



Global advocacy needed for sepsis in children

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Available online 23 June 2017

KEYWORDS

Sepsis;
Global health;
Infection;
Morbidity;
Mortality;
Pediatric infection;
Global sepsis alliance

Summary Sepsis in children is a complex syndrome that develops from various infections and results in 15–30% mortality in high-income countries and up to 50% or higher in low-income countries. Worldwide, this represents an annual burden of 30 million cases resulting in 8 million deaths. Not surprisingly, there is a significantly higher burden in low-income countries with children there being 18 times more likely to die before the age of 5 years compared to high-income countries. Factors such as commercial air travel, climate change, and unchecked population growth have contributed to the growing burden of infectious diseases and ensuing sepsis. In this article, we review the important role of *global advocacy* to improve public awareness of sepsis; increase access to essential medicines and vaccines; improve use of evidence-based treatment guidelines; raise awareness of antimicrobial resistance and encourage antibiotic stewardship; and, develop resilient health systems that can cope with health crises. Advocacy in these areas can assist nations in reaching the United Nations sustainable development goals (UN SDGs) of low rates of neonatal and under-5 mortality.

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Introduction

Sepsis is a complex syndrome characterised by pro- and anti-inflammatory markers, immunologic mediators, and hormones of the neuroendocrine and autonomic nervous systems.¹ Clinically, sepsis represents the end pathway of most systemic infections, and can result in organ dysfunction, multi-organ failure, and death. Globally, this translates into a significant burden of critical illness resulting in 15–30% mortality in high-income countries, and up to 50% or higher mortality in low-income countries.^{2,3}

Worldwide, sepsis remains a leading cause of pediatric and maternal mortality;^{4,5} however, sepsis has remained a neglected killer without clear status or recognition as a major cause of morbidity and mortality.^{6,7} In this article, we review the burden of pediatric sepsis, the global disparities in treatment and outcomes of sepsis, the need for a broad framework to tackle sepsis, and most importantly, the urgent need for concerted *global advocacy*. Our focus on advocacy includes educating people and healthcare providers given that 80–90% of people in North America and Europe were unfamiliar with the term 'sepsis' and were unaware that

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it was a leading cause of death.⁸ We will highlight the importance of advocacy in implementing interventions and monitoring progress in preventing and treating sepsis as well highlight organisations such as The Global Sepsis Alliance dedicated to advocating for all aspects of prevention and sepsis care, which will contribute to reducing the burden of sepsis.^{8,9}

The need to highlight the burden and disparities

Sepsis is a condition in which a known or suspected infection is associated with at least two of the four features of the systemic inflammatory response syndrome (SIRS): tachycardia, tachypnea, hypo- or hyperthermia, and leucopenia or leukocytosis. The SIRS criteria used, by the International Consensus Conference, to define sepsis was intended for research purposes but/and has not been very useful to clinicians for early recognition of sepsis. In resource rich areas this definition has not proven practical primarily because of its high sensitivity and low specificity. In low- and middle-income countries (LMICs), the SIRS based sepsis definition is not only poorly specific, but also difficult to apply since it requires laboratory parameters such as a leukocyte count, not routinely available in all settings.^{10,11} Thus research and advocacy for context specific definitions are needed.

Regardless of the definition used the global burden of sepsis is high. The SPROUT study tracked severe pediatric sepsis in 128 pediatric intensive care units across 26 countries (based in North America, Europe, South America, Asia, Australia/New Zealand, and Africa). Of 6,925 children screened, 569 had severe sepsis, resulting in 25% mortality and 17% moderate disability.¹² The prevalence of sepsis varied from 6.2% in Europe to 23.1% in Africa.¹² Nation specific registries have provided additional insights into the burden of pediatric sepsis: in high-income countries such as Canada (excluding Quebec), 20,130 children between 2004–2009 were hospitalised with sepsis resulting in 5.4% mortality.¹³ In the United States (US), data from seven states show that 17,542 children were hospitalised with severe sepsis in 2005, representing an 81% increase in cases from 1995, and 45% increase in cases from 2000.¹⁴ In 2005, there were over 75,000 cases of severe sepsis nationally, costing the healthcare system approximately USD 4.8 billion. High rates of hospitalisation and mortality have also been reported in pediatric intensive care units in New Zealand, Japan, and Spain.¹⁵ When data are extrapolated globally, there are an estimated 30 million cases of sepsis annually with mortality of 8 million,² with a higher proportion of deaths in lower income countries. The deaths are concentrated in low-income countries in that children are now 18 times more likely to die before the age of 5 years in these areas versus in high-income countries,¹⁶ with infections being a significant contributor to this disparity.

Aside from the concerns of mortality, morbidity is also of significant concern and should be highlighted. Globally, almost 39% of children who survived severe sepsis experienced some degree of functional deterioration at 28 days.¹⁷ In LMICs, because of the high burden of mortality and the social and economic context of these settings, the morbidity burden has largely been ignored although

it is likely to be higher, particularly when compounded by widely prevalent malnutrition. These observations present unique opportunities for the development and validation of outcome measures, such as health related quality of life and functional status measures to better understand and develop interventions for post-discharge morbidity in these complex settings.^{8,18}

The need for robust health systems

The health systems in several LMICs are fragile, with a limited capacity to respond to health crises. The world witnessed this fragility with the Ebola outbreak as systems struggled to contain the outbreak; in addition, essential supplies including medicines, blood products, and human resources were depleted such that the system could not support delivery of other core health services. This was particularly damaging to countries in Africa, where several people perished due to a health system that could not contain the disease or cope with the sudden surge in casualties. Health systems are thought to be resilient if they can respond to a health crisis, maintain core functions, and reorganise as needed.^{19,20} Establishing resilient health systems requires robust disease surveillance systems, infrastructure and capacity for pre-hospital and emergency care, staff and laboratory services, primary health services, external alliances with non-government organisations to help with mass communication and relief efforts, and quality improvement and efforts to assess, evaluate, implement, and innovate new strategies for care.^{21,22}

It is evident that a robust health system should be able to prevent, manage, and cure infectious conditions and sepsis, while remaining resilient in the face of unpredictable health crises. Many LMICs are on different trajectories towards developing a robust, resilient health system, and achieving this will require strong global advocacy.

Given the global burden of sepsis and disparity in outcomes in LMICs, along with factors that facilitate spread of infection including commercial air travel, global trade, urbanisation, unchecked population growth, and climate change,²³ strong advocacy is needed to identify local, regional, and international factors that increase the burden of sepsis. This in turn will allow nations and the World Health Organization (WHO) to build a global framework, develop and evaluate appropriate interventions, and track progress towards achieving the SDGs related to neonatal and under-5 mortality. Interventions that may reduce the burden of sepsis include preventing infection (including vaccination), recognising and treating sepsis aggressively, increasing access to antimicrobials and essential medicines, and educating the public to seek better care.

Preventing infection

Sepsis may result from several infections including meningitis, pneumonia, diarrhea, dengue, Ebola, measles, and human immunodeficiency virus/AIDS. A recent analysis of 79 pediatric health records from four US hospitals²⁴ observed that the most common causes were respiratory (29%) and gastrointestinal (24%) infections, resulting in 22% mortality, a risk that could be mitigated through improved access to pneumococcal, influenza^{25,26} and other vaccinations.²⁷ In

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