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Risks and Benefits of Fluid Bolus Therapy: The Need for a *Good Explanation*

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In his 1832 letter to *The Lancet*, Thomas Latta noted that, with intravenous delivery of a salt solution to a patient with hypovolemic shock from cholera, "improvement in the pulse and countenance is almost simultaneous, the cadaverous expression gradually gives place to appearances of returning animation, the livid hue disappears, the warmth of the body returns" (1). Since then, administration of intravenous fluids to restore circulating blood volume became the cornerstone of resuscitation for severe hypovolemia and shock. Numerous observational and some interventional studies have demonstrated an association of resuscitation protocols which include early fluid administration with improved patient outcomes in shock syndromes. However, missing from this pool of evidence were high-quality randomised trials that directly compared early bolus fluid resuscitation to an alternative strategy.

In 2011, the Fluid Expansion as Supportive Therapy (FEAST) study was published (Table). This study was designed to investigate early resuscitation with a saline or albumin bolus compared with no bolus in children with a severe febrile illness (57% positive for malaria and 32% with hemoglobin <5 g/dL) and impaired perfusion treated in sub-Saharan Africa. Children with severe hypotension, however, were treated with 40-60 mL/kg boluses without an option for no bolus. Mortality at 48 hours in the saline and albumin groups were 10.6% and 10.5%, respectively, but was significantly lower in the no bolus control group at 7.3%. These data—the first randomized high-quality evidence—demonstrated harm from early fluid bolus resuscitation in children. This study ignited an important debate over the potential risks and benefits of fluid resuscitation.

In this issue of *ADC*, Drs. Dewez, Nijman, and Yeung reviewed sepsis recommendations from the USA, Europe, and the Surviving Sepsis Campaign to ascertain the impact of the FEAST trial on guideline recommendations about fluid resuscitation in children (2). They reviewed 10

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guidelines that were published after FEAST. Four guidelines mentioned the trial, but only one (AHA-PALS) was noted to recommend cautious fluid bolus therapy if access to critical care was limited. However, the three other guidelines concluded that restriction of fluids, as in the FEAST trial, was not relevant when access to critical care was readily available. One other guideline by the World Health Organization was noted to consider restriction of fluids for children with malnourishment, malaria, and anaemia (which approximates the FEAST population). The authors conclude there is difficulty for incorporating evidence into the development of recommendations when it challenges current practice.

Unexpected observations have a disproportionate value in science. One result can change the way we think forever. A single sighting of a black swan immediately rejects the hypothesis that "all swans are white". No number of subsequent observations of white swans can resurrect this hypothesis. And yet, we share an inclination to ignore evidence that contradicts with established norms. A famous example is the medical community's rejection of Dr. Ignaz Semmelwies' 1847 observation that mortality from childbed fever decreased if doctors washed their hands. Are we doing the something similar with the FEAST data in how we prepare guidelines?

The specific challenge here is how to weigh the FEAST results to inform guidance in higher-resourced locations. Such places typically have very different case-mix and an ability to mitigate many of the potential harms of fluid resuscitation in ways that were not available to FEAST participants (e.g., positive-pressure ventilation, inotropic support, cardiac output monitoring, renal replacement therapy). Guidelines must consider the overall risks and benefits of a proposed intervention, acknowledging that this balance exists within, and is shaped by, a myriad of patient, provider, and environmental factors.

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The solution is likely to be complex. We increasingly appreciate the heterogeneity of treatment effects within critical care. Although studies often include broad clinical syndromes such as sepsis and acute respiratory distress syndrome (ARDS), several clinically-distinct phenotypes with variable biology, response to therapies, and outcomes can be delineated. For example, some ARDS cases benefit from increased positive end expiratory pressure (PEEP) to improve V/Q matching and oxygenation, while others suffer adverse haemodynamic consequences. The results from trials of high-PEEP strategies therefore depend on the proportional enrolment from these two groups. Similarly, Seymour et al projected in simulations that a higher proportional enrolment of an adult sepsis phenotype with hypotension, hyperlactatemia, transaminitis, and neurologic dysfunction in a trial of a structured resuscitation algorithm of "early goal-directed therapy" (EGDT) would be more likely to find harm from this intervention (3). Further, the efficacy of treatments in sepsis are highly dependent on baseline risk of mortality (4). Thus, the impact of many critical care therapies is demonstrably context-dependent.

To understand how fluid may work across contexts, ideally we need a *good explanation* as characterised by the physicist David Deutsch in his book, *The Beginning of Infinity: Explanations that Transform the World*. Good explanations are "hard to vary". This means they do not require adjustment for specific conditions, timing, or places. The law of general relativity does not alter on a Tuesday afternoon. An explanation that does require adjustment is not correct, or is at least incomplete. A related property is that a good explanation should have "reach" beyond its original scope. A good explanation of fluid bolus therapy, for example, would assist in every setting; it would clarify why, when, and how this therapy imparts risk versus benefit such that it can be appropriately individualized across patients and care settings.

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To do this we need to learn much more, including how best to detect and monitor shock. This is not an impossible idea. Something similar may be happening in mechanical ventilation where the deeper- and more complex- property of "mechanical power" appears to resolve inconsistencies between volutrauma, barotrauma, and atelectrauma theories of ventilator-induced lung injury (5). Unfortunately, attempts to determine the underlying mechanisms in the FEAST outcomes have produced conflicting results to date .

So, what are we do to in the meantime when confronted with a patient showing signs of impaired perfusion? Is FEAST, though internally valid, generalizable to children outside of sub-Saharan Africa to areas with unrestricted access to intensive care? The ultimate truth is, as of now, still not clear. Perhaps the best we can do to at the moment is to consider context-specific recommendations by applying largely observational data demonstrating a beneficial approach with a more liberal fluid resuscitation strategy when intensive care is available (and hypovolemia is present) and applying the highest quality evidence from the FEAST trial to restrict fluid resuscitation when access to intensive care is limited. Published guidelines to date have largely taken this context-specific approach, though we do agree with our colleagues' letter that some have been more or less transparent in this regard than others.

However, we respectfully disagree with the implied suggestion that FEAST has largely gone unnoticed, even when intensive care resources are available. Several recent and ongoing trials compare various fluid-liberal to fluid-restrictive resuscitation strategies for children with septic shock in highly-resourced settings (Table). Moreover, the results of the FEAST trial would benefit from replication in other limited-resource settings. In time, with such free and open enquiry, we may even discover a *good explanation*.

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Table: FEAST Trial and Other Select Clinical Trials Investigating Restrictive versus Liberal Fluid Resuscitation Strategies in Pediatric Septic Shock

Trial	Population	Intervention	Control	Outcome
FEAST[a]	Children preseting to African hospital with fever and impaired perfusion	Fluid boluses of 20-40 mL/kg in 1 hour	Maintenace fluids without bolus	48-hour mortality
FISH[b]	Children presenting to English ED with persistent septic shock after 20 mL/kg fluid	Fluid boluses of 10 mL/kg every 15 min for up to 4 hours	Fluid boluses of 20 mL/kg every 15 min for up to 4 hours	Hospital mortality
SQUEEZE[c]	Children presenting to Canadian ED with persistent septic shock after 40 mL/kg fluid	Fluid-sparing resuscitation with early initiation of vasoactives	At least 60 mL/kg total fluid followed by clinician option to continue fluid or start vasoactives	Time to shock reversal
Sankar et al[d]	Children presenting to Indian ED or PICU with septic shock	Fluid aliquots of 20 mL/kg administered over 15–20 minutes	Fluid aliquots of 20 mL/kg administered over 5–10 minutes	Mechanical ventilation or hypoxia within 24 hours of fluid resuscitation
Santhanam et al[e]	Children presenting to Indian ED with septic shock	Fluid bolus of 40 mL/kg followed by dopamine	Fluid aliquots up to 60 mL/kg followed by dopamine	Hospital mortality

[a]Maitland K, Kiguli S, Opoka RO*, et al.* Mortality after fluid bolus in African children with severe infection. *N Engl J Med*. 2011;**364**:2483-95
[b]Inwald DP, Canter R, Woolfall K*, et al.* Restricted fluid bolus volume in early septic shock: results of the Fluids in Shock pilot trial. *Arch Dis Child*. 2018.
[c]www.clinicaltrials.gov/NCT03080038
[d]Sankar J, Ismail J, Sankar MJ, C PS, Meena RS. Fluid Bolus Over 15-20 Versus 5-10 Minutes Each in the First Hour of Resuscitation in Children With Septic Shock: A Randomized Controlled Trial. *Pediatr Crit Care Med*. 2017;**18**:e435-e45.
[e]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;**24**:647-55

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3. Seymour CW, Kennedy JN, Wang S*, et al.* Derivation, Validation, and Potential Treatment Implications of Novel Clinical Phenotypes for Sepsis. *JAMA*. Epublished ahead of print 2019 May 19

4. Eichacker PQ, Parent C, Kalil A*, et al.* Risk and the efficacy of antiinflammatory agents: retrospective and confirmatory studies of sepsis. *Am J Respir Crit Care Med*. 2002;**166**:1197-205.

5. Gattinoni L, Tonetti T, Cressoni M*, et al.* Ventilator-related causes of lung injury: the mechanical power. *Intensive Care Med*. 2016;**42**:1567-75.

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