HHS Public Access

Author manuscript

Pediatr Crit Care Med. Author manuscript; available in PMC 2016 October 01.

Published in final edited form as:

Pediatr Crit Care Med. 2015 October ; 16(8): 789–790. doi:10.1097/PCC.0000000000000531.

Fluid resuscitation in pediatric sepsis: lack of data versus lack of equipoise

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Keywords

pediatric; fluid resuscitation; septic shock; guidelines; equipoise

The practice of pediatric acute care medicine, and especially pediatric critical care, has necessarily evolved often without the underpinning of a strong evidence base. Relative to adults, children are less commonly ill, have less comorbidity, and only rarely suffer mortality. As a result, pediatric critical care practice is often based on extrapolations from adult data or the application of biologically plausible yet unproven therapies. This reality is highlighted by Gelbart et. al. who in this issue of *Pediatric Critical Care Medicine* present the results of their systematic review of aggressive fluid resuscitation strategies for children with severe sepsis and septic shock (1). They found only a handful of randomized controlled trials with limited applicability to the developed world where pediatric intensive care resources are available. They conclude that an adequate scientific basis does not exist to support aggressive fluid resuscitation in children with severe septic disease, such as recommended in the ACCM Clinical Practice Parameters for the Hemodynamic Support of Pediatric and Neonatal Septic Shock (2) and the Surviving Sepsis Campaign (3). The work presented here is perhaps noteworthy in that it brings to light the general dearth of *prospective* clinical data in the field of critical care pediatrics, but this is a reality of which few are ignorant. However, despite this disappointing truth we must place Gelbart's study in its proper context and give credit to the worthy tradition of retrospective work and small-scale clinical trials that have been at least temporally associated with a dramatic fall in mortality from pediatric sepsis, at least in the developed world.

The ACCM Guidelines begin first and foremost with aggressive fluid resuscitation up to 60 mL/kg in the first 15 minutes after the diagnosis of severe sepsis followed by the titration of vasoactive medications based on shock phenotype and, if necessary, additional fluids (2, 4). Proper implementation of the guidelines in their current form requires the availability of

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Dr. Frazier disclosed that he does not have any potential conflicts of interest.

intensive care resources and the means to monitor (often invasively) cardiac output, perfusion pressures, and oxygen delivery. This ambitious goal is achievable (5), and subsequent studies of critically ill septic children showed an association between fluid resuscitation and early shock reversal and survival (6). Guidelines-based resuscitation has been used as a backbone strategy against which investigators have tested new hypotheses in randomized clinical trials (7). Isotonic boluses in the earliest stages of severe sepsis are also key elements of adult sepsis resuscitation clinical trials and subsequent guidelines (3, 8).

Here, Gelbart et. al. claim aggressive resuscitation lacks a firm evidence base, and this is perhaps true if the *only* evidence that will serve is the gold-standard prospective, randomized, blinded clinical trial. However, it can also be argued that at least with regard to the efficacy of aggressive fluid resuscitation for *pediatric* septic shock, the horse is out of the barn. With two iterations of practice parameters (2, 4) and the Surviving Sepsis Campaign (3), we must ask ourselves: how much clinical equipoise remains for the use of aggressive fluid resuscitation as an essential element of a goal-directed management? Gelbart point us to the FEAST study (9) in which critically ill children in several African nations without intensive care resources for monitoring hemodynamics and providing ongoing resuscitation experienced a higher mortality when randomized to receive fluid bolus with either saline or albumin. Although a large and well-conducted trial, the FEAST study fluid bolus treatment arms do not resemble the fluid bolus components of the ACCM pediatric guidelines: children in the study only received one or two bolus, up to 60 mL/kg total, over at least one hour, without the availability of respiratory support, additional resuscitative fluids, vasoactive support, or hemodynamic monitoring. It is unlikely these results will have much influence on future revisions of the ACCM guidelines which are targeted to relatively resource-rich settings, and they are not likely to greatly alter the practice of pediatric intensivists fortunate enough to treat patients in such environments. In short, the FEAST study likely does not much disturb clinical equipoise.

What then? Are pediatric intensive care professionals applying an untested and therefore unsafe treatment to their critically ill infected patients? Does a lack of prior prospective data obviate our current “ubiquitous use” (to quote Gelbart) of a trusted treatment? It is unlikely that such a state of uncertainty exists in the settings to which Gelbart aim their work – namely, resource-rich environments in the developed world. Gelbart et. al. recognize as much when they follow up their assertion that “randomized controlled trials are ethical, justified, and, probably, desirable” with the acknowledgement that “there may currently be insufficient equipoise for such a trial (1).” One solution is to adopt existing guidelines as a baseline therapeutic backbone from which to examine single aspects of resuscitation and management as was done by de Oliveira in 2008 (7) when examining the clinical utility of continuous central venous saturation monitoring. Alternatively, Gelbart et. al. call for prospective observational work, such as the large-scale multinational SPROUT study (10) and longitudinal studies of severe sepsis in the United States (11, 12). Indeed, one need look no further than Gelbart’s current work wherein Table 5 provides a sampling of the long-standing and worthy tradition of evidence collected and published to support pediatric fluid resuscitation for septic shock.

An important takeaway from Gelbart's work here is the way it challenges us to confront the tension within our field wherein we strive to provide the best care for critically ill and injured children despite a lack of high level evidence in most cases. Although it would be irresponsible to turn away from an established practice without a meaningful disruption of clinical equipoise (13) we must remain ever mindful of the scientific underpinning of our practice (be they ever so tenuous) and seek after opportunities to improve.

Acknowledgment

Dr. Muszynski's institution received grant support from the National Institutes of Health.

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