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

domestic product [34,35]. As a result, considerable research has been directed at the economic consequences of sepsis. Evidence confirms that malaria, tuberculosis, and HIV—all associated with sepsis—affect the young and economically active, thus affecting household income both from the perspective of paying for health care and reducing the ability to generate an income as a result of illness [36]. Emerging evidence indicates that sepsis results in substantial impairment in quality of life, which may be sustained for many years [37]. However, there is a paucity of data on the consequences of sepsis on families and long-term income-generating capabilities of patients. To help address this, the critical care community has recently initiated assessment of the long-term effect of sepsis on the quality of life [38].

PATHOPHYSIOLOGY

The trigger for sepsis is the presence of a virulent organism in sufficient quantity to produce a pro- and anti-inflammatory immune response in the host [39]. The proinflammatory state results in collateral organ damage, whereas the anti-inflammatory effect increases susceptibility to infection [39]. Abnormalities in leukocyte function, coagulation and complement activation, neuroendocrine function, and immune cell function occur concomitantly [39]. Organ failure is primarily the result of impaired oxygenation resulting from hypoperfusion (hypotension and altered regional blood flow), thrombosis, capillary leak, and mitochondrial dysfunction [39–41]. Outcome from sepsis depends on severity of hypoperfusion and organ failure (Table 2) [42].

Cardiovascular consequences of sepsis

All elements of the circulation are adversely affected in sepsis. Increased capillary permeability and fluid loss into the interstitium reduce pre-load whereas afterload is reduced by loss of vascular tone [43]. The etiology of myocardial dysfunction, frequently found in sepsis, is complex and incompletely understood [44]. Cytokines mediate reduction in contractility, whereas mitochondrial dysfunction and apoptosis also contribute to overall diminution of cardiac capacity [44]. Nitric oxide has a variable effect on cardiac function; deleterious and positive effects have been described depending on the type of nitric oxide expressed [44]. Sepsis-induced cardiomyopathy is a well-recognized entity and, similar to cardiomyopathy described in pheochromocytoma, the presence of high circulating catecholamines are thought to be responsible for this devastating complication [45–47]. The net effect of sepsis is reduction in contractility, impaired response to intravenous fluids, and myocardial dilation [44]. Tachycardia is a key compensatory response to hypotension based on the baroreflex [43]. To add to this conundrum of significant cardiovascular compromise in the face of excessive demand, it has recently been shown that new onset atrial fibrillation, which is common in sepsis, is associated with increased mortality [48]. Furthermore, this complication is associated with increased risk of long-term cardiac failure, ischemic stroke, and death [49].

Respiratory consequences of sepsis

Pneumonia is a leading cause of sepsis and produces hypoxia [9]. This occurs because of ventilation-perfusion mismatch from the infection but can also be the result of acute respiratory distress syndrome (ARDS). The development of ARDS is related to the inflammatory response associated with sepsis [39]. The most recent definition of ARDS includes the following: hypoxia despite mechanical ventilation; occurrence within a week from a known cause; chest infiltrates; and no cardiac etiology for edema [50]. Excessive fluid administration and inappropriate ventilation aggravate hypoxia and progression of lung injury [51,52]. ARDS is also known to aggravate organ dysfunction, hence the need for early effective treatment [52]. Lastly, ARDS results in significant long-term disability in survivors, which is related to the duration of mechanical ventilation and length of ICU stay [53].

Clinical features

Although cardiovascular and respiratory dysfunction are the cardinal manifestations of sepsis, all organ systems are involved [1]. Patients generally present with signs of systemic infection (fever, tachycardia, tachypnea, and altered white cell count), a site of infection and evidence of organ dysfunction (hypotension/hypoperfusion, hypoxia, altered sensorium, and/or low urine output) (Table 1). None of these features are sensitive or specific enough for the early recognition of sepsis. As a result, current recommendations are that sepsis must be considered when there is any evidence of infection and $\geq$1 clinical features of organ dysfunction [1].

The commonest site for sepsis is the respiratory tract followed by the abdomen, bloodstream, and urinary tract, which occur with similar frequency [12,54]. Respiratory tract infections are associated with the highest mortality from sepsis in HIC [55]. In addition, host factors such as age, sex, and race also influence chances of survival [55]. The causative organisms are typically gram-negative and gram-positive bacteria followed by fungi [12]. These data are primarily from HIC. Limited data from LMIC suggest that the spectrum of organisms and antimicrobial susceptibility patterns are different. Therefore, it is essential to consider regional endemic causes of sepsis before recommending antimicrobial prescribing practices [11,56,57].

MANAGEMENT OF SEPSIS

In HIC, the standard of care has been guided by SSG [10]. These guidelines cannot be directly applied in LMIC because of limited human capacity and infrastructure [8,9]. As a result, alternate approaches to care provision are essential. The Integrated Management of Adolescent and Adult Illness guideline was designed specifically for LMIC and is based on evidence and expert opinion [58].

Similarly, other approaches (e.g., adapting SSG) have been suggested to address this deficiency [9]. The ethical dilemma posed is whether we should implement a guideline based to a significant extent on the views of experts or await the accumulation of a sufficient body of evidence that can stand the test of scientific scrutiny. The accumulation of appropriate data will likely take several decades in which time many patients will receive care without suitable guidelines. On this basis, it is generally accepted that recommendations based on current data and expert opinion should be adopted and fervent efforts should be directed at addressing the gaps in key research questions in LMIC [17].

The basic principles in sepsis management that are not in dispute are early effective resuscitation, antimicrobial therapy, source control, and organ support (Fig. 1).

Resuscitation

Cardiovascular management. a. Fluid Resuscitation

The SSG recommend aggressive fluid resuscitation based on a single randomized study [39]. As part of a bundle of care (early goal directed therapy) in the first 6 h after presentation this has proven to be effective in HIC [59,60]. In LMIC, aggressive fluid resuscitation may be hazardous because unlike in HIC, diuretics, mechanical ventilation, and hemodialysis are not readily available to manage inadvertent fluid overload. For this reason, a moderate fluid administration regimen is advocated in this setting [9,58].

A single multicenter trial conducted among children with severe sepsis in LMIC in Africa showed an increase in mortality when saline or albumin boluses were compared with a nonbolus control group [61]. The investigators recommend that a conservative fluid strategy be applied in the pediatric population in similar settings. The same group suggested that the World Health Organization's Integrated Management of Adolescent and Adult Illness guidelines have failed to incorporate the findings of their study and should be revisited [62]. There are several reasons for caution to be applied to the adoption of a conservative strategy. This is the only large randomized trial addressing this question in LMIC. About 57% of the subjects in the study had malaria, a group in whom some clinicians would not have used an aggressive fluid resuscitation strategy [63].

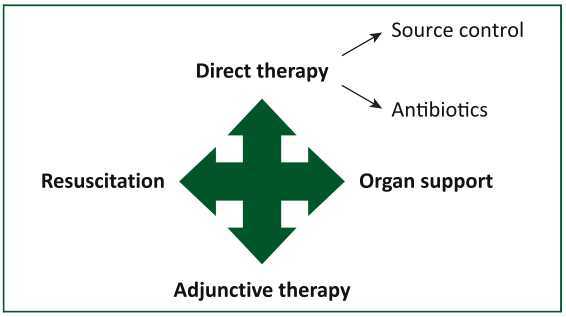

FIGURE 1. Therapy for sepsis.

Normal saline has been the resuscitation fluid of choice in most clinical trials but may not be the ideal fluid based on the associated risk, including saline-induced acidosis [43,64]. Synthetic starches have been shown to increase mortality and renal dysfunction and should not be used in LMIC [65]. Albumin is not routinely available in LMIC and should arguably be considered as a second line fluid intervention in this setting. Although albumin has been recommended as a suitable fluid in SSG [10], the general lack of availability of the fluid and equipoise regarding benefit mitigate against recommending this option [66]. Further research is essential before this approach can be uniformly recommended in LMIC.

b. Vasoactive Drugs

A significant reduction in afterload is the hallmark of early, florid septic shock. Initial resuscitation in HIC is therefore directed at increasing afterload with a vasopressor. Norepinephrine, vasopressin, epinephrine, and dobutamine are all suggested drugs to be added in the face of hypotension that does not respond to fluid therapy alone [10]. Dopamine on the other hand is not recommended based on the observation that there is an increased mortality when compared with epinephrine [67]. Norepinephrine is the drug of choice in many HIC because of its dominant alpha-agonist properties. Vasopressin is considered a second line agent for this purpose. Epinephrine is not commonly used in HIC, whereas dobutamine is reserved for refractory shock where an increase in inotropy is required.

The dilemma for most LMIC is that norepinephrine, vasopressin, and dobutamine are not available. Epinephrine and dopamine are more commonly available. The former cannot be easily administered via a peripheral intravenous line and central venous access is suggested. Central venous access, however, is not available in district-level healthcare facilities and often is not readily available even at the regional level. Dopamine can be administered via a peripheral line. Based on these realities, the recommendation currently is for the use of epinephrine when a central line can be placed and dopamine when peripheral administration only is available [58].

c. Target Blood Pressure

SSG recommend a target mean blood pressure of $\geq$65 mm Hg and systolic $>$90 mm Hg [10] to protect organ perfusion. In certain circumstances, for example, previous hypertension, recommendations suggest this goal should be higher [10]. Recently, a multicenter open-label trial showed no benefit from targeting a higher blood pressure [68]. Dünser et al. [69] also question blood pressure as a target of resuscitation and propose targeting perfusion to vital organs (heart, brain, kidney), purporting that permissive hypotension might be acceptable. It appears judicious to aim for a blood pressure that achieves adequate perfusion thereby preventing multiorgan dysfunction and death. To this end, identifying the

blood pressure that achieves adequate tissue oxygenation and acceptable urine output may be more appropriate in LMIC.

d. Finding the Resuscitation Balance

The ProCESS (Protocolized Care for Early Septic Shock) investigators have demonstrated no benefit from early goal directed therapy when compared with protocolized care without central venous access or usual care [70]. Based on the observed increase in mortality with acute onset atrial fibrillation in patients with sepsis, an open-label study comparing esmolol to standard care showed a reduction in fluid requirement and mortality when a heart rate target of 80 to 94 beats/min was attained [71]. The danger of post-sepsis cardiomyopathy was previously alluded to by Richard [47]. These data suggest that aggressive cardiovascular resuscitation may not be beneficial; indeed, this approach may be harmful.

Given the limited capacity for invasive monitoring and laboratory testing that is the norm for LMIC, as well as the nascent risk of aggressive intervention, it is appropriate to advocate for the following:

- moderate fluid resuscitation using balanced salt solutions;
- dopamine or epinephrine if a vasoactive drug is required;
- mean arterial pressures around 65 mm Hg, as long as indices of perfusion are adequate.

Respiratory management. Supplemental oxygen should be administered to all patients with severe sepsis and/or septic shock [10]. This is based on the goal of maximizing oxygen delivery. Where respiratory failure prevails from fatigue or ARDS, lung protective mechanical ventilation should be added [52]. Further respiratory maneuvers should include lung recruitment and prone positioning when hypoxia is persistent and a change from a moderate to a conservative fluid strategy for established ARDS without evidence of hypoperfusion [70].

In LMIC, mechanical ventilation is a luxury for most settings and is usually restricted to large cities and academic centers. Most of the critical respiratory therapeutic options are therefore unavailable to the majority of patients. Nasal oxygen should be used for severe sepsis or septic shock. A moderate fluid resuscitation strategy is essential to avoid unintentional fluid overload and the need for diuretics, mechanical ventilation, or dialysis.

Direct therapy

Source control. There are no randomized trials comparing effective source control to no source control, as such a trial would be unethical. Existing data sources depend on retrospective reviews and comparison of different techniques for source control. It is known that undue delays in source control adversely influence outcome [72]. Conversely, there is also a concern that attempts at source control in the unstable patient, or where there are long transit times to the operating room or interventional radiology suite, increase the risk of poor outcomes [72]. The balance rests between the need to move a patient for effective control and the need to achieve adequate resuscitation and antibiosis; good clinical judgment must be the arbiter. SSG recommend achieving source control within 12 to 24 h, and common sense would suggest that, within the constraints of other critical treatment needs, the sooner this is accomplished, the better [10,73].

Antimicrobial therapy. Each hour of delay in the institution of appropriate antimicrobial therapy for septic shock results in a dramatic increase in mortality (7.6% per hour) [74]. Effective therapy requires several important considerations: effective assessment of site of infection; likely pathogens; likely susceptibility; choice of agent; dose and duration of treatment; and escalation and de-escalation as appropriate. Furthermore, consideration of available antibiotics must also be considered; despite essential medicines lists and the best of intentions, many antibiotics are not available or must be paid for out-of-pocket by families. In LMIC, it is also important to recognize local endemic diseases such as tuberculosis, malaria, and dengue that have a crucial bearing on choice of antimicrobials [11]. It is common for there to be limited capacity for inpatient care or it is not feasible for families to afford or accommodate inpatient care. Under these circumstances, useful alternate strategies such as daily intramuscular injections on an outpatient basis may be appropriate [75]. Unique challenges call for novel solutions.

Organ support and adjunctive therapy. A comprehensive description of organ support is beyond the purview of this manuscript. It will suffice to submit that the same attention to each organ system is essential for a favorable outcome from sepsis. A major contribution of SSG is the recognition that adjunctive therapy such as the use of steroids and early enteral feeding are vital in the quest for total patient care. For each of these broad recommendations, local factors must be considered in determining appropriateness of interventions.

Socioeconomic and health system factors

The impact of the social and economic factors in all societies is easily underestimated in the classical medical model of care provision. A study looking at community awareness (in an HIC setting) identified poor public awareness about sepsis [76]. Patients come from communities (Fig. 2), and their health-seeking behavior is affected by their knowledge. Poor knowledge about a disease will result in slow or no response in the face of a serious life-threatening condition. It is likely that a similar or worse pattern of knowledge exists in LMIC. Illiteracy, poverty, and long travel times all seem to have an impact on time to receive medical attention in El Salvador, for example [77]. Furthermore, many patients may never actually present to a health facility because of these aforementioned challenges

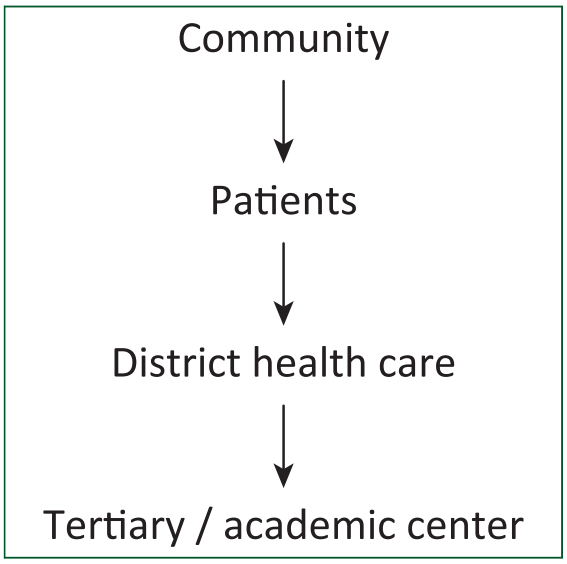

FIGURE 2. Socioeconomic and health system factors.

to accessing care. As shown previously, delays in accessing treatment significantly influence outcome from sepsis. A large proportion of patients in LMIC seek care at district-level facilities. These facilities lack the infrastructure and human capacity to deliver effective care [8,78]. Lastly, a proportion of patients will need to be transferred to higher level healthcare services. These services are usually available in larger cities or academic centers. These centers tend to be better staffed with appropriate infrastructure. The limiting factor is long transfer times and excessive demand for limited numbers of ICU beds [14].

The notion that implementing guidelines will improve outcomes is incorrect. The need for initiatives that embrace the community to be part of the solution is self-evident. Furthermore, improving outcomes from sepsis depends on understanding each of the elements in the healthcare chain and implementing steps that materially strengthen healthcare delivery and access to care.

SUMMARY

Sepsis is a complex disease entity that, to this day, we struggle to define. Whereas there is a large and relatively persuasive body of evidence to guide care for sepsis in HIC, we are challenged by the dearth of data from LMIC. This paucity of information makes recommendations and guidelines difficult to establish and to apply. Furthermore, the lack of skilled human resource capacity and infrastructure to recognize and treat sepsis as well as the difficult socioeconomic challenges in LMIC are significant hurdles to surmount to achieve better outcomes in sepsis treatment and mortality. The quest for data must be paralleled by the development and application of needed guidelines for care that are cognizant of current data and local realities. The final solution rests in the acknowledgment that only by taking small steps guided by data and common sense will we get closer to offering care to this vulnerable population.

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