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Sepsis and the Global Burden of Disease in Children

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In 2010, an estimated 25% of disability-adjusted life-years—a metric that incorporates premature death by years of life lost and years lived with disability—and 13% of all deaths worldwide were in children younger than 5 years.[1,2] While reductions in mortality in children younger than 5 years have occurred in many countries since 1990, mortality increased in young children in some parts of sub-Saharan Africa, with severe infections leading to sepsis being a major contributor.[1] For instance, in the neonatal period, diarrhea, lower respiratory tract infections, and meningitis were important contributors to mortality in 2010, while in the postneonatal period, nearly 1 million estimated deaths (half of all deaths) were due to lower respiratory tract infections (respiratory syncytial virus, *Haemophilus influenzae* type B, *Streptococcus pneumoniae*), diarrheal diseases (rotavirus, *Cryptosporidium*), and malaria.[2] Other infectious causes of death in children younger than 5 years were measles, pertussis, and human immunodeficiency virus/AIDS. We suggest that sepsis-related pediatric deaths are substantially underestimated and that efforts are needed to better assess the impact of sepsis on childhood mortality worldwide.

The Surviving Sepsis Campaign defines *sepsis* as the presence of infection together with systemic manifestations of infection; sepsis-induced organ dysfunction or tissue hypoperfusion is referred to as *severe sepsis*.[3] The common pathway to death for most children with systemic signs and symptoms associated with bacterial or viral infections is sepsis, whether death occurs at home or in a health care facility. These infections can result in a systemic inflammatory response and progress to severe sepsis and septic shock, often leading to multiorgan failure and death; survivors may have significant disabilities.[4,5] However, for the Global Burden of Disease Study 2010 estimates, sepsis as a cause of death is considered only for neonatal deaths.[2,6] Although this is likely due to a lack of data, such estimates underestimate the contribution of sepsis to mortality in the postneonatal period and in children aged 1 to 4 years. It is important to classify deaths according to specific causes as these data are needed for crafting and deploying preventive measures such as bed nets for

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malaria-endemic areas and vaccines such as for measles and pertussis. However, when faced with a child with severe multiorgan illness and systemic signs and symptoms of an infection, it is important to emphasize that the unifying feature of nearly all of these deaths is that they are due to sepsis.

Severe infections lead to systemic symptoms and organ dysfunction, which if untreated lead to death and disability. Moreover, pneumonia, diarrhea, malaria, and mixed infections commonly coexist; thus, there is considerable overlap of symptoms and organ involvement regardless of the etiologic agent. As a consequence, the clinician is faced with signs and symptoms consistent with syndromic sepsis, and practical interventions and pragmatic processes addressing sepsis can lead to greater efficiency and reduced deaths and disability as compared with focusing on specific infectious agents. From the clinician's viewpoint, a diagnosis of sepsis recognizes that children who die of infections, regardless of their source, develop various combinations of septic shock, cardiac failure, acute respiratory distress syndrome, or other organ dysfunction. This is the overwhelming experience in resource-rich countries such as the United States and Australia where infections leading to sepsis and septic shock confer a high burden of disease and mortality in pediatric intensive care units.[4,5] Moreover, generic support for the underlying pathophysiology in patients with sepsis syndrome has resulted in marked improvements in outcomes in resource-rich areas and, with a similar approach, may also do so in resource-poor areas. Indeed, the largest study of children with severe febrile illness and impaired perfusion in sub-Saharan Africa supports this contention in that all deaths were due to a combination of severe shock and acidosis with or without respiratory and neurological dysfunction.[7]

Highlighting sepsis as the result of severe illness from infections is important for ensuring provision of appropriate timely supportive care, especially in resource-limited environments where the disease burden is high and early intervention may circumvent multiorgan failure that demands resources such as ventilators or dialysis machines that are not available. Moreover, skilled health care workers are in short supply and care is being delivered by teams with limited training and clinical skills; the syndromic sepsis approach lends itself to a simple generic protocol for recognition and treatment that can be taught and implemented even in austere settings. Another common issue is the lack of laboratory services for microbiological diagnoses. Hence, highlighting severe illness with systemic signs and symptoms triggered by infections as sepsis helps the clinician because there is greater reliance on clinical acumen and less emphasis on laboratory pathogen confirmation. Indeed, the most important interventions to reduce sepsis morbidity and mortality must be made before a specific pathogen diagnosis is available.

That invasive infections lead to sepsis, severe sepsis, and septic shock is supported by clinical and robust pathophysiological evidence. It is often difficult to separate the 3 most common causes of death (pneumonia, malaria, and diarrheal diseases) in children with certainty in low-resource settings. These conditions often coexist and, when severe, lead to sepsis and septic shock. For instance, cerebral malaria is commonly associated with pneumonia, invasive bacterial infection is common in malaria, and pneumonia and diarrhea often occur concurrently in children in low-resource countries. A child presenting in septic shock may have pneumonia, malaria, or other invasive bacterial infection. Many children

with gastroenteritis die of dehydration and electrolyte disturbances. However, those who fail to improve after intravascular volume replacement and correction of electrolyte abnormalities are also likely to have a bacterial superinfection and sepsis. Thus, an approach by clinicians to manage the complex syndrome (severe sepsis) is indicated. The Surviving Sepsis Campaign international guidelines[3] address the role of antimicrobials (if available).

In most cases, identification of the specific etiologic agent(s) is not needed for initial management of children with sepsis. Separation into clinical syndromes is best made on clinical grounds and can signify the site of infection such as pneumonia or meningitis in some cases. However, the initial treatment options for most severe infections leading to sepsis are also limited and should include broad-spectrum antimicrobial administration, fluid administration (based on intravascular volume status), blood products (based on hemoglobin and platelet levels), oxygen administration (based on oxygenation status), and close monitoring. Thus, clinical management will be very similar—with minor variation in broad-spectrum antimicrobial choices based on cost and availability. Labeling pediatric sepsis as the final common pathway leading to critical illness and death from most infectious agents in resource-limited areas also simplifies educational materials and treatment protocols for health care workers with limited skills. The World Health Organization guidelines on integrated management of childhood illness use this approach by highlighting danger signs and therapies rather than specific diseases, thus highlighting sepsis and the emergency therapeutic interventions needed for treatment.

Given the efforts by the Surviving Sepsis Campaign to reduce sepsis-related deaths in all ages worldwide,[3] baseline estimates of sepsis-related deaths are needed to measure the success of such interventions. Therefore, we urge investigators who are assessing global mortality from infectious diseases to consider incorporating estimates of sepsis-related mortality for children of all ages.

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