

Pediatric Sepsis: Markers, Mechanisms, and Management

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Abstract: Sepsis is a significant health problem in both critically ill children and adults. While the mortality rate from sepsis is much lower in children, sepsis is directly responsible for over 4,000 childhood deaths per year in the United States alone. At face value, this number suggests that more children die per year in the United States from sepsis as the primary cause than from cancer. Unfortunately, there are few studies on the epidemiology, pathophysiology, and management of sepsis in children. Moreover, extrapolation of adult data to critically ill children is probably not appropriate due to several key developmental differences in the host response to infection and response to therapy. Therefore, additional studies targeting sepsis in the pediatric population are urgently required.

INTRODUCTION

Sir William Osler once stated that *to know syphilis is to know medicine*. Many years later, Zimmerman appropriately followed with the statement that *to know sepsis is to know critical care medicine* [1]. The early recognition, diagnosis, and management of critically ill patients with sepsis truly define the essence or sine qua non of the field of critical care medicine. Unfortunately, while sepsis defines our specialty, an exact, all-encompassing definition of the sepsis syndrome has been difficult to establish. Sepsis suffers from an identity crisis of sorts. For example, the lay public has very little knowledge of sepsis, especially compared to more commonly recognized causes of death, such as acute myocardial infarction, stroke, and cancer [2]. Health care workers are not much better. A recent international survey of over 1,058 physicians from a wide variety of disciplines, including critical care medicine, found that nearly two-thirds believed that a common definition for sepsis was lacking [3]. Part of the issue is that sepsis is not even really a disease in the strictest sense of the term, but rather a syndrome. The Merriam-Webster dictionary defines *syndrome* as *a group of signs and symptoms that occur together and characterize a particular abnormality or condition*. There are no specialized blood tests that can be used to diagnose sepsis with anything close to 100% certainty. Instead, sepsis remains primarily a clinical diagnosis based upon the identification of a constellation of several, fairly consistent clinical signs and symptoms that occur in association with an infection or other inciting event, e.g. trauma, pancreatitis, or burns. Based on this concept, Roger Bone initially coined the term sepsis syndrome in 1989 [4], and shortly thereafter, an international panel of experts from the Society of Critical Care Medicine (SCCM) and the American College of Chest Physicians (ACCP) proposed the now familiar consensus

definitions for the systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock (Table 1) [5]. These definitions have been subsequently modified for use in critically ill children with sepsis (Table 2) [6].

CHILDREN ARE NOT SMALL ADULTS

Why is an entire supplement dedicated to "Pediatric Sepsis" even necessary? The medical literature is replete with articles reviewing the pathophysiology of sepsis at the molecular, cellular, tissue, organ, and whole-organism levels. In addition, there have been entire volumes dedicated to the topic of sepsis. Are there any important differences between pediatric and adult sepsis that merit further discussion? The phrase *children are not small adults* is well-known to every pediatrician and certainly applies to critically ill patients with sepsis as well. In fact, there are several key developmental differences in the host response to infection and therapy that clearly delineate pediatric sepsis as a separate, albeit related, entity from adult sepsis. As a result, extrapolation of adult data to critically ill children with sepsis may not always be appropriate. One notable example is the vastly different results between two recently conducted multicenter, randomized, controlled trials of activated protein C in the management of sepsis. In the adult study (PROWESS), treatment with activated protein C was associated with an absolute reduction in the risk of death of 6.1 percent ($P=0.005$) [7]. Conversely, the pediatric study (RESOLVE) was stopped early for lack of therapeutic effect at the first planned interim analysis [8].

A GROWING PUBLIC HEALTH CRISIS?

According to the National Center for Health Statistics and the Centers for Disease Control and Prevention, sepsis was the 10th leading cause of death overall in 2004 [9]. In fact, annual deaths from sepsis in both children and adults far surpass the number of deaths from acute myocardial infarction (AMI), stroke, or cancer [10]. The cost of sepsis, in terms of annual health care expenditures, approaches close to \$17 billion and €6 billion every year in the U.S. and Europe, respectively [10, 11, 14]. These numbers are likely

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Table 1. American College of Physicians (ACCP)/Society of Critical Care Medicine (SCCM) Consensus Definitions for SIRS, Infection, Sepsis, Severe Sepsis, and Septic Shock

<p><u>Systemic Inflammatory Response Syndrome (SIRS)</u></p> <p>The presence of at least two of the following four criteria, one of which must be abnormal temperature or leukocyte count:</p> <ul style="list-style-type: none"> ▪ Core temperature > 38°C or <36°C (by rectal, bladder, oral or central catheter probe) ▪ Tachycardia, defined as heart rate > 90/min ▪ Tachypnea, defined as respiratory rate > 20/min or PaCO₂ < 32 mm Hg ▪ White blood cell count > 12,000 cells/μL or < 4,000 cells/μL <p><u>Infection</u></p> <p>A suspected or proven (i.e. by positive culture, tissue stain, polymerase chain reaction, etc) infection caused by any pathogen OR a clinical syndrome associated with a high probability of infection (e.g. presence of white blood cells in a normally sterile body fluid, chest radiograph consistent with pneumonia, petechial or purpuric rash, etc)</p> <p><u>Sepsis</u></p> <p>SIRS + Infection</p> <p><u>Severe Sepsis (Sepsis with Organ Dysfunction)</u></p> <p>Sepsis plus either cardiovascular dysfunction or acute respiratory distress syndrome (ARDS) OR two or more other organ dysfunctions</p> <p><u>Septic Shock</u></p> <p>Severe Sepsis with arterial hypotension defined by a systolic blood pressure below 90 mm Hg, mean arterial pressure (MAP) < 60 mm Hg, or a reduction in systolic blood pressure >40 mm Hg from baseline, despite adequate volume resuscitation and in the absence of other causes for hypotension.</p>

Adapted from [5].

Table 2. Consensus Definitions for Pediatric SIRS, Infection, Sepsis, Severe Sepsis, and Septic Shock

<p><u>Systemic Inflammatory Response Syndrome (SIRS)</u></p> <p>The presence of at least two of the following four criteria, one of which must be abnormal temperature or leukocyte count:</p> <ul style="list-style-type: none"> ▪ Core temperature > 38.5°C or <36°C (by rectal, bladder, oral or central catheter probe) ▪ Tachycardia, defined as mean heart rate >2 SD for age (in the absence pain, fever, drug therapy, etc) or otherwise persistent elevation over a 0.5-4 hour time period OR for children < 1 year of age: Bradycardia, defined as mean heart rate < 10th percentile for age (in the absence of drug therapy or presence of congenital heart disease) or otherwise persistent depression over a 0.5 hour time period ▪ Mean respiratory rate >2 SD above normal for age or mechanical ventilation (not for underlying neuromuscular disease or receipt of general anesthesia) ▪ Leukocyte count elevated or depressed for age (not due to chemotherapy-induced leucopenia) or >10% immature neutrophils <p><u>Infection</u></p> <p>A suspected or proven (i.e. by positive culture, tissue stain, polymerase chain reaction, etc) infection caused by any pathogen OR a clinical syndrome associated with a high probability of infection (e.g. presence of white blood cells in a normally sterile body fluid, chest radiograph consistent with pneumonia, petechial or purpuric rash, etc)</p> <p><u>Sepsis</u></p> <p>SIRS + Infection</p> <p><u>Severe Sepsis</u></p> <p>Sepsis plus either cardiovascular dysfunction or acute respiratory distress syndrome (ARDS) OR two or more other organ dysfunctions (see Table 2)</p> <p><u>Septic Shock</u></p> <p>Sepsis and cardiovascular organ dysfunction</p>

Adapted from [6].

to get worse. Recent estimates suggest that there are between 77 to 240 new cases of sepsis per 100,000 population each year [11, 12]. The incidence of sepsis is expected to further

increase by 1.5% every year, resulting in an additional 1 million cases per year by 2020 [10, 11, 13].

Just as important, and perhaps more relevant to the present discussion is the fact that sepsis accounts for

significant morbidity and mortality in the pediatric age group as well. Sepsis is the most common cause of death in infants and children worldwide [14]. Unfortunately, there are comparatively few studies on the epidemiology of sepsis in children. Proulx and colleagues [15] analyzed the incidence and outcome of sepsis using the aforementioned pediatric consensus definitions in a single tertiary care children's hospital. Out of 1,058 admissions analyzed over a one-year period, 82% of children admitted to the pediatric intensive care unit (PICU) met criteria for SIRS, while 23% had sepsis, 4% had severe sepsis, and 2% had septic shock. The overall mortality rate for this population was 6%, with the majority of deaths occurring in children with multiple organ dysfunction syndrome (MODS). These results were further corroborated by Watson and colleagues in the largest epidemiologic study of pediatric sepsis reported to date. In this study, sepsis accounted for nearly 4,500 deaths and close to \$2 billion per year in healthcare expenditures in the U.S. alone [16]. These statistics do not take into account the additional hidden costs attributed to the loss of productivity related to years of life lost for critically ill children who succumb to sepsis.

These sobering statistics suggest that pediatric sepsis is a growing public health problem that is reaching crisis proportions. At face value, more children die from sepsis every year in the U.S. than from cancer. Unfortunately, research funding specifically targeted towards pediatric sepsis is substantially lower than that for pediatric cancer. Additional research funding should be targeted at decreasing the morbidity and mortality from sepsis in children worldwide. Similarly, there is a growing need for educating the public on the dangers of sepsis, particularly in children. Finally, more studies on the epidemiology, pathophysiology, and treatment of pediatric sepsis are desperately required.

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