REVIEW ARTICLE / PREGLEDNI ČLANAK

MANAGEMENT OF SEPSIS AND SEPTIC SHOCK IN THE EMERGENCY DEPARTMENT

ZBRINJAVANJE SEPSE I SEPTIČKOG ŠOKA U HITNOM BOLNIČKOM PRIJAMU

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https://doi.org/10.64266/amu.2.5.3

Abstract

Sepsis, a rapidly progressing and life-threatening organ dysfunction, requires immediate action. Early recognition and timely intervention are critical because delays lead to high mortality. Current guidelines combine essential procedures for initial sepsis care into a one-hour bundle. This paper summarizes the most up-to-date evidence and recommendations for managing sepsis and septic shock in the emergency department. Accurate identification of sepsis and exclusion of non-infectious causes are essential. Key interventions include prompt initiation of empirical antibiotics after microbiological sampling, personalized to each patient, and initial treatment with electrolyte-balanced crystalloids guided by fluid tolerance and fluid responsiveness. Early vasopressor norepinephrine administration targets a mean arterial pressure of 65 mmHg; vasopressin may be added in refractory cases. Corticosteroids are reserved for patients with continued hemodynamic instability who do not achieve the target mean arterial pressure despite vasoactive therapy and bicarbonates for severe metabolic acidosis and acute kidney injury. Although implementing this comprehensive approach in the ED is challenging, evidence consistently shows that early, protocol-driven care improves patient outcomes.

Keywords: antibiotic; emergency medicine; sepsis; septic shock; vasopressor agents.

Sažetak

Sepsa je životno ugrožavajuća organska disfunkcija, s porastom incidencije i visokim mortalitetom. Liječenje je vremenski ovisno, te je nužno rano prepoznavanje ovih bolesnika, koji se vrlo često inicijalno zbrinjavaju u hitnom prijemu. Aktualne smjernice objedinjuju osnovne postupke početnog liječenja sepse u jednosatni snop postupaka. Cilj ovog rada je prikaz najnovijih spoznaja i rezultata studija te preporuka za osnovno liječenje sepse i septičkog šoka u hitnoj medicini. Iznimno je važno ispravno prepoznati sepsu, odnosno prepoznati neinfektivno zbivanje ako je ono uzrok stanja bolesnika. U liječenju sepse je ključna žurna primjena empirijske antibiotske terapije prilagođene osobitostima pojedinog bolesnika, odmah po uzimanju mikrobioloških uzoraka. U početno liječenje spada i volumna nadoknada, primjena elektrolitski balansiranih kristaloidnih otopina, koja je ovisna o procjeni tolerancije i osjetljivosti na primjenu tekućine, kao i rana primjena vazopresora noradrenalina s ciljem postizanja srednjeg arterijskog tlaka 65 mmHg žive, ali i izbjegavanja preopterećenja tekućinom. Ukoliko se radi o refraktornom šoku, preporučeno je uz primjenu noradrenalina dodati vazopresin. Kortikosteroidi se ne primjenjuju rutinski, ali imaju ulogu u liječenju kontinuirano hemodinamski nestabilnih bolesnika, odnosno onih u kojih se ne ostvaruje ciljna vrijednost srednjeg arterijskog tlaka usprkos vazoaktivnoj terapiji. Bikarbonati su indicirani kod bolesnika s teškom metaboličkom acidozom te akutnom ozljedom bubrega. Provođenje svih postupaka inicijalnog liječenja sepse u hitnom prijemu je osobito izazovno, ali brojne studije potvrđuju da omogućuje bolje ishode bolesnika.

Ključne riječi: antibiotici; hitna medicina; sepsa; septički šok; vazopresori

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Introduction

Early recognition, initial stabilization, and treatment of patients with sepsis in the hectic environment of the emergency department (ED) is extremely challenging. „Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection" (1). „Septic shock is defined as a subset of sepsis featuring profound circulatory, cellular, and metabolic abnormalities associated with a higher mortality risk than sepsis alone" (1). „Patients with septic shock require vasopressors to maintain a mean arterial pressure (MAP) of 65 mm Hg or higher, with a serum lactate level greater than 2 mmol/L in the absence of hypovolemia" (1). These two clinical features are associated with a hospital mortality of more than 40% (1). According to „The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis 3)", sepsis should be considered a possibility in patients with suspected infection from any source, and the use of „Quick Sequential Organ Failure Assessment (qSOFA) should be considered" (1). A score of 2 or higher indicates patients who are likely to have poor outcomes or are at increased risk of hospital mortality (1). However, the „2021 Surviving Sepsis Campaign (SSC) guidelines" do not support using qSOFA as the sole screening tool and recommend the „National Early Warning Score (NEWS), Modified Early Warning Score (MEWS), or Severe Inflammatory Response Syndrome (SIRS) score" (2). That is to say, a positive qSOFA score is a strong predictor of an unfavorable prognosis in patients with infection. It should certainly serve as a warning about the risk of sepsis, but it lacks sufficient sensitivity. There is a strong recommendation against its use as the sole tool for recognizing septic patients (2).

Early recognition of sepsis in the emergency setting is challenging, and timely prehospital assessment and treatment by emergency medical services are critical because outcomes are strongly time-dependent.

Sepsis and septic shock cases are rising worldwide, reaching 49 million yearly, and causing 11 million deaths (3). Even with better treatments, mortality remains high, about 20% or above (4, 5). Sepsis patients in emergency departments are among those with the highest mortality rates. The emergency medical service is the initial treatment site for sepsis and plays a particularly important role as the first link in the chain of care for these complex patients. Of interest are analysis data from the United States of America, which show that in 86% of patients, sepsis is diagnosed at admission. In about 80% of these patients, the ED is the place of initial management (6). Additionally, the out-of-the-hospital emergency medical services were taking care of more than 75% of the patients included in the study (7). Sepsis treatment outcomes are time-dependent, which is why protocols have been developed to help identify patients who need appropriate, strong therapy immediately. „The 2016 Surviving Sepsis Campaign" provided guidance for the management of these patients, and the 2018 update emphasized the importance of prompt treatment, presented as a „1-hour bundle" of resuscitation procedures (8). These include „measurement of serum lactate and remeasurement at 2-4 hours if ≥ 2 mmol/L, blood culture sampling before antibiotic administration, administration of broad-spectrum antibiotics, initiation of volume resuscitation of 30 ml/kg in hypotension or if lactate is ≥ 4 mmol/L, and administration of vasopressors in hypotension during or after the administration of volume replacement to maintain an MAP ≥ 65 mm Hg" (8). „The European Society for Emergency Medicine (EUSEM)" expressed concern in a position paper because of the feasibility of the „1-hour bundle", advocating evidence-based elements such as early identification of sepsis and early antibiotic administration, rather than strict time frames, and accomplishing all procedures from the bundle within an hour of triage (9). The key elements of the „1-hour bundle" are outlined in the SSC Guidelines 2021, but they ideally start within an hour of sepsis recognition and, for patients who are not in shock and are strongly suspected of infection, within three hours for starting antibiotic therapy (2). Another challenge in the acute environment of the ED is that these are often unexplained patients in whom early and quick recognition of sepsis is not easy, and some of them will have a different main diagnosis than sepsis after the completion of the assessment (10). This review will give a concise overview of sepsis and septic shock pathophysiology, accompanied by new findings and recommendations regarding the initial care of sepsis patients.

Methods

For the purposes of this review, we searched the PubMed database for literature published from 2020 to 2025. The strategy consisted of searching for given keywords from the Medical Subject Headings (MeSH) list. We further expanded the analysis by manually searching for references from the included studies.

Pathophysiology

The etiology of sepsis involves multiple factors and remains incompletely understood. Microorganisms and their toxic substances play a role in the rise of sepsis, as well as a significantly increased immune response of the organism (1,11). It also includes the activation of the complement system and the release of pro-inflammatory factors. Today's knowledge suggests that both pro-inflammatory and anti-inflammatory mediators play a role in the development of sepsis (11). However, the importance of prognostication lies in modulating large non-immune pathways (11,12). It is not entirely clear why an immune response that is normally localized can, in some cases, spread and cause sepsis. Cellular injury is a precursor to organ dysfunction.

But even with severe organ dysfunction, cell death is usually not significantly pronounced (1). Suggested processes underlying cell injury include „ischemia, apoptosis, and

cytopathic injury" (13). Recent findings emphasize the importance of patients' clinical and biological heterogeneity. Namely, their age, comorbidities, injuries, medications, and the infection site increase even more the complexity of this critical state (14,15). Sepsis can be partially presented as malignant intravascular inflammation. Malignant refers to the absence of control and self-sustainability, intravascular to the intravascular route of mediator spread through the blood, and inflammation to the features of sepsis, which are actually a markedly enhanced normal inflammatory response (16). When analyzing hemodynamic changes in these patients, septic shock is characterized by simultaneous changes in the macro- and microcirculations, ultimately resulting in an imbalance between the tissue's oxygen needs and the amount of oxygen delivered (17). One of the features of sepsis is the occurrence of absolute and relative hypovolemia, caused by pronounced arterial and venous vasodilation and increased vascular permeability.

Severe vasodilation and hypotension consequently lead to compensatory activation of the sympathetic nervous system by acting on alpha and beta adrenergic receptors. However, the effectiveness of these compensatory mechanisms is significantly lower than in other types of shock. The reasons are adrenal insufficiency, elevated levels of vasodilators such as nitric oxide (NO), and often reduced ventricular contractility in up to 60% of patients with sepsis (18). Septic cardiomyopathy is associated with endothelial and mitochondrial dysfunction, alterations in calcium metabolism, and alterations in beta-adrenergic receptors (18). It can occur immediately or during the first few days. This cardiomyopathy is reversible, but because it significantly affects compensatory mechanisms and the effectiveness of treatment, it is a key factor to consider in the care of these patients in the ED.

Sepsis causes profound microcirculatory and endothelial dysfunction, leading to impaired tissue perfusion despite changes in systemic hemodynamics.

Reducing the amount of capillaries that are fully functional is one of the key features of sepsis. It can be connected with tissue edema, external pressure on capillaries, endothelial swelling, or lumen obstruction by leukocytes and erythrocytes. Due to its role in regulating microcirculation, the endothelium is considered a crucial element in the sepsis development (19). Namely, it has a strong modulatory effect on coagulation processes and on signaling pathways for inflammatory and anti-inflammatory factors.

Endothelial cells interacting with the bacterial wall results with the changes described as „endothelial dysfunction, coagulation disorders, upregulation of adhesion molecules, and glycocalyx degradation" (13). The glycocalyx is part of the endothelium and is composed of glycoproteins and proteoglycans. Damage to its morphological and functional integrity manifests as increased vascular permeability and edema formation, elevated interstitial pressure, and, eventually, inadequate tissue perfusion (20).

Early recognition of sepsis

Sepsis is a clinical diagnosis. Anamnestic data and physical examination are particularly important, as they can reveal signs of infection and organic dysfunction. During the initial treatment of these patients, a wide range of possible differential diagnoses is often considered.

Correct diagnosis of sepsis often requires additional observation and diagnostic interventions.

Recognizing sepsis in immunosuppressed patients, the elderly, and those in the very early stages of the disease is particularly challenging. Analyses show that 20 to 40% of patients in whom sepsis is a working diagnosis during care in the ED are defined as a condition of a non-infectious nature upon completion of workup (10). Patients with these conditions, which can be called „sepsis mimics", are unlikely to benefit from all aspects of therapy aimed at treating sepsis (10). It is for these reasons that the SSC guideline has revised the timing of bundle initiation from arrival at the ED to sepsis diagnosis.

Various screening tools are helpful in the process of correctly recognizing sepsis. There are two basic forms: manual methods or the automated use of electronic health records (EHRs) (2). Commonly used clinical tools are „Systemic Inflammatory Response Syndrome (SIRS) criteria, qSOFA (Sequential Organ Failure Assessment), NEWS, and MEWS" (2). They have very different diagnostic accuracy but mostly low predictive value. So far, no validated tool has achieved reliable results.

No mortality benefit was observed with their use in the pooled analysis of three RCTs (2,21). Nevertheless, they constitute an important component of early sepsis identification, a basic prerequisite for early treatment.

A look into the near future is provided by a recent study on the child population that pointed to the possible application of the machine learning predictive model (22). It is based on the use of EHRs and can achieve positive likelihood ratios in predicting the development of sepsis over 48 hours, i.e., before the onset of organ dysfunction (22).

Initial treatment

The first step is a clinical examination and verification of the patient's vital parameters. Priority management includes airway protection (if necessary), administration of oxygen to maintain SpO2 ≥ 92%, establishment of venous access, and early application of crystalline solutions and antibiotics. Sepsis and septic shock are urgent conditions, and it is necessary to start treatment and resuscitation procedures immediately. It must not be forgotten that adherence to the applicable guidelines in their entirety is more important after sepsis is diagnosed than when it is only one of several possible reasons for the patient's condition. Therefore, a prerequisite for the

urgent initiation of therapy is the recognition of sepsis rather than other clinical diagnoses (10). Early Goal-Directed Therapy procedures, currently combined into a sepsis bundle, represent a common, standardized approach to treating sepsis. Various studies suggest that they reduce mortality, but in two meta-analyses from lower-resource countries, they were associated with increased mortality (23, 24).

Sepsis management requires immediate treatment once the diagnosis is established, while strict adherence to the full sepsis bundle may need to be adapted to the specific healthcare setting and available resources.

This points to the need for further development of guidelines tailored to different care settings and levels of care. An analysis of about 400 EDs across Europe found that only about half provided all elements of the 1-hour bundle (25). The most common deviations are due to the later recognition of these patients, which is associated with a large number of patients undergoing treatment and insufficient staff and training.

Intravenous fluids

Sepsis is characterized by severe vasoplegia that can lead to distributive shock. Early effective volume replacement is crucial in stabilizing tissue hypoperfusion caused by sepsis (2). Therefore, in clinical practice, it is important to initiate volume resuscitation immediately upon sepsis diagnosis. Knowing that these patients often have a wider list of possible causes of their condition at the beginning of treatment in the ED, if there is a high suspicion of sepsis, it is necessary to have a very low threshold for its initiation. There are two types of resuscitation fluids: crystalloid and colloid. There is a clear clinical advantage associated with crystalloid solutions compared to colloid solutions (26).

Albumin has a clear theoretical advantage in maintaining oncotic pressure. However, multiple meta-analyses and RCTs have shown that it is not associated with improved mortality (27,28). Its routine application is often limited by lower availability and higher costs, and without a clear benefit. Therefore, the „SSC guidelines 2021“ recommend considering the use of albumin in patients who have received large volumes of crystalloids (2). Colloid use, specifically hydroxyethyl starch (HES), carries significant risks in sepsis management.

HES increases the risk of acute kidney injury (AKI), which is associated with a higher mortality rate (29,30). Guideline recommendations continue to advise against its use in sepsis (2).

Crystalloid solutions, which are the fluids of choice in sepsis, are either chloride-rich [most commonly, normal saline (NS)] or balanced crystalloid solutions. For septic patients, balanced crystalloid solutions are preferred because their electrolyte composition is more similar to plasma, and because administering large amounts of saline can cause hyperchloremic acidosis. Based on available data, some studies advise using either balanced crystalloid solutions or NS for the first liter of volume compensation, but if a significant volume is required after the first liter, then balanced crystalloid solutions are recommended (31). Currently valid recommendations regarding the type of fluid for volumetric resuscitation of septic patients are actually quite uniform (2). The situation is rather different when it comes to the required total volume and the process of its application. According to the 2021 SCC guidelines, „septic patients with pronounced hypoperfusion and those in septic shock should receive at least 30 ml/kg of IV crystalloid within the first 3 hours“ (2).

In a large retrospective study that included septic patients in the ED, the group of patients who did not receive this adequate amount of volume had worse overall outcomes, regardless of comorbidities (32). However, this approach is the subject of numerous debates and, according to several studies, is questionable.

Namely, instead of aggressive volume compensation, the emphasis is increasingly on perfusion at the microcirculation level. Aggressive volume replacement may further worsen endothelial and glycocalyx dysfunction (33,34). The importance of microcirculation recovery as a key resuscitation outcome is increasingly being recognized (35). It is achieved through individualized treatment aimed at “glycocalyx resuscitation”, based on monitoring fluid tolerance and response.

Rooted in the knowledge available today, a gradual individualized method of initial volume resuscitation was proposed (36). It includes two key elements, repeated small boluses of crystalloid (250 ml to 500 ml) and continuous hemodynamic assessment (36,37). Early administration of vasopressors is necessary if there is no improvement in circulation (36). Continued fluid administration after initial resuscitation can cause volume overload, worsen acute renal injury, and increase mortality. Following a detailed initial exam, ongoing reassessment and repeated checks of the patient’s response are crucial. Around half of septic shock patients do not show increased cardiac output after a fluid bolus, or the response is short-lived. Identifying patients who respond to fluids helps guide appropriate volume therapy. It is recommended that volume resuscitation be conducted using dynamic measures (2,10).

Initial fluid resuscitation should use crystalloids, with balanced crystalloids preferred; fluid volume should be individualized according to the patient’s response, as excessive fluid administration may contribute to fluid overload and acute kidney injury.

In modern EDs, point-of-care ultrasound is a regular, significant aid in assessing the patient's condition. In this group of patients, the ultrasound role is primarily to assess volume status and fluid responsiveness. Assessment of volume status using ultrasound includes estimation of stroke volume and lung ultrasound (37). Also useful is the assessment of venous congestion by measuring intravascular distension, as indicated by a dilated inferior vena cava (IVC), or an elevated „VexUS score" (31, 37).

Interestingly, a recent RCT comparing liberal and restrictive volume administration in these patients did not show a difference in mortality at 90 days (38). Therefore, although an individualized method of application of volume resuscitation is preferred, further research is certainly necessary regarding the appropriate amount of fluids.

The management of the resuscitation process can be associated with various ways that provide insight into changes in hemodynamic status. We highlight two ways that are particularly useful and applicable in the ED. The resuscitation procedure can be guided by changes in serum lactate values as well as capillary refill time (CRT) values. In patients with elevated lactates, it is important to take into account the overall clinical situation and to consider other possible reasons for their increase. Especially from a clinical point of view, it is interesting to note that CRT is not inferior to serum lactate levels as an indicator of resuscitation efficiency (39). Consequently, CRT is recommended to guide resuscitation effects, but other perfusion methods can be used (2). The results of a recently published study, „The ANDROMEDA-SHOCK-2", suggest that the use of CRT as a clinical biomarker of tissue perfusion may reduce mortality in the early stages of septic shock (40).

Compared to usual treatment, there was no difference in mortality, but the group in which CRT and dynamic measurements were used to guide resuscitation had a 5% shorter duration of vital organ support. Furthermore, this group of patients received less fluid, and a higher proportion received vasopressor therapy.

These results further support the currently prevailing view of the key role of individualized hemodynamic resuscitation. CRT, as a practical and rapid clinical method, has a clear place in the assessment of changes in the patient's condition and the management of therapy. Given that the ED is the place of both diagnostic assessment and the beginning of treatment of septic patients, and that these patients certainly spend a certain amount of time there, hemodynamic monitoring may include some of the invasive methods, more commonly used in intensive care units, such as arterial catheters.

Finally, interestingly, the results of an RCT including more than 1,000 patients in a state of shock, half of whom had sepsis, did not show an association between arterial catheter placement and better outcomes compared with noninvasive blood-pressure monitoring (41). Mortality at 28 days was similar (34% versus 37%), and pain, bleeding, and hematomas were more common in the group with an arterial catheter (41).

Vasoactive agents

One of the key elements of the therapy of patients with sepsis is certainly vasoactive drugs. Septic shock is caused by, among other things, vasoplegia and consequent systemic vasodilation and hypotension. MAP is a key resuscitation target because it is essential for organ perfusion. Physiological mechanisms of autoregulation can preserve organ perfusion despite changes in the MAP, but when the MAP falls below a certain threshold, below 60 or 65 mmHg, autoregulation does not work, and there is a critical drop in perfusion, consequent ischemia, and organ injury. SSC guidelines 2021 define an „initial MAP target value of 65 mm Hg" (2).

In analyzing the outcomes of patients who did not achieve the target MAP, it is important to highlight the results of the permissive hypotension study (42). Namely, patients in septic shock aged 65 years and older did not show a difference in mortality between the MAP group of 60-65 mm Hg and the control group (42). Although the target value of the MAP has been defined, this is not the case when it comes to elevated values. Specifically, the upper limit of the MAP is not clearly defined. Organ injury due to vasoconstriction and microcirculatory impairment may be caused by high levels of MAP (31). However, certain groups of patients, such as those with heart failure or with increased intra-abdominal pressure, may benefit from higher MAP values (31). This was confirmed through a trial that included patients with chronic hypertension, who probably have a wider range of autoregulatory mechanisms (43). When caring for patients in septic shock, vasopressors are recommended to achieve the target MAP. According to current guidelines and recommendations, „norepinephrine is the first-line agent over other vasopressors" (2). Norepinephrine is an alpha-1 and beta-1 adrenergic agonist that primarily acts at the vascular level, causing vasoconstriction and a consequent increase in MAP (2). It also has a positive effect on myocardial contractility and cardiac output, but with very little effect on heart rate. Early norepinephrine administration may be associated with better outcomes in septic patients. One important factor is reducing the applied volume, which reduces the risk of fluid overload (44). The results of „the CENSER trial" clearly showed a correlation between more successful control of shock and early administration of norepinephrine (45).

Certainly, an important part of discussing the use of norepinephrine in the ED is the route of administration. The peripheral venous route is the preferred method of initial administration when the central venous route is unavailable or delayed (2). In patients with septic shock in whom the MAP target value has not been achieved despite norepinephrine administration, the addition of vasopressin to therapy is recommended, rather than further increasing the dose of norepinephrine

Thus, we can consider it as the second drug of choice among vasopressors that cause vasoconstriction, but by acting on other receptors, the vascular V1 receptors of smooth muscle (46). The meta-analysis showed a lower incidence of arrhythmias, especially atrial fibrillation, but no lower mortality with norepinephrine and vasopressin combined, compared to norepinephrine alone (47). The VASST study is one of the key studies in which a group comparison was conducted: one group received only norepinephrine, and the other received vasopressin added to norepinephrine (48). It showed that adding vasopressin was associated with reduced norepinephrine requirements and reduced 28-day mortality in patients with less severe septic shock (26, 48). The use of vasopressin prevents an additional increase in norepinephrine dose and reduces overall adrenergic stimulation, but its effect on mortality is unclear (31).

Early vasopressor therapy, particularly norepinephrine, may help achieve the target MAP while limiting excessive fluid administration and the risk of fluid overload.

Epinephrine is commonly considered the third-line treatment; it is suitable for patients in whom norepinephrine and vasopressin have not achieved MAP target values (2). It can be administered as an adjunct drug to norepinephrine, just like vasopressin. Its use has been associated with side effects such as tachycardia and tachypnea, but it is very useful in patients with refractory septic shock with cardiac dysfunction due to its strong beta-adrenergic effect (38).

It has a strong effect on beta-adrenergic receptors, with a positive effect on cardiac dysfunction (2). Its use is associated with side effects, including tachyarrhythmias and increased lactate levels (37).

Patients in septic shock experience pronounced hypotension, which is one of the main factors determining their mortality (46). In a crucial effort to achieve the target MAP while starting with crystalloid solutions, vasopressors are the only additional therapeutic option. Several authors agree on the justification for their use in patients who are euvolemic/hypervolemic, or in those in whom there is no increase in MAP after the administration of the initial crystalloid bolus, for example, from 5 to 10 ml per kilogram (31,46).

Recent studies strongly suggest the importance of the early initiation of vasopressors to ensure the perfusion of target organs. The proposed time frame of many authors is within an hour of diagnosis (46). This early treatment may be associated with reduced volume overload and better overall outcomes (37).

Antimicrobial therapy

Immediately after recognition of sepsis, the key role in pharmacological treatment is the urgent initiation of empirical antimicrobial therapy, after appropriate microbiological samples are obtained. Depending on the clinical evaluation, these may include blood, urine, cerebrospinal fluid, tissue samples, or other fluids. When taking blood samples for blood culture, it is important to take two vials, for aerobic and anaerobic organisms, in each set (10).

In the initial assessment of a patient with suspected sepsis, it is necessary to consider other possible causes of the patient's condition. Biomarkers such as procalcitonin (PCT) can provide very limited help in clinical evaluation and diagnosis. PCT is often used to differentiate bacterial infections from other inflammatory conditions (49). Several recent studies have suggested that, in patients with unclear clinical presentations, it can play a useful role in deciding whether to initiate antibiotics (50-52). However, it is interesting to note that PCT, along with clinical assessment, is less effective than clinical assessment alone in the decision to initiate antimicrobial therapy (2). This is also the position expressed in the SSC guidelines, as a weak recommendation (2).

Early appropriate antimicrobial therapy is crucial in sepsis, particularly in septic shock, where each hour of antibiotic delay is associated with increased mortality

When it comes to patients with suspected septic shock or those with a high suspicion of sepsis, the answer to the question of when to start antibiotic therapy is actually clear. In these two groups of patients, appropriate antibiotic therapy should be started "immediately, ideally within an hour of recognition of their condition" (2). Several studies have shown an association between the increase in mortality and the subsequent use of antibiotics, especially in septic shock (53). A retrospective analysis by Liu et al, which included 35,000 septic patients, showed that every hour of delay in antibiotic therapy is associated with an increase in mortality, which is particularly pronounced in the subgroup of patients in septic shock (54). The association is less pronounced in sepsis patients without signs of shock (54, 55).

Observational studies suggest a possible increase in mortality when the time interval exceeds 3 to 5 hours (56, 57). Therefore, SSC recommendations indicate that in this group of patients, antibiotic therapy should be initiated no later than 3 hours after the suspicion of sepsis is established (2). This period is important for carrying out the necessary diagnostic tests, confirming or excluding sepsis, and diagnosing the source. The need for early antimicrobial therapy should be weighed against the potential for unnecessary use in patients without infection.

In certain conditions, such as necrotizing infection, peritonitis, and intestinal ischemia, urgent source control is necessary. In these patients, outcomes depend on the „time to source control" (58). It's key to implement source control urgently

after diagnosis, within 6 hours, or up to 12 hours in some studies (58, 59).

Clinical and epidemiological factors guide decisions on empirical antibiotic therapy and are often complex and challenging. This is especially true in the hectic, stressful environment of the ED, where, with the inevitable dispersion of attention to a large number of critical patients and often incomplete anamnestic data, it is necessary to assess the complete clinical picture at the right time and choose the right antibiotic. The decision depends on the suspected source, anamnestic data (previous isolates and antibiotic therapy), comorbidities, and local resistance data. In septic patients initially treated in the ED, the two most common sites of infection are the respiratory tract (43%) and the urinary tract (16%) (60, 61). This should also be borne in mind when the source of infection is not clear from the clinical examination alone, and further diagnostic measures are considered.

The representation of certain microorganisms in sepsis changes over time. The microorganisms most commonly associated with sepsis are bacteria.

With the increasing number of immunosuppressed patients, the importance of fungal sepsis, particularly Candida spp.-related sepsis, is growing (10). Choosing the right antibiotic is crucial. The correct choice of antibiotic therapy is associated with better outcomes (2). However, inappropriate antibiotic selection reduces sepsis survival (62). Initial empirical antibiotic therapy depends on the source of infection and the clinical characteristics of the individual patient. In each individual case, the choice of antibiotics is conditioned by the causative agent we suspect, the presumed infection, and the condition of the specific patient. It is recommended that the broad-spectrum coverage include the most common pathogens, i.e., Gram-positive and Gram-negative bacteria (2). The most commonly isolated bacteria in septic patients whose coverage with therapy must be considered include: „Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus, Streptococcus pneumoniae“ (63).

In the selection of antibiotic therapy, the SSC guidelines provide general recommendations that should be adapted to the specific environment and clinical situation. A common initial selection of broad spectrum antibiotics includes beta lactam antibiotics (64). These are carbapenem or piperacillin-tazobactam. Third- or higher-generation cephalosporins may also be used (44). Empirical antibiotic therapy may include a single antibiotic or may be a combination of two or more antibiotics.

The multidrug therapy concept is also part of the guidelines and clinical practice.

Combination antibiotic therapy is based on the assumed higher efficiency and more reliable sensitivity of pathogens to empirical treatment. May be associated with better outcomes (65). Monotherapy, on the other hand, is associated with a lower incidence of new infections, a lower toxic effect, and lower costs. Its possible disadvantage is the lack of action on multidrug-resistant agents. A number of studies compare monotherapy and antibiotics from two different groups. Interestingly, the results of a meta-analysis did not confirm the superiority of combination versus monotherapy in patients with gram-negative agents (66,67). However, in patients with septic shock and suspected Gram-negative sepsis, combination therapy is justified, i.e., the use of two types of antibiotics that act on Gram-negative bacteria (2). For critically ill patients with multidrug-resistant pathogens (MDR), empirical treatment with two antibiotics active against Gram-negative bacteria is recommended, whereas for patients with low MDR risk, a single agent is preferred (2,68).

A particular challenge is the treatment of patients suspected of methicillin-resistant Staphylococcus aureus (MRSA). The group at high MRSA risk includes those with soft-tissue infections, line infections, hemodialysis patients, nosocomial infections, immunosuppressed individuals, and those with prior MRSA infections (31). Some studies show an increase in mortality when more than 24 hours have elapsed before administering antibiotics that cover MRSA in patients with MRSA infection (69, 70). However, an increase in mortality is also possible in those with undifferentiated sepsis, and early treatment with antibiotics covering MRSA is initiated (71).

Antibiotic selection should be individualized according to the suspected source of infection, patient characteristics, previous microbiology, and local antimicrobial resistance patterns

The guidelines therefore recommend empirical antibiotic coverage for MRSA in patients with sepsis and septic shock at high MRSA risk, but not in those at low MRSA risk (2). In the ED, vancomycin or linezolid is usually additionally used for patients with highly suspected MRSA sepsis who require dual coverage. Piperacillin-tazobactam is recommended if anaerobic coverage is required; an alternative is a combination of cefepime and metronidazole (31). For patients with septic shock and a strong suspicion of Pseudomonas infection, dual antibiotic therapy may be appropriate.

Addition of a third- or fourth-generation cephalosporin or a carbapenem should be considered to a fluoroquinolone or an aminoglycoside (8).

It is necessary to monitor and adhere to local guidelines and protocols, as they account for local antibiotic availability and patterns of resistance. When caring for patients in septic shock, it is initially necessary to administer a loading dose of broad-spectrum antibiotics. Further dosage should be adjusted based on renal and hepatic function, and the need for further therapy should be considered immediately upon receipt of culture test results.

Adjunctive therapies

Corticosteroid therapy in sepsis is still partially controversial.

Its proposed benefits in patients with septic shock include reducing adrenal insufficiency and systemic inflammation (72). However, current studies do not provide clear evidence to support their use (31, 73, 74). Studies on hydrocortisone in septic shock have shown more days without vasopressor therapy and a shorter duration of shock, but no reduction in mortality (75, 76). Based on current knowledge, corticosteroid therapy is not routinely used in patients with sepsis, but it may have benefits in selected groups of patients, such as those in refractory shock.

A recent meta-analysis demonstrated a reduction in mortality among patients treated with a combination of hydrocortisone and fludrocortisone, which warrants further investigation (77). The „SSC 2021 Guidelines" advise against routine corticosteroid use in the initial treatment of septic shock (2). They recommend intravenous corticosteroids only if the MAP target is not reached despite vasopressor therapy (2). The recommended dose of hydrocortisone is 200 mg per day, administered intravenously in 50 mg doses every 6 hours (2, 26).

Sodium bicarbonate has been considered in the treatment of septic patients because they tend to develop metabolic acidosis or lactic acidosis through various pathophysiological mechanisms.

Their use in septic patients is truly controversial, with disagreements among experts about the justification and indications for use. The studies conducted did not provide clear answers to questions about the justification for their use. Without exogenous bicarbonate, with effective therapeutic action on establishing adequate perfusion (i.e., by addressing the underlying disorder that causes shock), the expected effect is the desired correction of metabolic acidosis. The use of exogenous bicarbonate in therapy is associated with potential adverse effects, including increased carbon dioxide partial pressure, accelerated lactate formation, and increased serum sodium concentration (78). The SSC 2021 guidelines advise „against the use of bicarbonate to improve haemodynamic values for patients in septic shock and hypoperfusion induced lactic acidemia" (2).

Corticosteroids are not routinely indicated in sepsis but may be considered in refractory septic shock, while bicarbonate therapy remains reserved for selected patients with severe metabolic acidosis and acute kidney injury.

In patients with severe lactic acidosis, vasodilation, reduced left ventricular contractility, and an impaired catecholamine response result in hemodynamic instability (79). Although the use of bicarbonate is controversial, most experts agree that it is recommended in patients with metabolic acidosis, when bicarbonate levels are below 6 mEq/L, and pH is below 7.1 (79-81).

Bicarbonate therapy is not advised for patients with mild acidosis unless they also have severe acute kidney injury (82). The recent randomised controlled study did not show an association of bicarbonate administration with a reduction in mortality or organ failure in patients with severe metabolic acidosis (82). However, in a subgroup of patients with AKI, a reduction in mortality and the need for renal replacement therapy was observed.

The SSC 2021 guidelines "suggest the use of bicarbonate in patients with septic shock and severe metabolic acidosis and acute renal injury", albeit with a low level of evidence (2).

Conclusion

Sepsis is a life-threatening condition, and treatment success is time-dependent. The mortality rate of these patients is high, especially when septic shock develops. Combining the basic elements of care for septic patients into a one-hour bundle has become a common approach in the emergency department. Despite widespread acceptance, it is associated with numerous challenges. It is still questionable to what extent their full application is possible in overcrowded and overloaded EDs. It is important to note that in patients with suspected sepsis in the ED, a broader differential diagnosis should be considered, and the probability of sepsis should be assessed; therefore, diagnostic testing should be expanded early if necessary. It is crucial to balance early recognition of sepsis with early initiation of goal-directed therapy, while also recognizing and treating any other acute disorder that is causing the patient's critical condition. Early recognition of sepsis, early use of the right antibiotic, and appropriate volume resuscitation, along with early vasopressor and other supportive measures, can lead to better outcomes for patients with sepsis.

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