

Washington University Emergency Medicine Journal Club
Pediatric Shock Fluid Resuscitation in the Developing World

Vignette

The infamous SueLin Hilbert has brought you to Ghana to help staff the emergency department and train local Ghanaian physicians in the art and science of emergency medicine. Aside from the local beer, you are loving the experience and you are making a big positive impact on clinical care in this very underserved population. One night, you are covering the ED alone when a 4-year-old girl arrives in septic shock. She is febrile, hypotensive, tachycardic, barely responsive to painful stimulation, and has delayed capillary refill. You are not sure what the underlying diagnosis is and cannot find a specific diagnosis due to the fact that it is the middle of the night and the malaria lab techs are gone for the night and you are out of rapid malaria diagnostic tests. But, it is the rainy season and you are seeing tons of malaria, so you assume the child has malaria sepsis most likely or less likely Gram-negative bacterial sepsis.

Nevertheless, it is clear to you she is in septic shock. You manage to place an EJ line after the nurses fail to obtain peripheral access and you aggressively resuscitate her with normal saline at a dose of 60 mL/kg over half an hour, broad-spectrum antibiotics, and supplementary oxygen. You consider albumin and blood transfusions, but by the time you get back to this patient (since you have an ED full of other sick patients), you learn that her respiratory status worsened, she became more pale and cold, and ultimately died. Her mother is shrieking and crying. You are at the edge of tears since this is certainly not the first child that has died on your watch today.

In the morning after your shift, you go home, have a stiff drink, and ponder what you may or may not have done wrong. After discussing it with SueLin in the morning, she makes you think about whether the choice and volume of fluids you administered were ideal. You get on Pubmed to consider the role of fluid resuscitation in septic shock in the developing world and come across the following articles:

PICO Question

Population: Children with septic shock due to severe infection in the developing world.

Intervention: Fluid resuscitation with alternate fluids or rates.

Comparison: Standard resuscitation with 20 mL/kg normal saline.

Outcome: Survival and time to recovery from shock.

Search Strategy

PubMed was searched on October 11, 2013, using the strategy: (sepsis or malaria) AND (fluid resuscitation). This gave 1182 results. The “English” language filter was applied. This reduced the total to 1064 results. The “child” age filter was applied. This reduced the total to 169 results. The “10 years” publication date filter was applied. This reduced the total to 85 results (<http://goo.gl/cdn1r1>). The abstracts of these 85 articles were reviewed to assess for relevant studies conducted in the developing world.

Article 1: [Akech SO, Jemutai J, Timbwa M, Kivaya E, Boga M, Fegan G, Maitland K. Phase II trial on the use of Dextran 70 or starch for supportive therapy in Kenyan children with severe malaria. Crit Care Med. 2010 Aug;38\(8\):1630-6. \[Answer Key\]\(#\).](#)

Article 2: [Maitland K, Pamba A, English M, Peshu N, Marsh K, Newton C, Levin M. Randomized trial of volume expansion with albumin or saline in children with severe malaria: preliminary evidence of albumin benefit. Clin Infect Dis. 2005 Feb 15;40\(4\):538-45. \[Answer Key\]\(#\).](#)

Article 3: [Maitland K, Kiguli S, Opoka RO, Engoru C, Olupot-Olupot P, Akech SO, Nyeko R, Mtove G, Reyburn H, Lang T, Brent B, Evans JA, Tibenderana JK, Crawley J, Russell EC, Levin M, Babiker AG, Gibb DM; FEAST Trial Group. Mortality after fluid bolus in African children with severe infection. N Engl J Med. 2011 Jun 30;364\(26\):2483-95. \[Answer Key\]\(#\).](#)

Article 4: [Santhanam I, Sangareddi S, Venkataraman S, Kissoon N, Thiruvengadamudayan V, Kasthuri RK. A prospective randomized controlled study of two fluid regimens in the initial management of septic shock in the emergency department. Pediatr Emerg Care. 2008 Oct;24\(10\):647-55. \[Answer Key\]\(#\).](#)

Bottom Line

Circulatory shock is a [significant problem](#) in pediatric emergency medicine and critical care. The leading culprit is hypovolemia, usually [due to life-threatening infection](#). Consequently, current guidelines for the acute management of severe sepsis in [pediatric](#) (and [adult](#)) patients emphasize early, rapid, and substantial infusion of intravenous fluids. The optimal fluid choice, volume of fluid, and route of administration has been the topic of debate for 175 years. Indeed, this topic was the focus of at least two recent systematic reviews. ([Akech 2010](#), [Ford 2012](#)) Nonetheless, this remains a contentious issue as evidenced by numerous letters and commentaries. ([Ford 2011](#), [Ribeiro 2011](#), [Berend 2011](#), [Joyner 2011](#), [Kissoon 2011](#), [Scott 2011](#), [Myburgh 2011](#), [Hilton 2012](#))



The highest-quality (least biased) evidence to date is the Fluid Expansion as Supportive Therapy in Critically Ill African Children ([FEAST](#)) trial, although thus far no guideline revisions reflect the findings of this study. Although the FEAST trial represents landmark research, global medicine experts at our Journal Club identified several potentially serious flaws with it. First, the trial closed prematurely (with [pros](#) and [cons](#)), although the decision appears justified on ethical grounds. The authors provided much more detail about this decision in a [subsequent manuscript](#). Second, the investigators failed to provide or analyze the cause of death. One Journal Club attendee noted that a webinar conducted by several of the FEAST site investigators analyzing these findings identified “cardiac collapse” as the cause of death in most of these children. Identifying the cause of death will be important to guide subsequent management trials, as well as to fully understand the implications of this FEAST trial. Third, the authors failed to use the World Health Organization criteria for shock since the role of physical exam to stratify severity of illness [in normotensive children](#) is unproven. Whereas the WHO requires the presence of delayed capillary refill, weak pulse, and tachycardia to establish the diagnosis of “shock”, these investigators only required one of the three. Were the children in this FEAST trial septic shock patients? One [editorial](#) suggests that FEAST was “probably treating children with serious febrile illnesses due to the most common medical problems, namely pneumonia and malaria, but not hypovolaemic shock.”

What did the FEAST trial conclude? Routine IVF bolus therapy in clinically undifferentiated severely ill non-hypotensive febrile children with diminished perfusion increases 24-hour mortality whether normal saline or albumin is used. Increased mortality occurs regardless of malaria status, coma, severe anemia, base deficit, or lactate level. [Hypothetical mechanisms](#) include [non-blood product fluid resuscitation in severe anemia](#), rapid reversal of compensatory vasoconstrictor response, reperfusion injury, subclinical pulmonary compliance effects, [sepsis-related myocardial function](#), or intracranial pressure. Before extrapolating the [FEAST](#) findings to the developed world, future research would need to explore similar fluid resuscitation strategies in the context of readily available ICU and mechanical ventilation.

The rest of the evidence that we evaluated was of lesser quality and more focused on specific disease processes (malaria) or fluid types (Dextran vs. hydroxyl ethyl starch vs. normal saline or lactated ringers). The [PGY-1](#) manuscript demonstrated that in pediatric patients with severe malaria and moderate to severe acidosis in the developing world, IV albumin at 20-40 cc/kg plus standard antimicrobial and supportive therapy is superior to IV normal saline with an adjusted Number Needed to Treat ([NNT](#)) of 3 to prevent one death based upon a baseline mortality rate of 11%. Albumin is more effective in malaria patients presenting with coma.

The [PGY-2](#) manuscript demonstrated that in children with shock in India, more aggressive fluid and dopamine resuscitation within the first 20 minutes of ED arrival does not decrease mortality or increase intubation rates. If [clinical equipoise](#) remains despite these findings, future researchers should evaluate settings with >1 ED clinician and more ready access to ventilators to more accurately assess the internal and [external validity](#) of this intervention.

The [PGY-3](#) manuscript demonstrated that in severe (impaired consciousness or respiratory distress) pediatric malaria in the developing world, hydroxyl ethyl starch (HES) and Dextran are both safe for acute volume expansion therapy and no adverse outcomes observed among 80 patients. However, impressive trends were observed favoring HES (compared with Dextran) to reduce mortality and resolve acidosis at eight hours with [NNT](#)=5.

The consensus of our Pediatric EM and Critical Care Medicine experts was that the lack of access to ventilator support and Intensive Care Unit management in the FEAST trial limit prohibit extrapolation of these findings to the developed world at places like St. Louis Children's Hospital. As far as the experts were aware, no ongoing or future studies were planned to further evaluate the efficacy of aggressive fluid resuscitation in pediatric septic shock patients and neither guidelines nor local protocols would change based upon the [FEAST trial](#). Nonetheless, an expanding volume of research in the developed world using contemporary ICU management indicates that excessive fluid resuscitation contributes to preventable morbidity including [sepsis](#), [ARDS](#), [acute kidney injury](#), and [major surgery](#). [Several ongoing trials](#) will assess the effectiveness of [early goal directed therapy](#) (which includes aggressive fluid resuscitation) in septic shock management. However, Washington University School of Medicine global medicine experts Dr. [Indi Trehan](#) and Dr. [SueLin Hilbert](#) noted that the [FEAST trial](#) radically altered the approach to septic shock resuscitation in the developing world in that undifferentiated rapid fluid resuscitation is no longer the [standard of care](#).

One unintended consequence of this Pediatric EM-Pediatric Critical Care-Emergency Medicine Journal Club event was recognition of a potential niche in diagnostic research. Specifically, the [reproducibility of bedside features of shock](#) (and of history and physical exam in most of Pediatrics, as well as systematic reviews of diagnostic accuracy) is under-researched, largely unknown and poorly reported. How accurate and reliable are pediatric clinicians' physical exam skills for detecting "severe sepsis", organomegaly, etc.? This represents a tremendous opportunity (i.e. unfilled academic niche) for diagnostic researchers to contribute to the [JAMA Rational Clinical Exam](#) and [Academic Emergency Medicine Evidence Based Diagnostics series](#).