

REVIEW ARTICLE / ПРЕГЛЕД ЛИТЕРАТУРЕ

Sepsis and septic shock – recognize early, act fast, treat right

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SUMMARY

Sepsis is a medical emergency and therefore requires early identification and immediate management, which is not a matter of hours, but minutes. Since the first definition in 1991, sepsis remains a major challenge for clinicians and scientists. Despite significant advances in technology and therapy, mortality and cost of treatment are unacceptably high. Septic shock is the leading cause of mortality in critically ill patients. Cognitive impairment and functional disability were observed after survivors' long-term follow-up.

Since its foundation in 2002, Surviving Sepsis Campaign aims to implement global strategies and to raise awareness of the challenges associated with sepsis. The implementation of guidelines and sepsis care bundles resulted in significant decrease in mortality. Hospital mortality is lower in hospitals with high versus low bundle compliance. Still, epidemiological data for sepsis are missing for low- and middle-income countries.

Keywords: sepsis; septic shock; Surviving Sepsis Campaign; sepsis bundle

INTRODUCTION

Sepsis and septic shock are life-threatening clinical syndromes due to dysregulated host responses to infection that cause organ hypoperfusion and dysfunction. Sepsis is a medical emergency, similar to polytrauma, acute myocardial infarction, and stroke, indicating that only early identification and appropriate immediate management lead to better outcomes. Septic shock is the main cause of mortality in critically ill patients [1, 2]. Mortality due to sepsis in the intensive care unit (ICU) is estimated at 30% [1, 2]. A recent study is the first to produce global estimates of sepsis incidence and mortality across 195 countries, including data from low-income and middle-income countries in the period 1990–2017. Estimated 48.9 million cases of sepsis resulted in 11 million deaths in 2017 [3]. These fascinating estimates are more than double previous global figures, which is probably due to the inclusion of more data from low-income and middle-income countries. Furthermore, cognitive impairment and functional disability were observed after long-term follow-up of survivors [4].

Since its foundation in 2002, Surviving Sepsis Campaign (SSC) aims to implement global strategies and sepsis bundle and to raise awareness of the challenges associated with sepsis. The results of the 12-year-long study of the SSC performance demonstrated a significant decrease in mortality rates of sepsis, and lower mortality in hospitals with higher bundle compliance [5].

DEFINITION AND CLINICAL CRITERIA

The diagnosis of sepsis still remains a major problem. The definition of sepsis has been changed over the time in order to include the most important criteria for early recognition of sepsis. The first definition, Sepsis-1, made in 1991, was based on the presence of systemic inflammatory response syndrome (SIRS) due to infection. Diagnostic performance of this definition was suboptimal since SIRS criteria failed to distinguish between uncomplicated infection and severe life-threatening infection leading to multiple organ dysfunctions. In 2001, Sepsis-2 definition showed high sensitivity, but low specificity [6]. On the Third International Consensus Conference in 2016, the new Sepsis-3 definition defined sepsis as life-threatening organ dysfunction due to a dysregulated host response to infection [7]. Septic shock is a subset of sepsis with underlying circulatory and cellular/metabolic abnormalities that substantially increase mortality [7].

Organ dysfunction in sepsis is identified as an acute change of ≥ 2 points in the total Sequential (Sepsis-related) Organ Failure Assessment (SOFA) criteria (Table 1) [2]. Sepsis-3 definition propose quick SOFA score (qSOFA) as easy bedside tool to screen patients with infection for those at risk of organ dysfunction and death. A “positive” qSOFA Score (≥ 2) suggests high-risk patients who should be thoroughly assessed for evidence of organ dysfunction and to increase frequency of monitoring.

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Table 1. Sepsis-related Organ Failure Assessment score

System		Score				
		0	1	2	3	4
Respiratory	PaO ₂ /FiO ₂ , mmHg (kPa)	≥ 400 (53.3)	< 400 (53.3)	< 300 (40)	< 200 (26.7) with respiratory support	< 100 (13.3) with respiratory support
Coagulation	Platelet, 10 ³ /μl	≥ 150	< 150	< 100	< 50	< 20
Liver	Bilirubin, mg/dl (μmol/l)	< 1.2 (20)	1.2–1.9 (20–32)	2–5.9 (33–101)	6–11.9 (102–204)	> 12 (204)
Cardiovascular	MAP (mmHg)	≥ 70	< 70	Dopamine < 5 or dobutamine (any dose) ^a	Dopamine 5.1–15 or epinephrine ≤ 0.1 or norepinephrine ≤ 0.1 ^a	Dopamine > 15 or epinephrine > 0.1 or norepinephrine > 0.1 ^a
Central Nervous System	Glasgow Coma Scale (GCS)	15	13–14	10–12	6–9	< 6
Renal	Creatinine, mg/dL (μmol/l)	< 1.2 (110)	1.2–1.9 (110–170)	2–3.4 (171–299)	3.5–4.9 (300–400)	> 5 (440)
	Urine output, mL per day				< 500	< 200

FiO₂ – fraction of inspired oxygen; PaO₂ – partial pressure of oxygen; MAP – main arterial pressure; ^acatecholamine doses are given as μg/kg/min. for at least one hour

Comparing qSOFA and SIRS, qSOFA is superior to the SIRS criteria regarding content validity and feasibility, especially outside the ICU because no laboratory tests are required (Table 2) [8].

Table 2. Systemic Inflammatory Response Syndrome (SIRS) and quick Sepsis-related Organ Failure Assessment (qSOFA) score

Parameters	SIRS	qSOFA
Body temperature (C°)	< 36 or > 38	
Heart rate (beats/min)	> 90	
White blood cell count (10 ³ /μL)	> 12 or < 4 or > 10% immature bands	
Respiratory rate (breaths/min)	> 20	≥ 22
Systolic blood pressure (mmHg)	-	≤ 100
Glasgow Coma Scale	-	< 13 or abnormal mental status

Two or more parameters for positive SIRS and qSOFA score

Zhang et al. [8] tested the predictive validity of SIRS criteria in patients in the Sepsis-3 cohort and concluded that the increase in the SOFA score of 2 or more has greater prognostic significance for in-hospital mortality than SIRS or qSOFA score [7, 8].

INITIAL RESUSCITATION

Numerous studies and protocols showed that the successful management in septic shock is not the matter of hours, but minutes. In addition, SSC implemented a new “sepsis bundle” in 2018 which combined the previous three hour and six hour bundles into the single one “one hour bundle” [9]:

1. Measure lactate level; re-measure if the initial lactate is > 2 mmol/L;
2. Obtain blood cultures prior to antibiotics administration;
3. Administer broad-spectrum antibiotics;

4. Begin rapid administration of 30 ml/kg crystalloid for hypotension or lactate ≥ 4 mmol/L;
5. Apply vasopressors if the patient is hypotensive during or after fluid resuscitation to maintain MAP ≥ 65 mmHg.

Until 2016 SSC guidelines, early goal-directed therapy (EGDT), has been a key strategy for the resuscitation of patients with septic shock. According to EGDT protocol, initial resuscitation in the first six hours with intravenous fluids, vasopressors, inotropes, and blood transfusions are adjusted to reach pre-defined “goals” of central venous pressure, central venous oxygen saturation, mean arterial pressure (MAP) and urine output. Although this protocol was based on a single-center study, published by Rivers et al. [10] in 2001, this algorithm has changed the standards of sepsis treatment in the world.

After almost 15 years, the three large multicenter randomized controlled studies, the Protocolized Care for Early Septic Shock trial, the Australasian Resuscitation in Sepsis Evaluation trial, and the Protocolised Management In Sepsis trial, were conducted in order to test the accuracy of the Rivers protocol [11, 12, 13]. Studies compared the clinical outcomes of patients presenting with early septic shock in the emergency department with strict EGDT to patients with protocol-based standard therapy. All patients received early antibiotic therapy and appropriate hemodynamic management. Studies showed that EGDT is safe, and no harm was associated with interventional strategies. Yet, this protocol could not be recommended from its evidence base, since the cohort in the study by Rivers et al. [10] was unrepresentative (older and more severely ill patients, with higher initial serum lactate level on admission and higher mortality: 42% vs. 10–20%) compared to control group patients from the three recent studies.

According to current guidelines, initial resuscitation during the hyperdynamic phase of septic shock begins with rapid administration of 30 ml/kg crystalloid solution in order to increase oxygen delivery during circulatory failure. Reevaluation of the response to treatment should start with clinical

examination and physiological variables, such as heart rate, blood pressure, arterial oxygen saturation, respiratory rate, temperature, urine output, among others. Guidelines suggest that dynamic variables (passive leg raising, stroke volume measurements, pulse pressure variation) should be used rather than static, in order to predict fluid responsiveness [2, 9]. Growing literature suggested that bedside lung ultrasound can be useful in fluid resuscitation [14, 15].

The SSC recommends targeting MAP of at least 65 mmHg to maintain critical organs perfusion in patients with septic shock requiring vasopressors. However, studies showed that in certain subgroups of patients (older than 75 years and patients with chronic kidney disease) higher MAP (75–80 mmHg) is associated with lower hospital mortality rate and reduced need for renal replacement therapy [16, 17]. On the other hand, aiming to achieve a higher MAP may be harmful due to the significantly higher risk of arrhythmias and excessive vasopressor use [16].

Randomized controlled trials (RCTs) demonstrated that lactate-guided resuscitation therapy showed significant reduction in mortality in ICU patients [18, 19]. However, serum lactate level is not a direct measure of tissue perfusion and may be increased not only in anaerobic glycolysis due to hypoperfusion, but also in other conditions that accompany critically ill patients. For example, accelerated aerobic glycolysis where pyruvate production overcomes the capacity of pyruvate dehydrogenases occurs as a response to cytokine release, excess beta-adrenergic stimulation, or the accumulation of leukocytes at the site of inflammation.

After the resuscitation phase, during the optimization phase, the goal is to maintain adequate tissue perfusion. In addition, cautious titration of fluids with reassessment of hemodynamic status aimed to avoid fluid overload is mandatory. A recent multicenter study showed that 40% of septic shock patients experienced fluid overload defined as a body weight 10% higher than the baseline [20].

ANTIMICROBIAL THERAPY

One of the main determinants for sepsis and septic shock outcome is early systemic administration of appropriate antibiotic therapy. International guidelines recommended empiric antimicrobial therapy in the first hour of recognizing sepsis [2]. Cultures must be obtained before antibiotic administration with at least two sets of samples (aerobic and anaerobic).

In 2006, a retrospective study by Kumar et al. [21] showed correlation between increased survival in adults with septic shock and effective antimicrobial administration within the first hour of documented hypotension. According to this study, only 50% of septic shock patients received appropriate antimicrobial therapy within six hours of documented hypotension. Additionally, each hour delay in the administration of antibiotic is associated with an increase in mortality. Systematic review with meta-analysis of 70 prospective cohort studies assessing the effects of appropriate empirical antibiotic treatment on mortality showed overall, 46.5% of patients were given inappropri-

ate empirical antibiotic treatment [22]. Mortality was significantly higher with inappropriate empirical treatment.

The initial empirical regimen should be broad enough to cover all assumed pathogens [2]. Selection of antibiotics is very complex depending on the patient's medical history, clinical status, and local epidemiological map. Key patient factors include the nature of the site infection, concomitant underlying diseases, chronic organ failures, indwelling devices, the presence of immunosuppression, recent known infection, or colonization with a specific pathogen and recent administration of antimicrobials. Patients with neutropenia represent a subgroup of patients at risk for infections with atypical or resistant gram-negative bacilli and *Candida* species. In addition, patients with nosocomial infections and prolonged use of antibiotic can develop sepsis with methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococci*. Clinicians should also consider risk factors for multi drug resistant pathogen (*Pseudomonas*, *Acinetobacter*, *Klebsiella*) when deciding about the empirical antibiotic treatment.

Broad-spectrum carbapenem or extended-range penicillin/ β -lactamase inhibitor combination (meropenem, imipenem/ cilastatin or doripenem) or extended-range penicillin/ β -lactamase inhibitor combination (piperacillin/tazobactam or ticarcillin/clavulanate) or third- or fourth-generation cephalosporin is commonly used [2]. Vancomycin, teicoplanin, or another anti-MRSA agent can be added when risk factors for MRSA is present [23]. The anti-fungal agent should be considered in immunocompromised status (neutropenia, chemotherapy, transplant, diabetes mellitus), prolonged invasive vascular devices, total parenteral nutrition, necrotizing pancreatitis, and prolonged administration of broad-spectrum antibiotics.

Current guidelines suggest empiric combination therapy (using at least two antibiotics of different antimicrobial classes) for the initial management of septic shock [2, 23]. However, it is not recommended to be routinely used for most other serious infections, including bacteremia and sepsis without shock [2].

Dose-optimization should be based on antibiotic pharmacokinetic/pharmacodynamic (PK/PD) principles and specific drug properties in critically ill patients with sepsis and septic shock. Variety of conditions in critically ill (unstable hemodynamic, increased cardiac output, increased extracellular volume, variable kidney, and hepatic perfusion, reduced serum albumin), alter antimicrobial PK, affecting volume of distribution, drug clearance, drug binding. In addition, assessment of optimal antimicrobial dosing is individual and very demanding. Antimicrobial stewardship programs are recommended in order to help clinicians with antibiotic management and reduction of antimicrobial resistance.

Time-dependent antibiotics require drug concentrations greater than the minimum inhibitory concentration for a certain period between doses, which usually ranges 40–50% (for piperacillin/tazobactam 100%) of the inter-dose interval for their best action [24]. Experiments showed that the PK/PD target could be achieved only with extended or continuous infusion. Several clinical trials published

in recent years have assessed the benefit on continuous infusions over extended infusions for beta-lactam antibiotics. Although the data are not entirely consistent, recent meta-analysis of RCTs demonstrated protective effect of continuous therapy [25].

For vancomycin, it is suggested loading dose of 25–30 mg/kg (actual body weight) to rapidly achieve target plasma concentration [23]. Pre-dose monitoring of trough concentration of vancomycin is recommended. For aminoglycosides, concentration-dependent antibiotics, peak drug plasma concentrations should be attained with once daily dosing (i.e. 5–7 mg/kg daily gentamicin). Comparable studies showed decrease renal toxicity with this regimen compared to multiple daily dosing [26].

Empiric antimicrobial therapy should be narrowed when the pathogen is detected, and sensitivities are determined. Criteria for early de-escalation of antimicrobial therapy can be based on clinical progress, infection resolution as indicated by biomarkers, especially procalcitonin, and a relatively fixed duration of combination therapy. Although high-quality data on clinically driven de-escalation are limited, unnecessarily prolonged antimicrobial therapy is certainly associated with adverse effects (i.e. *Clostridium difficile* colitis). Studies have shown that daily assessment for de-escalation of antimicrobial therapy may be associated with improved mortality rates [27].

Current guidelines recommended 7–10 days antimicrobial treatment for most serious infections; however, longer treatment is necessary for patient with slow clinical response, undrainable focus of infection, bacteremia with *S. aureus*, some fungal and viral infection, or immunologic deficiencies [2]. Serum procalcitonin levels (together with clinical response) should be used for de-escalation of antibiotic therapy [28].

SOURCE CONTROL

Rapid source control should be performed as soon as possible following initial resuscitation [29]. Intra-abdominal infection along with necrotizing soft tissue infection and implanted device infection, are the sites where a rapid source control seems more feasible (drainage of infected collection, debridement of infected solid tissue, removal of devices, catheters or foreign bodies). Surgery gives an opportunity to take the first local microbiological samples.

VASOACTIVE MEDICATIONS

Norepinephrine is recommended as the first line vasopressor in septic shock [2]. The dosage may range 5–20 µg/min, and it is not based on the weight of the patient [30]. Data from the recent literature are in favor of early initiation of vasopressors during septic shock in order to prevent deep and durable hypotension. Moreover, early administration of norepinephrine in septic shock was significantly associated with lower rate of cardiogenic pulmonary edema and new-onset arrhythmia [30].

Recent systematic review and meta-analysis do not support routine use of dopamine since norepinephrine is more potent, reduces risk of tachycardia and arrhythmia, and therefore results in lower mortality compared to dopamine [31]. SSC guidelines suggest adding low dose vasopressin (up to 0.03 U/min) or epinephrine to norepinephrine in order to achieve target MAP and to decrease norepinephrine dosage [2].

Septic shock is a distributive shock, but it is important to think of combined cardiac dysfunction even in the early stages of disease. Inotropic agents should be considered if inadequate cardiac output is present.

CORTICOSTEROIDS AND METABOLIC RESUSCITATION PROTOCOL

The use of corticosteroids was controversial over the years. The large multicenter Adjunctive corticosteroid treatment in critically ill Patients With Septic Shock study showed shorter durations of shock and ICU stay in the glucocorticoid group compared with the placebo group [32]. Meta-analysis of 42 RCTs showed that corticosteroids result in small reduction in mortality in critically ill patients but increase the risk of neuromuscular weakness [33].

The retrospective study by Marik et al. [34] demonstrated that the administration of intravenous vitamin C, hydrocortisone, and thiamine is successful in preventing progressive organ dysfunction, especially acute kidney injury and even decreased mortality in patients with septic shock [34, 35]. However, further trials are needed to determine whether this metabolic resuscitation protocol can be recommended as a treatment for septic shock.

ACUTE RESPIRATORY DISTRESS SYNDROME / MECHANICAL VENTILATION

Acute respiratory distress syndrome (ARDS) is one of the most frequent organ dysfunction due to sepsis [36]. The mortality in this patient group is assessed to be as high as 40% [37]. ARDS is defined as a loss of aerated lung tissue as a result of edema and atelectasis, with reduced respiratory system compliance and impaired gas exchange. Mechanical ventilation and concept of protective lung strategy with reduction of tidal volume (VT) is imperative in the management of ARDS [38, 39]. Low VTs (4–6 ml/kg of predicted body weight) aim to maintain end-inspiratory plateau pressure, PPLAT ≤ 30 cmH₂O in order to prevent alveolar overdistension. Several meta-analyses supported Lachmann's "open lung concept" with higher levels of positive end-expiratory pressure to avoid collapse and reopening of alveolar units, combined with protective VTs [39]. Furthermore, the use of inspiratory pressure to open up atelectatic lung regions and end-expiratory pressure (so-called recruitment maneuvers), showed beneficial effect on the outcome, without increasing the risk of barotrauma [38, 39].

According to actual guidelines, prone position and extracorporeal membrane oxygenation are reserved only for

selected cases of severe ARDS (P/F ratio < 20 kPa) [36, 38]. By contrast, high frequency oscillation and inhaled nitric oxide are not recommended. Future investigations are suggested for corticosteroids and extracorporeal CO₂ removal [39]. Reported pilot study from Strategy of Ultra-Protective lung ventilation with Extracorporeal CO₂ Removal for New-Onset moderate to severe ARDS showed promising results with the strategy of ultra-protective lung ventilation (VT of 4 ml/kg predicted body weight and PPLAT ≤ 25 cmH₂O) and extracorporeal CO₂ removal to prevent severe respiratory acidosis [40]. According to LUNG safe study, non-invasive ventilation is associated with higher mortality in ARDS with P/F ration lower than 150 mmHg [41]. A fluid-conservative strategy to minimize fluid infusion and weight gain in patients with ARDS is associated with better outcome [36].

NUTRITION

Based on expert consensus, early enteral nutrition within 24–48 hours is standard for critically ill patients [2]. Early enteral nutrition should be initiated as soon as possible, right after initial resuscitation, taking care of gastrointestinal intolerance. According to the latest European Society for Clinical Nutrition and Metabolism guidelines, trophic feeding (defined as 10–20 kcal/h or up to 500 kcal/d) is recommended for the initial phase of sepsis advancing as tolerated after 24–48 hours to > 80% of target energy goal over the first week [42]. The delivery of 1.2–2 g protein/kg/d is suggested. Parenteral nutrition is more invasive, associated with greater risks and rates of complications.

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Due to the bacterial translocation mechanism, parenteral nutrition is associated with more infection than enteral nutrition [42]. Parenteral nutrition is reserved only for patients where enteral route is not possible or as addition to enteral nutrition to achieve full caloric support.

OTHER SUPPORTIVE THERAPIES

The current guidelines for transfusion and blood products management, stress ulcer prophylaxis, venous thromboembolism prophylaxis, renal replacement therapy, and immunoglobulins did not change significantly between the two revisions of SSC bundle [2, 43]

CONCLUSION

Sepsis is a clinical syndrome associated with high incidence, high mortality, and high cost of treatment. In order to reduce mortality and improve patients' outcomes, early recognition of sepsis and appropriate immediate management during the initial hour is of utmost importance for clinicians. The main goal of SSC is dissemination of evidence-based guidelines worldwide. However, new large multicenter trials are needed to develop further protocols. Development of new therapeutic agents and novel extracorporeal devices for multiple organ support are likely to be essential to further improve the outcome of patients with sepsis.

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Сепса и септични шок – рано препознај, брзо делуј, лечи исправно

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САЖЕТАК

Сепса је ургентно стање па стога захтева рано препознавање и што хитније спровођење терапијских поступака већ у првим минутима. Од прве дефиниције из 1991. године до данас сепса је остала главни изазов за клиничаре и научнике. Упркос напретку у технологији и терапији, смртност и трошкови лечења су неприхватљиво високи. Септични шок је главни узрок смрти критично оболелих болесника. После дугорочног праћења исхода преживелих запажени су когнитивно оштећење и функционална онеспособљеност.

Од свог оснивања 2002. године, Кампања за преживљавање сепсе има за циљ примену стратегија и подизање свести о изазовима повезаним са сепсом широм света. Имплементација препорука и мера за хитно збрињавање болесника довела је до значајног смањења mortalитета. Ипак, проблем представљају земље средњег и ниског економског развоја где не постоје ни тачни епидемиолошки подаци о сепси.

Кључне речи: сепса; септични шок; ургентно стање; препоруке