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Sepsis in the Pediatric Cardiac Intensive Care Unit

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Abstract

The survival rate for children with congenital heart disease (CHD) has increased significantly coincident with improved techniques in cardiothoracic surgery, cardiopulmonary bypass, and myocardial protection, and post-operative care. Cardiopulmonary bypass, likely in combination with ischemia-reperfusion injury, hypothermia, and surgical trauma, elicits a complex, systemic inflammatory response that is characterized by activation of the complement cascade, release of endotoxin, activation of leukocytes and the vascular endothelium, and release of pro-inflammatory cytokines. This complex inflammatory state causes a transient immunosuppressed state, which may increase the risk of hospital-acquired infection in these children. Postoperative sepsis occurs in nearly 3% of children undergoing cardiac surgery and significantly increases length of stay in the pediatric cardiac intensive care unit as well as the risk for mortality. Herein, we review the epidemiology, pathobiology, and management of sepsis in the pediatric cardiac intensive care unit.

Keywords

systemic inflammatory response syndrome (SIRS); sepsis; severe sepsis; septic shock; congenital heart disease; pediatrics; pediatric cardiac surgery; immunoparalysis; PIRO

Introduction

The survival rate for neonates, infants, and children with congenital heart disease (CHD) has increased significantly coincident with improved techniques in cardiothoracic surgery, cardiopulmonary bypass (CPB) and myocardial protection, and post-operative care. However, CPB, likely in combination with ischemia-reperfusion injury, hypothermia, and surgical trauma, elicits a complex, systemic inflammatory response that is characterized by activation of the complement cascade, release of endotoxin, activation of leukocytes and the vascular endothelium, and release of pro-inflammatory cytokines (1). This complex humoral and cellular-mediated immune response results in a transient and relative state of immune suppression, often referred to as "immunoparalysis" (1–3). Whole blood obtained from children following CPB stimulated *ex vivo* with lipopolysaccharide (LPS) results in markedly diminished pro-inflammatory cytokine production (2), consistent with the

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phenomenon known as “endotoxin tolerance” (4). This state of immunoparalysis may result in an increased risk of sepsis in children undergoing cardiac surgery for palliation or repair of CHD (5–7). In addition, chronic hypoxia and other co-morbid conditions associated with cyanotic CHD, as well as the need for invasive supportive devices may also increase the risk of sepsis in this population. Importantly, sepsis is a significant and independent risk factor for increased duration of mechanical ventilation, cardiac intensive care unit (CICU) length of stay (LOS), healthcare costs, and mortality in children with CHD (5, 7–10).

The Scope of the Problem

The diagnosis of sepsis is based upon the clinical recognition 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, cardiopulmonary bypass, or burns. Roger Bone first coined the term *sepsis syndrome* in 1989 (11), 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) (12). These definitions have been subsequently modified for use in critically ill children (Table 2) (13) and are certainly applicable to children with CHD.

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 2007 (14). Recent estimates suggest that there are between 77 to 240 new cases of sepsis per 100,000 population each year (15, 16). The population is growing older, and patients are living longer, even in the face of diseases that were previously considered universally fatal. Hospitalized patients are becoming more dependent upon the use of invasive devices and technology, all of which are associated with increased risk of infection. As such, the incidence of sepsis is expected to increase by 1.5% every year, resulting in an additional 1 million cases per year by 2020 (15, 17, 18). The story in children is fairly similar. There are between 20,000 – 42,000 cases of severe sepsis every year in the United States alone, half of which occur in children with underlying diseases like cancer and congenital heart disease (19, 20). Again, as more children survive diseases that were previously fatal (21), the incidence of sepsis will likely increase further.

While the management of critically ill patients with sepsis is certainly better now compared to 20 years ago (22–24), sepsis-associated mortality remains unacceptably high. Recent estimates suggest that there are approximately 4,500 children who die every year from sepsis in the United States alone (19, 25). The actual number of deaths associated with sepsis is likely to be much higher, as many patients usually die from sepsis during the course of an underlying disease, such as prematurity, congenital heart disease, or cancer. In many of these cases, deaths are frequently attributed to the underlying disease process, rather than to sepsis (17, 19, 26, 27). According to data from the World Health Organization (WHO), the United Nations Children’s Fund (UNICEF), and the Bill and Melinda Gates Foundation, nearly 70% of the 8 million deaths in children < 5 years of age were due to infectious disease (28). As sepsis is the final common pathway in many infectious diseases, such as malaria, dengue fever, pneumonia, influenza, and HIV, sepsis can and should be considered the #1 killer of children worldwide.

Unfortunately, there are relatively few studies that have determined the impact of sepsis on critically ill children with CHD (29–31). Most of these studies are limited to critically ill children who develop sepsis secondary to hospital-acquired infections (HAIs), including (in decreasing order of frequency and importance in the CICU) catheter-associated bloodstream infections (CA-BSIs), ventilator-associated respiratory infections (VARIs), surgical site

infections (SSIs), and catheter-associated urinary tract infections (CA-UTIs) (5, 6, 8, 9, 32–36). Barker and colleagues (31) reviewed 30,078 cases from 48 centers in the Society of Thoracic Surgeons Congenital Heart Surgery Database from 2002–2006 and found that 2.8% of these cases had a major infectious complication, of which 2.6% were sepsis. Mortality and postoperative length of stay were significantly greater in these patients. More studies on the epidemiology of sepsis in children with CHD are therefore necessary and warranted.

The PIRO concept

The consensus definitions for sepsis provide a general framework for epidemiologic investigation, as well as providing consistent and relatively straightforward inclusion criteria for clinical trials, most experts recognize that these definitions are far from perfect (37–39). As a result, several experts from SCCM and ACCP re-convened in December, 2001 and proposed a new staging system for sepsis (40). The “PIRO” staging system for sepsis is modeled after the TNM (Tumor, Nodes, Metastasis) system (41) for staging cancer and stratifies patients on the basis of their Predisposing conditions, the nature and extent of the insult (Infection), the nature and magnitude of the host Response, and the degree of concomitant Organ dysfunction. The PIRO staging system has many favorable attributes, but will require thorough validation and testing before it is widely adopted and applied in clinical practice (42–46).

Predisposition

There are numerous factors that may increase the risk and severity of sepsis. Certainly, age (increased mortality at the extremes of age – both young and old) (17, 19, 47), gender (increased severity of illness and mortality in males compared to females) (48, 49), nutritional status (increased morbidity and mortality with malnutrition or obesity) (50–52), and chronic diseases (17, 19, 24) are important. Genetic factors (see also below) likely play an important role as well, and there are several gene polymorphisms that have been linked with an increased susceptibility to sepsis (53). Aside from these factors, there are likely several reasons that children with CHD are at a particularly increased risk. First, there are several well-described malformation syndromes (e.g., 22q11 deletion or DiGeorge sequence) and chromosomal syndromes (trisomy 21) that are associated with congenital heart malformations and defects in immunity. Second, the chronic hypoxia associated with cyanotic CHD likely affects the host immune response. Third, children with CHD are exposed to invasive devices and technology, which carry an increased risk for HAI. Fourth, children who undergo heart or heart/lung transplantation require life-long immunosuppression to prevent graft rejection, which increases the risk of infection. Finally, ischemia-reperfusion injury following CPB frequently results in a state of functional immunoparalysis, which likely increases the risk of HAI as well.

Infection/Insult

There are likely important host-pathogen interactions that affect the response to therapy and outcome, which have been reviewed elsewhere (54–56).

Response

Individual differences in the host response to sepsis may also depend to a significant extent upon an individual's particular genetic make-up. While no clear “sepsis gene” has been identified, genetic factors undoubtedly play an important role in the pathophysiology of sepsis (53, 57–59). Sorensen and colleagues (60) conducted a longitudinal cohort study involving over 900 adopted children born between 1924 and 1926. The adopted children and both their biologic and adoptive parents were followed until 1982. The death of a biologic

parent before age 50 years resulted in a significantly increased risk of death in the adopted children (R.R. 1.71, 95% C.I. 1.14 to 2.57) for all causes. Of greater interest, if a biologic parent died of infection before the age of 50 years, the relative risk of death from infectious causes in the child was highly significant, with a relative risk of 5.81 (95% C.I. 2.47 to 13.7), which was higher than the increased risk of dying from cardiovascular disease or cancer, two conditions with well accepted genetic components. In contrast, the death of an adoptive parent from infectious causes did not confer a greater risk of death in the adopted child.

The prevailing evidence suggests that the individual response to sepsis is quite heterogeneous and that a “one-size fits all” approach to treatment is not likely to be successful. Sepsis results from a dysregulated host response, such that the balance between the pro-inflammatory mechanisms that are largely responsible for combating infection and the compensatory, anti-inflammatory mechanisms that counteract, “fine-tune”, and regulate these mechanisms largely determines the nature of the host response. For example, a shift in the homeostatic balance to a predominantly anti-inflammatory phenotype leads to a state of relative immune suppression or *immunoparalysis*, resulting in an inability to clear the pathogen and hence, an increased risk of HAI (61, 62). These patients would benefit from therapies that are designed to augment or stimulate the host immune response, e.g. interferon- γ (63–65) and/or granulocyte-macrophage colony-stimulating factor (GM-CSF) (66–70). Conversely, a shift in balance toward a predominantly pro-inflammatory phenotype results in further cellular injury, multiple organ failure, and death. These patients, on the other hand, would benefit from therapies that are designed to suppress or attenuate the host immune response. It is the nature of the host response, then, that largely determines the type of therapy required – either stimulation or attenuation of the host response to infection (59, 71). We believe that a strategy based upon “the right therapy, at the right time, in the right patient” will achieve the best possible outcome. The use of biomarkers (72) or gene expression profiling (73) will hopefully facilitate proper selection of the best therapy for critically ill children with sepsis.

Organ Dysfunction/Failure

Sepsis is characterized by a triad of inflammation, endothelial dysfunction, and alterations in the coagulation systems, which lead to perturbations in the delivery of oxygen and metabolic substrates to the tissues. These perturbations, in turn, lead to multiple organ dysfunction syndrome (MODS) (Table 4) and ultimately death. While relatively uncommon, MODS is associated with significant morbidity and mortality in critically ill children with CHD following cardiac surgery (74–76). For example, Ben-Abraham and colleagues (76) showed that 80% all deaths occurring during the first post-operative week in their series were caused by MODS. Mortality is higher with increased numbers of organ systems failures. Acute kidney injury (AKI), in particular, appears to be an independent risk factor for mortality in this population (77–80). Therefore, both the number and type of organ failures likely affects outcome in critically ill children with sepsis and CHD.

Management of Sepsis in the Pediatric CICU

The American College of Critical Care Medicine Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock were published in 2002 as a set of “best clinical practices” for the management of critically ill neonates and children with septic shock (81). While these guidelines have not been rigorously tested in a randomized, controlled clinical trial, early resuscitation and reversal of shock has improved outcome in critically ill children with septic shock (82, 83). In addition, a randomized open-label clinical trial in Brazil showed that management targeted to superior vena cava oxygen saturation (ScvO₂) using these guidelines resulted in a significant reduction in 28-day

mortality (39.2% vs. 11.8%, $p=0.002$) (84). These guidelines were updated and revised in 2007 (85).

Unanswered Questions

Several unanswered questions for the management of critically ill neonates and children with sepsis and underlying CHD remain. First, as discussed above, there are few epidemiologic studies available to assess the impact of the presence of underlying heart disease and/or chronic hypoxemia on the outcome from sepsis. Second, there is an urgent need for better biomarkers for risk stratification and therapeutic monitoring in this population. Third, we need to understand the impact of CHD, and in particular, the effects of cardiopulmonary bypass, on the subsequent risk for hospital-acquired infections, such as VARI, CA-BSI, and CA-UTI. Finally, we need to better understand the nuances of managing critically ill children with cyanotic CHD and sepsis.

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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

• **Systemic Inflammatory Response Syndrome (SIRS)**

The presence of at least two of the following four criteria, one of which must be abnormal temperature or leukocyte count:

- 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

Infection

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)

Sepsis

SIRS + Infection

Severe Sepsis (Sepsis with Organ Dysfunction)

Sepsis plus either cardiovascular dysfunction or acute respiratory distress syndrome (ARDS) OR two or more other organ dysfunctions

Septic Shock

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.

Adapted from (12)

Table 2**Consensus Definitions for Pediatric SIRS, Infection, Sepsis, Severe Sepsis, and Septic Shock****Systemic Inflammatory Response Syndrome (SIRS)**

The presence of at least two of the following four criteria, one of which must be abnormal temperature or leukocyte count:

- 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

Infection

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)

Sepsis

SIRS + Infection

Severe Sepsis

Sepsis plus either cardiovascular dysfunction or acute respiratory distress syndrome (ARDS) OR two or more other organ dysfunctions (see Table 4)

Septic Shock

Sepsis and cardiovascular organ dysfunction

Adapted from (13)

Table 3

The PIRO model of sepsis

P=PREDISPOSITION	I=INFECTION/INSULT	R=RESPONSE	O=ORGAN FAILURE
Age	Pathogen type	Immune Response	ALI/ARDS
Chronic diseases	Susceptibility patterns	Biomarker profile	Shock
Comorbidities	Virulence factors	Gene expression profile	AKI
Baseline severity of illness	Bacterial load	Clinical presentation	Liver Failure
Source of admission	Site of infection		MODS
Genetic polymorphisms			

Table 4**Consensus Definitions for Pediatric Organ Dysfunction****Cardiovascular dysfunction**

Despite administration of isotonic intravenous fluid bolus 40 mL/kg in 1 hr:

- Decrease in BP (hypotension) < 5th percentile for age or systolic BP < 2 SD below normal for age
- OR -
- Need for vasoactive drug to maintain BP in normal range (dopamine 5 µg/kg/min or dobutamine, epinephrine, norepinephrine, or vasopressin at any dose)
- OR -
- Two of the following:
 - Unexplained metabolic acidosis (base deficit > 5.0 mEq/L)
 - Increased arterial lactate > 2 times upper limit of normal
 - Oliguria (urine output < 0.5 mL/kg/hr)
 - Prolonged capillary refill (> 5 secs)
 - Core to peripheral temperature gap > 3°C

Respiratory dysfunction

One of the following criteria:

- $\text{PaO}_2/\text{FIO}_2 < 300$ in absence of cyanotic congenital heart disease or pre-existing lung disease
- $\text{PaCO}_2 > 65$ torr or 20 mm Hg over baseline PaCO_2
- Proven need or >50% FIO_2 to maintain saturation 92%
- Need for non-elective invasive or noninvasive mechanical ventilation

Neurologic dysfunction

One of the following criteria:

- Glasgow Coma Score 11
- Acute change in mental status with a decrease in Glasgow Coma Score 3 points from abnormal baseline

Hematologic dysfunction:

One of the following criteria:

- Platelet count < 80,000/mm³ or a decline of 50% in platelet count from highest value recorded over the past 3 days (for chronic hematology/oncology patients)
- International normalized ratio 2

Renal dysfunction:

- Serum creatinine 2 times upper limit of normal for age or 2-fold increase in baseline

Hepatic dysfunction:

One of the following criteria:

- Total bilirubin 4 mg/dL (not applicable for newborn)
- ALT 2 times upper limit of normal for age

Adapted from (13)