wheat allergy affect up to 6% of the general population, and they all share symptoms resulting from the harmful effects of gluten. Introducing a gluten-free diet for most patients leads to objective and subjective improvement of the disease [14,18].

Celiac disease

Celiac disease is a condition that should always be considered in patients with bloating. It affects 1-2% of the population and is the most common enteropathy. Special attention must be paid to it in all age groups, especially in patients with type 1 diabetes and Hashimoto's thyroiditis, where a lower threshold of suspicion for testing should be maintained [18,19]. Serological diagnostics play a role as a screening test, with the determination of IgA antibodies against tissue transglutaminase (IgAtTG) being the first-choice test. Despite the high specificity and sensitivity of serological testing, it is not sufficient for diagnosing celiac disease in adults. Confirmation through endoscopic examination and histological examination of duodenal mucosa biopsy is necessary for a definitive diagnosis. All patients with positive serological findings should be referred for endoscopic diagnosis. Regardless of the serological test result, endoscopic diagnosis is performed in patients with a high probability of celiac disease. Patients with symptomatic malabsorption, unexplained diarrhea with weight loss, unexplained iron-deficiency anemia, herpetiform dermatitis, or symptomatic patients who are first-degree relatives of celiac disease patients fall into this category [19]. Serological testing and endoscopic examination must be performed in patients following a gluten-containing diet. If the patient is on a gluten-free diet at the time of testing, they must be gluten-loaded. Recent studies have shown that even small amounts of gluten can induce inflammation. The gluten challenge should last at least 2 weeks, and if the patient tolerates the diet, it can be extended up to 6 weeks [20,21]. Genetic testing for celiac disease may be used in patients already on a gluten-free diet to determine the presence of HLA DQ2 and DQ8 alleles, which are necessary for celiac disease development; the absence of these alleles excludes the disease with a probability of over 99%. However, genetic testing is not used in routine practice and is indicated for unclear forms of celiac disease and diagnosing refractory forms of the disease [21].

Non-celiac gluten sensitivity (NCGS) has emerged as a separate nosological entity in recent years. Symptoms are varied and similar to those of celiac disease and other functional gastrointestinal disorders, associated with gluten consumption. Since the mechanism of the disease is poorly understood, there is still no diagnostic biomarker. Therefore, the diagnosis of non-celiac gluten sensitivity is made by excluding celiac disease. Wheat allergy, on the other hand, results from a classic allergic reaction (type 1 hypersensitivity) to proteins contained in wheat, including gluten. When antigens enter the body, the allergy can affect the skin, respiratory system, or digestive system. Gastrointestinal symptoms are nonspecific, including bloating, distension, diarrhea, but allergic reactions can also manifest as anaphylaxis. The diagnosis involves excluding celiac disease through serological testing and, if indicated, performing endoscopic examination and histopathological examination of duodenal mucosa biopsy. Allergy to wheat is confirmed through skin prick tests or by determining specific antibodies [23].

A gluten-free diet is crucial in gluten-related diseases. It involves eliminating all foods containing wheat, rye, barley, and related grains. Compared to a normal diet, a gluten-free diet is more expensive and less accessible. Patients must also pay close attention to hidden sources of gluten, as it appears in various sauces, soups, processed seafood, dried meat products, and dressings. Additionally, the managing physician must be aware that a gluten-free diet is not always balanced, and the patient may consume insufficient fiber, B-complex vitamins, iron, and trace elements (zinc, copper, selenium...) [24,25]. Celiac disease is a chronic, lifelong condition that, if left untreated, can lead to many serious complications (osteoporosis, the development of other autoimmune diseases, T-cell lymphoma). Therefore, strict lifelong dietary adherence is the cornerstone of therapy. A gluten-free diet in patients with celiac disease reduces symptom occurrence, improves quality of life, enhances nutritional status, and prevents disease complications. Symptoms disappear within 2-4 weeks, serological tests normalize within weeks to months, and the mucosa completely regenerates after about a year. Measurement of antibodies specific to

celiac disease is the most suitable test for assessing patient compliance with a gluten-free diet. If after 6-12 months of strict gluten-free diet, antibody levels in blood cells normalize but the patient still reports symptoms, further evaluation by a dietitian and gastroenterologist is required. It is necessary to exclude gluten contamination, refractory forms of the disease, or possible accompanying pathology [18,20,22].

A gluten-free diet is also the foundation of treatment for non-celiac gluten sensitivity. The goal is symptom remission and subjective well-being of the patient. Currently, there are no clear recommendations regarding the necessity of a lifelong gluten-free diet in these patients. There is insufficient research on whether non-celiac gluten sensitivity is only transient or a chronic disease state [18].

Pancreatic exocrine insufficiency (PEI) is a common and often overlooked cause of bloating, especially in older individuals. The causes of pancreatic exocrine insufficiency are divided into pancreatic or primary and non-pancreatic or secondary. In practice, elastase determination in stool is used in diagnostics, but lately, secretin MRCP (with much higher sensitivity and specificity) has been employed. PEI significantly reduces the quality of life and is diagnosed through clinical presentation and pancreatic function tests. Treatment involves lifestyle adjustments, vitamin supplementation, and pancreatic enzyme replacement therapy. Long-term goals include eliminating clinical symptoms and correcting malnutrition, addressing only the underlying disease when present. Enzyme replacement therapy has both diagnostic and therapeutic significance and leads to significant symptom improvement and better quality of life for patients [26].

The treatment of meteorism and abdominal distension caused by functional disorders, after excluding alarm signs and organic diseases, involves gradual, individualized treatment. Patients with mild functional bloating may only require reassurance that the condition is benign, well, and not indicative of any life-threatening disease.

Symptomatic treatment - Several agents are available for treating these disorders. Antispasmodics have shown some clinical benefit in alleviating symptoms in some patients [27]. Simethicone has been shown to reduce the frequency and severity of meteorism, distension, and bloating [28,29]. Peppermint oil reduced abdominal distension compared to placebo [30,31]. Despite their popularity, evidence is lacking regarding other commonly used agents such as activated charcoal, Iberogast, and magnesium salts.

Dietary intervention - The role of dietary therapy in managing bloating symptoms is crucial and is generally introduced early in the treatment plan. The main reason for dietary therapy is to identify foods that the patient does not tolerate and thus reduce excessive fermentation of food residues. Initially, empirical lactose and other poorly absorbed carbohydrate restrictions may be implemented [12]. Alternatively, FODMAP diet or other elimination diets may be offered to patients with meteorism and abdominal distension if they have not improved on a restrictive diet [32].

Addressing constipation - Patients with chronic idiopathic constipation (CIC) and irritable bowel syndrome with constipation (IBS-C) usually report bloating in their medical history. Lubiprostone has been found to reduce bloating in two placebo-controlled clinical trials involving patients with IBS-C [16,34]. Prucalopride, a selective 5-HT4 receptor agonist, enhances spontaneous bowel movements and reduces bloating [35]. Similarly, linaclotide, a guanylate cyclase C agonist, improves constipation symptoms and reduces abdominal pain and bloating in patients with CIC and IBS-C [36-42].

Microbiota modulation - Reducing gas-producing bacteria or inducing changes in their metabolic activities may reduce excessive fermentation and bloating. Rifaximin, a poorly absorbed broad-spectrum antibiotic, has been found to reduce bloating and flatulence in controlled trials in patients with and without IBS [45,46]. Probiotics may become a therapeutic option in FABD; however, studies have yielded different results, likely due to the lack of standardized study methods [47,48]. A recent review suggested that probiotics have a role in the treatment of functional gastrointestinal disorders [49]. In a double-blind study, Ringel et al. found that Lactobacillus acidophilus and Bifidobacterium lactis Bi-07 reduced bloating in patients with functional gastrointestinal disorders without constipation [50].

Abdominal biofeedback therapy - As described, postprandial meteorism and abdominal distension may result from abnormal relaxation of the anterior abdominal wall and diaphragmatic contraction. It has been shown that patients can be educated to use their abdominal and diaphragmatic muscles to reduce discomfort associated with meteorism and abdominal distension [51].

Modulation of the brain-gut axis - If heightened perception of bowel wall stretching and visceral hypersensitivity are key components in the pathogenesis of functional gastrointestinal disorders with

meteorism and abdominal distension, then modulation of the brain-gut axis appears to be a reasonable treatment option. The efficacy of antidepressants, such as tricyclic antidepressants (TCA) and selective serotonin reuptake inhibitors (SSRI), has been evaluated in patients with IBS. In a small, controlled crossover study, citalopram (SSRI) showed an increase in the number of days without bloating after 3 and 6 weeks. In another study, desipramine in combination with cognitive-behavioral therapy reduced bloating. Hypnotherapy and cognitive-behavioral therapy, also offered to patients with IBS, may be effective in patients with functional gastrointestinal disorders [55].

CONCLUSION

Meteorism and abdominal distension represent a common clinical problem. Like any other health condition, the clinical assessment of gastrointestinal disorders with meteorism and abdominal distension begins with a detailed medical history, physical examination, and appropriate diagnostic tests. It is crucial to exclude any organic cause of bloating and distension. Alarm symptoms, which may indicate more serious pathology, should not be overlooked. Depending on the frequency, gluten-related diseases should always be considered, and in the elderly, pancreatic exocrine insufficiency should also be considered. Celiac disease can be sufficiently excluded with serological testing, even at the level of primary or secondary medical facilities. In treatment, a gradual, multidisciplinary, individualized approach is desirable. Therapy may target bowel motility, muscle tone, microbiota, visceral sensitivity, nutrition, and/or psychological comorbidities. Additionally, an "ex juvantibus" response to treatment – improvement of symptoms with pancreatic enzyme replacement therapy – indicates pancreatic exocrine insufficiency.

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MELANONYCHIA AS A DIAGNOSTIC CHALLENGE

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Summary: Melanonychia involves black-brown discoloration of the nail plate and nail matrix epithelium caused by melanin accumulation. Etiologically, we distinguish simple melanocyte activation and melanocyte proliferation. Melanocyte proliferation can be benign (such as lentigo and nevus) and malignant (subungual melanoma). Although they have similar clinical characteristics, their prognoses are significantly different. The paper presents two cases of melanonychia. In the first case, a 13-year-old boy had linear black-brown discoloration of the nail plate of the index finger of the left, non-dominant hand. There was no nail plate dystrophy, periungual pigmentation, or bleeding. Medical and family histories were unremarkable. Onychoscopic examination diagnosed a nevus of the nail plate. In the second case, an adult woman had linear brown discoloration of the nail plate of the thumb of the right, dominant hand. The discoloration had discreetly irregular edges without signs of nail plate dystrophy, periungual pigmentation, or bleeding. Medical and family histories were unremarkable. After onychoscopic examination, longitudinal excisional biopsy was indicated, establishing the diagnosis of lentigo. Careful history taking, physical examination, onychoscopic examination, and ultimately biopsy with histological examination allow for determining etiology, as well as for an early diagnosis of subungual melanoma as the most important precondition for successful disease treatment.
Key words: nail, discoloration, nevus, lentigo, melanoma.

INTRODUCTION

The term "melanonychia" derives from the Greek words "Melas," meaning black or brown color, and "Onyx," meaning nail. It is characterized by black-brown discoloration of the nail plate and nail matrix epithelium caused by the accumulation of melanin. It can affect one or more nail plates, both on the hands and feet. It predominantly presents as a longitudinal black-brown streak starting from the matrix and extending to the free edge of the nail plate. Less commonly, the discoloration affects the entire nail plate or manifests as a transverse band.

The black-brown discoloration is caused by the accumulation of melanin produced by melanocytes in the nail matrix. Differentiation includes simple melanocyte activation, benign, and malignant melanocyte proliferation. Melanocyte activation can be induced by iatrogenic agents, pathogenic microorganisms, nutritional deficits, and trauma. Additionally, it can be present in certain physiological conditions, abnormalities of the nail plate or periungual tissue, dermatological conditions, tumors, systemic disorders, and syndromes. Melanocyte proliferation includes lentigo, nail matrix nevus, and subungual melanoma.

Melanonychia in childhood is rare. In adults, its prevalence varies (from 0.8% to 23%). Diagnosis is based on history, physical examination, onychoscopic examination, and biopsy with histological examination. Treatment depends on the etiology and nature of melanonychia.

CASE REPORT

During a systematic examination of a 13-year-old boy, a single black-brown, linear discoloration was observed on the index finger of his left, non-dominant hand (See Figure 1). There was no nail plate dystrophy, periungual pigmentation, or bleeding. The onset time of the change could not be determined. The boy was healthy, and his medical and family history were unremarkable. On onychoscopic examination, brown-black, parallel, longitudinal lines were observed on a brown background. The hyperpigmentation of the nail bed was visible through a thin cuticle and the distal part of the proximal nail fold. A diagnosis of nail matrix nevus was made, and regular follow-up by a dermatologist was advised.

During a follow-up examination of a 59-year-old female patient, a single melanonychia of the nail plate of the thumb of her right, dominant hand was observed. It was a brown, linear, uniformly pigmented, clearly demarcated discoloration with discreetly irregular edges from the proximal nail fold to the free edge of the nail plate. There were no signs of trauma, nail plate dystrophy, or bleeding. The change had been present for several months without altering in size or pigment intensity. The patient, a homemaker and non-smoker, had cardiomyopathy, irregular heart rhythm, high blood pressure, type 2 diabetes, and high cholesterol levels. She was on continuous therapy with 200mg of amiodarone, 4mg of acenocoumarol, 20mg of enalapril, 1000mg of metformin, and 10mg of rosuvastatin. On onychoscopic examination, brown-black longitudinal lines of varying width were visible through the cuticle and proximal nail fold on a brown background. A longitudinal excision biopsy was indicated, revealing an increased number of heavily pigmented melanocytes without signs of atypia in the basal epidermis. Thus, a diagnosis of nail plate lentigo was made, and the patient was advised regular dermatologist check-ups..

Figure 1. Nail matrix nevus

Figure 2. Lentigo of the nail matrix

DISCUSSION

Melanonychia implies nail pigmentation caused by simple activation of nail matrix melanocytes, either benign (lentigo or nail matrix nevus) or malignant (subungual melanoma) proliferation of the same [1].

Simple melanocyte activation (melanocyte stimulation, functional melanonychia) involves increased melanin production in secondarily activated melanocytes without an increase in the number of melanocytes [4].

Melanocytes are physiologically activated in ethnic melanonychia and pregnancy [7]. Ethnic melanonychia is predominantly present in individuals with darker pigmented skin types IV, V, and VI [1,7]. Its prevalence varies from 1% in Caucasians, 10%-20% in Asians, to 77–100% in African Americans [7]. It is most commonly found on the thumb and index finger of the hand and the big toe [1,7]. It often affects multiple nail plates, and its width increases with age [1,7]. Melanocyte activation during pregnancy involves several nails on the hands and/or feet [1]. It may disappear or persist after childbirth [1].

Melanocyte activation caused by drugs is often accompanied by skin and/or mucous membrane pigmentation [1]. Its form is variable (transverse or longitudinal stripes, solitary or associated) [1]. The majority of transverse melanonychias are caused by drugs [1]. Often, the changes involve several nails and fade partially or completely upon discontinuation of the drug [1,3]. Melanonychia can be caused by antiretroviral drugs (lamivudine, zidovudine), antimalarial drugs (mepacrine, amodiaquine, chloroquine, quinacrine), anticancer drugs (cyclophosphamide, doxorubicin, hydroxyurea, busulfan, taxanes, capecitabine, cisplatin, bleomycin, daunorubicin, dacarbazine, 5-fluorouracil, methotrexate) as well as simultaneous use of antiplatelet and anticoagulant drugs [1,2,3].

Melanocyte activation can also be induced by metals (arsenic, thallium, mercury), biological agents (clofazimine, infliximab, psoralen, phenytoin, fluconazole, cyclines, ketoconazole, phenothiazines), ultraviolet therapy, electron beam therapy, and conventional radiographic therapy (used in the 1950s and

1960s) [1,3]. The same effect is produced by henna, tobacco, potassium permanganate, tar, and silver nitrate [1].

Fungal melanocyte activation occurs as a result of onychomycosis, fungal infection of the nail plate [9]. So far, at least 21 different species of fungi that can cause fungal melanonychia have been described [9]. Its form is variable [1]. Dermatophytes (Scytalidium dimidiatum) form longitudinal stripes, yeasts (Candida albicans, Candida humicola, Candida parapsilosis) and molds (Trichophyton rubrum, Alternaria, Exophiala) form diffuse discoloration [9,10]. With eradication of the causative agent, the appearance of the nail plate usually normalizes [10,11]. The recurrence rate ranges from 10% to 50% [11].

Melanonychia can also be caused by gram-negative bacteria, including Pseudomonas aeruginosa, Escherichia coli, and Proteus mirabilis [1,12,13]. Immunocompromised states and working in a moist environment are risk factors [1]. Longitudinal stripes with a wider proximal edge or diffuse discolorations starting from the junction of the proximal and lateral nail folds and spreading irregularly along the medial edge are present on the nail plates [1].

The human immunodeficiency virus (HIV) predisposes to melanonychia (diffuse discoloration, multiple longitudinal or transverse stripes on multiple nail plates) accompanied by hyperpigmentation of the mucous membranes, palms, and soles [14].

Dark brown discoloration of the nail plate is observed in malnutrition (predominantly protein deficiency and vitamin D deficiency) [1,15]. It is also present in the absence of vitamin B12 (often found in vegetarians) due to decreased glutathione concentration and subsequent inhibition of tyrosinase, the main enzyme of melanogenesis [16].

Repeated local trauma caused by uncomfortable footwear, occupational trauma, onychophagia, onychotillomania, or carpal tunnel syndrome can activate nail matrix melanocytes [1,13]. Traumatic melanonychia is often accompanied by periungual signs of trauma [1]. Nail matrix melanocytes are often activated in a variety of inflammatory conditions and skin tumors, including Lichen planus, chronic paronychia, psoriasis, amyloidosis, chronic radiation dermatitis, Hallopeau acrodermatitis, myxoid pseudocyst, localized scleroderma, onychomatrix, subungual linear keratosis, Verruca vulgaris, subungual fibrous histiocytoma, Bowen's disease, basal cell carcinoma, subungual fibrous histiocytoma [1,13,14].

Multiple dark brown stripes or diffuse discoloration on multiple nail plates on the hands and feet are observed in Addison's disease, Cushing's syndrome, hyperthyroidism, acromegaly, alkaptonuria, hemosiderosis, hyperbilirubinemia, and porphyria [1]. Melanocyte activation is also present in the host reaction against transplantation (Graft versus host disease, GVHD) [1]. Laugier-Hunziker, Peutz-Jeghers, and Touraine syndromes are characterized by multiple dark brown stripes on the nail plates accompanied by pigmented mucous membrane macules on the lips and oral cavity [1,3]. Laugier-Hunziker syndrome occurs sporadically in white adults aged 20 to 40 years [1,3,18]. It does not have systemic manifestations or malignant potential [1,3,18]. Peutz-Jeghers and Touraine syndromes are predominantly present in children and are inherited in an autosomal dominant manner [1,3,18]. They are associated with intestinal polyps and an increased risk of gastrointestinal and pancreatic malignancies [1,3,18].

Melanocytic hyperplasia involves an increase in the number of melanocytes within the nail matrix [19,20]. We distinguish lentigo, nail matrix nevus, and subungual melanoma [19,20].

Lentigo and nail matrix nevus are benign changes [20]. Lentigo is melanocytic hyperplasia in the absence of melanocytic nests, usually present in adults (9% of longitudinal melanonychias in adults) [1,20]. Nail matrix nevus contains at least one melanocytic nest [19,20]. It accounts for 12% of longitudinal melanonychias in adults and 48% of longitudinal melanonychias in children [1]. We distinguish congenital and acquired nevus [20]. In children, especially under the age of 3, it is difficult to determine whether the nevus is congenital or acquired, considering that nail matrix nevus in the early stage can present as a colorless stripe [20].

In situ and invasive subungual melanoma belong to malignant melanocytic hyperplasias [3]. Subungual melanoma is a rare form of melanoma (1-3% of melanomas) [1]. The incidence varies among different races (from 10% to 25%), with higher incidences observed in Asian countries including Japan, China, and Korea [1]. There is no significant difference in incidence by gender [20]. The peak incidence is between the ages of 50 and 70 years [20]. Subungual melanoma is usually localized on the thumb, big toe, and middle toe [20]. In 38%-76% of cases, longitudinal melanonychia represents the first manifestation of the disease [20].

The medical history includes gender, age, occupation, hobbies, previous trauma, medical history, family medical history, continuous therapy, time of onset of melanonychia, location of melanonychia, color and width of the pigment strip, nail pain and/or bleeding, and nail deformity/brittleness [20]. In pregnant women, it includes a history of pregnancy and the relationship between pregnancy and the onset or progression of melanonychia [20].

The physical examination requires careful assessment of all twenty nails, skin, and mucous membranes [3]. During this examination, it is necessary to determine the following:

- Is one or more nails involved?
- Does one nail differ from the others (if multiple nails are involved)?
- Is the discoloration present on the surface, within, or beneath the nail plate?
- Is the discoloration linearly oriented?
- Is the discoloration wider or darker proximally?
- Is the discoloration associated with nail plate dystrophy (abrasion, splitting, cracking), periungual pigmentation, and bleeding?
- Is the discoloration accompanied by changes in the skin and mucous membranes? [1,3]

In the identification of subungual melanoma, the "ABCDE" (from English: Age, Nail band, Change, Digit involved, Extension, Family) rule established in 2000 by Levi and colleagues is applied (Table 1.) [20]..

Table 1. ABCDEF rule of identification of subungual melanoma

A	Age		From 50 to 70 years of age (Predominantly in African Americans, Asians, and Native Americans)
B	Stripe	Color	Black-brown band
		Width	Bands with a width of ≥3 mm
		Edges	Band with irregular or blurred edges
C	Change	Stripe	Sudden or rapid change in band size
		Nail	Change in nail morphology
D	Involved fingers	Finger	Thumb > Big toe > Index finger
		Hand	Dominant hand > Non-dominant hand
		Multiplicity	One finger > Multiple fingers
E	Extension		Extension of pigmentation to the cuticle, proximal or lateral nail folds (Hutchinson's sign), or free edge of the nail plate
F	Family and personal medical history		Family and personal history of melanoma or dysplastic nevus

Nail plate onychoscopy (with handheld dermoscope and digital videodermoscope) enables differentiation between melanin and non-melanin pigmentation (subungual hematoma, pigmentation caused by exogenous substances) [1,20]. Subungual hematoma is characterized by beads of varying sizes and colors (ranging from bright red to brown or black) depending on the depth and duration of bleeding [1]. It is important to note that subungual bleeding does not exclude the presence of subungual melanoma [1]. Additionally, Hutchinson's sign (extension of pigmentation into the cuticle, proximal, or lateral nail folds) of subungual melanoma and pseudo-Hutchinson's sign (hyperpigmentation of the nail bed visible through the thin cuticle and distal part of the proximal nail fold) should be distinguished [20,21]. Onychoscopic patterns of melanocyte activation, benign, and malignant proliferation have been convincingly confirmed in scientific research (Table 2) [1,20,22].

Table 2. Onychoscopic characteristics in relation to the cause of melanonychia 1

CAUSES OF MELANONYCHIA	ONYCHOSCOPIC CHARACTERISTICS
Melanocyte activation	Involvement of several nails. Homogeneous grayish background with regular gray lines.
Benign melanocytic proliferation	Brown background with brown-black longitudinal lines of identical color and width, with regular spacing (parallel).
Malignant melanocytic proliferation	Multicolored background with brown to black longitudinal lines of irregular width and spacing (loss of parallelism).

Intraoperative onychoscopy of the nail bed and matrix allows direct visualization of the changes in the nail bed and matrix [1]. Additionally, it facilitates determining margins and complete excision of the lesion [22].

Biopsy represents the gold standard in the diagnosis of subungual melanoma [6]. The type and location of the biopsy are determined by the morphological characteristics of melanonychia [1]. Histologically, subungual melanoma is characterized by asymmetry, infiltrative edges, significantly increased number of melanocytes in the basal layer (up to 39-136/mm), tendency to form compact aggregates in the suprabasal layers, presence of cytological atypia, and inflammatory processes [13]. Malignant melanocytes are multi-nucleated with large, atypical nuclei, exhibiting increased mitotic activity (Table 3).

Table 3. Histological characteristics in relation to the cause of melanonychia1,23

CAUSE OF MELANONYCHIA	HISTOLOGICAL CHARACTERISTICS
Melanocyte activation	Increased deposition of melanin in the epidermis without an increase in the number of melanocytes
Lentigo	Increased deposition of melanin and an increase in the number of individual melanocytes in the basal epidermis with the absence of atypia
Nevus	Increase in the number of individual melanocytes, irregular or slightly confluent melanocyte nests in the basal epidermis with the absence of atypia
Atypical melanocyte hyperplasia	Proliferation of melanocytes with mild cytological and architectural atypia
Melanoma in situ	Proliferation of melanocytes with significant cytological and architectural atypia, melanocytic fusion, and pagetoid spread
Invasive melanoma	Proliferation of melanocytes with significant cytological and architectural atypia, invasion beyond the epidermis

Treatment of melanonychia depends on the underlying cause [1]. Treatment of associated systemic or regional diseases, cessation of harmful medication use, avoidance of trauma, treatment of infections, or correction of nutritional deficiencies may result in regression of melanonychia [1]. Benign causes of melanonychia do not require treatment [23]. Treatment of subungual melanoma involves wide local excision of the nail or amputation of the finger [23].

CONCLUSION

Melanonychia represents a complex clinical entity whose etiology is often not easily determined. Simple activation of the nail matrix melanocytes, lentigo, nevus, and subungual melanoma have similar clinical characteristics, but their prognoses vary significantly. Careful medical history, physical examination, onychoscopic examination, and ultimately biopsy with histological examination allow for early diagnosis of subungual melanoma as a fundamental goal and precondition for successful treatment of the disease.

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CASE REPORT: TONSILLAR CANCER

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Summary: INTRODUCTION: Tonsillar cancers are most commonly squamous cell carcinomas, followed by lymphomas, mostly non-Hodgkin's type. The disease often remains asymptomatic for a long time, and patients typically present with odynophagia, dysphagia, and enlarged lymph nodes in the neck. It is increasingly seen in younger populations, with the most common cause being proven infection with high-risk types of human papillomavirus. CASE REPORT: A 62-year-old patient presented to their primary care physician complaining of ear pain and difficulty swallowing. Examination revealed an enlarged left tonsillar fossa with grayish deposits extending towards the soft palate. Biopsy confirmed squamous cell infiltrating carcinoma of the tonsil. HPV typing demonstrated the presence of human papillomavirus type 16. An oncology consultation first included two courses of chemotherapy, resulting in partial improvement in the patient's general condition, followed by bio-radiotherapy. After bio-radiotherapy, the patient experienced pain relief, denied swallowing difficulties, and the tumor mass was significantly reduced, barely visible. Further monitoring and treatment continued as per the recommendations of the Oncology Consultation.
Keywords: tonsillar carcinoma, HPV type 16, HPV vaccination.

INTRODUCTION

Oropharyngeal carcinomas are classified based on their localization into tonsillar carcinomas, which are the most common, carcinomas of the pharyngeal wall, and carcinomas of the soft palate and uvula. Tonsillar carcinomas account for about 90% of cases and are predominantly squamous cell carcinomas, followed by lymphomas. The most common risk factors for the development of this carcinoma include human papillomaviruses (HPV), smoking, alcoholism, Epstein-Barr virus, as well as a diet low in fiber, tobacco chewing, asbestos exposure, marijuana smoking, and certain genetic mutations. In recent years, the etiology of oropharyngeal carcinoma has changed significantly. While smoking and alcoholism are significant contributing factors, HPV infection, especially type 16, is the most common cause. HPV-related tonsillar carcinomas are more common in men, nearly three times more, with the average age at diagnosis being 55-60 years. This can be attributed to sexual behavior trends, increased oral sex at an earlier age than in previous generations, and differences in smoking habits.

Malignant tumors of the tonsils represent about 0.5% of all malignancies in humans, and if diagnosed early, it is a curable disease. However, in advanced stages, the average survival rate is less than 50%. Therefore, it is crucial to work on educating the population and increasing the HPV vaccination rate to reduce the incidence of oropharyngeal carcinomas and cervical carcinomas.

CASE REPORT

The patient, aged 62, has been smoking for 40 years, consuming 20 cigarettes a day, occasionally consuming alcohol, and has benign prostatic hyperplasia, receiving medication from a urologist.

In October 2023, he presented to his primary care physician due to a burning sensation in the throat and pain deep in the left ear, lasting almost a month, along with recent difficulty swallowing. He used locally administered dexamethasone-neomycin drops and azithromycin capsules 500mg without improvement. Examination revealed swollen left tonsillar fossa with grayish deposits spreading towards the soft palate. Otoscopic findings were normal bilaterally. He was referred to an otolaryngologist at the Health Center, who confirmed the same changes and referred him to a laryngologist. A biopsy conducted by the laryngologist at the Clinical Center revealed squamous cell carcinoma keratodes focalis infiltrativum. CT scan of the head and neck showed affected lymph nodes. Meanwhile, the patient experienced severe pain, increasing difficulty swallowing, even liquids. HPV typing isolated HPV type 16.

The Oncology Board recommended chemotherapy, two cycles following a schedule he received in November during his first hospitalization at the Institute of Oncology of Vojvodina, and additional cycles in December 2023. Between cycles, he experienced worsening difficulty swallowing, even water, with pain and occasional bloody sputum. Following chemotherapy, he felt significantly better, experiencing less pain, improved sleep, and examination revealed a reduction in the tumor mass in the left tonsillar fossa.

In January 2024, he was hospitalized at the Institute of Oncology to initiate bioradiotherapy of the oropharynx, per the recommendation of the oncology commission, including brachytherapy and Cetuximab. He developed erythema with pustules on his face due to the treatment, treated with doxycycline and a local cream with urea. In March, he received a reduced dose by 20% due to skin cancer. After completing bioradiotherapy, he reported feeling much better, without throat pain, denying swallowing difficulties, with minimal changes in the left tonsillar fossa, and non-palpable lymph nodes. A follow-up with a new head and neck CT scan and laboratory tests is planned for May.

DISCUSSION

Evidence from studies has shown that the prognosis of tonsillar carcinoma depends on the HPV status of the tumor, with HPV-positive tumors having a better prognosis, with a longer five-year survival rate of 71%, compared to 48% in HPV-negative tumors. Mortality rates are higher in smokers positive for HPV compared to non-smokers. Other factors influencing survival include the occurrence of carcinomas in younger patients without comorbidities, smaller tumor size, and absence of neck lymph node involvement, all of which lead to a better prognosis. There are currently no studies comparing survival differences between patients treated solely with surgical or oncological protocols.

In addition to advising patients to quit smoking and reduce alcohol consumption, raising awareness about the importance of HPV vaccination is crucial. While numerous studies have demonstrated the vaccine's significance in reducing gynecological diseases, there are still limited studies on its effectiveness in preventing oropharyngeal carcinomas. There is great hope that the vaccine will reduce the prevalence of oropharyngeal carcinomas in Australia, Canada, and the USA.

The rate of tonsillectomies has significantly decreased in recent decades, by up to 50%. A 2015 study demonstrated that tonsillectomy, previously mainly performed in childhood, is a preventive factor for tonsillar and oropharyngeal carcinomas in individuals under 60 years old, but increases the incidence of base of tongue carcinomas in those over 60. Due to significant heterogeneity among studies, firm conclusions cannot be drawn, and it is hoped that randomized trials on the immune-oncological role of tonsillectomy will be conducted.

Therapeutic effects of biological therapy for head and neck carcinomas, as well as other regions, are improving, with significant efforts being made to transform carcinomas into chronic and curable diseases. It is hoped that large, future studies will soon demonstrate this.

CONCLUSION

Approaching a patient with tonsillar carcinoma must be multidisciplinary. The most crucial aspect is to diagnose the condition in its early stages when the tumor is small, without local or distant metastases. A 62-year-old patient presents with throat burning, pain deep in the left ear, and difficulty swallowing. The diagnostic process is efficiently conducted. Examination reveals an enlarged left tonsillar bed with grayish deposits extending towards the soft palate. Biopsy confirms squamous cell infiltrating carcinoma of the tonsil. HPV typing confirms the presence of human papillomavirus type 16. CT scan of the head and neck shows affected lymph nodes. The oncology team initiates two courses of chemotherapy, resulting in partial improvement in the patient's overall condition, followed by bioradiotherapy. After bioradiotherapy, the patient experiences pain relief, denies swallowing difficulties, and the tumor mass is significantly reduced, barely visible. The patient continues with follow-up appointments and treatment as per the oncology team's recommendation.

In Serbia, a nonavalent HPV vaccine is available, proven to be effective against cervical cancer and oropharyngeal carcinoma. However, due to false and unverified information about vaccines in general disseminated in public media and social networks, vaccination coverage remains inadequate. Therefore, in the 21st century, the scientific community still faces a challenging and laborious process of educating the population for the benefit of humanity as a whole.

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CASE REPORT OF SUBACUTE THYROIDITIS FOLLOWING SARS-COV-2 INFECTION

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Sažetak: INTRODUCTION: SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) is a single-stranded RNA virus with an envelope that causes COVID-19 infection. The disease can be accompanied by mild cold-like symptoms, but it can also have potentially severe complications, some of which can be fatal. According to recent data, the virus can also be one of the causes of subacute thyroiditis (SAT). According to available data, the period of symptom manifestation of thyroiditis (SAT) after recovering from Covid-19 infection is 29 days. The disease may pass through stages of hyperthyroidism, hypothyroidism, and then return to a euthyroid state. In 10% of cases, permanent hypothyroidism may occur, requiring levothyroxine therapy. Treatment is usually symptomatic with high doses of aspirin at 600mg 3-4 times a day or nonsteroidal anti-inflammatory drugs. Corticosteroid therapy is introduced in more severe cases. CASE REPORT: A 69-year-old female patient presented to the Covid outpatient clinic complaining of weakness, fatigue, diarrhea, difficulty swallowing, and low-grade fever around 37.5°C. In her personal history, the patient reported being treated for Hashimoto's multinodular goiter with levothyroxine replacement therapy. She tested negative for the SARS-CoV-2 virus with a rapid antigen test and subsequently had a positive PCR test of the nasopharyngeal swab. An antibiotic, cefixime 400mg once daily, was initiated along with other therapy. After three days, her symptoms worsened. She experienced intense pain in the front of the neck, difficulty swallowing, a feeling of a lump in the throat, dry cough, and a body temperature reaching 38.5°C in the evening and at night. On physical examination, a slightly swollen neck was observed, and deeper palpation revealed the thyroid gland as hard and tender. The antibiotic was changed to azithromycin 500mg and ibuprofen 800mg daily. After 15 days, the patient achieved complete clinical recovery, indicating resolution of viral thyroiditis. Hormonal status remained normal throughout, and she was well substituted with levothyroxine. CONCLUSION: General practitioners should be aware of this complication of COVID-19 disease and analyze thyroid hormone levels in their clinics. Due to the population's exposure to the SARS-CoV-2 virus, subacute thyroiditis should be considered in general practice clinics. Suspicion should arise if fever persists, neck pain worsens, and inflammatory markers persist. Laboratory tests, thyroid hormone analysis, and consultation with an endocrinologist or nuclear medicine specialist should be sought as soon as possible.
Keywords: SARS-CoV-2, subacute thyroiditis, general practitioner

INTRODUCTION

Subacute thyroiditis (SAT) is likely a benign viral disease characterized by intense general and local symptoms, transient hyperthyroidism and hypothyroidism, followed by complete recovery of the thyroid gland. Subacute thyroiditis is 40 times less common than Hashimoto's thyroiditis. It most commonly affects women between the ages of 20 and 50, and is 3-6 times less common in men. The most common causative agents are influenza viruses, coxsackievirus, hepatitis E, adenovirus, parvovirus B19, dengue virus, cytomegalovirus, HIV, rubella, mumps, as well as Q fever and malaria. According to recent reports, it is necessary to add the SARS-CoV-2 virus to this list.

Previous data show that the period of symptom manifestation of thyroiditis (SAT) after recovering from Covid-19 infection is 29 days. The SARS-CoV-2 virus is the causative agent of coronavirus disease. The disease can manifest with mild cold-like symptoms, but also with severe acute respiratory distress syndrome with numerous complications, which are often fatal. The SARS-CoV-2 virus belongs to the genus of beta-coronaviruses, single-stranded RNA viruses. The envelope plays a crucial role in the virus's pathogenicity. Viral infection can induce an excessive immune reaction in the host, known as "cytokine storm," which results in extensive tissue damage. The virus enters the cell via angiotensin-

converting enzyme 2 (ACE-2). Rotondi and colleagues discovered that ACE-2 receptors, which have affinity for RNA, are expressed most in the thyroid gland, small intestine, heart, kidneys, suggesting that the virus can infect tissues other than the lungs. It is believed that the SARS-CoV-2 virus directly destructs the target cell or acts indirectly through the action of the "cytokine storm." According to published studies, common clinical symptoms of subacute thyroiditis (SAT) after Covid-19 infection are palpitations, fatigue, fever, and neck pain radiating to the jaw.

CASE REPORT

A 69-year-old female patient presented to the Covid clinic due to weakness, fatigue, diarrhea, and a low-grade fever of around 37.5°C. In her medical history, the patient reported treatment for hypertension (Prilenap H® 10mg+25mg once daily along with Bisprol® 5mg once daily), Hashimoto's multinodular goiter (Euthyrox® 50mcg for 3 days, then 25mcg for 4 days), and type 2B hyperlipidemia. She tested negative for the SARS-CoV-2 virus with a rapid antigen test initially, but a subsequent PCR test of the nasopharyngeal swab was positive. Symptomatic therapy was initiated with vitamin D, vitamin C, zinc, analgesics, and antipyretics. At the scheduled follow-up after seven days, the patient reported no improvement, with difficulty swallowing and a low-grade fever persisting. Cefixime 400mg once daily was added to her therapy regimen. Three days later, her symptoms worsened, with severe neck pain, difficulty swallowing, sensation of a lump in the throat, dry cough, and fever peaking at 38.5°C in the evenings and nights. On physical examination, she had a visibly swollen neck, and the thyroid gland was palpable during swallowing, feeling firm and tender on deeper palpation. Both sternocleidomastoid muscles were tender and very firm. Blood pressure was 124/83 mmHg with a pulse rate of 72 beats per minute. Oxygen saturation remained around 98%-99% throughout. An ECG was unremarkable, and chest auscultation revealed no abnormalities. Laboratory tests showed elevated inflammatory markers (CRP 113.1 mg/l; ESR 115mm/h), and a complete blood count indicated lymphopenia, monocytosis, and signs of anemia (HGB 104g/l, RBC 3.32, MCV 98.5, MCH 31.3, MCHC 318 g/l) with platelets within normal limits. Thyroid hormone levels after 14 days from the onset of illness were within reference ranges (TSH 1.35μIU/ml, FT3 3.37pmol/l, FT4 12.5pmol/l). Chest X-ray was normal. The patient was referred to an endocrinologist, where thyroid ultrasonography revealed significantly enlarged thyroid lobes, with a thickened isthmus measuring 10.2 mm. The lobes were predominantly hypoechoic and vascularized. The right lobe measured 40.4mm x 21.1mm x 16.2 mm, with a large hypoechoic nodule approximately 21.4mm x 11.9mm in the midsection. The left lobe measured 40.8mm x 19.6mm x 26.4 mm, showing clear hypoechoic areas suggestive of nodules. Inflammatory lymph nodes were visible around both neck muscles. The neck muscles appeared structurally altered and elevated due to enlarged lobes from the inflammatory viral process. The patient's therapy was adjusted, with azithromycin 500mg added to the existing cefixime regimen once daily, along with a probiotic, zinc, and selenium supplements before lunch, Vigantol® (vitamin D) drops (10 drops) after meals, and ibuprofen 800mg daily. After 15 days of this therapy, the patient's pain decreased, and she discontinued ibuprofen. On physical examination, the thyroid gland was palpable but non-tender. Skin moisture was normal, and tremor was very discreet, with a pulse rate of 71/min and blood pressure of 134/84mmHg. After one month from the onset of illness, laboratory tests showed a decrease in inflammatory parameters (CRP 6.5), while mild anemia persisted in the blood count (RBC 3.85x1012/l, HGB 109 g/l). Other findings were within reference values. A follow-up ultrasound was not performed, and the patient's hormonal status remained normal throughout. She was clinically well-substituted with levothyroxine, leading to recovery from viral thyroiditis.

DISCUSSION AND CONCLUSION

This case illustrates that any viral upper respiratory tract infection can be complicated by subacute thyroiditis (SAT). Several cases of SAT following Covid infection have been reported worldwide. SAT may manifest as described in our case, with fever, general symptoms of illness, difficulty swallowing, neck pain radiating to the jaw, and transient vocal cord paralysis, nervousness, tachycardia, increased sweating, and tremor. Symptoms may peak on the third and fourth days of illness, then gradually diminish and disappear within one week. However, in most cases, symptoms develop gradually over one to two weeks, with fluctuations in severity and prevalence over the next 3-6 weeks. Some patients may experience worsening symptoms for several months before complete recovery. Recovery from subacute

thyroiditis may be accompanied by transient hypothyroidism in a quarter of patients, with less than 10% experiencing permanent hypothyroidism.

A pathognomonic sign for SAT in the acute phase is transient elevation of FT3 and FT4 due to thyroid cell destruction, suppressed TSH, and increased erythrocyte sedimentation rate and other serum inflammatory markers (CRP, fibrinogen). Therefore, serum thyroglobulin concentration is elevated, while anti-thyroglobulin and anti-TPO antibodies are usually negative. Thyroid scintigraphy will show reduced radioactive iodine fixation <5% and technetium pertechnetate. Liver enzyme elevation may be present in serum in half of the patients and may persist for several months. Some patients may not require any medication therapy. Sometimes, aspirin at a dose of 600mg every 4-6 hours or nonsteroidal anti-inflammatory drugs (NSAIDs) may be necessary to reduce pain. In cases of severe symptoms, corticosteroid therapy is initiated with prednisone at a daily dose of 40mg, gradually reduced by 5mg every 7 days over 6 weeks. In the event of permanent hypothyroidism following an episode of SAT, levothyroxine replacement therapy is indicated.

Due to the prevalence of SARS-CoV-2 infection in the population, general practitioners should consider subacute thyroiditis as a complication of the disease. Suspect it if fever persists, neck pain intensifies, and inflammatory markers persist. Conduct laboratory tests, analyze thyroid hormone levels, and seek consultation with an endocrinologist or nuclear medicine specialist.

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THE SIGNIFICANCE OF DISTINGUISHING UNIPOLAR DEPRESSION AND DEPRESSIVE EPISODES IN BIPOLAR AFFECTIVE DISORDER - CASE REPORT

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Summary: Introduction. Mood disorders are the most prevalent mental disorders, divided into unipolar depression and bipolar affective disorders. Bipolar affective disorders manifest as mania, hypomania, mixed episodes, and depressive episodes, with depressive episodes occurring much more frequently. Hypomanic/ manic episodes often remain unrecognized by patients, their families, and even physicians due to insufficiently available heteroanamnestic data. It is crucial to raise awareness of the importance of thorough history taking, as therapy differs significantly between unipolar depression and bipolar affective disorder. The aim of this study is to emphasize the importance of distinguishing unipolar depression from depressive episodes in bipolar affective disorder and establishing an accurate diagnosis. Case presentation: We present a case of a 73-year-old female patient who has been undergoing outpatient psychiatric treatment for the past twenty years, diagnosed with recurrent depression. During her last hospitalization, she presented to the clinic accompanied by her children, who reported significant changes in her emotions and behavior, accompanied by paranoid-interpretative delusional ideas. Overall, this description corresponds to a manic psychotic episode within the framework of bipolar affective disorder. Further heteroanamnestic data revealed the patient's history of regularly seeking medical help when experiencing low mood and impaired functioning on a daily basis. However, episodes of hypomania, characterized by elevated mood, logorrhea, increased activity, decreased need for sleep, and the absence of accompanying fatigue, were perceived simply as her good mood by both her family members and herself. Consequently, the patient was perceived as having a recurrent depressive disorder, leading to therapy with antidepressants only, while in fact, the lack of data led to the oversight of bipolar affective disorder. Conclusion: From the presented case, we conclude that timely distinction and accurate diagnosis of these two disorders are crucial for prescribing appropriate therapy and preventing the occurrence of "switching" into mania.

Keywords: bipolar affective disorder, unipolar depression, recognition of hypomania, psychopharmacotherapy

INTRODUCTION

The most prevalent mental disorders are mood disorders. They often occur in association with other illnesses, which complicates the accurate diagnosis. Normal mood, such as feelings of happiness, sadness, or melancholy, differs from pathological mood by its duration, intensity, disturbance of sleep, appetite, altered perception of reality, and frequent suicidal attempts.

Mood disorders are divided into depressive disorders, which manifest solely with symptoms of depressive syndrome—unipolar depression, and bipolar disorders, which occur within the framework of bipolar affective disorder. Depressive disorders can occur at any age and are known to be twice as common in women. Approximately 350 million people worldwide suffer from depression.

Bipolar affective disorders are more common in younger age groups and occur equally in both men and women. Bipolar affective disorder is a progressive disease with a significant burden and complicated consequences, with depressive symptoms much more common than manic symptoms and responsible for most of the time during which patients experience symptoms of their illness.

Timely diagnosis and early initiation of appropriate treatment lead to a good prognosis. Patients with depressive disorders often complain of nonspecific somatic symptoms such as general weakness, body aches, and insomnia. They also mention feelings of emotional emptiness, sadness, tearfulness, and hypersensitivity. Thoughts of suicide are common because depressed individuals see no other way out of their condition.

It is essential to determine whether the patient has recurrent depressive disorder or a depressive episode within the framework of bipolar affective disorder. Typical symptoms of a depressive episode include depressed mood, loss of interest, and decreased energy. Other symptoms include decreased concentration and attention, reduced self-confidence, a pessimistic outlook on the future, disrupted sleep, decreased appetite, and suicidal thoughts. A depressive episode can be mild, moderately severe, or severe.

Depressive disorders must be distinguished from bipolar affective disorder, anxiety disorders, adjustment disorders, disorders due to harmful substance use, schizoaffective disorder depressive type, dementia, and personality disorders. Additionally, depressive syndrome should be differentiated from endocrine disorders, autoimmune diseases, neurological, and malignant diseases.

Bipolar disorders manifest as mania, hypomania, mixed episodes, and depressive episodes. What is characteristic of mood disorders is their episodic nature, meaning that after one depressive, manic, or hypomanic episode, a period of remission and recovery ensues, followed by the next episode. The risk of suicide and attempts is particularly high in the days following discharge from psychiatric hospitalization, associated with the delay or lack of appropriate care thereafter.

Distinguishing Unipolar from Bipolar Disorder

The most important thing is to recognize the depressive episode and determine whether it is recurrent depressive disorder or a depressive episode within bipolar disorder. The term unipolar depression is used in the literature to describe a condition where a person is solely depressed, without periods of mania or hypomania. Proper diagnosis (distinguishing between bipolar and unipolar disorder) is crucial for assessing the therapy needed for treatment.

The main challenge in diagnosing whether depression belongs to bipolar or unipolar disorder lies in the rare episodes of mania and hypomania in bipolar affective disorder compared to longer and more frequent periods of depression. In most patients diagnosed with bipolar affective disorder, the illness started with a depressive episode rather than mania. The aim of this study is to highlight the importance of distinguishing unipolar depression from a depressive episode in bipolar affective disorder and establishing an appropriate diagnosis.

CASE REPORT

The patient is a 73-year-old female, widowed, with two children she lives with, and holds a middle-level education as an accountant. She has been unemployed for thirty years since relocating from Croatia to Novi Sad as a refugee in 1991. She has not experienced any significant somatic illnesses aside from controlled hypertension with antihypertensive medication. There is no relevant psychiatric heredity data available. She does not consume alcohol or psychoactive substances. The patient has been receiving outpatient psychiatric treatment for the past twenty years, diagnosed with recurrent depression.

Currently, she presents at the clinic accompanied by her son and daughter, reporting significant behavioral changes. She exhibited accelerated speech, disturbed sleep-wake rhythm, spending sprees, and making unrealistic plans to earn additional money. Primarily, she displayed elevated mood, occasional irritability, and hostility towards family members, accompanied by paranoid delusions regarding her children stealing money from her. These symptoms persisted for approximately two months before culminating in hospitalization. Initially, the symptoms manifested as reduced sleep and increased activity without fatigue, along with persistent heightened mood and impulsive spending. Subsequently, paranoid ideation emerged towards her children, accusing them of stealing her savings left after her husband's death. Even after the money was returned, her symptoms worsened, demanding her daughter to evict her tenants because they were "taking her money." She also believed her family wanted to "institutionalize her" and exploit her finances during her hospital stay. The patient lacked insight into her condition. After three weeks of appropriate psychopharmacological therapy, including antipsychotics, mood stabilizers, and anxiolytics, her symptoms subsided, leading to behavioral and emotional stabilization.

Further details obtained from heteroanamnestic data revealed the patient's previous functioning. She regularly attended outpatient visits whenever she felt a lowered mood, experiencing difficulties in daily functioning, accompanied by fatigue, malaise, moodiness, and reluctance to perform daily tasks. She complained of sleep disturbances, decreased appetite, and forgetfulness. Loss of self-confidence with withdrawal tendencies was also common. Following the administration of psychopharmacotherapy and relief of depressive symptoms, the patient exhibited periods of elevated mood, sometimes excessive

cheerfulness, functioning with minimal sleep, and excessive movement. She became talkative, accelerated, and difficult to restrain, attributes attributed to her personality. Additionally, she always attended psychiatric appointments alone, refusing accompaniment, and since she did not perceive her elevated mood and acceleration as problematic but rather as excellent functioning, likely resulting in an inadequate description of her functioning between depressive episodes.

Consequently, the patient was initially considered to have recurrent depressive disorder, resulting in the prescription of antidepressant therapy alone. However, due to the lack of auto and heteroanamnestic data, the possibility of bipolar affective disorder was overlooked, specifically a manic psychotic episode within bipolar affective disorder, as described above..

DISCUSSION

As we can see from the presented case, this patient has been treated for twenty years under the diagnosis of unipolar depression, which, based on the current clinical picture and additional detailed heteroanamnestic data, leads us to the conclusion of previously unrecognized episodes of hypomania/mania. The clinical presentation of depressive episodes manifested through feelings of emptiness, sadness, tearfulness, and hypersensitivity. She responded slowly and quietly to questions, accompanied by limited facial expressions.

Typical symptoms of unipolar depression are classified into psychological, behavioral, and somatovegetative categories. Each diagnosis is primarily based on historical data, observed psychopathological phenomena, and disorder course. In this case, it was necessary to determine whether it was a recurrent depressive disorder or a depressive episode within bipolar affective disorder. Typical symptoms of a depressive episode include depressed mood, loss of interest, and decreased energy. Other symptoms include reduced self-confidence, feelings of guilt, a pessimistic view of the future, and suicidal ideation.

The primary symptoms of manic syndrome include emotional disturbances (euphoric or irritable mood), psychomotor symptoms and signs (hyperactivity), and increased self-confidence. In hypomania, symptoms are similar to mania but milder and shorter in duration. Delusions and hallucinations are absent in hypomanic states. Hypomanic episodes occur more frequently than diagnosed.

For these patients, obtaining information about previous hypomanic episodes during adolescence is essential (which was absent in the aforementioned patient) because, in that case, the diagnosis would not be recurrent depression but bipolar affective disorder. The treatment concept differs significantly in such cases. Treatment for unipolar depression involves a combination of antidepressant pharmacotherapy and psychotherapy, while bipolar affective disorder treatment involves a combination of several medications as it is divided into several phases: treatment of acute manic/hypomanic episodes, treatment of depressive episodes, maintenance phase, and prophylactic phase.

Medication treatment for acute mania involves the use of mood stabilizers and antipsychotics. Benzodiazepines are sometimes necessary in the initial days. The treatment of depressive episodes in bipolar disorder includes mood stabilizers and antidepressants. Antidepressants should not be used as monotherapy due to the risk of switching to mania. Moreover, prescribing antidepressants in bipolar disorder cases is often associated with mood destabilization, especially during maintenance therapy. Unfortunately, effective pharmacological treatments for bipolar affective disorders are not universally available, especially in countries with low to middle levels of healthcare.

Regarding mood stabilizers, lithium treatment requires careful monitoring of patients compared to most other mood stabilizing drugs. This facilitates the identification of new symptoms associated with suicidal behavior, including thoughts and suicidal ideation, early agitation, dysphoric mood, anger, and disrupted circadian rhythms. Antidepressants may not produce the desired effect or may even increase agitation and suicide risk. In contrast, with the use of mood stabilizers, especially long-term maintenance of lithium salts, greater effectiveness is expected in comprehensive treatment aimed at suicide prevention.

One treatment option is electroconvulsive therapy, which is applied in treatment-resistant or psychotic depressive episodes, severe psychotic or treatment-resistant mania. It is also the therapy of choice for bipolar affective disorder during pregnancy.

For such patients, it is crucial to differentiate between unipolar depression and depressive episodes of bipolar affective disorder. Incorrectly diagnosing unipolar depression in patients with bipolar depression has many harmful consequences, including the use of inadequate psychopharmacotherapy, the

possibility of switching to mania, and increased suicidal risk. Bipolar and unipolar disorders are also associated with increased impulsivity, although it is more common in bipolar disorders. Approximately one million people die by suicide each year. It is essential to effectively treat depression, as many people suffer from it, and only half achieve complete remission with treatments such as pharmacotherapy and psychotherapy within two years of starting treatment. Some patients may experience reduced effectiveness of antidepressant therapy because a significant number of patients do not adhere to prescribed treatment. There is also no evidence that adjunctive antidepressants improve response rates or depressive symptoms in acute bipolar depression. Depression in patients with bipolar affective disorder is a significant clinical challenge as it is associated with higher morbidity, mortality, and a high risk of suicide.

In bipolar depression, the risks of diabetes mellitus, cardiovascular disorders, and metabolic syndrome are several times higher than those in the general population or patients with other psychiatric disorders.

CONCLUSION

Depression can occur as a symptom within various psychiatric disorders or as an independent entity. Symptoms of depression encompass combinations of psychological, psychomotor, and somatic symptoms that manifest with varying intensity. Depression affects all aspects of life. Unipolar and bipolar depressive episodes entail differences in etiology, phenomenology, as well as in the course and treatment process. Bipolar depression is more strongly associated with mood lability, psychomotor retardation, and hypersomnia. In these patients, symptoms manifest early, there is a higher frequency of depressive episodes, and the presence of bipolar disorder in the family is more common. Diagnosing bipolar disorder is nonspecific and lengthy, often being diagnosed and treated as unipolar depression. One reason for this is the failure to recognize hypomanic or manic symptoms by the patient or family members who attribute them to good mood or the patient's personality. It may take more than ten years to establish the correct diagnosis. For such patients, it is crucial to identify the presence of manic or hypomanic episodes. Depression in patients with bipolar affective disorder is a significant clinical challenge because in such patients, depression is associated with more frequent morbidities, as well as mortality and a high risk of suicide. Above all, it is essential to consider the specificities of each patient to achieve the full effect of treatment.

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DOCTOR VOJISLAV SUBOTIĆ – LIFE AND WORK OF THE FOUNDER OF SERBIAN SURGERY

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Summary: Doctor Vojislav Subotić was born in Novi Sad in 1859. He was a leading surgeon in Serbia in the late 19th and early 20th centuries. He is known for inventing a splint for immobilizing the fractured femur and introducing innovations in ligating blood vessels. Surgeon Subotić successfully performed surgeries at a time when modern medical technological advances such as endotracheal anesthesia, parenteral rehydration, blood transfusion, and antibiotics did not exist. His feats were heroic as he managed to save patients' lives and treat various diseases and injuries using limited resources and knowledge available at that time. His courage, skill, and dedication to medicine made him an exceptional surgeon whose operations often meant life-saving interventions. He published a large number of papers in the fields of abdominal surgery, urology, and orthopedics.
Keywords: Vojislav Subotić, surgery, ligating blood vessels, splints for femur immobilization

INTRODUCTION

The goal of this paper is to explore the life, family, education, career, and contributions to medicine of the renowned surgeon Vojislav Subotić. Born in Novi Sad, Subotić was a leading surgeon in Serbia at the end of the 19th and beginning of the 20th century. He lived for 64 years, studied in Vienna and Paris, and achieved significant medical innovations such as inventing a splint for immobilizing fractured femurs and introducing innovations in ligating blood vessels. He was one of the founders of the Medical Faculty in Belgrade and the head of the surgical department at the General State Hospital in Belgrade. His name is associated with the development of operative medicine in Serbia, earning him the title of the father of practical surgery in the country. Additionally, he served as a volunteer physician in several wars, including the Serbo-Turkish War and World War I. The legacy of the Subotić family, donated to the Museum of the City of Belgrade in 1975, includes 56 items, as well as family albums and documents, mostly related to Dr. Vojislav Subotić, his elder brother General Dejan, and their father, the writer Dr. Jovan Subotić.

The family of Vojislav Subotić had a significant impact on Serbian history. His mother, Savka Polit, came from a Greek (Vlach) family that migrated to Novi Sad from Constantinople. Savka was actively involved in the educational sector and fought for women's rights. She founded various educational institutions and women's organizations in different cities, such as the "Udruženje gospođa" in Zagreb, the "Ženska zadruga" in Novi Sad, and the "Viša ženska škola" in Pančevo and Novi Sad. She was also one of the founders and the first president of the "Kolo srpskih sestara," where she emphasized the importance of educating children for the future of the nation. Savka was known for her dedication and enthusiasm in promoting Serbian women's folk art and crafts at domestic and international exhibitions. She particularly praised the Pirot carpets, calling them "poetry of women's hands in line with Serbian folk songs." Savka was recognized as the "mother of her people" by the poet Aleksa Šantić. Her contribution to the struggle for women's rights and the promotion of Serbian culture was significant and left a mark in history.

Vojislav Subotić's father, Jovan Subotić, was also a notable figure in Serbian history. He held a doctorate in law and philosophy and worked as a lawyer, poet, and playwright. Jovan Subotić was the editor of the Letopis Matice srpske, a leader of the Serbian people in Vojvodina, the organizer of the Assembly of Serbs in Pest in 1848, a participant in the May Assembly in Sremski Karlovci, the founder of the Karlovci Patriarchate, and the president of the Matica srpska in Novi Sad. He was also involved in

editing the newspaper "Narod" and overseeing the financing of the Theater. He worked on connecting Serbian and Croatian political centers such as Novi Sad, Zagreb, Osijek, and Belgrade.

Jovan and Savka Subotić had six children: Vida, Verica, Branislav, Ozren, Dejan, and Vojislav. Vida and Ozren died at a young age from smallpox. Branislav became a diplomat, while Dejan served in the Russian army. He joined the Serbian army in the First Serbo-Turkish War in 1876/7. Afterward, he became an honorary Serbian consul general in Crimea and participated in both Balkan Wars and World War I. He died in 1920 and was buried in the family tomb at the Zemun cemetery.

BIOGRAPHY OF VOJISLAV SUBOTIĆ

Vojislav Subotić was born in Novi Sad. He received his education in Zagreb and Novi Sad, where he completed his secondary education. He studied medicine in Vienna and Paris. During his education, he worked as a demonstrator under Professor Karl Rokitansky in Vienna. Subotić completed his medical studies in 1881, at the age of only 22. He pursued his specialization under Professor Eduard Albert in Vienna, who was the head of the First University Surgical Clinic.

Picture 1. Doctor Vojislav Subotic

Albert was known for introducing antisepsis, new surgical procedures in surgery such as junostomy and nephrectomy, as well as for performing the first nerve transplant and many other achievements. Subotić also studied under Karel Maydl, who introduced colostomy in abdominal surgery. After acquiring knowledge from these great surgeons, Subotić was appointed as a physician and primary care physician in Zemun, where he founded the Surgical Department and became the head of the hospital. There, he performed complex surgeries and published papers in prestigious scientific journals in Austria-Hungary and Germany. He assumed the position of head of the Surgical Department at the General State Hospital in Belgrade at the beginning of 1889. He immediately began significant work on the development and advancement of Serbian surgery. Some publications add the word "Elder" to distinguish him from another Vojislav, Vojislav M. Subotić, the first Serbian neuropsychiatrist. Both gentlemen contributed to Serbian medicine in different ways, leaving a significant impact on society. The surgeries performed by Dr. Subotić successfully, at a time when modern medical technological advancements such as endotracheal anesthesia, parenteral rehydration, blood transfusion, and antibiotics did not exist, were truly heroic endeavors. Today, many of the complex surgeries he successfully performed can only be performed by a small number of surgeons in our country, demonstrating how great and skilled he was in his profession.

In Serbia today, almost every branch of surgery can be associated with the work of Dr. Subotić, who performed surgeries on all organs. Evidence of this can be found in available literature. Unlike other nations who proudly record the beginnings of their surgery, due to insufficient knowledge of the history of Serbian surgery, even distinguished surgery professors date the beginnings of "their" branches of surgery decades after Subotić and his colleagues routinely performed them. Dr. Vojislav Subotić, a surgeon of great reputation, was known for his modesty. He always operated with closed doors, restricting access only to physicians, avoiding any advertising that he considered inappropriate for a serious physician. Dr. Mihailo Petrović praised his stance on advertising. Today, such behavior could serve as an example for the majority. Dr. Subotić made sketches for projects that a design firm in Budapest used to build Surgical Pavilions on West Vračar in 1907. Those pavilions were among the most modern in Europe at the time. They were used until the 1970s when they were demolished. Subotić edited a compendium entitled "The First Yugoslav Meeting for Operative Medicine" in 1912. The compendium was printed by "Nova štamparija" of Save Radenković and his brother and comprised 538 pages of text, including all papers and discussions in full, as well as 108 images and one color table. Additionally, the Second Yugoslav Meeting for Operative Medicine was held on September 5th and 6th, 1921, organized by Miroslav Čačković, a professor at the Medical Faculty in Zagreb. Subotić was elected president of the Serbian Medical Society five times in a five-year period, described as a "period of scientific momentum" by Dr. Bukić Pijade.

Dr. Subotić was an exceptionally important Serbian patriot who participated in multiple wars and provided aid to the wounded. As a surgeon and physician, he was active in wars against Turkey and Bulgaria, as well as in World War I. He organized meetings with surgeons from different countries to analyze and share their wartime experiences in treating war injuries. In this way, he contributed to the exchange of knowledge and the advancement of surgical practice in caring for the wounded. In 1913, he initiated one of the first clinical programs that emphasized reconstruction, instead of ligating, injured arteries and veins. Surgeons from around the world visited his clinic to assist in this program, and at a presentation in London (1913), there were discussions about the experience in managing 77 injured major blood vessels, resulting in 32 vascular reconstructions - 19 arteriorrhaphies and 13 venorrhaphies. Ironically, it took almost 40 years before similar successful efforts were achieved during the latter part of the Korean War (1952 to 1953). Dr. Subotić was a surgeon who in World War I was destined to surrender to the Bulgarian occupiers, but instead decided to retreat through Albania. After the war, he served as a delegate of the Kingdom of Serbia in the Interallied Medical Commission in London and Paris. Upon returning to Thessaloniki, he decided to decline the offered position of surgeon in the rear hospital and worked in the legendary Surgical Field Hospital in Dragoman, founded by Duke Stepa Stepanović. Upon returning to Belgrade, he began the restoration of the Surgical Department of the General State Hospital, which was devastated and looted.

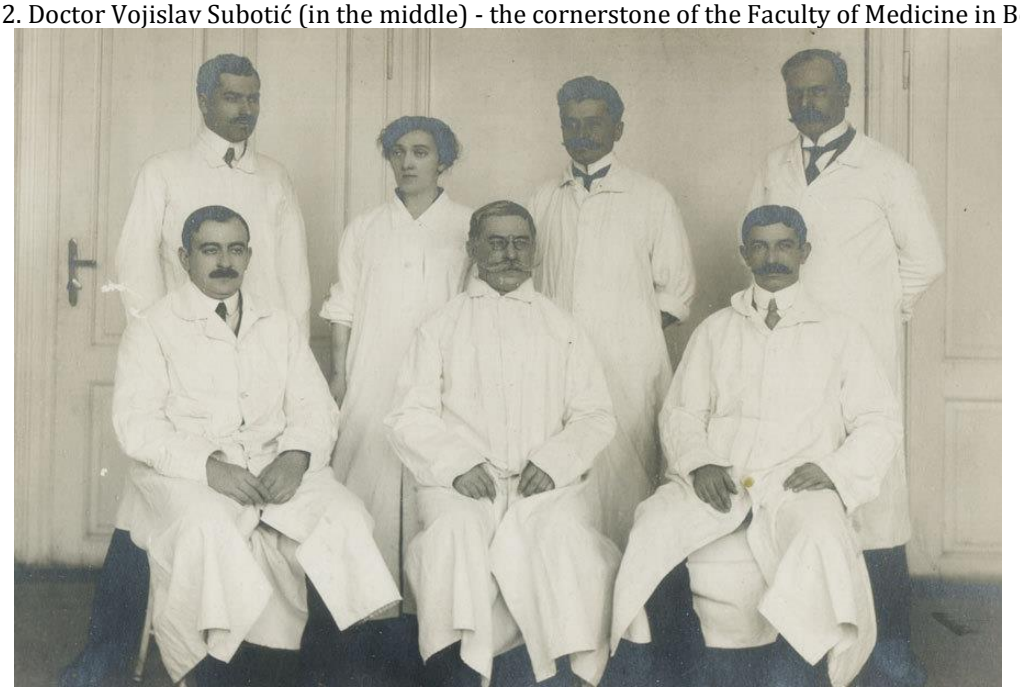
Vojislav Subotić, a member of numerous prestigious foreign professional societies, passed away on December 17, 1923, at the table where he was supposed to give a lecture. Instead, his successor at the Department, Associate Professor Milivoje Kostić, delivered the lecture. Subotić was the recipient of numerous domestic and foreign decorations and honors, and he began publishing his professional works in 1886. He described various medical cases, such as actinomycosis and operative cases of pancreatic cysts. Additionally, in 1898, he reviewed the War Sanitary Service by Colonel Dr. Mihailo Mika Marković, providing useful advice and suggestions. At the First Congress of Serbian Physicians and Naturalists, held from September 5th to 7th, 1904, he delivered a lecture entitled "Contribution to the Pathology of Appendicitis." Moreover, he published several papers on splenic cysts and other spleen diseases, described injury to the hepatic duct during abdominal trauma, and wrote about ileus, ulcer, acute and chronic pancreatitis, intestinal tuberculosis, hernias, and a range of other surgical diseases, as well as immobilization of fractures of the long bones of the legs. He also wrote about the epidemic of typhoid fever in Serbia and other important topics. His most significant work, "Army Experience of Traumatic Aneurysms," was published in 1913 in the journal "The Lancet."

It is not possible to compile a complete bibliography of Subotić, but the available list includes at least 38 papers, mostly published in leading foreign journals, at least 31 reviews of books or articles from foreign literature, several hundred reviews and discussions recorded in the minutes of meetings of the Serbian Medical Society on operated patients. His discussions on non-surgical diseases at these meetings demonstrate his broad knowledge of medicine as a whole. Subotić, raised in the orderly state of Austria-Hungary, regularly wrote Reports on the work of the Surgical Department of the General State Hospital in

Belgrade. These reports were sent to the Sanitary Department of the Ministry of Internal Affairs, and from 1892 were almost regularly printed in the "Serbian Archive for Comprehensive Medicine." He published a total of 39 factual reports, thanks to which it is possible to reconstruct the work and development of surgery at the Surgical Department of the General State Hospital in Belgrade with almost complete certainty. Unfortunately, his successor did not publish any such reports after his death, which greatly complicates the study of the development of interwar surgery in Serbia.

After all, the question arises: What have the post-war generations done to honor this great son of the Serbian people? The correct answer would be: "Enough, but not as much as it should." The street where the Dean's Office of the Medical Faculty is located was named after Vojislav Subotić. The former Second Surgical Clinic under the leadership of Professor Vojislav K. Stojanović placed a bust of Subotić in the clinic's amphitheater, the work of academician Nikola (Koka) Janković. Professor Zoran Gerzić wrote a contribution about Subotić in the first book of the edition of the Serbian Academy of Sciences and Arts "Life and Work of Serbian Scientists" in 1996. The author of these lines published "Memory" about Subotić in the "Serbian Archive for Comprehensive Medicine" in 2003, on the occasion of the 80th anniversary of Professor Subotić's death. The Surgical Section of the Serbian Medical Society restored the Subotić family tomb at the Zemun cemetery on the 80th anniversary of Professor Subotić's death, placed a memorial plaque and a copy of the bust in the lobby of the Serbian Medical Society building, and placed his photograph and a picture of the house where he lived in Zemun in the meeting room of the Serbian Medical Society. A new portrait of Professor Subotić, made in Vienna, was placed in the ceremonial hall of the Dean's Office of the Medical Faculty, with his biography in the background. Additionally, lectures about him were held, and the most comprehensive bibliography was compiled.

Picture 2. Doctor Vojislav Subotić (in the middle) - the cornerstone of the Faculty of Medicine in Belgrade



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The following is a SUMMARY (Abstract), up to 300 words is best. A summary cannot have footnotes, tables, images, or references. A summary of **the original papers** should include: Introduction (state the objective in the last sentence), **Material and methods, Results and Conclusions**. Write each of the segments listed at the beginning of the sentence in bold. Provide the most important results (numerical values) of the statistical analysis and the levelofsignificance. The conclusion must not be general, but must be directly linked to the results of the work. **For case reports, the summary** should have the following parts: **Introduction** (state the objective in the last sentence), **Case report, Conclusion**. For other types of papers the summary has no specific structure.

The summary must not contain any claims that are not contained in the text of the article. It must be written in such a way that even an educated nonexpert can understand the content of the article. After the summary, write 3 to 8 keywords. The words in the title should not be repeated and the keywords should be relevant or descriptive and in accordance with MESH rules (available at https://www.nlm.nih.gov/mesh).

The next part of all the papers is an **INTRODUCTION** (with a subtitle of the same name), which must be brief, with a brief overview of the literature on the problem in question, and with a clear statement of **the purpose of the article** in a separate paragraph at the end of the introduction.

MATERIALS AND METHODS (with the same subtitle) must contain sufficient information to enable other researchers to repeat similar research without further information. Patient names and medical history numbers should not be used nor other details to help identify patients. The names of the apparatuses, software and statistical methods used must be indicated.

Show the **results** (with the subtitle of the same name in BOLD) clearly and concisely. You should not display the same data both in tables and charts.

DISCUSSION (with the subtitle of the same name) should discuss the interpretation of the results, their meaning in comparison with other, similar research and in accordance with the hypotheses of the research. The results already written should not be repeated.

CONCLUSION (with the subtitle of the same name) should be given in a separate chapter.

Each table, chart, or illustration must be self-explanatory, i.e. even without reading the text in the manuscript. Above the table, chart, orimage,there should be a serial number and a title. Put the legend in a footnote below the table, chart, or image and explain any non-standard abbreviations there. Illustrations (images) should be sharp and contrasting, no larger than 1024x768 pixels. The number of images should be limited to the most necessary (generally no more than 4-5). If the image, table, or chart is downloaded from the Internet or another source, the source must be indicated.

REFERENCES

LITERATURE. At the end of the paper, write a list of cited literature, which should be as current as possible and most references should not be older than 5 years. References are numbered in the order they appear in the text. Mark the references in the text with an Arabic number in square brackets [...]. The literature lists the first 3 to 6 authors of the article cited, followed by "et al". Journal titles can only be abbreviated as in Index Medicus. The journal abbreviation can be found at: http://www.nlm.nih.gov/. If the abbreviation is not known, give the name of the journal as a whole. The literature is cited as follows:

Journal articles

Standard journal article:

Gao SR, McGarry M, Ferrier TL, Pallante B, Gasparrini B, Fletcher JR, et al. Effect of cell confluence on production of cloned mice using an inbred embryonic stem cell line. Biol Reprod. 2003; 68 (2): 595-603.

Organization as author:

WHO collaborative study team on the role of breastfeeding on the prevention of infant mortality. Effect of breastfeeding on infant and child mortality due to infectious diseases in less developed countries: a pooled analysis. Lancet. 2000; 355: 451–5.

No authors listed:
Coffe drinking and cancer of the pancreas [editorial]. BMJ. 1981; 283 628.

A volume with a supplement:
Magni F, Rossoni G, Berti F. BN-52021 protects guinea pig heart anaphylaxis. Pharmacol Res Commun. 1988; 20 Suppl 5: 75–8.

Books and other monographs

The author is a person (s):
Carlson BM. Human embryology and developmental biology. 3rd ed. St. Louis: Mosby; 2004.

Editor (s) as authors:
Brown AM, Stubbs DW, editors. Medical physiology. New York: Wiley; 1983.

Chapter in a book:
Blaxter PS, Farnsworth TP. Social health and class inequalities. In: Carter C, Peel JR, editors. Equalities and inequalities in health. 2nd ed. London: Academic Press; 1976. p. 165–78.

Meeting announcements: Harris AH, editor. Economics and Health: 1997: Proceedings of the 19th Australian Conference of Health Economists; 1997 Sep 13-14; Sydney, Australia. Kensington, N.S.W.: School of Health Services Management, University of New South Wales; 1998.

Conference Articles:
Anderson JC. Current status of chorion villus biopsy. In: Tudenhope D, Chenoweth J, editors. Proceedings of the 4th Congress of the Australian Perinatal Society; 1986: Brisbane, Queensland: Australian Perinatal Society; 1987. p. 190-6.

Dissertation:
Cairns RB. Infrared spectroscopy studies of solid oxygen. Dissertation. Berkley, California: University of California, 1965.

Electronic material

Article in aninternetmagazine:
Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs. 2002; 102 (6). Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm

Article published electronically before the printed version:
Yu WM, Hawley TS, Hawley RG, Qu CK. Immortalization of yolk sac-derived precursor cells. Blood. 2002-Nov-15; 100 (10): 3828-31. Epub 2002 Jul 5.

CD-ROM:
Anderson SC, Poulsen KB. Anderson's Electronic Atlas of Hematology [CD-ROM]. Philadelphia: Lippincott Williams & Wilkins; 2002.

Online monograph:
Foley KM, Gelband H, editors. Improving palliative care for cancer [monograph on the Internet]. Washington: National Academy Press; 2001 [cited 2002 Jul 9]. Available from: http://www.nap.edu/books/0309074029/html/.

Website:
Cancer-Pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources, Inc.; c2000-01 [updated 2002 May 16; cited 2002 Jul 9]. Available from: http://www.cancer-pain.org/.

Part of awebsite:
American Medical Association [homepage on the Internet]. Chicago: The Association; c1995-2002 [updated 2001 Aug 23; cited 2002 Aug 12]. AMA Office of Group Practice Liaison; [about 2screens]. Available from: http: //www.ama-assn.org/ama/pub/category/1736.html

NOTE. A paper that does not meet the requirements of this guide cannot be referred for review and will be returned to the authors for completion and correction. Adhering to the preparation instructions will significantly shorten the time of the entire process until the paper is published, which will positively affect the quality of the articles and the regularity of the publication of the journal.

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