Abstract:
The approach to sepsis in a global setting can appear challenging at first, complicated by differences in infectious etiologies, limitations in resources, variability in treatment and prevention strategies, controversies in application of clinical trial results, public health policy, and variation in cultural norms. In reality, however, the basic approach to sepsis in any context follows core principles within the practice of emergency medicine and critical care. Here, we discuss pediatric sepsis from a global health perspective and review simple strategies to reduce morbidity and mortality.

Keywords:
pediatric; infection; sepsis; septic shock; global; developing countries; FEAST trial

*Northwestern University Feinberg School of Medicine, Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL.
Reprint requests and correspondence: Ajay Khilanani, MD, Department of Pediatrics, Division of Pediatric Critical Care, Northwestern University Feinberg School of Medicine, Ann and Robert H. Lurie Children's Hospital of Chicago, 225 E Chicago Ave, Box #205, Chicago, IL 60611.
ajay.khilanani@gmail.com

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Pediatric Sepsis in the Global Setting

Ajay Khilanani, MD*, Mjaye Mazwi, MD*, Erin Talati Paquette, MD, JD, MBe*

Louis Pasteur, recognized for his profound contributions to germ theory of disease and principles in vaccination and pasteurization, is quoted as saying, "One does not ask of one who suffers: What is your country and what is your religion? One merely says: You suffer, that is enough for me. …" This statement gracefully describes the sentiment in which many physicians approach challenges in global health including sepsis.

The approach to sepsis by the emergency medical physician in a global setting can appear challenging at first, complicated by factors such as differences in infectious etiologies, limitations in resources, variability in treatment and prevention strategies, controversies in application of clinical trial results, public health policy, and variation in cultural norms. In reality, however, the basic approach to sepsis in any context follows core principles within the practice of emergency medicine—triage, timely recognition, resuscitation and stabilization, and medication administration. Everything else is secondary to these guiding concepts. Here, we will discuss sepsis from a global health perspective and review simple strategies to reduce morbidity and mortality.

SEPSIS AS A GLOBAL HEALTH PROBLEM CAN BE LIMITED

Sepsis results from a wide variety of infectious pathogens and is a leading cause of morbidity and mortality in the world. Whereas the overall mortality of children with severe sepsis and septic shock in industrialized countries is estimated at 2 to 10%,[1,2] the mortality in developing countries has been documented to be as high as 50%.[2] Developing countries such as India, Nigeria, Democratic Republic of the Congo, Pakistan, and China account for approximately half of all deaths in children younger than 5

years that result from infection.[3] As expected, variation exists between children who are previously healthy and those with chronic illness. Of the 7.5 million deaths that occur annually in children younger than 5 years, the majority (60-80%) are associated with sepsis—the common inflammatory pathway resulting from infectious disease that can lead to organ dysfunction, shock, and death.[4–6] According to data from the World Health Organization (WHO), the United Nations Children's Fund, and the Bill and Melinda Gates Foundation, nearly 70 to 80% of these deaths result from severe infections due to pneumonia, malaria, measles, neonatal sepsis, or diarrhea.[5,7] Infection also plays a large role in neonatal mortality, which makes up nearly half of child mortality in developing countries.[8] For these reasons, the common infectious pathway of sepsis should be considered the number 1 cause of childhood death globally.

Despite its significance globally, sepsis is a neglected entity.[7] This is particularly true in resource-constrained environments.[4] In part, this may occur because of the vertical nature of clinical and research programs that tend to focus on specific infectious diseases (eg, malaria, diarrhea, HIV) rather than managing the common syndrome of inflammation that results from numerous infectious diseases. Despite this, we know through multiple trials that simple interventions such as immunizations, vitamin and mineral supplementation, antibiotics, fluid resuscitation, and inotropic support can reduce morbidity and mortality 10- to 100-fold in a cost-effective manner.[5] This knowledge should empower any emergency medicine physician hoping to have a lasting impact on global health—from a clinical, educational, organizational/process improvement, or public policy standpoint.

REVIEW OF DEFINITIONS

Sepsis, as defined by the Surviving Sepsis Campaign,[1] is based on probable or documented infection in the presence of general clinical and/or laboratory evidence of systemic inflammation. The diagnosis must include 2 of 4 clinical criteria: abnormal temperature, tachycardia, tachypnea, and abnormal leukocyte count, with a requirement that 1 of the criteria must include abnormal temperature or abnormal leukocyte count. *Severe sepsis* is defined as sepsis with evidence of sepsis-induced organ dysfunction or tissue hypoperfusion.[1] *Septic shock* is defined as sepsis-induced hypotension despite adequate fluid resuscitation.[1]

LIMITATIONS IN TRADITIONAL DEFINITIONS

These traditional definitions, although adequate for developed and resource-abundant regions, cannot always be applied in settings of resource and/or cost limitations. At present, all 3 definitions (*sepsis*, *severe sepsis*, and *septic shock*), based on the Surviving Sepsis Campaign and the International Pediatric Sepsis Consensus Conference definitions, require laboratory tests to establish systemic inflammation (white blood cell count), organ dysfunction, and tissue hypoperfusion (PaO_2/FIO_2 ratio, $PaCO_2$, platelet count, international normalized ratio, serum creatinine, bilirubin, aminotransferases, and/or lactate levels). Given these limitations of applying definitions of sepsis globally, it is practical to create alternative definitions that are based solely on clinical criteria.

Need for Modified Definitions to Apply to Resource-Limited Areas

One possibility is to establish the systemic inflammatory component of sepsis based on 2 of 3 criteria (abnormal temperature, tachycardia, and tachypnea). Because leukocyte count is not part of this diagnostic definition, abnormal temperature would be required as 1 of the 2 criteria.[4] A recent study performed in Latvia involving 943 children identified all but 1 child while screening for systemic inflammation based on these criteria. Only 1 additional child with a normal temperature met criteria for systemic inflammation based on abnormal white count.[4,9] This study demonstrates a high level of predictive capability in these clinical criteria along with a low percentage of false negatives.

A second modified definition is derived from the integrated management of childhood illness guidelines developed by WHO to aid health workers in identifying children with infection.[4,10] Berkeley et al[11] applied observable criteria from these guidelines (Figure 1) to establish those in need of antibiotic therapy in a cohort of 11,874 pediatric admissions between 1999 and 2001. This clinical criterion was successful in identifying 80% of all invasive bacterial infections. Only 1% of children not identified by these criteria died, resulting in a 99% negative predictive value for mortality.

Modified definitions of sepsis represent pragmatic and noninvasive diagnostic alternatives that can facilitate early recognition. Further research, however, is required to validate clinical criteria with high sensitivity to reduce the risk of missing disease in resource-constrained areas. Because this may be associated with limited specificity, underlying