SEPTIČNO STANJE U DIFERENCIJALNOJ DIJAGNOZI NEJASNOG FEBRILNOG STANJA

ORIGINALNI RAD

ORIGINAL ARTICLE

SEPTIC STATE IN THE DIFFERENTIAL DIAGNOSIS OF FEVER OF UNKNOWN ORIGIN

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43.SAŽETAK

Uvod: U savremenom svetu nejasno febrilno stanje je sve češći entitet sa raznovrsnom etiologijom. Septično stanje značajno participira kao etiološki faktor nejasnog febrilnog stanja a često se previdi, tj. lečenje se započinje kasno.

Cilj rada: Utvrditi učestalost sepse, ustanoviti demografske karakteristike, kliničku prezentaciju oboljenja, utvrditi proporciju dokazanih izazivača i njihovu raspodelu po vrstama, predstaviti laboratorijske analize bolesnika sa dijagnozom sepse po prijemu i po otpustu iz bolnice.

Materijal i metode: Ispitivanjem su obuhvaćeni pacijenti lečeni na Klinici za infektivne i tropske bolesti Kliničkog centra Srbije, na Odeljenju kliničke farmakoterapije u periodu od 1.12.2014. do 31.12.2017. godine, a kod kojih je u toku ispitivanja etiologije nejasnog febrilnog stanja dokazana sepsa.

Rezultati: Među 420 ispitivanih pacijenata, kod 50 (11,9%) je dokazana sepsa. U istraživanje je bilo uključeno 29 (58%) žena i 21 (42%) muškarac, prosečne starosti 63,76 ± 13,6 (24-90) godina. Kod 40 (80%) pacijenata je iz hemokulture dokazan uzročnik oboljenja, dok kod 10 (20%) pacijenata nije. Povišena telesna temperatura se javila kod 49 (98%) ispitanika, kod 24 (47%) postojala je jeza i drhtavica, 13 (25,5%) pacijenata imalo je mučninu, 16 (31,4%) povraćanje. Glavobolja se javila kod 8 (16%) pacijenata, dok su dijareja, dizurične tegobe, kao i poremećaj svesti registrovani kod 11 (21,6%) obolelih. Upoređivanjem srednjih vrednosti biohemijskih analiza pacijenata dobijenih po prijemu i po otpustu iz bolnice, utvrđeno je da postoji statistički značajna razlika (p<0,01) koja ukazuje na smanjenje vrednosti laboratorijskih parametara kao što su sedimentacija eritrocita, C-reaktivni protein, ukupan broj leukocita i procenat segmentiranih leukocita.

Zaključak: U posmatranom uzorku sepsa se, kao etiološki faktor nejasnog febrilnog stanja, sreće relativno često (11,9%). I pored značajnog napretka i razvoja sofisticiranih dijagnostičkih postupaka, u diferencijalnoj dijagnozi nejasnog febrilnog stanja treba uvek razmišljati o potencijalnoj sistemskoj infekciji kao mogućem uzroku u sklopu koje septično stanje zauzima važno mesto, čak i kada nas inicijalna ispitivanja ne navode na takav zaključak.

Ključne reči: sepsa, SIRS, nejasno febrilno stanje, infektivne bolesti

SUMMARY

Introduction: In the modern world, fever of unknown origin is becoming an increasingly common entity with varied etiologies. Septic condition has a significant role as an etiological factor of fever of unknown origin, often being overlooked or treated late.

Objective: To determine the frequency of sepsis, to establish demographic characteristics, clinical presentation of the disease, to identify the proportion of proven pathogens and their distribution by type, and to present laboratory analyses of patients diagnosed with sepsis upon admission and discharge from the hospital.

Materials and Methods: The study included patients treated at the Clinic for Infectious and Tropical Diseases of the Clinical Center of Serbia, in the Department of Clinical Pharmacotherapy, from December 1, 2014, to December 31, 2017, with documented sepsis during the investigation of the etiology of FUO.

Results: Among 420 patients studied, sepsis was documented in 50 (11.9%). The study included 29 (58%) women and 21 (42%) men, with an average age of 63.76 ± 13.6 (24-90) years. The causative agent of the disease was detected in blood cultures in 40 (80%) patients, while not in 10 (20%). Elevated body temperature occurred in 49 (98%) patients, whilst 24 (47%) experienced chills and shivering, 13 (25.5%) nausea, and 16 (31.4%) vomiting. Headache occurred in 8 (16%) patients, while diarrhea, urinary symptoms, and altered consciousness were observed in 11 (21.6%) patients. By comparing the median values of biochemical analyses of patients obtained upon admission and discharge from the hospital, a statistically significant difference (p<0,01) was found, indicating a decrease in laboratory parameter values such as erythrocyte sedimentation rate, C-reactive protein, total leukocyte count, and percentage of segmented leukocytes.

Conclusion: In the observed sample, sepsis occurs relatively frequently (11.9%) as an etiological factor of FUO. In the differential diagnosis of fever of unknown origin, despite significant progress and development of sophisticated diagnostic procedures, one should always consider potential systemic infection as a possible cause, among which septic condition occupies an important place, even when initial examinations do not lead to such a conclusion.

Keywords: sepsis, SIRS , fever of unknown origin, infectious diseases

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UVOD

Febrilno stanje nejasnog porekla označava prisustvo telesne temperature >38,3°C registrovane u više mahova koja traje duže od 3 nedelje, a dijagnoza nije postavljena uprkos adekvatnom ispitivanju koje obuhvata osnovna biohemijska ispitivanja, radiološka snimanja pluća, ultrazvučni pregled abdomena, bris grla, urinokulturu, kao i ginekološki pregled kod žena, odnosno urološki kod muškaraca sprovedenom u toku tri posete lekaru, odnosno nakon tri dana boravka u bolnici [1-3].

Septično stanje označava sistemski inflamatorni odgovor (*SIRS – "systemic inflammatory response syndrome"*) dokazane ili verovatne mikrobne etiologije, bez obzira da li se mikroorganizmi raznose krvlju, što se najčešće dešava, ili ostaju u lokalnom žarištu. SIRS je imunsko-metabolička reakcija organizma na različite, pa i biološke agense koji ga napadaju, a kog karakterišu najmanje dva od sledećih kliničkih znakova:

- febrilnost (> 38°C) ili hipotermija (< 36°C)
- tahipneja (> 24 udaha/min)
- tahikardija (>90 otkucaja/min)
- leukocitoza (> 12x 10^9/l), leukopenija (<4x 10^9/l) ili više od 10% nezrelih formi leukocita

Kako se radi o disregulaciji imunskog odgovora na infektivni agens i kako se on često karakteriše poremećajem telesne temperature, od izuzetnog je značaja pravovremeno pomisliti na ovo stanje [4-6].

U savremenom svetu nejasno febrilno stanje je sve češći entitet sa raznolikom etiologijom. Sepsa značajno participira kao etiološki faktor nejasnog febrilnog stanja, a često se previdi tj. lečenje se započinje kasno. Cilj ovog rada je bio da se utvrdi učestalost sepse, da se predstave demografske karakteristike, klinička prezentacija oboljenja, proporcija dokazanih izazivača i njihova raspodela po vrstama, kao i da se predstave laboratorijske analize pacijenata sa dijagnozom sepse po prijemu i po otpustu iz bolnice.

MATERIJAL I METODE

Ispitivanjem su obuhvaćeni pacijenti lečeni na Klinici za infektivne i tropske bolesti Kliničkog centra Srbije, na Odeljenju kliničke farmakoterapije u periodu od 1.12.2014. do 31.12.2017. godine, a kod kojih je u toku ispitivanja etiologije nejasnog febrilnog stanja dokazana sepsa. U posmatranom periodu je ispitivano 420 pacijenata tokom kojeg je sepsa dokazana kod 50 ispitanika. U ispitivanje nisu uključene osobe mlađe od 18 godina, jer Odeljenje kliničke farmakoterapije u sklopu Klinike za infektivne i tropske bolesti Kliničkog centra Srbije ne leči pedijatrijsku populaciju. U dijagnostici su korišćene standardne biohemijske metode

INTRODUCTION

Fever of unknown origin denotes the presence of body temperature >38.3°C recorded on multiple occasions lasting longer than 3 weeks, with no diagnosis established despite adequate investigation including basic biochemical tests, chest radiographs, abdominal ultrasound examination, throat swab culture, urine culture, and gynecological examination in women, or urological examination in men, conducted during three visits to the doctor or after three days of hospital stay [1-3].

Septic condition signifies a systemic inflammatory response (SIRS - "systemic inflammatory response syndrome") of proven or probable microbial etiology, regardless of whether microorganisms are disseminated in the blood, which commonly occurs, or remain in a local focus. SIRS is the immune-metabolic reaction of the body to various, including biological, agents attacking it, characterized by at least two of the following clinical signs:

- fever (> 38°C) or hypothermia (< 36°C)
- tachypnea (> 24 breaths/min)
- tachycardia (> 90 beats/min)
- leukocytosis (> 12x10^9 /L), leukopenia (< 4x10^9 /L), or more than 10% immature forms of leukocytes

Given that it involves dysregulation of the immune response to infectious agents and is often characterized by disturbances in body temperature, timely consideration of this condition is of utmost importance [4-6].

In the modern world, fever of unknown origin is an increasingly common entity with diverse etiology. Sepsis significantly participates as an etiological factor of fever of unknown origin, often overlooked, i.e., treatment is initiated late. This study aimed to determine the frequency of sepsis, present demographic characteristics, clinical presentation of the disease, proportion of proven pathogens, and their distribution by types, and to present laboratory analyses of patients diagnosed with sepsis upon admission and discharge from the hospital.

MATERIALS AND METHODS

The study included patients treated at the Clinic for Infectious and Tropical Diseases of the Clinical Center of Serbia, in the Department of Clinical Pharmacotherapy, from December 1, 2014, to December 31, 2017, who were diagnosed with sepsis during the investigation of the etiology of fever of unknown origin. During the observation period, 420 patients were examined, among whom sepsis was confirmed in 50 individuals. Persons under 18 years old were not included in the study, as the Department of Clinical Pharmacotherapy within the

koje uključuju nespecifične faktore inflamacije (*CRP, SE*), kompletnu krvnu sliku (*Leu*, % granulocita, *Er, Tr, Hgb*), ispitivanje enzima od značaja (*AST, ALT*, *LDH*, *CPK*) i mikrobiološke metode koje podrazumevaju uzimanje uzoraka krvi i urina radi izolacije i kultivisanja potencijalnog infektivnog agensa, kao i izrade antibiograma prema kome bi se uvela tj. korigovala terapija.

Statističke metode

Za statističko analiziranje podataka korišćeni su programi SPSS-a (*Statistical Package for the Social Sciences*) i EZR (*Easy R*). U cilju ispitivanja statističke značajnosti razlike srednjih vrednosti dva nezavisna uzorka korišćeni su Studentov t-test i Wilcoxon-ov test. Kao kriterijum statističke značajnosti razlike primenjene su vrednosti $p < 0,01$.

REZULTATI

Rezultati ovog istraživanja pokazali su da je među 420 ispitivanih pacijenta u datom periodu kod 50 (11,9%) dokazana sepsa (Grafikon 1).

Među pacijentima koji su bili uključeni u istraživanje bilo je 29 (58%) žena i 21 (42%) muškarac (Grafikon 2). Prosečna starost pacijenata bila je 63,76 ± 13,6 (24–90) godina.

Kod 40 (80%) pacijenata je iz hemokulture dokazan uzročnik oboljenja, dok kod 10 (20%) pacijenata nije (Tabela 1).

Clinic for Infectious and Tropical Diseases of the Clinical Center of Serbia does not treat pediatric patients. Standard biochemical methods were used in the diagnosis, including non-specific inflammation factors (CRP, ESR), complete blood count (WBC, % granulocytes, RBC, platelets, Hgb), examination of significant enzymes (AST, ALT, LDH, CPK), and microbiological methods involving blood and urine sampling for isolation and cultivation of potentially infectious agents, as well as antibiotic susceptibility testing to guide or adjust therapy.

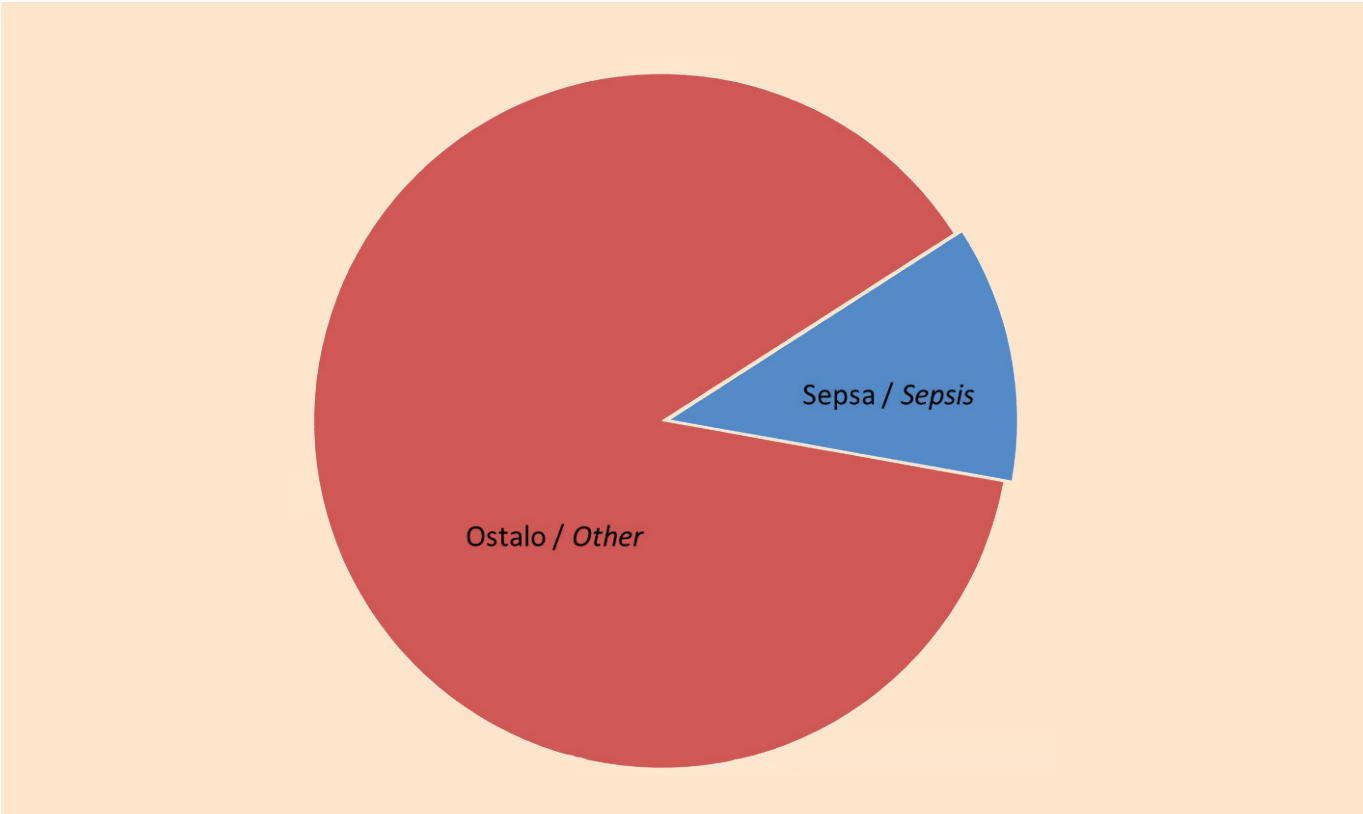
Statistical Methods

SPSS (Statistical Package for the Social Sciences) and EZR (Easy R) programs were used for statistical analysis of the data. Student's t-test and Wilcoxon's test were used to assess the statistical significance of the difference in mean values of two independent samples. A criterion of statistical significance was applied with $p < 0.01$.

RESULTS

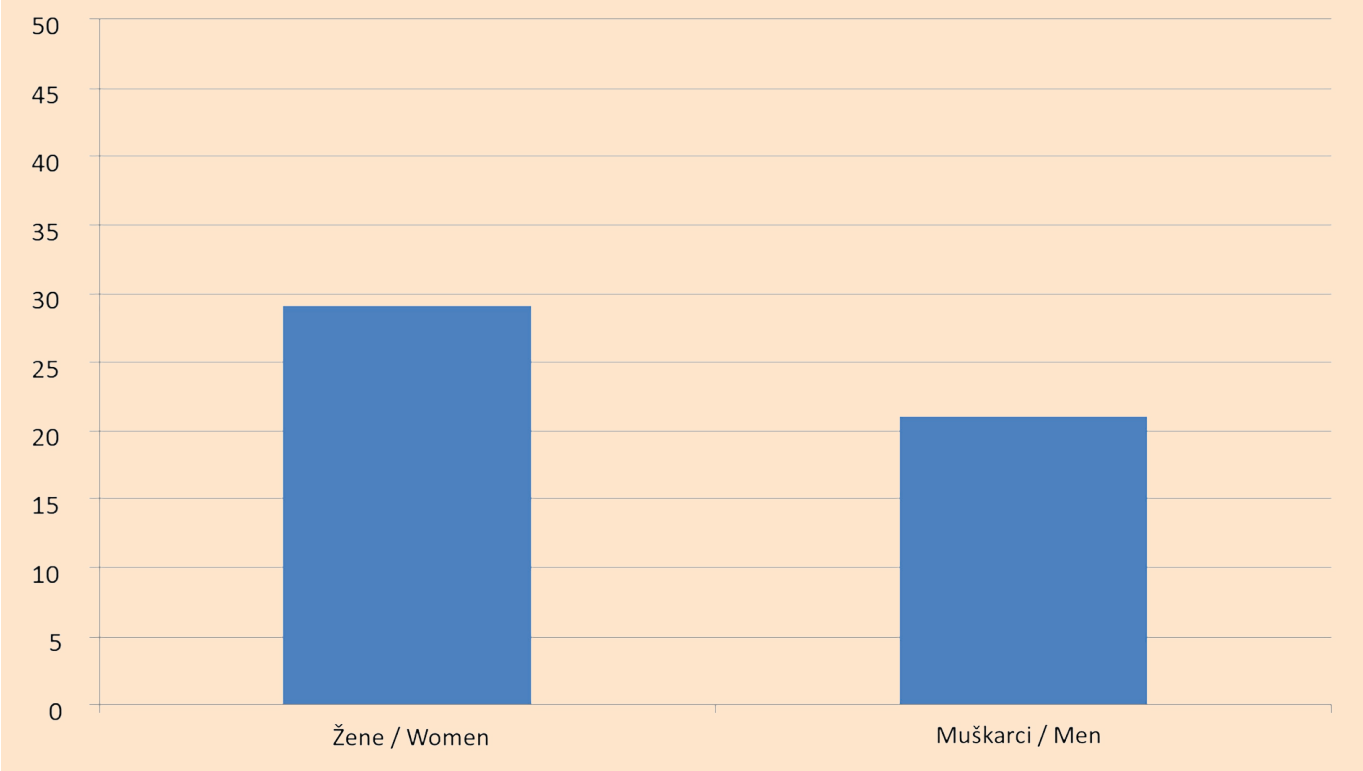
The results of this study showed that among the 420 examined patients during the given period, sepsis was confirmed in 50 (11.9%) cases (Graph 1).

Among the patients included in the study, there were 29 (58%) females and 21 (42%) males (Graph 2). The average age of the patients was 63.76 ± 13.6 (24-90) years.



Grafikon 1. Učestalost sepse u ispitivanoj grupi pacijenata

Figure 1. The frequency of sepsis within the examined group of patients



Grafikon 2. Demografski prikaz bolesnika sa dijagnozom sepse

Figure 2. Demographic display of patients diagnosed with sepsis

Kod pacijenata sa pozitivnom hemokulturom, najveći broj njih imao je izolovane bakterijske uzročnike među kojima dominiraju izazivači urosepse kao što su *Escherichia coli* koja se javila kod 17 (34%) i *Klebsiella* spp. kod 8 (16%) ispitanika. Svi ostali infektivni agensi prikazani su u sklopu priloga (Tabela 2).

Praćenjem osnovnih kliničkih manifestacija oboljenja i glavnih tegoba koje su pacijenti navodili po prijemu u bolnicu, rezultati prikazanog istraživanja pokazuju da se povišena telesna temperatura javila kod 49 (98,04%) pacijenata. Takođe, kod njih 24 (47%) postojala je jeza i drhtavica, 13 (25,5%) pacijenata imalo je mučninu kao jedan od simptoma bolesti, 16 (31,4%) je imalo povraćanje. Glavobolja se javila kod 8 (16%) pacijenata, dok su dijareja, dizurične tegobe, kao i poremećaj svesti registrovani kod 11 (21,6%) obolelih (Tabela 3).

Tabela 1. Proporcija dokazanih i nedokazanih mikrobioloških uzročnika septičnog stanja

Table 1. Proportion of proven and unproven microbiological pathogens of septic conditions

	Učestalost / *Frequency*	%
Dokazani / *Proven*	40	80
Nedokazani / *Unproven*	10	20
Ukupno / *Total*	50	100

In 40 (80%) patients, the causative agent of the disease was identified from blood culture, while in 10 (20%) patients it was not (Table 1).

Tabela 2. Prikaz uzročnika septičnog stanja prema učestalosti javljanja

Table 2. Display of pathogens of septic condition according to frequency of occurence

	Učestalost / *Frequency*	%
E. coli	17	34
K. pneumoniae	8	16
Staphylococcus aureus	3	6
Enterococcus spp.	3	6
Streptococcus gallolyticus	2	4
Bacteroides spp.	1	2
Streptococcus pneumoniae	1	2
Streptococcus viridans	1	2
Streptococcus dysgalactiae	1	2
Coagulase-negative staphylococcus	1	2
Candida parapsilosis	1	2
Listeria monocytogenes	1	2
Nepoznato / *Unknown*	10	20
Ukupno / *Total*	50	100

Tabela 3. Kliničke karakteristike bolesnika sa dijagnozom sepse

Table 3. Clinical characteristics of patients diagnosed with sepsis

	Ukupno / *Total*	%
Povišena temperatura / *Elevated temperature*	49	98.04
Jeza i drhtavica / *Chills and shivering*	24	47.06
Mučnina / *Nausea*	13	25.49
Povraćanje / *Vomiting*	16	31.37
Dijareja / *Diarrhea*	11	21.57
Dizurične tegobe / *Dysuric disorders*	11	21.57
Poremećaj svesti / *Altered consciousness*	11	21.57
Glavobolja / *Headache*	8	16

Upoređivanjem srednjih vrednosti rutinskih biohemijskih analiza pacijenata sa dijagnozom sepse dobijenih po prijemu i po otpustu iz bolnice, utvrđeno je da postoji statistički značajna razlika (p<0,01) koja ukazuje na smanjenje vrednosti sledećih laboratorijskih parametara: sedimentacija eritrocita (78,6 / 55,16), C–reaktivni protein (344,6 / 30,6), ukupan broj leukocita (13,77 / 7,56), procenat segmentiranih leukocita (82,6 / 67,2) (Tabela 4).

DISKUSIJA

Na osnovu dostupnih podataka američkog Centra za kontrolu i prevenciju bolesti (CDC – "Centers for Disease Control and Prevention") na teritoriji Sjedinjenih Američkih Država registruje se više od 1.5 miliona slučajeva septičnog stanja na godišnjem nivou, sa oko 250.000 smrtnih ishoda, a kod jednog od tri hospitalizovana pacijenta sa letalnim ishodom dokazana je sepsa. U odraslih pacijenata najčešća ishodišta infekcije koja dovode do razvoja septičnog stanja su: infekcije respiratornog sistema (35%), infekcije urinarnog sistema i bubrega (25%), infekcije digestivnog trakta (11%) i kožne infekcije (11%) [7-8].

Prema podacima dobijenim na osnovu velikih kohortnih studija koje su sprovedene u 5 razvijenih zemalja (Velika Britanija, Francuska, SAD, Australija i Novi Zeland) pokazano je da godišnja incidencija sepse značajno varira u rasponu od 51 (Velika Britanija) do 300 (SAD) obolelih na 100.000 stanovnika, a beleži se i rast incidencije (8-13%) u odnosu na prethodne dve decenije. Ovaj trend pripisuje se starenju stanovništva, produženju života bolesnika sa hroničnim bolestima i infekcijama (tumori, diabetes mellitus tip 2, AIDS), širokoj upotrebi antimikrobnih lekova, glukokortikoida, trajnih katetera, mehaničkih naprava i mehaničke ventilacije [9-13].

Tabela 4. Srednje vrednosti rutinskih biohemijskih analiza pacijenata sa dijagnozom sepse dobijenih po prijemu i po otpustu iz bolnice

Table 4. Median values of routined biochemical analyses of patients diagnosed with sepsis upon admission and discharge from the hospital

	Pre prijema / *Before admission*	Po otpustu / *After discharge*	p (< 0,01)
SE (mm/h)	78.66	55.16	<0.001**
CRP (mg/l)	344.578	30.581	<0.001**
ALT (IU/l)	48.35	29.11	0.002**
AST (IU/l)	41.35	23.97	0.001**
LDH (IU/l)	325.98	252.29	<0.001**
CPK (IU/l)	234.96	41.00	0.001**
HgB (x 10^{12}/l)	118.02	112.28	0.079*
Tr (x 10^{12}/l)	213.34	256.08	<0.001**
Le (x 10^{12}/l)	13.767	7.556	<0.001**
Segmentirani / *Segmented* %	82.65	67.16	<0.001*

*Studentov t-test / **Wilcoxon-ov test*

**Student's t-test / **Wilcoxon's test*

Among patients with positive blood cultures, the majority had isolated bacterial pathogens, with urosepsis-causing agents such as Escherichia coli occurring in 17 (34%) and Klebsiella spp. in 8 (16%) subjects. All other infectious agents are presented in the appendix (Table 2).

Monitoring the basic clinical manifestations of the disease and the main complaints reported by patients upon admission to the hospital, the results of the presented study show that elevated body temperature occurred in 49 (98.04%) patients. Additionally, 24 (47%) experienced chills and shivering, 13 (25.5%) had nausea as a symptom of the disease, and 16 (31.4%) experienced vomiting. Headache occurred in 8 (16%) patients, while diarrhea, urinary symptoms, and altered consciousness were reported in 11 (21.6%) patients (Table 3).

By comparing the median values of routine biochemical analyses of patients diagnosed with sepsis upon admission and upon discharge from the hospital, a statistically significant difference (p<0.01) was found, indicating a decrease in the values of the following laboratory parameters: erythrocyte sedimentation rate (78.6 / 55.16), C-reactive protein (344.6 / 30.6), total leukocyte count (13.77 / 7.56), percentage of segmented leukocytes (82.6 / 67.2) (Table 4).

DISCUSSION

Based on available data from the Centers for Disease Control and Prevention (CDC) in the United States, over 1.5 million cases of septic conditions are registered an-

Ukoliko posmatramo samo pojedinačne oblasti Evrope, kao značajnu izdvajamo veliku retrospektivnu analizu sprovedenu na tlu Katalonije, autonomne oblasti Španije, u kojoj se navodi incidencija sepse tj. septičnog stanja od 1,72% na godišnjem nivou. Od ukupnog broja obolelih, 56,1% činili su pripadnici muškog pola, dok je prosečna starost pacijenata sa dijagnozom sepse bila 71,2 ± 19,7 godina. U najčešća ishodišta infekcije koja su dovela do razvoja septičnog stanja navode se infekcije urinarnog trakta (37,2%) i infekcije respiratornog sistema (32,5%). Rezultati studije pokazuju da je iz hemokulture dokazan uzročnik kod 84,2% pacijenta, a kod 15,8% ispitanika nije. Kao najčešće izolovani infektivni agensi navode se *Escherichia coli* (8%), *Streptococcus* spp. (7%), koagulaza-negativni *Staphylococcus* spp. (6%) i *Staphylococcus aureus* (6%) [14,15].

Na Klinici za infektivne i tropske bolesti KCS-a, na Odeljenju kliničke farmakoterapije, među 420 ispitivanih pacijenata, u periodu od 1.12.2014. do 31.12.2017., kod 50 (11,9%) pacijenata se javila sepsa; od čega je njih 29 (58%) pripadalo ženskoj populaciji i 21 (42%) muškoj populaciji, a prosečna starost ispitanika bila je 63,76 ± 13,6 (24-90) godina. Rezultati studije takođe su pokazali da su kod pacijenata sa pozitivnom hemokulturom najčešće izolovani etiološki agensi bile bakterije i to: *Escherichia coli* koja se javila kod 17 (34%) i

Klebsiella spp. kod 8 (16%) ispitanika. Ostali izolati, kao što su na primer *Staphylococcus aureus* (6%), *Streptococcus gallolyticus* (6%) *i Streptococcus pneumoniae* (2%), govore u prilog bakterijskih mikroorganizama kao najčešćih uzročnika ovog stanja. Kod jednog pacijenta (2%) dokazana je gljivična etiologija *(Candida parapsilosis)*.

Upoređivanjem ovih rezultata sa rezultatima prethodnih studija, registruju se veća učestalost septičnog stanja i niža prosečna starost bolesnika. Značajnije odstupanje vezano za procenat pozitivnih hemokultura, kao i izolovanih uzročnika se ne zapaža.

Sepsa može biti odgovor na infekciju uzrokovanu bilo kojom vrstom mikroorganizama. Premda gram-negativne i gram-pozitivne bakterije čine najčešće infektivne agense koji su u osnovi *SIRS-a*, sepsa može biti uzrokovana gljivicama, mikobakterijama, protozoama [16].

Na sepsu se lako posumnja kod bolesnika sa lokalnom infekcijom koji naglo dobije povišenu telesnu temperaturu, groznicu, tahikardiju, tahipneju, poremećaj svesti i hipotenziju. Međutim, septički odgovor se može razvijati mnogo sporije i imati suptilnije manifestacije. U jednom proučavanju 36% bolesnika sa sepsom bilo je afebrilno, 44% je imalo uredno stanje svesti, 60% eupnoično, 10% je imalo broj srčanih otkucaja u okviru fizioloških granica. Odsustvo febrilnosti najčešće je u starijih osoba i bolesnika sa uremijom, ili kod alkoholičara [17-19].

nually, resulting in approximately 250,000 fatalities. Sepsis is proven in one out of three hospitalized patients with a fatal outcome. The most common sources of infection leading to the development of septic conditions in adults include respiratory infections (35%), urinary tract and kidney infections (25%), gastrointestinal infections (11%), and skin infections (11%) [7-8].

According to data obtained from large cohort studies conducted in five developed countries (the United Kingdom, France, the United States, Australia, and New Zealand), the annual incidence of sepsis significantly varies from 51 (the United Kingdom) to 300 (the United States) cases per 100,000 population, with an increasing incidence trend (8-13%) over the past two decades. This trend is attributed to population aging, prolonged lifespan of patients with chronic diseases and infections (such as tumors, type 2 diabetes mellitus, AIDS), widespread use of antimicrobial drugs, glucocorticoids, indwelling catheters, mechanical devices, and mechanical ventilation [9-13].

If we focus solely on individual regions of Europe, a significant retrospective analysis conducted in Catalonia, an autonomous region of Spain, reports an incidence of sepsis or septic conditions of 1.72% annually. Of the total number of cases, 56.1% were male, with an average age of 71.2 ± 19.7 years among patients diagnosed with sepsis. The most common sources of infection leading to the development of septic conditions include urinary tract infections (37.2%) and respiratory system infections (32.5%). The study results indicate that the causative agent was identified from blood culture in 84.2% of patients, while it was not in 15.8% of subjects. The most frequently isolated infectious agents include Escherichia coli (8%), Streptococcus spp. (7%), coagulase-negative Staphylococcus spp. (6%), and Staphylococcus aureus (6%) [14,15].

At the Clinic for Infectious and Tropical Diseases of the Clinical Center of Serbia, in the Department of Clinical Pharmacotherapy, among the 420 examined patients from December 1, 2014, to December 31, 2017, sepsis occurred in 50 (11.9%) patients. Among them, 29 (58%) were female and 21 (42%) were male, with an average age of 63.76 ± 13.6 (24-90) years. The study results also showed that the most commonly isolated etiological agents in patients with positive blood cultures were bacteria, namely Escherichia coli occurring in 17 (34%) and Klebsiella spp. in 8 (16%) subjects. Other isolates, such as Staphylococcus aureus (6%), Streptococcus gallolyticus (6%), and Streptococcus pneumoniae (2%), support bacterial microorganisms as the most common causative agents of this condition. A fungal etiology (Candida parapsilosis) was confirmed in one patient (2%).

Osnovne kliničke manifestacije oboljenja i glavne tegobe koje su pacijenti navodili po prijemu u bolnicu bili su povišena telesna temperatura koja se javila kod 98% ispitanika, jeza i drhtavica 47%, mučnina 25,5%, povraćanje 31,4%, glavobolja 16%, dok su dijareja, dizurične tegobe i poremećaj svesti registrovani kod 21,6% bolesnika.

Povišen ili snižen broj leukocita, kao i pojava mladih formi granulocita, deo je definicije SIRS-a u okviru kojeg se nalazi i sepsa. Leukocitoza, sa izrazitom predominacijom polimorfonukleara se najčešće sreće u ranoj fazi sepse izazvane gram-pozitivnim bakterijama, dok je leukopenija karakterističnija za sepsu izazvanu gram-negativnim bakterijama. Ubrzana sedimentacija eritrocita, povišen nivo fibrinogena, C-reaktivnog proteina, alfa 2- globulina nespecifični su pokazatelji zapaljenja i po pravilu su prisutni i u sepsi [6-9].

Tokom ispitivanja pacijenata po prijemu u ustanovu, kod većine je zabeležena leukocitoza sa porastom procenta segmentiranih leukocita, kao i ubrzana sedimentacija eritrocita i povišen nivo C-reaktivnog proteina. Kontrolnim biohemijskim analizama po otpustu pacijenata iz bolnice ustanovljeno je statistički značajno sniženje ovih parametara.

U savremenom svetu nejasno febrilno stanje je sve češći entitet sa raznovrsnom etiologijom. Septično stanje značajno participira kao etiološki faktor nejasnog febrilnog stanja, a često se previdi tj. lečenje se započinje kasno.

Na osnovu rezultata možemo zaključiti da je procenat obolelih od ovog infektivnog stanja veći među učesnicima prikazane studije zbog lošijih socijalno-ekonomskih uslova naše zemlje i zdravstvenog sistema uopšte, koji dovode do slabijih rezultata primarne dijagnostike u odnosu na zdravstvene sisteme razvijenih zemalja. Takođe, ovo se može opravdati većom zastupljenošću infektivnih bolesti u našem okruženju, kao i većim procentom radno aktivnih koji zbog loše medicinske kulture kasnije dolaze u medicinske ustanove.

ZAKLJUČAK

U posmatranom uzorku sepsa se kao etiološki faktor nejasnog febrilnog stanja sreće relativno često (11,9%). Na osnovu rezultata ovog istraživanja zaključuje se da češće obolevaju pripadnice ženskog pola (58%), starije životne dobi, a da u najčešće izolovane uzročnike spadaju *Escherichia coli* (34%) i *Klebsiella* spp. (16%) što ukazuje na to da je najčešće ishodište infekcije urinarni trakt. Glavne tegobe ne moraju obavezno biti specifične, te kod svake produžene febrilnosti u razmatranje treba uključiti i sistemsku infekciju.

U diferencijalnoj dijagnozi nejasnog febrilnog stanja, i pored značajnog napretka i razvoja sofisticiranih dija-

Comparing these results with those of previous studies, a higher frequency of septic conditions and a lower average patient age are observed. Significant deviations regarding the percentage of positive blood cultures and isolated pathogens are not noted.

Sepsis can be a response to an infection caused by any type of microorganism. Although gram-negative and gram-positive bacteria are the most common infectious agents underlying SIRS, sepsis can also be caused by fungi, mycobacteria, protozoa [16].

Sepsis can be easily suspected in patients with a local infection who suddenly develop elevated body temperature, fever, tachycardia, tachypnea, altered consciousness, and hypotension. However, the septic response can develop much more slowly and have subtler manifestations. In one study, 36% of patients with sepsis were afebrile, 44% had normal consciousness, 60% were eupneic, and 10% had heart rates within physiological limits. Absence of fever is most common in older individuals, patients with uremia, or alcoholics [17-19].

Basic clinical manifestations of the disease and main complaints reported by patients upon hospital admission included elevated body temperature in 98% of respondents, chills and shivering in 47%, nausea in 25.5%, vomiting in 31.4%, headache in 16%, while diarrhea, urinary symptoms, and altered consciousness were reported in 21.6% of patients.

Elevated or decreased leukocyte count, as well as the presence of young forms of granulocytes, are part of the definition of SIRS, within which sepsis is encompassed. Leukocytosis, with a marked predominance of polymorphonuclear cells, is most commonly encountered in the early stage of sepsis caused by gram-positive bacteria, while leukopenia is more characteristic of sepsis caused by gram-negative bacteria. Elevated erythrocyte sedimentation rate, increased fibrinogen level, C-reactive protein, and alpha 2-globulin are nonspecific indicators of inflammation and are typically present in sepsis [6-9].

During the examination of patients upon admission to the institution, leukocytosis with an increase in segmented leukocyte percentage, accelerated erythrocyte sedimentation rate, and elevated C-reactive protein level were recorded in most cases. Statistical analysis of biochemical parameters upon discharge from the hospital revealed a significant decrease in these parameters.

In the modern world, fever of unknown origin becoming increasingly common entities with diverse etiologies. Septic conditions significantly contribute as an etiological factor in fever of unknown origin, often overlooked, i.e. leading to delayed treatment.

gnostičkih postupaka, treba uvek razmišljati o potencijalnoj sistemskoj infekciji kao mogućem uzroku u sklopu koje septično stanje zauzima važno mesto, čak i kada nas inicijalna ispitivanja ne navode na takav zaključak.

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Based on the results, we can conclude that the percentage of individuals affected by this infectious condition is higher among the participants in the presented study due to the poorer socio-economic conditions of our country and the healthcare system in general. These conditions lead to poorer primary diagnostic results compared to healthcare systems in developed countries. Additionally, this can be justified by a higher prevalence of infectious diseases in our environment, as well as a higher percentage of working individuals who, due to poor medical culture, tend to seek medical attention later.

CONCLUSION

In the observed sample, sepsis emerges relatively frequently as an etiological factor in a fever of unknown origin (11.9%). Based on the results of this study, it is concluded that females are more often affected (58%), particularly those of older age, with Escherichia coli (34%) and Klebsiella spp. (16%) being the most commonly isolated pathogens, indicating that the most common origin of infection is the urinary tract. The main symptoms may not necessarily be specific, thus systemic infection should be considered in the differential diagnosis of prolonged fever.

Despite significant advancements and the development of sophisticated diagnostic procedures, differential diagnosis of fever of unknown origin should always include the consideration of potential systemic infection, among which septic conditions hold a significant position, even when initial investigations do not suggest such a conclusion.

Conflict of interest: None declared.

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