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Managing septic shock

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Abstract

Although several successful clinical trials in the last 2-3 years have been greeted with enthusiasm by intensivists, severe sepsis and septic shock still have increasing incidence and more or less unchanged mortality. Within the last few years, the progress in sepsis research covering definitions, epidemiology, pathophysiology, diagnosis, and standard and adjunctive therapy as well as general measures such as treatment bundles is encouraging. In this report, a small selection of recent publications, focusing on the current discussion of activated protein C as well as the relevance of the Surviving Sepsis Campaign bundle therapy, is presented and the possible impact on clinical routine is discussed.

Introduction and context

Sepsis is a leading cause of hospital mortality in adult patients, and the incidence is increasing [1]. There is considerable variation between countries, with a strong correlation between the frequency of sepsis and intensive care unit (ICU) mortality rates [2]. In a prospective study of 3877 patients in 454 German ICUs, the prevalence of sepsis was 12.4% [3]. The prevalence of severe sepsis, defined as sepsis associated with organ dysfunction, was 11.0%. Of those with severe sepsis, nearly half had septic shock, defined as sepsis with hypotension despite adequate fluid replacement. The incidence of severe sepsis was estimated to be 76-110 cases/year per 100,000 inhabitants. Outcome data revealed ICU and hospital mortality rates of 48.4% and 55.2%, respectively [3]. Patients surviving sepsis have a lower quality of life than the age- and sex-adjusted population as much as 1.5 years later [4]. The economic burden of severe sepsis is immense. The daily cost is estimated to be 1090 euros (approximately USD $1600), and the overall costs per hospital stay are estimated to be 2-fold to 11-fold higher than the general cost per patient [5].

Currently available strategies for the management of sepsis patients include timely patient identification and diagnosis, rapid identification of causative organisms, appropriate and early antimicrobial therapy, improved ventilatory techniques, goal-directed hemodynamic support, targeted immunological therapy, glycemic control, appropriate nutrition, effective supportive therapies, and patient management by highly qualified clinicians and nursing staff. These multifaceted approaches to patient management, the use of evidence-based methods, and the adoption of incremental, goal-oriented strategies are vital to combat this complex, aggressive, and increasingly prevalent condition.

Recent advances

Pathophysiology

Sepsis is a complex phenomenon that remains incompletely understood. Infectious pathogens possess unique structural components called pathogen-associated molecular patterns; examples include lipopolysaccharide in Gram-negative bacteria and peptidoglycan in Gram-positive bacteria [6]. These molecules bind to host cell receptors known as 'pattern recognition receptors', which include the cell-surface Toll-like receptors and several types of cytoplasmic receptors [7]. Receptor binding results in the activation of intracellular signaling pathways that lead to a variety of responses, including increased

transcription of inflammatory cytokines, upregulation of adhesion molecule expression, stimulation of humoral and cell-mediated immune responses, and activation of vascular endothelial cells. A detailed discussion of the pathogenesis of sepsis is beyond the scope of this article, but the subject has been addressed in a number of recent reviews [8-11].

An important feature of the pathophysiology of sepsis is the development of a procoagulant state [12]. Inflammatory cytokines activate the coagulation cascade and inhibit fibrinolysis. In turn, components of the coagulation and fibrinolytic systems have proinflammatory effects. Disseminated intravascular coagulation, one of the most feared complications of sepsis, is a manifestation of the dysregulation of coagulation seen in this disorder [12].

Activated protein C

In severe sepsis, treatment of the underlying cause of infection requires early and meticulous attention to source control, including the use of antimicrobial agents and, where appropriate, surgical drainage. Physiological support of organ dysfunction with inotropes, mechanical ventilation, and renal replacement therapy should be instituted depending upon the individual clinical circumstances. Specific drugs such as corticosteroids are broadly used, although the benefit of such therapy remains uncertain [13,14].

Protein C is a soluble, vitamin K-dependent, plasma serine protease that plays a central role in endogenous anticoagulation [15]. The activated form is generated when thrombin, bound to the cofactor thrombomodulin, interacts with and cleaves the zymogen protein C. Activated protein C (APC) is a potent anticoagulant and profibrinolytic enzyme capable of inactivating clotting factors Va and VIIIa and plasminogen activator inhibitor 1. The exact role of APC in the treatment of septic shock is eagerly debated, and a recent review from our group gives an overview [15].

Unexpected reversal of refractory septic shock with APC was recently described [16]. The 23 patients included in this observational study had a 100% risk of death, according to a score based on the response to early continuous veno-venous hemodiafiltration. The actual 28-day mortality rate of the 23 patients who received APC was only 39% and was associated with a decrease in the magnitude of lactic acidosis and the dose of norepinephrine required. In a double-blind randomized placebo-controlled trial, the safety and efficacy of extended APC treatment were evaluated in 64 ICUs in nine countries. Patients (n = 193) received APC for a maximum of 3 days. However, extended APC treatment was not associated with reductions in day-28 all-cause mortality or in-hospital mortality or with an increase in serious adverse events [17]. Heparin used concomitantly with APC was explored in a large randomized study, and no heparin effect on mortality was observed [18]. Further analyses revealed that the coadministration of APC with low-dose heparin in patients with severe sepsis did not increase the incidence of serious bleeding. Fewer ischemic strokes in the heparin group suggest that heparin cessation should be avoided during APC infusion [18]. Finally, recent observational data from a large international sepsis registry demonstrated a beneficial effect of the treatment with APC [19].

Implementing treatment bundles

In 2002, the Surviving Sepsis Campaign (SSC) was launched. This international group of investigators developed evidence-based guidelines through a formal and transparent process. The initial guidelines were published in 2004, and an updated version was published in 2008 [20]. The development and publication of guidelines often do not lead to changes in clinical behavior, and guidelines are rarely, if ever, integrated into bedside practice in a timely fashion [21]. Recognizing that implementing guidelines presents a significant challenge, the SSC set out to develop and evaluate a multifaceted model to change bedside practice for patients with severe sepsis and septic shock by the definition of 'sepsis resuscitation bundles' as well as 'sepsis management bundles' [22]. A central part of that program was an international registry that providers could use to monitor the performance of their institution and to recruit and enter patients. A Spanish cohort study demonstrated significant benefit after implementing these bundles [23]. In January 2010, the first analysis of the worldwide registry data described the global initiative and its implementation and reported its impact on process improvement and patient outcomes [24]. Data from 15,022 subjects at 165 sites were analyzed to determine the compliance with bundle targets and association with hospital mortality. Compliance with the entire resuscitation bundle increased linearly from 10.9% in the first site quarter to 31.3% by the end of 2 years ($P < 0.0001$). Unadjusted hospital mortality decreased from 37% to 30.8% over 2 years ($P = 0.001$). The adjusted odds ratio for mortality improved the longer a site was in the SSC, resulting in adjusted absolute decreases of 0.8% per quarter and 5.4% over 2 years (95% confidence interval 2.5-8.4%) [24].

Implications for clinical practice

The management of sepsis in hospitals is significantly better today than it was 10 years ago. However, sepsis-associated mortality rates remain unacceptably high, and

new strategies to improve patient outcomes will have to be embraced further still. The recent improvement in outcomes of patients with severe sepsis and septic shock has been characterized by the successive introduction of multiple interventions and therapies, which is an ongoing process. The results of the aforementioned studies [23,24] demonstrate that the use of a multifaceted performance improvement initiative was successful in changing sepsis treatment behavior as evidenced by a significant increase in compliance with sepsis performance measures. This compliance was associated with a significant reduction in hospital mortality in patients with severe sepsis and septic shock over the duration of the 2-year study, but the study design does not allow us to say, with certainty, whether this was due to some or all bundle elements, increased awareness of severe sepsis, or other unrelated factors [24]. There are still many unanswered questions – including the mortality trend in hospitals that have not implemented the bundles and confirmation of which components of the bundles reduce mortality – that could provide direction for future research. The results of this study should encourage similar efforts to implement guidelines and treatment protocols as a means to improve outcomes. Finally, the importance of the wholehearted involvement of the entire health care team and the provision of strong public and political support in achieving these objectives cannot be stressed enough.

Abbreviations

APC, activated protein C; ICU, intensive care unit; SSC, Surviving Sepsis Campaign.

Competing interest

The authors declare that they have no competing interests.

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