Sepsis in Vulnerable Populations

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ABSTRACT

Despite the acquisition of a large body of evidence, there are many unanswered questions about sepsis. The definition of this disease is plagued by the lack of a simple pathophysiological description linking cause to effect and the activation of host immune responses that hinders disease progression at the same time producing multiorgan dysfunction. A plethora of inconsistent clinical features has served to obfuscate rather than illuminate. The Surviving Sepsis Guidelines (SSG) are a major advance because it comprehensively interrogates all aspects of care for the critically ill. For vulnerable populations living in low- and middle-income countries, this guideline is ineffectual because of the lack of region-specific data, differences in etiology of sepsis and burden of disease, limited human capacity and infrastructure, as well as socioeconomic realities. Appropriate care must be guided by common sense guidelines that are sensitive to local realities and adapted as relevant data are acquired.

Common sense is not so common
—Voltaire 1765

Hippocrates recognized sepsis as the disease that caused flesh to rot and wounds to fester. Centuries after the entity was first recognized, a complete understanding of sepsis continues to elude us. It was only at the end of the last century that we recognized that sepsis was a more complex process involving an organism and the host's response. Although triggered by an infecting agent, an exaggerated immune response is a major contributor to the self-destructive clinical picture. The host response is not limited to the primary initiating organism, but it produces multiorgan failure that has since been recognized as the hallmark of sepsis [1]. Baue [2] later emphasized the importance of the host's immune response to any major insult including surgery, trauma, and an infecting agent by its invoking the "horror autotoxicus" (described earlier by Ehrlich) whereby the host launches an autoimmune response that challenges the insult (septic or nonseptic) with significant self-injury manifested by multiorgan failure. Sepsis is present when a source is suspected or identified and there are clinical and laboratory indicators of the systemic inflammatory response syndrome (Table 1). "Severe sepsis" is defined as sepsis with evidence of hypoperfusion and organ dysfunction, whereas "septic shock" is heralded by the presence of severe sepsis with the need for vasoactive drugs to maintain blood pressure and perfusion. This progression of sepsis is important to distinguish because the development of hypoperfusion and organ dysfunction directly influences mortality rate (Table 2) [3—5]. Recently, this gradation of sepsis has been challenged by the notion that it is the organ dysfunction that is the key factor that predicates outcome [6]. Further interrogation of the definition has prompted the view that a more complete description requires an adaptation of the TNM (or tumor, node, metastases) classification used in describing cancer, namely PIRO [7], which would include the following: predisposition (factors that influence the character of the host response); insult (the nature of the primary insult); response (host response to the insult); and organ dysfunction (extent to which organs are dysfunctional). This approach is attractive because it allows for a more specific description of the organism-host interaction. Studies adopting this approach are currently in progress.

For sepsis in resource-limited settings, this nebulous reality of an evolving definition of sepsis is compounded by the dearth of data about sepsis in low- and middle-income countries (LMIC) [8,9]. The Surviving Sepsis Guidelines (SSG) represent the synthesis of current evidence and are considered the standard of care for sepsis in high-income countries (HIC) [10]. Although the pathogenesis of sepsis may be similar in LMIC and HIC, the plethora of infectious diseases that affect LMIC is vastly different [11,12]. Furthermore, LMIC lack the human resources and infrastructure to apply the guidelines [13—16]. Given these realities, the vexing question is whether guidelines are appropriate in LMIC. Several investigators have argued for the implementation of modified guidelines while the quest for data in LMIC continues [9,17,18].

As we continue to unravel this disease, it would be prudent to adopt a common sense approach to sepsis in LMIC. This paper provides a review of sepsis in resource-limited settings. It examines the epidemiology and demography of sepsis, its pathophysiology, and the clinical spectrum of sepsis with special attention to the cardiovascular and respiratory effects of sepsis. It then provides a review of management to provide guidance on treatment and improving outcomes.

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TABLE 1. Clinical features of sepsis

	Documented or Suspected Infection Plus 1 or More of the Following
General	Fever or hypothermia Tachycardia Tachypnea Delirium or obtundation Edema or positive fluid balance Hyperglycemia without diabetes mellitus
Inflammatory variables	Leukocytosis, leucopenia, normal WCC plus immature cells Elevated C-reactive protein or procalcitonin
Hemodynamic changes	Hypotension Elevated mixed venous saturation or cardiac index
Organ dysfunction	Arterial hypoxia Oliguria, elevated creatinine Coagulation abnormalities, thrombocytopenia Paralytic ileus Hyperbilirubinemia
Tissue perfusion variables	Elevated lactate, decreased capillary refill or mottling
Severe sepsis	Sepsis plus organ dysfunction
Septic shock	Sepsis plus hypotension unresponsive to fluids or hyperlactatemia

WCC, white cell count.
Adapted, with permission, from Levy et al [1].

EPIDEMIOLOGY AND DEMOGRAPHICS OF SEPSIS

The global burden of disease is extensively reported based on commonly used descriptions of disease [19,20]. These data describe mortality and morbidity (measured by disability-adjusted life years) by country. The epidemiologic transition indicates a general increase in noncommunicable diseases with a concomitant decrease in communicable diseases [17,18]. There are several limitations to assessing the burden of disease imposed by sepsis if traditional approaches are adopted. First, sepsis is not seen as a distinct entity in the medical community. The usual approach is to describe infectious diseases by site with no reference to sepsis. It would be simplistic to estimate the burden of sepsis by adding all infectious diseases such as lower respiratory tract infection and diarrhea (the fourth and seventh leading causes of death) because the definitions for sepsis may or may not have been satisfied [21]. Second, underreporting of sepsis is possible because some diseases may have sepsis as the underlying cause of death. For example, patients with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome commonly present with sepsis as the cause of mortality, but the cause of death is not documented as such [22]. Lastly, the pattern of infectious diseases varies between and within countries [11,12]. As a result, it is difficult to entertain effective solutions in resource-constrained environments in the face of a limited understanding of the burden of illness.

Studies generated from intensive care units (ICU) have the advantage of having addressed sepsis specifically but are largely cross-sectional prevalence studies and are predominantly from HIC [3,12,23–25]. There is a significant difference in infection rates and causative organisms when comparing U.S. with European ICUs [23,26]. Few reports exist for LMIC [4,27,28]. For all of these reasons, Adhikari et al. [29] argue that the global estimates of critical illness are underestimated. The burden of sepsis may be as much as 56% in Sub-Saharan Africa (representing LMIC) with a global contribution to mortality of 23% [29].

There is a relatively consistent relationship between the severity of sepsis as defined by the consensus criteria and mortality rate [1] (Table 2). It is worth noting that there are significant variations in mortality based on the population being considered (Table 2). The presence of shock, however, is uniformly associated with a higher mortality rate. It follows therefore that interventions applied early in the illness, before the onset of shock are likely to produce the greatest reduction in mortality. The caveat demonstrated in Table 2 is that low mortality from sepsis/severe sepsis (a LMIC cohort [5]) probably reflects a younger patient population who present to ICU following acute trauma with minimal previous comorbidity.

TABLE 2. Mortality from sepsis: relation to severity

	Mortality			
Country	Sepsis	Severe Sepsis	Septic Shock	Source
Brazil	35	47	52	Silva et al., 2004 [4]
Italy	36	52	82	Salvo et al., 1995 [3]
South Africa	10	14	66	Muckart and Bhagwanjee, 1997 [5]

Values are %.

The Millennium Development Goals have heightened awareness about maternal and child health, and addressing sepsis in resource-limited countries is central to improving these outcomes. A high prevalence of neonatal infections is described in LMIC with a large proportion of surviving neonates having neurodevelopmental impairment [30]. Mortality in Brazilian children with sepsis was about 20% [31]. A recent review of maternal deaths in HIC identified an underestimation of the burden of maternal death from sepsis [32], which can be extrapolated to be worse in lower-income countries. The HIV epidemic had a devastating effect on maternal well-being in Africa where HIV-related complications (primarily sepsis) have taken over as the leading cause of maternal death [33].

It is evident that both maternal illness and death are consistently associated with a negative effect on gross