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Clinical trials in pediatric sepsis: What's the (end) point?

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Selecting the primary endpoint or outcome measure is critical to the design and sample size determination of a clinical trial. To date, most sepsis trials have used short-term all-cause mortality endpoints, such as death at 28 days or hospital discharge (1). However, mortality within this relatively arbitrary time period has been questioned as the most appropriate endpoint for sepsis trials, particularly in pediatrics (2–4).

In this issue of *Pediatric Critical Care Medicine*, Menon et al. reviewed endpoints used in randomized trials of pediatric septic shock (including Dengue shock) conducted in a pediatric intensive care unit (PICU) and published between 1986 and 2016 in English-language journals (5). The authors determined if primary endpoints met a “feasibility” metric, which they defined as 1) recruitment of at least 90% of the targeted sample size and agreement of the predicted-to-observed outcome rate to within 10% in the control group or 2) finding a statistically significant difference in the primary outcome. Of the 19 trials included, 14 specified a primary outcome of which short-term mortality endpoints were most common (used in eight trials). Other primary endpoints included duration of shock (four trials) and organ dysfunction (1 trial). No trial used morbidity or health-related quality of life (HRQL). The primary endpoint was deemed “feasible” in only three trials, all of which used 28-day mortality. Two of the “feasible” trials reported a statistically significant mortality reduction (both conducted in developing countries). Challenges to using mortality as an endpoint were over-estimating both the expected mortality and the anticipated impact of the intervention, as well as insufficient recruitment capacity to meet the sample size goal. Ultimately, the authors concluded that mortality, though commonly used, may not be appropriate as a sole primary endpoint for pediatric sepsis trials in all settings, particularly in developed countries where sepsis-related deaths continue to decline.

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This systematic review raises several questions for pediatric sepsis investigators: 1) Do children still die from septic shock? 2) Can we “afford” to use mortality as an endpoint in pediatric sepsis trials? 3) Are interventions valuable even if they do not decrease death?

Do children still die from septic shock?

The answer, unfortunately, is yes. Although quantifying the public health burden of sepsis-related deaths in children is difficult, U.S.-based estimates range from a few percent in population-based studies to greater than 20% for patients requiring PICU admission (6–10). On the surface, then, it would seem reasonable to target mortality in clinical trials. However, the reasons that children die from sepsis are highly variable and thus the mechanisms through which an intervention may be expected to impact mortality need consideration. For example, trials targeting earlier sepsis recognition and resuscitation therapies are most likely to reduce deaths from refractory shock. Conversely, a novel biologic therapy targeting persistent or progressive organ dysfunction should more readily lower subacute deaths for children who have been stabilized in a PICU but fail to clinically improve. But most trials group all mortalities together as an “all-cause” endpoint without regard to the types of death the intervention is most likely to impact. In addition, children with the highest risk of death from sepsis are also most likely to have comorbidities that independently limit survival, making it difficult to attribute the cause of death to sepsis (1, 2).

Can we “afford” to use mortality as an endpoint in pediatric sepsis trials?

“Afford” refers both to the high cost of conducting large trials that are adequately (and realistically) powered for mortality as an endpoint, as well as the prolonged timeframe needed to complete very large trials. For example, even with a relatively high PICU mortality of 24%, the SPROUT study estimated that 2,118 patients would need to be enrolled from 58 modestly-sized PICUs over three years to achieve 80% power to detect a 5% absolute reduction in mortality (10). Such an extensive trial across numerous PICUs may be prohibitively expensive, but utilizing fewer sites would prolong enrollment and delay results. Incorporation of adaptive and enrichment designs to test multiple interventions targeted to patients most likely to benefit may help to curtail costs and hasten trial completion, but any methodological advantages are tempered by rare endpoints, such as mortality (4). Shifting focus to more common endpoints with a greater public health impact has seemingly become a matter of practical necessity.

Are interventions valuable even if they do not decrease death?

Surrogate endpoints provide a substitute for patient-centered outcomes in which the effect of the intervention on the surrogate predicts an effect on the “real” clinical outcome. Duration of shock and organ dysfunction are two surrogate endpoints that were commonly utilized in the review by Menon et al (5). Although both of these surrogates are associated with mortality in sepsis, it is less clear if reducing duration of shock or organ dysfunction will translate into fewer deaths (11, 12). But does it matter? Surely, shortening duration of shock and minimizing organ dysfunction will lower resource utilization, length of stay, and costs—all valuable benefits. Moreover, many of the same factors that increase risk of mortality also

lead to functional morbidity (13). Thus, interventions that improve functional morbidity and enhance HRQL for sepsis survivors certainly have value, even if there is minimal impact on death itself.

Although preventing death remains a fundamental tenet of critical care, the review by Menon et al. sheds new light on the “feasibility” of mortality as a primary endpoint for pediatric sepsis trials. Future trials should consider that mortality may not be the best measure of success and consider endpoints that are both more common and important to survivors, such as composite measures of mortality and HRQL that more fully capture the public health impact of pediatric sepsis. Mortality may still have utility in some settings, but care should be taken to set realistic expectations for mortality and the anticipated impact of the intervention. After reviewing thirty years of pediatric sepsis trials, perhaps the clearest message that Menon et al. have conveyed is that if we fail to learn from history we are doomed to repeat it.

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