Abstract:
Sepsis and septic shock remain one of the leading causes of morbidity and mortality in children. Collaboration of clinicians and researchers in the fields of infectious diseases, basic science, genetics, genomics, and critical care has resulted in significant progress in understanding the pathophysiology, advances in prevention, early identification of patients at risk, and the development of coordinated therapies, resulting in improved outcomes.

Keywords:
sepsis; septic shock; children; early identification; prevention; guidelines; Surviving Sepsis Campaign

The History of Sepsis Management Over the Last 30 Years

Zehava L. Noah, MD

Northwestern University Feinberg School of Medicine, Division of Pediatric Critical Care, The Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL.
Reprint requests and correspondence: Zehava L. Noah, MD, Northwestern University Feinberg School of Medicine, Division of Pediatric Critical Care, The Ann & Robert H. Lurie Children's Hospital of Chicago, 225 E. Chicago Ave, Box 73, Chicago, IL 60611.
znoah@luriechildrens.org

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Sepsis, a word of Greek derivation implying biological decay, was described in ancient Greek and Roman literature. Physicians have sought for over 2700 years (from Hippocrates, Galen, to Lister, Fleming Semelweis, and Pasteur) for ways to prevent and cure this malady.[1] Progress in medicine is an evolution; each generation of physicians and researchers builds on the discoveries of their predecessors. Today, infectious diseases account for almost 60% of the 7.6 million annual deaths of children less than the age of 5 years worldwide, mostly in Asia and sub-Saharan Africa.

In the resource-rich countries, the best estimates come from the United States. Approximately 40 000 children develop severe sepsis every year. The incidence is estimated at 0.6 per 1000 population. Since the 1960s, mortality from severe sepsis has decreased from 97% to 4 to 7% for patients with severe sepsis and 13 to 34% for patients with septic shock. Severe sepsis is one of the leading causes of death in children; 4400 deaths occur annually in the United States.[2,3]

This article will attempt to summarize the developments over the last 30 years that have led to this reduction in mortality in spite of an increase in the absolute number of cases (rising approximately 13% per year).[2]

EVOLUTION OF MANAGEMENT FROM EDWARD FRANK TO THE PRESENT

In 1964, Dr Edward Frank, a vascular surgeon at Beth Israel Hospital in Boston, published a protocol for the management of

septic shock that he thought would give the patient the best chance of survival.[4] He based his recommendations on his work with animal septic shock models. He advocated for constant bedside attendance by a team of well-trained senior physicians who would assume total responsibility for the patient's management. Continuous monitoring of systemic arterial pressure, central venous pressure, cardiac output monitoring by the dye-dilution technique, urinary output, blood volume, blood chemistries, gases, pH, and electrolytes, all at bedside.

After resuscitation to restore cardiac and respiratory function, he recommended correction of hypovolemia, support for respiratory insufficiency or failure with mechanical ventilation via a tracheostomy, and recommended digitalization for inotropic support with cautious use of pressors for hypotension. He also recommended antiadrenergic drugs in selected cases, correction of electrolytes and acid-base balance, and, above all, the identification and prompt treatment of the causative infections.

Few hospitals were equipped to follow these recommendations in the 1960s. Although some of his pharmacologic recommendations are odd, many of the suggestions are as acceptable today as they were 50 years ago.

WHAT THEN HAS CHANGED?

Early Identification of Patients at Risk for the Development of Sepsis and Septic Shock

Strategies to improve management and outcome for sepsis in the pediatric population have been facilitated through the early identification of those children with an increased risk for disease, including:

1. Patients on immune suppressive therapy for the treatment of malignancy, for the prevention of rejection after transplants, and for the suppression of severe inflammatory response.
2. Immune suppression caused by human immunodeficiency virus/acquired immunodeficiency syndrome, malignancy, and congenital immune deficiencies.
3. Age-related factors such as extreme prematurity and higher risk for neonates, infants, and young children.
4. Children with chronic conditions such as chronic lung disease, congenital heart disease, neuromuscular disease, and hematologic/oncological disease.
5. Genetics and genomic factors:

(a) Although no single gene has been associated with increased risk for septic shock, there is tantalizing evidence that suggests genetic predilection. For instance, children with meningococcemia that are homozygous for the 4 g allele, produce higher amounts of plasminogen activator inhibitor 1 and are at risk for worse outcomes.
(b) Serum interleukin 8 measurements can predict a 95% probability survival of pediatric septic shock with standard care.
(c) Ongoing research aims to generate genomic subclassifications, which will allow clinicians using a gene expression mosaic at the bedside, to differentiate between 3 classes of septic shock (subclass A represents the highest severity).[5,6]

Prevention

Prevention has been another strategy deployed to reduce the burden of disease related to sepsis. These activities include:

1. The development of vaccines and the implementation of widespread immunization programs.[7] Before *Haemophilus influenza* type b immunization, *H influenza* was the leading invasive infection and a leading cause of sepsis in children under the age of 5 years. Since routine *H* influenza type b vaccine was implemented, the infection rate has declined dramatically. With the widespread implementation of pneumococcal vaccine, the rate of invasive pneumococcal infection and sepsis has declined similarly.
2. Meticulous attention to isolation precautions, to aseptic techniques, and prompt removal of lines, tubes, and catheters when no longer needed.

Identification and Treatment of the Causative Agent

Bacteria, viruses, fungi, and parasites can all trigger the inflammatory response leading to the development of clinical sepsis and septic shock. Prompt identification of the causative agent and rapid initiation of treatment are extremely important.

Although cultures are the criterion standard for the identification of bacteria, additional methods such as polymerase chain reaction and gene expression profiling were developed. Gene expression profiling can differentiate viral from bacterial infection and similarly can differentiate between gram-positive vs