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KNOWLEDGE AND ATTITUDES TOWARDS HUMAN PAPILLOMAVIRUS INFECTION AMONG THE FIRST YEAR STUDENTS OF THE FACULTY OF MEDICINE, UNIVERSITY OF NOVI SAD, SERBIA

ZNANJA I STAVOVI STUDENATA PRVE GODINE MEDICINSKOG FAKULTETA, UNIVERZITETA U NOVOM SADU, O INFEKCIJI HUMANIM PAPILOMA VIRUSOM

Ljiljana MLADENOVIĆ SEGEDI[1, 2], Aljoša MANDIĆ[1, 3], Miloš PANTELIĆ[1, 2], Artur BJELICA[1, 2] and Aleksandra VEJNOVIĆ[1, 2]

Summary

Introduction. Persistent infection with highly oncogenic human papillomavirus is associated with premalignant cervical lesions and cervical cancer, as well as cancers of the vulva and vagina. The aim of the study was to determine the level of knowledge and attitudes towards human papillomavirus infection, its risk factors, clinical manifestations and the use of contraception. **Material and Methods**. A total of 355 first-year students of the Faculty of Medicine, University of Novi Sad, filled in a non-standardized, self-administered questionnaire designed for the purpose of this study. The collected data included: sexual history of the respondents, the use and knowledge of contraception, human papillomavirus infection, and human papillomavirus vaccine. **Results**. About 89% of students have heard of human papillomavirus infection, while 75.5% of them knew that human papillomavirus infection is a sexually transmitted disease. Accurate knowledge about human papillomavirus infection was low, while female students showed higher levels of knowledge compared to the male (4.03 ± 3.07 versus 5.56 ±3.37; $p < 0.01$). Only 27.6% of students knew that young women are at a higher risk of human papillomavirus infection, 45.9% of the respondents knew that the risk of human papillomavirus infection depends on the number of sexual partners, 34.09% of them knew that a condom does not provide complete protection against human papillomavirus infection, 53.5% knew that human papillomavirus can cause cervical cancer, and only 19.7% of students knew that human papillomavirus infection can cause penile cancer. **Conclusion.** The first-year medical students showed a lack of knowledge about human papillomavirus infection and human papillomavirus-related diseases. General education and health education of young people is necessary primarily in secondary schools, in order to preserve the reproductive health and prevent human papillomavirus-related cancers.

Key words: Papillomavirus Infections; Uterine Cervical Neoplasms; Health Knowledge, Attitudes, Practice; Students, Medical; Risk Factors; Contraception; Sexual Behavior

Sažetak

Uvod. Perzistentna infekcija visoko-onkogenim humanim papiloma virusom povezana je s pojavom premalignih cervikalnih lezija i raka grlića materice, kao i raka vulve i vagine. Cilj nam je bio da utvrdimo nivo znanja i stavove studenata medicine o infekciji humanim papiloma virusom, o njenim faktorima rizika, kliničkim manifestacijama kao i upotrebi kontracepcije. **Materijal i metode.** 355 studenata prve godine Medicinskog fakulteta Univerziteta u Novom Sadu popunilo je nestandardizovani, za studiju konstruisan upitnik. Prikupljeni podaci uključivali su: anamnezu seksualnih odnosa ispitanika, znanje o kontracepciji i njena upotreba, znanje o infekciji humanim papiloma virusom i vakcini. **Rezultati.** Oko 89% studenata je čulo za infekciju humanim papiloma virusom, dok 75,5% njih zna da se infekcija humanim papiloma virusom prenosi seksualno. Tačno poznavanje infekcije humanim papiloma virusom bilo je nisko, a devojke su pokazale viši nivo znanja u odnosu na muškarce (4,03 ±3,07 vs 5,56 ± 3,37; $p < 0,01$). Samo 27,6% studenata zna da mlade žene imaju veći rizik od infekcije humanim papiloma virusom, 45,9% ispitanika zna da rizik od infekcije zavisi od broja seksualnih partnera, 34,09% zna da kondom ne predstavlja potpunu zaštitu od infekcije humanim papiloma virusom, 53,5% zna da humani papiloma virus može uzrokovati rak grlića materice, a samo 19,7% studenata zna da infekcija humanim papiloma virusom može uzrokovati rak penisa. **Zaključak.** Studenti prve godine medicine nemaju dovoljno znanja o infekciji i bolestima povezanim sa humanim papiloma virusom. Obrazovanje i zdravstveno prosvećivanje mladih ljudi, već u srednjim školama, potrebno je kako bi se očuvalo reproduktivno zdravlje i sprečio nastanak karcinoma uzrokovanih humanim papiloma virusom.

Ključne reči: infekcije papiloma virusom; karcinom grlića materice; znanje o zdravlju, stavovi, praksa; studenti medicine; faktori rizika; kontracepcija; seksualno ponašanje

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Abbreviations
HPV – human papillomavirus
STD – sexually transmitted disease

Introduction

Today, human papillomavirus (HPV) infection is one of the most prevalent sexually transmitted diseases and the most common viral infection of the genital region [1, 2]. It is believed that about 70 - 80% of sexually active women will be infected with HPV during their lifetime [3, 4]. The highest prevalence rate is reported in female student population, that is, between 18 and 25 years of age, while men are at constant risk of a new HPV infection during their entire life [4]. In about 80 – 90% of infected persons, the infection is transient and a spontaneous elimination of the virus from the organism occurs in the period of 2 years [4].

A persistent HPV infection with low risk oncogenic HPV types (HPV 6 and 11, in more than 90% of cases) can clinically manifest with the appearance of genital warts [5].

A persistent infection with high risk oncogenic HPV types (HPV 16 and 18, in 70 - 80% of cases) is associated with cervical premalignant lesions and cervical cancer, as well as development of cancer of the vulva, vagina, anus, penis, oropharynx, mouth, and larynx [1, 6–8].

Cervical cancer is the third most common cancer in women worldwide, with about 569,847 new cases and 311,365 deaths in 2018 according to Global Cancer Incidence [9, 10]. However, in the population of women aged 15 – 44, cervical cancer is the second most common cancer [9]. In Serbia, the annual standardized incidence of cervical cancer is around 20.3 [9].

A prophylactic HPV vaccine has been introduced into the regular primary prevention of HPV infection and HPV-related carcinomas in more than 100 countries of the world, particularly in the developed countries. HPV vaccine is recommended for girls and boys aged 9 – 13, or younger persons aged 13 – 26 years who had not been in contact with HPV [4, 11]. In several large clinical trials, vaccines were confirmed (bivalent vaccine against HPV types 16 and 18, and quadrivalent HPV types 6, 11, 16 and 18) as highly immunogenic, safe, well-tolerated and highly effective in the prevention of HPV infection [7, 12, 13]. Nevertheless, they are poorly accepted in most countries of the world [4, 11–14,]

Vaccines are available in Serbia as well, but they have not been introduced into the National Immunization Program yet.

It has been determined that accurate and correct knowledge of HPV infection, its etiology and transmission, possible consequences as well as the possibilities of prevention are very important when making a decision whether to receive the vaccine or not [5, 6, 11, 13]. Moreover, correct knowledge and attitude towards HPV vaccination is in direct positive correlation with the recommendation for the vaccine to future adolescents [2, 4, 13].

Our goal was to determine the level of knowledge and attitudes of the first year students at the Faculty of Medicine towards HPV infection, its risk factors, means of protection, its clinical manifestations, as well as to raise their awareness and knowledge about HPV infection to a higher level through organizing educational workshops.

We believe that they, as future doctors and healthcare workers, will play a significant role in further dissemination of information about HPV infection and its consequences as well as prevention possibilities in our society and community.

Material and Methods

The a cross-sectional study included 355 first year students of the Faculty of Medicine, University of Novi Sad, and it was conducted in November of 2016. The research was approved by the Ethics Committee of the Faculty of Medicine as part of the City Administration of Novi Sad Health Care Project entitled "My Gynecological Reminder". Students were given information on the objectives of this research, after which they were asked to fill in a non-standardized, self-administered questionnaire, designed for the purpose of this study.

The questionnaire consisted of 32 questions, which were divided into 5 parts. The first group (three questions) was related to gender, previous education and the Department they enrolled at the Faculty of Medicine. The second group (4 questions) was related to the attitudes towards visiting a counseling service for the young and seeing a gynecologist. The third group (9 questions) was related to their past sexual life and the use of contraception, as well as their attitudes towards contraception. The fourth group of 13 questions was related to the knowledge of HPV infection. The purpose of the fifth group of three questions was to gather information on whether they wanted to learn more about HPV infection and cervical cancer, and whether they were willing to receive the HPV vaccine.

The students' unwillingness to participate in the study was the only exclusion criterion from the research.

Students were asked to circle one of the provided answers showing their attitudes and knowledge about reproductive health and contraception (the second and the third group of questions). Their knowledge of HPV infection was estimated based on the number of correct answers to 13 questions from the fourth group. Each correct answer was worth 1 point, while incorrect answers were worth 0 points. The students answered 12 questions by circling one of the three possible answers: "Yes", "No" and "I do not know". Four answers were provided for the question: "How is HPV infection transmitted?" a) via blood, b) through sexual contact, c) by dirty hands, d) I do not know.

The correct answer was worth 1 point. The total score of the test was 13 points. The number of correct answers equal to or over 10 = excellent knowledge, 6 – 10 = moderate, less than 6 = poor knowledge.

Table 1. General characteristics of the respondents
Tabela 1. *Opšte karakteristike ispitanika*

Characteristic/*Karakteristika*	Number (%, percentage)/*Broj (%, procenat)*
Gender/*Pol*	
Male/*Muški*	108 (30.4)
Female/*Ženski*	247 (69.6)
Department at the FM/*Smer na fakultetu*	
General Medicine/*Opšta medicina*	258 (72.75)
Nursing/*Zdravstvena nega*	74 (20.8)
Others/*Ostali*	23 (6.45)
Previous school/*Završena škola*	
High school/*Gimnazija*	274 (77.2)
Secondary medical school/*Srednja medicinska škola*	69 (19.4)
Others/*Ostalo*	12 (3.4)

The statistical package for the social sciences 21 was used for data processing. Frequency analysis, descriptive statistics and χ^2 test were used for the analysis of the sample structure as well as the analysis of the correct answers on the HPV infection. Differences in knowledge with respect to demographic variables were examined by Student's t-test and analysis of variance.

Results

The study included 355 students, 108 (30.4%) male and 247 (69.6%) female. The examined sample included 72.75% of medical students and 20.8% of nursing students. The vast majority of students were high school graduates (77.2%), while a significantly smaller number, 19.4% of students were secondary medical school graduates **(Table 1)**.

Attitudes towards visiting a counseling service for young people and having a gynecological examination

Ninety one point five percent of students thought that preventive gynecological examinations were necessary. However, 88.2% of students have never visited a youth counseling service; they obtained information on reproductive health from media and the Internet (39.4%), followed by parents/family members (20.6%), health workers (20.3%), and friends (18.6%) **(Graph 1)**.

About 73% of students did not want to talk to a gynecologist or an expert about their sex life, because 49.9% did not like talking about their sex life, while 22.8% of students had no dilemmas about their sex life. Only about 27% of students thought they needed a conversation with a gynecologist or an expert about their sex life.

Sex life of students and their attitudes towards contraception

Two hundred and two students (56.9%) have had sexual intercourse and they had their first sexual experience at the age of 17 (min. 15, max. 19 years). By the moment of examination, they have changed 2 partners on average (min. 1, max. 6 partners). At the moment of examination, 42.8% of students had a sexual partner.

About 34.2% of sexually active students had only vaginal sex, while 65.8% of sexually active students had vaginal, oral and anal sex. Sexually transmitted diseases (STDs) were not reported by 87.9% of students **(Table 2)**.

The majority of students (51%) used condoms against unplanned pregnancy, 15.7% had interrupted sexual intercourse, and only 11.3% used oral contraceptives, while 14.7% used a combination of two methods **(Graph 2)**.

Forty seven percent of students thought that condoms were the most effective means to prevent unwanted pregnancy. Only 14.1% of students believed that intrauterine devices provided complete preven-

Table 2. Characteristics of the prior sexual life of students
Tabela 2. *Karakteristike seksualnog života ispitanika*

Had sexual relations (number (%))/*Imao/la seksualne odnose (broj (%))*	202 (56.9)
Currently has a partner (number (%))/*Trenutno ima partnera (broj (%))*	152 (42.8)
Age of the first sexual relation intercourse ($\overline{X}$ ± SD)/*Starost kod prvog polnog donosa* ($\overline{X} \pm SD$)	17.2 ± 1.27
Number of previous sex partners ($\overline{X}$ ± SD)/*Broj dosadašnjih seksualnih partnera* ($\overline{X} \pm SD$)	2.11 ± 1.16
Type of sexual relation (%)/*Tip polnih odnosa (%)*	
Vaginal/*vaginalni*	34.2
vaginal + anal + oral/*vaginalni + analni + oralni*	65.8
Had a sexually transmitted infection (number (%))/*Imao/la seksualno prenosivu infekciju (broj (%))*	43 (12.1)

Legend/*Legenda*: $\overline{X}$= mean value/*srednja vrednost;* SD = standard deviation/*standardna devijacija*

Table 3. Correct answers to the questions about HPV infection
Tabela 3. *Tačni odgovori o infekciji humanim papiloma virusom*

Question *Pitanje*	Correct answer (%) *Tačan odgovor (%)*
Young women are at higher risk of HPV infection (yes) *Mlade žene imaju veći rizik za HPV infekciju (da)*	27.6
HPV infection is transmitted by sexual intercourse (yes) *HPV infekcija se prenosi seksualnim kontaktom (da)*	75.5
The risk of HPV depends on the number of sexual partners (yes) *Rizik od HPV-a zavisi od broja seksualnih partnera (da)*	45.9
Early sexual intercourse is a risk of HPV infection (yes) *Rano stupanje u seksualne odnose je rizik za HPV infekciju (da)*	32.1
HPV infections can affect men (yes)/*Od HPV infekcije mogu da obole muškarci (da)*	37.7
HPV is the cause of genital warts (condyloma) (yes) *HPV su uzrok nastanka polnih bradavica (kondiloma) (da)*	41.1
HPV infection can be cured (yes)/*HPV infekcija se može izlečiti (da)*	31.55
HPV infection always has pronounced symptoms (no) *HPV infekcija uvek daje izražene simptome (ne)*	36.6
Condom provides a complete protection against HPV (no)/*Kondom je potpuna zaštita od HPV-a (ne)*	34.09
There is a vaccine against HPV (yes)/*Postoji vakcina protiv HPV-a (da)*	28.7
HPV can cause cervical cancer (yes)/*HPV može da izazove rak grlića materice (da)*	53.5
HPV can cause penile cancer (yes)/*HPV može da izazove rak penisa (da)*	19.7

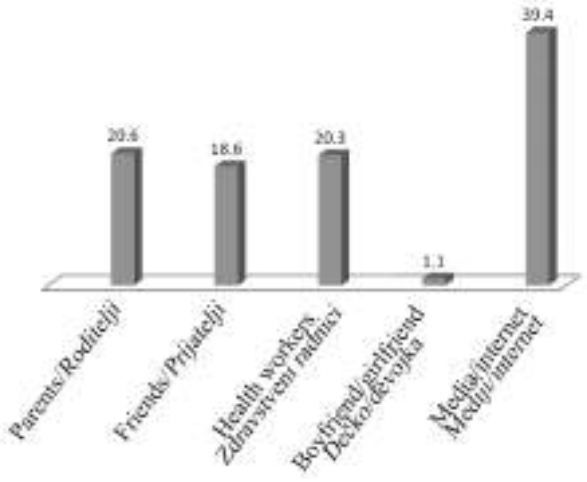
HPV – humani papiloma virus

tion of pregnancy, 11.2% of them believed in contraceptive pills, or a combination of two methods (11.2%). About 17% of students did not know the answer to this question **(Graph 3)**.

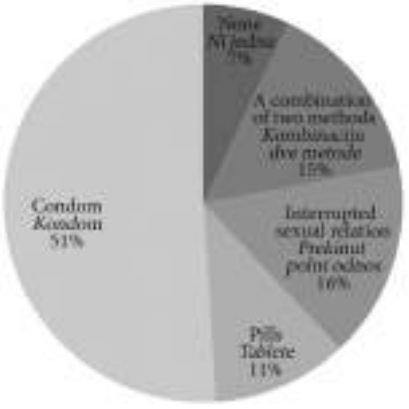
Forty eight point seven percent of students thought that pregnancy termination was dangerous and that it should be avoided using contraception, while 27.6% of students believed that it was very dangerous for health.

Students' knowledge of HPV infection

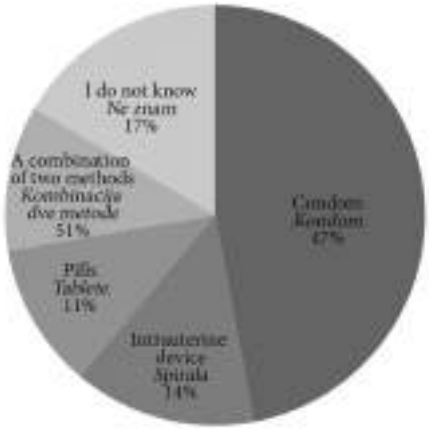
Eighty nine percent of students have heard about HPV infection, while 75.5% of them knew that HPV infection is transmitted through sexual intercourse. Only 27.6% of students knew that young women are at a higher risk of HPV infection, that the risk of HPV infection depends on the number of sexual partners (45.9%), that early sexual intercourse is a risk of getting HPV infection (32.1%), that HPV infection may also affect men (37.7%), that HPV infection causes genital warts (41.1%), that HPV infection can be cured (31.55%), that HPV infection does not always have symptoms (36.6%), that condoms do not provide complete protection against HPV infection (34.09%), 28.7% have heard of HPV vaccine, while 53.5% knew that HPV can cause cervical cancer, and only 19.7% of students knew that HPV infection may cause penile cancer **(Table 3)**.



Graph 1. Sources of information on reproductive health
Grafikon 1. *Izvori informacija o reproduktivnom zdravlju*



Graph 2. Contraceptive methods used by students
Grafikon 2. *Tipovi kontracepcije koju studenti koriste*



Graph 3. The most effective means to prevent pregnancy according to students
Grafikon 3. *Najefikasnije sredstvo za zaštitu od trudnoće prema mišljenju studenata*

The total score of the knowledge test was 5.09 +/- 3.35, which means that students of the first year showed poor knowledge about HPV infection.

The female students showed better results than male students (t (353) = - 4.192; $p < 0.01$). There was also a statistically significant difference in the knowledge of students related to the secondary school they attended. The best results were achieved by students who attended medical high schools ($F_{(2. 352)} = 10.177$; $p < 0.01$). In addition, students of nursing showed better knowledge of HPV infection than students from other departments ($F_{(2. 352)} = 10.177$; $p < 0.01$), than students who have not had sexual intercourse yet ($t_{(353)} = -5.699$; $p < 0.01$), and students who have not had sexually transmitted infections so far ($t_{(353)} = -3.946$; $p < 0.01$).

Students' opinions on HPV vaccine

About 75% of the total number of respondents thought that they were not sufficiently informed of HPV infection and cervical cancer and wanted to learn more through lectures and workshops. More than half (53.2%) of students did not want to receive HPV vaccine, while only 18.6% of them would receive a vaccine if they were advised by a doctor.

Discussion

Previous studies have shown that medical students have a higher level of knowledge compared to students of other sciences, as well as compared to general population [11, 13]. A research which was conducted in our country on HPV infection, as a sexually transmitted disease, showed that students of the Faculty of Medicine have statistically significantly higher knowledge, compared to the respondents from secondary medical schools and other high schools (84% versus 65.8% versus 60.3%), but with low awareness of the existence and role of HPV vaccine (55% versus 23.1% vs. 14.7%) [15]. The aim of our research was to determine the actual level of students' knowledge of HPV infection.

In our research, the majority of students (89%) have heard of HPV infection and knew that the infection is transmitted through sexual intercourse (75.5%); however, accurate knowledge of HPV infection was low, with female students showing a higher level of knowledge (4.03 ± 3.07 versus 5.56 ± 3.37; $p < 0.01$). Overall, female students showed a higher level of knowledge compared to male students than students who had previously graduated from a secondary medical school, students of general medicine, students who have not had sexual intercourse yet, and those who have not had a sexually transmitted infection [3, 14].

On average, students answered 5 out of 13 questions about HPV infection correctly. Our results do not differ from the results of other authors, who have also found that, in general, there is a low level of knowledge about HPV infection among students of the Faculty of Medicine and that female students have a higher level of knowledge than male students [3, 6, 8, 14]. The results of other authors are diverse. According to a research of McCusker SM et al., among students of medicine in Scotland, 96% of girls and 100% of boys knew that HPV was a sexually transmitted infection, while another study conducted in Germany showed that less than 50% of students knew that HPV was a sexually transmitted infection [4, 6].

The results of our study show that there is an insufficient level of knowledge about the correlation between HPV infection and cancer of the genital region. Just over half of the students (53.5%) knew that HPV infection is associated with cervical cancer and genital warts (41.1%).

However, only about 19.7% of students knew that HPV infection can cause penile cancer. Our results are slightly worse than the results of other authors. In a study by Choudhary et al., conducted in India, 78% of medical students who participated in the study knew that HPV is sexually transmitted, 54% knew that HPV causes cervical cancer, 53% knew that it causes genital warts, while 25% knew about the correlation between HPV infection and penile cancer [8]. In the study conducted by Khan et al. in Pakistan, 57% of students have heard of HPV infection, but 55% knew that HPV can cause cervical cancer, while 47% knew that HPV causes penile and anal cancer [1]. In China, 76.5% of students have heard of HPV infection, 46.8% knew that it is sexually transmitted, 49.4% knew that HPV causes genital warts, while 67.4% knew that HPV causes cervical cancer [3].

In addition, students' knowledge about the risk factors of HPV infection, as well as the possible ways of prevention, is incomplete and imprecise [16]. In our study, one third of students knew that HPV infection does not always have symptoms (37%), that it can be cured spontaneously (31.55%) and that condoms do not provide complete protection against HPV infection (34%), which is consistent with the results of other authors [1].

However, almost two-thirds of students do not know that having early sexual relations poses a risk for getting HPV infection (67.9%), that HPV infection depends on

the number of sex partners (54.1%), that young women are at a higher risk (72.4%), and that men can also get infected (62.3%). In the study conducted by Yoruk et al., students knew that risk factors for HPV infection are having early sexual relations (61.8%) and having multiple sex partners (83.3%) [16].

The lack of knowledge about HPV infection and its possible consequences, as well as the ways of preventing it, can be explained by the lack of education of young people in secondary schools about STDs. Statistically speaking, a better level of knowledge in our research was demonstrated by students who had previously graduated from secondary medical schools, which suggests that in secondary schools young people get insufficient education on reproductive health and STDs, which is in line with the results of other authors [3, 14].

In our research, 88.2% of students have never visited a youth counseling service, while information on reproductive health are obtained from media and the Internet (39.4%), followed by parents or family members (20.6%), health workers (20.3%) and friends (18.6%). Furthermore, data that about 73% of students do not want to talk to a gynecologist or an expert about their sex life (they do not like talking about their sex life (50%), they have no dilemmas regarding their sex life (22.8%), are also a sign of insufficient health awareness. Other authors have come to similar conclusions [6].

Good knowledge of HPV infection and its association with cervical and other genital carcinomas is a significant factor in deciding whether to receive the vaccine or not [6]. In our study, only 28.7% of students knew that there is an HPV vaccine, but more than half (53.2%) of them do not want to receive it. Only 18.6% of students would receive the vaccine if the doctor recommended it. The results of other authors are diverse.

In Khan's study, 47% of students knew that there is an HPV vaccine, and a vast majority would receive it if it was recommended by a doctor [1]. In the study of Tripathy S et al., 36.1% of medical students would receive an HPV vaccine, while in the study of Mehta S et al., as many as 88% of students would receive an HPV vaccine [17, 18]. This attitude of students is expected, given the low level of knowledge about HPV infection and the severity of its possible consequences.

Conclusion

There is a lack of knowledge among medical students, future health workers, about human papillomavirus infection, ways of its spreading, diseases it causes, and about its prevention. Education and health awareness of young people is necessary in secondary schools, in order to preserve reproductive health and prevent human papillomavirus-related cancers. Better awareness and higher level of knowledge about human papillomavirus vaccine will contribute to increase acceptance of vaccination, which will reduce the morbidity and mortality from cervical and other human papillomavirus-induced carcinomas.

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ANALYSIS OF ACADEMIC SELF-EFFICACY OF MEDICAL STUDENTS LEARNING ENGLISH FOR SPECIFIC PURPOSES

ANALIZA AKADEMSKE SAMOEFIKASNOSTI STUDENATA MEDICINE KOJI UČE ENGLESKI JEZIK KAO JEZIK STRUKE

Staša ĐOKIĆ[1], Nina BRKIĆ JOVANOVIĆ[2], Zoran MAROŠAN[1] and Vuk MARKOVIĆ[1]

Summary

Introduction. English for Specific Purposes focuses on teaching and learning subject specific knowledge which includes specific language skills that particular learners need for a specific purpose. Self-efficacy is determined by subjective beliefs about one's own abilities, which also applies to the academic setting of studying English for Specific Purposes. Academic self-efficacy represents the conviction of students about their own abilities to successfully fulfil academic tasks at designated levels. The goal of this research is to examine the degree of academic self-efficacy of medical students who learn English for Specific purposes at the Faculty of Medicine of the University of Novi Sad, with respect to their gender, year of study, grade achieved in the previous course in English, and the length of learning English before enrolling in the Faculty. **Material and Methods**. The study included 58 medical students. The researchers used the College Academic Self-Efficacy Scale questionnaire developed by Owen and Froman (1988) to assess academic self-efficacy. **Results**. Three significant factors were identified: general self-competence, communication with the professor, and attendance at lectures, with general self-competence being the most significant factor. Considering the independent variables, only the grade showed statistical significance. Establishing the grade as such a significant predictor can be explained by the fact that good grades and a high grade point average are presented as very desirable outcomes. However, a good grade does not necessarily mean having better knowledge or correct use of language. **Conclusion**. Further research into this topic is necessary, with expanding the number of participants, study programs and variables.

Key words: Self Efficacy; Self-Assessment; Language; Academic Success; Surveys and Questionnaires; Students, Medical; Communication

Sažetak

Uvod. Engleski jezik kao jezik struke fokusira se na predavanju i usvajanju znanja koje je vezano za specifičnu oblast, što uključuje specifične jezičke veštine koje su određenim učenicima potrebne za određenu svrhu. Samoefikasnost određuju subjektivna ubeđenja o sopstvenim sposobnostima, što se odnosi i na akademsko okruženje učenja engleskog jezika kao jezika struke. Akademska samoefikasnost predstavlja ubeđenje studenata o sopstvenim sposobnostima u uspešnom izvršavanju akademskih aktivnosti na zadatom niovu. Cilj ovog istraživanja je da istraži stepen akademske samoefikasnosti studenata medicine koji uče engleski jezik kao jezik struke na Medicinskom fakultetu Univerziteta u Novom Sadu, u zavisnosti od pola, godine studija, ocene ostvarene u prethodnom kursu engleskog jezika i dužine učenja engleskog jezika pre upisa na fakultet. **Materijal i metode.** Istraživanje je obuhvatilo 58 studenata medicine. Istraživači su koristili upitnik pod nazivom Skala akademske samoefikasnosti na fakultetu koju su formulisali Oven i Froman (Owen and Froman, 1988) za procenu akademske samoefikasnosti. **Rezultati.** Uočavaju se tri značajna faktora: opšta samokompetencija, razgovor sa profesorom i prisustvo na predavanju, dok je opšta samokompetencija najznačajniji faktor. Uzimajući u obzir nezavisne varijable, pokazalo se da je samo ocena statistički značajna. Utvrđivanje ocene kao veoma značajnog prediktora može se objasniti činjenicom da su dobre ocene i visok prosek predstavljeni kao vrlo poželjni ishodi. Međutim, visoka ocena ne obezbeđuje uvek kvalitetno znanje i pravilnu upotrebu jezika. **Zaključak.** Neophodno je dalje istraživanje ove oblasti, sa proširivanjem broja učesnika, studijskih programa i varijabli.

Ključne reči: samoefikasnost; samoprocena; jezik; akademski uspeh; istraživanja i upitnici; studenti medicine; komunikacija

Introduction

The purpose of this research is to examine the degree of academic self-efficacy of medical students who learn English for Specific purposes (ESP) at the Faculty of Medicine of the University of Novi Sad. The aim of this paper is to present the results of a survey which was designed to explore academic self-efficacy in learning ESP in respect to the gender, year of study, grade achieved in the previous course in English, and the length of learning English before enrollment. The research focused on discovering whether a connection can be established between the aforementioned independent

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Abbreviations

ESP – English for Specific Purposes
ESAP – English for Specific Academic Purposes
EFL – English as a Foreign Language
SPSS – Statistical Package for the Social Sciences
CASES – College Academic Self-Efficacy Scale

variables and the students' academic self-efficacy, i.e. the dependent variable. Furthermore, the research aimed at determining which variables had the most impact on self-efficacy, and if these variables exerted positive or negative influence on self-efficacy. The purpose of examining possible influences is to gain insight into medical students' academic self-efficacy beliefs and to find ways to enhance it, if that is necessary.

English for Specific Purposes "involves teaching and learning the specific skills and language needed by particular learners for a particular purpose" [1]. The "purpose" refers to a professional purpose which is to acquire knowledge and a set of skills necessary for a certain profession. Learning ESP differs from learning General English, which is intended for a wider scope of learners, while the key factor in ESP is subject specific knowledge (e.g. of legal procedures or engineering methods), [1], where emphasis is put on the understanding and use of professional terminology [2].

In ESP classes, learners with similar needs can form study groups. This is relatively easy to organize in the context of universities where students have similar needs, which is to master, for example English for Media Studies. Furthermore, this branch of ESP can be referred to as English for Specific Academic Purposes (ESAP), as well. The ESP classes can also be designed for workers in a certain profession, such as organizing English lessons for employees at a law firm [1].

The participants in this study are the students of the Integrated Academic Studies of Medicine who have two mandatory courses in ESP in the area of Medical English. However, apart from subject specific knowledge, these courses also include units in English grammar and general vocabulary. Apart from mastering medical terminology, there is also a need for mastering General English skills for university level, because not all students enroll in the faculty with the same level of language proficiency.

Literature Review

According to Bandura, people's degree of motivation, affective states and actions are greatly influenced by what they believe rather than by what is true, making subjective perceptions often more significant than objectives facts. Therefore, people make most of their decisions based on personal efficacy beliefs. In other words, "perceived self-efficacy refers to beliefs in one's capabilities to organize and execute the courses of action required to produce given attainments" [3], meaning that it is "concerned with judgments of how well one can execute courses of action required to deal with prospective situations" [4]. Self-efficacy beliefs are not always completely rational and may not reflect people's real capabilities, but they are often the result of the connection between subjective estimations of task demands and difficulty, the resources people believe to possess, and their ability to use these resources in order to fulfil tasks [5]. In order to function competently, people need to find balance between their beliefs and their real knowledge and skills [6]. Accordingly, academic self-efficacy refers to the students' judgments or convictions about their capabilities to successfully perform academic tasks at required levels [7–9], being "a powerful motivation construct that works well to predict academic self-beliefs and performances at varying levels" [10].

Concerning gender, Pajares, Johnson and Usher found that female students showed greater mastery experience, vicarious experience, and social persuasions, as well as a lower degree of anxiety [7]. In a broader study, Bong established that male students exhibited more confidence in different academic domains, while female students more precisely distinguished between their verbal and mathematic academic capabilities [11]. The reason for this could be that male students are more likely to overestimate their verbal abilities than female students [11, 12]. Furthermore, Khatib & Maarof established that the female students exhibited a significantly higher level of self-efficacy compared to male students concerning ability [13].

When it comes to the year of study, Sachitra and Bandara found that students in degree part IV exhibited the highest level of academic self-efficacy compared to the degree parts II and III, indicating that gaining academic experience leads to the rise of academic self-efficacy [14]. Similarly, Khatib and Maarof established that the fifth semester students exhibited higher self-efficacy compared to the first semester students, in terms of ability, attitude and aspiration, indicating that longer exposure to English positively influences self-confidence [13].

Considering the grade achieved in the previous course in English, Wood and Locke explored how academic performance can be influenced by students' academic self-efficacy and desired grades. It was found that self-efficacy had a significant impact on academic performance [15]. In a more recent study, Tilfarlioğlu and Cğnkara found that self-efficacy significantly affected the students' EFL grades at the end of the year, concluding that students can benefit from a high level of self-efficacy because it can result in "a higher intrinsic motivation, lower anxiety, perseverance in the face of difficulty, and, therefore, the attainment of desirable outcomes" [16].

Regarding the length of learning English before enrolling in the faculty, Lampert claims that children's self-efficacy beliefs begin to influence their future goals at a very young age. Therefore, a child who exhibits a higher degree of self-efficacy is expected to be more successful academically and pro-

fessionally than a child with a lower degree of self-efficacy. However, "efficacy is dynamic and changes as individual socialization patterns change" [17]. Furthermore, it can be assumed that students who have been exposed to English for a longer time have more experience in language learning and perhaps a better understanding of language which enhances self-esteem [18].

Material and Methods

The questionnaire used in this study was distributed electronically among the medical students of the Faculty of Medicine in Novi Sad. A quantitative research design was applied in order to get an answer to the following research question: Which individual learner characteristics have independent influence on the medical students' academic self-efficacy in learning ESP, and 4 null hypotheses were set: (1) gender does not affect the degree of academic self-efficacy; (2) study year does not affect the degree of academic self-efficacy; (3) the grade achieved in the previous course in English does not affect the degree of academic self-efficacy; and (4) the length of learning English before enrolling in the Faculty does not affect the degree of academic self-efficacy.

The Participants

The study included a sample of 58 students of the Integrated Academic Studies of Medicine at the University of Novi Sad. The questionnaire examined the students' academic self-efficacy with respect to their ESP learning experience during the 2019/20 school year. When the selection process is concerned, convenient sampling was used since only those students who were willing to complete the questionnaire participated in the study. The questionnaire was distributed electronically via Google Forms through social network groups, and the time needed for completing it was estimated at about ten minutes. Socio-demographic characteristics of the participants are presented in **Table 1.**

Instrumentation

For the purpose of this study, the researchers used the questionnaire developed by Owen and Froman, concerned with "the development and estimation of measurement properties of the College Academic Self-Efficacy Scale (CASES)", which was tested both for reliability and validity showing encouraging preliminary measurements [18, 19].

The questionnaire was adapted for this research, firstly by translating it from English into Serbian language and then by modifying the original 33 statements into 15 statements. The statements were tested on a Likert scale ranging from 1 to 5 (1 being the lowest degree and 5 being the highest degree). The statements are presented in **Table 2.** The independent variables include gender, year of study, grade achieved in the previous course in English, and the length of learning English before enrollment, which were included in the first part of the questionnaire. The students' academic self-efficacy in ESP was tested as a dependent variable.

Variables in the Study

Regarding the independent variables, only the variable of gender was used from the original, while the following variables were added: year of study, grade achieved in the previous course in English, and the length of learning English before enrolling in the Faculty. The students' academic self-efficacy in ESP was tested as a dependent variable.

Statistical data analysis

The Statistical Package for the Social Sciences (SPSS) 22.0 program was used for data entry and analysis. In order to analyze and describe the sam-

Table 1. Socio-demographic characteristics of the examined sample
Tabela 1. *Socio-demografske karakteristike ispitivanog uzorka*

Sample description/*Deskripcija uzorka*	
Gender/*Pol*	
men/*muškarci*	10 (17.2%)
women/*žene*	48 (82.8%)
Grade in the English language/*Ocena iz engleskog jezika*	
7	1 (1.7%)
8	5 (8.6%)
9	22 (37.9%)
10	27 (46.6%)
Year of study/*Godina studija*	
1st year/*1. godina*	37 (41.2%)
2nd year/*2. godina*	21 (36.2%)
The length of learning the English language/*Dužina učenja engleskog jezika*	
8 years/*8 godina*	13 (22.4%)
12 years/*12 godina*	45 (77.9%)

Table 2. Pattern matrix of the acquired three-factor solution
Tabela 2. *Matrica sklopa dobijenog trofaktorskog rešenja*

Items *Stavke*	General self-competence *Opšta samokompetencija*	Communication with the professor *Razgovor sa profesorom*	Attendance at lectures *Prisustvo na predavanju*
1. I believe that I can successfully take notes during the lecture and organize my notes well. *Verujem da uspešno mogu da zapisujem u toku predavanja i svoje beleške dobro organizujem.*	.786		
2. I believe that I can successfully participate in discussions during the lecture. *Verujem da uspešno mogu da učestvujem u diskusijama na predavanju*	.691	.414	
3. I believe that I can successfully follow a lecture about a complex topic. *Verujem da uspešno mogu da pratim predavanje kada se obrađuje kompleksna tema.*	.874		
4. I believe that I can successfully teach other students. *Verujem da uspešno mogu da podučavam druge studente.*	.747		
5. I believe that I can ask the professor to explain a certain part of the lecture which I did not understand again during the lecture. *Verujem da mogu da zamolim profesora na predavanju da ponovo objasni određeni deo gradiva koji nisam razumeo/la.*	.361		.557
6. I believe that I can regularly attend lectures. *Verujem da mogu redovno da prisustvujem predavanjima.*			.764
7. I believe that I can understand most of the content presented in lectures. *Verujem da uspešno mogu da razumem većinu gradiva koje se obrađuje na predavanju.*	.865		
8. I believe that I can successfully communicate with the professor privately in order to get to know him/her better. *Verujem da uspešno mogu da razgovaram nasamo sa profesorom kako bih njega ili nju bolje upoznao/la.*		.727	
9. I believe that I can successfully make connections between content in the English language and content in other courses. *Verujem da uspešno mogu da povezujem gradivo iz engleskog jezika sa gradivom iz drugih predmeta.*	.595		
10. I believe that I can successfully answer the professor's questions during the lecture. *Verujem da uspešno mogu da odgovaram na pitanja koja postavlja profesor u toku predavanja.*	.837		
11. I believe that I can successfully master content in the general vocabulary of the English language./*Verujem da uspešno mogu da savladam gradivo iz opšteg vokabulara engleskog jezika.*	.913		
12. I believe that I can successfully master content in the medical vocabulary of the English language. *Verujem da uspešno mogu da savladam gradivo iz stručnog vokabulara engleskog jezika.*	.814		
13. I believe that I can successfully master content in grammar of the English language. *Verujem da uspešno mogu da savladam gradivo iz gramatike engleskog jezika.*	.675		
14. I believe that I can successfully pass the written exam. *Verujem da uspešno mogu da položim pismeni ispit.*	.756		
15. I believe that I can successfully pass the oral exam. *Verujem da uspešno mogu da položim usmeni ispit.*	.833		

Table 3. Characteristic roots and coverage of variance of isolated factors in the measured space of the Questionnaire for the Evaluation of Self-efficacy after the application of the promax rotation
Tabela 3. *Karakteristični koreni i obuhvat varijanse izolovanih faktora prostora merenja Upitnika za procenu samoefikasnosti nakon primene promax rotacije*

Component/*Komponenta*	Initial solution/*Inicijalno rešenje*		
	Characteristic root *Karakteristični koren*	Percentage of variance *Procenat varijanse*	Cumulative percentage *Kumulativni procenat*
Questionnaire/*Upitnik*			
1	7.663	51.08	51.08
2	1.727	11.51	62.60
3	1.168	7.78	70.38

ple structure according to relevant variables, representations of frequencies and percentages were used, with the aim of exploring to which extent certain categories or answers are present. Methods of descriptive statistics were applied in order to determine the measures of central tendencies (arithmetic mean), measures of variability (standard deviation) and extreme values (minimum and maximum) of the explored numerical characteristics. Exploratory factor analysis was used along with the principal axis factoring for the purpose of factorization. In order to evaluate the reliability of the scale as a whole, the measurement of internal consistency expressed by the Cronbach's alpha coefficient was used. Within the comparative statistics, a series of multivariate regression analyses were conducted. In the applied tests, limits of risk probability were set at the significance level of 95% ($p < 0.05$) (significant difference in statistical parameters) and 99% ($p < 0.01$) (highly significant difference in statistical parameters). In the case of the Questionnaire for the Evaluation of Self-efficacy, the initial set of variables included answers to 15 statements of the questionnaire. Further analyses included three dimensions/factors of the questionnaire, which are operationally defined as factor scores. These factor scores were created according to the solution suggested by the implemented Exploratory factor analysis in the latent space of the aforementioned questionnaire.

Results

Latent structure of the questionnaire

Verification of the assumption of the questionnaire dimensionality was performed by Exploratory factor analysis and Principal axis factoring in the SPSS 22 program. The statistically significant Bartlett's test of sphericity [$\chi^2(105) = 633{,}252$; $p < .001$] indicates that the intercorrelation matrix is factorable. By using the Exploratory factor analysis, three factors were identified based on the solutions of parallel analysis. The factors included 70.38% of common variance after the extraction. The factors were tested by the promax rotation and interpreted based on the pattern matrix **(Table 2)**. Only factor loadings of 0.32 and higher were taken into consideration [20]. The values of the characteristic roots, percentage of the explained variance, and cumulative percentage of the explained variance are shown in **Table 3**.

After examining the factorial pattern matrix in the promax position **(Table 2)**, three clear interpretable factors are identified. After rotation, the first factor encompasses 51.08% of common variance and it is largely explained by the items: 11, 3, 7, as well as 10 and 15. The first factor can be referred to as 'general self-competence'. The second factor encompasses 11.51% of common variance and it is explained by the items 2 and 8. The second factor can be referred to as 'communication with the professor'. The third factor encompasses 7.78% of common variance and it is largely explained by items 5 and 6. The third factor can be referred to as 'attendance at lectures'.

Reliability of the questionnaire

Internal consistency of the Questionnaire for the Evaluation of Self-efficacy was determined by calculating the Cronbach's alpha coefficient.

Based on the data obtained from this study, it was determined that the reliability of the Questionnaire for the Evaluation of Self-efficacy is $\alpha = 0.914$ in total, which is significantly high.

Description of the participants' answers to scales and statements are given in **Table 4.**

Multiple regression analyses

Multiple regression analyses were applied in order to examine to which extent score variance on subscales and total score reported by students on the Self-efficacy scale can be explained by the variance of different socio-demographic variables and other significant variables. The set of predictors included the following variables: gender, year of study, grade achieved in the previous course in English, and the length the students had been learning English before enrolling in the Faculty. The criterion variable was the total score on the applied scale and scores on three subscales. Preliminary analysis was conducted to determine if there were significant deviations from the expected normality, linearity, multicollinearity and homoscedascity.

Table 4. Mean values and basic characteristics
Tabela 4. *Prosečne vrednosti i osnovne karakteristike*

Components *Komponente*	Descriptive characteristics *Deskriptivne karakteristike*			
	min	max	AS	SD
Total score/*Ukupni skor*	30.0	75.0	61.36	11.19
General self-competence/*Opšta samokompetencija*	24.0	70.0	57.65	10.71
Communication with the professor/*Razgovor sa profesorom*	2.0	10.0	7.32	2.18
Attendance at lectures/*Prisustvo na predavanju*	4.0	10.0	8.41	1.56
1. I believe that I can successfully take notes during the lecture and organize my notes well. *Verujem da uspešno mogu da zapisujem u toku predavanja i svoje beleške dobro organizujem.*	1.0	5.0	3.82	1.25
2. I believe that I can successfully participate in discussions during the lecture. *Verujem da uspešno mogu da učestvujem u diskusijama na predavanju.*	1.0	5.0	3.75	1.32
3. I believe that I can successfully follow a lecture about a complex topic. *Verujem da uspešno mogu da pratim predavanje kada se obrađuje kompleksna tema.*	1.0	5.0	4.10	1.29
4. I believe that I can successfully teach other students./*Verujem da uspešno mogu da podučavam druge studente.*	1.0	5.0	3.41	1.33
5. I believe that I can ask the professor to explain a certain part of the lecture which I did not understand again during the lecture. *Verujem da mogu da zamolim profesora na predavanju da ponovo objasni određeni deo gradiva koji nisam razumeo/la.*	1.0	5.0	4.27	1.13
6. I believe that I can regularly attend lectures. *Verujem da mogu redovno da prisustvujem predavanjima.*	1.0	5.0	4.13	1.01
7. I believe that I can understand most of the content presented in lectures. *Verujem da uspešno mogu da razumem većinu gradiva koje se obrađuje na predavanju.*	1.0	5.0	4.39	1.02
8. I believe that I can successfully communicate with the professor privately in order to get to know him/her better. *Verujem da uspešno mogu da razgovaram nasamo sa profesorom kako bih njega ili nju bolje upoznao/la.*	1.0	5.0	3.56	1.35
9. I believe that I can successfully make connections between content in the English language and content in other courses. *Verujem da uspešno mogu da povezujem gradivo iz engleskog jezika sa gradivom iz drugih predmeta.*	1.0	5.0	4.00	1.19
10. I believe that I can successfully answer the professor's questions during the lecture. *Verujem da uspešno mogu da odgovaram na pitanja koja postavlja profesor u toku predavanja.*	1.0	5.0	4.05	1.05
11. I believe that I can successfully master content in the general vocabulary of the English language. *Verujem da uspešno mogu da savladam gradivo iz opšteg vokabulara engleskog jezika.*	1.0	5.0	4.62	.79
12. I believe that I can successfully master content in the medical vocabulary of the English language. *Verujem da uspešno mogu da savladam gradivo iz stručnog vokabulara engleskog jezika.*	1.0	5.0	4.34	1.00
13. I believe that I can successfully master content in grammar of the English language. *Verujem da uspešno mogu da savladam gradivo iz gramatike engleskog jezika.*	1.0	5.0	4.39	1.007
14. I believe that I can successfully pass the written exam. *Verujem da uspešno mogu da položim pismeni ispit.*	1	5	4.59	.92
15. I believe that I can successfully pass the oral exam. *Verujem da uspešno mogu da položim usmeni ispit.*	1	5	4.34	1.10

Legend**:** * Sk (Skewness) curvature indicator; Ku (Kurtosis) flatness indicator
*Legenda: * Sk (Skjunis) pokazatelj zakrivljenosti; Ku (Kurtozis) pokazatelj spljoštenosti*

Table 5. Evaluation of the statistical significance of the regression model
Tabela 5. *Procena statističke značajnosti regresionog modela*

	Sum of squares df *Suma Kvadrata*		Mean square *Prosečan vadrat*	R	R^2	F	p-level *p-nivo*
Total/*Ukupno*	1180.916	4	295.229	.415	.172	2.603	.047
General self-competence *Opšta samokompetencija*	1237.510	4	309.377	.441	.130	3.024	.026
Communication with the professor *Razgovor sa profesorom*	7.920	4	1.980	.178	.032	.407	.803
Attendance at lectures *Prisustvo na predavanju*	11.898	4	2.974	.292	.085	1.167	.337

Table 6. Partial contributions of the Beta (β) predictor
Tabela 6. *Parcijalni doprinosi prediktora Beta (β)*

	Sum *Ukupno*	General self-competence/*Opšta samokompetencija*	Communication with the professor/*Razgovor sa profesorom*	Attendance at lectures/*Prisustvo na predavanju*
Gender/*Pol*	.016	.028	-.098	-.043
Year of study/*Godina studija*	-.134	-.155	-.016	-.123
Grade/*Ocena*	.370*	.370*	.082	.192
Length of learning/*Dužina učenja*	.131	.180	.090	.157

* $p < 0.05$

Four multiple regression analyses were conducted. The results are presented in **Table 5** and **Table 6**. In two cases, the model was not statistically significant – F (4) = .407, p = 0.803 for the second subscale and F (4) = 1.167, p = 0.337 for the third subscale. For the second subscale the coefficient of multiple correlation was *R* = 0.178, while the percentage of variance of this subscale explaining the predictor variables was 3.2%. None of the predictor variables exhibited a significant individual contribution within the set model. For the third subscale, the coefficient of multiple correlation was R = 0.292, while the percentage of variance of this subscale explaining the predictor variables was 8.5%. None of the predictor variables exhibited a significant individual contribution within the set model.

By observing the total score and the score of the first subscale, it was determined that the models are statistically significant. The model value of the total score is F (4) = 2.603, p = 0.047, while the model value of the first subscale is F (4) = 3.024, p = 0.026. In the total score, the coefficient of multiple correla-tion is R = 0.415, while the percentage of scale vari-ance explaining the predictor variables is 17.2%. By examining individual contributions, it can be con-cluded that only the grade in the English language is a significant predictor. Students who reported having a higher grade also exhibited a higher level of self-efficacy. On the first subscale, the coefficient of multiple correlation is R = 0.441, while the percentage of variance of this subscale explaining the predictor variables is 13.0%. Also, only the significant positive influence of the grade variable was identified.

Discussion

Using the exploratory factor analysis, three significant factors were identified: general self-competence, communication with the professor, and attendance at lectures. Since it encompasses many different aspects of learning, such as mastering general vocabulary in English, complex topics and content in whole, as well as the confidence to communicate with the professor and pass the exam, it could be expected that this factor would exhibit the most significance regarding the degree of academic self-efficacy.

General self-competence is followed by the factor of communication with the professor. This factor is significant because successful communication with the professor may help the students' confidence and resolve any issues the students may experience in their learning process.

Finally, the third factor is attendance at lectures. Sometimes, only attending lectures can help students feel confident about the course because they know that they will not miss anything in terms of content and important information. Moreover, if the students feel safe to ask the professor to repeat certain parts of lectures, they probably believe that all misunderstandings can be easily resolved which positively affects self-efficacy. The items which reflect these three factors represent language skills and components which make the largest contribution to the level of self-efficacy.

The variables of gender, year of study and the length of learning English before enrolling in the Faculty did not exhibit statistical significance. How-

ever, it is important to consider that there were significantly more female participants in the study, which could have affected the results. Namely, studies which indicated that female students showed a higher level of self-efficacy in the academic setting included a sample of even gender distribution [7, 13]. In contrast, some studies did not find gender differences, but included a sample with a notably higher number of either male or female participants [21, 22]. Considering the length of learning English, it was established that children who started learning a language at an early age are likely to achieve better academic and professional results [17], since longer exposure to language may result in higher self-confidence [18]. However, the results of this study did not establish a connection between the number of years of English language learning and self-efficacy. These findings indicate that the results could have been influenced by uneven gender distribution and a significant difference in the number of participants who have been learning English for 8 years and those who have been learning English for 12 years.

On the other hand, it was determined that the grade achieved in the previous course in English was the only statistically significant variable. The higher the grade, the higher the academic self-efficacy. Moreover, the variable of grade exhibited only positive influence. These results are in accordance with the findings that there is a strong connection between the grade and the degree of academic self-efficacy [15, 16]. Establishing the grade as a crucial predictor of the degree of self-efficacy can be explained by the fact that a lot of importance is assigned to having high grades and a high point average. Namely, high grades can ensure scholarships for studying in the country or abroad, University awards, an impressive resume, or even employment right after completing studies.

However, a lot of questions about the validity of grades have been raised [23] and since there is no definitive answer whether grades accurately reflect academic achievement and knowledge [23], it seems that the grade should not be the most important criterion for success, and, therefore, the most significant influence on self-efficacy. A high grade does not necessarily guarantee the quality of knowledge or correct language use. Since motivation plays a significant role in the learning process, professors should focus on raising their student's motivation and developing positive beliefs about language learning [24] and on promoting the use of effective learning strategies [25].

Conclusion

Further research into this topic is necessary. Since only one independent variable proved to be significant, a new set of variables should be considered so that professors can gain more insight into their students' self-efficacy. Perhaps another study can include variables which are more closely related to the learning process. Moreover, future studies should involve a significantly larger number of participants so that results can be observed on a larger sample and the student population can be wholesomely represented, while ensuring equal distribution between male and female participants. These results provide a valuable insight for the professors of English and emphasize the need for further research of academic self-efficacy, with expanding the number of participants, study programs and variables.

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BLOODSTREAM INFECTIONS IN PATIENTS WITH HEMATOLOGIC MALIGNANCIES AND FEBRILE NEUTROPENIA – A SINGLE CENTER EXPERIENCE

BAKTERIJEMIJE KOD BOLESNIKA SA MALIGNIM HEMOPATIJAMA TOKOM FEBRILNE NEUTROPENIJE – ISKUSTVO JEDNOG CENTRA

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Summary

Introduction. Bacterial blood infections during febrile neutropenia episodes are urgent medical conditions which were and still are the main cause of morbidity and mortality among patients with hematologic malignancies. The aim of this study was to determine the incidence and clinical characteristics of bacteremia, infectious agents, presence and incidence of antibiotic resistance, as well as the treatment outcome of bloodstream infections in patients with hematologic malignancies. **Material and Methods.** A three-year retrospective study included 107 patients with hematologic malignancies and positive blood culture results during febrile neutropenia. **Results.** The most common isolates were Gram-negative bacteria (58.5%), with Escherichia coli being the most frequent pathogen. The Gram-negative microorganisms were mostly sensitive to carbapenems in 70.7%, whereas sensitivity to other antibiotics was as follows: piperacillin/tazobactam 62%, amikacin 58.5%, and third-generation cephalosporins 50.5%. Acinetobacter spp. was sensitive only to colistin (94.1%). The antibiotic sensitivity among Gram-positive bacteria was highest to linezolid (97.1%), followed by teicoplanin (81.4%) and vancomycin (81.4%). In our patients, the mortality rate during the first 28 days from the moment of positive isolates was high (37.4%). Most patients died within the first seven days. Bacterial blood infections caused by Gram-negative bacteria were associated with significantly higher mortality ($\chi^2 = 4.92$, $p = 0.026$). Acinetobacter spp. was isolated in almost half of the patients with fatal outcome, of whom 62.5% died in the first 24 hours. **Conclusion.** Bacterial bloodstream infections are severe complications with a high rate of mortality in febrile neutropenic hematological patients. Gram-negative bacteria were the most common isolates in our Clinic, with high mortality. It is of utmost importance to constantly monitor the resistance of bacteria to antibiotics, as well as to prevent and control the spread of resistant strains. Antibiotics resistance patterns should regularly be followed.

Key words: Febrile Neutropenia; Hematologic Neoplasms; Bacteremia; Blood Culture; Mortality; Drug Resistance, Bacterial; Gram-Negative Bacteria

Sažetak

Uvod. Bakterijske infekcije krvi tokom febrilne neutropenije su hitna medicinska stanja koja su bila i još uvek su glavni uzrok morbiditeta i mortaliteta kod bolesnika sa hematološkim malignitetima. Cilj rada je utvrđivanje učestalosti i kliničkih karakteristika bakterijemija, infektivnih agenasa, prisustva i učestalosti rezistencije na antibiotike, kao i ishod lečenja bakterijskih infekcija krvotoka kod pacijenata sa hematološkim malignitetima. **Materijal i metode.** Retrospektivna, trogodišnja studija obuhvatila je 107 bolesnika sa hematološkim malignitetima koji su imali pozitivne hemokulture tokom perioda febrilne neutropenije. **Rezultati.** Najčešći izolati su bile Gram-negativne bakterije (58,5%)−*Escherichia coli* koja je bila najčešće izolovani patogen. Gram-negativni mikroorganizmi bili su uglavnom osetljivi na karbapeneme u 70,7%, dok je osetljivost na druge antibiotike bila: piperacilin/tazobaktam 62%, amikacin 58,5% i cefalosporini treće generacije 50,5%. Bakterija *Acinetobacter spp* bila je osetljiva samo na kolistin (94,1%). Osetljivost na antibiotike među Gram-pozitivnim bakterijama bila je najveća za linezolid (97,1%), zatim za teikoplanin (81,4%) i vankomicin (81,4%). Kod naših bolesnika stopa smrtnosti tokom prvih 28 dana od momenta pozitivnih izolata bila je visoka (37,4%). Većina bolesnika je preminula u prvih sedam dana. Bakterijske infekcije krvi izazvane Gram-negativnim bakterijama povezane su sa značajno većim mortalitetom ($\chi^2 = 4,92$, $p = 0,026$). Kod skoro polovine bolesnika kod kojih je nastupio smrtni ishod bila je izolovana bakterija *Acinetobacter spp*, od kojih je 62,5% umrlo u prva 24 sata. **Zaključak.** Bakterijske infekcije krvi su teške komplikacije febrilnih neutropenija kod hematoloških bolesnika sa visokom stopom smrtnosti. Gram-negativne bakterije bile su najčešći izolati na našoj klinici, sa visokim mortalitetom. Veoma je važno stalno praćenje rezistencije bakterija na antibiotike, kao i preduzimanje preventivnih mera za kontrolu i širenje rezistentnih sojeva.

Ključne reči: febrilna neutropenija; hematološki maligniteti; bakteriemija; hemokultura; mortalitet; bakterijska rezistencija; Gram-negativne bakterije

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Abbreviations

FN – febrile neutropenia
GN – Gram-negative
GP – Gram-positive
MDR – multi-drug resistant
CoNS – coagulase-negative staphylococci
MRSA – methicillin-resistant Staphylococcus aureus
VRE – vancomycin-resistant enterococci
AML – acute myeloid leukemia
CVC – central venous catheters

Introduction

Patients with hematologic malignancies are subjected to intensive myelosuppressive and immunosuppressive therapy. They are at high risk for developing severe, life-threatening infections [1].

Bacterial infections are the most common of all microbial infections, and their resistance is a major global problem [2]. Bacteremia is the most significant cause of mortality during neutropenic episodes. It is found in one-third of all cases of febrile neutropenia (FN) and it is the leading cause of death in patients with FN [3].

Over the past decades, there has been a significant change in the spectrum of bacterial pathogens isolated in FN patients [4]. While the incidence of Gram-negative (GN) infections was high during the 1960s and the 1970s, the increase in catheter use, prophylactic administration of quinolones, and the use of broad-spectrum antibiotics led to a rise in the incidence of Gram-positive (GP) infections in the 1990s. However, recent studies showed another shift towards GN isolates [5].

Increased resistance to penicillin and cephalosporin and increased use of broad-spectrum antibiotics like carbapenems, led to a higher incidence of fungal infections and Clostridium difficile colitis [1, 6]. Knowing the local antibiotic resistance pattern is essential for the choice of empiric antibiotic therapy in neutropenic patients.

This study aimed to examine the epidemiology of bloodstream infections during episodes of FN in patients with hematologic malignancies and to present the features of isolated pathogens and their drug sensitivity pattern. The second objective of the study was to analyze the outcomes of these infections.

Material and Methods

A single-center retrospective study was carried out at the Clinic of Hematology, Clinical Center Vojvodina. The medical records of all patients hospitalized between January 1st, 2015 and December 31st, 2017 were reviewed, and data of all positive blood cultures taken in FN were obtained. The FN was defined as oral temperature higher than 38.5°C or two consecutive measurements higher than 38.0°C, two hours apart, while the absolute neutrophil count was less than 0.5 x 10^9/l [6].

Data about the age, gender, underlying disease, chemotherapy, blood culture isolates, sensitivity pattern, and outcome after 7 and 28 days from the diagnosis of bacteremia were collected.

The bacterial isolation and identification was done in the laboratories of the Microbiology Center of the Institute of Public Health of Vojvodina in Novi Sad. In vitro, the antibiotic sensitivity pattern of blood isolates was determined by the Kirby-Bauer disc diffusion method. The results were interpreted using the guidelines of the Clinical and Laboratory Standards Institute and the European Committee on Antimicrobial Susceptibility Testing. They were classified as fully sensitive (S), moderately sensitive (M), and resistant (R). Strains showing moderate sensitivity were classified as resistant.

The collected data were analyzed using standard statistical methods. Statistical significance was set at $p < 0.05$. The study was approved by the Ethics Committee of the Clinical Center of Vojvodina. All procedures involving human participants were performed in accordance with the ethical standards of the institutional and national research committees and with the 1964 Helsinki declaration.

Results

Clinical characteristics of the study subjects

During the study period, excluding double positive results during the same febrile episode, there were 153 positive blood cultures in 107 patients. Forty-nine patients were male (45.8%), 58 were female (54.2%), and the average age was 53 ± 15.54 years (ranging from 19 to 80 years). The highest number of positive blood cultures was found in patients with acute leukemia. Out of 107 patients, 15 (14%) patients were in relapse, while 24 (22.4%) patients were treatment-resistant **(Table 1)**.

All but nine patients (8.4%) received high-dose chemotherapy regimens. Fourty-seven positive blood cultures (30.7%) were identified after remission induction treatment **(Graph 1)**. In those cases, bacteremia was most commonly diagnosed on the 17th day after chemotherapy was initiated.

Fourteen patients (13%) had positive blood cultures on two occasions, 6 patients (5.6%) on three, 3 patients (2.8%) on four, and 1 patient (0.93%) on each seven occasions. Most patients with acute myeloid leukemia had two or more positive blood cultures.

Types of isolated pathogens

Out of 153 positive blood cultures, a bacterial pathogen was identified in 150 (98%), while a fungal agent was isolated in the remaining three (2%) **(Table 2)**. Polymicrobial bacterial blood cultures were found in 12.66%, 17 were positive for two bacterial agents, and two were positive for 3 bacterial agents. Since 19/150 (12.66%) bacterial blood episodes were polymicrobial, a total of 169 bacteria were identified.

The GN bacteria were isolated in 58.5% (99/169). The most commonly isolated species were Escherichia coli, followed by Pseudomonas aeruginosa, Acinetobacter species (spp.), and Klebsiella pneumoniae. The most common GP isolate was coagulase-negative staphylococci (CoNS). Enterococcus species were found in 17 positive blood cul-

Table 1. The incidence of hematologic malignancies among patients with febrile neutropenia
Tabela 1*. Incidencija malignih hemopatija kod bolesnika tokom febrilne neutropenije*

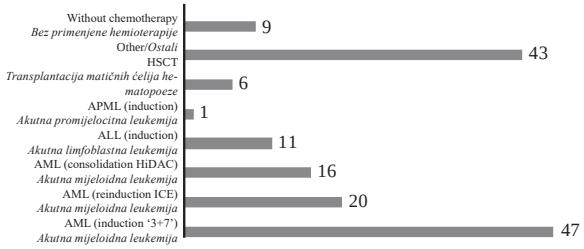
Diagnosis *Dijagnoza*	Number of positive hemocultures (%) *Broj pozitivnih hemokultura (%)*
Acute myeloid leukemia/*Akutna mijeloidna leukemija*	86 (56.2%)
Acute lymphoblastic leukemia/*Akutna limfoblastna leukemija*	24 (15.7%)
Non-Hodgkin's lymphoma/*Non-Hočkin limfom*	15 (9.8%)
Multiple myeloma/*Multipli mijelom*	11 (7.2%)
Myelodysplastic syndrome/*Mijelodisplastični sindrom*	6 (4%)
Chronic lymphocytic leukemia/*Hronična limfocitna leukemija*	5 (3.2%)
Hodgkin's lymphoma/*Hočkinov limfom*	3 (2%)
Acute plasmocytic leukemia/*Akutna promijelocitna leukemija*	1 (0.63%)
Aplastic anemia/*Aplastična anemija*	1 (0.63%)
Hairy-cell leukemia/*Leukemija vlasastih ćelija*	1 (0.63%)
Total/*Ukupno*	153 (100%)

Table 2. The most common microbial isolates
Tabela 2*. Najčešći mikrobiološki uzročnici*

Microbial agent/*Uzročnik*	n (%)	Microbial agent/*Uzročnik*	n (%)
Gram+ isolates/*Gram+ bakterije*	70 (41.5)	Gram– isolates/*Gram–bakterije*	99 (58.5)
CoNS*	37 (52.9)	Escherichia coli	29 (29.3)
Enterococcus	17 (24.3)	Pseudomonas aeruginosa	23 (23.2)
Streptococcus	9 (12.8)	Acinetobacter spp.	17 (17.8)
Staphylococcus aureus	7 (10)	Klebsiella pneumoniae	17 (17.8)
		Enterobacter spp.	9 (9.1)
Fungal isolates/*Gljivični izolati*	3 (2)	Other/*Drugo*	4 (4)

CoNS* – Coagulase negative Staphylococcus species/*Koagulaza-negativni stafilokok*

tures (24.9%) **(Table 2)**. Fungal isolates were Candida parapsilosis and Candida albicans. No resistance to caspofungin treatment was observed.



Graph 1. The incidence of positive blood cultures according to the chemotherapy protocol, n
Grafikon 1. *Incidencija pozitivnih hemokultura prema vrsti hemioterapijskog protokola, n*

Legend/*Legenda***:** AML – acute myeloid leukemia, remission induction treatment '3+7' – daunorubicin during 3 days and cytarabine during 7 days/*akutna mijeloidna leukemija, indukciona terapija '3 + 7' - daunorubicin tokom 3 dana i citarabin tokom 7 dana*; ICE – ifosfamide, carboplatin and etoposide/*ifosfamid, karboplatin i etopozid*; HiDAC – high-dose cytarabin/*visoke doze citarabina*; ALL – acute lymphoblastic leukemia/*akutna limfoblastna leukemija*; APML – acute promyelocytic leukemia/*akutna promijelocitna leukemija*; HSCT – hematopoietic stem cell transplantation/*transplantacija matičnih ćelija hematopoeze*; Without chemotherapy/*Bez primenjene hemioterapije;* Other/*Ostali*

Pathogens' sensitivity to antibiotics

In our center, Ceftazidime 2 x 2 g and amikacin 2 x 500 mg is a standard first-line empiric antibiotic treatment for FN. Around half of GN isolates in this study were sensitive to this combination. The GN isolates showed higher susceptibility to piperacillin/tazobactam monotherapy (4.5 g/6 h) which is a standard second-line treatment in our center. The standard third-line therapy (carbapenem with or without vancomycin) showed the highest sensitivity **(Table 3)**. Escherichia coli, as the most frequent GN isolate, was sensitive to the first- and second-line therapy almost in 90% of cases. Pseudomonas aeruginosa also showed high sensitivity to all standard lines of antibiotics. Therefore, in our study, Pseudomonas aeruginosa was not classified as multidrug resistant (MDR). On the other hand, due to resistance to cephalosporins, piperacillin/tazobactam, amikacin, and ciprofloxacin, Klebsiella pneumoniae was classified as MDR. Nevertheless, sensitivity was high to carbapenems, tigecycline, and colistin. Acinetobacter spp. was pan-resistant in our study. We detected a high percentage of resistance to ciprofloxacin in GN isolates, although in our center fluoroquinolone prophylaxis is not employed **(Table 3)**.

The GP isolates were mostly resistant to methicillin, but showed a sensitivity to piperacillin/tazobactam and

Table 3. Incidence and sensitivity pattern of Gram-negative bacteria, n (%)
Tabela 3. *Incidencija i senzitivnost Gram-negativnih bakterija, n (%)*

Gram– bacterial agents *Gram– bakterije*	Total *Ukupno*	pip/ tazo	ceftazi/ ceftri	carbep	amk	cipro	amox clav	Vanco	Colis
Escherichia coli	29	26/29 (89.6%)	20/29 (69%)	29/29 (100%)	26/29 (89.6%)	17/29 (58.6%)	17/29 (58.6%)	/	/
Pseudomonas aeruginosa	23	21/23 (91.3%)	17/23 (74%)	16/23 (69.5%)	16/23 (69.5%)	15/23 (65.2%)	/	/	23/23 (100%)
Acinetobacter spp	17	0	0	0	0	0	0	0	16/17 (94.1%)
Klebsiella pneumoniae	17	7/17 (41.2%)	6/17 (35.2%)	16/17 (94.1%)	9/17 (53%)	10/17 (58.8%)	4/17 (23.5%)	/	17/17 (100%)
Enterobacter spp	9	7/9 (77.7%)	7/9 (77.7%)	9/9 (100%)	7/9 (77.7%)	7/9 (77.7%)	2/9 (22.2%)	/	
Total sensitivity/*Ukupna senzitivnost*		61.9%	50.5%	70.7%	58.5%	44.4%			98.2%

Legend/*Legenda*: Pip/tazo – piperacillin/tazobactam; Ceftazi/ceftri – ceftriaxone/ciprofloxacin; Carbep – carbapenem; Amk – amikacin; Cipro – ciprofloxacin; Amox/clav – amoxicillin/clavulanic acid; Vanco – vancomycin; Colis – colistin

Table 4. Incidence and sensitivity pattern of Gram-positive bacteria, n (%)
Tabela 4. *Incidencija i senzitivnost Gram-pozitivnih bakterija, n (%)*

Gram+ bacterial agents *Gram+ bakterije*	Total *Ukupno*	pip/tazo	ceftazi/ ceftri	Carbep	cipro	amox/ clav	vanco	Linez	Teicopl
Staphylococcus spp coag-	37	16/37 (43%)	/	/	12/37 (32.5%)	26/37 (70.3%)	36/37 (97.3%)	37/37 (100%)	35/37 (94.6%)
Enterococcus	17	6/17 (35.2%)	/	8/17 (47%)	12/16 (70.6%)	2/17 (11.7%)	7/17 (41.1%)	17/17 (100%)	6/17 (35.3%)
Streptococcus	9	9/9 (100%)	5/9 (55.5%)	/	9/9 (100%)	/	7/9 (77.7%)	7/9 (77.7%)	9/9 (100%)
Staphylococcus aureus	7	7/7 (100%)	/	/	7/7 (100%)	/	7/7 (100%)	7/7 (100%)	7/7 (100%)
Total sensitivity/*Ukupna senzitivnost*		56.3%			57.1%		81.4%	97.1%	81.4%

Legend/*Legenda*: Pip/tazo – piperacillin/tazobactam; Ceftazi/ceftri – ceftriaxone/ciprofloxacin; Carbep – carbapenem; Cipro – ciprofloxacin; Amox/clav – amoxicillin/clavulanic acid; Vanco – vancomycin; Colis – colistin

fluoroquinolones in around half of the cases. There were no methicillin-resistant Staphylococcus aureus (MRSA) isolates. The majority of Enterococci were vancomycin-resistant enterococci (VRE). All VRE were sensitive to linezolid and tigecycline. The sensitivity to vancomycin in other GP isolates was high; CoNS, as the most frequently GP isolate, was highly susceptible to amoxicillin/clavulanic acid, vancomycin, and linezolid **(Table 4)**.

Infection outcome

Forty patients (37.4%) died within 28 days after the diagnosis of bacteremia, the majority of them within the first seven days. Bacteremias caused by GN bacteria were associated with significantly higher mortality ($\chi^2 = 4.92$, $p = 0.026$). Acinetobacter spp. was isolated in almost half of the fatalities, of whom 62.5% died within the first 24 hours. Acute leukemia was the most common underlying disease in deceased patients; acute myeloid leukemia in 18/40 (45%), acute lymphoblastic leukemia in 5/40 (12.5%), non-Hodgkin's lymphoma in 5/40 (12.5%), chronic lymphocytic leukemia in 4/40 (10%), myelodysplastic syndrome in 4/40 (10%), multiple myeloma in 3/40 (7.5%), and Hodgkin's lymphoma in 1/40 (2.5%).

Discussion

In our center, bacteremia was most commonly detected in patients with acute myeloid leukemia (AML) after remission induction treatment, which is in accordance with other studies [8–11]. High incidence of FN in AML is in part the consequence of high dose chemotherapy that leads to deep and prolonged neutropenia. However, acute leukemia and myelodysplastic syndrome are also independent risk factors for the development of severe complications of FN [8].

Fungal agents, Candida species, showed a decreased incidence in our center compared to the previous study by Savić et al. 17 years ago [12]. Our results correlate with other studies [10, 13, 14]. Despite a decreased incidence due to antifungal prophylaxis, fungal infections still represent a major health problem, because prophylaxis is given sporadically, mostly in patients with prolonged neutropenia. Fungal infections are acquired through invasion from the gastrointesti-

nal tract or via central venous catheters (CVC). Removal of CVC is essential in infections with Candida spp. and other fungi, Staphylococcus aureus, Pseudomonas aeruginosa and rapidly growing nontuberculosis mycobacteria [15, 16]. It is also recommended in cases of catheter entry site infection, septic thrombosis, endocarditis, hemodynamic instability (septic shock), and persistence of sepsis for more than 72 hours despite adequate antibiotic therapy [17].

In the present study, GN isolates were found in 58.2% of all bacteremia cases, which correlates with currently available data [18, 19]. Numerous studies suggest that in the last two decades there has been a change in the microbiological spectrum of bacteremia and that GP isolates are more often the cause of bacteremia in patients with hematologic malignancies [20, 21]. Ramphal explains this by the increased use of Hickman's catheters, followed by colonization and infection of the surrounding skin by flora, which is generally GP. Studies show that the prophylactic use of fluoroquinolones, which suppresses the colonization of the gastrointestinal tract with aerobic GN bacteria, but not with the microaerophilic GP bacteria, in part leads to the increased incidence of bacteremia caused by GP agents [11, 15, 22].

Escherichia coli was the most common GN isolate, while CoNS were the most common GP isolates. Most of the CoNS isolates were probably contaminants from the skin, and in most cases they were multisensitive. The bacterial spectrum of isolated agents in this study is similar to other international studies [9–11, 23]. On the other hand, it somewhat differs from the spectrum reported in the survey conducted in our center nearly two decades ago with Acinetobacter spp. being the most common GN isolate [12].

Except for Acinetobacter spp., the sensitivity of GN isolates to the first- (third generation cephalosporin with amikacin) and second-line (piperacillin/tazobactam) antibiotics were reasonably good in our study. Apart from Acinetobacter spp. and Klebsiella pneumoniae, there was a high sensitivity to carbapenems. Our results have changed over the last two decades when the reported sensitivity of GN isolates to carbapenems was mearly 47% [12]. The lower percentage of Acinetobacter isolates in our study comparing to seventeen years ago may explain this fact. Pseudomonas aeruginosa was highly sensitive to piperacillin/tazobactam (91.3%), which correlates with previously published results [24].

On the other hand, some studies have reported a significantly lower rate of Pseudomonas aeruginosa sensitivity to piperacillin/tazobactam [21, 25]. Unlike the results of Savić et al. seventeen years ago, Acinetobacter spp. is not so common, isolated in 13% of cases, but pan-drug resistant with a high mortality rate. Menzo et al. have detected Acinetobacter spp. at a much lower rate, below 3%, which is also the case in other studies [21, 25, 26]. In addition to colistin, which is the go-to antibiotic for treating multidrug resistant Pseudomonas aeruginosa and Acinetobacter spp. infections, tigecycline plays an essential role in the treatment of those infections [27].

Our results showed that GP isolates show a low sensitivity to fluoroquinolones (57.2%). Low sensitivity to fluoroquinolones was observed in other studies as well, especially in patients in whom fluoroquinolones were administered as prophylaxis [28]. In our study, GP isolates were highly sensitive to vancomycin, teicoplanin and linezolid. The VRE was detected in 14.3% of GP isolates, which is a lot less than in current data where it accounts for about 25% of GP isolates [29]. However, Gedik et al. detected VRE only in 4% of cases [17]. They stated that VRE bacteremia is associated with a severe clinical condition and that decreasing the frequency of invasive procedures, including bone marrow biopsy and CVC installation, reduces the incidence of VRE sepsis in patients with VRE colonization [17]. The rarest of all GP isolates was Staphylococcus aureus (4.11%), while MRSA was not isolated at all, which in part can be explained by the infrequent use of CVC in our center [11].

The bacteremia mortality rate in our study was 37.4%, higher than in most published data [11, 21, 24]. The GN bacteremias were associated with a significantly higher mortality rate than GP bacteremias. The high death rate in our center can be explained by a higher degree of antibiotic resistance, especially in GN isolates, mainly, Acinetobacter spp. isolated in 40% of the deceased patients. The most common GN isolate, Escherichia coli, seldom led to fatal outcome. Although being the most common GP isolate, CoNS did not lead to fatal outcomes. These results correlate with current published data [17, 21, 30].

Although the survival of patients with hematologic malignancies has improved over the past decade, these patients remain at high risk of developing life-threatening infections. Bacteremia is a severe complication with a high mortality rate.

There were some limitations and insufficiencies in our study. First, it is a single center retrospective study and bacteremia spectrum was analyzed in a heterogeneous group of hematologic malignancies which makes it difficult to generalize the findings for all groups. By including only bloodstream isolates, the applicability of our results may be difficult to extrapolate to other sites of infection. And finally, we did not take into consideration the initiation time of antibiotic or antimicrobial therapy, nor the treatment modifications made during FN.

Conclusion

Our results showed a different epidemiological situation in our clinic compared to two decades ago. Escherichia coli was the predominant isolate. The first- and the second-line of empirical antibiotics in our center are still reasonably efficient. On the other hand, high mortality rate, especially in case of Acinetobacter spp., indicates a need to revise our approach in treating febrile neutropenia in hematologic patients. For that matter, continuous surveillance of the spectrum of locally prevalent pathogens and their susceptibility patterns is essential in making local protocols for empirical antibiotic treatment.

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RESULTS OF SURGICAL TREATMENT OF THE PATELLAR TENDON RUPTURE

REZULTATI OPERATIVNOG LEČENJA POVREDA ČAŠIČNE VEZE

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Summary

Introduction. The aim of the study was to report surgical treatment results of complete patellar tendon ruptures reconstructed by different surgical procedures. **Material and Methods.** This study included 35 patients, 26 males and 9 females, with an average age of 39 (range, 16 - 66) years. Seventeen patients had the risk factors (48.6%), including 11 with prior surgeries of the same knee: 7 reconstructions of the anterior cruciate ligament, 3 total knee replacement surgeries, and one intramedullary nailing. In 27 patients (77.1%), the surgery was performed during the first seven days after the injury. The following procedures were applied: patellar tendon repair with suture anchors in 5 cases; 13 transpatellar suturing through transpatellar tunnels; additional strengthening with wires and screws was performed in 7 patients; 7 reconstructions with bone-tendon-bone allograft taken from the bone bank, and in 3 patients contralateral bone-tendon-bone autografts were used. **Results and Discussion.** The average Lysholm score was 86.1 (range, 27 - 100). Excellent results were found in 19 cases (54.2%), satisfactory in 10 (28.6%), and unsatisfactory in 6 patients (17.1%) who had chronic diseases and total knee replacement. The patients with timely diagnosis had significantly better results (90.1) than patients with chronic tendon injuries (72.6 points). **Conclusion.** Good results of acute rupture reconstruction are achieved by transosseous techniques or suture anchors. The surgery is much more complicated in neglected and chronic ruptures, and the results are worse. Surgical procedures, such as the patellar tendon reconstruction by bone-tendon-bone graft, additionally strengthened with wiring and screws, contribute to stable fixation, enable early rehabilitation, and prevent stiffness and muscle weakness.

Key words: Patellar Ligament; Tendon Injuries; Reconstructive Surgical Procedures; Treatment Outcome; Risk Factors; Lysholm Knee Score; Range of Motion, Articular; Bone-Patellar Tendon-Bone Grafts

Sažetak

Uvod. Cilj studije predstavlja prikaz rezultata lečenja kompletnih prekida čašične veze, rekonstruisanih različitim tehnikama. **Materijal i metode.** Studijom je obuvaćeno 35 pacijenata: 26 muškaraca i devet žena, prosečne starosti 39 godina (16−66). Sedamnaestoro pacijenata je imalo faktore rizika (48,6%), uključujući 11 prethodnih operacija istog kolena, u vidu: sedam rekonstrukcija prednjeg ukrštenog ligamenta, tri ugradnje totalne proteze i jednog intramedularnog klina. Kod 27 pacijenata (77,1%) operacija je izvršena u toku prvih sedam dana posle povrede. Šivenje ligamenta i njegovo pripajanje za čašicu ankerima je primenjeno kod pet pacijenata; u 13 slučajeva postavljani su šavovi kroz tunele u čašici; dodatno ojačanje šavova žicom i zavrtnjima vršeno je kod sedam pacijenata; u sedam slučajeva rekonstrukcija je vršena kost–tetiva–kost alograftom uzetim iz koštane banke, a kod tri pacijenta kontralateralnim kost–tetiva–kost kalemom. **Rezultati i diskusija.** Prosečna vrednost Lišolmovog skora iznosila je 86,1 poen (27−100). Odlični rezultati postignuti su kod 19 (54,2%), zadovoljavajući kod 10 (28,6%), a nezadovoljavajući kod šest pacijenata (17,1%) jer su imali sistemska oboljenja ili raniju ugradnju totalne proteze kolena. Pacijenti čija je povreda pravovremeno dijagnostikovana imali su značajno bolje rezultate (90,1) od operacije hroničnih slučajeva (72,6 poena). **Zaključak.** Zadovoljavajući rezultati svežih ruptura postižu se rekonstrukcijama uz pomoć transosealnih šavova ili ankera. Kod previđenih i hroničnih slučajeva, operacija je znatno komplikovanija a rezultati lošiji. Operativne tehnike, poput supstitucije ligamenta kost–tetiva–kost kalemom, koji se dodatno ojačava žicama i zavrtnjima, doprinose stabilnoj fiksaciji, omogućavaju ranu rehabilitaciju i preveniraju kontrakturu i atrofiju mišića.

Ključne reči: tetiva čašice kolena; povrede tetive; rekonstruktivne hirurške procedure; ishod lečenja; faktori rizika; Lišolmov skor; obim pokreta zgloba; kost- tetiva-kost kalem

Introduction

The patellar tendon is the final connection of the extensor mechanism of the knee. It is basically a ligament, connecting the sesamoid bone (patella) with another bone (tibial tubercle), but also a tendon, because the strong quadriceps muscle ends with it in the tibia. A patellar tendon rupture is the third most common injury of the extensor mechanism, right after patella fracture and quadriceps

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Abbreviations

ACL – anterior cruciate ligament
MRI – magnetic resonance imaging
BTB – bone-tendon-bone
N – Newton
BPTB – bone-patellar-tendon-bone

tendon rupture [1–4]. A current study [1] that followed 230 middle aged people (on average 44 years old), without symptoms associated with the knee joints, concluded that as much as 97% of them had asymptomatic magnetic resonance imaging (MRI) verified lesions of the following structures: 30% of menisci, 57% of cartilage, 21% of tendons and 3% of ligaments [1]. Moderate lesions of patellar tendon were found in 11% of knee joints, and serious asymptomatic lesions in 2% of all cases [1].

A patellar tendon rupture most often occurs at patellar insertion or its middle part [4–6]. In younger patients it occurs due to repeated microtrauma and as a result of taking out the medial part of the tendon during anterior cruciate ligament (ACL) reconstruction procedure, or after inrtamedullary nailing [5, 7, 8]. However, this injury is a result of degenerative changes in the tendon, corticosteroid infiltration, knee prosthesis and systemic diseases in older patients [6, 7, 9, 10].

The patellar tendon rupture is diagnosed by symptoms such as pain, palpable infrapatellar defect, inability to extend the knee against gravity, too high position of patella (confirmed by lateral radiography) as well as by ultrasonography and MRI in less obvious cases, such as partial ruptures and associated injuries [1].

Patellar tendon ruptures, especially chronic and neglected ones, are technically difficult to repair and the main goal of treatment is to reconstruct the extensor mechanism to allow painless full range motion of the knee joint, regain the muscle strenght and non-restricted everyday activities. However, there is still a dilemma about an optimal surgical procedure, choice of implants, duration of wearing a cast, and rehabilitation procedures [5, 11]. Therefore, the aim of this study is to present our results of surgical treatment of the ruptured patellar tendon and to determine if there is a significant difference between the results among the patients with and without risk factors, as well between acute and chronic reconstructions.

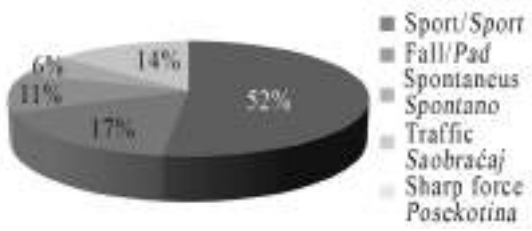
Material and Methods

This retrospective multicentric study was performed at the Clinic of Orthopedic Surgery and Traumatology of the Clinical Center of Vojvodina, and at the General Hospital Subotica, with the prior approval of the Ethics Committee. In the period from 2008 to 2018, there were 52 patients with a complete patellar tendon rupture who underwent surgery. This study included 35 of them, who volunteered to complete a questionnaire available on the internet [12] and had X-rays of their knee and measurements of the range of motion in the operated knee joint and girth of the thigh (10 cm above the patella). The average follow up was 4 years (range, 2 – 10).

The study included 26 males (74%) and 9 females (26%), with an average age of 39 (range, 16 – 66) years, among whom there was one case with a bilateral patellar tendon injury. The left knee was injured in 20 cases, the right in 16. The main cause of injury was a sport related activity (51.6%), because 15 athletes, mainly male, experienced a trauma during jumps (8 in basketball, 4 in soccer, 3 in handball), and three patients during weight lifting. Other causes were falls from a height in 6 patients, sharp objects causing bleeding wounds in 5 cases, old patients had four injuries with no serious trauma, and two ruptures happened in traffic accidents **(Graph 1)**. A subgroup included 7 patients, 6 males and 1 female, aged between 18 and 25 years, with prior ACL reconstruction with complications of patellar tendon rupture,.

The participants were divided into two groups, a group with risk factors and a group without them **(Table 1)**. Risk factors for patellar tendon rupture were found in 17 patients (48.6%). Chronic diseases were registered 8 times, 11 patients had former operations of the same knee joint, and three athletes had chronic tendinitis (one of them received a local corticosteroid therapy). Present comorbidities were as follows: two cases with diabetes, secondary hyperparathyroidism, reumatoid artritis, gout, and renal failure, each in one patient. Eleven patients with a predisposition for tendon rupture underwent the following surgeries: anterior ligament reconstruction (7), total knee prosthesis (3), and intramedullar nail that migrated proximally into the tendon after tibial fracture management (1).

The injury was diagnosed on time and the surgery was performed within the first seven days in 27 patients (77.1%). Different surgical procedures were used: surgical repair of 5 tendons with nonabsorbable Bunnell or Krackow-type sutures fixed with anchors; 13 repairs with sutures through patellar tunnels **(Figure 1)**, and 17 cases with additional wires and screws placed through the tibial tubercle **(Table 2)**. In eight cases (22.9%) the surgery was not performed in the acute phase (between 3 weeks and 2 months after the injury), so due to tendon proximal retraction, we used contralateral bone-tendon-bone (BTB) autograft, or BTB allograft



Graph 1. Causes of patellar tendon rupture
Grafikon 1. *Uzroci povrede čašične veze*

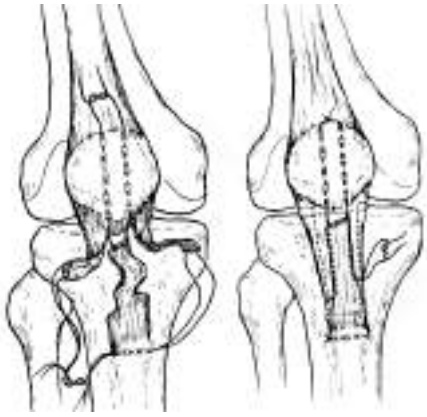


Figure 1. Surgical repair of acute patellar tendon rupture
Slika 1. *Operativna tehnika akutne rupture ligamenta patele*

from the bone bank, with augmentation using wires and screws [6] **(Figure 2)**.

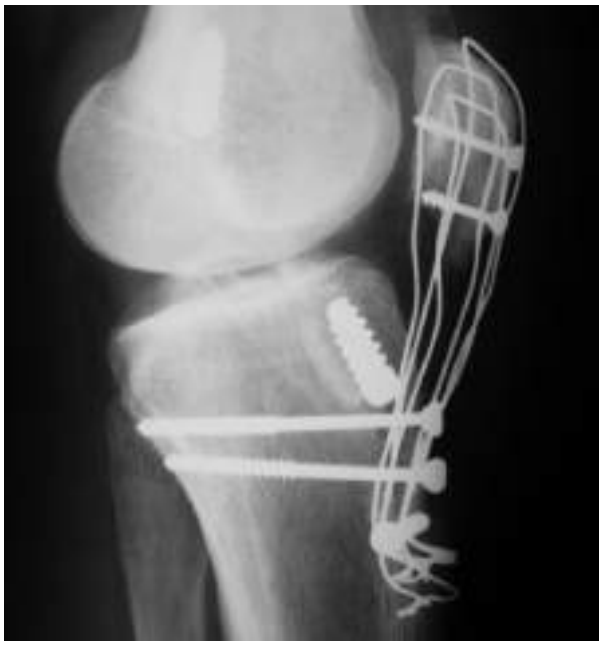


Figure 2. Lateral X-ray of a knee after chronic patellar tendon reconstruction with BTB graft, wires and screws [8]
Slika 2. *Profilni rendgenski snimak kolena nakon rekonstrukcije hronične rupture ligamenta patele KTK (kost-tetiva-kost) kalemom, žicama i zavrtnjima [8]*

All patients with acute ruptures wore their orthosis for three weeks, in order to reduce pain and swelling, because they underwent passive exercises from the second postoperative day, with partial weight-bearing. Postoperatively, the knee joint was immobilized for six weeks with delayed partial weight-bearing in patients with chronic rupture surgery. All of the patients underwent at least a three-month rehabilitation protocol.

The results were based on the average Lysholm score [13], which takes into account pain, swelling, instability, weight-bearing, climbing stairs, limping and squatting. Postoperative outcome was rated excellent in the range from 90 to 100 points, satisfactory from 80 to 89 points, and poor below 79 points. This scale was also used to compare the results between different patient groups and surgical procedures. The difference in volumes of the left and the right thigh exceeding 2 cm indicated hypotrophy of the quadriceps muscle.

Seventeen patients who did not respond to the invitation or did not want to fill the questionnaire were excluded from the study. The exclusion criteria were also partial rupture of this tendon and improper rehabilitation.

The results were statistically analyzed by Student's T-test and presented in tables and graphs. The values of $p < 0.05$ were considered statistically significant. Some of the surgical procedures were shown in figures.

Results

The highest Lysholm score was 100 points, the lowest 27, and the average score was 86.1 points. A statistically significant difference was found between the group of patients with chronic diseases and prior surgeries, with an average of 79.0 points, in comparison to the group without risk factors who scored 92.1 points ($p = 0.0197$; $p < 0.05$). The best results were found in patients with acute ruptures without risk factors, and the worst in two patients with chronic ruptures that had infection after total knee replacement with prosthesis, and a patient on dialysis **(Table 1)**.

According to the Lysholm scale, 19 patients had excellent postoperative results (54.2%), 10 achieved satisfactory (28.6%), and all of the 6 patients with unsatisfactory (17.1%) results were in the group with chronic diseases and prior total knee replacement.

Twenty one patients (60.0%) returned to the activities of daily living without reduction, whereas in 14 (40.0%) the activities were reduced or modified.

Table 1. Average results among different types of injuries and patient groups
Tabela 1. *Prosečni rezultati između različitih vrsta povreda i grupa pacijenata*

	No/*Br.*	Average Lysholm score/*Prosečni Lišolm skor*
Acute ruptures/*Sveže povrede*	27	90.1
Chronic ruptures/*Zastarele povrede*	8	72.6
With risk factors/*Prisustvo faktora rizika*	16	79.0
Without risk factors/*Odsustvo faktora rizika*	19	92.1
Total/*Ukupno*	35	86.1

Table 2. Comparison between results of different surgical procedures
Tabela 2. *Poređenje rezultata različitih operativnih tehnika*

Surgical procedures *Operativna tehnika*	Number of patients *Broj pacijenata*	Average Lysholm score *Prosečni Lišolm skor*
Sutures with anchors/*Ankerisani šavovi*	5	84.2
Sutures through patella/*Šavovi kroz čašicu*	13	86.0
Sutures with wires and screws/*Šavovi sa žicom i zavrtnjem*	7	92.4
BTB allograft + wires + screws/*KTK alokalem + žice + zavrtnji*	7	88.7
BTB autograft + wires + screws/*KTK autokalem+ žice + zavrtnji*	3	68.6

Legenda: KTK – kost-tetiva-kost

The patients with timely diagnosis, within 7 days after injury, had better results (90.1 points) than those with a chronic tendon tear (72.6 points) ($p = 0.008$; $p < 0.01$).

The surgical procedures used in the treatment of acute ruptures showed better average results than more complicated and technically demanding reconstructions with grafts and implants (87.0 versus 81.8 points) ($p < 0.05$) **(Table 2)**. The transpatellar technique showed slightly better average results in acute repairs than anchor technique (86.0 vs. 84.2). The only group that achieved an excellent average result of 92.0 points included all the 7 patients with acute rupture. We used transpatellar sutures with wires and screws in these cases.

A subgroup including 7 patients with prior ACL reconstruction showed an average score of 88.7 points (80 - 100), and all of the athletes successfully returned to sports activities. Four athletes returned to sports activities after 6 months, one after 8, and two 12 months after the patellar tendon surgery.

One patient with a former tibial osteosynthesis showed a satisfactory result scoring 85.0 points, while the subgroup with prior arthroplasty scored significantly poorer with 51.7 points on average, and there were two cases with unsatisfactory results.

Thirteen patients (37.1%) had a thigh muscle hypotrophy, associated with limited range of motion in eight cases. Our participants had no serious complications such as rerupture, but two of them with total knee arthroplasty had infections.

Out of 17 cases where wires and screws for strengthening was performed, in 12 (71.0%) the fixation material was extracted three months after the surgery on average, especially in case of wire breakage, over tightening the implants, or they protruded under the skin.

Discussion

In contrast to quadriceps tendon injuries, which usually occur in population older than 40 years [2, 3, 14], patellar tendon is mainly injured in males under the age of 40 [14–17]. This was confirmed in our sample as well. When we analyzed patients with former ruptures of the quadriceps tendon, the average age was 54 years [2, 3], while the mean age in our sample was 39. Complete rupture of the patellar tendon is very rare [1, 4, 8]. We annually have 5 operatively treated cases in the population of 800.000 citizens covered by two institutions. That is in line with an average incidence of 0.68 annual ruptures in 100.000 citizens [1]. The main cause of the patellar tendon injury is athletic trauma [14–18] during landing or stumbling, when the quadriceps muscle contracts eccentrically while the knee is flexed [18], thus more than a half our patients were injured during sports activities. The most common mechanism of injury was basketball landing (47% in a greater study) [14], followed by soccer injuries and weight lifting.

The knee extensor mechanism injuries occur due to overuse, during direct trauma or in iatrogenic way [2, 3, 6–8]. An unchanged patellar tendon has a substantial strength and the average force needed for its rupture is 4366 Newtons (N) [18], but measured forces that affect it during sports activities, that include sudden deceleration after landings or weight lifting, range between 8 and 10 thousand N [19]. The tendon load is maximal at its insertions where collagen fibers are tougher, during active extension when the knee is at an angle of 60 degrees with a planted foot. Repetitive micro-injuries leading to tendon weakness usually precede the rupture. Ruptures of the patellar tendon can occur secondary to trauma, in association with systemic diseases [2, 8, 9], after total knee arthroplasty [20–22] or ACL reconstruction [5, 7, 8, 23], as a late complication of tibial nailing [24, 25], or after local corticosteroid or anabolic administration and redressement force under an anesthetic [4, 6]. In case of associated systemic diseases, which lead to collagen weakness, such as rheumatoid arthritis, diabetes, chronic renal insufficiency or secondary hyperparathyroidism, the patellar tendon rupture may occur even without a significant trauma [6, 9]. Described risk factors also include Osgood-Schlatter's osteochondrosis and systemic lupus erythematosus [10]. Nowadays, anabolic steroid and fluoroquinolone use is also associated with increased risk for tendons [26]. It is well documented that ciprofloxacin can cause rupture of Achilles tendon, rotator cuff, biceps, wrist extensors, quadriceps muscle, even bilateral rupture of patellar tendon in a young person without risk factors [26]. Almost half of our patients had some of the mentioned risk factors. One of them received local corticosteroids due to the pain in the top of the kneecap ("jumper's knee").

Fresh ruptures should be repaired immediately, if skin conditions are optimal. Preoperatively, the Insall-

Salvati ratio of the contralateral knee serves as a baseline to restore the patellar height of the operative knee. The lenght of patella and its tendon should be equal (4 – 5 cm) to avoid patella baja and patella alta [27]. In 12 cases we drilled four 3 mm tunnels vertically through the patella and placed mattress sutures through the proximal end of the tendon drawing it securely to the inferior pole of patella. Afterwards, the sutures were tightened over the superior part of patella. If secure fixation cannot be obtained with this method, some techniques use augmentation with semitendinosus or gracilis tendon autografts. It is also important to pay close attention intraoperatively to the tension of the suture to allow 90 to 100 degrees of passive flexion [28]. We agree with the authors, Shelbourne et al., who suggest that knee immobilization is necessary only for two weeks to achieve 90 degrees of flexion. After four weeks of rehabilitation, flexion is 110 degrees, after three months it is 130 degrees, and after 6 months 140 degrees is achieved [28]. They used augmentation of the repair with special cable placed through the patella and tibial tubercle and tensioned it at 60 degrees of flexion, to prevent rerupture, but provide immediate postoperative movements. With this aggressive rehabilitation protocol, all of their 12 patients had returned to their previous levels of activity [28]. We have also registered excellent results in acute ruptures (90 points on average). In contrast, earlier views that have been overlooked claimed that braces should be removed six weeks after the surgery of acute rupture of patellar tendon [29].

It was thought that chronic ruptures are more than 6 weeks old [4] and the majority of authors moved the timing for safe surgery forward into the first two weeks after the injury [5, 8, 23, 27]. When a rupture is more than 6 weeks old, the soft tissues undergo irreversible changes, the patella is retracted proximally 3 – 5 cm and may require extensive surgical release of scar tissue and quadricepsplasty [29–31]. There are many techniques described in literature used to repair chronic patellar ruptures. Some use hamstring tendon autografts [32], some Achilles tendon grafts [24, 26, 27], some, like we did, a BTB grafts [5, 8, 23]. Some techniques reconstruct the neglected rupture with Z-shaped shortening of patellar tendon and Z-lengthening of quadriceps tendon to achieve adequate length of extensor mechanism [33]. In comparison to patellar tendon, there are no significant differences in outcomes related to the timing of ACL reconstruction [34], but in case of patellar tendon surgery, the time of reconstruction is an important factor for the final outcome.

The postoperative rehabilitation after chronic rupture surgery usually differs from more aggressive rehabilitation in acute injuries [23, 27]. That may be the reason why the results are not so good. In chronic ruptures, casts are removed usually after 6 weeks [4, 8, 29, 33] when active and passive exercises begin.

Cases of bilateral patellar tendon rupture are very rare, published mainly as case reports [4, 6, 8, 15–17, 26]. Since bilateral patellar tendon rupture is often unrecognized (up to 28% of cases) [29], it causes delays in diagnosis and treatment, because it is often nontraumatic and misdiagnosed with paraplegia. We also had a patient with bilateral rupture who had been on long-term hemodialysis due to renal insufficiency. The final outcome was unsatisfactory, due to comorbidities and late diagnosis. In this case we used BTB allograft augmented with wires [8], while the length was determined on profile X-ray of the patient's uninjured knee (Insall-Salvati ratio). O'Dowd et al. followed 361 patients, 13 with bilateral repairs, with an incidence of 5.8% [14].

Anterior knee pain is the most common complication after tibial nailing. Its occurrence has been reported in 30 to 47% of cases, particularly in young and active patients [24, 25]. The choice of surgical approach, transpatellar or parapatellar, has been reported as a contributory factor for knee pain after nail insertion. The parapatellar approach is suggested, when patellar tendon and well vascularized retropatellar fat pad are retracted. Bad choice of proximal entry point in the tibial plateau and possible proximal migration of the nail, dammaged the patellar ligament in one of our patients. Removal of the nail and suturing led to a satisfactory result.

Rupture of the patellar tendon may also occur after total knee arthroplasty. This serious postoperative complication happens in 0.17 to 0.55% of cases [20–22]. Intraoperative factors include over-resected patella, improper lateral release, too big components, and patellar maltracking [2, 20–22]. Postoperatively, a trauma may be the result of a revision procedure, with necessary appropriate extensile exposures. This increases the chances for infection and soft tissue adhesion [20–22]. Autografts and allografts (from the bone bank) are usually used in such cases, mostly Achilles tendon or BTB allograft [8, 23, 27]. In chronic ruptures, it is important to determine the length of allograft, because a too short leads to lack of flexion and too long results with lack of extension [35]. The results of direct repair of extensor mechanism failure are dismal (up to 90% unsatisfactory) because older population with knee replacement has a poor quality of tendon fibers [20, 21]. We had only one good outcome in three patients. Reconstructions with grafts can replace the retracted patella up to 3 cm distally [21, 22]. However, a large series of reported extensor allografts showed reasonable results after this complication of total knee arthroplasty in a group of 36 patients [36]. These patients were extremely challenging, because one third of them had previous infections. Eight patients had reruptures. After repeated revisions, two of them had recurrent ruptures [36]. It is important to perform graft tensioning in full knee extension to avoid failure [36].

A rupture of the patellar tendon after harvesting a BTB autograft occurs very rarely, in 0.1 – 0.24% of all reconstructions [5, 8, 23, 28]. In 6 of our 7 patients, rupture of patellar tendon occurred 10 months (7 – 12) after ACL reconstruction on average, during forced jumping. The etiology of patellar tendon rupture after ACL reconstruction lies in devascularization of the tendon during graft harvesting, its avascular degeneration, and because the donor tendon may be mechanically weak when the central third is removed [18]. Experimental measurements have proved

that the remaining two thirds of patellar fibers can absorb only a half of original tendon force, before the rupture (2227 N). We tried to prevent the disruption of the knee extensor apparatus during ACL reconstruction by avoiding harvesting too excessive BTB graft. Precise cutting tools should be used, without damaging the surrounding tissue, and careful closure of the peritendineum. The use of bone-patellar tendon-bone (BPTB) autograft is not recommended if patellar tendinopathy is obvious or there is a suspicion of partial tendon tear. It is known that patellar tendinopathy increases the risk of BPTB graft failure, when used for ACL reconstruction. In such cases, the surgeon should consider using a different graft [37, 38].

The most common surgical treatment of the acute patellar tendon rupture is simple suturing. This method provides lesser morbidity, so other studies also have reported excellent results in the treatment of patients with acute patellar tendon rupture [4, 39]. However, the gold standard for acute patellar tendon repair is transosseous technique, where sutures are passed through bone tunnels in the patella and tied over a bony bridge proximally [14, 28]. But there is a recent study that compared the results between 321 transosseous and 53 anchor repairs that showed that gold standard had 3.24 times the odds of reoperation versus anchor repair [14]. Other studies that followed the complications of anchor technique had reruptures more often (5 – 21%) [40, 41]. Our specimen is ten times smaller, but without reruptures in both groups.

The average operative results depend on the percentage of chronic ruptures in the whole sample, but the majority of them scored between 81 and 90 points according to Lysholm scale [4, 5, 8, 39]. We achieved the similar results with an average of 86 points. Our results of patellar tendon rupture surgery are also similar to quadriceps tendon reconstructions [2, 3], but not as good as the average results of ACL reconstruction, which range between 92 and 95 points [35, 38–41]. The average result of reconstruction of patellar tendon in our 7 patients with BTB graft **(Figure 2)** was almost excellent, with an average of 89 points (80 – 100), so all of them continued with sports activities [23]. Benner et al. [7] also treated 13 ruptures of patellar tendon after prior ACL reconstruction, but with anchors and wires. They achieved full range of motion in 11 of 13 cases (85%) after aggressive rehabilitation. Our results are similar, because 80% of our patients have no knee motion limitations. In our subgroup with prior ACL reconstructions, the results are even better.

An important issue to consider when reconstructing patellar tendon rupture after ACL reconstruction is whether to reinforce the tendon repair site with single or multiple wire loops [8, 23, 28, 42] or use postoperative immobilization instead. We reinforced the tendon repair site with multiple wire loops in 17 cases and secured immediate postoperative mobilization [23, 39]. In 71% of cases, removal of a multiple wire loop was required. Additional operation for removing the tension cerclage wiring is not always necessary, and it is recommended three months after the reconstruction [4, 23].

The most common early complications of patellar tendon surgery are deep venous thrombosis and local infection (both happen on average in 2.5%). The most common late complications are reruptures, that occurred in 6.5% of cases [14], as well as reduced mobility of the patella, low lying patella, limited flexion of the knee, persistent pain, and muscle weakness [4, 30, 31, 40]. The most frequent complication in our study was hypotrophy of the quadriceps muscle, which can be explained by insufficiently aggressive physical therapy in old patients with chronic ruptures. On the other hand, aggressive physical therapy may lead to patellar tendon rerupture, which was not the case in our study.

One of the disadvantages of our study is inclusion of non-uniformed groups. In some cases we compared the results between the young patients with risk factors and results of older patients without risk factors. This study compared the results of reconstructions among, for example, persons older than 40 years with risk factors and the same age group without them. A small sample does not allow proper comparison between transpatellar suturing and anchor technique. A histopathology analysis of the ruptured tendon could provide answers how to improve the strength of patellar tendon, especially in athletes in the fourth decade of life. This could prevent chronic tendinitis and injury. The future studies should follow the development of new surgical procedures, especially those that treat neglected and chronic cases. Some of them could provide more stable fixation, safer and earlier rehabilitation in order to prevent limited range of motion and muscle weakness.

Conclusion

Proper history taking and clinical examination with lateral radiography of a knee joint are sufficient for the diagnosis of complete rupture of the patellar tendon. These factors have a significant effect on the final treatment outcome. Mistakes and negligence in prior surgeries and during the examination can hardly be fixed with a late surgery.

The best surgical results of complete rupture of patellar tendon are achieved if the surgery is performed soon after the injury, in patients without prior surgeries of the same knee and without chronic diseases, no matter which technique is used. Good results of acute rupture repair can be achieved with transpatellar sutures or anchors.

All young athletes with prior surgeries of anterior cruciate ligament successfully achieved the level of former non-restricted activities after the reconstruction of patellar tendon.

Surgery is more complicated in neglected and chronic ruptures and the results are not so good. In these cases, surgical procedures using bone-tendon-bone grafts, taken from contralateral knee or from a bone bank, and augmented with wires and screws, may be successful. Similar surgical procedures provide stable fixation and early rehabilitation, preventing knee stiffness and muscle weakness.

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SUBJECTIVE AND OBJECTIVE ACOUSTIC VOICE ANALYSIS OF PRIMARY SCHOOL TEACHERS

SUBJEKTIVNA I OBJEKTIVNA AKUSTIČKA ANALIZA GLASA NASTAVNIKA RAZREDNE NASTAVE

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Summary

Introduction. Voice disorders in primary school teachers, as vocal professionals, are very common and often an inevitable phenomenon, which is unfortunately given little importance. Primary school teachers are at greater risk compared to other educators, because they rarely have opportunities for vocal rest during their working hours. The aim of this paper was to determine the acoustic voice characteristics of primary school teachers and their subjective experience of voice quality. **Material and Methods.** The study included 30 female teachers employed at the elementary school "Branko Radičević" in Banja Luka. For the purpose of objective acoustic analysis, the computer program Praat was used; for the purposes of subjective acoustic analysis the Grade, Instability, Roughness, Breathiness, Asthenia, and Strain scale was used, whereas the Voice Handicap Index was used for voice self-assessment. The effects of work experience, number of classes per week, bad habits and chronic diseases on voice quality were analyzed. **Results.** Statistically significant differences were found only in subjects who reported bad habits in the domain of subjective acoustic analysis, where pathological values were obtained for subscales grade, instability, roughness, breathiness and strain ($p < 0.05$), whereas the second statistically significant difference was observed in participants without previous history of chronic diseases, and who had significantly better speech intensity and lower harmonics-to-noise ratio ($p < 0.05$). **Conclusion.** In our research, objective and subjective acoustic analysis showed that about half of primary school teachers have voice disorders. Unhealthy habits and chronic diseases have a greater impact on the quality of voice of the primary school teachers than the length of work experience and the number of classes per week.

Key words: School Teachers; Speech Acoustics; Voice Quality; Voice Disorders; Acoustics; Occupational Exposure; Risk Factors; Diagnostic Self Evaluation

Sažetak

Uvod. Poremećaji glasa kod profesora razredne nastave, kao vokalnih profesionalaca, vrlo su česta i neretko obavezna pojava, a kojoj se nažalost pridaje mali značaj. Učiteljice su pod većim rizikom od drugih prosvetnih radnika i zbog toga što tokom radnog vremena retko imaju prilike za vokalni odmor. Cilj ovog istraživanja jeste utvrđivanje akustičkih karakteristika glasa profesora razredne nastave i njihovog subjektivnog doživljaja kvaliteta glasa. **Materijal i metode.** U istraživanju je učestvovalo 30 učiteljica iz OŠ „Branko Radičević" u Banjoj Luci. U svrhu objektivne akustičke analize korišten je kompjuterski program *Praat*, u svrhu subjektivne akustičke analize *Grade, Instability, Roughness, Breathiness, Asthenia, and Strain scale*, a za samoprocenu glasa upitnik Indeks glasovnog oštećenja. Analiziran je uticaj dužine radnog staža, nedeljnog broja časova, prisustva štetnih navika i hroničnih bolesti na kvalitet glasa. **Rezultati.** Statistički značajne razlike su se ispoljile kod ispitanica koje su prijavile prisustvo štetnih navika – u domenu subjektivne akustičke analize, gde su dobijene patološke vrednosti za supskale ($p < 0,05$), a druga statistički značajna razlika je zabeležena kod ispitanica koje nemaju hronične bolesti, a koje su imale značajno bolji intenzitet govora i niži odnos šuma i harmoničnog glasa ($p < 0,05$). **Zaključak.** Naše istraživanje pokazuje da oko polovine profesora razredne nastave ima odstupanja u pogledu glasa, bilo da se radi o objektivnoj ili subjektivnoj akustičkoj analizi. Štetne navike i hronične bolesti imaju veći uticaj na kvalitet glasa profesora razredne nastave u odnosu na dužinu radnog staža i nedeljno opterećenje časovima.

Ključne reči: nastavnici razredne nastave; govorna akustika; kvalitet glasa; poremećaji glasa; akustika; profesionalna izloženost; faktori rizika; samoprocena

Introduction

In modern society, about one third of the labor force works in occupations for which voice is the primary tool [1]. Voice is the essential element of verbal communication; for persons classified as vocal professionals – singers, actors, teachers, speech therapists, doctors, television presenters, etc., voice is one of the prerequisites for successful job performance. In vocal professionals, dysphonia may have a significant negative effect on job performance, it can lead to a decrease in income due to

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Abbreviations

F_0	– fundamental frequency
GIRBAS	– G - Grade; I - Instability; R - Roughness; B - Breathiness; A - Asthenia; S - Strain
HNR	– harmonics-to-noise ratio
VHI	– voice handicap index
SD	– statistical difference

absence from work, or even job loss, eventually leading to lower quality of life [2].

The voice of primary school teachers is daily affected by a number of factors which lead to vocal disorders: yelling, noise, often poor room acoustics and other negative environmental conditions, overloaded weekly schedules, and additional vocal activities [3]. Furthermore, compared to subject teachers and professors, primary school teachers have less vocal rest, considering the fact that classes are mostly continuous. Munier et al. [4] claim that a regular day for primary school teachers in an elementary school consists of 5 hours of continuous teaching on average, with short breaks in between, and a 30 minute lunch break. On the other hand, high school teachers have more opportunities for vocal rest as their classes last 45 minutes, and they often have a break between two classes. When we take into consideration certain harmful habits, such as smoking and alcohol drinking, the chance of developing phonatory system disorders in primary school teachers is even greater. Most studies in this field included female teachers, since most teachers are female, but also due to the fact that women have twice as many vocal problems compared to men [5]. Studies across the world show that vocal issues in teachers are associated with continuous vocal production and vocal exhaustion affects the acoustic characteristics of speech, leading to the change of acoustic quality during voice production [3]. The percentage of primary school teachers who reported having vocal issues was higher (11.0%) compared to persons with vocal issues who were not in the teaching profession (6.2%) [6], while an Italian study showed that the percentage of teachers who reported having ongoing vocal issues was 8.7%, as opposed to 2.9% in the general population, and the percentage of the development of vocal disorders in the entire lifetime was 51.4% in teachers, as opposed to 25.9% in the general population, making the difference significant [7].

When it comes to vocal intensity, vocal use in teachers outside of working hours (from 4PM to 10 PM on workdays and during the weekend) does not differ much from vocal use during working hours – the intensity was only 2.5 dB lower on average. It can be concluded that voice used during free time, can only additionally harm their already overburdened voice [8]. Many of these characteristics can be prevented or decreased by following the principles of vocal hygiene, which consists of a series of recommendations and advice about changing one's lifestyle, conditions of life, and daily habits.

Vocal performers need to have a high level of vocal flexibility, agility and ability to perform fast maneuvers, such as yelling or whispering. According to the research of Ferreir et al. [9], the following factors were recognized to affect vocal hoarseness: decreased water intake, shouting/loud speech, talking too much, difficulties with mouth opening while chewing and getting less than 6 hours of sleep. In the presence of noise, 94.6% of teachers increase their voice intensity, and 83.8% confirmed that it leads to a throat discomfort while teaching [10].

The literature data show that vocal symptoms in teachers during holidays do not appear, while they do appear during school months when teachers continuously use their voice [3]. Vocal disorders in teachers that develop due to inadequate use of the phonation apparatus combined with certain environmental factors are categorized as functional vocal disorders. Untreated functional dysphonia can lead to laryngeal lesions, which leads to hoarseness [11].

The aim of this research was to determine the acoustic characteristics of female school teachers and their subjective perception of voice quality. The next step was to analyze the acoustic vocal characteristics of school teachers, comparing them to standardized parameters, and if possible, connecting them to the acquired data and potential risk factors. Additionally, the purpose of this study was raising awareness about vocal disorders in this category of vocal professionals.

Material and Methods

The prospective study was conducted in the "Branko Radičević" Elementary School in Banja Luka, during September, 2020 and it included 30 female primary school teachers with their voice in good condition.

All the participants were given a written explanation of the purpose of the study. Participation in the study was completely anonymous and voluntary. The participants were asked questions by interviewers who then recorded their answers in writing. The study was approved by the Ethical Committee of the Faculty of Medicine Novi Sad.

The research consisted of four parts: 1. Filling out the general information form; 2. Objective acoustic voice analysis; 3. Subjective acoustic voice analysis; 4. Voice self-evaluation of the participants.

The participants first filled out the general information form, providing data on age, years of work experience, number of classes per week, existence of any chronic diseases that may affect voice quality (such as asthma, allergy to inhaled allergens, thyroid disease, reflux disease etc.), prescription drugs for these conditions, and any harmful habits, such as smoking, drinking alcohol or taking drugs, as well as vocal abuse.

Objective (computerized) acoustic voice analysis was done using the Praat (Dutch for "talk") computer software [12]. The phonation of the vowel /a/ was recorded first, using a pleasant pitch and intensity, and the recorded parameters were used for the following variables: fundamental frequency F_0 (Hz), intensity (dB), jitter (%), shimmer (%) and harmonics-to-noise ratio (HNR) (dB), as suggested by Maryn

et al. [13]. Afterwards, a short spoken statement was recorded, of an emotionally neutral tone – "I'll be back soon" in Serbian language, recording the height and intensity of speech. The voice of the participants was recorded using a computer microphone (Gembird MIC-D- 01), placed 5 cm away from the mouths of the participants.

Subjective acoustic analysis was done using the GIRBAS (G – grade, I – instability, R – roughness, B – breathiness, A – asthenia, and S – strain) scale, where voices of the participants were recorded while saying their first and last name and scoring from 1 to 10, and in the end it was evaluated by two independent listeners. The parameters on the scale were evaluated with grades from 0 to 3 (0 – normal voice, 1 – slight disturbance, 2 – moderate disturbance, 3 – severe disturbance) [14].

Finally, the participants filled out the Voice Handicap Index (VHI) self-evaluation questionnaire [15]. The VHI-30 is divided into three 10-item subscales: physical, which represents the participant's perception of his or her voice; emotional, representing the participant's emotional experience of his or her problem with his or her voice; and functional, which refers to the participant's problems in communication. Participants evaluated their vocal symptoms on a 4 point Likert scale – never, almost never, sometimes, often, and always.

For the purpose of data entry and statistical analysis, the Statistical Package for the Social Sciences 20.0 software was used. Due to a small number of participants, comparative analysis was conducted using the following techniques: Mann-Whitney U-test for comparing differences between the two groups of participants and the Phi square test.

The parameters of the objective voice analysis were measured in continuous speech, because using categorical variables leads to cross tabulations with insufficient data variability, and because at least one group consisted of fewer than 5 participants, so such calculations were not possible. Mann-Whitney test was used for comparing data regarding objective voice analysis and voice self-evaluation.

In order to test the hypothesis that there were higher deviations in subjective acoustic voice analysis, participants were divided into 2 x 2 groups, so that every group included a minimum of 5 participants. The Chi square test was used to test differences in response frequency by category.

The border risk probability values of the applied tests were at a 95% significance level ($p < 0.05$) (significant difference of statistical parameters) and 99% significance level ($p < 0.01$) (highly significant difference of statistical parameters).

Results

The average age of the participants was 41.23 with statistical difference (SD) of 9.42. The youngest teacher was 24, and the oldest 57 years old. All the participants were female. In regard to the years of experience, the sample was divided in two groups, those with less and

Table 1. Average values of parameters and frequency in regard to voice categories
Tabela 1. *Prosečne vrednosti parametara i frekvencija u odnosu na kategorije glasa*

Parameter *Parametar*	$\overline{X}$ $\overline{X}$	SD *SD*	Normal (N) *Normalan (N)*	Pathological (P) *Patološki (P)*
Vocal F_0 (Hz)/*F_0 glasa (Hz)*	174.06	51.04	13	17
Jitter %/*Nervoza %*	0.80	1.02	24	6
Shimmer %/*Treperavost %*	12.48	4.09	0	30
HNR (dB)/*HNR (dB)*	10.34	3.07	13	17
Voice intensity (dB)/*Intenzitet glasa (dB)*	70.90	4.29	16	14
Speech F_0 (Hz)/*F_0 pri govoru (Hz)*	177.46	29.94	12	18
Speech intensity (dB)/*Intenzitet pri govoru (dB)*	66.00	5.22	5	25
Deviations/*Odstupanja*	Without/*Bez*	Low/*Manje*	Average/*Srednje*	High/*Veće*
G – grade/*G – stepen*	15	12	3	0
I – instability/*I – intenzitet*	16	12	2	0
R – roughness/*R – hrapavost*	12	12	3	3
B – breathiness/*B – dahtavost*	15	9	5	1
A – asthenicity/*A – asteničnost*	26	3	1	0
S – strained/*S – napregnutost*	16	11	3	0
Voice self-evaluation/*Samoprocena glasa*	Min/*Min*	Max/*Maks.*	AS/*AS*	SD/*SD*
VHI/*VHI*	2.0	38.0	12.86	8.26
VHI physical scale/*VHI fizička skala*	0	20.0	6.50	4.49
VHI functional scale/*VHI funkcionalna skala*	0	9.0	4.30	2.79
VHI emotional scale/*VHI emocionalna skala*	0	9.0	2.06	2.36

Legend: VHI – voice handicap index; HNR – harmonics-to-noise ratio, F_0 – fundamental frequency
Legenda: VHI – indeks glasovnog oštećenja; HNR – odnos harmoničnog glasa i šuma, F_0 – osnovna frekvencija glasa

Table 2. Analysis of objective acoustic voice parameters in relation to work experience
Tabela 2. *Analiza objektivnih akustičkih parametara glasa u odnosu na radno iskustvo*

Objective voice analysis *Objektivna analiza glasa*	Years of work experience *Godine radnog iskustva*	$\overline{X}$ $\overline{X}$	SD *SD*	U *U*	P *p*
Vocal F_0 (Hz)/*F_0 glasa (Hz)*	≤ 20	180.90	49.16	67.000	0.344
	> 20	155.25	54.70		
Jitter %/*Nervoza %*	≤ 20	0.85	1.14	85.500	0.909
	> 20	0.63	0.57		
Shimmer %/*Treperavost %*	≤ 20	12.63	4.34	82.000	0.801
	> 20	12.08	3.55		
HNR (dB)/*HNR (dB)*	≤ 20	10.08	2.95	67.500	0.344
	> 20	11.06	3.46		
Voice intensity (dB)/*Intenzitet glasa (dB)*	≤ 20	70.72	3.84	71.500	0.437
	> 20	71.37	5.63		
Speech F_0 (Hz)/*F_0 pri govoru (Hz)*	≤ 20	180.50	24.12	65.000	0.275
	> 20	169.12	43.12		
Speech intensity (dB)/*Intenzitet pri govoru (dB)*	≤ 20	65.54	4.83	71.000	0.425
	> 20	67.25	6.36		

Legenda: HNR – odnos harmoničnog glasa i šuma, F_0 – osnovna frekvencija glasa

those with more than 20 years of experience. There were 22 (73.3%) teachers with less than 20, while 8 (26.7%) participants had over 20 years of experience. In regard to the number of classes per week, the participants were also divided in two groups. Only 8 (26.7%) participants had up to 20 classes per week, whereas the rest (73.3%) had more than 20 classes per week. Most of the participants did not suffer from any diseases, and only 6 (20%) had a disease that could eventually affect the quality of voice (4 with a thyroid disease, and 2 had allergies to inhaled allergens). Also, 6 (20%) of the participants were taking prescription drugs (for thyroid diseases and allergies). With reference to harmful habits, the participants were divided in two groups. Most of the participants did not report having any harmful habits (63.3%). Eleven participants (36.7%) reported having harmful habits (smoking and voice abuse).

When it comes to the characteristics of the assessed variables in the whole sample, the following variables: vocal F_0, shimmer, HNR, speech F_0 and speech intensity were found in more participants with pathological scores than in those with normal scores **(Table 1)**. It is interesting that all scores of the shimmer parameter were found to be pathological.

Regarding the subjective acoustic analysis, the GIRBAS scale, most participants were without dysphonic elements on all subscales, and the fewest participants showed severe disorders, but only on the following subscales: R – roughness and B – breathiness **(Table 1)**. When it comes to self-evaluation, or the VHI questionnaire, the lowest overall VHI score was 2, and the highest 38. Scale-wise, the highest score was recorded on the physical, and the lowest on the emotional scale **(Table 1)**.

We assumed that higher deviations of the parameters of objective acoustic voice analysis would be found in teachers with over 20 years of work experience, compared to participants with fewer years of experience. In order to test this hypothesis, participants were divided into two groups according to years of experience, so that every tested group included a minimum of five participants. The Mann-Whitney test was used to test for intergroup differences.

As shown in **Table 2**, the results of the U-test showed no differences between the values of objec-

Table 3. Analysis of subjective acoustic voice parameters in relation to work experience
Tabela 3. *Analiza subjektivnih akustičkih parametara glasa u odnosu na radno iskustvo*

Parameter/*Parametar*	Chi square test/*Hi kvadrat test*	p/*p*
G – grade/*G – stepen*	0.682	0.409
I – instability/*I – intenzitet*	1.099	0.295
R – roughness/*R – hrapavost*	1.023	0.312
B – breathiness/*B – dahtavost*	0.682	0.409
A – asthenicity/*A – asteničnost*	0.007	0.935
S – strained/*S – napregnutost*	3.519	0.061

Table 4. Analysis of voice self-evaluation in relation to work experience
Tabela 4. *Analiza samoprocene glasa u odnosu na radon iskustvo*

Objective voice analysis *Objektivna analiza glasa*	Years of work experience *Godine radnog iskustva*	$\overline{X}$ $\overline{X}$	SD *SD*	U *U*	p *p*
VHI/*VHI*	≤ 20	12.09	6.80	87.500	0.982
	> 20	15.00	11.66		
VHI physical scale/*VHI fizička skala*	≤ 20	6.09	3.57	80.500	0.730
	> 20	7.62	6.58		
VHI functional scale/*VHI funkcionalna skala*	≤ 20	4.18	2.61	83.000	0.836
	> 20	4.62	3.42		
VHI emotional scale/*VHI emocionalna skala*	≤ 20	1.81	2.19	64.500	0.277
	> 20	2.75	2.81		

Legend: VHI – voice handicap index, U – Mann-Whitney U-test/*Legenda: VHI – indeks glasovnog oštećenja, U – Man-Vitnijev U-test*

tive acoustic voice analysis parameters in participants with less or more than 20 years of work experience.

As shown in **Table 3**, the results of the Chi square test showed no differences in the subjective voice analysis parameters of the participants with more or less than 20 years of work experience.

We were also interested whether higher deviations regarding voice self-evaluation were seen in teachers with more than 20 years of work experience compared to participants with fewer years of work experience. The Mann-Whitney test was used to test for intergroup differences.

As shown in **Table 4**, the results of the U-test showed no significant differences in the values of self-evaluation parameters between participants with more or less than 20 years of work experience.

The next step was to examine whether a higher number of classes per week affected the parameters. The differences in objective voice analysis parameters between participants with less or over 20 classes per week were tested using the Mann-Whitney U-test for independent samples. The results of the U-test showed no differences between subjective and objective acoustic analysis parameters with regard to the number of classes per week ($p > 0.05$).

The differences in subjective voice analysis parameters between participants with less or over 20 classes per week were tested using Chi square test. It also did not show statistically significant differences between the groups ($p > 0.05$).

We also tested whether higher deviations in voice self-evaluation were observed in teachers with over 20 classes per week compared to participants with fewer classes per week. The differences in voice self-evaluation parameters between both groups of participants were tested using the Mann-Whitney U-test for independent samples. Results showed no differences in the values of parameters of voice self-evaluation between the participants.

Furthermore, we tested whether a lower quality of voice in regard to the parameters of subjective and objective acoustic analysis is seen in teachers who reported having harmful habits compared to participants who reported having no harmful habits.

In order to test this hypothesis, participants were divided into two groups (with and without harmful habits) and the Mann-Whitney test for testing intergroup differences was used. The results of the U-test showed no differences between the values of objective acoustic voice analysis parameters in participants with and without harmful habits ($p > 0.05$).

The differences in subjective voice analysis parameters in participants with and without harmful habits were tested using the Chi square test. The **Table 5** shows test results and significance levels.

As seen in **Table 5**, the results of the Chi square test show differences in the number of participants across groups formed according to the existence of harmful habits and the subjective acoustic voice analysis in all parameters except for voice asthenicity. The pathological finding of the subjective evaluation of voice in the G, I, R, B and S areas is more commonly seen in participants with harmful habits.

Table 5. Analysis of subjective acoustic voice parameters in relation to harmful habits
Tabela 5. *Analiza subjektivnih akustičkih parametara glasa u odnosu na štetne navike*

Parameter/*Parametar*	Chi square test/*Hi kvadrat test*	p/*p*
G – grade/*G – stepen*	7.033	0.008
I – instability/*I – intenzitet*	4.739	0.029
R – roughness/*R – hrapavost*	6.914	0.009
B – breathiness/*B – dahtavost*	7.033	0.008
A – asthenicity/*A – asteničnost*	0.353	0.552
S – strained/*S – napregnutost*	4.739	0.029

Table 6. Analysis of objective acoustic voice parameters in relation to chronic diseases
Tabela 6*. Analiza objektivnih akustičkih parametara glasa u odnosu na hroničnе bolesti*

Objective voice analysis *Objektivna analiza glasa*	Disease *Bolest*	$\overline{X}$ $\bar{X}$	SD *SD*	U *U*	p *p*
Vocal F_0 (Hz)/*F_0 glasa (Hz)*	No/*Ne*	170.50	50.46	58.000	0.494
	Yes/*Da*	188.33	55.62		
Jitter %/*Nervoza %*	No/*Ne*	0.87	1.12	69.500	0.900
	Yes/*Da*	0.48	0.24		
Shimmer %/*Treperavost %*	No/*Ne*	12.90	4.27	51.000	0.274
	Yes/*Da*	10.83	3.07		
HNR (dB)/*HNR (dB)*	No/*Ne*	9.84	3.09	34.000	0.046
	Yes/*Da*	12.33	2.16		
Voice intensity (dB)/*Intenzitet glasa (dB)*	No/*Ne*	70.79	4.48	65.000	0.715
	Yes/*Da*	71.33	3.77		
Speech F_0 (Hz)/*F_0 pri govoru (Hz)*	No/*Ne*	176.04	31.95	62.500	0.6225
	Yes/*Da*	183.16	21.31		
Speech intensity (dB)/*Intenzitet pri govoru (dB)*	No/*Ne*	67.04	4.94	30.000	0.029
	Yes/*Da*	61.83	4.44		

Legend: U – Mann-Whitney U-test, F_0 – fundamental frequency/*Legenda: U – Man-Vitnijev U-test, F_0 – osnovna frekvencija glasa*

In the final step, in order to test the hypothesis that lower voice quality in regard to the parameters of subjective and objective acoustic analysis can be seen in participants who reported presence of a chronic disease compared to participants who did not report any, the participants were divided into two groups (with and without chronic diseases). The Mann-Whitney test for intergroup differences was used.

The results of the U-test showed no differences in the values of parameters of objective acoustic voice analysis between participants with and without chronic diseases, except for the HNR parameter and intensity of speech **(Table 6)**. Participants without chronic diseases showed significantly better speech intensity and lower HNR.

The results of the Chi square test showed no differences in the values of subjective acoustic voice analysis parameters between participants with and without chronic diseases ($p > 0.05$).

Discussion

A concerning fact that has been identified by this research is that more than half of the primary school teachers had a voice disorder, due to F_0 of the voice or voice intensity, during continuous speech and pronunciation of isolated vowel /a/. This study, as well as studies of other authors, indicates the sensitivity of teachers' voice to be due to the professional voice workload [4, 6–8, 16]. Regarding the subjective acoustic analysis of the voice, it was found that slightly less than half of the respondents have deviations in all aspects except for asthenic voice. These results are consistent with those obtained by objective acoustic measurements in this research. The results of the voice self-evaluation show slight deviations of the voice in relation to the objective and subjective acoustic analysis of the voice. This can be explained by the fact that voice disorders in teachers do not occur suddenly, but gradually. Over the years, there has been a gradual change in phonation automatism.

When it comes to number of classes, the length of work experience and weekly workload are often considered to be primary factors associated with voice quality. Our sample consisted of 27% of primary school teachers with more than 20 years of work experience and 73.3% of teachers with a workload over 20 classes per week; however, no assessment showed statistically significant differences in the quality of voice in primary school teachers with longer work experience or higher weekly workload, and such results were presented in two different studies conducted in Brazil [17, 18]. On the other hand, in 2009, a study was conducted in Naples, Italy, showing that 60.3% of primary school teachers with dysphonia had more than 15 years of work experience. Furthermore, the study of Rossi-Barbosa et al. [10] showed that primary school teachers who had more than 15 years of work experience reported having chronic vocal disorders (lasting longer than 3 weeks).

Harmful habits, such as smoking and vocal abuse, are often considered when analyzing and comparing results. When it comes to the prevalence of smokers in our sample, it is rather low – 26.7% and the same "trend" can be seen in some other studies which focused on primary school teachers [9]. With regard to voice comparison in persons who smoke and those who do not, the results of objective acoustic analysis showed no statistically significant difference. Still, the research of Sorensen and Horrii [19] showed that the values of F_0 in women smokers are lower than in women non-smokers, even though that difference was not statistically significant, and these results coincide

with ours. The authors of the mentioned research attributed this result to possible compensation of effects which cigarette consumption has on women's voices. The authors emphasize that, considering that society does not find women with deep voices appealing, it is possible that women smokers consciously modify their vocal behavior to conceal the effect that cigarettes have on their fundamental vocal frequency. For example, women smokers may change the degree of strain in their larynx in order to maintain a relatively acceptable F_0, and if they did not, it is possible that a statistically significant difference would appear in the results. Nevertheless, this represents another hypothesis which should be tested. Statistically significant differences were found by Šehović et al. [20], comparing the quality of voice shown by objective acoustic analysis between women teachers who smoke and those who do not, where the teachers who smoked showed variable values characterizing vocal pathology. What's important to emphasize is that these results were seen during the articulation of the vowels *o* and *u,* but not the vowel *a,* which is the only vowel that this research focused on.

In regard to the comparison of subjective acoustic analysis results, in this case, using the GIRBAS scale, there were few studies which used this method in the literature. This was the topic of the Perez Serey and Ortiz Araya [21] study, which analyzed methods used in published literature on the topic of vocal analysis of class and subject teachers in the period between 2006 and 2010 in English, Spanish and Portuguese languages, concluding that only 7% of studies used the GRBAS voice assessment scale. In this study, a statistically significant difference in subjective acoustic analysis was shown only in participants with a history of harmful habits, smoking and voice abuse. Namely, in these participants, a pathological finding was present on the G scale (grade), I (instability), R (roughness), B (breathiness) and S (strain). Furthermore, the connection between vocal abuse, which among other things, includes daily yelling, and roughness, was presented in the study of Ferreire and colleagues [9].

Subjective acoustic analysis of the voice provides insight into the quality of the voice during continuous speech, while objective acoustic analysis of the voice provides data that may be a consequence of voice imposition control which provides a higher F_0 of the voice.

In regard to voice self-evaluation, no statistically significant differences were found between groups created based on the years of work experience and weekly workload. It is important to emphasize that no participants had a VHI score zero, and previous research shows that both teachers and subject teachers scored significantly higher when talking about vocal disorder symptoms and on self-evaluation questionnaires compared to the rest of the population [22]. Even though the research of Gadepalli et al. [16] shows teachers with a VHI-10 score zero, 72.7% of teachers reported having some vocal issue in this questionnaire. This research also found no statistically significant difference between weekly workload and the results of voice self-evaluation. Furthermore, the lowest average score was reported on the emotional scale, which is consistent with the usual expectations in regard to the results of this questionnaire, as the emotional score is usually always the lowest [23].

The results of this study show that primary school teachers with no history of chronic diseases had a significantly better speech intensity compared to participants who reported having a chronic disease. The results shown in the study of Rossi-Barbosa et al. [10] might explain this finding. Namely, the authors claimed that the noise factor had a higher effect on the primary school teachers with a chronic disease, as they, naturally for all human beings, habitually increased the intensity of their voice in the presence of noise (phenomenon known as the Lombard effect), so that students could hear them better. Data show that vocal intensity should be 10 dB higher than the background noise in order to ensure coherency of speech. Based on this, in time, this vocal strain due to the noise can overburden the larynx, which is possibly already affected with some sort of chronic disease, which in turn may affect the quality of voice [18].

The result considering the shimmer parameter is notable in this study, showing pathologically increased values in all 30 primary school teachers. The reasons for this may be manifold. On the one hand, the reason could be the conditions of the study, or insufficient sound insulation of the testing room, and on the other, the fact that has already been considered, which is that the intensity of voice in primary school teachers is often chronically increased due to the nature and conditions of their job. The study of Mahato et al. [11] showed that primary school teachers, when having their voice assessed after classes, scored significantly higher on the shimmer parameter, which was attributed to decreased muscle tone and pathological neuro-motor laryngeal control caused by vocal cord exhaustion.

The main limitation of this study is the small sample size and the impossibility of performing more detailed medical examination of the participants (such as aerodynamic vocal assessment and video-stroboscopy), due to the current epidemiological situation. The research could be also improved by repeating the entire survey during or at the end of school year, and by conducting the research in general population or other professions.

Conclusion

The findings so far suggest that primary school teachers are at a significantly higher risk for the development of vocal disorders. Our research showed that about half of the examined teachers presented with voice disorders, no matter if the acoustic analysis was objective or subjective. Years of work experience and weekly workload of teachers did not affect parameters of objective or subjective acoustic voice analysis. Harmful habits, such as smoking and voice abuse lead to poorer voice quality, in terms of subjective acoustic analysis. Unlike the previous one, chronic diseases, such as thyroid diseases and

respiratory allergies, affect the parametric harmonics-to-noise ratio and intensity of the voice.

Considering that functional vocal disorders are rare disorders, that they are completely preventable by good vocal education and hygiene, the aim of all professions dealing with vocal disorders, primarily speech therapists and speech-language pathologists, should be to promote solutions to this problem.

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SPEECH DISORDERS IN PARKINSON'S DISEASE – CHARACTERISTICS, ASSESSMENT AND TREATMENT

POREMEĆAJ GOVORA KOD PARKINSONOVE BOLESTI – KARAKTERISTIKE, PROCENA I TRETMAN

Lana JERKIĆ, Mirjana PETROVIĆ LAZIĆ and Mile VUKOVIĆ

Summary

Introduction. Parkinson's disease belongs to the group of extrapyramidal neurodegenerative diseases and occurs as a consequence of the loss of dopaminergic neurons in the substantia nigra of the mesencephalon. Persons with Parkinson's disease may experience a wide range of motor and non-motor symptoms. **Material and Methods.** A literature search was conducted using electronic databases on the Internet and electronic databases of Serbian libraries. **Results.** Speech disorders in Parkinson's disease are classified in the group of hypokinetic dysarthria. Empirical data show that the basic characteristics of dysarthria in people with Parkinson's disease are changes in voice quality, difficulties in articulating consonants, abnormalities in vowel production, monotonous speech, changes in speech rate, rough and breathy voice, increased voice nasality, reduced intensity of voice, involuntary pauses during speech, and palilalia. Methods used in the assessment of speech disorders include perceptual voice analysis, such as the overall dysphonia Grade, Roughness, Breathiness, Asthenia, Strain and Consensus Auditory Perceptual Evaluation of Voice scales, acoustic voice analysis (e.g., Multi-Dimensional Voice Program), and voice quality self-assessment methods (e.g., Voice Handicap Index and the Dysarthria Impact Profile). In the treatment of dysarthria, various behavioral methods of speech therapy are used, among which the Lee Silverman method is particularly important. **Conclusion.** Speech disorders in Parkinson's disease manifest as altered patterns of respiration, phonation, resonance, articulation and prosody. The best results in the treatment are achieved by combination of medical, surgical, and behavioral therapy, through the cooperation of experts of different profiles as well as with family members of the patient.

Key words: Parkinson Disease; Speech Disorders; Dysarthria; Voice Quality; Voice Training; Speech Acoustics; Phonation; Diagnostic Self Evaluation

Sažetak

Uvod. Parkinsonova bolest ubraja se u grupu ekstrapiramidnih neurodegenerativnih bolesti i javlja se kao posledica gubitka dopaminergičkih neurona u supstanciji nigra mezencefalona. Kod osoba sa Parkinsonovom bolešću javlja se čitava lepeza motornih i nemotornih simptoma. **Materijal i metode.** Uvid u relevantnu literaturu izvršen je pomoću pretraživanja specijalizovanih pretraživača na internetu i elektronskih baza biblioteka Srbije. **Rezultati.** Govorni poremećaji u Parkinsonovoj bolesti su svrstani u grupu hipokinetičkih disartrija. Empirijski podaci pokazuju da su osnovne karakteristike disartrije kod osoba sa Parkinsonovom bolešću promene kvaliteta glasa, teškoće u artikulaciji konsonanata, abnormalnosti u produkciji vokala, jednoličan i monoton govor, promene tempa govora, grub i zadihan glas, hipernazalnost, smanjen intenzitet glasa, nevoljne pauze u govoru i palilalija. U proceni govornog poremećaja koriste se metode perceptivne analize glasa (kao što je, na primer, *Grade, Roughness, Breathiness, Asthenia, Strain* ili *Consensus Auditory Perceptual Evaluation of Voice scales*), akustičke metode analize glasa (npr. *Multi-Dimensional Voice Program*) i metode samoprocene kvaliteta glasa (npr. *Voice Handicap Index* i *The Dysarthria Impact Profile*). U tretmanu disartrije koriste se različite bihevioralne metode govorne terapije među kojima poseban značaj ima Li Silverman metoda. **Zaključak.** Poremećaj govora u Parkinsonovoj bolesti manifestuje se izmenjenim obrascima respiracije, fonacije, rezonancije, artikulacije i prozodije. Najbolji rezultati u tretmanu postižu se kombinacijom medikametnog, hirurškog i bihevioralnog pristupa, kroz saradnju stručnjaka različitog profila i kao i sa članovima porodice obolelog.

Ključne reči: Parkinsonova bolest; poremećaji govora; disartrija; kvalitet glasa; trening glasa; govorna akustika; fonacija; samoprocena

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Introduction

Parkinson's disease (PD) belongs to the group of neurodegenerative disorders that mostly occurs sporadically and then it is referred to as idiopathic Parkinson's disease [1]. It affects about 2 – 3% of people over the age of 65 as a consequence of the loss of nerve cells in the substantia nigra in the mesencephalon, whose main role is production of dopamine, an inhibitory neurotransmitter [1, 2]. The accumulation of Lewy bodies (deformed proteins responsible neuronal cell death) is also evident in the brain stem and cortical and subcortical structures [3]. According to DeLong and Wichmann, cited by Pavlović [4], cortical-subcortical-cortical circuits are disrupted. Circuits start in certain

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Abbreviations
PD – Parkinson's disease
F_{0} – fundamental frequency
KoBSON – Serbian Library Consortium for Coordinated Acquisition

parts of the cerebral cortex, then go to parts of the basal ganglia and return to the parts of the cortex from which they originated. In case of a disease, a wide range of motor (tremor at rest, rigidity, bradykinesia, and impaired posture) as well as non-motor signs (depression, psychosis, and signs of cognitive decline) are manifested [4–6].

Production of speech is a complex process that depends on the mutual coordination of different subsystems of all basic motor processes of speech such as respiration, phonation, resonance, articulation, and prosody [7]. As coordination and interdependence of all mentioned mechanisms is necessary for adequate speech production, deficits in one subsystem can lead to abnormal functioning of other subsystems. For example, abnormalities in the functioning of the respiratory and phonatory subsystems are reflected in prosody and articulation [8].

Speech disorder in PD, referred to as hypokinetic dysarthria, is also known as Parkinson's dysarthria in recent literature [7].

Material and Methods

This paper deals with the presentation and interpretation of voice and speech disorders in persons with PD. The present paper aims to systematically present data on the manifestations of dysarthria, as well as on the possibilities of its assessment and treatment, with special emphasis on the behavioral approach. The following electronic databases were used to search the relevant literature: the Serbian Library Consortium for Coordinated Acquisition (KoBSON), Google Scholar, PubMed, and Science Direct. The following terms were used as search key words: hypokinetic dysarthria, speech disorders in PD, voice disorders in PD, assessment of hypokinetic dysarthria, and treatment of hypokinetic dysarthria.

Results

Characteristics of hypokinetic dysarthria in persons with Parkinson's disease

Various factors (such as progressive neuronal loss, compensation mechanisms one uses, type of treatment - pharmacological or behavioral, and other factors) affect the manifestation of speech disorders in persons with PD. These factors shape the clinical picture of dysarthria [9]. It is estimated that dysarthria occurs in about 90% of individuals with PD. It impairs the intelligibility of speech, which consequently affects the communication of these patients with people from their environment and also the quality of life [10].

An important characteristic of dysarthria in PD is that it changes the voice quality. Voice disorders in people with PD occur as a consequence of two types of anatomical abnormalities: asymmetric stiffness of the internal muscles of the larynx and incomplete closure of the glottis due to vocal cord hypokinesis. They may be an early indicator of motor dysfunction in PD [11].

Speech disorders in persons with PD manifest as dysfunction of the respiratory organs, phonation, and articulation. As a consequence, changes occur in the pattern of respiration, voice quality, and difficulties in articulating some sounds. Besides, soft palate dysfunction leads to changes in voice resonance, while changes in voice quality and speech rate lead to deficits in resonance and prosody. The following is an overview of the characteristics of speech production components in persons with PD.

1. Abnormalities in respiration

The basic role of the respiratory system is to enable normal breathing. In addition to respiration, it is important in voice activation and voice production [12].

Persons with PD have an altered breathing pattern and they rely more on the strength of active respiratory muscles, which results in increased effort and fatigue during the act of speaking. These individuals begin and end speech at levels either above or below the normal lung volume [13]. The inconsistency of such findings results from the use of different types of speech tasks in the assessment [14]. Chest rigidity, weakness of expiratory muscles and reduced coordination between breathing and speech production reduce the lung capacity, and during speech breathing, a greater effort of expiratory muscles is also noticeable [15].

Because of the decreased contraction of the chest and diaphragm muscles, there is a decrease in airflow to the upper respiratory tract and, as a result, changes in the vibration of the vocal cords [16]. Increased subglottic pressure is a reflection of laryngeal resistance during phonation, due to vocal rigidity and reduced tension, which are also characteristics of this disease [17]. Patients do not inhale enough air, which causes interruption of speech [18]. Due to the speech breathing, individuals with PD may produce a reduced length of utterance [14].

2. Disorders of phonation

Phonation is a learned skill that is developed, maintained, and controlled through acoustic, kinesthetic, and visual feedback mechanisms and it is controlled by the central nervous system. The most important organ of phonation is the larynx and it represents the voice generator [12]. According to studies, people with PD can have incomplete glottic closure and laryngeal tremor [19].

Reduced duration of phonation is a consequence of respiratory muscle weakness, reduced vital capacity, and glottal insufficiency [18]. According to Sachin et al., as cited in Ferrand [17], due to the rigidity of the vocal cords, their normal vibration is not possible. Reduced loudness occurs as a consequence of general laryngeal weakness and highly affects the ability to speak in a noisy environment [20]. Even when they can speak with normal voice intensity, PD patients sometimes avoid doing it, because they are

afraid that other people will perceive their speech as shouting. This phenomenon is due to disturbances in perception and sensorimotor integration that are responsible for adjusting voice intensity [21]. Bradykinesia and tremor mostly affect the ability to produce speech: bradykinesia often results in hypophonia and monotony of the voice, while tremor often affects the lips, tongue, and chin [1].

The empirical data demonstrate abnormalities in minimum, average, and maximum fundamental frequency (F_0), jitter, and shimmer [22, 23]. Some authors believe that changes in speech are universal during disease progression [23]. There is an opinion that changes can be detected early by certain acoustic measurements and that reduced F_0 variability in spontaneous speech (especially intonation patterns) can be an early indicator of the disease even several years before diagnosis and clinical onset [24].

3. Resonance disorders

Vocal resonators are areas in which the primary laryngeal tone is amplified and higher harmonic tones are created and modified at the same time [12]. Although hypernasality is not usually considered to be a key feature of hypokinetic dysarthria, individual variations are possible [20]. Empirical data suggest that hypernasality may occur in these patients as a consequence of limited soft palate movements and velopharyngeal dysfunction [18, 20].

4. Articulation disorders

Articulation is the process of planning and executing sequences of speech organ movements [25] for speech production. Inaccuracy in the production of consonants is the basic characteristic of articulation disorders in persons with PD and it mainly occurs as a consequence of a reduced range of motion of the articulators [1].

It was previously thought that the affectation of sounds in PD depends on the place of articulation. For example, according to Logeman, as cited in Read et al. [5] the disease primarily affects posterior sounds and then those sounds whose articulation takes place in the anterior parts of the oral cavity. In their empirical study, Read et al. [5] concluded that the limitation of oral musculature mobility in PD affects all sounds of spoken language equally and simultaneously. The disorders are most noticeable during the production of sounds that require a wide jaw angle for articulation (such as sounds A, O, L, R, K, and G) and those that require the engagement of different groups of articulatory muscles [18].

Some authors point out that disorders in the articulation of vowels can also be an early marker of PD and that they can be specially manifested in more complex speech acts such as monologues [26]. Although limited movements of articulators may be due to rigidity and hypokinesia [9], some authors believe that vowel articulation disorders may occur regardless of global motor dysfunction or stage of the disease [27]. Domestic authors found significant differences in the position of formants in persons with PD and hypokinetic dysarthria for most vowels (E, I, O, U) in the Serbian language, especially the second formant that has the greatest dynamics in vowels [28].

5. Prosody disorders

Prosody is the systematic organization of different linguistic units in pronunciation and its realization includes both segmental and non-segmental features of speech to convey not only linguistic but also paralinguistic and non-linguistic information [29]. Prosodic abnormalities can be the main cause of impaired speech intelligibility and they negatively affect communication with other people [9]. The voice quality in these individuals is usually described as rough and breathy [23]. Most persons with PD experience difficulty varying the pitch and intensity of their voice due to the inability to perform fine vocal cord movements. There are also disturbances in auditory perception, and these people mostly complain that their voice is of reduced intensity and that they sound monotonous because they are not able to vary the pitch of their voice [17]. The voice range can also be reduced [30]. There are also palilalia and speech rate abnormalities, so the speech of these people may be accelerated or slow [23, 31]. At first, the person speaks loudly. As the length of speech increases, the speech tempo accelerates and the intensity of the voice decreases [18].

Harris et al., [32] compared the results of individuals with PD and a control group and observed that individuals with PD showed abnormalities of linguistic prosody compared to the control group, but did not show music dysprosody. The authors suggest that this finding could serve as a valuable resource for the treatment of linguistic prosody in people with PD.

Assessment of dysarthria in persons with Parkinson's disease

Speech disorders can manifest in the initial phase of the disease, which is why these people often seek help from speech and language pathologists [1]. Clinicians can use a variety of tests and scales to assess dysarthria.

Clinical assessment of voice consists of extended phonation of vowels, assessment of automatic speech (e.g., counting from 1 to 10), reading of sentences and texts, and assessment of narrative discourse (e.g., description of a picture illustrating an event). In clinical practice, the GRBAS scale (Grade, Roughness, Breathiness, Asthenia, Strain) and the Consensus Auditory-Perceptual Evaluation of Voice (CAPE-V) scale are used [33], as well as various applications offered by modern technology [34], the Unified Parkinson Disease Rating Scale (UPDRS) for speech and swallowing [35] and other assessment methods and techniques.

Acoustic analysis of speech and voice in patients with PD may be a valuable source for examining the characteristics of hypokinetic dysarthria [10]. When assessing hypokinetic dysarthria, clinicians usually focus on measuring the fundamental frequency (F_0) and its variations, intensity, speech rate, etc. These characteristics can be associated with specific man-

ifestations of hypokinetic dysarthria and this is their main advantage [36]. The Multi-Dimensional Voice Program (MDVP) is widely used to detect voice disorders and facilitates extraction of as many as 33 voice parameters [37] being an objective method in assessing voice characteristics in persons with PD.

Considering that the articulation subsystem is the most affected after the phonation mechanism, rapid syllable repetition tasks are used to assess its kinematic characteristics in addition to the traditional method of testing articulatory abilities [8].

Patient self-assessment questionnaires are also a valuable resource for clinicians for a better insight into the impact of the disorder on the daily functioning of patients. The best-known self-assessment questionnaires are the Voice Handicap Index [38] and The Dysarthria Impact Profile [9].

Approaches to the treatment of dysarthria in persons with Parkinson's disease

Treatment of dysarthria can be carried out in different ways: 1) by directing therapeutic procedures to a certain mechanism of speech production (respiration, phonation, resonance, or articulation); 2) using strategies to improve communication (e.g., maintaining eye contact, using gestures to increase understanding, etc.); 3) modification of the environment; and 4) using assistive technology [39].

Different approaches are used in the treatment of speech-language and communication deficits: pharmacological (drugs), surgical (deep brain stimulation), and non-pharmacological (such as the intensive Lee Silverman program, traditional approaches in the treatment of voice and speech disorders, music therapy, etc.) [40].

1. Pharmacological approach

According to some empirical data, the severity of speech and voice symptoms should be taken into account in studies of levodopa effectiveness [41]. While some authors report positive effects of levodopa on some features of dysarthria such as e.g., vowel articulation [42], other authors found no significant improvements in voice and speech after taking levodopa [43].

In the study by Cushni-Sparrow et al., [41] the effect of levodopa on the acoustic and perceptual characteristics of voice was examined by having people with PD prolonged phonation of vowels when not taking levodopa and then being retested after taking the drug. The authors found that patients with poor voice quality who did not take levodopa had an improvement in voice quality after taking it, and vice versa. The authors proposed the "speech severity responsiveness" hypothesis, which suggests that variations in symptom severity are potentially responsible for individual differences in response to levodopa and that the effects of levodopa are better in severe speech disorders.

2. Surgical approach

Pallidotomy and thalamotomy were used to treat symptoms in PD before using dopamine therapy. However, their application seems to have led to worsening of speech disorders. Deep brain stimulation may have some positive effects on speech, but there is still a risk of its deterioration [44].

3. Behavioral approach

Lee Silverman Voice Treatment is an intensive method specifically designed for the treatment of dysarthria symptoms in patients with PD. Some of the positive effects attributed to this method are improved loudness, intonation and intelligibility of speech, pitch, speech rate, improved facial expression, and swallowing [44, 45]. This program is also suitable for patients with cognitive deficits since the procedures are simple and can be easily understood by patients [17].

Some authors point out that behavioral techniques, such as biofeedback and techniques that slow down the speaking rate, give better results in the treatment of prosodic deficits compared to surgical and pharmacological methods [46]. Various studies report on the benefits of programs such as SPEAK UP and the Loud Crowd program [3], group singing aimed at increasing the pitch and intensity of voice and slowing its deterioration [47], using techniques to improve the mechanisms of the effector system, assistive technology [48], and other programs.

The treatment of articulatory deficits can be performed in the traditional way through exercises to strengthen the oral muscles and by pronouncing sounds in different phonetic positions and phonetic sets [1]. Giving feedback in any type of behavioral therapy significantly helps these patients [45].

Hypokinetic dysarthria considerably impairs the quality of communication of persons with PD with people in their environment. The advancement of behavioral techniques provides various benefits for improving speech abilities in people with PD [49]. Trail et al., [50] claim that pharmacological and surgical approaches alone are insufficient, and that they must be combined with behavioral methods such as Lee Silverman method, which appears to be the most effective method for treating speech disorders in persons with PD.

Conclusion

Parkinson's disease is a widespread neurodegenerative disease that manifests itself through motor and non-motor symptoms. Hypokinetic dysarthria is a speech disorder that is also a characteristic symptom of Parkinson's disease. Dysarthria is manifested by changes in the patterns of respiration, phonation, resonance, articulation, and prosody.

Inadequate respiratory and altered breathing patterns affect the ability to produce speech. Speech breathing is often inadequate due to respiratory muscle weakness and incoordination, which consequently affects the ability of phonation and vibration of the vocal cords. Normal functioning of the resonance subsystem is affected by soft palate weakness and velopharyngeal incompetence, and hypernasality also occurs. Imprecision in consonant pronunciation is the most noticeable symptom of articula-

tory disorders, but some studies also report abnormalities in vowel production, which can be an early sign of the disease and it is most noticeable in more complex speech acts. The quality of voice of patients with Parkinson's disease is often described as monotonous, of reduced intensity, rough and short of breath, and there are involuntary pauses in speech. Palilalia and speech disorders also occur. In addition to disturbances in production, these persons also have disturbances in the perception of the intensity of their voice.

When assessing the state of voice and speech abilities, clinicians have access to various perceptual scales and objective acoustic methods. Voice quality self-assessment questionnaires have also been specifically made and designed for patients with Parkinson's disease.

Speech is the primary means of communication among people so manifestations of hypokinetic dysarthria greatly complicate communication of patients with Parkinson's disease with people in their environment. Although levodopa is widely used in the treatment of motor symptoms, research results on its effectiveness in dysarthric symptoms are inconsistent. When it comes to the non-pharmacological treatment of dysarthria, it seems that the behavioral approach gives the best results. When treating speech disorders, a combination of different approaches provides the best results. A multidisciplinary approach and collaboration of experts of various profiles (neurologists, phoniatritians, speech therapists, physiotherapists, and other experts) as well as cooperation with family members are required when assessing and treating hypokinetic dysarthria. Drug therapy, with the application of physical and speech therapy, contributes to slowing the progression of the disease and improving the quality of life in patients with Parkinson's disease.

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NOSOCOMIAL INFECTIONS IN A PEDIATRIC SURGICAL INTENSIVE CARE UNIT: AN UNICENTRIC CROSS-SECTIONAL STUDY

BOLNIČKE INFEKCIJE U PEDIJATRIJSKOJ JEDINICI HIRURŠKOG INTENZIVNOG LEČENJA: UNICENTRIČNA STUDIJA PRESEKA

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Summary

Introduction. Nosocomial infections are a common complication in patients hospitalized in intensive care units. The aims of this research were to examine the incidence of nosocomial infections in patients admitted to the pediatric surgical intensive care unit, the impact of hospital length of stay and type of surgical disease on the incidence of nosocomial infections, the frequency of microorganisms causing nosocomial infections and their antibiotic susceptibility profile. **Material and Methods.** Data on 50 subjects were extracted from the database. The following data were taken from the medical histories of the examinees: age, sex, diagnosis, number of days at the hospital before admission to the intensive care unit, number of days in the intensive care unit, levels of C-reactive protein, applied antimicrobial drugs, isolated microorganisms and their susceptibility to antibiotics. **Results.** The incidence of nosocomial infections in the study period was 52%. Patients who developed nosocomial infection remained longer in the intensive care unit than those who did not develop it ($p = 0.003$). Patients with the diagnosis of acute abdomen had a statistically significantly higher incidence of nosocomial infections compared to other patients ($p = 0.001$). Gram-negative bacteria were the most commonly isolated pathogens (46.8%). Acinetobacter baumanii proved to be the most resistant species in this study, since 80% of the strains did not show sensitivity to any of the tested antibiotics. **Conclusion.** Nosocomial infections are present in slightly more than half of the patients treated at the pediatric surgical intensive care unit. Patients who developed nosocomial infections stayed longer in the pediatric surgical intensive care unit, which had negative consequences for their health and treatment costs.

Key words: Intensive Care Units, Pediatric; Cross Infection; Child; Acinetobacter Infections; Drug Resistance, Multiple, Bacterial; Gram-Negative Bacteria; Microbial Sensitivity Tests

Sažetak

Uvod. Bolničke infekcije su česta komplikacija kod pacijenata hospitalizovanih u jedinicama intenzivnog lečenja. Ciljevi ove studije bili su da se ispita učestalost bolničkih infekcija pacijenata primljenih u pedijatrijsku jedinicu hirurškog intenzivnog lečenja, uticaj dužine hospitalizacije i vrste hirurške bolesti na pojavu bolničke infekcije, učestalost mikroorganizama koji uzrokuju bolničke infekcije i njihov profil osetljivosti na antibiotike. **Materijal i metode.** Iz baze podataka izdvojeni su podaci o 50 ispitanika. Iz medicinske dokumentacije ispitanika su preuzeti sledeći podaci: uzrast, pol, dijagnoza, broj dana u bolnici pre prijema u jedinici intenzivnog lečenja, broj dana u jedinici intenzivnog lečenja, vrednosti C-reaktivnog proteina, primenjivani antimikrobni lekovi, izolovani mikroorganizmi i njihova osetljivost na antibiotike. **Rezultati.** Učestalost bolničkih infekcija u ispitivanom periodu iznosila je 52%. Pacijenti koji su razvili bolničku infekciju ostajali su duže u jedinici intenzivnog lečenja u odnosu na one koji je nisu razvili ($p = 0,003$). Pacijenti sa dijagnozom akutnog abdomena imali su statistički značajno veću incidenciju razvijenih bolničkih infekcija u odnosu na ostale grupe ($p = 0,001$). Gram-negativne bakterije su najčešće izolovani patogeni (46,8%). *Acinetobacter baumanii* pokazao se najrezistentnijom bakterijom u studiji, s obzirom da 80% sojeva nije pokazalo senzitivnost ni na jedan ispitivan antibiotik. **Zaključak.** Bolničke infekcije su prisutne kod nešto više od polovine pacijenata pedijatrijske hirurške jedinice intenzivnog lečenja. Pacijenti koji su razvili bolničke infekcije ostajali su duže u jedinici intenzivnog lečenja, što je imalo posledice na njihovo zdravstveno stanje i troškove lečenja.

Ključne reči: pedijatrijske jedinice intenzivne nege; bolničke infekcije; dete; infekcije izazvane Acinetobakterijama; bakterijska multirezistencija; Gram-negativne bakterije; testovi mikrobne osetljivosti

Introduction

A nosocomial infection is defined as an infection that is not present or in the incubation phase at the time when the patient is admitted to hospital or other health care facility. Since the incubation period for most infections is about 48 hours, a nosocomial infection is considered to be an infection that

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Abbreviations
ICU – intensive care unit
CRP – C-reactive protein

occurred during any period of hospitalization, but after 48 hours from admission [1].

Patients in intensive care units (ICUs) are five to ten times more likely to develop nosocomial infections than those in general wards [2]. The most common nosocomial infections in ICUs are sepsis, blood infections associated with vascular catheters, ventilator-induced pneumonia, and urinary tract infections associated with urinary catheters [3]. Patients in surgical ICUs are at additional risk to develop nosocomial infections due to the length of preoperative hospitalization, surgical intervention itself, existence of a surgical wound, need for blood transfusions etc. They are also exposed to surgical site infections [4].

There are many differences between children and adults in terms of nosocomial infections. Factors unique to pediatric patients include differences in the healthcare process, such as the type and amount of physical contact between patients and healthcare professionals (e.g. feeding, changing diapers etc.); differences in developmental immunity; congenital anomalies that disrupt anatomical barriers; increased susceptibility to certain pathogens; social interactions that may increase microbial transmission (such as visiting family members) [5].

The aim of this cross-sectional study was to analyze the incidence of nosocomial infections, the impact of hospital length of stay and type of surgical intervention on the incidence of nosocomial infections, the incidence of microorganisms causing nosocomial infections and their antibiotic susceptibility and resistance profile in patients admitted to pediatric surgical ICUs.

Material and Methods

The research was designed as a retrospective unicentric cross-sectional study. It was approved by the local departmental Ethics Committee. Quarterly data from the databases of the Department of Pediatric Anesthesiology, Intensive Care and Pain Therapy (surgical ICU), Clinic of Pediatric Surgery, Institute for Child and Youth Health Care of Vojvodina were analyzed for a three-month period.

The research included 50 patients, who were hospitalized in the surgical ICU during the period from July to September 2019. There were no exclusion criteria. The following parameters were taken from the medical histories of all subjects included in the study: age, sex, diagnosis, number of days at the hospital, and number of days at the surgical ICU. The nosocomial infection diagnosis was made based on the increase in C-reactive protein (CRP) level by more than 50% in relation to the value on admission. Also, data related to the use of antimicrobial drugs, isolated microorganisms from biological samples and their sensitivity to various antibiotics and antifungals were analyzed.

The children included in the study were divided into 4 groups according to the primary diagnosis that caused admission to the surgical ICU. The first group included newborns and infants admitted due to various congenital anomalies. The second group included children after elective surgeries. The third group included patients admitted after trauma or burns, and the fourth group included children admitted due to the diagnosis of acute abdomen.

For the needs of the research, a special protocol and database were designed, and all data were subsequently statistically processed and analyzed using appropriate tests. Comparison of the analyzed variables was performed by Mann-Whitney, Kruskal-Wallis as well as χ^2-test. Spearman's correlation analysis examined the correlation of the examined parameters. Statistical significance was set at $p < 0.05$.

Results

Our study included 50 children who were admitted to the Department of Pediatric Anesthesiology, Intensive Care and Pain Therapy (surgical ICU), Clinic of Pediatric Surgery, Institute for Child and Youth Health Care of Vojvodina, in the period between July and September 2019.

General data

The age of children included in the study ranged from the first day of life to less than 18 years. The mean age of the children was 8.14 ± 7.01 years. There were 27 (54%) male and 23 (46%) female children. The average age of male children was 10.41 ± 6.42 years and of female children 5.48 ± 6.87 years.

The children included in the study were divided into 4 groups according to the primary diagnosis that caused admission to the surgical ICU. Most children were in the group admitted after trauma or burns (15, 30%). The second most numerous group of 14 (28%) children included newborns and infants admitted due to various congenital anomalies. The condition of the acute abdomen was the admission diagnosis in 11 (22%) cases, while 10 (20%) children underwent elective surgery. The number of admitted children distributed by the primary diagnosis is shown in **Graph 1**.

Nosocomial infections

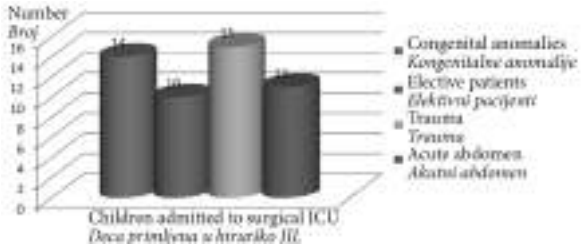
The initial CRP level on admission to the surgical ICU was measured in each patient. The mean CRP level, upon ICU admission, in all patients was 50.1 ± 80.1 mg/l. The CRP level was monitored daily until discharge from the surgical ICU. Patients with an increase in CRP levels by more than 50% in relation to the initial level on admission were defined as patients with a nosocomial infection. There were 24 patients (48%) without clear signs of infection, while the number of those with nosocomial infection was 26 (52%).

Comparison of patients with and without nosocomial infection by age, length of stay at the hospital and length of stay at the surgical ICU is shown on **Table 1**.

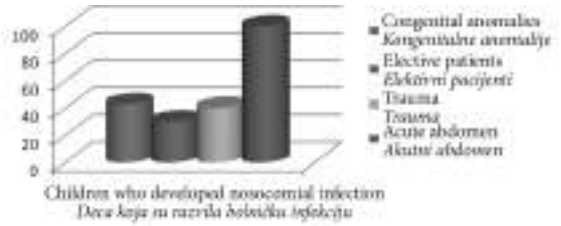
Table 1. Comparison of patients with and without nosocomial infections
Tabela 1. *Poređenje pacijenata bez razvijene bolničke infekcije i pacijenata sa razvijenom bolničkom infekcijom*

	Without infection *Bez razvijene infekcije* (n = 24)	Nosocomial infection *Bolnička infekcija* (n = 26)	p-value* *p-vrednost**
Age (years) - Mean ± SD/*Starost (godine)* AS ± SD	7.5 ± 1.6	8.73 ± 2.26	0.48
Length of stay in hospital (days) - Mean ± SD *Dužina boravka u bolnici (dani) AS ± SD*	12,3 ± 2.5	14.3 ± 2	0.2
Length of stay in surgical ICU (days) - Mean ± SD *Dužina boravka u hirurškoj JIL (dani) AS ± SD*	4 ± 2.8	8.4 ± 7.5	0.003

Legend/*Legenda:* * Mann–Whitney test: p < 0.05 was considered statistically significant/* *Man–Vitnijev test: p < 0,05 je smatrana statistički značajnom vrednošću;* Mean/*AS – aritmetička sredina; SD – standard deviation/SD – standardna devijacija;* ICU - intensive care unit/*JIL – jedinica intenzivnog lečenja*



Graph 1. Number of admitted children in surgical ICU grouped by primary diagnosis (congenital anomalies, elective patients, trauma, acute abdomen)
Grafikon 1. *Broj dece primljene u Jedinicu intenzivnog lečenja grupisanih po vodećoj dijagnozi (kongenitalne anomalije, elektivni pacijenti, trauma, akutni abdomen)*



Graph 2. Percentage of children who developed nosocomial infection in diagnostic-related groups
Grafikon 2. *Procenat dece koja su razvila bolničku infekciju po dijagnostičkim grupama*

The mean age of patients without clear signs of infection was 7.5 ± 1.6 years, while mean age of patients with nosocomial infection was 8.73 ± 2.26 years. The Mann-Whitney test showed that there was no statistically significant difference between the age of patients and presence of nosocomial infection in surgical ICU (p = 0.48).

The Mann-Whitney test showed that there was a statistically significant difference between the presence of nosocomial infection and the length of stay at the surgical ICU (p = 0.003). Spearman's correlation test showed a moderately strong correlation between the level of CRP and the hospital length of stay (q = +0.42).

The average length of stay of patients with a nosocomial infection was 14.3 ± 2.0 days and 12.3 ± 2.5 days in the group without nosocomial infection. This difference was not statistically significant (Mann-Whitney test p = 0.2).

We also investigated the incidence of nosocomial infections between the groups. The Chi-square test showed that there was a significant difference between the groups (p = 0.001). The difference was significant due to the group of patients with the diagnosis of acute abdomen on admission, because all of these patients had elevated CRP. There were 6 patients (42.8%) in the group with congenital anomalies, 6 (40%) in the group with traumas, and 3 (30%) in the group of patients undergoing elective surgery who developed nosocomial infection **(Graph 2)**.

Microorganisms and their antibiotic sensitivity

During our study, we investigated the biological sample taken for microorganism analysis determined by the hospital protocol. A positive throat swab was found in 6 (12%) patients. The obtained antibiogram showed the presence of Escherichia coli, Stenotrophomonas maltophilia, Staphylococcus aureus and Acinetobacter spp. A positive blood culture was found in 7 (14%) patients. The obtained antibiogram showed the presence of coagulase-negative staphylococci in 5 patients, while in one patient Enterobacter spp. and Candida parapsilosis were isolated. Positive stool tests were found in 11 (22%) patients. Fungi (Saccharomyces or Candida spp.) were found in all samples. A positive abdominal swab was found in 7 (14%) patients. The most commonly isolated bacterium was Escherichia coli, in one patient associated with Providencia rettgeri, or Pseudomonas aeruginosa. In one case, we isolated Acinetobacter spp. A positive drain tip culture was found in 4 (8%) patients. The isolated bacteria were Bacillus spp, Escherichia coli and coagulase-negative staphylococci. A positive wound swab was found in 3 (6%) patients. The isolated bacteria were Enterococcus faecium and coagulase-negative staphylococci. **Graph 3** shows the overall incidence of positive antimicrobial susceptibility testing results.

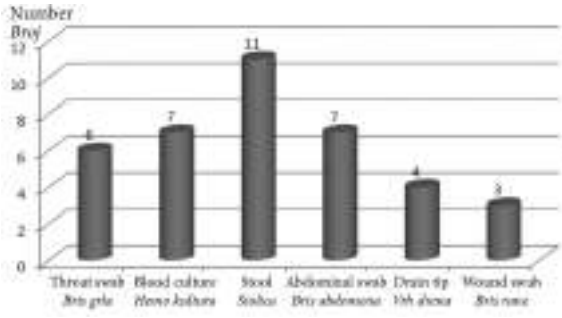
Of the 62 isolated pathogens, most were Gram-negative bacteria (46.8%), followed by Gram-positive bacteria (30.6%), while the remaining microorganisms were fungi (22.6%). The most common microorganisms were: Escherichia coli (24.7%), fungi (22.6%), coagulase-negative staphylococci (19.3%), Acinetobacter spp. (8.1%) and Enterococcus spp. (6.5%). The remaining microorganisms (Staphylococcus aureus, Bacillus spp., Proteus mirabilis,

Table 2. The sensitivity of the most commonly isolated bacteria to antibiotics
Tabela 2. *Senzitivnost najčešće izolovanih bakterija na antibiotike*

Antibiotic *Antibiotik*	Escherichia coli *Escherichia coli*	Coagulase-negative staphylococci/*Koagulaza negativan stafilokok*	Acinetobacter spp. *Acinetobacter spp.*	Enterococcus spp. *Enterococcus spp.*
Ampicillin/*Ampicilin*	23.5%	/	/	50%
Amoxicillin/*Amoksicilin*	23.5%	/	/	50%
Amoxicillin clavulanic acid *Amoksicilin klavulanska kiselina*	41.2%	16.7%	/	50%
Imipenem/*Imipenem*	100%	/	20%	/
Meropenem/*Meropenem*	100%	/	20%	/
Ertapenem/*Ertapenem*	100%	/	/	/
Amikacin/*Amikacin*	94%	/	20%	/
Vancomycin/*Vankomicin*	/	100%	/	50%
Tigecycline/*Tigeciklin*	/	/	/	100%
Linezolid/*Linezolid*	/	93,3%	/	100%
Teicoplanin/*Teikoplanin*	/	/	/	50%
Tetracyclines/*Tetraciklini*	/	60%	/	/
Fusidic acid/*Fusidinska kiselina*	/	53%	/	/

Stenotrophomonas maltrophilia, Providentia rettgeri, Pseudomonas aeruginosa, Enterobacter spp.) were present in only one or two isolates.

The antibiograms show that bacteria may be sensitive, moderately sensitive, or resistant to certain antibiotics. Thus, the most effective antibiotics for isolated strains of Escherichia coli were from the carbapenem group imipenem, meropenem and ertapenem (100% of sensitive strains), followed by amikacin from the aminoglycoside group (94% of sensitive strains). Ampicillin and amoxicillin from the group of beta-lactam antibiotics were the least effective (23.5% of sensitive strains). Coagulase-negative staphylococci strains were 100% sensitive only to vancomycin from the group of glycopeptide antibiotics. The next in efficiency were linezolid from the class of oxazolidinone (93.3% of sensitive strains), tetracyclines (60% of sensitive strains), fusidic acid (53% of sensitive strains), while staphylococci were mostly resistant to all other tested antibiotics. Acinetobacter spp. proved to be the most resistant bacteria in this study, since 80% of strains did not show sensitivity to any of the tested antibiotics.



Graph 3. Incidence of positive samples submitted for microbiological analysis
Grafikon 3. *Incidencija pozitivnog uzorka na mikrobiološku analizu*

Among them, only one strain was intermediate to antibiotics from the penicillin group – ampicillin/sulbactam. The only antibiotic to which 100% of Enterococcus spp. strains showed sensitivity were linezolid from the oxazolidine class and tigecycline from the glycylcycline class. Half (50%) of the isolated strains of Enterococcus spp. showed sensitivity to ampicillin, amoxicillin and amoxicillin/clavulanic acid from the group of penicillins, vancomycin and teicoplanin from the class of glycopeptide antibiotics. The **Table 2** shows the sensitivity of the most commonly isolated bacterial pathogens to antibiotics.

Discussion

Prevention, control and treatment of infections in ICUs requires detailed knowledge of local epidemiological data: incidence of infections, incidence of microorganisms and their antimicrobial resistance profiles, as well as potential risk factors for infection [6].

Numerous studies indicate that one-third to one-half of critically ill patients develop a nosocomial infection [7]. These results are in line with the incidence of nosocomial infections in our surgical ICU, which is 52%. In most foreign studies, pediatric ICUs are usually multidisciplinary, so they do not separate children with surgical pathology from other children, which may be the reason for a significantly lower incidence of infections in their ICUs (20%) compared to ours [8, 9]. Also, they usually have separate neonatal ICUs, which is different in our clinic. Finally, in our ICU there are plenty of emergency patients who are prone to infections in general.

According to our study results, patients with nosocomial infections stayed longer in surgical ICU than those without a nosocomial infection. Similar results were reported by Baviskar A. et al. in their study conducted in surgical ICU, as well as Becerra M. et al.

whose study was conducted in a pediatric ICU [9, 10]. Patients with a nosocomial infection stay longer in the ICU, because it takes a certain period of time to recover from the infection. Also, our study shows that nosocomial infections are more common in patients diagnosed with acute abdomen than in other groups of patients. In the group of patients who developed nosocomial infection in the surgical ICU in the study of Baviskar A. et al., most patients were also those whose admission diagnosis was acute abdomen/abdominal surgery (65%). The higher incidence of nosocomial infections in patients with abdominal surgery/acute abdomen can be explained by a higher incidence of surgical wound infections. These patients underwent emergency surgery with suboptimal preoperative bowel preparation, which leads to wound contamination [11].

As in the study by Baviskar A. et al., the most common isolated organisms that cause nosocomial infections were Gram-negative bacteria - 72.3% (in our study - 46.8%). Also, among the most common gram-negative causes of infections were Escherichia coli - 26.6% and Acinetobacter spp. - 18.1% (in our study - 24.7%; 8.1%, respectively) [9]. Regarding the sensitivity of the most commonly isolated pathogens, the results of Bayram A. and Balci I. differ from ours in terms of resistance of coagulase-negative staphylococci, since in their surgical ICU they were all (100% of strains) resistant to tetracyclines, and in ours about 40% [6]. As in the study by Tran G. et al., Acinetobacter spp. appears to be the most resistant bacteria in their ICU, since most strains (80 to 90%) showed to be resistant to antibiotics such as imipenem, meropenem, and amikacin (in our study - 80%) [11]. Escherichia coli strains showed similar sensitivity in our and the study of Bayram A. and Balci I., in whose surgical ICU the most effective antibiotics were imipenem - 90% and amikacin - 95% (in our study - 100%; 94%) [6].

Multidrug-resistant bacteria are microorganisms resistant to 3 or more groups of antibiotics. In this study, Acinetobacter spp. shows the highest percentage of multidrug-resistant strains (80%), and the results of other studies are similar, such as the study of Baviskar A. et al., where Acinetobacter spp. is the leading bacteria with the highest number of strains resistant to several different groups of antibiotics (65%) [9].

Conclusion

Higher percentage of nosocomial infections in intensive care unit patients, especially pediatric patients, is probably multifactorial: immature immune system, insufficient number of nurses, irrational use of antibiotics, longer hospitalization, invasive monitoring and generally inadequate hygiene, etc. Thus, control of infections in intensive care units primarily means their prevention. The most important aspect of prevention is the implementation of strict hygiene measures. Hospital hygiene is also extremely important. Supervision of antibiotic use is a special segment and it is carried out with the aim of their rational use, since it largely contributes to the development of antimicrobial resistance.

These data show the current state of the epidemiological situation in a surgical intensive care unit and indicates the importance of infection control in it. High percentage of nosocomial infections, which is most likely the cause of longer treatment and stay of children in the intensive care unit, have more severe consequences for their health and the cost of treatment. Since this is a cross-sectional study, it is not possible to determine the direct reason for this situation, but it is certain that the cause is multifactorial. Future research should monitor further development of the epidemiological situation in pediatric intensive care units.

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CASE REPORTS
PRIKAZI SLUČAJEVA

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COMBINATORIAL PHARMACOGENOMIC TEST FOR SUCCESSFUL ANTIDEPRESSANT TREATMENT OF A MAJOR DEPRESSIVE DISORDER

KOMBINATORNI FARMAKOGENOMSKI TEST USPEŠNO JE ODREDIO ANTIDEPRESIVNU TERAPIJU ZA TEŽAK DEPRESIJSKI POREMEĆAJ

Slađana VOJVODIĆ[1, 2], Gabor KATONA[1] and Miroslav SARAČ[1]

Summary

Introduction. The combinatorial pharmacogenomic test has shown the potential to predict antidepressant response, tolerability, selection, and dosage in the treatment of a major depressive disorder. A case of successful management of antidepressant therapy adjustment is reported by using the combinatorial pharmacogenomic test. **Case Report.** A 53-year old man, severely disabled due to a rare genetic disease, Usher syndrome type 3, was treated with numerous antidepressants. However, episodes of major depression recurred, along with frequent suicidal thoughts. A combinatorial pharmacogenomic test was considered to design a potentially effective antidepressant therapy. **Conclusion.** According to the results of the combinatorial pharmacogenomic test, the patient constantly received inadequate antidepressant therapy, which did not lead to an improvement of depression due to moderate gene-drug interaction. The patient was prescribed nortriptyline, which proved to be one of the few most adequate according to the test. He showed improvement with subjectively more tolerable depression without suicidal thoughts and episodes of major depression. This case showed that the combinatorial pharmacogenomic testing may contribute to better selection of antidepressant therapy.

Key words: Depressive Disorder, Major; Depressive Disorder, Treatment-Resistant; Antidepressive Agents; Signs and Symptoms; Pharmacogenomic Testing; Treatment Outcome

Sažetak

Uvod. Kombinatorni farmakogenomski test je pokazao potencijal za predviđanje antidepresivnog odgovora, podnošljivosti, selekcije i doziranja prilikom lečenja teškog depresijskog poremećaja. Prikazan je slučaj uspešnog upravljanja prilagođavanjem terapije antidepresivima korišćenjem kombinatornog farmakogenomskog testa. **Prikaz slučaja.** Ovaj 53-godišnji muškarac, teško onesposobljen zbog retkog genetskog sindroma Usher 3, bio je na terapiji brojnim antidepresivima. Međutim, epizode teške depresije su se ponavljale, zajedno sa čestim samoubilačkim mislima. Kombinatorni farmakogenomski test je razmatran za oblikovanje moguće uspešne antidepresivne terapije. **Zaključak.** Prema rezultatima kombinatornog farmakogenomskog testa, pacijent je neprekidno bio na neadekvatnoj antidepresivnoj terapiji, koja nije dovela do poboljšanja njegovog stanja depresije zbog umerene interakcije gen-lek. Pacijentu je prepisan nortriptilin, koji se pokazao kao jedan od nekoliko najadekvatnijih prema testu. On je pokazao poboljšanje sa subjektivno podnošljivijom depresijom bez samoubilačkih misli i epizoda teške depresije. Ovaj slučaj je pokazao da kombinatorni farmakogenetski test može pomoći u boljem oblikovanju terapije antidepresivima.

Ključne reči: težak depresivni poremećaj; depresivni poremećaj otporan na lekove; antidepresivna terapija; znaci i simptomi; farmakogenomsko testiranje; ishod lečenja

Introduction

Depression is a significant human blight [1]. Globally, it is responsible for more disabilities than any other condition. According to the World Health Organization, approximately 350 million people suffer from depression. It is one of the leading causes of disability, and is in the ninth place as a general cause of mortality after cardiovascular diseases, stroke, and human immunodeficiency virus infection. Generally, depression is widely undiagnosed and not treated properly. One of the possible reasons is that there is still a stigma, lack of treatment and lack of mental health resources. Additionally, some clinical studies have shown that patients with depression do not have a satisfactory therapeutic outcome [2].

Clinically significant depression is present in one of every four persons with diabetes mellitus type 2 [3] and patients with multimorbidity including disability [4]. Depression is a frequent complication after stroke [5] and cardiovascular diseases [6]. Generally, depression is common in the elderly, but still stays undiagnosed and improperly treated in

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Abbreviations

MDD – major depressive disorder
CPGx – combinatorial pharmacogenomic
MTHFR – methylenetetrahydrofolate reductase
PCR – polymerase chain reaction
PHQ-9 – Patient health questionnaire-9
SBQ-R – Suicide Behaviors Questionnaire-Revised
QIDS – Quick Inventory of Depressive Symptomatology
TMS – transcranial magnetic stimulation
rTMS – repetitive transcranial magnetic stimulation

clinical settings [7–9]. Depression is a prevalent and fatal disorder, and approximately one in five adults in the United States had at least one severe episode of major depression in their lifetime [10].

Major depression is a common disabling condition, first diagnosed and treated predominantly in primary care setting, followed by treatment in psychiatric clinics. Some severe medical conditions, including visible and invisible disability, sleep disorders, grief, and other psychiatric conditions, may co-occur and mimic the symptoms of major depressive disorder (MDD). Healthcare providers should assess for the presence of these conditions when diagnosing MDD and consider comorbid conditions to tailor management interventions [11]. In some cases, antidepressant therapy requires special attention of healthcare providers. Multiple changes of antidepressant medications without success may point to drug-resistant depression, and further diagnostic tests should be considered to prevent a severe episode of depression when a patient is suffering from frequent suicidal thoughts.

In this article, we present a case of MDD in a severely disabled patient due to rare genetic disorder, Usher syndrome type 3, treated with many antidepressants for an extended period without success and frequent periods of relapse when the patient suffered from significant depressive episodes and persistent suicidal thoughts. Physicians should prescribe antidepressants based on educated guesses because it is impossible to predict the effectiveness of any particular antidepressant in an individual patient [12]. Pharmacogenomics has opened the door for better treatment of MDD and treatment with antidepressants. Commercially available combinatorial multigene pharmacogenomic (CPGx) tests, in previous studies, predicted patients whose antidepressant therapy for MDD resulted in poor efficacy and significantly increased the healthcare costs [13–16]. Thus, they can reduce overall healthcare costs in patients with drug-resistant MDD [17]. Some studies showed that CPGx is reproducible and suitable for clinical use [18]; some studies are controversial regarding the utilization of CPGx; however, there are clinical cases in which the technology may be informative [19, 20].

Case Report

A 53-year old Caucasian man, born and raised in Europe, was severely disabled due to a rare genetic disease, Usher syndrome type 3 (vision, hearing, and balance impairment), and Meniere's disease that fully expressed itself in his 40s. The patient was placed into a rehabilitation program for the visually impaired and blind, through the state rehabilitation services. The patient's written consent was obtained for this case study.

Past medical history: chronic obstructive pulmonary disease, diagnosed in 2000, and two spontaneous pneumothorax events in 1992 and 1993. Past surgical history: none. Current medications: diazepam 10 mg for dizziness if necessary, prescribed by a neuro-otologist for Meniere's disease, nortriptyline hydrochloride 150 mg (prescribed according to the results of CPGx), oxcarbazepine 300 mg (prescribed according to the results of CPGx), L-methylfolate 15 mg (prescribed according to the results of CPGx), albuterol, ibuprofen 400 mg/day for arthritic pain and doxylamine succinate 25 mg as a nighttime sleep-aid. Allergies: penicillin, doxycycline. Social history: smoking, one pack per day.

The patient experienced the first episode of MDD due to a developed, acquired disability. First, he received escitalopram. Since 2008, he has received several antidepressants, such as venlafaxine (initially 75 mg to 375 mg/day), escitalopram (10 mg – 20 mg/day), bupropion hydrochloride (150 mg – 400 mg), fluoxetine (20 mg – 80 mg), sertraline (50 mg – 200 mg), and paroxetine (10 mg – 40 mg). Each medication showed only a slight improvement for a brief period (approximately two to four months) and an episode of MDD relapsed. The patient exhibited significant weight gain and altered lipid profile during antidepressant therapy without improvement of depression. A home-bound and sedentary lifestyle of a deaf-blind person significantly contributed to his agonizing bouts of depression even though he was treated for depression using multiple antidepressants prescribed by a physician.

The Diagnostic and Statistical Manual of Mental Disorders-5 of the American Psychiatric Association criteria used by a psychiatrist pointed to the diagnosis of MDD, According to the International Classification of Diseases, the tenth revision, the diagnosis code was F32.2. More than five depressive symptoms were detected, such as depressed mood most of the day, loss of interest and pleasure, weight gain on higher doses of each antidepressant, and weight loss during the episodes of MDD with suicidal thoughts, insomnia, fatigue, feeling worthless with reduced self-esteem, decreased concentration and attention, pessimistic views of the future, suicidal/death thoughts. In addition, the patient exhibited additional four required criteria, such as symptoms that cause clinically significant distress or impairments in social, professional/occupational, or other important areas of functioning; there was no history of manic and hypomanic episodes, episodes not explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders, episodes not attributable to physiological effects of a substance or another medical condition. Over several years, psychiatric and psychological evaluation and assess-

ment included Montgomery-Asberg Depression Rating Scale, Hamilton Depression Rating Scale, Patient Health Questionnaire-9, Suicide Behaviors Questionnaire-Revised, and Quick Inventory of Depressive Symptomatology was used for evaluation of the patient's improvement.

His depression significantly worsened and he started developing MDD with suicidal thoughts. The psychiatrist seriously took into consideration the diagnosis of treatment-resistant depression along with MDD and dysthymia. With MDD, dysthymia may include more than one cause, including impaired brain chemistry and impaired pharmacokinetics and pharmacodynamics (relevant for this case), genetics such as having a first degree relative with depressive disorder (in this case, father and brother), life events/environmental factors such as loss of a parent during childhood (relevant for this case), traumatic events (in this case acquired severe disability), and personality traits that include negativity, low self-esteem, pessimistic view of the future, excessive dependence on others, such as the primary caregiver (relevant for this case). After that, a combinatorial pharmacogenomic test (GeneSight® Psychotropic) was recommended by a psychiatrist for shaping a potentially successful antidepressant therapy to treat his MDD. The GeneSight® Psychotropic test was developed in a unit Myriad Genetics of the Myriad Neuroscience clinical laboratory that analyzes clinically significant genetic variations that may impact the way a patient metabolizes and responds to certain psychiatric medications. The test results provide clinicians with information regarding which medications may require dose adjustments, those that may be less likely to work, or may have an increased risk of side effects based on the patient's genetic makeup. GeneSight® Psychotropic test has been performed by laboratory Assurex Health Inc., Mason, OH, United States of America. Deletion/duplication analysis was done by polymerase chain reaction (PCR) and electrophoresis and Targeted Variant Analysis allele-specific primer extension by Agena Bioscience Mass ARRAY system PCR and electrophoresis.

The combinatorial pharmacogenomic test revealed the following findings: after the buccal swab sample was collected, genomic deoxyribonucleic acid was isolated, and the relevant genomic regions were amplified by PCR. Analysis of ADRA2A, COMT CYP2D6, HLA-B*1502, SLC6A4, CYP1A2, CYP2B6, CYP2C9, CYP3A4, HTR2A, rs1061235 (indicating presence of the HLA-A*3101 allele or specific HLA-A*33 alleles), UGT1A4, UGT2B15, CYP2D6, MTHFR genes was performed.

The genetic test for the methylenetetrahydrofolate reductase (MTHFR) gene exhibited significantly reduced folic acid conversion. The patient was recessive homozygous for T allele of the C677T polymorphism in the MTHFR gene. This genotype is associated with considerably decreased folic acid metabolism, significantly reduced serum folate levels, and significantly increased homocysteine levels. Additionally, the combinatorial pharmacogenomic test provided information about the best choice for mood stabilizer therapy, anxiolytics, hypnotics, antipsychotics, and attention deficit hyperactivity disorder (ADHD) therapy.

Discussion

According to CPGtest results, the patient was continuously using antidepressant therapy, but it did not improve his condition due to moderate and significant gene-drug interactions such as bupropion, escitalopram, fluoxetine, sertraline, venlafaxine, and paroxetine. The serum levels, according to clinical and pharmaceutical considerations, may be too high, and lower doses may be necessary for all these medications. Thus, practically, the patient was permanently on antidepressant therapy, which was not the best option for improving his MDD and severe episodes of depression with frequent suicidal thoughts. The patient exhibited an increased sensitivity phenotype for the genotype in HTR2A gene G/G, potentially putting the patient at an increased risk of adverse drug reactions with specific selective serotonin reuptake inhibitors. The patient exhibited standard results (phenotype) for the serotonin transporter. Also, genetic testing revealed a lower risk phenotype for severe dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) when taking specific mood stabilizers.

The pharmacogenomic genes exhibited potential phenotypes such as increased enzyme activities for CYP1A2 as an ultra-rapid metabolizer and UGT1A4 and UGT2B15; intermediate metabolizer for CYP2B6, CYP2C19, and CYP2C9 and normal extensive metabolizer for CYP3A4, CYP2D6.

The patient started treatment with antidepressant nortriptyline 150 mg and a mood stabilizer oxcarbazepine, which was established as the most appropriate according to the results of CPGx. Nortriptyline and oxcarbazepine are two of the very few medications that were not found in the patient genotypes that may impact medications response and moderate or significant gene-drug interactions. The patient was recessive homozygous for the T allele of the C677T polymorphism in the MTHFR gene, significantly reducing folic acid conversion into the active form L-methylfolate, so he received L-methylfolate 15 mg per day. This genotype is associated with considerably decreased folic acid metabolism, significantly reduced serum folate levels, and significantly increased homocysteine levels, confirmed by laboratory testing (three times elevated homocysteine compared to the average level). The lack of L-methylfolate is well known as a factor that significantly contributes to depression (so-called MTHFR depression) and other pathologies such as cardiovascular diseases, neurological abnormalities, and numerous metabolic abnormalities.

Since the patient started receiving nortriptyline antidepressant therapy combined with mood stabilizer oxcarbazepine and L-methylfolate, according

to the results of CPGx, he showed improvement with subjectively more tolerable depression without suicidal thoughts and episodes of severe depression. The scores improved on the Montgomery-Asberg Depression Rating Scale (MADRS), Patient Health Questionnaire (PHQ-9), Suicide Behaviors Questionnaire-Revised (SBQ-R), and Quick Inventory of Depressive Symptomatology (QIDS), performed by a psychiatrist and clinical psychologist-psychotherapist. The patient started psychotherapy conducted by a clinical psychologist and less frequent psychiatric evaluation. Even though without suicidal thoughts and episodes of severe depression, the patient subjectively felt that depression was more tolerable but still present without significant fluctuations.

Additionally, in 2017, the psychiatrists proposed a combination of current antidepressant therapy prescribed according to results of the pharmacogenomic test with alternative repetitive transcranial magnetic stimulation (TMS). The TMS is an alternative non-invasive procedure in psychiatry that uses magnetic fields to stimulate the brain to treat symptoms of depression. It is used when other depression treatments have not been effective as expected. This treatment involves delivering repetitive magnetic pulses, so it is called repetitive TMS (rTMS) [21, 22]. The patient underwent 36 consecutive rTMS treatments. The treatments were performed on Neuronetics (Inc. NeuroStar®, Malvern, PA, USA) conducted and supervised by a trained psychiatrist in TMS treatment. During rTMS treatments, the evaluation and assessment were performed by PHQ-9, SBQ-R, and QIDS. The improvement of depression was substantial and it lasted about a year. Still, on treatment by nortriptyline, oxcarbazepine, and L-methyl folate every day, the patient was without suicidal thoughts with subjectively tolerable depression. However, in the interview, the patient reported that 36 consecutive rTMS treatments were pretty exhausting; he did not feel any positive effects until the 20th treatment, and that support from family was crucial in this long term treatment which took 36 days. Additionally, it was a substantial financial burden as this alternative treatment in mental healthcare is not fully covered by health insurance.

In 2019, the patient started receiving ketamine infusions (racemic ketamine, a subanesthetic, 0.5 mg/kg administered over 40 minutes) performed by an anesthesiologist and psychiatrist with electrocardiography and vital signs monitoring. The patient received the initial six infusions over the first two weeks and then boosters every three to six weeks. Ketamine infusions along with prescribed nortriptyline, oxcarbazepine, and L-methyl folate significantly improved the depression, he was completely without suicidal thoughts, and it enhanced everyday functioning. Ketamine is effective for treatment-resistant depression, suicidal thoughts, posttraumatic stress disorder, bipolar depression, and multiple other mood disorders [23, 24]. Ketamine has immediate effects, so it is now being used in patients with suicidal ideations. However, the impact of an initial treatment usually lasts for 1 – 3 days, and repeated treatments are needed to sustain more extended relief from treatment-resistant depression and other depressive symptoms. Prior, during, and after initial ketamine infusions, the evaluation and assessment were performed by PHQ-9 and QIDS. They exhibited a substantial increase in the scores and well overall patient subjective feeling regarding depression. Unfortunately, this alternative treatment is still not covered by health insurance, and it may be a substantial financial burden.

With increasing evidence of ketamine efficacy in persons with treatment-resistant depression and its potential anti-suicidal effect, a research was performed on elucidating its effects on the brain. Of particular interest and therapeutic potential is the ability of ketamine to exert rapid antidepressant properties as early as several hours after administration. This is in contrast with the delayed effects observed with traditional antidepressants, mostly requiring several weeks or months of therapy for a favorable clinical outcome. Ketamine appears to have the mechanism of action involving glutamate modulation via activities at the N-methyl-D-aspartate and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors. Additionally, downstream activation of brain-derived neurotrophic factor and mechanistic target of rapamycin signaling pathways potentiate synaptic plasticity [25].

Currently, the patient is under prescribed nortriptyline, oxcarbazepine, and L-methylfolate (L-5-MTHF, the fourth generation of L-methylfolate in combination with methylcobalamin B12). In addition, approximately every three to five months (if necessary), he receives ketamine infusion booster. It seems that both alternative treatments in psychiatry, such as rTMS and ketamine infusions, in combination with the proposed therapy according to pharmacogenomic test results, exhibited substantial overall improvement and alleviated severe depression. However, we should not underestimate the effect of metabolically active L- methylfolate in the current therapy. The patient was detected as recessive homozygous for the T allele of the C677T polymorphism in the MTHFR gene, significantly reducing folic acid conversion into the active form L-methylfolate. The C677T gene mutation leads to depression in several ways [26, 27]. Firstly, this gene mutation indirectly affects the cause of depression through the inability to use vital essential nutrients and the utilization of specific amino acids needed to synthesize neurotransmitters and affect the homocysteine cycle. Secondly, if folate metabolism is impaired and generally methylation, it sets up a chain reaction leading to depression.

Surely, pharmacogenomic testing is a promising diagnostic means in clinical practice, including psychiatry. For example, antidepressants help alleviate depression by altering brain chemicals like serotonin, dopamine, norepinephrine, etc. However, it is a clinical balancing act to find what actually works with each patient and typically takes several weeks or months to find what works or if antidepressants will

work at all. Even though some patients exhibit a substantial improvement in depression, some patients do not show adequate and expecting response to antidepressants. Suppose a patient does not show any signs of improvement after two or three antidepressants. In that case, it is a warning sign that pharmacogenomic testing should be considered for further shaping an antidepressant therapy. Also, relatively new alternative treatments, such as rTMS and ketamine infusions, should be considered in cases of treatment-resistant depression when a patient shows no substantial improvement after two to four antidepressants. According to the current protocols for alternative treatments (rTMS and ketamine infusions), patients are eligible for these treatments if there is no positive response to 2 – 4 or more antidepressant medications.

Conclusion

Without doubt, pharmacogenomics can improve clinical outcomes by guiding antidepressant selection and dosing. In this case of major depressive disorder, inadequately treated for a long time with inappropriate antidepressant therapy, it caused episodes of severe depression with suicidal thoughts, pointing to the fact that combinatorial pharmacogenomic testing could help in shaping antidepressant therapy better with mood stabilizers, anxiolytics, hypnotics, and antipsychotics. Unfortunately, there are very few studies to support clinical utilization of pharmacogenomic testing.

Reporting successful outcomes accomplished by using combinatorial pharmacogenomic testing for depression may contribute to its more frequent use in clinical practice as well as selection of proper medications for depression and other psychiatric pathologies. Additionally, high cost of treatment with antidepressants would be avoided, improving the psychiatric healthcare and psychotherapeutic services. Also, repetitive transcranial magnetic stimulation and ketamine infusions exhibited promising signs in treating patients who suffer from treatment-resistant depression, major depressive disorder, and inadequate response to antidepressant medications.

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TICAGRELOR IN UNSTABLE CAROTID STENOSIS – A CASE REPORT

TIKAGRELOR U NESTABILNOJ KAROTIDNOJ STENOZI – PRIKAZ SLUČAJA

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Summary

Introduction. Ticagrelor is an oral, reversible, direct-acting inhibitor of adenosine diphosphate receptor P2Y12, which has a faster onset of action and stronger inhibition of platelet aggregation than clopidogrel. **Case Report.** This case report describes a 54-year-old male patient with repeated, transient ischemic attacks due to ipsilateral, significant carotid stenosis registered by carotid duplex ultrasound. In addition to aspirin, clopidogrel and rosuvastatin were added to the therapy. Despite optimal treatment, the patient was continuously unstable with frequent but transient neurological symptoms. A magnetic resonance imaging of the brain showed acute, cortical-subcortical ischemic lesions in the left frontal and parietal lobes, while the computed tomography angiography of the endocranium showed progression of findings and occlusion of the left common carotid artery. Subsequently, laboratory platelet aggregation analysis confirmed aspirin resistance and poor response to clopidogrel. Episodes of transient ischemic attacks were stabilized after the exclusion of dual antiplatelet therapy and introduction of ticagrelor. After that, the patient's symptoms did not recur and he remained stable. **Conclusion.** The incidence of resistance to antiplatelet therapy in patients with stroke or transient ischemic attack varies greatly and ranges from 3% to 85% for aspirin, and 28% to 44% for clopidogrel. Our case showed that platelet aggregation analysis is reasonable if patients with transient ischemic attack or minor acute ischemic stroke are neurologically unstable, despite optimal medical treatment and when other therapeutic options, such as carotid revascularization, are not indicated. In such situations, ticagrelor may be a suitable alternative to dual antiplatelet therapy.

Key words: Ischemic Attack, Transient; Ischemic Stroke; Carotid Stenosis; Ticagrelor; Clopidogrel; Platelet Aggregation Inhibitors; Aspirin; Secondary Prevention

Sažetak

Uvod. Tikagrelor je oralni, reverzibilni, direktni inhibitor adenozin-difosfatnog receptora P2Y12, koji ima brži početak dejstva i snažniju inhibiciju agregacije trombocita nego klopidogrel. **Prikaz slučaja.** Prikazan je slučaj muške osobe, starosti 54 godine, sa ponovljenim, tranzitornim ishemijskim atacima nastalim usled ipsilateralne, signifikantne karotidne stenoze, registrovane neurosonološkom obradom. Pored aspirina, klopidogrel i rosuvastatin su bili uključeni u terapiju. Uprkos optimalnom tretmanu, pacijent je bio kontinuirano nestabilan sa čestim, ali tranzitornim neurološkim simptomima. Na snimku magnetne rezonancije mozga registrovane su akutne, kortiko-supkortikalne ishemijske lezije u frontalnim i parijetalnim režnjevima levo, dok je na angiografiji kompjuterizovanom tomografijom endokranijuma opisana progresija nalaza i okluzija leve zajedničke karotidne arterije. Nakon toga, laboratorijskom analizom agregabilnosti trombocita potvrđena je rezistencija na aspirin i slab odgovor na klopidogrel. Epizode tranzitornih ishemijskih ataka bile su stabilizovane nakon isključenja dvojne antiagregacione terapije i uvođenja tikagrelora, nakon čega se tegobe pacijenta nisu ponavljale i nadalje je bio stabilnog neurološkog statusa. **Zaključak.** Incidencija rezistencije na antiagregacionu terapiju kod pacijenata sa moždanim udarom ili tranzitornim ishemijskim atacima varira u opsegu od 3% do 85% za aspirin i 28% do 44% za klopidogrel. Pokazali smo da je testiranje agregabilnosti trombocita opravdano kod pacijenata sa tranzitornim ishemijskim atacima ili blagim ishemijskim moždanim udarom koji su neurološki nestabilni, uprkos optimalnom lečenju i kada ostale terapijske opcije, kao što je karotidna revaskularizacija, nisu indikovane. U takvim situacijama, tikagrelor bi mogao biti odgovarajuća alternativa dvojnoj antiagregacionoj terapiji.

Ključne reči: tranzitorni ishemijski atak; ishemijski moždani udar; karotidna stenoza; tikagrelor; klopidrogel; antiagregaciona terapija; aspirin; sekundarna prevencija

Introduction

Ticagrelor is an oral, reversible, direct-acting inhibitor of adenosine diphosphate (ADP) receptor P2Y12, which has a faster onset of action and stronger inhibition of platelet aggregation than clopidogrel [1]. The PLATO trial showed that in patients with acute coronary syndrome (ACS) ticagrelor significantly reduced the death rate from vascular causes, myocardial infarction, and stroke compared to clopidogrel [2]. On the other hand, Ticagrelor is not recommended over aspirin for treatment of patients with minor acute stroke [1].

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Abbreviations

TIA – transient ischemic attack
MRI – magnetic resonance imaging
CT – computed tomography
ADP – adenosine diphosphate
MRA – magnetic resonance angiography
CDU – carotid duplex ultrasonography
CCA – common carotid artery
ICA – internal carotid artery
AIS – acute ischemic stroke

Case Report

A 54-year-old man with a medical history of hypertension, diabetes and smoking was admitted to the emergency department due to transient diplopia, speech difficulties and right-sided central facial palsy which self-resolved within 30 minutes. One week before, he had temporary double vision in the car while driving and transient right arm numbness, both lasting up to 5 minutes. General physical examination showed no abnormalities, the blood pressure was 150/90 mmHg, the neurological examination revealed only a moderate divergent strabismus, and the National Institutes of Health Stroke Scale (NIHSS) score was 0. Laboratory test results and electrocardiography were normal and cranial non-contrast computed tomography (CT) scan did not show acute or chronic ischemic lesions. Aspirin (100 mg/day) was administered on the day of the admission to the hospital. Carotid duplex ultrasonography (CDU) showed significant (> 70%) stenosis of the left common carotid artery (CCA) and internal carotid artery (ICA), while the repeated head CT scan showed subcortical, temporal hypodense areas on the left. In addition to aspirin, clopidogrel (75 mg/day) and rosuvastatin (20 mg/day) were added to the therapy. The magnetic resonance imaging (MRI) of the brain was delayed by two days because of a questionable dental implant. Meanwhile, the patient had several short episodes of transient dysphasia, diplopia, and weakness of the right hand with complete self-resolution. Brain MRI showed acute, cortical-subcortical ischemic lesions in the left frontal and parietal lobe (**Figure 1a** and **Figure 1b**, respectively). MR angiography (MRA) showed occlusions of the left CCA and proximal part of the left ICA **(Figure 1c)**. The CDU was repeated and revealed a near-occlusion of the left CCA, and subsequent CT angiography confirmed the left CCA occlusion **(Figure 1d)**.

Despite the optimal treatment, the patient was continuously unstable with frequent but transient neurological symptoms. Therefore, the platelet sensitivity to aspirin and clopidogrel was tested using multiple electrode aggregometry and the obtained results (AGR COL/ADP 95 seconds (ref. 62 – 100 seconds), AGR COL/EPI 139 seconds (ref. 82 – 150 seconds)) revealed that the patient was resistant to aspirin and had a poor response to clopidogrel. The dual antiplatelet therapy was discontinued and ticagrelor at initial loading dose of 180 mg followed by the dose of 90 mg twice per day was initiated. Repeated platelet sensitivity test showed good response to ticagrelor (AGR P2Y12 > 300 seconds (ref. < 106 seconds)). After that, the patient's symptoms did not recur, and he remained stable. Repeated CDU confirmed occlusion of the left CCA by the unstable, ruptured atherosclerotic plaque (**Figure 1e** and **Figure 1f**). The patient was discharged with ticagrelor at a dose of 90 mg twice per day, without neurological deficits. After three months of follow-up, the patient was still without neurological symptoms or bleeding complications and the control MRI of the brain did not reveal new ischemic lesions.

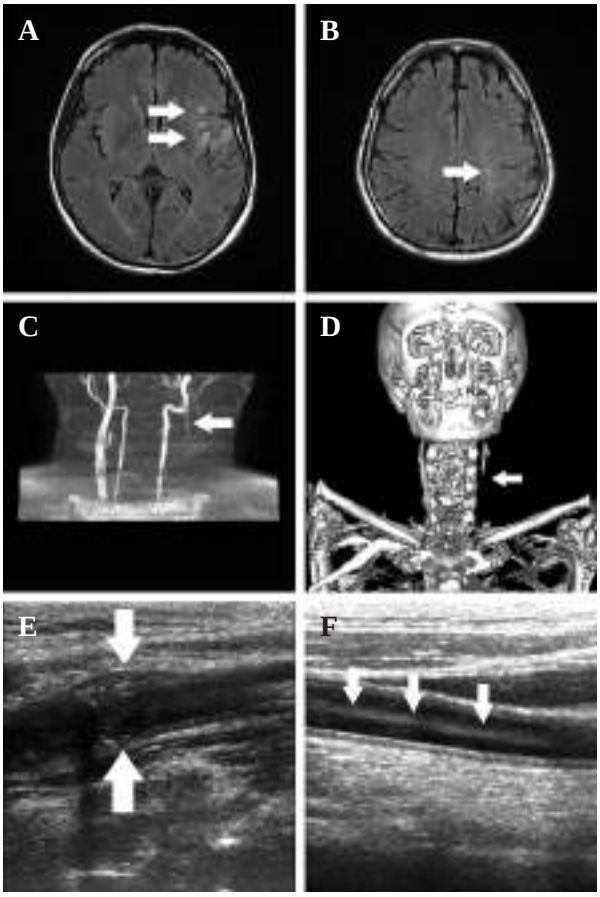

Figure 1. MRI showing acute cortical-subcortical ischemic lesions in the left frontal (A) and parietal lobe (B); MRA showing an occlusion of the left CCA and proximal part of the left ICA (C); CTA reconstruction with the left CCA occlusion (D); CDU showing the ruptured atherosclerotic plaque (E) and occlusion of the left CAA (F)

Slika 1. *Snimak magnetne rezonancije sa akutnim, kortiko-supkortikalnim ishemijskim lezijama u frontalnom (A) i parijetalnom (B) režnju levo; Magnetna rezonantna angiografija prikazuje okluziju leve ACC i proksimalnog dela leve ACI (C); CTA rekonstrukcija sa okluzijom leve ACC (D); DUZ prikazuje rupturirani aterosklerotski plak (E) i okluziju leve ACC (F)*

Legend**:** MRI – magnetic resonance imaging; CCA – common carotid artery; ICA – internal carotid artery; CTA – computed tomography angiography; CDU – carotid duplex ultrasonography

*Legenda**:** ACC – zajednička karotidna arterija; ICA – unutrašnja karotidna arterija; CTA – kompjuterizovana tomografija angiografija; DUZ – dupleks ultrazvuk karotida*

Discussion

According to the guidelines, aspirin is recommended in patients with acute ischemic stroke (AIS) within 24 to 48 hours after the onset of symptoms, while in patients presenting with minor stroke, treatment with dual antiplatelet therapy (aspirin and clopidogrel) during three weeks may be beneficial for secondary stroke prevention [1]. Significant carotid artery stenosis is most effectively treated with endarterectomy or stenting, and dual antiplatelet therapy is recommended if they are contraindicated [1]. After the results of SOCRATES study, ticagrelor was not recommended in the treatment of patients with AIS. This study compared the efficacy and safety of ticagrelor versus aspirin over a period of 90 days in the treatment of patients with minor AIS or TIA [3]. The results showed that 7.5% of patients who were given aspirin and 6.8% of patients who got ticagrelor had some of primary end point incidents (stroke, myocardial infarction, or death); the secondary end point, ischemic stroke, was found in 6.6% of patients in aspirin group and 5.9% of patients in ticagrelor group [3]. In addition, authors of SOCRATES trial performed a subgroup analysis classifying the patients into non-atherosclerotic and atherosclerotic group in which approximately the same number of patients were treated with aspirin (n=1539) or ticagrelor (n = 1542). The primary end point (time to occurrence of stroke, myocardial infarction, or death within 90 days) occurred in 6.7% of patients in the ticagrelor group, compared with 9.6% in the aspirin group ($p = 0.003$). The authors concluded that ticagrelor was superior to aspirin in preventing stroke, myocardial infarction, or death during the first three months in patients with AIS or TIA associated with ipsilateral atherosclerotic stenosis [4]. A meta-analysis of 13 randomized controlled trials compared the efficacy and safety outcomes, all-cause mortality, and major bleeding events among patients with cerebral or cardiovascular risk factors treated with ticagrelor vs. other antiplatelet agents or placebo. The authors concluded that ticagrelor reduced the risk of incidental ischemic stroke, combined ischemic and hemorrhagic stroke and composite stroke/miocardial infarction/cerebrovascular cisease when compared with other antithrombotic therapies or placebo in patients with cardiovascular and cerebrovascular risk factors [5]. The official guideline recommendations regarding dual antiplatelet therapy relies on the results of CHANCE and POINT studies, which showed lower risk from repeated cerebrovascular events and death in patients treated with clopidogrel and aspirin compared to aspirin alone [1, 6, 7]. The results of recent THALES study, which explored the efficacy of ticagrelor and aspirin versus aspirin in the group of patients with mild to moderate non-cardioembolic stroke and TIA, pointed out that while the severe bleeding was more frequent with ticagrelor, the overall risk of the composite stroke or death within 30 days was lower with ticagrelor-aspirin combination than aspirin alone, but the incidence of disability did not differ significantly between the two groups [8]. Despite the results of this study, ticagrelor might prove its place in the therapy of AIS especially considering the percentage of aspirin and/or clopidogrel resistance in patients with stroke or TIA. In situation of repeated, transient neurological deficit, regardless of antiplatelet therapy, testing the platelet sensitivity to aspirin and/or clopidogrel should be considered [8] since the incidence of antiplatelet resistance in patients with stroke or TIA varies greatly and ranges from 3% to 85% for aspirin and 28% to 44% for clopidogrel [9, 10].

Conclusion

Our case showed that testing of platelet sensitivity is reasonable if patients with transient ischemic attack or minor acute ischemic stroke are neurologically unstable despite optimal treatment (aspirin, clopidogrel and statins), and when carotid revascularization is contraindicated [1]. In such situations ticagrelor may be a reasonable alternative to dual antiplatelet therapy.

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USE OF BETA BLOCKERS IN PATIENTS WITH ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

PRIMENA BETA BLOKATORA KOD PACIJENATA SA ASTMOM I HRONIČNOM OPSTRUKTIVNOM BOLESTI PLUĆA

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Summary

Introduction. Beta blockers play an essential role in the treatment of cardiovascular diseases, but also various other endocrinological, gastroenterological, ophthalmological and neurological disorders. The most important effects of beta blockers are a reduction in myocardial oxygen consumption and inhibition of renin secretion. Beta blockers are divided into three generations according to their selectivity – non-selective, cardioselective and vasodilating beta blockers. **Beta blockers and obstructive pulmonary diseases.** Patients with obstructive pulmonary diseases are significantly more likely to develop cardiovascular diseases compared to general population, largely due to common risk factors such as smoking, systemic inflammation, age, and genetic predisposition. The use of non-selective beta blockers carries a great risk for patients with obstructive pulmonary diseases, while cardioselective beta blockers can be used more extensively. Reversible airway obstruction is predominantly present in asthma, so that the adverse effects of beta blockers on the airways are significantly more pronounced in asthma compared to chronic obstructive pulmonary disease. **Conclusion.** In both asthma and chronic obstructive pulmonary disease, the use of highly cardioselective beta blockers such as bisoprolol and nebivolol is preferred. The use of beta blockers in patients with asthma requires great caution due to the possibility of bronchial obstruction, while in patients with chronic obstructive pulmonary disease they are somewhat safer. Patients must be closely monitored by a physician, with special attention focused on clinical signs of airway obstruction such as wheezing, shortness of breath, and prolonged expiration.

Key words: Pulmonary Disease, Chronic Obstructive; Asthma; Adrenergic beta-Antagonists; Risk Factors; Drug-Related Side Effects and Adverse Reactions; Myocardial Ischemia

Sažetak

Uvod. Beta blokatori zauzimaju važno mesto u lečenju kardiovaskularnih bolesti, ali i različitih drugih endokrinoloških, gastroenteroloških, oftalmoloških i neuroloških poremećaja. Najznačajniji efekti beta blokatora su smanjenje potrošnje kiseonika u miokardu i inhibicija lučenja renina. Beta blokatori su prema selektivnosti podeljeni u tri generacije – neselektivni, kardioselektivni i vazodilatatorni. **Beta blokatori i opstruktivne bolesti pluća.** Pacijenti sa opstruktivnim bolestima pluća znatno češće obolevaju od kardiovaskularnih bolesti u odnosu na opštu populaciju, za šta su u velikoj meri zaslužni zajednički faktori rizika kao što su pušenje, sistemska inflamacija, starost i genetska predispozicija. Za pacijente sa opstrukcijom disajnih puteva najveći rizik nosi primena neselektivnih beta blokatora, dok kardioselektivni beta blokatori mogu slobodnije da se koriste. Reverzibilnost opstrukcije disajnih puteva dominantno je prisutna u astmi, tako da su neželjena dejstva beta blokatora na disajne puteve u znatno većoj meri izražena kod astme u odnosu na hroničnu opstruktivnu bolest pluća. **Zaključak.** U astmi i hroničnim opstruktivnim bolestima pluća preferira se primena visoko kardioselektivnih beta blokatora kao što su bisoprolol i nebivolol. Za primenu beta blokatora kod pacijenata sa astmom potreban je veliki oprez zbog mogućnosti bronhoopstrukcije, dok se kod pacijenata sa hroničnim opstruktivnim bolestima pluća mogu nešto bezbednije primenjivati. Važno je da lekar temeljno prati pacijenta, uz posebnu pažnju usmerenu na znakove opstrukcije disajnih puteva kao što su zviždanje, kratak dah i produžen ekspirijum.

Ključne reči: hronična opstruktivna bolest pluća; astma; beta blokatori; faktori rizika; neželjeni efekti i neželjene reakcije; ishemijska bolest srca

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Abbreviations

COPD – chronic obstructive pulmonary disease
LABA – long-acting β2 agonists
FEV1 – forced expiratory volume in the first second
ESC – European Society of Cardiology
ESH – European Society of Hypertension

Introduction

Beta adrenergic receptors

Beta (β) adrenergic receptors are postsynaptic receptors that regulate the autonomic nervous system. Structurally, they are transmembrane proteins located on the cell surface. Their activation by catecholamines causes functional changes inside the cells, which vary depending on the tissue and organs **(Table 1)**. There are three subtypes of β receptors (β1, β2 and β3), although the latest studies propose introduction of the fourth subtype into the classification [1, 2].

The heart contains mainly β1 adrenergic receptors. Their stimulation has positive chronotropic and inotropic effects, resulting in cardiac output increase by rise in both factors in its equation (cardiac output = heart rate x stroke volume). Beside the heart, β1 receptors are also present in the juxtaglomerular cells of the kidneys, which cause renin release and activation of the renin-angiotensin-aldosterone system, resulting in sodium and water retention. This mechanism has a significant role in the pathophysiology of heart failure [1, 3].

The β2 adrenergic receptors are predominantly expressed in the smooth muscle cells of the airways. Their activation causes relaxation of these smooth muscles, leading to bronchodilation. This mechanism is used in the treatment of asthma and chronic obstructive pulmonary disease (COPD), where the use of selective β2 agonists stimulates these receptors and causes airway dilatation [4]. Apart from the airways, smooth muscles in other organs are also relaxed as a result of β2 receptors stimulation, so vasodilation is one of the effects as well. Activation of β2 receptors inside the liver induces gluconeogenesis and glycogenolysis, leading to hyperglycemia [5].

The β3 receptors are found in adipose tissue and mainly have metabolic effects. Stimulation of β3 receptors in the white adipose tissue causes lipolysis, whereas in the brown adipose tissue (mostly present in children) they cause thermogenesis. Due to their positive metabolic effects, β3 agonists are being intensively studied for their potential use in the treatment of metabolic disorders such as obesity and diabetes, but also in the prevention and treatment of cardiovascular diseases [6].

Pharmacology of beta receptors

Non-selective β stimulation is achieved by endogenous catecholamines (adrenaline, dopamine) and sympathomimetics (ephedrine). These medications, along with selective β1 agonists (dobutamine), have a crucial role in treatment of acute heart failure and shock. Their mechanism and clinical use is less important for the subject of this paper, so they will not be discussed further.

Drugs that cause selective β2 stimulation are essential for the management of patients with bronchoconstriction. Stimulation of β2 receptors in smooth muscles decreases the intracellular concentration of calcium ions, which disables their contraction and causes relaxation. This effect leads to bronchodilation in the airways and enables the treatment of diseases such as asthma and COPD [7].

Table 1. Localization and effects of β adrenergic receptors
Tabela 1. *Lokalizacija i dejstvo β adrenergičnih receptora*

Receptor/*Receptor*	Organ (tissue)/*Organ (tkivo)*	Effect/*Dejstvo*
β1	Heart/*Srce*	Heart rate/*Srčana frekvencija* ↑
		Contractility/*Kontraktilnost* ↑
	Kidney/*Bubreg*	Renin release/*Oslobađanje renina* ↑
β2	Smooth muscles/*Glatki mišići*	Tone/*Tonus* ↓
	Airways/*Disajni putevi*	Bronchodilation/*Bronhodilatacija*
	Blood vessels/*Krvni sudovi*	Vasodilation/*Vazodilatacija*
	Gastrointestinal tract/*Gastrointestinalni trakt*	Relaxation/*Relaksacija*
	Urinary bladder/*Mokraćna bešika*	Relaxation/*Relaksacija*
	Uterus (pregnancy)/*Materica (trudnoća)*	Gluconeogenesis/*Glikoneogeneza* ↑
	Liver/*Jetra*	Glycogenolysis/*Glikogenoliza* ↑
β3	Fat tissue/*Masno tkivo*	Lipolysis/*Lipoliza* ↑

Table 2. Classification of β2 agonists regarding their duration of action
Tabela 2. *Podela β2 agonista prema dužini delovanja*

Short-acting/*Kratkodelujući*	Long-acting/*Dugodelujući*	Ultra-long-acting/*Ultradugodelujući*
Salbutamol/*Salbutamol*	Salmeterol/*Salmeterol*	Indacaterol/*Indakaterol*
Terbutaline/*Terbutalin*	Formoterol/*Formoterol*	Olodaterol/*Olodaterol*
Levosalbutamol/*Levosalbutamol*		Vilanterol/*Vilanterol*
Pirbuterol/*Pirbuterol*		Formoterol/*Formoterol*
Fenoterol/*Fenoterol*		

Table 3. Classification of beta blockers
Tabela 3. *Klasifikacija beta blokatora*

Non-selective *Neselektivni*	No vasodilatory effect *Bez vazodilatatornog efekta*	Alprenolol/*Alprenolol* Bupranolol/*Bupranolol* Pindolol/*Pindolol* Propranolol/*Propranolol* Sotalol/*Sotalol*
	With vasodilatory effect *Sa vazodilatatornim efektom*	Carvedilol/*Karvedilol* Labetalol/*Labetalol*
Cardioselective *Kardioselektivni*	No vasodilatory effect *Bez vazodilatatornog efekta*	Acebutolol/*Acebutolol* Atenolol/*Atenolol* Bisoprolol/*Bisoprolol* Metoprolol/*Metoprolol*
	With vasodilatory effect *Sa vazodilatatornim efektom*	Celiprolol/*Celiprolol* Nebivolol/*Nebivolol*

According to the duration of their action, β2 agonists are divided into short-acting β2 agonists (SABA) and long-acting β2 agonists (LABA), with an additional subgroup of the novel ultra-long-acting β2 agonists (ultra-LABA) **(Table 2)** [8, 9].

Beta blockers

Beta blockers are a large group of medications that have been in use for more than 50 years. With their antagonistic effect on β adrenergic receptors, they provide sympathetic system blocking in various physiological processes, which makes them essential in the treatment of cardiovascular diseases, but also in various endocrinological, gastroenterological, ophthalmological and neurological disorders.

The most important effect of beta blockers is to reduce heart oxygen consumption. With their antagonistic impact on the heart β1 receptors, beta blockers reduce the heart rate and myocardial contractility, resulting in lower oxygen demand. This effect of beta blockers has made them essential in the treatment of all forms of ischemic heart diseases (stable and unstable angina pectoris, myocardial infarction). Moreover, blocking of β1 receptors in juxtaglomerular cells of the kidneys inhibits renin secretion and blocks the renin-angiotensin-aldosterone system, which makes them useful in the treatment of chronic heart failure and hypertension [10, 11].

The first generation of beta blockers has the same affinity for β1 and β2 receptors, which is why they are called non-selective beta blockers. Due to their non-selective characteristics and β2 receptors antagonism, their application is frequently associated with adverse effects including respiratory airway obstruction and spasm, as well as increase in peripheral vascular resistance [12]. The most significant representative of non-selective beta blockers is propranolol, whose current application is reserved mostly for "non-cardiac" conditions, such as portal hypertension, prevention and treatment of esophageal variceal bleeding, hyperthyroidism and thyrotoxicosis, pheochromocytoma, migraine, essential tremor and anxiety.

The second generation beta blockers exhibits only affinity for β1 receptors; they primarily reduce the cardiac output and inhibit renin secretion without effects on β2 receptors. Because of their predominant effects on the heart, this group is called cardioselective beta blockers, represented with atenolol, metoprolol and bisoprolol **(Table 3)**.

The third generation is the most recently developed group of beta blockers. The major difference comparing to the first two generations is an additional vasodilatory effect, which earned them the name vasodilatory beta blockers **(Table 3)**. Their mechanism of action is either through alpha-1 adrenergic receptor antagonists (labetalol, carvedilol) or nitric oxide release stimulation (nebivolol). By reducing peripheral vascular resistance, these medications additionally decrease myocardial oxygen demand, and are also more efficient in lowering the blood pressure compared to the first two generations of beta blockers [10, 12, 13].

Beta blockers and obstructive pulmonary diseases

Patients with obstructive pulmonary diseases suffer from cardiovascular diseases more often compared to general population, which is due to common risk factors such as smoking, systemic inflammation, age, and genetic predisposition. Hypoxia caused by respiratory pathway obstruction additionally increases the cardiovascular risk [14–16]. On the other hand, beta blockers are among the most commonly prescribed medications in cardiovascular pathology, because of their proven reduction in mortality in these patients. Beta blockers are recommended in a wide spectrum of cardiovascular diseases, including ischemic heart disease [17], arterial hypertension [18, 19], cardiac arrhythmias [20, 21] and chronic heart failure [22].

The β2 agonists are the most widely used in the treatment of obstructive pulmonary disease, due to their main effect - bronchodilation. However, there is emerging evidence that patients on this therapy have increased risk for developing adverse cardiovascular events [23], which is explained by the fact that these medications are only relatively selective, and that β1 receptors are also stimulated during long term application. This evidence is supported by the fact that beta

Table 4. Meta-analyses on the effects of beta blockers in asthma and COPD
Tabela 4*. Meta-analize o efektima beta blokatora na astmu i HOBP*

Study *Studija*	No. of trials included *Broj uključenih studija*	Investigated topic *Tema istraživanja*
Salpeter et al. 2002 [25]	29	Cardioselective beta blockers in asthma and COPD *Kardioselektivni beta blokatori u astmi i HOBP*
Salpeter et al. 2005 [26]	20	Cardioselective beta blockers in COPD *Kardioselektivni beta blokatori u HOBP*
Etminan et al. 2012 [27]	9	Impact of beta blockers on COPD mortality *Uticaj beta blokatora na mortalitet od HOBP*
Ni et al. 2012 [28]	5	Cardioselective beta blockers in COPD *Kardioselektivni beta blokatori u HOBP*
Du et al. 2014 [29]	15	Beta blockers in COPD/*Beta blokatori u HOBP*
Morales et al. 2014 [30]	32	Acute beta blocker exposure in asthma *Akutno izlaganje beta blokatoru u astmi*
Yang et al. 2020 [31]	49	Beta blockers in COPD/*Beta blokatori u HOBP*
Gulea et al. 2021 [32]	37	Beta blockers in COPD/*Beta blokatori u HOBP*
Huang et al. 2021 [33]	24	Beta blockers in asthma/*Beta blokatori u astmi*

Legend: COPD – chronic obstructive pulmonary disease/*Legenda: HOBP – hronična opstruktivna bolest pluća*

blockers neutralize negative effect of β2 agonists on the cardiovascular system, and have cardioprotective effect in patients with COPD [24]. The **Table 4** shows a list of recent large scale meta-analyses that investigated the benefits and adverse effects of beta blockers in patients with COPDs.

Prior studies showed that taking beta blockers increases respiratory pathway hyperreactivity due to blocking effects of β2 agonists, thus increasing the risk of bronchial obstruction and respiratory adverse effects. In theory, using cardioselective beta blockers should only block β1 receptors, while maintaining normal functioning of β2 receptors in the lungs. However, even these cardioselective beta blockers are only partially selective, meaning that, although to a lesser degree, they do antagonize β2 receptors as well [34]. Nonetheless, using non-selective beta blockers is associated with a greater risk for patients with COPDs, while cardioselective beta blockers can be used more extensively. After using β2 agonists, reversible airway obstruction is predominantly present in asthma, so that the adverse effects of beta blockers on the airways are significantly more pronounced in asthma compared to COPD.

Studies have shown that the use of propranolol, a non-selective beta blocker in patients with asthma leads to significant decrease in forced expiratory volume in the first second (FEV1) [30]. In these asthma patients, short term use of low doses, as well as chronic use of higher doses of non-selective beta blockers increases the risk of severe asthma exacerbations [35].

The situation is somewhat better with COPD, but not enough to completely justify the use of non-selective beta blockers. The COPD patients that use non-selective beta blockers are at proportionally higher risk for developing severe exacerbations depending on the therapy dose and duration. Using non-selective beta blockers in patients with COPD leads to moderate decrease in FEV1 and weaker response to therapy with β2 agonists [36].

On the other hand, the use of cardioselective beta blockers is a much safer option. It has been established that the use of selective beta blockers in asthma patients, although they do cause FEV1 decrease in some cases, does not contribute to clinical symptoms [30]. Conclusion derived from this is that the use of cardioselective beta blockers has minor adverse effect on asthma, but still carries some risk. Therefore, cardioselective beta blockers do present a better treatment option for asthma patients with cardiovascular comorbidity [14].

Large meta-analyses and clinical trials showed that the use of selective β1 blockers has no significant adverse effect on FEV1, β2 agonist therapeutic response, occurrence of respiratory symptoms, and the overall condition in patients with COPD [4]. Moreover, cardioselective beta blockers can even have complementary effects with β2 agonists, because β1 blockers increase the sensitivity of β2 receptors to β2 agonists in COPD patients. There is evidence that the use of selective beta blockers in COPD patients lowers the mortality rate, number of hospitalizations and ambulatory visits, as well as number of COPD exacerbations [4, 37].

The current 2016 European Society of Cardiology (ESC) Guidelines for the diagnosis and treatment of acute and chronic heart failure [22] specify that application of beta blockers is not contraindicated in COPD patients, while asthma represents a relative contraindication **(Table 5)**. Therefore, strictly β1 selective blockers, like bisoprolol and nebivolol, are preferred and recommended in these patients.

It is believed that beta blockers are considered contraindicated in asthma as a result of some outdated studies from 1980s and 1990s, which were conducted with very high initial doses in patients with severe forms of asthma. Nevertheless, using lower doses of

Table 5. Recommendations of relevant international guidelines for the use of beta blockers in asthma and COPD
Tabela 5. *Preporuke relevantnih internacionalnih vodiča za primenu beta blokatora kod astme i HOBP*

Guideline/*Vodič*	Recommendation/*Preporuka*
2020 ESC Guidelines for the diagnosis and management of atrial fibrillation [19] *2020 ESC Vodič za dijagnozu i zbrinjavanje atrijalne fibrilacije*	For heart rate control in atrial fibrillation in case of **asthma** use **selective β1 blockers.** *Za kontrolu srčane frekvencije u atrijalnoj fibrilaciji u slučaju postojanja **astme** koristiti **selektivne β1 blokatore**.*
2018 ESC/ESH Guidelines for the management of arterial hypertension [18] *2018 ESC/ESH Vodič za zbrinjavanje arterijske hipertenzije*	Calcium channel blockers, ACE inhibitors or angiotensin receptor blockers are recommended as the initial drugs of choice for the management of arterial hypertension in patients with **COPD**. If the response is poor, **selective β1 blockers** can be considered. *Blokator kalcijumskih kanala, ACE inhibitor ili blokator receptora angiotenzina preporučuje se kao inicijalni lek izbora za lečenje arterijske hipertenzije kod pacijenata sa **HOBP**. U slučaju slabog odgovora mogu se razmotriti **selektivni β1 blokatori.***
2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure [21]/*2016 ESC Vodič za dijagnozu i lečenje akutne i hronične srčane slabosti*	**Beta blockers** are only relatively contraindicated in **asthma**, but not in **COPD**, although the use of **selective β1 blocker** is preffered. ***Beta blokatori** su samo relativno kontraindikovani u **astmi**, ali ne i u **HOBP**, iako se preferira primena **selektivnog β1 blokatora**.*
2020 GINA Global strategy for asthma management and prevention [33] *2020 GINA globalna strategija za zbrinjavanje i prevenciju astme*	For people with **asthma**, a decision to prescribe **beta blockers** should be made on a case-by-case basis, and treatment should only be initiated under close medical supervision by a specialist. *Odluku o prepisivanju **beta blokatora** kod pacijenata sa **astmom** treba donositi individualno, od slučaja do slučaja, i lečenje treba započeti pod pažljivim medicinskim nadzorom specijaliste.* **Asthma** should not be regarded as an absolute contraindication to use **cardioselective beta blockers** when they are indicated for acute coronary events, but the relative risks and benefits should be considered. ***Astmu** ne treba smatrati apsolutnom kontraindikacijom za primenu **kardioselektivnih beta blokatora** kada su indikovani zbog akutnih koronarnih događaja, ali treba razmotriti relativne rizike i benefite.*
2020 GOLD Global strategy for diagnosis, management, and prevention of chronic obstructive pulmonary disease [34] *2020 GOLD Globalna strategija za dijagnozu, zbrinjavanje i prevenciju hronične opstruktivne bolesti pluća*	There is no evidence that **beta blockers** should be used in patients with **COPD** who do not have a cardiovascular indication for their use. *Nema dokaza da treba koristiti **beta blokatore** kod pacijenata sa **HOBP** koji nemaju kardiovaskularnu indikaciju za njegovu primenu.* There is no evidence that in patients with **COPD** and increased cardiovascular risk **beta blockers** reduce the benefits of treatment with LABA. *Nema dokaza da kod pacijenata sa **HOBP** i povišenim kardiovaskularnim rizikom primena **beta blokatora** smanjuje efikasnost terapija LABA.*
2018 ETA Guideline for the management of Graves' hyperthyroidism [35] *2018 ETA Vodič za zbrinjavanje Grejvsovog hipertiroidizma*	**Non-selective beta blockers** are recommended in all suitable patients with Graves' hyperthyroidism to control symptoms such as palpitations and tremor. **Cardioselective beta blockers** represent an alternative, especially in patients with **asthma**. ***Neselektivni beta blokatori** se preporučuju kod svih pacijenata sa Grejvsovim hipertiroidizmom za kontrolu simptoma kao što su palpitacije i tremor. **Kardioselektivni beta blokatori** predstavljaju alternativu, naročito kod pacijenata sa **astmom**.*

Legend: COPD - chronic obstructive pulmonary disease; LABA - long-acting β2 agonists
Legenda: HOBP – hronična opstruktivna bolest pluća; LABA – β2 agonisti sa dugim dejstvom

highly selective beta blockers is acceptable in clinical practice, especially in patients with mild forms of asthma but with careful monitoring of clinical signs of airway obstruction (wheezing, shortness of breath, prolonged expiration).

Arterial hypertension is by far the most common comorbidity in patients with COPD [38]. The 2018 ESC/European Society of Hypertension (ESH) Guidelines for the management of arterial hypertension [18] recommend calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers as the initial antihypertensive therapy in patients with COPD, and only in case of a poor therapeutic response, addition of selective β1 blockers to the therapy is considered **(Table 5)**. There are no particular recommendations for the antihypertensive therapy in asthma patients.

Ischemic heart disease is one of the most common and particularly important indication for beta blockers, but neither of three latest ESC guidelines covering this topic (2017 ESC Guidelines for the management of acute myocardial infarction in patients pre-

senting with ST-segment elevation [39], 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation [40] and 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes [17]), despite multiple recommendations for the use of beta blockers, gives specific instructions for their use in patients with asthma and COPD. In the older, now outdated 2013 ESC Guidelines, on the management of stable coronary artery disease [41], it was pointed out that beta blockers were contraindicated in asthma, while cardioselective beta blockers could be used with caution in COPD if the patient was fully treated by inhalatory corticosteroid and LABA. However, in 2019, these guidelines were replaced by the aforementioned ESC Guidelines for chronic coronary syndromes, where the use of beta blockers is not considered in asthma and COPD.

Conclusion

Asthma and chronic obstructive pulmonary disease are often associated with diverse cardiovascular comorbidities, for which beta blockers represent a standard care. Due to their adverse effects on respiratory airway obstruction, the use of beta blockers is limited in patients with asthma and chronic obstructive pulmonary disease.

In both asthma and chronic obstructive pulmonary disease, highly cardioselective beta blockers, such as bisoprolol and nebivolol, are preferred. The use of beta blockers in asthma patients requires more caution because of possible bronchial obstruction, while in patients with chronic obstructive pulmonary disease their use is somewhat safer. Patients must be thoroughly monitored for clinical signs of bronchial obstruction, such as wheezing, shortness of breath and prolonged expiration.

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IN MEMORIAM
IN MEMORIAM

DR PETAR ŠVARC
(1890–1981)

Dr Petar Švarc je rođen u Šandorfalvi, u Mađarskoj 1890. godine a umro je u Jevrejskom staračkom domu u Zagrebu 1981. godine. Otac mu je bio vlasnik velike ćurčijske radnje u Budimpešti. U Šandorfalvi su imali 300 lanaca zemlje i parni mlin.

Posle završene gimnazije u Nađvaradu, upisao je studije medicine u Budimpešti gde je i diplomirao 1917. godine. Mobilisan je u mađarsku Crvenu gardu, a posle dolaska nove vlasti seli se u Zagreb gde je radio na proizvodnji vakcine protiv velikih boginja. Dr Andrija Štampar i tadašnja Svetska zdravstvena organizacija uputili su dr Švarca, kao preventivca međunarodnog značaja, u Kinu da tamo pomogne organizovanje preventivne službe. Godine 1920. šalju ga kao specijalistu u Novi Sad.

Doktorat medicinskih nauka odbranio je u Berlinu. Pre toga je objavio pedesetak naučnih radova iz bakteriologije. Od 1934. do 1958. godine imao je privatnu laboratoriju zajedno sa dr Milošem Aranickim. Držao je niz stručnih predavanja u Budimpešti, Beču, Cirihu, Minhenu, Berlinu i Rimu.

Za vreme Drugog svetskog rata odlazi preko Turske u Palestinu gde ulazi u sastav engleske vojske. Bio je kapetan-vojni lekar, a supruga Kornelija radila je kao medicinska sestra. U Jugoslaviju se vraća 1944. godine i stupa u JNA.

Bio je upravnik Stanice za transfuziju krvi, a kasnije Bakteriološke laboratorije u Novom Sadu. Demobilisan je u činu majora. Istovremeno ponovo vodi svoju privatnu laboratoriju. Zahvaljujući poznavanju osam jezika predavanja je držao ne samo u Evropi već i u SAD.

Kao vrstan sportista bio je začetnik sportskog mačevanja u gradu. Kao član državne reprezentacije učestvovao je na olimpijadi u Amsterdamu 1924. godine. Kao predsednik sportskog kluba „Juda Makabi“ potpisao je sporazum sa ovdašnjim sportskim društvom „Vojvodina“ o zajedničkoj izgradnji stadiona „Karađorđe“.

Bio je predsednik Jevrejske opštine od 1952. do 1961. godine.

Osnovao je posle Prvog svetskog rata biohemijsku i bakteriološku laboratoriju, jedinu tako velikog obima u Vojvodini. Kvantitativno je određivano tridesetak biohemijskih i bakterioloških analiza. Takvu laboratoriju u Vojvodini nisu imale ni bolnice, a dijapazon analiza postepeno je proširivao. Njegovo poboljšanje Majnikeove metode za utvrđivanje luesa prihvaćeno je daleko šire od Novog Sada. Kada je ukinuta privatna praksa, preneo je svoju laboratoriju u Glavnu pokrajinsku bolnicu u Novom Sadu.

Savladan bolešću prestao je da radi i sa suprugom otišao u pomenuti staračk dom.

Bio je faktički osnivač medicinske, biohemijske i bakteriološke službe u Novom Sadu i pomogao stvaranje takve službe u celoj Vojvodini. Danas u Novom Sadu, pa ni u celoj Vojvodini ne postoji ustanova, ulica, ili neka znamenitost koja nosi njegovo ime.

Josip Šosberger, dipl. ekonomista

(Pavle Šosberger, otac pisca ovog teksta, neposredno pre nego što je preminuo, predao je sav materijal koji je pripremio o znamenitim Jevrejima Novog Sada Arhivu Vojvodine. Njegov sin, Josip uzeo je podatke iz tog materijala.)

Doc. dr OLJA NIĆIFOROVIĆ ŠURKOVIĆ (1965–2021)

S tugom se opraštamo od naše drage načelnice Centra za promociju zdravlja i člana Upravnog odbora Instituta za javno zdravlje Vojvodine, doc. dr Olje Nićiforović Šurković, specijaliste socijalne medicine, koja je bila prvi načelnik ovog centra, osnovanog 2007. godine.

Olja Nićiforović Šurković je rođena 1965. godine, u Novom Sadu, gde je završila Medicinski fakultet i specijalizirala, magistrirala i doktorirala iz oblasti socijalne medicine. Od 1993. godine zaposlena je u Institutu za javno zdravlje Vojvodine, gde se od početka usmerava ka oblasti promocije zdravlja i zdravstvenom vaspitanju. Svoju akademsku karijeru ostvaruje i na Katedri za socijalnu medicinu i zdravstvenu statistiku sa informatikom Medicinskog fakulteta Univerziteta u Novom Sadu.

Doc. dr Olja Nićiforović Šurković ostavila je neizbrisiv trag u različitim, domaćim i međunarodnim, primenjenim i istraživačkim projektima iz oblasti socijalne medicine, promocije zdravlja i zdravstvenog vaspitanja u zemlji i inostranstvu. Autor je i koautor više od 100 stručnih i naučnih radova, udžbenika, priručnika, voljeni mentor studenata, vrsni predavač, jedna od najproduktivnijih autorki programa kontinuirane medicinske edukacije, omiljena saradnica i rukovodilac.

U svom društveno-angažovanom radu dala je nemerljiv doprinos principima i vrednostima Crvenog krsta u Novom Sadu i Vojvodini, gde je nakon dugogodišnjeg volontiranja izabrana za potpredsednicu Crvenog krsta Novog Sada i člana Upravnog odbora Crvenog krsta Vojvodine.

Pamtićemo je po njenom neiscrpnom optimizmu, poletu i ljubavi prema poslu, koji će nam biti inspiracija u budućem radu.

Prof. dr Vesna Mijatović Jovanović

UPUTSTVO ZA AUTORE

Časopis ***Medicinski pregled*** objavljuje radove koji prethodno nisu objavljeni niti poslati u drugi časopis. U Časopisu mogu biti objavljeni radovi iz različitih oblasti biomedicine, koji su namenjeni lekarima različitih specijalnosti.

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Primaju se samo radovi koji su napisani na engleskom jeziku, uz sažetak rada i naslov rada koji treba da budu napisani na engleskom i srpskom jeziku.

Radove koji su pristigli u časopis *Medicinski pregled* pregleda jedan ili više članova Uređivačkog odbora Časopisa. Oni radovi koji su napisani prema pravilima Časopisa šalju se na anonimnu recenziju kod najmanje dva recenzenta, stručnjaka iz odgovarajuće oblasti biomedicine. Načinjene recenzije radova pregleda glavni urednik ili članovi Uređivačkog odbora i one nisu garancija da će rad biti prihvaćen za štampu. Materijal koji je pristigao u časopis ostaje poverljiv dok se rad nalazi na recenziji, a identitet autora i recenzenata su zaštićeni, osim u slučaju ako oni odluče drugačije.

U časopisu *Medicinski pregled* objavljuju se: uvodnici, originalni članci, prethodna ili kratka saopštenja, pregledni članci, stručni članci, prikazi slučajeva, članci iz istorije medicine i drugi članci.

1. Uvodnici – do 5 strana. Sadrže mišljenja ili diskusiju o posebno značajnoj temi za Časopis, kao i o podacima koji su štampani u ovom ili nekom drugom časopisu. Obično ih piše jedan autor po pozivu.

2. Originalni članci – do 12 strana. Predstavljaju rezultate istraživanja autora rada i njihovo tumačenje. Istraživanje treba da bude obrađeno i izloženo na način da se može ponoviti, a analiza rezultata i zaključci jasni da bi se mogli proveriti.

3. Pregledni članci – do 10 strana. Predstavljaju sistematsko, sveobuhvatno i kritičko izlaganje problema na osnovu analiziranih i diskutovanih podataka iz literature, a koji oslikavaju postojeću situaciju u određenom području istraživanja. Literatura koja se koristi u radu mora da sadrži najmanje 5 radova autora članka iz uže naučne oblasti koja je opisana u radu.

4. Prethodna ili kratka saopštenja – do 4 strane. Sadrže izuzetno važne naučne rezultate koje bi trebalo objaviti u što kraćem vremenu. Ne moraju da sadrže detaljan opis metodologije rada i rezultata, ali moraju da imaju sva poglavlja kao originalni članci u sažetoj formi.

5. Stručni članci – do 10 strana. Odnose se na proveru ili prikaz prethodnog istraživanja i predstavljaju koristan izvor za širenje znanja i prilagođavanja originalnog istraživanja potrebama postojeće nauke i prakse.

6. Prikazi slučajeva – do 6 strana. Opisuju retke slučajeve iz prakse. Slični su stručnim člancima. U ovim radovima prikazuju se neuobičajeni oblici i tokovi oboljenja, neočekivane reakcije na primenjenu terapiju, primene novih dijagnostičkih procedura ili retke i nove bolesti.

7. Članci iz istorije medicine – do 10 strana. Ovi članci opisuju događaje iz prošlosti sa ciljem da omoguće očuvanje medicinske i zdravstvene kulture. Imaju karakter stručnih članaka.

8. Ostali članci – U časopisu Medicinski pregled objavljuju se feljtoni, prikazi knjiga, izvodi iz strane literature, izveštaji sa kongresa i stručnih sastanaka, saopštenja o radu pojedinih zdravstvenih organizacija, podružnica i sekcija, saopštenja Uredništva, pisma Uredništvu, novosti u medicini, pitanja i odgovori, stručne i staleške vesti i članci napisani u znak sećanja (*In memoriam).*

Priprema rukopisa

Kompletan rukopis, uključujući tekst rada, sve priloge i propratno pismo, treba poslati na elektronsku adresu koja je prethodno navedena.

Propratno pismo:

– mora da sadrži izjavu svih autora da se radi o originalnom radu koji prethodno nije objavljen niti prihvaćen za štampu u drugim časopisima;

– autori svojim potpisom preuzimaju odgovornost da rad ispunjava sve postavljene uslove i da ne postoji sukob interesa i

– autor mora navesti kategoriju članka (originalni rad, pregleni rad, prethodno saopštenje, stručni rad, prikaz slučaja, rad iz istorije medicine, itd.).

Rukopis

Opšta uputstva

Tekst rada treba da bude napisan u programu *Microsoft Word* za *Windows*, na A4 formatu stranice (sve četiri margine 2,5 cm), proreda 1,5 (isto važi i za tabele), fontom *Times New Roman*, veličinom slova 12 *pt*. Neophodno je koristiti međunarodni sistem mernih jedinica (*SI*), uz izuzetak temperature (° *C*) i krvnog pritiska (*mmHg*).

Rukopis treba da sadrži sledeće elemente:

1. Naslovna strana

Naslovna strana treba da sadrži: kratak i sažet naslov rada, bez skraćenica, skraćeni naslov rada (do 40 karaktera), imena i prezimena autora (ne više od 6) i afilijacije svih autora. Na dnu strane treba da piše ime, prezime i titula autora zaduženog za korespondenciju, njena/njegova adresa, elektronska adresa, broj telefona i faksa.

2. Sažetak

Sažetak ne može da sadrži više od 250 reči niti skraćenice. Treba da bude strukturisan, kratak i sažet, sa jasnim pregledom problema istraživanja, ciljevima, metodama, značajnim rezultatima i zaključcima.

Sažetak originalnih i stručnih članaka treba da sadrži uvod (sa ciljevima istraživanja), materijale i metode, rezultate i zaključak.

Sažetak prikaza slučaja treba da sadrži uvod, prikaz slučaja i zaključak.

Sažetak preglednih članaka treba da sadrži Uvod, podnaslove koji odgovaraju istima u tekstu i Zaključak.

Navesti do 10 ključnih reči ispod sažetka. One su pomoć prilikom indeksiranja, ali autorove ključne reči mogu biti izmenjene u skladu sa odgovarajućim deskriptorima, odnosno terminima iz *Medical Subject Headings, MeSH.*

Sažetak treba da bude napisan na srpskom i engleskom jeziku. Sažetak na srpskom jeziku trebalo bi da predstavlja prevod sažetka na engleskom, što podrazumeva da sadrži jednake delove.

3. Tekst članka

Originalni rad treba da sadrži sledeća poglavlja: Uvod (sa jasno definisanim ciljevima istraživanja), Materijal i metode, Rezultati, Diskusija, Zaključak, spisak skraćenica (ukoliko su

korišćene u tekstu). Nije neophodno da se u posebnom poglavlju rada napiše zahvalnica onima koji su pomogli da se istraživanje uradi, kao i da se rad napiše.

Prikaz slučaja treba da sadrži sledeća poglavlja: Uvod (sa jasno definisanim ciljevima), Prikaz slučaja, Diskusija i Zaključak.

Uvod

U poglavlju Uvod potrebno je jasno definisati predmet istraživanja (prirodu i značaj istraživanja), navesti značajne navode literature i jasno definisati ciljeve istraživanja i hipoteze.

Materijal i metode

Materijal i metode rada treba da sadrže podatke o vrsti studije (prospektivna/retrospektivna, uslove za uključivanje i ograničenja studije, trajanje istraživanja, demografske podatke, period praćenja). Detaljno treba opisati statističke metode da bi čitaoci rada mogli da provere iznesene rezultate.

Rezultati

Rezultati predstavljaju detaljan prikaz podataka koji su dobijeni istraživanjem. Sve tabele, grafikoni, sheme i slike moraju biti citirani u tekstu rada i označeni brojevima po redosledu njihovog navođenja.

Diskusija

Diskusija treba da bude koncizna, jasna i da predstavlja tumačenje i poređenje rezultata studije sa relevantnim studijama koje su objavljene u domaćoj i međunarodnoj literaturi. U poglavlju Diskusija potrebno je naglasiti da li su postavljene hipoteze potvrđene ili nisu, kao i istaknuti značaj i nedostatke istraživanja.

Zaključak

Zaključci moraju proisteći isključivo iz rezultata istraživanja rada; treba izbegavati uopštene i nepotrebne zaključke. Zaključci koji su navedeni u tekstu rada moraju biti u saglasnosti sa zaključcima iz Sažetka.

4. Literatura

Potrebno je da se literatura numeriše arapskim brojevima redosledom kojim je u tekstu navedena u parentezama; izbegavati nepotrebno velik broj navoda literature. Časopise bi trebalo navoditi u skraćenom obliku koji se koristi u *Index Medicus* (*http://www.nlm.nih.gov/tsd/serials/lji.html*). Pri citiranju literature koristiti Vankuverski sistem. Potrebno je da se navedu svi autori rada, osim ukoliko je broj autora veći od šest. U tom slučaju napisati imena prvih šest autora praćeno sa *et al*.

Primeri pravilnog navođenja literature nalaze se u nastavku.

Radovi u časopisima

∗ Standardni rad

Ginsberg JS, Bates SM. Management of venous thromboembolism during pregnancy. J Thromb Haemost 2003;1:1435-42.

∗ Organizacija kao autor

Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. Hypertension 2002;40(5):679-86.

∗ Bez autora

21st century heart solution may have a sting in the tail. BMJ. 2002;325(7357):184.

∗ Volumen sa suplementom

Magni F, Rossoni G, Berti F. BN-52021 protects guinea pig from heart anaphylaxix. Pharmacol Res Commun 1988;20 Suppl 5:75-8.

∗ Sveska sa suplementom

Gardos G, Cole JO, Haskell D, Marby D, Pame SS, Moore P. The natural history of tardive dyskinesia. J Clin Psychopharmacol 1988;8(4 Suppl):31S-37S.

∗ Sažetak u časopisu

Fuhrman SA, Joiner KA. Binding of the third component of complement C3 by Toxoplasma gondi [abstract]. Clin Res 1987;35:475A.

Knjige i druge monografije

∗ Jedan ili više autora

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

∗ Urednik (urednici) kao autor (autori)

Danset J, Colombani J, eds. Histocompatibility testing 1972. Copenhagen: Munksgaard, 1973:12-8.

∗ Poglavlje u knjizi

Weinstein L, Shwartz MN. Pathologic properties of invading microorganisms. In: Soderman WA Jr, Soderman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: Saunders; 1974. p. 457-72.

∗ Zbornik radova sa kongresa

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer; 2002. p. 182-91.

∗ Disertacija

Borkowski MM. Infant sleep and feeding: a telephone survey of Hispanic Americans [dissertation]. Mount Pleasant (MI): Central Michigan University; 2002.

Elektronski materijal

∗ Članak iz časopisa u elektronskom formatu

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [Internet]. 2002 Jun [cited 2002 Aug 12];102(6):[about 1 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htmArticle

∗ Monografija u elektronskom formatu

CDI, clinical dermatology illustrated [monograph on CD-ROM]. Reevs JRT, Maibach H. CMEA Multimedia Group, producers. 2nd ed. Version 2.0. San Diego:CMEA;1995.

∗ Kompjuterska datoteka

Hemodynamics III: the ups and downs of hemodynamics [computer program]. Version 2.2. Orlando (FL): Computerized Educational Systems; 1993.

5. Prilozi (tabele, grafikoni, sheme i slike)

BROJ PRILOGA NE SME BITI VEĆI OD ŠEST!

Tabele, grafikoni, sheme i slike se postavljaju kao posebni dokumenti.

– Tabele i grafikone bi trebalo pripremiti u formatu koji je kompatibilan programu u kojem je napisan tekst rada. Slike bi trebalo poslati u jednom od sledećih oblika: *JPG, GIF, TIFF, EPS*.

– Svaki prilog mora biti obeležen arapskim brojem prema redosledu po kojem se navodi u tekstu rada.

– Naslovi, tekst u tabelama, grafikonima, shemama i legende slika bi trebalo da budu napisani na srpskom i engleskom jeziku.

– Nestandardne priloge označiti u fusnoti uz korišćenje sledećih simbola: *, †, ‡, §, | |, ¶, **, † †, ‡ ‡ .

– U legendi slika trebalo bi napisati korišćeno uveličanje okulara i objektiva mikroskopa. Svaka fotografija treba da ima vidljivu skalu.

– Ako su tabele, grafikoni, sheme ili slike već objavljene, navesti originalni izvor i priložiti pisano odobrenje autora za njihovo korišćenje.

– Svi prilozi će biti štampani kao crno-bele slike. Ukoliko autori žele da se prilozi štampaju u boji, obavezno treba da plate dodatne troškove.

6. Dodatne obaveze

AUTORI I SVI KOAUTORI RADA OBAVEZNO TREBA DA PLATE GODIŠNJU PRETPLATU ZA ČASOPIS *MEDICINSKI PREGLED*. U PROTIVNOM, RAD NEĆE BITI ŠTAMPAN U ČASOPISU.

INFORMATION FOR AUTHORS

Medical Review publishes papers (previously neither published in nor submitted to any other journals) from various fields of biomedicine intended for broad circles of doctors.

Since January 1th, 2013 the Medical Review has been using the service e-Ur: Electronic Journal Editing. All users of the Registration system, i.e. authors, reviewers, and editors have to be registered users with only one e-mail address. Registration should be made on the web address:

http://aseestant.ceon.rs/index.php/medpreg/user/register.

Manuscript submission should be made on the web address:

http://aseestant.ceon.rs/index.php/medpreg/

A SUPPLEMENTARY FILE, WITH THE STATEMENT THAT THE PAPER HAS NOT BEEN SUBMITTED OR ACCEPTED FOR PUBLICATION ELSEWHERE AND A CONSENT SIGNED BY ALL AUTHORS, HAVE TO BE ENCLOSED WITH THE MANUSCRIPT.

Authors may not send the same manuscript to more than one journal concurrently. If this occurs, the Editor may return the paper without reviewing it, reject the paper, contact the Editor of the other journal(s) in question and/or contact the author's employers.

Papers should be written in English language, with an abstract and title page in English, as well as in Serbian language.

All papers submitted to ***Medical Review*** are seen by one or more members of the Editorial Board. Suitable articles are sent to at least two experts to be reviewed, thier reports are returned to the assigned member of the Editorial Board and the Editor. Revision of an article gives no guarantee of acceptance and in some cases revised articles are rejected if the improvements are not sufficient or new issues have arisen. Material submitted to *the Journal* remains confidential while being reviewed and peer-reviewers' identities are protected unless they elect to lose anonymity.

Medical Review publishes the following types of articles: editorials, original studies, preliminary reports, review articles, professional articles, case reports, articles from history of medicine and other types of publications.

1. Editorials – up to 5 pages – convey opinions or discussions on a subject relevant for the Journal. Editorials are commonly written by one author by invitation.

2. Original studies – up to 12 pages – present the authors' own investigations and their interpretations. They should contain data which could be the basis to check the obtained results and reproduce the investigative procedure.

3. Review articles – up to 10 pages – provide a condensed, comprehensive and critical review of a problem on the basis of the published material being analyzed and discussed, reflecting the current situation in one area of research. Papers of this type will be accepted for publication provided that the authors confirm their expertise in the relevant area by citing at least 5 self-citations.

4. Preliminary reports – up to 4 pages – contain scientific results of significant importance requiring urgent publishing; however, it need not provide detailed description for repeating the obtained results. It presents new scientific data without a detailed explanation of methods and results. It contains all parts of an original study in an abridged form.

5. Professional articles – up to 10 pages – examine or reproduce previous investigation and represent a valuable source of knowledge and adaption of original investigations for the needs of current science and practice.

6. Case reports – up to 6 pages – deal with rare casuistry from practice important for doctors in direct charge of patients and are similar to professional articles. They emphasize unusual characteristics and course of a disease, unexpected reactions to a therapy, application of new diagnostic procedures and describe a rare or new disease.

7. History of medicine – up to 10 pages – deals with history with the aim of providing continuity of medical and health care culture. They have the character of professional articles.

8. Other types of publications – The journal also publishes feuilletons, book reviews, extracts from foreign literature, reports from congresses and professional meetings, communications on activities of certain medical institutions, branches and sections, announcements of the Editorial Board, letters to the Editorial Board, novelties in medicine, questions and answers, professional and vocational news and In memoriam.

Preparation of the manuscript

The complete manuscript, including the text, all supplementary material and covering letter, is to be sent to the web address above.

The covering letter:

– It must contain the proof given by the author that the paper represents an original work that it has neither been previously published in other journals nor is under consideration to be published in other journals.

– It must confirm that all the authors meet criteria set for the authorship of the paper, that they agree completely with the text and that there is no conflict of interest.

– It must state the type of the paper submitted (an original study, a review article, a preliminary report, a professional article, a case report, history of medicine).

The manuscript:

General instructions.

Use Microsoft Word for Windows to type the text. The text must be typed in font *Times New Roman*, page format A4, space 1.5 (for tables as well), margins set to 2.5 cm and font size 12pt. All measurements should be reported in the metric system of the International System of Units – SI. Temperature should be expressed in Celsius degrees (°C) and pressure in mmHg.

The manuscript should contain the following elements:

1. The title page.

The title page should contain a concise and clear title of the paper, without abbreviations, then a short title (up to 40 characters), full names and surnames of the authors (not more than 6) indexed by numbers corresponding to those given in the heading along with the full name and place of the institutions they work for. Contact information including the academic degree(s), full address, e-mail and number of phone or fax of the corresponding author (the author responsible for correspondence) are to be given at the bottom of this page.

2. Summary.

The summary should contain up to 250 words, without abbreviations, with the precise review of problems, objectives, methods, important results and conclusions. It should be structured into the paragraphs as follows:

– Original and professional papers should have the introduction (with the objective of the paper), materials and methods, results and conclusion

– Case reports should have the introduction, case report and conclusion

– Review papers should have the introduction, subtitles corresponding to those in the paper and conclusion.

The authors should provide up to 10 keywords below the summary. These keywords will assist indexers in cross-indexing the article and will be published with the summary, but the authors' keywords could be changed in accordance with the list of Medical Subject Headings, MeSH of the American National Medical Library.

The summary should be written in both languages, English as well as Serbian. The summary in Serbian language should be the translation of the summary in English; therefore, it has to contain the same paragraphs.

3. The text of the paper.

The text of original studies must contain the following: introduction (with the clearly defined objective of the study), materials and methods, results, discussion, conclusion, list of abbreviations (if used in the text) and not necessarily, the acknowledgment mentioning those who have helped in the investigation and preparation of the paper.

The text of a case report should contain the following: introduction (with clearly defined objective of the study), case report, discussion and conclusion.

Introduction contains clearly defined problem dealt with in the study (its nature and importance), with the relevant references and clearly defined objective of the investigation and hypothesis.

Materials and methods should contain data on design of the study (prospective/retrospective, eligibility and exclusion criteria, duration, demographic data, follow-up period). Statistical methods applied should be clear and described in details.

Results give a detailed review of data obtained during the study. All tables, graphs, schemes and figures must be cited in the text and numbered consecutively in the order of their first citation in the text.

Discussion should be concise and clear, interpreting the basic findings of the study in comparison with the results of relevant studies published in international and national literature. It should be stated whether the hypothesis has been confirmed or denied. Merits and demerits of the study should be mentioned.

Conclusion must deny or confirm the attitude towards the 0based solely on the author's own results, corroborating them. Avoid generalized and unnecessary conclusions. Conclusions in the text must be in accordance with those given in the summary.

4. References are to be given in the text under Arabic numerals in parentheses consecutively in the order of their first citation. Avoid a large number of citations in the text. The title of journals should be abbreviated according to the style used in Index Medicus (http://www.nlm.nih.gov/tsd/serials/lji.html). Apply Vancouver Group's Criteria, which define the order of data and punctuation marks separating them. Examples of correct forms of references are given below. List all authors, but if the number exceeds six, give the names of six authors followed by 'et al'.

Articles in journals

∗ *A standard article*

Ginsberg JS, Bates SM. Management of venous thromboembolism during pregnancy. J Thromb Haemost 2003;1:1435-42.

∗ *An organization as the author*

Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. Hypertension 2002;40(5):679-86.

∗ *No author given*

21st century heart solution may have a sting in the tail. BMJ. 2002;325(7357):184.

∗ *A volume with supplement*

Magni F, Rossoni G, Berti F. BN-52021 protects guinea pig from heart anaphylaxix. Pharmacol Res Commun 1988;20 Suppl 5:75-8.

∗ *An issue with supplement*

Gardos G, Cole JO, Haskell D, Marby D, Pame SS, Moore P. The natural history of tardive dyskinesia. J Clin Psychopharmacol 1988;8(4 Suppl):31S-37S.

∗ *A summary in a journal*

Fuhrman SA, Joiner KA. Binding of the third component of complement C3 by Toxoplasma gondi [abstract]. Clin Res 1987;35:475A.

Books and other monographs

∗ *One or more authors*

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

∗ *Editor(s) as author(s)*

Danset J, Colombani J, eds. Histocompatibility testing 1972. Copenhagen: Munksgaard, 1973:12-8.

∗ *A chapter in a book*

Weinstein L, Shwartz MN. Pathologic properties of invading microorganisms. In: Soderman WA Jr, Soderman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: Saunders; 1974. p. 457-72.

∗ *A conference paper*

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer; 2002. p. 182-91.

∗ *A dissertation and theses*

Borkowski MM. Infant sleep and feeding: a telephone survey of Hispanic Americans [dissertation]. Mount Pleasant (MI): Central Michigan University; 2002.

Electronic material

∗ *A journal article in electronic format*

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [Internet]. 2002 Jun [cited 2002 Aug 12];102(6):[about 1 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htmArticle

∗ *Monographs in electronic format*

CDI, clinical dermatology illustrated [monograph on CD-ROM]. Reevs JRT, Maibach H. CMEA Multimedia Group, producers. 2nd ed. Version 2.0. San Diego:CMEA;1995.

∗ *A computer file*

Hemodynamics III: the ups and downs of hemodynamics [computer program]. Version 2.2. Orlando (FL): Computerized Educational Systems; 1993.

5. Attachments (tables, graphs, schemes and photographs).

THE MAXIMUM NUMBER OF ATTACHMENTS ALLOWED IS SIX!

– Tables, graphs, schemes and photographs are to be submitted as separate documents, on separate pages.

– Tables and graphs are to be prepared in the format compatible with Microsoft Word for Windows programme. Photographs are to be prepared in JPG, GIF, TIFF, EPS or similar format.

– Each attachment must be numbered by Arabic numerals consecutively in the order of their appearance in the text

– The title, text in tables, graphs, schemes and legends must be given in both Serbian and English languages.

– Explain all non-standard abbreviations in footnotes using the following symbols *, †, ‡, §, | |, ¶, **, † †, ‡ ‡ .

– State the type of color used and microscope magnification in the legends of photomicrographs. Photomicrographs should have internal scale markers.

– If a table, graph, scheme or figure has been previously published, acknowledge the original source and submit written permission from the copyright holder to reproduce it.

– All attachments will be printed in black and white. If the authors wish to have the attachments in color, they will have to pay additional cost.

6. Additional requirements

SHOULD THE AUTHOR AND ALL CO-AUTHORS FAIL TO PAY THE SUBSCRIPTION FOR MEDICAL REVIEW, THEIR PAPER WILL NOT BE PUBLISHED.