

# Pediatric Sepsis

## Challenges and Adjunctive Therapies

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### KEYWORDS

- Epidemiology • Outcomes • Antibiotics • Quality improvement • Corticosteroids
- Hemofiltration • Hemoadsorption • Plasmapheresis

### KEY POINTS

- Sepsis continues to be a major challenge in pediatric critical care medicine.
- Studies of sepsis outcomes should include both short-term and long-term outcomes, and should also focus on functional outcomes.
- The issue of timeliness and appropriateness of antibiotics is an appropriate and important area for quality improvement in pediatric sepsis.
- The issue of corticosteroids as an adjunctive therapy in pediatric septic shock remains largely unresolved and requires formal testing by way of clinical trials.
- Hemofiltration, hemoperfusion, and plasmapheresis are potential adjunctive therapies for pediatric sepsis, but require formal testing by way of clinical trials.
- A new multi-biomarker-based model has been developed to reliably stratify the outcome risk in children with septic shock.

### INTRODUCTION

Sepsis remains a major challenge in pediatric critical care medicine. Several recent publications cover the general principles of sepsis management, as well as pathophysiology in a developmental context.<sup>1–5</sup> This review intends to provide an appraisal of adjunctive therapies for sepsis and to highlight opportunities for meeting selected challenges in the field.

### EPIDEMIOLOGIC AND QUALITY-IMPROVEMENT CHALLENGES

Sepsis is estimated to be the leading cause of death in infants and children worldwide, with an annual mortality of approximately 1.6 million per year. In the United States,

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approximately 42,000 cases of severe sepsis occur annually and in-hospital mortality is estimated at 10.3%.<sup>6,7</sup> The mean length of stay and cost for a child with severe sepsis in the United States are estimated to be 31 days and more than \$40,000, respectively. Clearly sepsis remains an important public health issue in both underdeveloped and developed countries, and consequently brings many opportunities for translational research and efforts at quality improvement.

The ability to benchmark outcomes, based on a reliable outcome metric (ie, reliable outcome prediction), is fundamental to quality-improvement efforts and improvement science.<sup>8</sup> Unfortunately, there is no quality metric or outcome benchmark specific to pediatric sepsis. Scoring systems based on physiologic and clinical variables, such as the Pediatric Risk of Mortality (PRISM) score and the Pediatric Index of Mortality (PIM), are very robust for predicting outcomes of general pediatric intensive care unit (ICU) populations, but begin to perform less well when applied to specific diseases, such as sepsis.<sup>9</sup> Recently a multi-biomarker-based outcome risk model that reliably predicts outcome in children with severe sepsis and septic shock was developed and validated.<sup>10,11</sup> Although the model requires further prospective testing, it is hoped it will enhance currently available scoring systems and therefore provide a sepsis-specific quality metric to better assess short-term outcomes of pediatric sepsis.

While short-term outcomes (ie, acute mortality or survival) will continue to be important considerations in translational research efforts and clinical trials, increasingly greater attention is now focused on sepsis-related morbidity and mortality beyond the acute phase. Quartin and colleagues<sup>12</sup> reported that adults who initially recover from the acute stage of sepsis have an increased risk of death for up to 5 years after discharge, even after accounting for the effects of comorbidities. Karlsson and colleagues<sup>13</sup> documented a 2-year mortality rate of 45% for adults after severe sepsis and decreased quality of life in sepsis survivors at a median of 17 months after the acute episode of severe sepsis.

Similar data are now being reported in pediatric survivors of severe sepsis. Czaja and colleagues<sup>14</sup> retrospectively studied more than 7000 pediatric cases of severe sepsis. Almost one-half of the patients who were discharged after the initial admission were readmitted at least once, at a median of 3 months after discharge. Respiratory infection was the most common indication for readmission, and greater than 30% of these readmissions were in children without comorbidities. An additional 6.5% of patients died during these readmissions. Thus sepsis has important long-term consequences and there is a need to more robustly assess long-term outcomes, as well as functional outcomes beyond the acute dichotomy of alive or dead.

The Functional Status Scale (FSS) was recently developed to specifically meet the need of assessing functional outcomes of critically ill children.<sup>15</sup> The FSS incorporates several relevant functional assessments including mental status, sensory functioning, communication, motor functioning, feeding, and respiratory status, and is designed to be applied in diverse and time-limited environments. The FSS appears to have very good interrater reliability, and its performance compares favorably with more complex and labor-intensive functional outcome tools. A major challenge moving forward, as stated by the FSS investigators, is the development of subgroup-specific versions of FSS (eg, sepsis specific).<sup>15</sup>

## **APPROPRIATENESS AND TIMING OF ANTIBIOTICS**

Along with aggressive fluid resuscitation, prompt and appropriate administration of antibiotics continues to be a cornerstone of therapy for patients with severe sepsis

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