



# SEPSIS DEFINITION: WHAT'S NEW IN THE TREATMENT GUIDELINES

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**SUMMARY** – Sepsis is a life-threatening organ dysfunction caused by an unregulated response of a host. Septic shock is its most severe form. It is manifested by a drop in blood pressure, which decreases tissue perfusion pressure, causing hypoxia that is characteristic of shock. Sepsis is still one of the leading causes of mortality worldwide. Its incidence has increased since the first consensus definitions were established in 1991. Raising sepsis awareness, its significance and the need for better treatment, has led to an improvement in defining sepsis and the development of guidelines for its treatment. The first guidelines were published in 2004, the second 2008, the third 2013, the fourth 2016, and the last revised guidelines appeared in 2021. This paper will describe the previous and new definitions of sepsis and septic shock, the previous guidelines for the recognition and treatment, and the latest recommendations for treatment. Timely diagnosis is crucial for the outcomes for patients with sepsis and septic shock. The fact is that the sepsis care bundles have been modified to increasingly shorter time determinants, which emphasizes the importance of emergency physicians, who frequently first recognize and begin emergency treatment of septic patients.

*Key words: sepsis, septic shock, treatment, definition, bundles*

## Introduction

Sepsis is often the immediate cause of death of critically ill patients in an intensive care unit (ICU). It is still one of the leading causes of morbidity and mortality in the world. The incidence of sepsis and septic shock has been steadily increasing since the first consensus definition in 1991. The appropriate definition of sepsis also plays a role in correct and rapid recognition. Research has shown that early identification and timely care of patients has the greatest impact on reducing mortality. Until recently, sepsis was defined as a clinical syndrome that manifests as a systemic inflammatory response syndrome (SIRS) to infection. How-

ever, there are no specific clinical, imaging or biochemical indicators to indicate this condition. The non-specificity of the signs of SIRS, on which the definition of sepsis was based, was the reason for a significant discrepancy in the presentation of the incidence and mortality of sepsis in epidemiological studies. The latest redefinition of sepsis (2016), which highlights the host's inadequate response to infection, makes it easier to recognize sepsis in daily clinical practice. The results of scientific research demonstrate that the incidence of sepsis is increasing, but thanks to the efforts of the Surviving Sepsis Campaign (SSC) and the development of guidelines or recommendations in the form of bundles for the treatment of sepsis, there has been a reduction in mortality. However, the total number of deaths due to sepsis is still rising, as more people are getting sick. The sepsis care bundles are a set of evidence-based components that, if implemented togeth-

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er, can lead to a better treatment outcome than if applied individually.

### How the definition of sepsis has changed over time

The first definition of sepsis dates to 1992 and was the result of an agreement among world experts in the field of intensive care. Sepsis is defined as the systemic immune response syndrome (SIRS). In addition to sepsis, the term severe sepsis is defined as sepsis associated with organic dysfunction, hypoperfusion and hypotension, and the term septic shock as a condition of sepsis with arterial hypotension insensitive to fluid replacement. The diagnosis of sepsis was based on the presence of a suspected infection and clinical or microbiological evidence of infection in the presence of at least two of the four systemic inflammatory response criteria (SIRS). The following SIRS criteria were established: body temperature above 38 ° C or below 36 ° C, heart rate greater than 90 beats per minute, respiratory rate greater than 20 beats per minute or carbon dioxide partial pressure below 4.3 kPa, and neutrophilia above 12000 / mm<sup>3</sup> or neutropenia below 4000 / mm<sup>3</sup> with 10% or more of non-segmented peripheral blood neutrophils.<sup>1</sup> Severe sepsis is sepsis with organic dysfunction, hypoperfusion or hypotension. Septic shock is sepsis-induced hypotension despite adequate fluid resuscitation in the presence of perfusion abnormalities. The first definition of sepsis was not specific enough to distinguish sepsis patients from those patients who had a normal inflammatory response to infection or an inflammatory condition not caused by infection.

To improve the diagnosis of sepsis, in 2001 the definition of sepsis was supplemented by an expanded list of clinical and laboratory indicators that made it easier for clinicians to diagnose sepsis<sup>2</sup>. According to this definition, septic patients are grouped according to the severity of the clinical condition. Sepsis is classified as a clinical syndrome ranging from septicemia to severe sepsis followed by the failure of vital organ function and septic shock as the most severe form of sepsis, in which deep hypotension is the dominant sign<sup>2</sup>. The new definition has not yet solved the problem of "specificity," but the incidence of sepsis and septic shock has increased significantly. The reason is the higher number of patients with many associated dis-

eases, a higher proportion of those who are immunocompromised, but also the lack of specificity of the definition according to which the group of patients with sepsis includes those patients with uncomplicated infection or mild cold.<sup>3,4</sup> On the other hand, following these guidelines provides sufficient time for timely detection of sepsis and early inclusion of valid therapy, which is extremely important in preventing the progression of this condition to severe sepsis, and especially septic shock, which is accompanied by significantly higher mortality rates<sup>5</sup>.

The third redefinition of sepsis was made in 2016.<sup>6</sup> Due to the already mentioned insufficient specificity of the existing (old) definition of sepsis, there was a need for a new definition that would be more specific than the previous one and allow easier recognition of sepsis in everyday clinical practice. It is based on the pathobiology and pathophysiology of the host's response to infection, which is described as "non-homeostatic." The most important changes are the elimination of the terms "SIRS" and "severe sepsis." Sepsis is now defined as a life-threatening organ failure caused by the host's inappropriate response to infection. Organ failure is now considered if there is a change in sequential, sepsis-related organ failure assessment (SOFA), where two points or more are associated with a hospital mortality rate greater than 10%. Septic shock is defined as a subtype of sepsis, and is manifested by circulatory, cellular, and metabolic instability associated with a higher risk of death than sepsis itself. The criteria for diagnosing septic shock are: hypotensions requiring vasopressor therapy to maintain mean arterial pressure >65 mmHg and serum lactate levels greater than 2 mmol/L after appropriate management of hypovolemia. This combination is associated with a hospital mortality rate of more than 40%. To avoid delays in the start of treatment for patients who are placed outside the ICU, a new simplified version of the SOFA scale has been designed - a fast SOFA scoring system called quick SOFA (qSOFA). It is recommended for rapid diagnosis in outpatients and emergency hospital admissions for patients with suspected infection and sepsis. The qSOFA scale assesses the patient's mental, cardiovascular and respiratory status. The criterion for hypotension is systolic pressure <100 mmHg, for tachypnea respiratory rate >22 breaths per minute and Glasgow coma scale (GCS) <15. They emphasize that qSOFA does not de-

fine sepsis but allows rapid identification of all patients at potential risk of sepsis because it is an indicator of an increased risk of clinical deterioration.<sup>7</sup> The key advantages of qSOFA are that it is easy to measure and does not require laboratory testing. It can be performed quickly and repeatedly.

### Previous sepsis survival campaign recommendations

Despite significant advances in understanding pathophysiology and supportive treatment options, mortality from sepsis and septic shock remains very high. It is estimated that one in five patients diagnosed with sepsis dies. Mortality is also high in patients in whom transient improvement is achieved through intensive treatment, and the reason for this is most often complications associated with existing diseases or irreversible impairment of the function of one of the vital organs<sup>3,8,9</sup>. Sepsis and septic shock have been identified as important public health issues, prompting intensive care professionals to develop guidelines, the SSC, that could guide clinicians in treating septic patients. The campaign to introduce the guidelines was initiated at a meeting in Barcelona, based on all previous guidelines based on evidence and renewed research on more than 30,000 patients<sup>10</sup>. The main idea was to define global criteria for early detection of sepsis with recommendations for the implementation of certain therapeutic procedures in order to improve their effectiveness and reduce mortality by 25% over five years. The guidelines have undergone many changes over the years as part of the latest clinical research and new pathophysiological findings on sepsis. The first original guidelines were published in 2004<sup>3</sup>, and have been updated and supplemented on several occasions to date in 2008, 2012, 2016 and 2018. The last renewal and amendment of the SSC was performed in 2021. Evidence based methodology was used in the renewal of the guidelines.

The first SSC guidelines from 2004 included two bundles called “Sepsis resuscitation bundle” and “Sepsis management bundle” for the care of patients who had to be completed as soon as possible within 6 hours and 24 hours, respectively. The 6-hour initial care package included serum lactate extraction, exclusion of blood culture samples, administration of broad-spectrum antibiotics within 3 hours of hospital admission,

hypotension or serum lactates  $>4$  mmol / L fluid replacement 20 ml / kg, and the introduction of vasopressor support at MAP  $<65$  mmHg despite fluid replacement. It was recommended that central venous pressure  $>8$  mmHg be maintained in persistent hypotension (septic shock) despite fluid and / or lactate replacement  $>4$  mmol / L. The 24-hour beam included GUK glycemic control  $<8.3$  mmol / L, peak pressure  $<30$  cm H<sub>2</sub>O in patients on mechanical ventilation, steroid use in patients on continuous vasopressor therapy, and recombinant human activated protein C (rhAPC).

The second edition of the 2008 amended guidelines incorporated the previous two bundles for the management of sepsis and septic shock with minimal changes, but now with incorporated recommendations for clinicians. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system has been adopted, which is a link between clinical research and everyday practice and describes the levels of recommendations with the strength of evidence.<sup>11</sup>

The SSC campaign updated and revised the sepsis guidelines in 2012.<sup>12</sup> The update introduced several important changes to recommendations important for the treatment of severe sepsis and septic shock in emergency departments. The guidelines have been changed to a “3-hour bundle” and a “6-hour bundle” with similar elements but recommends that interventions be carried out in a shorter period of time. The 3-hour bundle requires: measurement of serum lactates, exclusion of blood culture samples prior to antibiotic administration, broad-spectrum antibiotic administration, and crystalloid replacement of 30 ml / kg for hypotension or serum lactates  $\geq 4$  mmol / L. within 3 hours of patient triage. The 6-hour bundle recommends the use of vasopressor support for hypotension that does not respond to initial fluid resuscitation or lactate  $\geq 4$  mmol / L. The guidelines advise measuring central venous pressure and oxygen saturation of venous blood. They also recommend re-measuring lactate if initial lactate levels are  $\geq 4$  mmol / L. The 24-hour bundle is no longer recommended.

Following the redefinition of sepsis in 2016,<sup>4</sup> a new updated edition of the SSC recommendations was published. According to the 2016 guidelines, sepsis and septic shock are emergencies and treatment should be started as early as possible, immediately after the

presentation of a patient with sepsis or septic shock criteria.<sup>6</sup> Thirty-two-strong recommendations, 39 weak recommendations, and 18 best practice statements were published. The 3-hour and 6-hour bundles were revised or remained the same but with the elimination of central venous pressure measurements and venous blood oxygen saturation. In the case of sepsis accompanied by severe hypotension, the guidelines require aggressive volume compensation (administration of 30 ml / kg intravenous crystalloid solution within the first three hours). Prior to initiating antimicrobial therapy, at least two blood samples should be taken for blood cultures, and empirical administration of one or more broad-spectrum antimicrobial drugs should be initiated to address all possible causes. If the patient's clinical condition indicates septic shock, antimicrobial drugs should be administered within one hour. If hemodynamic stabilization is not achieved with volume compensation, vasoactive support should be included. Noradrenaline is recommended as the first-choice vasopressor. If the expected therapeutic effect of noradrenaline is absent (a target mean arterial pressure of 65 mmHg or more), adrenaline or a combination of vasopressin and adrenaline or vasopressin alone may be added to reduce the noradrenaline dose. Dopamine has been used as a good substitute for norepinephrine according to the updated guidelines, but only in patients at low risk for tachyarrhythmias. The use of corticosteroids has been recommended in patients with septic shock whose volume resuscitation and vasopressor support have not achieved hemodynamic stability. Appropriate mechanical support should be used in patients with sepsis failure. Protective ventilation is recommended, so that the target inspiratory volume does not exceed 6 ml / kg. Also, using the SOFA identify patients with sepsis to more quickly, a new "qSOFA" scoring system is proposed for quick screening of patients outside the ICU who are at risk of developing sepsis.<sup>7</sup>

With the revision of the SSC guidelines in 2018, 3-hour and 6-hour bundles are combined into a revised Hour -1 bundle with the intention of starting the care for septic patient's immediately<sup>12</sup>. It takes more than an hour to complete all recommendations, but it is crucial to start all treatment recommendations immediately. Zero time is defined as the time of triage in the emergency department or from the time the sepsis criteria are recorded in the medical documents.

The new 1-hour bundle includes 5 steps: measurement of serum lactates, and re-measurement in 2-4 hours if  $\geq 2$  mmol / L, exclude blood cultures before antibiotics, administration of broad-spectrum antibiotics, volume resuscitation 30 ml / kg in case of hypotension or if lactate  $\geq 4$  mmol / L and vasopressor administration in hypotension during or after volume replacement to maintain MAP  $\geq 65$  mmHg.

### Latest SSC guidelines

The fourth updated SSC campaign guidelines were published in 2021.<sup>13</sup> They include recommendations for recognition and early care, source diagnosis and treatment of infection, hemodynamic care, ventilation, and additional therapeutic treatment recommendations. A new strong recommendation in the guidelines is the use of programs and tools like qSOFA, National Early Warning Result (NEWS), and Modified Early Warning Result (MEWS)) to improve care, including recognition in the populations of acutely ill and high-risk patients. It is recommended that qSOFA not be used as the only method for recognizing sepsis and septic shock, without SIRS, NEWS or MEWS. MEWS is a simple physiological result that helps to improve quality and safety in patient care. Five physiological parameters are measured: respiratory rate, systolic blood pressure, heart rate, level of consciousness and body temperature. NEWS is a scoring system for physiological measurements that are routinely recorded next to the patient's bed. Its purpose is to identify acutely ill patients, including those with sepsis. It measures six physiological parameters and evaluates values from 0 to 3: respiratory frequency, oxygen saturation, systolic blood pressure, pulse rate, neurological level of consciousness and body temperature. The guidelines emphasize that a systematic screening process is key to early identification of patients with sepsis.

For patients with sepsis-induced hypoperfusion or septic shock, we suggest that at least 30 mL/kg of IV crystalloid fluid should be given within the first three hours of resuscitation. The recommendation has now been moved from a strong to a weak recommendation level (caution in patients with heart failure and kidney disease). It is also recommended to lower serum lactate levels (weak recommendation), and an additional new recommendation (weak) is to monitor capillary filling to assess tissue perfusion.

If septic shock is suspected, it is recommended to use antimicrobial drugs immediately or within one hour of recognition (weak recommendation), and if sepsis is suspected without shock, consider non-infectious causes but administer antimicrobials within three hours from the time recognition of sepsis (weak recommendation). It is recommended to exclude microbiological samples before initiating therapy. In patients with suspected sepsis / shock but without confirmation of infection, continuous reevaluation and research of alternative diagnoses is recommended, as well as discontinuation of empirical antibiotic therapy if there is a suspicion of a cause other than infection (best practice statement), because 1/3 of patients with suspected sepsis eventually have a non-infectious disease.

For hemodynamic resuscitation, the use of balanced crystalloids instead of saline is recommended. The old guidelines recommended balanced crystalloids or saline. The use of albumin is recommended in patients who have received a large volume (moderate level), and the use of hydroxyethyl starch or gelatin is not recommended (strong recommendation). For septic shock on vasopressors, an initial target mean arterial pressure (MAP) of 65 mm Hg **over** higher MAP targets is recommended (strong recommendation). The new recommendation is to initiate vasopressor therapy peripherally to restore mean arterial pressure, rather than delaying onset until central venous access is provided (weak recommendation). Noradrenaline is still the vasopressor of first choice (high level of evidence). In the absence of the expected therapeutic effect of norepinephrine (target mean arterial pressure of 65 mmHg or more), vasopressin may be added to reduce the dose of norepinephrine (moderate level). As a third line alternative, adrenaline (weak recommendation) may be added. For shock with cardiac dysfunction and persistent hypoperfusion despite adequate volume status, the use of dobutamine in addition to norepinephrine is recommended (weak recommendation). The new guidelines suggest that levosimendan not be used. There is insufficient evidence to recommend a restrictive versus a liberal approach to fluid replacement during the first 24 hours of treatment in patients with sepsis / shock who continue to show signs of hypoperfusion and volume depletion.

New guidelines for sepsis-induced respiratory failure recommend the use of high flow nasal oxygen (HFNO) over noninvasive ventilation (NIV) (weak recommendation). Another new recommendation is

that in severe acute respiratory distress syndrome caused by sepsis, the guidelines suggest the use of venous extracorporeal membrane oxygenation when conventional mechanical ventilation fails in experienced centers with infrastructure supporting its use.

The guidelines suggest that vitamin C should not be used to treat sepsis or septic shock (weak recommendation). The use of hemoperfusion with polymyxin B is not recommended (weak recommendation) and there is insufficient evidence for other blood purification techniques. It is recommended that corticosteroids be administered to patients in septic shock who require vasopressor therapy (weak recommendation) in a dose of hydrocortisone 200 mg / day, 50 mg every six hours or as a continuous infusion. In 2016, there was insufficient evidence for their use if hemodynamic stability was achieved by volume or vasopressor support. For suspected sepsis or septic shock, they suggest against using procalcitonin plus clinical evaluation to decide when to start antimicrobials, compared to clinical evaluation alone (weak recommendation). New guidelines for the first time place increased emphasis on improving care for sepsis patients after they are discharged from the intensive care unit. Recommendations for survivors of sepsis or septic shock include assessment and follow-up for physical, cognitive, and emotional problems after hospital discharge.

## Conclusion

The incidence of sepsis is still on the rise, although data from sepsis campaign efforts have shown some positive results. Further education and dissemination of knowledge that sepsis must be treated as a medical emergency is needed. The fact that the bundles for the care of septic patients have changed with their revision to shorter and shorter time determinants emphasizes the importance of emergency physicians as the first to recognize and begin emergency resuscitation and treatment for septic patients. Education, further clinical research, and adherence to recommendations and guidelines are important both in treatment and in further efforts to reduce mortality.

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## Sažetak

### DEFINICIJA SEPSE: "ŠTO JE NOVO U SMJERNICAMA ZA LIJEČENJE"

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Sepsa je po život opasna disfunkcija organa uzrokovana nereguliranim odgovorom domaćina na infekciju. Septički šok je najteži oblik sepse koji se očituje padom krvnog tlaka prilikom kojeg se smanjuje tlak perfuzije tkiva što uzrokuje hipoksiju tkiva koja je karakteristična za šok. Sepsa je još uvijek jedan od vodećih uzroka morbiditeta i mortaliteta u današnjem svijetu. Incidencija je u porastu još od prvog konsenzusa definicije iz 1991. Podizanje razine svijesti o sepsi, njenom značenju, prepoznavanju i potrebi što boljeg liječenja dovelo je i do usavršavanja definicije sepse te razvoja smjernica za liječenje. Prve smjernice su objavljene 2004. god., druge 2008., treće 2013., četvrte 2016. a zadnje revidirane smjernice 2021. godine. U ovom radu bit će opisana dosadašnja i nova definicija sepse i septičkog šoka, prikaz dosadašnjih smjernica za prepoznavanje i liječenje te najnovije preporuke. Pravovremena dijagnoza ključna je za ishod liječenja u bolesnika sa sepsom i septičkim šokom. Činjenica da su se snopovi postupaka za zbrinjavanje septičnih bolesnika svakom izmjenom mijenjali do sve kraćih vremenskih odrednica, naglašava ulogu i važnost liječnika hitne medicine kao onih koji prvi prepoznaju i započinju hitno zbrinjavanje septičnih bolesnika.

Ključne riječi: *sepsa, septički šok, liječenje, definicija, snopovi*