EDITORIAL VIEW

Sepsis in my view

Said Abuhasna, MD

Chairman, Department of Critical Care Medicine; Associate Professor in Medicine, FMHS - UAEU;
Chairman of Ethics and Consultation Service, Tawam Hospital, Al Ain, (United Arab Emirates)
E-mail: sabuhasna@tawamhospital.ae

Sepsis is a disease process that exists on a spectrum that increases in severity from sepsis to severe sepsis to septic shock. The common thread between these elements is a disseminated inflammatory response to infection characterized by clinical and laboratory findings. Severe sepsis is complicated by organ dysfunction. It is the number one cause of death in the noncoronary intensive care unit. More than 750,000 Americans develop severe sepsis each year in the USA, while the worldwide toll is unknown. Cases of severe sepsis are expected to rise in the future with the increase in the awareness and sensitivity for the diagnosis, number of immunocompromised patients, use of invasive procedures, number of resistant microorganisms, and the growth of the elderly populations[1]. Septic shock is sepsis with refractory hypotension. Over the last decade several strategies to manage septic patients have emerged and have been summarized in international guidelines supported by international medical specialty organizations. Despite extensive research indicating the benefits of these therapies in the management of sepsis, the debate is continuing and research is gearing up[2].

In the past three decades, enormous investment has been made in enhancing critical care resources, yet, mortality from severe sepsis ranges from 28% to 50% or greater. A 2001 study reported that the treatment of severe sepsis resulted in an average cost of $2200 per case, with a nationwide annual total cost of over $16.7 billion. [2,3]

Any type of bacteria, and fungi and (rarely) viruses may produce this condition. Toxins released by the bacteria or fungi may cause tissue damage, and may lead to low blood pressure and poor organ function. Some researchers think that blood clots in small arteries are responsible for low blood flow and poor organ function.

Septic shock occurs most often in the very old and the very young. It also occurs in people who have other illnesses; and has a crude mortality rate of 45% and claims the lives of 90,000 people each year in the USA alone.[3] An epidemiological survey in France of over 100,000 intensive care unit (ICU) admissions, indicates the incidence of septic shock before or following admission to ICU is rising and now affects almost 10% of this patient population.[4] Given the scale and associated costs of this problem,[3,5] it is not surprising that developing solutions has been a focus of researchers, clinicians, and the pharmaceutical industry. The intensive care specialists took the challenge to overcome the current situation and to reduce sepsis mortality significantly by implementing evidence based clinical standards for the diagnosis and treatment of sepsis worldwide. New strategies, including tight glycemic control, early hemodynamic goal-directed therapy, infusion of activated protein C, and use of corticosteroids (still for debate), have shown some promise in prevention and/or treatment of sepsis and septic shock..

Risk factors for septic shock include; diabetes, diseases of the genitourinary system or intestinal system, AIDS, indwelling catheters (those that remain in place for extended periods, especially intravenous lines and urinary catheters and plastic and metal stents used for drainage), leukemia, long-term use of antibiotics, recent use of steroid medications and many more.

Sepsis is defined as the presence of infection in association with SIRS. The presence of SIRS is, of course, not limited to sepsis, but in the presence of infection, an increase in the number of SIRS criteria observed should alert the clinician to the possibility of endothelial dysfunction, developing organ dysfunction, and the need for aggressive therapy. Certain biomarkers have been associated with the endothelial dysfunction of sepsis; however, the use of sepsis-specific biomarkers has not yet translated to establishing a clinical diagnosis of sepsis in the emergency department (ED). There is a promise of procalcitonin use as a marker in early identification of such septic patients.

With sepsis, at least one of the following manifestations of inadequate organ function/perfusion is typically seen:

- Alteration in mental state
- Hypoxemia; PaO_2 < 72 mmHg at F_iO_2 of 0.21; overt pulmonary disease not the direct cause of hypoxemia
- Elevated plasma lactate level
- Oliguria (urine output < 30 ml or 0.5 ml/kg for at least 1 h)

Severe sepsis is defined as sepsis complicated by end-organ dysfunction, as signaled by altered mental status, an episode of hypotension, elevated creatinine concentration, or evidence of disseminated intravascular coagulopathy (DIC).

Septic shock is defined as a state of acute circulatory failure characterized by persistent arterial hypotension despite adequate fluid resuscitation or by tissue hypoperfusion (manifested by a lactate concentration greater than 4 mg/dl) unexplained by other causes. Patients receiving inotropic or vasopressor agents may not be hypotensive by the time that they manifest hypoperfusion abnormalities or organ dysfunction.

We all agree that treatment strategies of sepsis should start in the emergency room and we should start the antibiotics within the hour after blood work is drawn. The success of treatment depends upon early detection of high-risk patients, appropriate antimicrobials, source control, hemodynamic optimization (clarity in fluid therapy and vasopressor selection), and the results of large-scale efforts to implement bundles of care. Recently, the sepsis surviving campaign has issued the latest recommendations for treatment of septic shock, but the debate about the use of steroids is still going on. In my opinion, it has a definitive role and should be used in refractory hypotension.

In 2001, a landmark paper, "Early goal-directed therapy in the treatment of severe sepsis and septic shock", altered the clinical landscape of sepsis management. Two hundred and sixty-three patients with severe sepsis, defined as two SIRS criteria, a source of infection, and a serum lactate>4 mmol/l, and systolic blood pressure <90 mmHg after adequate fluid challenge, were randomized to receive either standard therapy or early goal-directed therapy (EGDT). During the first six hours of care, patients in the EGDT arm received statistically significantly more intravenous fluids, inotropes, and blood transfusions. By moving an aggressive, algorithmic resuscitation strategy to the proximal phase of critical infection and inflammation, Rivers and colleagues demonstrated a 16% absolute reduction in in-hospital mortality. This reduction in mortality was accompanied by a decreased use of vasopressors and mechanical ventilation over the first 72 hours of hospitalization. These results spurred a renewed interest in improving sepsis management in the ED and led to numerous implementation studies and quality improvement initiatives, showing improved in-hospital, 28 day, and up-to-one-year mortality with implementing EGDT [5].

We recognized more than a decade ago that the widespread and perhaps indiscriminate use of an extremely expensive and marginally effective therapy for septic shock could have serious economic implications for many hospitals. One of these is Drotrecogin Alpha Activated protein C[6].

Many times in humans, sepsis is caused by fungi or gram-positive bacteria. Drugs that are effective against endotoxin or gram-negative bacteria may not have the same effect on other pathogens. The report continues: In sepsis there are multiple clinical, microbiologic, and host derived indicators of prognosis that are difficult to control, such as severity of underlying disease, co-morbidities, degree of organ dysfunction, and adequacy of antibiotic therapy. Remarkably, Bernard and his colleagues, in a landmark New England Journal of Medicine article describing the so-called PROWESS trial, demonstrated that drotrecogin alfa or recombinant human activated protein C has anti-thrombotic, anti-inflammatory and pro-fibrinolytic properties. Treatment with this human activated protein C (marketed by Eli Lilly as Xigris®), significantly reduces mortality in patients with severe sepsis. The treatment was effective regardless of age, severity of illness, the number of dysfunctional organs or systems, the site of the infection and the type of infecting organism.[5,6]

At the integrated hospital system level, I believe drotrecogin alfa requires widespread coordination of pharmacy department efforts to appropriately utilize this new entity. Intrasystem coordination is essential in the sharing of data about the number of sepsis cases, their clinical characteristics, and outcomes with and without the use of drotrecogin alfa[7]. Integrated systems should have a systemwide approach to drotrecogin alfa use , emphasizing a judicious and circumspect prescribing behavior on the part of all clinicians.

A retrospective analysis using electronic database for patients who received drotrecogin alfa from June 2008 until April 2011 was conducted at our 20-bed intensive care unit (ICU) at a governmental hospital in Al Ain, United

Arab Emirates. Among the 41 patients who recei ved drotrecogin alfa, the indication w as appropriate for 32 (78%). We conclude that strictly following the institutional protocols can have a big impact in minimizing wastage by better selection of candidates for drotrecogin alfa.

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NOT-TO-BE-USED ABBREVIATIONS

In 2001, The Joint Commission issued a Sentinel Event Alert on the subject of medical abbreviations, and just one year later, its Board of Commissioners approved a National Patient Safety Goal requiring accredited organizations to develop and implement a list of abbreviations not to use. In 2004, The Joint Commission created its "do not use" list of abbreviations as part of the requirements for meeting that goal.

On the list used by the European Association of Science Editors (www.ease.org.uk), Tom Lang has posted a link to a list of abbreviations that one organization has recommended should not be used, apparently because they have been associated with confusion leading to serious adverse events (http://www.jointcommission.org/facts_about_the_official_/).

Some of these abbreviations are very common in health research. Experience with manuscripts from different parts of the world shows that some of them -particularly the ones that use Greek letters and other symbols not available on the keyboard- - may cause character conversion errors, and that these errors are not always detected at proof stage. If dosages of radiation or drugs are involved, the potential for accidents may be worth considering.