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Sepsis in Pediatric Cardiac Intensive Care

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Abstract

Objectives—In this review we will discuss risk factors for developing sepsis; the role of biomarkers in establishing an early diagnosis, monitoring therapeutic efficacy, stratification, and for the identification of sepsis endotypes; and the pathophysiology and management of severe sepsis and septic shock, with an emphasis on the impact of sepsis on cardiovascular function.

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Conclusion—There is a lot of excitement in the field of sepsis research today. Scientific advances in the diagnosis and clinical staging of sepsis, as well as a personalized approach to the treatment of sepsis, offer tremendous promise for the future. However, at the same time, it is also evident that sepsis mortality has not improved enough, even with progress in our understanding of the molecular pathophysiology of sepsis.

Keywords

severe sepsis; pediatrics; biomarkers; pathophysiology; outcomes

Introduction

The Italian philosopher Niccolo Machiavelli described a condition in his masterpiece The Prince that was “in the beginning of the malady...easy to cure but difficult to detect, but in the course of time, not having been either detected or treated in the beginning, it becomes easy to detect but difficult to cure...” While he was talking specifically about a condition known at the time as hectic fever (now known to be caused by tuberculosis), the same statement still applies to the syndrome we know as sepsis over five centuries later. Tuberculosis, like all infectious diseases, can trigger a systemic inflammatory response that is manifest clinically as fever, tachycardia, tachypnea, hypotension, and capillary leak, that is to say sepsis. Indeed, because all infections share sepsis as the final common pathway, sepsis has become one of the leading killers of children worldwide (1). In the United States, almost 4,500 children die from sepsis every year (2).

Unfortunately, there have only been a few studies on the epidemiology of sepsis in children. Proulx and colleagues (3) analyzed the incidence and outcome of sepsis using the now familiar Society of Critical Care Medicine/American College of Chest Physicians consensus definitions, modified specifically for use in pediatrics (4, 5) in a single tertiary care

children's hospital. The hospital's pediatric intensive care unit (PICU) admitted slightly over 1,000 critically ill children over a 12-month period - 82% of these children met criteria for the systemic inflammatory response syndrome (SIRS), while 23% had sepsis, 4% had severe sepsis, and 2% had septic shock. More recently, Weiss and colleagues reported the results from an international point prevalence study of pediatric sepsis conducted in 128 sites from 26 countries on 5 separate days throughout 2013–2014. The point prevalence of severe sepsis was 8.2% with a reported hospital mortality of 25% (6), which is much higher than previously reported rates of mortality (2, 3, 7–9).

While mortality statistics are certainly an important consideration, children who survive from sepsis often experience significant morbidity as well (10). Approximately 17% of children hospitalized with severe sepsis will develop at least moderate disability (6), which is associated with a greater risk of readmission to the hospital and/or death after initial discharge from the hospital (9). The “economic morbidity” is an important consideration as well. In at least one study, pediatric sepsis accounted for over \$2 billion per year in the U.S. alone (2). However, these statistics tend to ignore the hidden costs attributed to the loss of productivity from the years of life lost for critically ill children who die of sepsis, as well as the often substantial additional hidden costs of caring for those children who survive sepsis with long-term morbidities, as described above. Collectively, these studies describe a worldwide problem of immense importance to the health and welfare of children (7, 8).

Risk Factors for Sepsis in Pediatric Cardiac Intensive Care

Critically ill children with congenital heart disease are at an increased risk for sepsis (11). For example, there are several well-described malformation syndromes (e.g., 22q11 deletion or DiGeorge sequence) and chromosomal syndromes (trisomy 21) that have been linked with an increased risk of congenital heart disease, as well as defects in the host immune response. In addition, these children are exposed to invasive devices, which carry an increased risk for infection. Children who undergo heart or heart/lung transplantation require life-long immunosuppression to prevent graft rejection, which also increases the risk of infection. Finally, cardiopulmonary bypass (CPB) has a number of effects on the innate and adaptive immune system, including activation of the complement cascade, release of endotoxin, activation of leukocytes and the vascular endothelium, and release of pro-inflammatory cytokines (12). The impact of this transient, but potent pro-inflammatory immune response on clinical outcomes is not well understood (13), though several centers now routinely treat these patients with corticosteroids in an attempt to suppress or at least ameliorate this inflammatory response (14, 15). Studies have also shown that the immunologic response to CPB can produce a transient state of immune suppression, often referred to as “immunoparalysis” (12, 16–18). For example, whole blood obtained from children following CPB stimulated *ex vivo* with lipopolysaccharide (LPS) results in markedly diminished pro-inflammatory cytokine production (16), consistent with the phenomenon known as “endotoxin tolerance” (19). The significance of immunoparalysis remains in question, though some studies suggest that these children are at a greater risk for hospital-acquired infections (HAI), such as central line-associated bloodstream infections (CLA-BSI), ventilator-associated respiratory infections (VARI), surgical site infections (SSI), and catheter-associated urinary tract infections (18, 20–22). HAIs are an independent

risk factor for increased post-operative CICU length of stay (LOS) following the arterial switch operation (23). Similarly, others have also shown that HAI significantly increase duration of mechanical ventilation, ICU and hospital LOS, and healthcare costs in children (20, 22, 24–28).

Pathophysiology of Sepsis in Children

Pediatric sepsis is different from adult sepsis and has been reviewed extensively elsewhere (29–31). It is important to recognize, however, that sepsis affects literally every organ system to some degree. The effects of sepsis on cardiac function, vascular function and cardiac output are of particular interest. For example, adult septic shock is classically characterized by a hyperdynamic state with high cardiac output and low systemic vascular resistance (SVR) (in other words, “warm shock”). Cardiovascular support is therefore focused on increasing SVR with vasopressors, such as norepinephrine. Children, on the other hand, often exhibit low cardiac output and high SVR (in other words, “cold shock”) (32). Left ventricular (LV) systolic function during early infancy is critically sensitive to increases in afterload, in that increased afterload, as occurs in the setting of shock and peripheral vasoconstriction, results in markedly diminished stroke volume and cardiac output (33, 34). Importantly, the pediatric vascular endothelium responds to stress with increased vasoconstriction, creating conditions that therefore favor the “cold shock” phenotype (high SVR, low cardiac output). Myocardial excitation-contraction coupling is not completely developed in early childhood, resulting in a relatively greater sensitivity and dependence to calcium and β -adrenergic tone compared with adults (35). Moreover, reduced left ventricular muscle mass leads to a relative decrease in left ventricular reserve capacity, such that the left ventricle is unable to sufficiently increase contractility in response to stress. As such, infants in particular are unable to augment stroke volume to increase cardiac output and are therefore dependent upon heart rate alone for this purpose (35).

These cardiovascular and hemodynamic differences were described in what is now considered a classic study by Ceneviva and colleagues (36). These investigators categorized 50 children with fluid-refractory shock based upon hemodynamic data obtained with a pulmonary artery (PA) catheter into one of three possible hemodynamic derangements (i) the adult “warm shock” phenotype, characterized by high cardiac index (CI) and low SVR (< 800 dynes sec/cm^5); (ii) the “cold shock” phenotype characterized by low CI and high SVR; and (iii) an intermediate phenotype characterized by low CI and low SVR. The most common phenotype observed in these critically ill children was the “cold shock” phenotype, as discussed above (36). These findings have been demonstrated in multiple studies (37–44). Based on these hemodynamic differences, historically the treatment of pediatric septic shock has focused on augmenting cardiac output with fluid resuscitation (to augment preload), increasing contractility with the addition of inotropic agents (e.g., dopamine, low-dose epinephrine, and milrinone) (29).

Sepsis-induced Cardiomyopathy

Myocardial dysfunction appears to play a prominent role in the pathophysiology of septic shock in both critically ill children and adults. Unfortunately, there is no universally

accepted definition of myocardial depression in sepsis, though some authors have defined “septic cardiomyopathy” by the presence of global (systolic and diastolic) dysfunction of both the right and left sides of the heart (45, 46). There are three distinguishing features of septic cardiomyopathy (47). First, patients typically have evidence of left ventricular dilatation with normal or low filling pressures due to increased left ventricular compliance (48). Volume loading (as would occur with fluid resuscitation) leads to an abnormal increase in left ventricular end-diastolic volume (EDV) (49). Second, left (and probably right as well) ventricular ejection fraction is decreased (50–52). Third, septic cardiomyopathy is generally reversible, as function typically improves in 7–10 days (48, 53).

The exact mechanism of sepsis-induced cardiomyopathy is not fully understood. Several studies suggest that pro-inflammatory mediators, released during the host immune response, act as “myocardial depressant factors.” For example, some of the earliest studies showed that myocardial contraction velocity is significantly decreased in rat cardiomyocytes treated with serum obtained from critically ill adults with septic shock (54). Suffice it to say that there is no one single so-called “myocardial depressant factor,” but rather a number of inflammatory cytokines (e.g., tumor necrosis factor (TNF) - α , interleukin (IL) -1, and IL-6), ion channels (e.g., calcium channels, potassium channels), and other factors (e.g., nitric oxide and endothelin-1) have been shown to adversely impact myocardial function both *in vitro* and *in vivo* (47). In addition, structural modifications in the myocardium (e.g., apoptosis, necrosis, myocardial infiltration with leukocytes, edema, disruption of the contractile apparatus, etc.) and alterations in myocardial bioenergetics are also likely to play a significant role (45, 55–57). For example, increased serum concentrations of cardiac troponin I (cTnI) (a marker of cardiomyocyte cell necrosis) correlates with diminished cardiac function, increased inotrope requirements, and severity of illness in critically ill children with septic shock (58, 59).

Importantly, while echocardiography is an important non-invasive tool for assessing cardiac function in critically ill children, standard echocardiographic measures of left ventricular function (i.e., ejection fraction and fractional shortening) are influenced greatly by both preload and afterload, potentially limiting echocardiography’s utility in critically ill children with septic shock. Newer echocardiographic techniques, such as spectral tracking imaging (STI), do not have these limitations and have been shown to detect myocardial depression even when traditional echocardiography does not (60). There clearly is a gap in our understanding of the complex pathophysiology of septic cardiomyopathy in critically ill children (61, 62), and further studies using tools such as STI echocardiography in this population are clearly justified. Treatment of septic cardiomyopathy is largely supportive and discussed further below.

The Emerging Role of Sepsis Biomarkers

There is substantial interest in the development and discovery of biomarkers to better manage patients with sepsis. Such biomarkers can serve a variety of functions including early diagnosis, monitoring for therapeutic efficacy, stratification, and identification of sepsis endotypes (see below) (63). A large number of biomarkers have been described for diagnosing sepsis, but currently procalcitonin and CRP are the only ones in routine clinical use (64). The clinical performance of these two biomarkers has been quite variable, thereby

stimulating the search for more reliable biomarkers. One such biomarker is interleukin-27 (IL-27). Using a transcriptomic approach, IL-27 was identified as a candidate sepsis biomarker, and serum IL-27 concentrations greater than 5 ng/mL were reported to have greater than 90% sensitivity and positive predictive value for identifying critically ill children with bacterial infection (65). In this initial study, IL-27 outperformed procalcitonin, and a combination of IL-27 and procalcitonin performed better than either biomarker alone. Additional studies are ongoing to further assess the validity of IL-27 as a sepsis diagnostic biomarker. Interestingly, IL-27 appears to perform better as a sepsis diagnostic biomarker in children, compared to adults (66).

Recent studies reported on the derivation and validation of the Pediatric Sepsis Biomarker Risk Model (PEREVERE) (67–69). PERSEVERE is a multi-biomarker-based risk model that assigns a baseline mortality risk for children with septic shock. There are several potential applications for PERSEVERE including stratification for clinical trials, serving as a benchmark for quality improvement efforts, and informing clinical decision making based on a reliable baseline mortality risk estimate. Recently, PERSEVERE was applied to conduct risk stratified analyses of clinical data (70, 71). A temporal version of PERSEVERE that monitors biomarker changes over the initial three days of septic shock, and how those changes associate with outcome, has the potential to serve as a monitor for therapeutic efficacy (72).

An endotype is a subclass of a condition or syndrome, as defined by function or biological process. Given that sepsis is a syndrome, it is likely that sepsis endotypes exist and that the endotypes are associated with clinical phenotype, outcome, and response to therapy. Using whole genome expression profiling, gene expression endotypes of sepsis were reported and subsequently validated (73–75). Recently, the approach to identifying these sepsis endotypes was adapted for clinical application using an endotype-defining gene signature consisting of 100 genes, gene expression mosaics, and a rapid mRNA quantification platform (76). Importantly, allocation to one of the endotypes is independently associated with increase mortality and organ failure burden. The gene signature that defines the endotypes is enriched for genes corresponding to adaptive immunity and the glucocorticoid receptor signaling pathway, thus opening the possibility for a theranostic approach to pediatric sepsis. Indeed, in a *post hoc* analysis the prescription of adjunctive corticosteroids was independently associated with four times the risk of mortality in one of the endotypes.

Management of Sepsis in Pediatric Cardiac Intensive Care

There are no “magic bullets” with which to treat critically ill children with sepsis. Several promising treatments, many of which have been targeted at specific mediators of the host inflammatory response in sepsis have universally failed to live up to initial expectations in subsequent clinical trials (77). Given the lack of specific treatments, the crux of pediatric sepsis management rests upon three important therapeutic principles or pillars – (i) early recognition, (ii) early source control and antibiotic administration, and (iii) early reversal of the shock state.

Early recognition, particularly in children with cardiac disease, is particularly difficult. A recently published retrospective registry review involving close to 110,000 critically ill adults showed that the SIRS criteria, on which the diagnosis of sepsis is based, excluded one in eight patients with infection, organ failure, and subsequent death (78). While this was an adult study, the SIRS criteria likely perform just as poorly in critically ill children (79–81). The so-called PIRO approach (P=Predisposition, I=Insult/Infection, R=Response, O=Organ dysfunction) (11, 82, 83) may prove to be more useful for clinically staging patients with sepsis, though the use of this model for the diagnosis of sepsis requires further study. Regardless, early recognition is of absolute importance, given that delays in recognition and treatment have been associated with poor outcomes (84–86). Interestingly, expert clinicians may use completely different contextual cues to recognize children with sepsis (87) – this is an area of active research in our own center (Wheeler, *unpublished data*).

Once the diagnosis of sepsis is suspected, early treatment measures focused on antibiotic administration and reversal of shock are of utmost importance. For example, the American College of Critical Care Medicine Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock were published in 2002 as “best practices” for the management of critically ill neonates and children with septic shock (88) – these guidelines were updated in 2007 (89). While these guidelines have not been rigorously tested in a randomized, controlled clinical trial, early antibiotic administration and reversal of shock are associated with improved outcomes in critically ill children with severe sepsis/septic shock (84, 90–93).

The landmark early, goal-directed therapy (EGDT) in sepsis was published in 2001 (94). At the time, this study was one of the first clinical trials in sepsis to show a reduction in overall mortality. Several subsequent trials have failed to demonstrate any improvement in outcomes with protocolized, goal-directed therapy of critically ill patients with sepsis (95–97). Rather than discarding EGDT as a concept, it is important to remember that one of the fundamental reasons that Rivers and colleagues performed this trial was to address the widespread problem of “medical boarding” of critically ill patients in the emergency department (ED) setting. The paradigm shift here was that these patients were treated in the ED, rather than waiting for admission to the ICU. As early treatment of sepsis has become widespread, particularly following the Surviving Sepsis Campaign (98), it is not surprising that there is no difference in outcome between early treatment of patients using either a goal-directed protocol or standard therapy. The key here is that treatment, regardless of approach, is instituted early!

Conclusion

There is a lot of excitement in the field of sepsis research today. Scientific advances in the diagnosis, clinical staging, and personalized approach to treatment to sepsis offer tremendous promise for the future. However, at the same time, it is also evident that sepsis mortality has not improved enough, even with the progress in our understanding of the molecular pathophysiology of sepsis. It is clear that we do not know enough about sepsis in children with cardiac disease – this is an area that deserves further research.

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