

DEVELOPMENT OF THE DEFINITION OF SEPSIS

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SAŽETAK

Sepsa predstavlja veliki zdravstveni problem, imajući u vidu da svake godine preko 20 miliona ljudi u svetu oboli od sepe. Uprkos značajnom razvoju medicine poslednjih decenija, stopa mortaliteta sepe je izuzetno visoka (oko 26%). Razvoj definicije sepe tekao je uporedo sa razumevanjem mehanizma nastanka sepe. Početkom devedesetih godina dvadesetog veka nastala je prva definicija sepe, prema kojoj je sepsa definisana kao sindrom sistemskog inflamatornog odgovora (engl. *systemic inflammatory response syndrome – SIRS*), uz prisustvo sumnje ili dokaza o postojanju infekcije. Zbog velikog broja neadekvatno dijagnostikovanih pacijenata sa sepsom nastala je druga definicija, po kojoj je sepsa definisana kao klinički sindrom. Zbog nedovoljne preciznosti prethodnih definicija sepe, ali i novih saznanja o patofiziološkom mehanizmu sepe, 2016. godine je nastala i treća definicija sepe. Prema ovoj definiciji, sepsa je životno ugrožavajuće stanje u čijoj osnovi se nalazi organska disfunkcija nastala kao posledica neadekvatnog odgovora organizma na infekciju. Septički šok se manifestuje cirkulatornom, ćelijskom i metaboličkom nestabilnošću i karakteriše se nivoom laktata u serumu većim od 2 mmol/l i prisutnom hipotenzijom, koja nakon primene intravenskih rastvora, zahteva terapiju vazopresorima. Ova definicija sepe i septičkog šoka omogućava rano prepoznavanje i lečenje bolesnika sa sepsom, što su ključni koraci u smanjenju incidencije i mortaliteta od ove bolesti.

Ključne reči: sepsa, definicija, mortalitet

ABSTRACT

Sepsis is a significant health problem, considering that, annually, over 20 million people fall ill from sepsis. Despite the significant development of medicine in recent decades, the mortality rate of sepsis is exceptionally high (about 26%). The definition of sepsis developed together with the understanding of the mechanism of sepsis. At the beginning of the 1990s, the first definition of sepsis was created, according to which sepsis was defined as systemic inflammatory response syndrome (SIRS), with the presence of suspicion or evidence of infection. Due to many inadequately diagnosed patients with sepsis, another definition was created, according to which sepsis is defined as a clinical syndrome. As the result of the lack of clarity of the previous definitions and the new information on the pathophysiological process of sepsis, a third definition of sepsis was developed in 2016. According to this definition, sepsis is a life-threatening condition based on organic dysfunction resulting from the body's inappropriate response to infection. Septic shock manifests as circulatory, cellular and metabolic instability. It is characterized by a serum lactate level higher than 2 mmol/l and hypotension, which requires vasopressor therapy after the administration of intravenous solutions. This definition of sepsis and septic shock enables early recognition and treatment of patients with sepsis, which are critical steps in reducing the incidence and mortality from this disease.

Key words: sepsis, definition, mortality

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UVOD

Sepsa i septički šok su veliki zdravstveni problemi, koji svake godine pogađaju milione ljudi širom sveta [1]. Naime, godišnje, oko 20 miliona ljudi u svetu oboli od sepse. Usled visoke stope mortaliteta (oko 26%), sepsa je potencijalno odgovorna za preko pet miliona smrtnih slučajeva svake godine [2]. I pored napretka u medicini, ukupan broj umrlih od sepse i dalje raste, jer sve više ljudi oboleva [3]. Razvoj definicije sepse povezan je sa razumevanjem mehanizma nastanka sepse. Naime, pre više od 100 godina, Viljem Osler je zaključio: „izgleda da pacijent umire od odgovora tela na infekciju, a ne od same infekcije“. Danas znamo da oslobađanje inflamatornih medijatora od strane urođenih imunih ćelija, nakon prepoznavanja patogena, dovodi do aktivacije koagulacione kaskade, vazodilatacije, ekstravazacije neutrofila i inflamatornih medijatora u ekstravaskularni prostor, te posledične disfunkcije organa i hipotenzije tokom sepse [4].

ISTORIJAT DEFINICIJE SEPSIS

Reč *sepsa* potiče od grčke reči *σήψη*, koja označava raspadanje životinjske, biljne ili organske materije u prisustvu bakterija. Prva upotreba ovog termina u medicinske svrhe je dokumentovana pre oko 2.700 godina, u Homerovim poemama, i označavala je trulež. Kasnije se ovaj termin pronalazi u spisima velikog grčkog lekara i filozofa Hipokrata. Prema Hipokratu, ovaj termin je označavao opasno i neprijatno biološko raspadanje, koje nastaje u čovekovom telu, najverovatnije u debelom crevu, i koje može dovesti do sistemske intoksikacije. Nakon starih Grka, definisanju sepse okreću se stari Rimljani na čelu sa Galenom, koji su sepsu smatrali rezultatom proizvodnje nevidljivih stvorenja (mikroorganizama), koja emituju trula isparenja [5].

Na nove definicije sepse čekalo se nekoliko stotina godina. Početkom 19. veka, sa otkrićem prvog mikroskopa, nastala je „teorija klica“, nakon koje je postalo izvesno da sepsa nastaje kao posledica prisustva štetnih mikroorganizama. Po ovoj teoriji, klice (mikroorganizmi) predstavljaju uzrok svih infekcija, a svaka infektivna bolest se može izlečiti ubijanjem klica [6]. Hugo Šotmiller je, 1914. godine, zaključio da je „sepsa prisutna ako se razvilo žarište iz kojeg patogene bakterije, stalno ili periodično, upadaju u krvotok i to na takav način da to izaziva subjektivne i objektivne simptome“ [7].

Sredinom 20. veka sepsa je definisana kao teško, generalizovano, infektivno oboljenje izazvano uglavnom gnojnom klicom, koja iz primarnog ognjišta sukcesivno ulazi u krvotok, stvarajući metastaze [8]. Krajem 20. veka dolazi do nastanka prve savremene definicije sepse.

INTRODUCTION

Sepsis and septic shock are major health problems affecting millions of people worldwide, each year [1]. Namely, around 20 million people around the world fall ill with sepsis, annually. Sepsis has a high mortality rate (roughly 26%), making it potentially responsible for almost five million fatalities each year [2]. Despite the advances in medicine, the total number of deaths from sepsis continues to rise as more and more people become ill [3]. The development of the definition of sepsis is related to understanding the mechanism of sepsis. Namely, more than 100 years ago, William Osler concluded: “it seems that the patient dies from the body’s response to the infection, not from the infection itself”. Today, we know that releasing inflammatory mediators by innate immune cells after pathogen recognition leads to the activation of the coagulation cascade, vasodilation, extravasation of neutrophils and inflammatory mediators into the extravascular space and consequent organ dysfunction and hypotension during sepsis [4].

HISTORY OF THE DEFINITION OF SEPSIS

The word *sepsis* comes from the Greek word *σήψη*, which denotes the decomposition of animal, vegetable or organic matter in the presence of bacteria. The first use of this term for medical purposes was documented around 2.700 years ago, in Homer’s poems, denoting putrefaction. Later, this term can be found in the writings of the great Greek physician and philosopher Hippocrates. According to Hippocrates, this term denoted dangerous and unpleasant biological decomposition, occurring in the human body, most likely in the large intestine, and potentially leading to systemic intoxication. After the ancient Greeks, the ancient Romans, most notably Galen, also attempted to define sepsis. They considered sepsis to result from the production of invisible creatures (microorganisms), which emit putrid fumes [5].

Several hundred years passed before new definitions of sepsis were formulated. At the beginning of the 19th century, with the discovery of the first microscope, the “germ theory” was developed, after which it became indisputable that sepsis occurs due to harmful microorganisms. According to this theory, germs (microorganisms) cause all infections, and any infectious disease can be cured by killing the germs causing it [6]. In 1914, Hugo Schottmüller concluded that “sepsis is present if a focus has developed from which pathogenic bacteria, constantly or periodically, enter the bloodstream in such a way that it causes subjective and objective symptoms” [7].

In the middle of the 20th century, sepsis was defined as a severe generalized infectious disease caused mainly by a purulent germ, which successively enters

PRVA SAVREMENA DEFINICIJA SEPSE

Početkom devedesetih godina dvadesetog veka, osnovan je međunarodni konzorcijum stručnjaka, sa ciljem da se smanji mortalitet od sepse, pomoću posebnog programa usmerenog na rano postavljanje dijagnoze i primenu adekvatne terapije [9]. Naime, na osnovu konsenzusa iz 1992. godine, sepsa je definisana kao postojanje najmanje dva kriterijuma sindroma sistemskog inflamatornog odgovora (engl. *systemic inflammatory response syndrome – SIRS*), uz prisustvo visokog stepena sumnje na infekciju ili uz dokazano prisustvo infekcije [10]. Utvrđeni su sledeći kriterijumi SIRS-a:

1. telesna temperatura iznad 38 °C ili ispod 36 °C;
2. srčana frekvencija veća od 90 otkucaja u minutu;
3. brzina disanja veća od 20 respiracija u minutu ili parcijalni pritisak ugljen-dioksida ispod 4,3 kPa;
4. leukocitoza (broj leukocita iznad 12.000/mm³) ili leukopenija (broj leukocita ispod 4.000/mm³, sa 10% ili više nesegmentiranih neutrofila periferne krvi), (Tabela 1).

Nespecifičnost znakova SIRS-a, na kojima se zasnivala definicija sepse, dovela je do značajnog odstupanja u prikazu incidencije i mortaliteta sepse u epidemiološkim studijama. Pored sepse, definisani su i termini *teška sepsa* i *septički šok*. Teška sepsa je definisana kao sepsa povezana sa organskom disfunkcijom, hipoperfuzijom i hipotenzijom, dok je septički šok definisan kao stanje sepse sa arterijskom hipotenzijom neosetljivom na intravensku nadoknadu tečnosti. Ova definicija sepse nije bila dovoljno precizna da razlikuje pacijente sa sepsom od onih pacijenata koji su imali normalan inflamatorni odgovor na infekciju ili inflamatorno stanje koje nije uzrokovano infekcijom [11]. Ipak, od prve definicije sepse, naše znanje o mehanizmima odgovora domaćina na patogene značajno se poboljšalo [12].

DRUGA SAVREMENA DEFINICIJA SEPSE

Zbog velikog broja nedijagnostikovanih ili neadekvatno dijagnostikovanih pacijenata sa sepsom, prvobitna definicija sepse je promenjena, 2001. godine, sa ciljem da se kliničarima olakša postavljanje dijagnoze. Prema ovoj definiciji, sepsa je označena kao klinički sindrom, a septični pacijenti su klasifikovani prema težini kliničkog stanja – od septikemije do teške sepse praćene disfunkcijom vitalnih organa i septičkim šokom, kao najtežim oblikom sepse [13]. Nakon ove definicije, incidencija sepse i septičkog šoka je značajno porasla, a razlog tome je bilo prisustvo velikog broja imunokompromitovanih i pacijenata sa brojnim komorbiditetima, ali i nedovoljna preciznost definicije, prema kojoj su u grupu pacijenata sa sepsom spadali i pacijenti sa nekomplikovanom ili blagom infekcijom [14]. Ipak, ova definicija je

the bloodstream from the primary focus, creating metastases [8]. At the end of the 20th century, the first contemporary definition of sepsis was formulated.

THE FIRST CONTEMPORARY DEFINITION OF SEPSIS

In the early 1990s, an international consortium of experts was established, with the aim of reducing sepsis-related mortality, through the application of a specifically designed program focused on early diagnosis and application of the appropriate therapy [9]. Namely, based on the 1992 consensus, sepsis was defined as the presence of at least two criteria of systemic inflammatory response syndrome (SIRS), with a high degree of suspicion of infection or with proven presence of infection [10]. The following SIRS criteria were established:

1. body temperature above 38 °C or below 36 °C;
2. heart rate of over 90 beats per minute;
3. respiratory rate of over 20/min or carbon dioxide partial pressure below 4.3 kPa,
4. leukocytosis (number of leukocytes above 12,000/mm³) or leukopenia (number of leukocytes below 4,000 /mm³, with 10% or more of unsegmented peripheral blood neutrophils), (Table 1).

Tabela 1. Kriterijumi sindroma sistemskog inflamatornog odgovora – SIRS kriterijumi

Table 1. Expanded Disability Status Scale - EDSS

Dva ili više od sledećih / Two or more of the following:
Telesna temperatura > 38 °C ili < 36 °C / Body temperature > 38 °C or < 36 °C
Broj otkucaja srca > 90/min / Heart rate > 90/min
Broj respiracija > 20/min ili PaCO ₂ (PaCO ₂) < 32 mmHg (4,3 kPa) / Respiratory rate > 20/min or PaCO ₂ (PaCO ₂) < 32 mmHg (4.3 kPa)
Broj leukocita > 12.000/mm ³ ili < 4.000/mm ³ ili > 10% nezrelih formi / Leukocytes > 12,000/mm ³ or < 4,000/mm ³ or > 10% immature forms

The non-specificity of SIRS signs, which the definition of sepsis was based on, led to a significant discrepancy in the presentation of sepsis incidence and sepsis-related mortality in epidemiological studies. In addition to sepsis, the terms *severe sepsis* and *septic shock* were also defined. Severe sepsis was defined as sepsis associated with organ dysfunction, hypoperfusion, and hypotension, while septic shock was defined as the state of sepsis with arterial hypotension unresponsive to intravenous fluid replacement. This definition of sepsis was not specific enough to distinguish patients with sepsis from those with a normal inflammatory response to infection or an inflammatory condition not caused by infection [11]. Nevertheless, since the first definition of

obezbedila rano dijagnostikovanje sepse i rano započinjanje terapije, što je od izuzetnog značaja u sprečavanju progresije ovog stanja u tešku sepsu i septički šok, koji su praćeni znatno višim stopama mortaliteta [15].

Treća savremena definicija sepse

Decenijama se sepsa smatrala sistemskom diseminacijom infekcije koja dovodi do sistemskih kliničkih manifestacija, uključujući tu i oštećenje više organa i sistema organa, sa visokim morbiditetom i mortalitetom [16]. Najveći problem prve i druge definicije sepse su uske granice u definisanju infekcije i sepse. Zaista, SIRS kriterijumi, koji definišu sepsu, pripadaju normalnom odgovoru na infekciju, kao što su pneumonija ili infekcija urinarnog trakta, i sami po sebi ne predstavljaju znak komplikovanog toka [15].

Zbog pomenute nedovoljne preciznosti prethodnih definicija sepse, ali i novih saznanja o patofiziološkom mehanizmu sepse, 2016. godine se ukazala potreba za novom definicijom, koja bi bila konkretnija od prethodne i koja bi omogućila lakše prepoznavanje sepse u svakodnevnoj kliničkoj praksi [17]. Prema ovoj definiciji, u osnovi sepse je patofiziološki odgovor domaćina na infekciju, koji je opisan kao „nehomoeostatski“. Naime, ono što razlikuje sepsu od infekcije jeste aberantni ili neregulisani odgovor domaćina i prisustvo disfunkcije organa, što odražava značaj faktora domaćina u nastanku sepse. Novom definicijom izbačeni su termini SIRS i teška sepsa, dok se sepsa definiše kao životno ugrožavajuća organska disfunkcija uzrokovana neadekvatnim odgovorom domaćina na infekciju, pri čemu se organska disfunkcija definiše kao akutna promena u ukupnom Skoru procene sekvencijalnog popuštanja organa (engl. *Sequential Organ Failure Assessment – SOFA*) za dva i više poena, a koja je uzrokovana infekcijom [18]. Septički šok se definiše kao podtip sepse, a manifestuje se cirkulatornom, ćelijskom i metaboličkom nestabilnošću i povezan je sa mortalitetom većim od 40%. Pacijent se nalazi u septičkom šoku ukoliko je, pored pomenute organske disfunkcije karakteristične za sepsu, prisutan i nivo serumskog laktata veći od 2 mmol/l (18 mg/dl), ali i hipotenzija koja nakon intravenske primene infuzionih rastvora, zahteva terapiju vazopresorima da bi se srednji arterijski pritisak održao iznad 65 mmHg [19].

Glavna prednost treće definicije sepse je to što su novi dijagnostički kriterijumi ispitani i potvrđeni u velikim retrospektivnim studijama u razvijenim zemljama, kao što su SAD i Nemačka [20,21]. Ipak, osim u razvijenim zemljama, efikasnost treće definicije sepse procenjena je i u manje razvijenim zemljama. Prognostička vrednost ove definicije sepse je procenjena u jednom centru intenzivne nege, pokazavši povećanje

sepsis, our knowledge of the mechanisms of the host's response to pathogens has improved significantly [12].

THE SECOND CONTEMPORARY DEFINITION OF SEPSIS

Due to a high number of undiagnosed or inadequately diagnosed patients with sepsis, in 2001, the original definition of sepsis was adapted to make the diagnosis easier for clinicians. According to this definition, sepsis is designated as a clinical syndrome. Septic patients are classified according to the severity of the clinical condition – from septicemia to severe sepsis, accompanied by the dysfunction of vital organs and septic shock as the most severe form of sepsis [13]. After this definition was introduced, the incidence of sepsis and septic shock increased significantly, and the reason for this was the presence of a large number of immunocompromised patients and patients with numerous comorbidities, but also the lack of specificity of the definition, according to which the group of patients with sepsis also included patients with uncomplicated or mild infection [14]. Nevertheless, this definition ensured the early diagnosis of sepsis and the early initiation of therapy, which are extremely important in preventing the progression of this condition to severe sepsis and septic shock, which are accompanied by significantly higher mortality rates [15].

THE THIRD CONTEMPORARY DEFINITION OF SEPSIS

For decades, sepsis was considered a systemic dissemination of infection leading to systemic clinical manifestations, including multiple organ and organ system damage, with high morbidity and mortality [16]. The greatest problem with the first and second definitions of sepsis are the narrow boundaries in defining infection and sepsis. Indeed, the SIRS criteria defining sepsis belong to the normal response to infection, such as pneumonia or urinary tract infection, and do not, in themselves, represent signs of complications in the clinical course of disease [15].

Due to the above-mentioned insufficient specificity of the previous definitions of sepsis, as well as new knowledge regarding the pathophysiological mechanism of sepsis, in 2016, there was a need for a new definition that would be more specific than the previous one and would enable easier recognition of sepsis in everyday clinical practice [17]. This concept places the 'non-homeostatic' pathophysiological host response to infection at the core of sepsis. Namely, what distinguishes sepsis from infection is an aberrant or unregulated host response and the presence of organ dysfunction. It reflects the importance of host factors in the development of sepsis. The new definition elim-

mortaliteta u sve tri kategorije: infekcija bez organske disfunkcije, sepsa i septički šok [22]. Ovim studijama je pokazano da ova definicija sepse definitivno olakšava prepoznavanje sepse u svakodnevnoj kliničkoj praksi.

SKOR PROCENE SEKVENCIJALNOG POPUŠTANJA ORGANA – SOFA SKOR

Glavni razlozi brojnih smrtnih ishoda nastalih kao posledica obolevanja od sepse jesu kasno prepoznavanje i dijagnostikovanje sepse i kasno započinjanje terapije. Da bi se mortalitet od sepse smanjio, napravljeni su posebni algoritmi koji pomažu u dijagnostikovanju ove bolesti [23]. Najpoznatiji među njima je Skor procene sekvencijalnog popuštanja organa (engl. *Sequential Organ Failure Assessment*) – SOFA skor, pri čemu akutna promena u ukupnom SOFA skoru za dva i više poena označava postojanje organske disfunkcije, koja je uzrokovana infekcijom. Računa se da je početni SOFA skor 0, kod pacijenta bez prethodne organske disfunkcije (Tabela 2) [24].

Za brzo dijagnostikovanje sepse kod pacijenata smeštenih van jedinica intenzivnog lečenja, dizajnirana je nova, pojednostavljena verzija SOFA skora – Brzi SOFA skor (engl. *Quick SOFA – qSOFA*). Ovaj skor pomaže u procenjivanju mentalnog, respiratornog i kardiovaskularnog statusa pacijenta, a zbog brzog i lakog izvođenja, koristi se u prijemnim ambulantama i na bolničkim odeljenjima. Kriterijumi qSOFA skora su:

inates the terms *SIRS* and *severe sepsis*, while sepsis is defined as life-threatening organ dysfunction caused by inappropriate host response to infection, and organ dysfunction is defined as an acute change in the total Sequential Organ Failure Assessment (SOFA) score by two or more points, as the result of infection [18]. Septic shock is defined as a subtype of sepsis, manifesting as circulatory, cellular, and metabolic instability and associated with mortality greater than 40%. A patient is in septic shock if, in addition to the above-mentioned organ failure associated with sepsis, their blood lactate level is above 2 mmol/l (18 mg/dl), they have hypotension, and they need vasopressor medication to raise their mean arterial pressure above 65 mmHg [19].

The main advantage of the third definition of sepsis is that the new diagnostic criteria have been tested and confirmed in extensive retrospective studies in developed countries, such as USA and Germany [20,21]. In addition to developed countries, the effectiveness of the third definition of sepsis has also been evaluated in less developed countries. The prognostic value of this definition of sepsis was evaluated in one intensive care center, showing an increase in mortality in all three categories: infection without organ dysfunction, sepsis, and septic shock [22]. These studies have shown that this definition of sepsis facilitates the recognition of sepsis in daily clinical practice.

Tabela 1. Kriterijumi sindroma sistemskog inflamatornog odgovora – SIRS kriterijumi

Table 1. Expanded Disability Status Scale - EDSS

Kriterijum	0	1	2	3	4
PaO ₂ /FiO ₂ mmHg (kPa)	≥ 400 (53,3)	< 400 (53,3)	< 300 (40)	< 200 (26,7) uz respiratornu potporu / respiratory support	< 100 (13,3) uz respiratornu potporu / respiratory support
Srednji arterijski pritisak / Mean arterial pressure	MAP ≥ 70 mmHg	MAP < 70 mmHg	Primena dopamina ili dobutamina / Use of dopamine or dobutamine	Dopamin / Dopamine 5,1 – 15 l ili / or epinefrin / epinephrine ≤ 0,1 ili norepinefrin / or norepinephrine ≤ 0,1 (µg/kg/min)	Dopamin / Dopamine > 15 l ili / or epinefrin / epinephrine > 0,1 ili norepinefrin / or norepinephrine > 0,1 (µg/kg/min)
Trombociti / Platelets (x10 ³ /µl)	≥ 150	< 150	< 100	< 50	< 20
Skor na Glazgovskoj skali kome / Glasgow coma score	15	13 – 14	10 – 12	6 – 9	< 6
Kreatinin / Creatinine mg/dl (µmol/l)	< 1,2 (110)	1,2 – 1,9 (110 – 170)	2,0 – 3,4 (171 – 299)	3,5 – 4,9 (300 – 400)	> 5,0 (440)
Bilirubin / Bilirubin mg/dl (µmol/l)	< 1,2 (20)	1,2 – 1,9 (20 – 32)	2,0 – 5,9 (33 – 101)	6,0 – 11,9 (102 – 204)	> 12,0 (204)

1. izmenjena mentalna aktivnost, $GCS^1 < 15$
2. hipotenzija, sistolni krvni pritisak ≤ 100 mmHg
3. tahipneja, broj respiracija $\geq 22/\text{min}$.

Ipak, *qSOFA* skor ne definiše sepsu, ali omogućava brzu identifikaciju svih pacijenata sa potencijalnim rizikom od sepse, jer je pokazatelj povećanog rizika od prisustva organske disfunkcije. U tom smislu, prisustvo najmanje dve varijable sugerise da je pacijent pod visokim rizikom od nepovoljnih ishoda, kao što su smrt u bolnici ili dugotrajni boravak na intenzivnoj nezi [25]. Studije su pokazale da je *qSOFA* skor specifičniji, ali manje osetljiv od *SIRS* kriterijuma za ranu identifikaciju organske disfunkcije izazvane infekcijom [26].

Primena *qSOFA* skora rezultirala je većom prognostičkom tačnošću u pogledu bolničkog mortaliteta nego što je to bio slučaj sa *SIRS*-om ili teškom sepsom [27]. Dodavanjem vrednosti nivoa laktata, *qSOFA* skor je statistički dodatno poboljšalo prediktivnu validnost ovog testa [28]. Glavne prednosti ovog „testa upozorenja“ su jednostavnost izvođenja, mogućnost čestog ponavljanja i praćenja, velika brzina izvođenja (dovoljno je nekoliko sekundi), kao i to što ne zahteva korišćenje posebne opreme [29].

ZAKLJUČAK

Sepsa je životno ugrožavajući klinički sindrom sa visokom incidencijom i stopom mortaliteta, kako u nerazvijenim, tako i u razvijenim zemljama. Zbog antimikrobne rezistencije, koja je posebno izražena nakon epidemije KOVID-19 oboljenja, smatra se da će stopa mortaliteta imati još veći porast. Nova definicija sepse omogućava rano prepoznavanje i rano lečenje bolesnika sa sepsom i bolesnika pod povećanim rizikom od nastanka sepse. Rano postavljanje sumnje na sepsu i odgovarajuća terapija u prvim satima nakon razvoja sepse predstavljaju ključne korake u lečenju ovih bolesnika, jer se jedino tako može poboljšati preživljavanje pacijenata obolelih od sepse. Uprkos ogromnom napretku medicine poslednjih decenija, definisanje, dijagnostika i lečenje sepse i dalje predstavljaju veliki izazov.

Sukob interesa: Nije prijavljen.

SEQUENTIAL ORGAN FAILURE ASSESSMENT (SOFA) SCORE

The main reasons for numerous deaths resulting from sepsis are late recognition and diagnosis and late initiation of therapy. In order to reduce mortality from sepsis, unique algorithms have been created to help diagnose this disease [23]. The most prominent among them is the SOFA score, wherein an acute change in the total SOFA score by two or more points indicates the existence of an organ dysfunction caused by infection. The initial SOFA score is considered to be 0 in a patient without previous organ dysfunction (Table 2) [24].

A new, simplified version of the SOFA score, i.e., the Quick SOFA score (*qSOFA*), was designed to rapidly diagnose sepsis in patients outside intensive care units. The *qSOFA* helps assess the patient's mental, respiratory and cardiovascular status, and is used in admission units and hospital wards due to its quick and easy execution. The *qSOFA* criteria are, as follows:

1. altered mental activity, $GCS^2 < 15$
2. hypotension, systolic blood pressure ≤ 100 mmHg
3. tachypnea, respiratory rate $\geq 22/\text{min}$.

However, the *qSOFA* does not define sepsis, but does allow for the rapid identification of all patients at potential risk of sepsis, because it indicates an increased risk of organ dysfunction. Thus, the presence of at least two variables suggests that the patient is at high risk of adverse outcomes, such as in-hospital death or prolonged ICU stay [25]. Studies have shown that *qSOFA* is more specific but less sensitive than the *SIRS* criteria for early identification of organ dysfunction caused by infection [26].

The application of *qSOFA* resulted in greater prognostic accuracy regarding in-hospital mortality than *SIRS* or severe sepsis [27]. The predictive validity of this test was significantly enhanced by adding lactate levels to *qSOFA* [28]. The main advantages of this 'warning test' are the simplicity of execution, the possibility of frequent repetition and monitoring, the high speed of execution (a few seconds are enough), and the fact that it does not require special equipment [29].

CONCLUSION

Sepsis is a life-threatening clinical syndrome with high incidence and a high mortality rate, both in developing and developed countries. It is believed that antimicrobial resistance, which has become more pronounced since the COVID-19 pandemic, will contribute to an even higher death rate. The new definition of sepsis enables early recognition and treatment of patients with sepsis and patients at increased risk of develo-

1 Glazgovska skala/skor kome (engl. *Glasgow coma scale/score* – GSC)

2 Glasgow coma scale/score (GSC)

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- ping sepsis. Early suspicion of sepsis and appropriate treatment in the first hours after the onset of sepsis are vital steps, as this is the only way of improving survival in sepsis patients. Despite substantial advances in medicine in the previous decades, defining, diagnosing, and treating sepsis remains a significant challenge.

Conflict of interest: None declared.

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