Critical Review Form
Therapy

Mortality after Fluid Bolus in African Children with Severe Infection, *NEJM* 2011; 364: 2483-2495

Objectives: **"To investigate the practice of early resuscitation with a saline bolus as compared with no bolus (control) and with an albumin bolus as compared with a saline bolus." (p. 2484)**

Methods: **Two stratum, multicentre, six-center, open-labeled RCT in Kenya, Tanzania and Uganda from January 2009 thru January 2011. Stratum A consisted of children without severe hypotension, whereas Stratum B had severe hypotension defined as SBP <50 mmHg in children under 1 year, <60mmHG ages 1-5 years and <70 mmHg above age 5. In Stratum A, investigators randomized children in a 1:1:1 ratio to either 20 cc/kg of 0.9% saline or 20 cc/kg of 5% human albumin or no bolus (control). Children in Stratum B received either albumin or saline bolus at 40 cc/kg. In both strata (but not the control group) children received an additional 20 cc/kg bolus at one hour if impaired perfusion persisted. No cross over between bolus groups was permitted. The initial boluses were increased to 40 mL/kg (60mL/kg in Stratum B) in June 2010. An independent data and safety monitoring committee reviewed the interim analysis twice each year and in January 2011 recommended stopping enrollment due to safety concerns in the saline bolus and albumin bolus groups.**

Inclusion criteria included age 60 days – 12 years with severe febrile illness complicated by impaired consciousness (prostration or coma), and/or respiratory distress with impaired perfusion as evidenced by one or more of the following: capillary refill > 3 seconds, lower-limb temperature gradient, weak radial pulse volume or severe tachycardia (180 age <1year, >160 age 1-5, >140 age >5). Exclusion criteria included severe malnutrition, gastroenteritis, non-infectious shock etiology (trauma, surgery, burns), or contraindications to volume expansion (renal failure? CHF?). Children received care on general pediatric wards where assisted ventilation was unavailable. Children also received IV maintenance fluids (2.5-4.0 cc/kg/hour), antibiotics, antimalarial, antipyretic, and anticonvulsant drugs. Transfusion occurred if Hg was less than 5 g/dL. A structured clinical case-report was completed at admission, 1-, 4-, 8-, 24-, and 48-hours. Assessment of neurologic sequelae occurred at 4 weeks by an independent clinician unaware of study assignment.

The primary outcome was 48-hour mortality. Secondary outcomes included 4-week mortality, neurologic sequelae at 4 and 24 weeks, hypotensive shock within 48-hour and fluid-related adverse events (pulmonary edema, increased intracranial pressure, and severe allergic reaction). The study was initially powered at 80% with adjusted two-sided alpha of 0.025 with 2800 patients if 33% relative reduction with saline and

40% relative mortality reduction with albumin bolus. However, a protocol amendment in June 2010 increased the sample size to 3600 because the risk of death being observed in the combined groups was lower than expected. The three treatment groups were compared using chi-square tests for proportions and adjusted for clinical center and randomization date using a Mantel-Haenszel adjustment. Comparisons between the three groups were also performed for predefined subgroups: coma status, malaria status, severe anemia (hg <5), age, gender, severe acidosis (base deficit ≥ 8 mmol/L, lactate level ≥ 5 mmol/L, and date of randomization.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	
1.	Were patients randomized?	Yes. "Randomization was performed in permuted blocks of random sizes and was stratified according to clinical center." (p. 2485)
2.	Was randomization concealed (blinded)?	Yes. "The trial statistician at the Medical Research Council Clinical Trials Unit, London generated and kept all the randomization schedules. The schedule for each center contained a list of trial numbers and the randomly assigned intervention. Trial numbers were kept inside opaque, sealed envelopes, which were numbered consecutively and opened in numerical order by a study clinician." (p. 2485)
3.	Were patients analyzed in the groups to which they were randomized?	Yes. "All the analyses were performed according to the intention-to-treat principle…" (p. 2487) "A total of 99.5% of the children in the albumin-bolus group (1045 of 1050 children) and 99.4% of the children in the saline-bolus group (1041 or 1047) received the treatment to which they had been randomly assigned." (p. 2487)
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. "The baseline characteristics of the children were similar across groups." (p. 2487)
B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	

1.	Were patients aware of group allocation?	Yes. This was an open trial so patients and parents/caregivers were aware of group allocation leaving open the possibility of ascertainment or recall bias.
2.	Were clinicians aware of group allocation?	Yes, open trial so clinicians aware leaving open possibility of co-intervention bias.
3.	Were outcome assessors aware of group allocation?	Sometimes. Open trial and presumably the same clinicians who identified patients as eligible for the trial were completing the clinical care report form at admission and up to 48-hours. However, "at 4 weeks, assessment of neurologic sequelae were performed, and these were reviewed by an independent clinician who was unaware of the treatment assignments." (p. 2487)
4.	Was follow-up complete?	No. 1.4% (43/3141) were lost to follow-up (16 from albumin group, 14 from saline group, and 13 from control group). No children in Stratum B lost to follow-up. (p. 2487)
II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect?	• Investigators randomized 3141 children with median age 24 months, including 62% with prostration, 15% comatose, 83% in respiratory distress, 51% with $\geq$ 1 feature of acidosis, and 39% with lactate $\geq$ 5 mmol/L. • In total, 57% had malaria and 4% HIV. • Over the course of 8-hours, the median volume of fluid infused was 40 cc/kg (IQ range 30-50) in the albumin group, 40 cc/kg (IQ range 30-50) in the saline group, and 10 cc/kg (IQ range 10-26) in the control group. • **Significant mortality differences observed at 48-hours favoring the control group (7.3%) over albumin (10.6%) or saline (10.5) groups. Relative risk of death saline 1.44 (95% CI 1.09-1.90, p=0.01) vs. no bolus and albumin or saline bolus vs. no bolus 1.45 (95% CI 1.13-1.86, p=0.003) with absolute risk increase 3.3% (NNH=30)** • In Stratum B (hypotensive patients) there was no difference between saline and albumin with relative risk 1.23 (95% CI 0.70 – 2.16, p=0.45). • No evidence of heterogeneity according to center or date of randomization (I^2 = 0%, Figure 3 page 2493) • The risk of death was similar at 1-hour with a persistent trend for increased mortality up to day 2 in the two fluid bolus groups. Most (87%) of deaths occurred within the first 24-hours and very few occurred after 48-hours. • **Investigators identified no subgroup (coma, malaria, severe anemia, age, gender, severe acidosis) for who fluid resuscitation was beneficial.**

		• Suspected pulmonary edema occurred in 26 children (14 albumin, 6 saline, 6 control) and increased intracranial pressure in 45 (16 albumin, 18 saline, 11 control). • No differences in neurologic sequelae at 4 weeks: 2.2% albumin, 1.9% saline, 2.0% control.
2.	How precise was the estimate of the treatment effect?	See 95% CI above.
III.	**How can I apply the results to patient care (answer the questions posed below)?**	
1.	Were the study patients similar to my patient?	Unlikely since immunization and nutrition status of African children likely less desirable than in the developed world as is access to tertiary medical care (ventilator support). In addition, the malaria (57%) and HIV (4%) exposure rates of children with "severe febrile illness" is not the norm in North America, Australia, or most of Europe and developed Asia. However, this child is quite similar to that in our vignette.
2.	Were all clinically important outcomes considered?	Yes, mortality and neurological sequelae.
3.	Are the likely treatment benefits worth the potential harm and costs?	No, based on this data the role of aggressive fluid resuscitation in the developing world management of severe febrile illness (not trauma, surgery, or burns) must be questioned. The external validity of these findings in the developed world with ready access to vent support and ICU care is uncertain. Furthermore, these findings do not apply to patients with febrile illness who present with hypotension since the sample size in Stratum B was too small to draw conclusions.
4.	How will you communicate the findings of this study with your patients to facilitate shared decision-making?	Routine use of bolus resuscitation (either salt water or human protein) undifferentiated severely ill non-hypotensive febrile children with decreased blood flow in African hospitals appears to increase mortality within 24-48° and is not recommended.

Limitations

1) **Uncertain external validity to developed world (but certainly raises pertinent concerns about EGDT sepsis management). In particular, the small sample size in Stratum B (29 total patients) precludes extrapolation of results to hypotensive patients.**

2) **Premature trial closure (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.**

3) **Failure to provide or analyze the cause of death. One Journal Club attendee noted that a webinar conducted by several of the 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 more fully elucidating the implications of this FEAST trial.**

4) **Failure to use 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."**

Bottom Line

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, myocardial function, or intracranial pressure. Before extrapolating these findings to the developed world, future research should explore similar fluid resuscitation strategies in the context of readily available ICU and mechanical ventilation.