Update on the Management of Infection in Patients With Severe Sepsis

Dominique M. Vandijck, PhD, MSc, MA, RN; Stijn I. Blot, PhD, MSc, RN; Johan M. Decruyenaere, MD

Morbidity and mortality associated with the development of severe sepsis remain unacceptably high. However, with the introduction of a protocol called early goal-directed therapy, significant benefits in terms of patient’s outcome have been demonstrated. In an aim to improve outcome and to increase awareness, practical evidence-based guidelines for the management of severe sepsis and septic shock were developed under the auspices of the Sepsis Surviving Campaign, easy to apply by the bedside medical and nursing staff. The treatment of severe sepsis includes 3 main essentials: (1) eradication of the inciting infection using source control measures and empiric antimicrobials, (2) hemodynamic resuscitation of tissue hypoperfusion using fluids and inotropic drugs to prevent life-threatening organ damage, and (3) sustained organ support using mechanical interventions to diminish organ injury. This review article highlights the anti-infective approach of the management of sepsis.

Keywords: Infection management, Sepsis, Septic shock, Severe sepsis

Because of sociological evolution and major progress made in medicine over the past decades, sepsis has put itself to the foreground as one the most serious health problems. Mortality rates associated with sepsis have been estimated to be 30% to 40% for severe sepsis (sepsis + infection-induced organ dysfunction) and 50% to 60% for septic shock (severe sepsis + persistent hypotension not reversed with fluid resuscitation). The number of sepsis cases is projected to grow at a rate of 1.5% per year, making a total of nearly 18 million new cases to occur worldwide each year. This is almost equivalent to the combined population of all Scandinavian countries together. Sepsis is an extremely complex disease; the pathophysiology is only beginning to be unravelled, and the symptoms are often unspecific, making them easily misattributed to other conditions.

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Signs signalling the presence of a possible septic response are shown in Table 1.5

**Sepsis is an extremely complex disease.**

Despite the recent evolutions made in the field of sepsis in terms of epidemiology, pathophysiology, and monitoring, particularly in early diagnosis and therapy, continued progress is urgently needed.7 This review will provide information on the management of infection in critically ill patients with severe sepsis.

**TREATMENT OF SEPSIS**
The treatment of severe sepsis and septic shock still remains a major challenge. In 2003, international critical care and infectious disease experts came together under the auspices of the Surviving Sepsis Campaign to develop a set of practical guidelines for the management of severe sepsis and septic shock.8 The key objectives of this conference were to (1) build awareness of sepsis, (2) improve early detection of patients with sepsis, (3) educate healthcare professionals taking care of patients with sepsis; and (4) increase the use of appropriate treatments and interventions.8

The mainstays for the treatment of severe sepsis includes the following principles: (1) treatment of the infection (antimicrobial therapy and, if possible, surgical eradication of the inciting infectious focus), (2) resuscitation and hemodynamic support (fluids and vasopressor therapy), (3) full organ support (renal replacement therapy and mechanical ventilation), (4) modulation of the inflammatory response (recombinant human activated protein C), (5) sedation and analgesia as needed, and (6) adequate nutrition.8-11

In one randomized study, the investigators evaluated early goal-directed therapy (EGDT).12 Endpoints of this EGDT represented an attempt to improve cardiac preload, afterload, and contractility to balance oxygen delivery with oxygen demand. Goals of this approach were to achieve a central venous pressure of 8 to 12 cm H2O, a mean arterial pressure greater than or equal to 65 mm Hg, urine output greater than or equal to 0.5 mL/kg/h, and a central venous or mixed venous oxygen saturation of 70% or greater within 6 hours. Significant benefits were demonstrated in patients managed with EGDT compared with those who received standard therapy.12

**INFECTION MANAGEMENT OF SEVERE SEPSIS**
The optimum treatment of sepsis is a dynamic and evolving process requiring a multidisciplinary and individual approach. It is likely that, in most cases, only a combination of therapies will yield the greatest benefit.13 Patients whose hospital stay is complicated with severe sepsis should be managed in an intensive care unit.

**Diagnosis**
Early and adequate treatment within the first hours after the onset of a septic episode is associated with increased favorable outcome.12,14 Thus, the management of a patient with sepsis should begin as soon as the syndrome is recognized and should not be delayed pending intensive care unit admission. Consequently, such early recognition requires clear definitions as well as experienced healthcare providers able to both anticipate and discern the sometimes subtle and often rapidly changing symptoms progressing clinical course.15

The diagnosis of sepsis is difficult and is generally guided by a mixture of alterations in both physiologic (arterial blood pressure, body temperature, heart rate, etc) and biochemical (C-reactive protein, white blood cell count, platelets, procalcitonin, inflammatory mediators, lactate, etc) parameters.16,17 Sampling for blood cultures should be obtained in any critically ill patient with sepsis. Approximately 30% to 50% of patients presenting with a clinical picture of severe sepsis have positive blood cultures.18,19 Collecting appropriate blood cultures (ie, at least a set of 2 pairs of cultures, 1 drawn peripherally and 1 drawn through each vascular access

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**TABLE 1  Possible Signs of Sepsis**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Signs</th>
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<tbody>
<tr>
<td>General variables</td>
<td>Fever, hypothermia, chills, transpiration, confusion/drowsiness</td>
</tr>
<tr>
<td>Hemodynamic variables</td>
<td>Arterial hypotension, tachycardia, decreased cardiac output</td>
</tr>
<tr>
<td>Respiratory variables</td>
<td>Tachypnea, hyperventilation</td>
</tr>
<tr>
<td>Coagulation variables</td>
<td>Increased INR, APTT</td>
</tr>
<tr>
<td></td>
<td>Decreased platelets, PT</td>
</tr>
<tr>
<td>Inflammatory variables</td>
<td>Increased CRP, PCT, IL-1, IL-6, HGMB, sTREM</td>
</tr>
<tr>
<td>Metabolic variables</td>
<td>Increased lactate, altered insulin requirements, mottling</td>
</tr>
<tr>
<td>Organ dysfunction variables</td>
<td>Increased creatinine, bilirubin</td>
</tr>
</tbody>
</table>

Abbreviations: APTT, activated partial thromboplastin time; CRP, C-reactive protein; HGMB, high-mobility group box 1 protein; IL, interleukin; INR, international normalized ratio; PCT, procalcitonin; PT, prothrombin time; sTREM, soluble triggering receptor expressed on myeloid cells.
device, and preferably spread out in time) before initiation of empiric antimicrobials offers the best hope of identifying the causative pathogen. Failure to check blood cultures before the start of antimicrobial therapy will potentially influence the growth of blood-borne bacteria and prevent a culture from becoming positive later. However, treatment cannot be delayed while awaiting the results of blood cultures. If indicated, cultures of other sites (urine, drain fluids, wounds, and sputum) should also be performed before antibiotics are initiated. Indications suggestive of the presence of bacteremia are listed in Table 2.

**Antimicrobial Therapy**

In case of a clinical suspicion of systemic infection, empiric antimicrobials must be started as soon as blood cultures are sampled, improving the odds of survival. This early initiation of antimicrobials with in vitro activity against the isolate within 48 hours of specimen collection demonstrated 3 to 4 times better survival rates in contrast when inappropriate drugs were used. The initial choice of an empirical antimicrobial regimen should be broad enough, covering all likely causative pathogens because there is little margin for error in this subgroup of critically ill patients. Furthermore, this choice should be guided by the local ecology, susceptibility patterns, selection pressure, type of infection, colonization status, and the underlying conditions of the patient.

When microbiological results of cultures are known, mostly within a few days, reassessment of the antibiotic regimen is needed. If possible, antimicrobial therapy should be downgraded to a narrower spectrum to avoid unnecessary risk of the development of a subinfection with resistant pathogens, as well as to reduce associated costs, antimicrobial resistance, and drug toxicity. When the sepsis-like syndrome is considered to be due to a noninfectious cause, antibiotics should be stopped.

**TABLE 2**

<table>
<thead>
<tr>
<th>Clinical Signs Suggestive of Bacteremia</th>
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<tbody>
<tr>
<td>Spiking fever</td>
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<tr>
<td>Unexplained hypothermia</td>
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<tr>
<td>Neutropenia</td>
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<tr>
<td>Hypotension not explained by noninfectious causes</td>
</tr>
<tr>
<td>Local infections (meningitis, intra-abdominal infection, pneumonia, etc)</td>
</tr>
<tr>
<td>Unexplained deterioration of mental status</td>
</tr>
<tr>
<td>Unexplained arrhythmias (eg, tachycardia, atrial fibrillation)</td>
</tr>
<tr>
<td>Unexplained renal or hepatic dysfunction</td>
</tr>
</tbody>
</table>

When the sepsis-like syndrome is considered to be due to a noninfectious cause, antibiotics should be stopped.

Once a causative pathogen is identified, there is no evidence that combination therapy is more effective than monotherapy. The duration of therapy is recommended at a minimum of 7 to 10 days and must be guided by clinical response. A full loading dose of each drug administered should be given initially. However, severe sepsis and septic shock frequently are accompanied by profound changes in the organism that can all affect therapy. In some patients, higher doses may be needed because of changed distribution volumes due to aggressive fluid infusion. Appropriate serum concentrations may already be ensured when lower doses are prescribed in those patients with renal or hepatic dysfunction.

**Source Control**

Sometimes, antimicrobial treatment is not sufficient, making timely surgical removal of the source of infection indispensable. Therefore, every patient presenting with a systemic inflammatory response should be evaluated for the presence of a possible focus of infection, using diagnostic interventions such as computer tomography, endoscopy, and surgery. If present, this inciting focus (eg, abscess, necrotic tissue, intravascular catheter, or other invasive devices) needs to be removed. When considering the best way to eradicate the infectious focus, benefits and risks of the different potential interventions must be considered.

**CONCLUSION**

Severe sepsis is a common disease process in the critically ill and is associated with substantial morbidity and mortality. Numbers of fatal cases are intolerable, making sepsis one of the most challenging disease entities in intensive care medicine. In this rapidly moving field, continued research has provided considerable insights, enabling various aspects to be targeted.

First, it is of the utmost importance to diagnose severe sepsis as early as possible. Therefore, it is necessary to recognize historical, clinical, and laboratory findings, either alone or in combination, that are indicative of a beginning infection, organ dysfunction, and global tissue hypoperfusion. Both epidemiologic and individual patient risk factors must first be considered, and focal findings of infection should be sought.
on medical records and physical examination. Second, keeping in mind the substantial reduction in mortality observed when appropriate empiric antimicrobials are used, these drugs must be started within 1 hour after sampling blood cultures as recommended. Third, in patients with severe sepsis and sepsis shock, source control is an integral part of therapy. Early detection of the site of infection determines the presumptive microbiologic cause and potentially facilitates eradication by source control measures. Such measures include percutaneous drainage, debridement, and surgical removal of devitalized infected tissue or endoprostheses.

With the advent of intensive care medicine, mortality of patients with life-threatening infections has been reduced. Nevertheless, efficient strategies in the prevention of infection (eg, antibiotic prophylaxis, semirecumbe nt positioning, hand hygiene, isolation, and selective decontamination of the digestive tract) are also crucial in diminishing the incidence of sepsis. Also, organizing a routine protocol of performing surveillance cultures, indicating colonization with opportunistic pathogens, can be used to focus empiric anti-infective therapy. Finally, good communication and rapid reporting of culture results between microbiologists and intensivists is also a cornerstone in achieving better patient outcome.

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To summarize, early recognition of sepsis during the critical “golden hours,” followed by prompt and aggressive therapeutic interventions, is of key importance to reduce sepsis-related morbidity and mortality.

References


ABOUT THE AUTHORS

Dominique M. Vandijck, PhD, MSc, MA, RN, is a researcher in the intensive care department of the Ghent University Hospital and a researcher in the interfaculty center for health economic research of the faculty of medicine and health sciences at Ghent University.

Stijn I. Blot, PhD, MNSc, RN, is a professor in the faculty of medicine and health sciences at Ghent University and Ghent University College and a researcher in the infectious diseases department of the Ghent University Hospital.

Johan M. Decruyenaere, MD, is director of the intensive care department of the Ghent University Hospital and a professor in the faculty of medicine and health sciences of Ghent University.

Address correspondence and reprint requests to: Dominique M. Vandijck, PhD, MSc, MA, RN, Department of Intensive Care Medicine, Faculty of Medicine and Health Sciences, Ghent University-Ghent University Hospital, De Pintelaan 185, 9000 Ghent, Belgium (Dominique.Vandijck@UGent.be).

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