Epidemiology of Pediatric Septic Shock

Daniela Carla de Souza^{1,2} Flávia Ribeiro Machado³

¹ Pediatric Intensive Care Unit, Department of Pediatrics, Hospital Sírio-Libanês, São Paulo, São Paulo, Brazil

² Pediatric Intensive Care Unit, Department of Pediatrics, Hospital Universitário da Universidade de São Paulo, São Paulo, São Paulo, Brazil

³ Department of Anesthesiology, Pain and Intensive Care, Universidade Federal de São Paulo, São Paulo, São Paulo, Brazil

Address for correspondence Daniela Carla de Souza, UTIP, Hospital Sírio-Libanês, Rua Alves Guimarães, 470 ap 113, Pinheiros, São Paulo, SP, Brazil, 05410-000 (e-mail: daniela@hu.usp.br).

J Pediatr Intensive Care 2019;8:3–10.

Abstract

Sepsis, or dysregulated host response to infection, is considered a worldwide public health problem. It is a major childhood disease both in terms of frequency and severity, and severe sepsis is still considered the main cause of death from infection in childhood. This review provides an overview of the epidemiology of pediatric septic shock. The prevalence of severe sepsis and septic shock among hospitalized children ranges from 1 to 26%. Mortality is high, ranging from 5% in developed countries to up to 35% in developing countries. However, 10 years after the publication of pediatric sepsis definitions, a global perspective on the burden of this disease in childhood is still missing. Major obstacles to a better knowledge of sepsis epidemiology in children are the absence of an adequate disease definition and not having sepsis as a cause of death in the World Health Organization Global Burden of Disease Report, which is one of the most important sources of information for health policies decision-making in the world. Several studies performed in both developed and developing countries have shown that mortality from septic shock is high and is associated with delayed diagnosis, late treatment, and nonadherence to the treatment guidelines. Reducing mortality from sepsis in childhood is a worldwide challenge, especially in developing countries, where the highest number of cases and deaths are recorded and where financial resources are scarce. Many specialists consider that prevention, education, and organization are key to achieve a reduction in the burden of sepsis.

Keywords

- severe sepsis
- septic shock
- prevalence
- incidence
- outcome
- mortality
- epidemiology
- pediatrics

Introduction

Sepsis, or dysregulated host response to infection, is considered a worldwide public health problem.¹ It is a major childhood disease both in terms of frequency and severity. Retrospective studies show that its frequency is increasing in the pediatric population, mainly due to the increased survival of very low birth weight infants and children with chronic conditions.^{2,3} Despite numerous efforts,^{3–6} severe sepsis and septic shock are still considered the main cause of death from infection in childhood.⁷ It is estimated that there were more than 4 million deaths worldwide in 2013 due to infectious

diseases in children under 5 years old, and the vast majority is due to severe sepsis and septic shock.⁷ The estimated healthcare cost of pediatric sepsis in the United States in 2005 was \$4.8 billion.⁸

Despite the importance of the disease and the efforts of several organizations, epidemiology data about global sepsis in children is still scarce. Studies in the 1990s, using the adult sepsis definitions proposed by Bone et al⁹ and adapted for children, reported a prevalence of septic shock in pediatric intensive care units (PICUs) of 2 to 3% in developed countries,^{10–12} and 18 to 46% in developing countries.^{13–15} These studies also reported high mortality from septic shock, with

received
November 1, 2018
accepted after revision
November 11, 2018
published online
December 28, 2018

Issue Theme Advances in Pediatric
Septic Shock; Guest Editor: E. Scott
Halstead, MD, PhD.

Copyright © 2019 by Georg Thieme
Verlag KG, Stuttgart · New York

DOI <https://doi.org/10.1055/s-0038-1676634>.
ISSN 2146-4618.

rates up to 80%.^{10–15} More recently, researchers have reported a decrease in mortality from septic shock in children, with rates around 10%.^{2,8}

It is important to raise awareness about the current burden of septic shock in children to establish appropriate prevention and treatment strategies and to improve the prognosis of the disease, as well as to better allocate health-care resources. This review provides an overview of the epidemiology of pediatric septic shock, focused on children beyond the neonatal period.

Definitions

Sepsis is a dynamic disease with a complex pathophysiology that has a varied and unspecific clinical presentation and affects a heterogeneous group of people. For these reasons, a simple definition is not feasible. Therefore, the definition of sepsis has evolved throughout history and studies published until the end of the 1980s used a variety of definitions and terminologies, for example, sepsis, septicemia, generalized infection, and sepsis syndrome, which made it difficult to compare results from different studies.

In 1992, the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) published the diagnostic criteria and definition of Systemic Inflammatory Response Syndrome (SIRS), sepsis, severe sepsis, septic shock, and organ dysfunction.⁹ These definitions were intended to diagnose sepsis in its early stage allowing rapid interventions capable of saving lives. Despite the high sensitivity and low specificity, these definitions helped to improve septic patients care and prognosis.

The improvement in knowledge of clinical, epidemiological and therapeutic aspects of sepsis pointed out limitations in the definitions proposed by the ACCP/SCCM.⁹ Thus, revised definitions for adults (Sepsis-3) were published in 2016.¹⁶ In these new definitions, sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection. Septic shock is defined by the presence of persistent hypotension which requires the use of a vasopressor to maintain mean arterial pressure above 65 mm Hg and serum lactate greater than 2 mmol/L, despite adequate fluid resuscitation. Finally, organ dysfunction is defined as a change of two points in the Sequential Organ Failure Assessment (SOFA) score. A major advantage of these new definitions was the simplification of the nomenclature, which replaced severe sepsis by sepsis, allowing the distinction between patients with uncomplicated infection and critically ill patients who have high death risk. However, these definitions raised a lot of controversy because the strict use of the SOFA score variations will select more severely ill patients and will lose sensitivity. For instance, patients with hypotension or a Glasgow coma score of 13 to 14 do not fit the strict criteria of organ dysfunction neither do the patients with hyperlactatemia, as lactate is not part of the score. In quality improvement programs, SOFA score calculation is not feasible and the detection of sepsis still needs to be based on the presence of any organ dysfunction. Although the SIRS criteria are no longer required for the definition of sepsis,

they are still relevant as a screening tool for infected patients with suspected sepsis. Many questions still remain such as its applicability in countries with limited resources and the potential delay in diagnosis.

Despite the advances for the adult population, until 2004 there was no consensus on pediatric sepsis definitions. Some researchers used the definitions proposed by Hayden,¹⁷ while others adopted Bone et al¹⁸ criteria, modified and adapted for pediatric patients. The difficulty to establish a consensus is related to the dynamic and complex nature of the disease, together with certain childhood peculiarities (different age groups, physiological changes in vital signs, different infectious agents, and predisposing factors). The absence of consensus on pediatric sepsis represents a major obstacle to a better understanding of its epidemiology.

In 2005, members of the International Pediatric Sepsis Consensus Conference (IPSCC) published new definitions for the pediatric group.¹⁹ Unlike the sepsis definitions proposed in 1992⁹ for the adult population, which were designed to improve early diagnosis at the bedside and thus allow immediate therapeutic intervention, pediatric sepsis definitions were primarily designed for research purposes. However, IPSCC definitions have been used in daily clinical practices all around the world and are the cornerstone for the development of treatment guidelines. According to IPSCC, sepsis is defined by the presence of two or more signs of SIRS, one of which being a change in temperature or in leukocytes counts, with confirmed or suspected infection. Severe sepsis in children is characterized by the presence of sepsis and cardiovascular or respiratory dysfunction, or two or more organ dysfunctions (neurological, hepatic, hematologic, renal). Septic shock is defined as sepsis and cardiovascular dysfunction. Cardiovascular dysfunction is defined by the presence of hypotension or the need for vasoactive drug to maintain systolic arterial pressure in the normal range or at least two of the hypoperfusion criteria: unexplained metabolic acidosis, hyperlactatemia (lactate > 2 times the reference value), oliguria, prolonged capillary refill and core to peripheral temperature gap > 3°C despite administration of isotonic intravenous fluid bolus in 1 hour. The IPSCC sets criteria for the diagnosis of organ dysfunctions based on both clinical and laboratory variables, which make its application difficult in limited resource settings.

Epidemiology of Severe Sepsis and Septic Shock in Children in Developed Countries

The prevalence of severe sepsis and septic shock is highly variable and one of the reasons responsible for that is the different ways to measure it. There are basically two ways of assessing data: from clinical registries in which the diagnosis is based on retrospective or prospective clinical assessment and from administrative assessment of hospital discharge databases in which diagnosis is made using the International Classification of Diseases, 9th Revision, (ICD)-9 or ICD-10 codes. The first approach typically assesses patients treated in ICUs, while the second approach usually measures all admissions and allows estimates of sepsis incidences in the whole population.

Until recently, the most relevant studies of sepsis in children were based on discharge data record from American hospitals.^{2,8} Two of these studies have described the incidence and mortality from severe sepsis in American children.^{2,8} Over 10 years (1995–2005), the authors reported an increase in the incidence of severe sepsis in children, ranging from 56 to 89 cases per 100,000. Notwithstanding the growth in all pediatric age groups, the increase was greater among newborns, where the incidence of severe sepsis has more than doubled (from 4.5 to 9.7 cases/1,000 births), and among adolescents, where an increase of 30% was observed (from 37 to 48 cases/100,000 children from 15 to 19 years old). During the study period, the authors observed a decrease of 13.6% in the mortality rate due to severe sepsis in children; of note the mortality rate in 2005 was 8.9%.⁸

Also, in the United States, two recent studies have reported epidemiological data on pediatric sepsis obtained from national information systems of pediatric hospitals.^{20,21} Both studies used the same diagnostic criteria to identify severe sepsis and septic shock in children and observed wide variations in prevalence. Balamuth et al²⁰ observed that the prevalence of severe sepsis in hospitalized children varies up to seven times depending on the strategy used to identify the disease. While sepsis prevalence was 0.45% when the codes for severe sepsis and septic shock of the ICD-9 were used, it increased to 3.1% when using the combined strategy validated by Angus et al in adults. In the same period (2004–2012), Ruth et al²¹ analyzed only PICUs and estimated that in the United States, the prevalence of severe sepsis was 7.7% when using either the ICD-9 codes for severe sepsis and septic shock or the combined strategy.

These authors observed a decrease in severe sepsis mortality in children that varied according to the diagnostic criteria adopted. In the study of Balamuth et al,²⁰ mortality from severe sepsis and septic shock was 2.6 times higher when the ICD-9 codes were adopted than when the combined strategy was used (21.2% [95% confidence interval, CI, 20.7–21.8] vs. 8.2% [95% CI, 8.0–8.3]). Ruth et al²¹ reported that mortality from severe sepsis in PICUs was 14.4%, with a significant decrease during the study period (18.9–12.0%, $p < 0.001$).

Also using administrative data from hospital record systems, Thompson and Kissoon²² reported that between 2004 and 2009, sepsis accounted for 4,000 hospital admissions of children and 200 deaths per year in Canada. Among children with sepsis, 22% had severe sepsis. Newborns (56.3%) and infants (18.8%) represented the majority of cases. The authors demonstrated a significant decline in age-adjusted hospitalization rates for all children with diagnostic code for sepsis. In that study, mortality from severe sepsis declined significantly across the study period, ranging from 20 to 17%.

Other epidemiological studies of severe sepsis and septic shock in developed countries reported a lower frequency of the disease in PICUs when compared with American data. In Italy²³ and Japan,²⁴ the prevalence of severe sepsis in PICUs was 1.6 and 1.4% respectively. In a retrospective study that analyzed the incidence and mortality from severe infections in children under 16 years old in Australia and New Zealand, Schlapbach et al²⁵ reported that among the 97,127 children

admitted in participant PICUs from 2002 to 2013 (ANZPIC Registry), 6.9% had invasive infections, 2.9% had sepsis, and 2.1% had septic shock. Over the 12 years of study, the authors observed an increase of 0.09 and 0.08 cases per 100,000 children per year in the incidence of sepsis and septic shock, respectively. The low incidence of the disease was attributed to different health policies such as immunization programs, in the etiology of the disease and in the diagnostic criteria used in the studies. In Spain, Vila Pérez et al²⁶ evaluated the incidence of sepsis and septic shock in seven tertiary PICUs prospectively and estimated that the incidence of sepsis was ~5.6 cases per 100,000 inhabitants per year.

The mortality from severe sepsis and septic shock in these countries remains high.^{22–25} A study from Italy²³ reported a 51% mortality rate from septic shock, and 30.6% rate of early mortality (<24 hours). The high mortality from septic shock in Italian PICUs was attributed to the inadequate treatment of shock, because in the study period, none of the PICUs adopted the algorithm for severe sepsis and septic shock treatment in children proposed by American College of Critical Care Medicine - Pediatric Advanced Life Support. In Australia and New Zealand,²⁵ the mortality rate of children with septic shock was 17%. When the authors compared the data from the periods between 2002–2007 and 2008–2013 (after the publication of IPSCC¹⁸ and the Surviving Sepsis Campaign⁵), they observed a 20% decrease in mortality from septic shock, similar to the overall improvement in survival of children hospitalized in ICUs for noninfectious causes. These data suggest that the decline in septic shock mortality is not dependent on specific interventions for sepsis, but rather on the general improvements in ICUs quality of care.

In a recent multicenter, prospective, population-based cohort study in Switzerland, Agyeman et al²⁷ estimated an age-standardized incidence of pediatric blood culture-proven bacterial sepsis of 25 cases per 100,000 children per year. In this study, the incidence of pediatric bacterial sepsis was age-dependent, with highest incidence in neonates and infants. The 30-day in-hospital mortality was 7% and was related to the presence and number of organ dysfunction. Children with pediatric blood culture-proven bacterial sepsis without organ dysfunction had a mortality of less than 1%.

Epidemiology of Severe Sepsis and Septic Shock in Children in Low- and Middle-Income Countries

Despite the major impact of sepsis in developing countries, both in medical and social and economic aspects, epidemiological data from low and middle-income countries remains scarce and is not representative. In Brazil, Mangia et al²⁸ evaluated the incidence and mortality from sepsis in hospitalized children from 1992 to 2006 with data extracted from the Hospital Information System of the Unified Health System (SIH-SUS in Portuguese). During the study period, infectious and parasitic diseases accounted for 16% of admissions, while sepsis accounted for 1%. Unlike data from developed countries, the authors observed a 64% reduction in hospitalization due to sepsis in Brazil during the 14 years of study. This decrease was

attributed, in part, to the implementation of the Millennium Development Goals, which aim to reduce child mortality through immunization and sanitation programs, improvement in the availability of drinking water, reduction in the frequency of diarrhea, and increase in the use of oral rehydration and of programs to improve the nutritional status. Despite these measures, mortality from sepsis in children in Brazil was high (19.1%) and virtually no decrease was observed over the studied period.

In China, Wang et al²⁹ conducted a prospective, multi-center study of pediatric sepsis in hospitalized children and reported that the prevalence of sepsis was 5.5%. Among the 1,530 children who met the criteria of sepsis, 121 (7.9%) had severe sepsis and 32 (2.1%) had septic shock. Based on these data, the incidence of sepsis in Chinese children was estimated to be 181 cases per 100,000 children. In China, the overall case fatality rate was 3.5% in all cases of sepsis, the mortality from severe sepsis and septic shock was 34.6%, and over 70% of these deaths occurred in the first 72 hours after admission. According to the authors, the high mortality from septic shock in Chinese children was not influenced by previous medical conditions that could increase the chance of a complicated infection, since most of the children were previously healthy. Instead, it was attributed to the delay in diagnosis and in hospital admission, which occurred on average in the third day of the disease; delay in treatment; and to the non-adherence to international guidelines for severe sepsis and septic shock treatment.

In South America, de Souza et al³⁰ observed that both the prevalence of severe sepsis (25.9%) and septic shock (19.8%) at admission to the PICUs were high. In that study, sepsis-related mortality was 14.2% and was consistently higher with increasing sepsis severity: 4.4% for sepsis, 12.3% for severe sepsis, and 23.1% for septic shock. One in four deaths of sepsis patients occurred within the first 24 hours after admission to the PICU. The authors found that the prevalence of sepsis was higher in children under 1 year of age (50.4%) and decreased in adolescents (1.9%). Multivariate analysis showed that higher Pediatric Risk of Mortality (odds ratio [OR], 1.06; 95% CI, 1.02–1.11; $p = 0.005$) and Pediatric Logistic Organ Dysfunction (OR, 1.06; 95% CI, 1.02–1.11; $p = 0.015$) scores, the presence of two or more chronic conditions (OR, 2.74; 95% CI, 1.4–5.36; $p = 0.003$), and admission from pediatric wards (OR, 2.44; 95% CI, 1.19–5.01; $p = 0.015$) were independently associated with death. Jaramillo-Bustamante et al³¹ reported that half of children with sepsis admitted in 19 PICUs in Colombia were in advanced stage of the disease (i.e., septic shock) and over 40% had multiple organ dysfunction syndrome which probably have contributed to the high mortality rate of septic shock (34%).

Global Perspective on Epidemiology of Severe Sepsis and Septic Shock in Children

The Sepsis PRevalence, OUtcomes, and Therapies Study (SPROUT Study)³² published in 2015 assessed the prevalence and mortality from severe sepsis in 6,925 children admitted to 128 PICUs from 26 countries. The study was conducted for 5 non-consecutive days from June 2013 to March 2014. They

reported a severe sepsis prevalence of 8.2%. The authors also observed a wide variation in the prevalence of severe sepsis in children among the continents, ranging from 6.2% in Europe to 23.1% in Africa ($p < 0.001$). It is possible that the shortage of ICU beds influences the prevalence by favoring admission of more severely ill patients, which usually includes the septic ones. The hospital mortality rate for severe sepsis was 25%. Surprisingly, the authors found no difference in mortality in PICUs when comparing developed and developing countries (23 vs. 29%, $p = 0.23$). Early mortality (<24 hours) and cumulative mortality at the second, seventh, and fourteenth day of PICU admission was 0.7 (one child), 5.0, 16.6, and 40.3%, respectively.

In a recent systematic review and meta-analysis of epidemiology of pediatric sepsis,³³ the incidence of sepsis in children was 48 cases per 100,000 person-years and the incidence of severe sepsis was 22 cases per 100,000 person-years. The authors estimated an incidence of 1.2 million cases of pediatric sepsis in children per year. The mortality of pediatric severe sepsis ranged from 9 to 20%. These data were probably underestimated because no study from low-income countries was included in the systematic review, where the incidence and mortality of pediatric sepsis are probably higher.

Given the alarming mortality rate from infectious diseases in children, the World Federation of Pediatric Intensive and Critical Care Societies (WFPICCS) launched the “Global Pediatric Sepsis Initiative” in 2007.³⁴ The initiative was based on previous studies showing that simple interventions such as immunization programs, vitamin and mineral supplements, early use of antibiotics, fluid resuscitation, and inotropic drugs may reduce mortality from sepsis. Importantly, this program recognizes resource disparity between regions as a crucial issue and proposes specific recommendations for the treatment of sepsis in children based on the degree of regional socioeconomic development and health resources availability. According to the data released by WFPICCS in 2011,⁴ mortality from sepsis in childhood does not seem to be directly related to the financial resources availability and the socioeconomic development level of each region, but rather to the adherence to treatment guidelines of severe sepsis and septic shock, which is still very low, both in developed and developing countries. Mortality from severe sepsis was higher in developing countries (30 vs. 11%), where adherence rates to guidelines were lower (23.8 vs. 51.9%) than in developed countries.

All these studies have limitations which compromise our ability to understand the epidemiology of septic shock in children. Some studies excluded newborns who are known to be at higher risk of developing and dying from sepsis; other studies used a convenient sampling of ICUs and were usually located in metropolitan areas where the population's socioeconomic status is higher, and other studies were retrospective and the diagnosis of septic shock was based on administrative data. Even the SPROUT study,³² the most representative one, has its own limitations, since most participants PICUs were located in North America and Europe and 87% were located in academic institutions. Furthermore, none of the studies provides information on the prevalence and mortality of septic shock before admission

to the hospital. This would be important, since according to Cvetkovic et al.,³⁵ 25% of the deaths from septic shock in children occur before arrival at the hospital.

Why Is There No Global Perspective on the Epidemiology of Severe Sepsis and Septic Shock in Children?

More than 10 years after the publication of pediatric sepsis definitions,¹⁹ there is no global perspectives on the burden of the sepsis in childhood. We believe that there are several obstacles to the complete knowledge of the epidemiology of sepsis and septic shock in children.

First, the prevalence of sepsis varies depending on the settings and the sepsis diagnostic criteria adopted, the methodology used, the time of data collection, the data source used, the clinical and demographic characteristics of the study population and the country or region (e.g., level of socioeconomic development, health policies), selection bias and even as a result of chance.^{20,21,36}

Another major obstacle is the absence of proper disease definitions in pediatric patients. The current definitions¹⁹ have been proposed to assist in the standardization of observational studies and evaluation of therapeutic interventions in clinical trials. They involve clinical and physiological variables that are difficult to memorize and thus hard to apply at bedside and in resource-limited settings.

Studies have shown a few disagreements between the definitions proposed by IPSCC and the clinical criteria.^{37,38} In 2015, Weiss et al³⁸ evaluated the degree of agreement between the clinical diagnosis and IPSCC criteria to identify children with severe sepsis in an international PICU network. The authors observed a moderate agreement between the two diagnostic criteria. From 706 children who were diagnosed with severe sepsis, 19.4% were identified only by clinical criteria during daily bedside practice, 42.6% by the two diagnostic criteria, and 38% only through the IPSCC criteria. These findings suggest that the results of sepsis studies using the IPSCC diagnostic criteria might not be applied to a third of children diagnosed with sepsis admitted to PICUs. Moreover, in about half of patients with severe sepsis identified by IPSCC, and therefore eligible to participate in clinical trials, the diagnosis was not confirmed during daily practice in the PICU.

Another critical point refers to the redundancy between the definition of severe sepsis with cardiovascular dysfunction and septic shock as both may describe the same stage of the disease. Thus, the classification of a patient in the categories of severe sepsis or septic shock depends on medical judgment. It should also be noted that children, unlikely adults, may experience shock without the presence of hypotension. Thus, in children, the distinction between severe sepsis and septic shock may be artificial and both categories represent the same medical urgency.

Despite the limitations of the IPSCC such as: imprecision, moderate degree of concordance between the clinical diagnosis and the criteria of IPSCC and difficulty of its use in scenarios with resource limitations, the 2005 definitions of

pediatric sepsis are still valid. These limitations make difficult to understand the full extent of the real burden of pediatric sepsis.³⁹

A third obstacle is the absence of sepsis as a reportable cause of death in the World Health Organization (WHO) Global Burden of Disease Report (GBDR),^{7,40} which is one of the most important sources of information for health policies decision-making in the world. Although ~60% of deaths in children under 5 years old are secondary to infectious diseases, the GBDR only considers sepsis as a cause of death in neonates, leading to an underestimation of the sepsis burden beyond the neonatal period. As suggested by Kissoon and Uyeki,⁴¹ it is of utmost importance to clarify that sepsis is the final pathway of severe infections that kill children worldwide and this is the way to simplify the diagnosis and treatment and educate health professionals who work in areas with limited resources.

Experts in pediatric sepsis around the world agree that we need urgently new pediatric sepsis definition.^{39,42,43} These new definitions need to be easy to apply in any environment and should attend the needs of physicians and scientists. Sepsis is a life-threatening disease regardless of patients' location, whether in the emergency room, in the ward, or in the PICU; in developed and developing countries; for physicians or researchers. Certainly, the definitions proposed in 2005¹⁹ have limitations and failed to solve the problems related to the diagnosis of this important disease of childhood and the discrepancies of their epidemiological data.

Why Are Children with Septic Shock Still Dying?

Mortality from infectious diseases and septic shock in childhood is multifactorial, and is associated with factors related to the host, to the agent, and to the environment. In developed countries, the host characteristics, such as the presence of chronic disease, especially neoplastic, hematological and immunological, and the characteristics of the infectious agent, are associated with higher mortality from septic shock. On the other hand, in low- and middle-income countries, in addition to the previously mentioned factors, poverty, malnutrition, low vaccination coverage rates, poor sanitary conditions and characteristics of the health system, such as the decentralization of care, absence of specialized transportation services for critically ill children, the difficulty of access to health services, and the shortage of intensive care beds are important factors associated with mortality.

Several studies in both developed and developing countries have shown that mortality from septic shock is associated with suboptimal care: delayed diagnosis and treatment and nonadherence to the treatment guidelines.^{4,44,45} In a retrospective observational study at emergency departments and ICUs at two academic children's hospital, Weiss et al⁴⁶ observed that early pediatric sepsis mortality was high (49% in the first 7 days from sepsis recognition). In this study, children who died on the first 3 days from sepsis recognition were younger, more likely to be developed community-acquired sepsis and more likely to

be previously healthier than children who died later. These children died from refractory shock due to late diagnosis and treatment. In another study, Cvetkovic et al³⁵ related that 26% of children with sepsis died before PICU admission and half of the deaths in children referred for intensive care with severe sepsis occurred within the first 24 hours of referral.

Like other studies,^{47–49} we believe that one of the main explanations for the delay in diagnosis and treatment and poor adherence to the sepsis treatment guidelines is the insufficiency of education and inadequate process of care. Although limitation of resources might play a role, other factors seem to be more relevant in determining the poor adherence to guidelines and consequently a high mortality from sepsis in the pediatric population, such as educational and institutional factors like the unfamiliarity with the disease, failures in the process of development and implementation of guidelines, absence of alignment with the structure of each service, lack of training, interest and motivation of healthcare workers and the institutions themselves, added to that cultural barriers.

A critical point is the limited knowledge of physicians in the diagnosis and treatment of sepsis and the low quality in terms of education and training of health professionals who provide care to children with sepsis. Both Kissoon⁴⁷ and Nadel et al⁴⁸ suggested that one of the main factors that contributes to the low adherence to sepsis treatment guidelines is the inability of the doctor to recognize sepsis as a disease, and their lack of familiarity with the warning signs and the treatment guidelines. In Brazil, Assunção et al⁵⁰ showed that the knowledge of sepsis definition among these professionals is unsatisfactory. In India, Santhanam et al⁵¹ assessed the knowledge of pediatricians and anesthesiologists regarding sepsis and its treatment. In that study, although ~40% of physicians have demonstrated adequate knowledge of the treatment guidelines, 90% did not apply these guidelines in clinical practice. Failure to adhere to the flow chart proposed by ACCM/PALS was due to insufficient skills in the use of vasoactive drugs, in airway management, and in carrying out procedures in the emergency department: 20% of doctors had never performed an intubation, 78% had never passed central venous catheter, and 76% had never done a catheter insertion for invasive blood pressure monitoring. The authors concluded that the guidelines of the ACCM/PALS could not be applied in India and inferred that the implementation of educational programs for pediatricians and the development of simpler guidelines appropriate to local conditions could save many children's lives.

Is It Possible to Reduce the Burden of Pediatric Sepsis?

Sepsis is a cause of death that could be prevented through the adoption of simple and inexpensive measures. To reduce the burden of sepsis, it is necessary to think about the disease and to simplify it. The primary measures are prevention, education, and organization. Another important point for the pediatric sepsis is to increase awareness of the disease both between family and healthcare professionals. However, all

these measures depend on the understanding of the epidemiology of the disease, which in turn depends on clear definitions that are simple and easy to apply.

Studies in adults and children have shown that educational programs are effective in increasing knowledge related to sepsis, adherence to treatment of severe sepsis and septic shock bundles, and in reducing mortality from this disease.^{52–54} Implementation of guidelines to treat pediatric severe sepsis results in early identification of children with sepsis and promotes a significant reduction in the starting-time of the intervention and in the variability of treatment, decreases the rates of acute renal failure and the need for renal-replacement therapy, and improves outcomes.^{55–60} Larsen et al⁵⁵ observed a significant increase in adherence to the early administration of antibiotics (<3 hours), the fluid bolus administration in the first hour, and the oxygen supply after implementing a screening and a treatment protocol for septic shock in the emergency room. The protocol implementation also led to a significant reduction in the length of hospitalization, although without a significant reduction in mortality from septic shock. Balamuth et al⁵⁶ observed that the treatment of children with sepsis through well-defined protocols in emergency departments is associated with the resolution of organ dysfunction in the second day of hospitalization. The implementation of guidelines to treat sepsis is cost-effective.⁵² However, it is unclear whether the benefits observed are due to specific measures for the treatment of sepsis or are inherent to the educational process involved in the implementation of these protocols.

All the difficulties associated with the diagnosis and treatment of children with sepsis can be overcome with leadership, commitment, education, training, creativity, advocacy, provision, and motivation.^{47,49} WFPICCS reaffirms that the limitation in resources should not be a barrier to adherence to guidelines, since several studies have shown that the decline in mortality from sepsis can be achieved through simple measures such as educational programs, implementation of scientific knowledge at the bedside, and the efficient use of resources.^{4,34} That entity recommends that sepsis treatment guidelines for children can and should be adapted to each region or setting. The key is not to delay the diagnosis and treatment of sepsis.

Conclusion

Sepsis is undoubtedly a public health problem worldwide. Its prevalence has increased over the years and despite numerous efforts, severe sepsis and septic shock remain a major cause of morbidity and mortality in the pediatric population. The reduction in mortality from sepsis in childhood is a worldwide challenge, especially in developing countries, where the highest number of cases and deaths are recorded and the financial resources are scarce. The problem does not seem to be primarily the availability of resources, but rather the absence of education, which determines a delay in diagnosis and treatment, and low adherence to treatment guidelines. To achieve the goal of improving treatment, the first step is the recognition by the lay people, healthcare

professionals, and authorities that sepsis is a medical emergency that, if not recognized and treated early, culminates in serious consequences.

Funding and Conflict of Interest

No external funding supported this study. The authors declare no potential conflicts of interest.

References

- Reinhart K, Daniels R, Kissoon N, Machado FR, Schachter RD, Finfer S. Recognizing sepsis as a global health priority - a WHO resolution. *N Engl J Med* 2017;377(05):414-417
- Watson RS, Carcillo JA, Linde-Zwirble WT, Clermont G, Lidicker J, Angus DC. The epidemiology of severe sepsis in children in the United States. *Am J Respir Crit Care Med* 2003;167(05):695-701
- Brierley J, Carcillo JA, Choong K, et al. Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. *Crit Care Med* 2009;37(02):666-688
- Kissoon N, Carcillo JA, Espinosa V, et al; Global Sepsis Initiative Vanguard Center Contributors. World Federation of Pediatric Intensive Care and Critical Care Societies: global sepsis initiative. *Pediatr Crit Care Med* 2011;12(05):494-503
- Dellinger RP, Levy MM, Rhodes A, et al; Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013;41(02):580-637
- Davis AL, Carcillo JA, Aneja RK, et al. American College of Critical Care Medicine Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock. *Crit Care Med* 2017;45(06):1061-1093
- Liu L, Oza S, Hogan D, et al. Global, regional, and national causes of child mortality in 2000-13, with projections to inform post-2015 priorities: an updated systematic analysis. *Lancet* 2015;385(9966):430-440
- Hartman ME, Linde-Zwirble WT, Angus DC, Watson RS. Trends in the epidemiology of pediatric severe sepsis*. *Pediatr Crit Care Med* 2013;14(07):686-693
- Bone RC, Balk RA, Cerra FB, et al; The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest* 1992;101(06):1644-1655
- Proulx F, Fayon M, Farrell CA, Lacroix J, Gauthier M. Epidemiology of sepsis and multiple organ dysfunction syndrome in children. *Chest* 1996;109(04):1033-1037
- Kutko MC, Calarco MP, Flaherty MB, et al. Mortality rates in pediatric septic shock with and without multiple organ system failure. *Pediatr Crit Care Med* 2003;4(03):333-337
- Leclerc F, Leteurtre S, Duhamel A, et al. Cumulative influence of organ dysfunctions and septic state on mortality of critically ill children. *Am J Respir Crit Care Med* 2005;171(04):348-353
- Sáez-Llorens X, Vargas S, Guerra F, Coronado L. Application of new sepsis definitions to evaluate outcome of pediatric patients with severe systemic infections. *Pediatr Infect Dis J* 1995;14(07):557-561
- Goh A, Lum L. Sepsis, severe sepsis and septic shock in paediatric multiple organ dysfunction syndrome. *J Paediatr Child Health* 1999;35(05):488-492
- Tantaleán JA, León RJ, Santos AA, Sánchez E. Multiple organ dysfunction syndrome in children. *Pediatr Crit Care Med* 2003;4(02):181-185
- Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016;315(08):801-810
- Hayden WR. Sepsis terminology in pediatrics. *J Pediatr* 1994;124(04):657-658
- Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. 1992. *Chest* 2009;136:e28
- Goldstein B, Giroir B, Randolph A; International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med* 2005;6(01):2-8
- Balamuth F, Weiss SL, Neuman MI, et al. Pediatric severe sepsis in U.S. children's hospitals. *Pediatr Crit Care Med* 2014;15(09):798-805
- Ruth A, McCracken CE, Fortenberry JD, Hall M, Simon HK, Hebbard KB. Pediatric severe sepsis: current trends and outcomes from the Pediatric Health Information Systems database. *Pediatr Crit Care Med* 2014;15(09):828-838
- Thompson GC, Kissoon N. Sepsis in Canadian children: a national analysis using administrative data. *Clin Epidemiol* 2014;6:461-469
- Wolfler A, Silvani P, Musicco M, Antonelli M, Salvo I; Italian Pediatric Sepsis Study (SISPe) group. Incidence of and mortality due to sepsis, severe sepsis and septic shock in Italian Pediatric Intensive Care Units: a prospective national survey. *Intensive Care Med* 2008;34(09):1690-1697
- Shime N, Kawasaki T, Saito O, et al. Incidence and risk factors for mortality in paediatric severe sepsis: results from the national paediatric intensive care registry in Japan. *Intensive Care Med* 2012;38(07):1191-1197
- Schlapbach LJ, Straney L, Alexander J, et al; ANZICS Paediatric Study Group. Mortality related to invasive infections, sepsis, and septic shock in critically ill children in Australia and New Zealand, 2002-13: a multicentre retrospective cohort study. *Lancet Infect Dis* 2015;15(01):46-54
- Vila Pérez D, Jordan I, Esteban E, et al. Prognostic factors in pediatric sepsis study, from the Spanish Society of Pediatric Intensive Care. *Pediatr Infect Dis J* 2014;33(02):152-157
- Agyeman PKA, Schlapbach LJ, Giannoni E, et al; Swiss Pediatric Sepsis Study. Epidemiology of blood culture-proven bacterial sepsis in children in Switzerland: a population-based cohort study. *Lancet Child Adolesc Health* 2017;1(02):124-133
- Mangia CM, Kissoon N, Branchini OA, Andrade MC, Kopelman BI, Carcillo J. Bacterial sepsis in Brazilian children: a trend analysis from 1992 to 2006. *PLoS One* 2011;6(06):e14817
- Wang Y, Sun B, Yue H, et al. An epidemiologic survey of pediatric sepsis in regional hospitals in China. *Pediatr Crit Care Med* 2014;15(09):814-820
- de Souza DC, Shieh HH, Barreira ER, Ventura AM, Bousso A, Troster EJ; LAPSES Group. Epidemiology of sepsis in children admitted to PICUs in South America. *Pediatr Crit Care Med* 2016;17(08):727-734
- Jaramillo-Bustamante JC, Marín-Agudelo A, Fernández-Laverde M, Bareño-Silva J. Epidemiology of sepsis in pediatric intensive care units: first Colombian multicenter study. *Pediatr Crit Care Med* 2012;13(05):501-508
- Weiss SL, Fitzgerald JC, Pappachan J, et al; Sepsis Prevalence, Outcomes, and Therapies (SPROUT) Study Investigators and Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network. Global epidemiology of pediatric severe sepsis: the sepsis prevalence, outcomes, and therapies study. *Am J Respir Crit Care Med* 2015;191(10):1147-1157
- Fleischmann-Struzek C, Goldfarb DM, Schlattmann P, Schlapbach LJ, Reinhart K, Kissoon N. The global burden of paediatric and neonatal sepsis: a systematic review. *Lancet Respir Med* 2018;6(03):223-230
- Kissoon N, Argent A, Devictor D, et al. World Federation of Pediatric Intensive and Critical Care Societies-its global agenda. *Pediatr Crit Care Med* 2009;10(05):597-600

- 35 Cvetkovic M, Lutman D, Ramnarayan P, Pathan N, Inwald DP, Peters MJ. Timing of death in children referred for intensive care with severe sepsis: implications for interventional studies. *Pediatr Crit Care Med* 2015;16(05):410–417
- 36 Gaieski DF, Edwards JM, Kallan MJ, Carr BG. Benchmarking the incidence and mortality of severe sepsis in the United States. *Crit Care Med* 2013;41(05):1167–1174
- 37 Weiss SL, Parker B, Bullock ME, et al. Defining pediatric sepsis by different criteria: discrepancies in populations and implications for clinical practice. *Pediatr Crit Care Med* 2012;13(04):e219–e226
- 38 Weiss SL, Fitzgerald JC, Maffei FA, et al; SPROUT Study Investigators and Pediatric Acute Lung Injury and Sepsis Investigators Network. Discordant identification of pediatric severe sepsis by research and clinical definitions in the SPROUT international point prevalence study. *Crit Care* 2015;19:325
- 39 Souza DC, Brandão MB, Piva JP. From the International Pediatric Sepsis Conference 2005 to the Sepsis-3 Consensus. *Rev Bras Ter Intensiva* 2018;30(01):1–5
- 40 GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015;385(9963):117–171
- 41 Kissoon N, Uyeki TM. Sepsis and the global burden of disease in children. *JAMA Pediatr* 2016;170(02):107–108
- 42 Schlapbach LJ, Kissoon N. Defining pediatric sepsis. *JAMA Pediatr* 2018;172(04):312–314
- 43 Piva JP, Garcia PC. Sepsis: from the stone age to nowadays without a precise definition. *Pediatr Crit Care Med* 2016;17(08):794–795
- 44 Oliveira CF, Nogueira de Sá FR, Oliveira DS, et al. Time- and fluid-sensitive resuscitation for hemodynamic support of children in septic shock: barriers to the implementation of the American College of Critical Care Medicine/Pediatric Advanced Life Support Guidelines in a pediatric intensive care unit in a developing world. *Pediatr Emerg Care* 2008;24(12):810–815
- 45 Ninis N, Phillips C, Bailey L, et al. The role of healthcare delivery in the outcome of meningococcal disease in children: case-control study of fatal and non-fatal cases. *BMJ* 2005;330(7506):1475
- 46 Weiss SL, Balamuth F, Hensley J, et al. The epidemiology of hospital death following pediatric severe sepsis: when, why, and how children with sepsis die. *Pediatr Crit Care Med* 2017;18(09):823–830
- 47 Kissoon N. Sepsis guideline implementation: benefits, pitfalls and possible solutions. *Crit Care* 2014;18(02):207
- 48 Nadel S, Britto J, Booy R, Maconochie I, Habibi P, Levin M. Avoidable deficiencies in the delivery of health care to children with meningococcal disease. *J Accid Emerg Med* 1998;15(05):298–303
- 49 Kissoon N. Sepsis guidelines: suggestions to improve adherence. *J Infect* 2015;71(Suppl 1):S36–S41
- 50 Assunção M, Akamine N, Cardoso GS, et al; SEPSSES Study Group. Survey on physicians' knowledge of sepsis: do they recognize it promptly? *J Crit Care* 2010;25(04):545–552
- 51 Santhanam I, Kissoon N, Kamath SR, Ranjit S, Ramesh J, Shankar J. GAP between knowledge and skills for the implementation of the ACCM/PALS septic shock guidelines in India: is the bridge too far? *Indian J Crit Care Med* 2009;13(02):54–58
- 52 Noritomi DT, Ranzani OT, Monteiro MB, et al. Implementation of a multifaceted sepsis education program in an emerging country setting: clinical outcomes and cost-effectiveness in a long-term follow-up study. *Intensive Care Med* 2014;40(02):182–191
- 53 Ferrer R, Artigas A, Levy MM, et al; Edusepsis Study Group. Improvement in process of care and outcome after a multicenter severe sepsis educational program in Spain. *JAMA* 2008;299(19):2294–2303
- 54 Booy R, Habibi P, Nadel S, et al; Meningococcal Research Group. Reduction in case fatality rate from meningococcal disease associated with improved healthcare delivery. *Arch Dis Child* 2001;85(05):386–390
- 55 Larsen GY, Mecham N, Greenberg R. An emergency department septic shock protocol and care guideline for children initiated at triage. *Pediatrics* 2011;127(06):e1585–e1592
- 56 Balamuth F, Weiss SL, Fitzgerald JC, et al. Protocolized treatment is associated with decreased organ dysfunction in pediatric severe sepsis. *Pediatr Crit Care Med* 2016;17(09):817–822
- 57 Akcan Arikan A, Williams EA, Graf JM, Kennedy CE, Patel B, Cruz AT. Resuscitation bundle in pediatric shock decreases acute kidney injury and improves outcomes. *J Pediatr* 2015;167(06):1301–5.e1
- 58 Cruz AT, Perry AM, Williams EA, Graf JM, Wuestner ER, Patel B. Implementation of goal-directed therapy for children with suspected sepsis in the emergency department. *Pediatrics* 2011;127(03):e758–e766
- 59 Paul R, Neuman MI, Monuteaux MC, Melendez E. Adherence to PALS sepsis guidelines and hospital length of stay. *Pediatrics* 2012;130(02):e273–e280
- 60 Paul R, Melendez E, Stack A, Capraro A, Monuteaux M, Neuman MI. Improving adherence to PALS septic shock guidelines. *Pediatrics* 2014;133(05):e1358–e1366