Foreword

Advances in Pediatric Sepsis and Shock

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In this special issue of the *Journal of Pediatric Intensive Care*, we have compiled a series of articles addressing various aspects of the disease process termed “pediatric sepsis,” including its epidemiology, advances in diagnostic biomarkers as well as an increased understanding of sepsis-related inflammation, the emergence of antimicrobial resistant organisms, pulmonary complication of sepsis, and new insights into sepsis immune modulation.

The first article details the epidemiology of pediatric septic shock. Of course, to quantitate something, it must be defined. Defining septic shock, especially in pediatric patients, has been difficult. The first definition of pediatric septic shock was published in 2002 and was defined as the presence of fever or hypothermia and tachycardia and five signs of hypoperfusion: altered mental status, capillary refill of more than 2 seconds or flash capillary refill, diminished or bounding peripheral pulses, mottled extremities, and decreased urine output.¹ Using this definition, according to the recent Sepsis PRevalence, OUTcomes, and Therapies Study (SPROUT), the prevalence of severe pediatric sepsis is high worldwide, varying ranging from 6.2% in Europe to 23.1% in Africa.² More recently, in 2016, the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) developed a new definition of septic shock as being “a subset of sepsis in which underlying circulatory, cellular and metabolic abnormalities are associated with a greater risk of mortality than sepsis alone,” with adult patients identified as having hypotension requiring vasopressor therapy to maintain mean blood pressures of at least 65 mm Hg, and having a serum lactate level greater than 2 mmol/L after fluid resuscitation.³ However, the new Sepsis-3 consensus statement was designed for adults and not children, as such there is an urgent need to for Sepsis-3 to develop pediatric-specific definitions and clinical para-

eters.⁴ But regardless of the specific definitions, it is clear that in both developed and developing countries, mortality from septic shock is high, and is associated with delayed diagnosis and treatment.

Sepsis is the result of a dynamic interplay between the pathogen and the host immune system. Given that defining pediatric sepsis is challenging, one can imagine that it would be particularly difficult to develop biomarkers to predict sepsis pathogenesis and prognosis. In the second article of this issue, Dr. Hector Wong offers his insights into the development of biomarkers for just this purpose. More importantly, however, he provides an exceptional review of the field of biomarkers in general. With the field moving toward more personalized medicine, his thoughts on *enrichment*, defined as the selection of a patient cohort that is more likely to respond to a therapeutic intervention, compared with an unselected cohort, are apropos.⁵

Even when pediatric sepsis is recognized and treated early, it is increasingly possible that the antibiotics delivered to patients will not eradicate the organism due to multidrug resistance (MDR). The third article of this issue focuses on the emerging threat of MDR organisms in both pediatric and neonatal populations. While infections from antibiotic-resistant Gram-negatives, such as extended spectrum β -lactamase-producing organisms and carbapenem-resistant Enterobacteriaceae, have been associated with poor outcomes in adults, little data are available for children. Furthermore, since fewer antimicrobials have been tested and approved for the use in children, the therapeutic options are more limited. The development and approval of antimicrobials for use in children need to be a focus of future research given this emerging threat.

Unfortunately, the common final pathway of refractory sepsis and shock is multiple organ dysfunction syndrome

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(MODS). MODS was first defined in 1991 by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference concerning sepsis and its sequelae as the “presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention⁶.” But MODS may present in “different flavors” in children such as thrombocytopenia-associated multiple organ failure, which is a spectrum of thrombotic microangiopathies due to various insults^{7,8}; and immune paralysis as defined by inadequate monocyte human leukocyte antigen-DR expression and tumor necrosis factor production in response to stimuli.⁹ The fourth article of this issue highlights the roles of cytokines and danger-associated molecular patterns and the pathogenesis of MODS. Although an exuberant proinflammatory response to the infectious insult is a trigger for subsequent activation of downstream pathways, the lack of a precise pathophysiological mechanism has led to the paradigm that metabolic shutdown of cellular mitochondria may play a key role in MODS. Future research is needed to define precise cellular pathogenesis to create new treatment modalities.

Sepsis and shock often lead to respiratory failure, with the most severe form of respiratory failure defined as acute respiratory distress syndrome (ARDS). For years in pediatric critical care, we used the same ARDS criteria as defined in adult patients. However, these ARDS definitions may not capture the nuances of pediatric ARDS. The fifth article describes the present interpretation of the 2015 Pediatric Acute Lung Injury Consensus Conference (PALICC) that was sponsored by the Pediatric Acute Lung Injury and Sepsis Investigators to propose pediatric-specific definitions for pediatric ARDS (PARDS).¹⁰ The 2015 PALICC definitions of PARDS differ from ARDS criteria in the use of oxygenation index instead of $\text{PaO}_2/\text{FIO}_2$, alternative stratification based on SpO_2 rather than PaO_2 (oxygen saturation index), and less restrictive radiographic criteria (unilateral infiltrates). It remains to be seen whether these modifications will increase, or decrease, the sensitivity and specificity for PARDS, but it provides a starting point.

As previously mentioned, sepsis is a dynamic interplay between the pathogen and the host immune system. While elimination of the nidus of infection is a staple of sepsis management, it is being increasingly recognized that sepsis/shock may be due to either a paralyzed or over-exuberant immune response. Numerous clinical trials in septic adults have unsuccessfully attempted anti-inflammatory therapies in an effort to ameliorate the proinflammatory surge. What has been recognized is that the excessive immune responses are typically paired with overly robust compensatory anti-inflammatory responses. The sixth article delves into this complex subject and highlights some potential strategies for immune monitoring and immunomodulation in pediatric sepsis with a goal of restoring immunologic homeostasis.

Pediatric sepsis remains a significant cause of mortality in children around the world. We, as pediatric critical care physicians, need better protocols, criteria, and technology to more quickly and precisely characterize infections and associated pathogens. Additionally, to intelligently deliver immune modulation in patients with poor prognosis, we need methods to quickly classify the timing, magnitude, and quality of the immune response in pediatric sepsis patients. Future research is needed specifically in pediatric sepsis to fill these knowledge gaps.

Conflict of Interest

None declared.

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