2008 update of international guidelines for the management of severe sepsis and septic shock: should we change our current clinical practice?

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Introduction

Sepsis is a common clinical syndrome characterized by infection accompanied by systemic inflammation. The systemic inflammation (systemic inflammatory response syndrome – SIRS), which may be also related to non-infectious causes (Fig. 1), manifests itself as changes in temperature (>38°C or <36°C), tachycardia (>90 per minute), tachypnea (>20 per minute), or changes in white blood cell count in peripheral blood (<4000 or >12,000 cells per µl, or >10% immature forms of granulocytes [bands]). More recent publications point to other systemic manifestations of infection than the four original SIRS criteria, although lists of such manifestations are more difficult to use in clinical practise than the original SIRS definition (Appendix) [1,2]. Once symptoms of tissue hypoperfusion (elevated lactate or altered mental status), arterial hypotension, or other organ dysfunction occur due to the systemic manifestations of infection we are dealing with severe sepsis; when blood pressure remains decreased despite adequate fluid resuscitation we are faced with septic shock (Fig. 1) [2].

Well over half a million patients in the USA develop severe sepsis each year. The mortality from severe sepsis or septic shock varies according to the severity of condition from 15% to over 50%. No other clinical syndrome occurs so often, so suddenly, and with such devastating results at the same time. It is estimated that in the US alone over 200,000 patients die each year sepsis and almost as many in Europe [1,3]. Extrapolating this number to Polish population would put the number of deaths at about 15,000 per year.

The recognition of the importance of severe sepsis and septic shock continues to grow. A group of clinicians interested in the sepsis management representing eleven international organizations came together in early 2000s to develop „Surviving Sepsis Campaign guidelines for the management of severe sepsis and septic shock" first published in 2004 [4]. The recently published 2008 revision represents the most recent effort of this group, now sponsored by fourteen international organizations [5].

Key changes in the methodology of development of this revision of Surviving Sepsis Campaign guidelines

First, recognizing an increasing role of clinical practice guidelines in shaping clinical practice around the world and the methodological advances in guideline development, Surviving Sepsis Campaign guideline panel implemented an even more transparent process that resulted in more evidence-based and clinically useful recommendations. The group repeated the same careful search and analysis of evidence that characterized the first edition. A new systematic way of grading the quality of available evidence and strength of recommendations according to the GRADE system was used [6].

For each recommendation, the authors assessed whether the desirable effects of following their recommendation will outweigh the undesirable effects (harm, burden, and cost), or vice versa. If they were confident that desirable effects outweigh the undesirable ones, or vice versa, they made a strong recommendation for or against a particular management strategy. If the panel was not confident (e.g. best available evidence was low-quality and thus there was uncertainty about

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the magnitude of benefits or risks, or benefits and harms were closely balanced) they made a weak recommendation. In this document a "strong" recommendation is worded as "we recommend" and a weak recommendation as "we suggest."

Another new development is the explicit identification of areas of controversies and disagreements. Please refer to the full text of the guidelines to find discussions of pros and cons for making particular recommendations and, where applicable, a characterization of the level of disagreement with the presentation of voting results.

The issue of potential conflict of interest that many guideline panels face was also directly addressed. Successful researchers in the field and "content experts" are often involved in guideline development on behalf of professional organizations. In many cases, these same researchers and experts receive industry funding to conduct their research, consult, lecture, participate in industry scientific advisory boards, or provide other services.

These relationships with industry may result in real or perceived conflicts of interest. For this edition of "Surviving Sepsis Campaign guidelines" potential conflicts were addressed by identification of relationship with the industry, discussion of potential conflicts of interest during each of the panel meetings, and an option to abstain from discussion or voting on particular recommendation.

Because of the methodological rigour of selecting, analysing, and describing the evidence, aiming at explicitness and transparency, and consideration given to potential conflicts of interest, we believe these new "Surviving Sepsis Campaign guidelines" provide the best current recommendations for the management of sepsis and septic shock.

Key issues and changes in clinical recommendations

Main impact of these new guidelines is more in reinforcing principles of sepsis management than in refining recommendations related to specific medications. The most important single general principle in sepsis management remains the need for rapid assessment and treatment.

We all know that we need to act fast when confronted by patients with acute myocardial infarction. We strive to achieve "door to needle" time of 30 minutes and "door to cath lab" of 60 minutes, we use helicopters to transfer these patients to the nearest experienced and equipped center. We remember, however, less frequently that whichever therapy these patients receive, the benefits turn out to be less than we can gain by giving an appropriate antibiotic to a patient in septic shock one hour earlier than otherwise we would.

An observational study performed by Kumar et al. [7] between 1989 and 2004 among Canadian and US patients with septic shock (patients with decrease in blood pressure requiring fluids and pressors) serves to reinforce this message. The median time to effective antimicrobial therapy was 6 hours (25–75th percentile: 2.0 to 15.0 hours). In other words 50% of

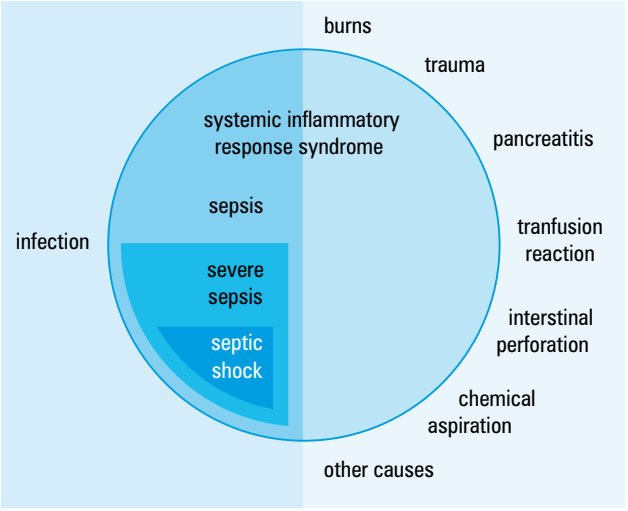

Fig. 1. Severe inflammatory response syndrome, infection, and different stages of sepsis. See text for explanation (based on [2])

septic shock patients received effective antimicrobial therapy within 6 hrs of documented hypotension, but it took longer in another 50%. If this delay appears unusual let us recall that in a pivotal study of rapid sepsis management by Rivers et al. [8], 10% of patients did not receive any antibiotic within first 6 hours after randomization! Kumar et al. [7] observed that administration of an antimicrobial effective for an isolated or suspected pathogens within the first hour of documented hypotension was associated with a mortality rate of 21.1%. In contrast, patients who received an appropriate antimicrobial later than one hour after presentation suffered higher in-hospital mortality that those receiving therapy within the first hour (OR 1.67, 95% CI 1.12–2.48). Each hour of delay in antimicrobial administration over the subsequent 6 hours was associated with an average decrease in survival of over 7%! The time to antibiotic use was prognosticaly more important than the full range of differences in the APACHE score. Figure 2 represents the mortality of patients with septic shock in relation to the time when the therapy directed at isolated or suspected pathogens was initiated.

The strongest evidence supporting rapid management of septic shock in addition to giving prompt antimicrobial therapy comes from the study by Rivers et al. [8]. The investigated management strategy –"early goal directed resuscitation" – was guided by physiological targets of central venous pressure, urine output, arterial blood pressure and central venous blood oxygen saturation, and consisted of rapid fluid infusion, vasoactive drug use and blood transfusion. Although previous studies of increasing oxygen delivery to hypoperfused tissues had failed to show a difference in clinical outcomes, the application of such management strategy during the first 6 hours in sepsis induced tissue hypoperfusion was associated with large survival advantage.

Recommendations related to the currently controversial topic of using corticosteroids in septic shock, recombinant hu-

man activated protein C (rhAPC) use and glycemic control in severe sepsis encountered much discussion and underwent some changes. Results of the recently published CORTICUS study [9] undermined the confidence of the panel that the administration of corticosteroids brings more benefit than harm even among those most hemodynamically compromised. Although corticosteroids are suggested in patients with blood pressure poorly responsive to fluid infusion and vasopressor therapy, this recommendation is weak and based on low quality (inconsistent) evidence.

Similar sequence of events occurred regarding use of rhAPC. The results of the earlier PROWESS study that enrolled patients at very high risk (30.8% mortality in the placebo group) appeared very strong and convincing (6% risk difference for mortality) [10] until a second study in a population with less severe disease (17% mortality in the placebo group) showed essentially no effect [11]. The guidelines currently suggest the use of rhAPC in patients with severe sepsis and clinical assessment of high risk of death, typically those with multiple organ failure or APACHE II score of 25 or more. A new study in patients with septic shock is ongoing.

Finally the degree of enthusiasm for tight glucose control generated by the results of the first study by van den Berghe and colleagues [12] continues to be tempered by the risk of hypoglycemia confirmed in a second study from the same group conducted in critically ill medical patients [13] and by just published results of a study among septic patients that was stopped early due to high risk of hypoglycemia and lack of clear benefit [14]. The guidelines still strongly recommend glycemic control, but only a weak recommendation was formulated about the level of control suggesting a target glucose level of less than 150 mg/dl (8.25 mmol/l) – not the 80–110 mg/dl (4.4–6.0 mmol/l) tight control limits. Results of a large ongoing NICE-SUGAR trial in which patients are randomized to strict or more liberal glucose control are awaited [15].

Comprehensiveness is one of the goals of "Surviving Sepsis Campaign guidelines", hence the recommendations are not restricted to the specific management of sepsis, including source control, but take into account also other strategies of general treatment including prevention of ventilator associated pneumonia, venous thromboembolism, and gastrointestinal bleeding, as well as the best approaches to ventilation and sedation, etc. There are questions that remain to be addressed in next iteration of the guidelines, such as the use of intravenous immunoglobulin in severe sepsis [16] or the impact of rapid response teams on sepsis management [17].

More evidence and more controversies await us. As a result, we will conclude this editorial with a reminder that severe sepsis and septic shock are more deadly in the short term than any other common disease with which we deal in clinical practice. Despite controversies that will never be eliminated, only replaced with different content area, we can likely make a tremendous impact ensuring that the treatments we currently believe to be the best for severe sepsis are instituted. Clinicians should maintain a high level of suspicion and vigilance identifying patients with sepsis, rapidly recognize the progression to severe sepsis, while ensuring prompt decision making regarding initial treatment. All considerations surrounding diagnosis and treatment of sepsis and septic shock require widespread recognition of the problem at many different levels (patients, clinicians, and organizations), education of health care professionals (multispecialty and multidisciplinary), and system changes allowing rapid delivery of evidence-based care. We hope that the new "Surviving Sepsis Campaign guidelines" and the supplementary education and implementation initiatives, including those conducted in Poland, will help to accomplish this goal. For more information on Surviving Sepsis Campaign performance improvement program, including its presence in Poland, please go to: www.survivingsepsis.org and www.sepsa.pl.

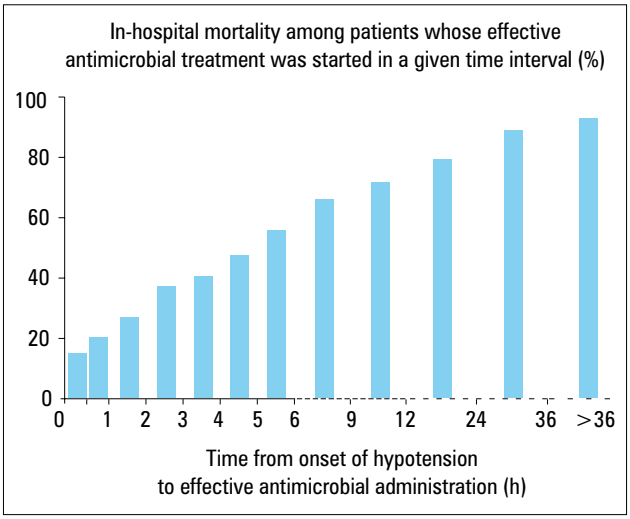

Fig. 2. Probability of death from septic shock depending on time to initiation of effective antimicrobal therapy (based on [7])

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Appendix. Possible systemic manifestation of sepsis (based on [1])

General variables:

- Fever (temperature >38.3°C)
- Hypothermia (core temperature <36.0°C)
- Heart rate >90/min or >2 SD above the mean normal value for age
- Tachypnea
- Altered mental status
- Significant edema or positive fluid balance (>20 ml/kg over 24 h)
- Hyperglycemia (plasma glucose >140 mg/dl [7.7 mmol/l]) in the absence of diabetes

Inflammatory variables:

- Leukocytosis (WBC count >12,000 μl^{-1})
- Leukopenia (WBC count <4000 μl^{-1})
- Normal WBC count with >10% immature forms
- Plasma C-reactive protein >2 SD above the mean normal value
- Plasma procalcitonin >2 SD above the mean normal value

Hemodynamic variables:

- Arterial hypotension (SBP <90 mm Hg, MAP <70, or a SBP decrease of >40 mm Hg in adults or <2 SD below mean normal for age)

Organ dysfunction variables:

- Arterial hypoxemia (PaO_2/FiO_2 <300)
- Acute oliguria (urine output <0.5 ml/kg/h for at least 2 h despite adequate fluid resuscitation)
- Creatinine increase >0.5 mg/dl [44 μmol/l])
- Coagulation abnormalities (INR >1.5 or aPTT >60 s)
- Ileus
- Thrombocytopenia (platelet count <100,000 μl^{-1})
- Hyperbilirubinemia (plasma total bilirubin >4 mg/dl [70 μmol/l])

Tissue perfusion variables:

- Hyperlactatemia (above the upper limit of lab normal)
- Decreased capillary refill or mottling

Diagnostic criteria for sepsis in the pediatric population are signs and symptoms of inflammation plus infection with hyper- or hypothermia (rectal temperature >38.5°C or <35°C), tachycardia (may be absent in hypothermic patients), and at least one of the following indications of altered organ function: altered mental status, hypoxemia, increased serum lactate level or bounding pulses.

Abbreviations: aPTT – activated partial thromboplastin time, FiO_2 – fraction of inspired oxygen, INR – international normalized ratio, MAP – mean arterial pressure, PaO_2 – pressure of oxygen in arterial blood, SBP – systolic blood pressure, SD – standard deviation, WBC – white blood cells