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Pediatric Sepsis From Start to Finish

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"Understanding the true risk of death in an episode of severe sepsis or septic shock in childhood is surprisingly complex." This conclusion reported by Cvetkovic and colleagues from London (1), nicely summarizes a database investigation that provides new insight into pediatric sepsis epidemiology. Once again, these investigators have ascertained that sepsis (and critical illness in general) begins and ends outside of the confines of the pediatric intensive care unit (PICU) (2).

This study group interrogated the Children's Acute Transport Service database culling seven years of data over the interval, 2005–2011. It is notable that the database records transfer information from 44 referring hospitals and seven receiving PICUs. It is also pertinent that the vast majority of pediatric sepsis cases in England are admitted following transport from a referring hospital (3).

In this investigation, 703 children were identified with a diagnosis of severe sepsis, and of these 627 had one-year survival data. The study cohort reflected approximately 5% of all Children's Acute Transport Service referrals and approximately 10% of all cases of severe sepsis/septic shock in England. Fifty-five percent of the deaths in the cohort occurred within the first 24 hours of referral to a PICU. Twenty-six percent of these early deaths occurred before ever reaching the referral PICU, including 5% of children who died at local referring hospitals. These early sepsis deaths largely involved unsuccessful multiple organ dysfunction syndrome resuscitation. A significant proportion of cases were attributable to meningococcemia. Overall, 24-hour mortality was 11% while 30-day mortality was 18%, and one-year mortality was 21%. The risk of death at one month was similar to that observed in the RESOLVE trial that examined the potential benefit of activated protein C among children with severe sepsis (4). In the RESOLVE investigation, all subjects exhibited both cardiovascular (need for vasoactive-inotropic support) and pulmonary (need for mechanical ventilation) organ dysfunctions.

Although the focus of the investigation was clearly early deaths attributable to pediatric severe sepsis/septic shock, the authors also confirm risk for long term mortality following an episode of pediatric sepsis, a finding that was previously reported in a large cohort of septic

children in the United States (5). This investigation also confirmed that children with chronic comorbid conditions exhibited a 3–4 fold higher risk of death during the first year after the sepsis event as compared to previously healthy children (5–7). This risk is strikingly demonstrated in the Kaplan-Meier survival curve (Figure 2) that diverges after 24 hours and reflects the excess burden of late mortality among children with chronic comorbid conditions. In the study cohort, children with previous prematurity, immunodeficiency, cardiac disease, and neurologic disease were at particular risk for long term mortality following an episode of severe sepsis/septic shock.

From their data, the investigators conclude that early sepsis deaths in children may in fact delay and limit the impact of sepsis treatment that is largely delivered in PICUs. In pediatric sepsis interventional trials, subject ascertainment bias may occur because of delays in consent and hence delays in administration of potentially beneficial novel therapy. For example, such an effect was observed in the trial of recombinant bacterial permeability increasing protein for pediatric meningococcemia (8). Early deaths were particularly common in this investigation, and clearly impacted the intention-to-treat population. In this trial, children randomized to the treatment drug arm frequently died before administration of the study drug.

The authors point out that the results of their investigation may be limited by the relatively large population of children with meningococcemia as well as a relatively small population of children with chronic comorbid conditions (14%.) However, even as the incidence of meningococcemia has gradually decreased, the percentage of children with chronic comorbid conditions admitted to PICUs has gradually increased and now comprises 40–50% of admissions in many PICUs (7, 9).

A recent 7.5-year evaluation of compliance with the Surviving Sepsis Campaign resuscitation bundle among 29,470 adults with sepsis demonstrated a clear survival benefit (29.0% vs. 38.6%) when comparing institutions with high versus low bundle compliance (10). Similarly, there exist multiple reports documenting the benefit of early resuscitation for pediatric sepsis (11–15). However, the report by Cvetkovic and colleagues emphasizes that the resuscitation bundle needs to move out of the PICU and into the field. It has been well-established that pediatric sepsis resuscitation is time-sensitive (16–18). Every effort must be made to identify the patient with sepsis as early as possible in order to initiate the earliest resuscitative measures. In this regard, in the discussion of their findings, the authors provide two suggestions to improve sepsis resuscitation at the source: Intensive care unit retrieval teams could facilitate experienced pediatric critical care at referring hospitals assuming earlier sepsis recognition and referral--this approach could be augmented with telemedicine while awaiting arrival of the transport team (19). This is essentially analogous to a rapid response team with boundaries beyond the walls of the referral hospital. In addition, the authors advocate serious discussion regarding deferred consent for sepsis interventional trials (20). This approach could potentially save hours of critical time involving the transfer and consent processes. Such an approach would require community education, discussion, feedback, and ultimately support of a deferred consent process, and would likely have a secondary effect of increasing public awareness of the lethality of pediatric sepsis and promote earlier community sepsis recognition.

In conclusion, Cvetkovic and colleagues remind us of the risk of late death associated with an index case of pediatric sepsis during the first year following discharge from the hospital; that children with chronic comorbid conditions have a particularly high risk of death from sepsis; and that the majority of children who die of sepsis do so within the first 24 hours of referral to a PICU, half of these before ever reaching the PICU. As intensivists, we have been trained to resuscitate multiple organ dysfunction syndrome associated with sepsis in PICUs. The report by Cvetkovic challenges us to acknowledge that to further reduce pediatric sepsis mortality, we need to turn our attention to events that are occurring hours before PICU admission and acknowledge that ongoing risk of death associated with pediatric sepsis continues long after PICU discharge.

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