

## VIEWPOINT

# Surviving Sepsis Guidelines

## A Continuous Move Toward Better Care of Patients With Sepsis

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**Sepsis is a life-threatening condition** that affects more than 1 million patients a year in the United States and even more patients around the globe and is one of the leading causes of death. Since the Declaration of Barcelona in 2002, the European Society of Intensive Care Medicine and the Society of Critical Care Medicine (SCCM) have launched several initiatives to decrease the mortality of patients with sepsis. The Surviving Sepsis Campaign (SSC) was launched in 2002 and has a 7-point agenda: building awareness of sepsis, improving diagnosis and recognition, defining and increasing the use of appropriate treatment and care, educating health care professionals, improving post-intensive care unit care, developing guidelines of care, and implementing a performance improvement program.

The mortality of patients with sepsis has improved over time.<sup>1</sup> In an observational study that included 29 470 patients in sepsis worldwide, every quarter of participation in the SSC initiative was associated with a significant decrease in the odds of hospital mortality (odds ratio, 0.96; 95% CI, 0.95-0.97;  $P < .001$ ).<sup>2</sup>

The Surviving Sepsis Guidelines were first published in 2004, with revisions in 2008 and 2012. In January 2017, the fourth revision of the Surviving Sepsis Guidelines was presented at the 46th annual SCCM meeting and published online jointly in *Critical Care Medicine* and *Intensive Care Medicine*.<sup>3,4</sup> A synopsis of the guidelines also has been published.<sup>5</sup>

The updated guideline was generated by 55 international experts representing 25 international organizations involved in the care of patients with sepsis and providing 93 recommendations on early management of sepsis and septic shock. There are numerous major advances in the revision of the guidelines. Among the various topics covered, initial resuscitation and antibiotic therapy are the domains in which the most important changes and advances were made.

For initial resuscitation, previous guidelines were mostly based on early goal-directed therapy, which has been challenged by recent trials,<sup>6</sup> and this approach is no longer recommended. Of note, no harm was demonstrated in those trials, so there was not a recommendation to avoid early goal-directed therapy targets. The guidelines recommend (mostly as best practice statements) the use of hemodynamic assessment for further fluid administration after the initial fluid bolus (including available physiological variables but also noninvasive or invasive hemodynamic monitoring) and hemodynamic assessment to determine the type of shock if the clinical diagnosis does not lead to clear diagnosis (this is particularly important in complex

cases; for example, those with a history of cardiac dysfunction who develop pneumonia, when the nature of circulatory failure is not always obvious).

Another important advance is that the new guidelines recommend the use of dynamic (ie, pulse or stroke volume variations induced by mechanical ventilation or passive leg raise test) over static variables (intravascular pressures or volumes) to predict fluid responsiveness. This is a significant change, as previous guidelines recommended that clinicians should target specific values of central venous pressure. Subsequent data have shown that central venous pressure has limited value for the prediction of the response to fluids.<sup>7</sup> Importantly, the guidelines recommend that when fluid administration is initiated, clinicians should use the fluid challenge technique to evaluate the effect (and safety) of fluid administration. When hemodynamic factors continue to improve in response to fluids, further fluid administration can be considered. However, fluid administration should be discontinued when the response to fluids is no longer beneficial, a step often neglected in clinical practice.<sup>7</sup> This is particularly important because multiple studies have shown that excessive net fluid status is associated with a poorer outcome, including an increase in mortality. Hence, the guidelines moved from a protocolized, quantitative resuscitation strategy to a more patient-centered resuscitation approach guided by hemodynamic assessment including dynamic variables for fluid responsiveness and ongoing reevaluation of the response to treatment.

Infection source control (eg, retrieval of catheter/device suspected to be infected, surgical procedure) and early antibiotic therapy remain mainstays of treatment. Source control should always be obtained as rapidly as possible. The new guidelines recommend that antibiotics should be administered as soon as possible and within 1 hour maximum. This recommendation is based on multiple observational studies showing that any delay in antibiotic administration is associated with an increased risk of death. In addition to the timing of antibiotics, it is important to ensure the adequacy of antibiotics in terms of both doses and drug selection. The new guidelines state that best practice includes the use of dosing strategies based on pharmacokinetics/pharmacodynamics principles in patients with sepsis when such tests are available. This statement is based on the observation that recommended initial doses of antibiotics are often insufficient because of an increase in volume of distribution and also, in some patients, augmented renal clearance.<sup>8</sup>

The issue of combination therapy, which reflects the use of 2 different classes of antibiotics to cover a single putative pathogen sensitive to both agents, is also addressed in the new guidelines. Even though combination therapy is not recommended for routine treatment of neutropenic sepsis (even with bacteremia), a weak recommendation was made for the use of empirical combination therapy in patients with septic shock (but not in sepsis without shock). The latter was based on the increasing frequency of pathogen resistance to antimicrobial agents and that multidrug combinations of different classes of antibiotics decrease the likelihood of inadequate coverage. Several observational studies have suggested benefit with empirical combination therapy in high-risk but not low-risk patients, justifying this quite complex 3-level recommendation on combination therapy.

The SSC has also developed other initiatives. The Sepsis in Resource Limited Nations initiative is designed to improve the quality and reliability of patient-centered care to patients in developing and emerging countries, based on the adaptation of the current evidence to these specific areas. Unlike previous editions, the 2016 iteration of the SSC guidelines does not include recommendations for the care of pediatric patients with sepsis. The specific aspects involved in treatment of pediatric patients could not be covered in

a few paragraphs in the adult guidelines, and the evolving evidence justified the development of the SSC Pediatric Guideline. Thus, a new guideline development committee specifically designed to develop pediatric guidelines has been established as part of the SSC. The pediatric committee will include pediatric intensivists and other experts in pediatrics involved in the care of children with sepsis, and publication of these guidelines is expected to occur in approximately 2 years. In addition, an SSC research committee has now been established with the aim of outlining research priorities in sepsis care, with particular attention to areas of the current guidelines in which inadequate information exists.

Finally, the SSC guidelines will be translated into bundles that are key elements in sepsis improvement efforts. In a 1-day observational study conducted in 62 countries worldwide, adherence to the bundles, even though not present in the majority of patients, was associated with a marked reduction in the odds of death.<sup>9</sup> In response to the changes in the SSC guidelines, these bundles will be updated later this year and will be available online.<sup>10</sup>

This fourth revision of the SSC guidelines based on up-to-date evidence should prove helpful for clinicians to continue to improve the care of patients with sepsis and improve the outcome of these critically ill patients.

#### ARTICLE INFORMATION

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**Additional Information:** Dr De Backer is immediate past cochair of the Surviving Sepsis Campaign and immediate past president of the European Society of Intensive Care Medicine. Dr Dorman is president of the Society of Critical Care Medicine.

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