Editorial

Sepsis and Septic Shock

Yatin Mehta[1] Gaurav Kochhar[1]

[1] Medanta Institute of Critical Care and Anesthesiology, Medanta–The Medicity, Gurugram, Haryana, India

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The term "sepsis" is derived from Greek word "sepo" meaning "I rot" and was first introduced in the poems of Homer (ca. 18th century BC). Sepsis and septic shock are among the major causes of mortality in critically ill patients. Recent Sequential Organ Failure Assessment (SOAP) study across Europe estimated that more than 35% of intensive care unit (ICU) patients had sepsis at some point during their ICU stay.[1]

As per the World Health Organization (WHO), pneumonia is the leading cause of sepsis. Data for sepsis-related death in low-income group countries are not readily available, but if we consider deaths due to pneumonia as surrogate for sepsis-related deaths, in 2012, a threefold higher death rate (91 deaths per 100,000 persons) has been reported in low-income countries than in high-income countries.[2,3]

To determine the incidence and outcome of severe sepsis among adult patients, a multicenter, prospective, observational study was conducted in four intensive therapy units in India from June 2006 to June 2009, which reported the incidence of severe sepsis as 16.45% of all admissions and a hospital mortality of 65.2%.[4] Economic impact of ICU admission in a country like India cannot be ignored. As per one estimate, one episode of hospitalization is enough to account for 58% of per capita expenditure pushing 2.2% below the poverty line, and more than 40% of those admitted to an ICU borrow money or sell assets.[5]

Historically, the mortality associated with sepsis and septic shock has been approximately 50 to 75%.[6–8] Introduction of antibiotics approximately 50 to 60 years ago brought the mortality rate in the range of 30 to 50%, and subsequent advancement in treatment reduced mortality to approximately 18%. However, despite reduction in mortality rate, the overall number of patients dying from sepsis is increasing.[9]

After the introduction of the term "sepsis" approximately 2,700 years ago, it was only in 1914 that Hugo Schottmüller formally defined *septicemia* as a disease caused by microbial invasion into bloodstream. Despite this early definition, terms such as "septicemia," "sepsis," "toxemia," and "bacteremia" were all used interchangeably. There was a need for standard definition, and in 1991, a joint conference of American College of Chest Physicians (ACCP) and Society of Critical Care Medicine (SSCM) established the first definition of sepsis and introduced the terms "systemic inflammatory response syndrome" (SIRS), "severe sepsis," and "septic shock."

In 2001, SCCM, ACCP, and the European Society of Critical Care Medicine (ESCIM) revised sepsis definition by consensus and added an expanded diagnostic criterion. They also recognized stages of sepsis designated by the acronym PIRO (predisposition, infection, response to the infectious challenge, and organ dysfunction). Both the 1991 and 2001 definitions were based on SIRS. Moving forward, not only was the need for two or more SIRS criteria found to be insufficiently specific, but it also failed to identify patients at risk of death. It was also argued that SIRS neither reflects the severity of the disease nor indicates that there is maladaptive host response.[10]

In 2016, SCCM and ESICM gave us the Third International Consensus Definitions for Sepsis and Septic Shock aimed at identifying patients with increased risk of both mortality and prolonged ICU stay. A Delphi process was used to reach a consensus definition, which resulted in use of increment in SOFA score by 2, elevated lactate levels despite fluid resuscitation, and vasopressor-dependent hypotension as criteria in the new definition.[11]

As per 2016 definition, sepsis is a life-threatening organ dysfunction due to a dysregulated host response to infection. Organ dysfunction is defined as an increase of ≥ 2 points in the SOFA score. Septic shock is defined as a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality. The clinical criteria to identify septic shock are the presence of sepsis and persistent hypotension requiring vasopressors to maintain mean arterial pressure (MAP)

Address for correspondence
Dr. Yatin Mehta, MD, MNAMS, FRCA, FAMS, FICCM, FIACTA, FTEE, Medanta Institute of Critical Care and Anesthesiology, Medanta–The Medicity, Sector 38, Gurugram, Haryana 122001, India
(e-mail: yatinmehta@hotmail.com).

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$\geq$ 65 mm Hg, along with lactate $\geq$ 2 mmol/L despite adequate volume resuscitation. The term "severe sepsis" has been discarded.

The major implications of the new definition include the recognition of role of dysregulated host response in pathogenesis of sepsis and septic shock, the use of increment of SOFA score by 2 to identify the patients with sepsis, and the use of quick SOFA (qSOFA) score to identify septic patients outside of ICU.

Basic components in management of sepsis and septic shock include initial resuscitation, vasopressor/inotropic and hemodynamic support, early antibiotic, source control, diagnosis (cultures and imaging), supportive care (ventilation, dialysis, transfusion, etc.), and infection prevention. In 2004 and subsequently in 2004 and 2012, SCCM and ESCIM published protocol-based "surviving sepsis" guidelines (►**Table 1**). The bundle approach advocated by these guidelines was shown to reduce mortality.[12]

Early goal-directed therapy introduced by Rivers et al in 2001 remained an important component of protocol in all the three guidelines. In 2014, however, the protocol-based resuscitation was challenged by ARISE (Australasian Resuscitation in Sepsis Evaluation), ProMISe (Protocolized Management In Sepsis), and ProCESS (Protocolized Care for Early Septic Shock) trial, and this led to a changes in the 6 hours bundle (3 hours bundle remained unchanged) by the surviving sepsis guideline. The measurements of central venous pressure and central venous oxygen saturation are not required as per the new bundle.

The situation is far from perfect, however, and some problems with the new definitions have been pointed out. SOFA is complex to calculate and qSOFA has been validated only out of ICU and retrospectively. Sepsis 3 did not include data from low-income group countries.

The strengthening of basic care and preventive strategies are extremely important in a developing country such as India. For example, in an international study, it was found that device-associated infections in the ICUs in developing countries pose greater threats to patient safety than in US ICUs.[13]

Moving forward, new developments offer a peek into the changes we can expect in future. Multiple clinical studies have demonstrated an independent association between an increasingly positive fluid balance and increased mortality in patient with sepsis.[1,14–23] The concept of fluid administration guided by fluid responsiveness is gaining grounds, and tools such as carotid Doppler peak velocity, passive leg raising, and echocardiography have been shown to help gauge fluid responsiveness.[24,25] Counterintuitively, the use of β-blockers to control heart rate in patients with septic shock on high dose of norepinephrine has been shown to reduce mortality.[26]

Table 1 For management of sepsis, severe sepsis, and septic shock

	Old	New
Sepsis	SIRS + suspected infection *The 2012 definition required suspected infection and presence of some of the following: general variables, inflammatory variables, hemodynamic variables, organ dysfunction variables, and tissue perfusion variables	Suspected or documented infection + Increase in SOFA score by $\geq$ 2 *or* For out-of-ICU patients 2 out of 3 criteria for qSOFA Hypotension systolic BP $\leq$ 100 mm Hg GCS $\leq$ 13 Respiratory rate $\geq$ 22 breaths/min
Severe sepsis	Sepsis-induced tissue hypoperfusion or organ dysfunction • Sepsis-induced hypotension • Lactate above upper limits laboratory normal • Urine output $<$ 0.5 mL/kg/h for $>$ 2 h despite adequate fluid resuscitation • Acute lung injury with $Pao_2/Fio_2 < 250$ in the absence of pneumonia as infection source • Creatinine $>$ 2.0 mg/dL (176.8 μmol/L) • Bilirubin $>$ 2 mg/dL (34.2 μmol/L) • Platelet count $<$ 100,000 μL • Coagulopathy (INR $>$ 1.5)	
Septic shock	Sepsis + hypotension despite adequate fluid resuscitation	Sepsis + Vasopressor requirement to maintain MAP $\geq$ 65 + Lactate $>$ 2 mmol despite adequate fluid resuscitation

Abbreviations: BP, blood pressure; GCS, Glasgow coma scale; ICU, intensive care unit; INR, international normalized ratio; MAP, mean arterial pressure; qSOFA, quick SOFA; SIRS, systemic inflammatory response syndrome; SOFA, Sequential Organ Failure Assessment.
Adapted from Singer M, Deutschman CS, Seymour CW, et al. International Guidelines for Management of Severe Sepsis and Septic Shock: 2012 Surviving Sepsis Campaign. Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:801–810.

Search and evaluation for molecular methods for rapid detection of infection, therapeutic targets (angiopoietin 1, Slit2-N, sphingosine 1 phosphate, histones, pentraxins, etc) may yield practice changing results in future. New sepsis alerts tools based on concepts such as wearable physiologic monitoring devices, cognitive ergonomics, human-centered interface design, use of more sophisticated mathematical modeling, and machine learning techniques may become available in future. The availability of new biomarkers may enable better prognostication. Pediatric sepsis biomarker risk model (PERSEVERE) is one such example that has been recently validated.

Long-term consequences of septic shock such as neuropsychological impairment, physical impairment, sepsis-induced inflammation and cardiovascular risk, sepsis-induced immunosuppression, health care resource use, long-term health-related quality of life, and mortality are being recognized, and they provide impetus to changes and additions in management strategy.

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