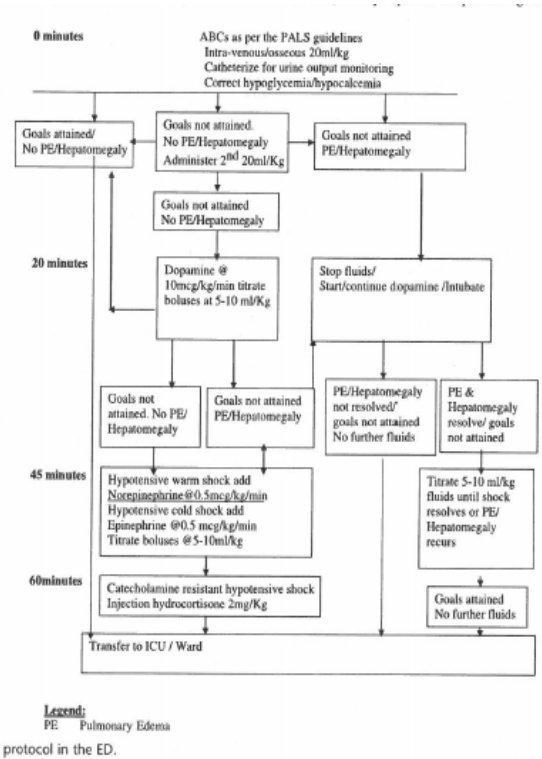
Critical Review Form
Therapy

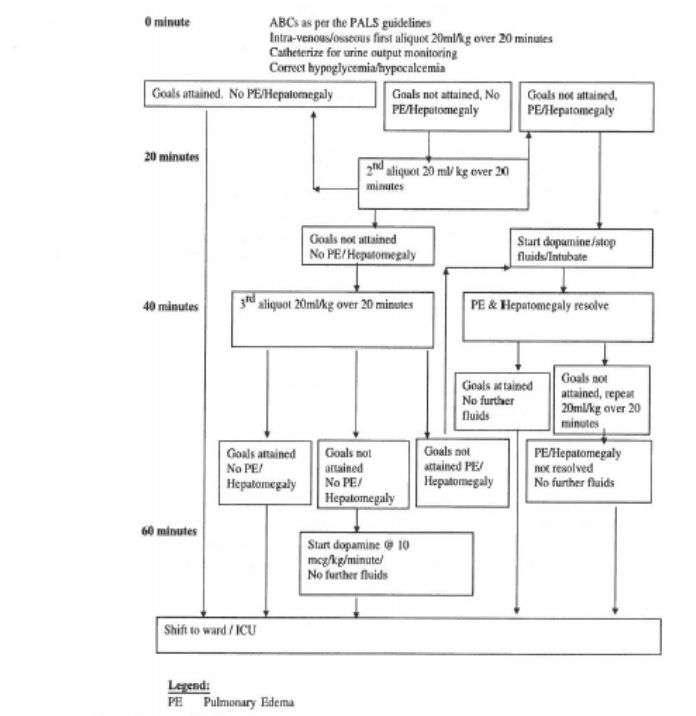
A Prospective Randomized Controlled Study of Two Fluid Regimens in the Initial Management of Septic Shock in the Emergency Department, *Ped Emerg Care* 2008; 24: 647-655

Objectives: **"To determine whether the study group (40mL of LR [lactated ringers] over 5 minutes followed by dopamine) would achieve similar resolution of shock, less need for ventilation and similar outcomes as compared with the control protocol (up to 60 mL/kg over an hour followed by dopamine)." (p. 647)**

Methods: **Convenience sampling RCT conducted from Nov 2003 thru Dec 2004 at the Institute of Child Health ED in India. This is a specialty center in Chennai India with 14 ICU beds and over 5000 pediatric visits requiring resuscitation in the ED each year. The authors sought to compare the effectiveness of two interventions (see below) on previously healthy children between ages 1 month and 12 years who presented in septic shock when the PI was available. Exclusion criteria included age < 30d, shock 2° to hypovolemia, hemorrhage, anaphylaxis, or envenomation; DKA inborn errors of metabolism, drug toxicity, trauma, burns, stridor, severe asthma, severe malnutrition, chronic systemic co-morbidities, genetic disorders, malignancies, HIV or other immune compromising disorder, DNR orders, physician decision not to treat, pre-hospital fluid resuscitation or cardiopulmonary arrest.**



Study protocol in the ED.



Control protocol in the ED.

A stop clock was used to time all interventions. After each aliquot of 20 cc/kg, a well-defined "rapid cardiopulmonary assessment" occurred that included: airway patency, respiratory rate, grunt, retractions, abdominal respiration, air entry, adventitious sounds, color, heart rate, differences in pulse, volume between femoral and dorsal pedis pulses, core-peripheral temperature gradient, capillary refill time, blood pressure, liver span, mental status (Alert, Voice response, Pain response, Unresponsive scale), urine output and pupillary response. The therapeutic goal was attainment of normal BP for age, warm peripheries, cap refill <2 seconds, and urine output > 1cc/kg. Assessments were performed by resident and PI.

The study protocol required 20 to 40 cc/kg of lactated ringers solution to be administered over 15 minutes using a 3-way stopcock and a rapid push-pull method. Dopamine was initiated if therapeutic objectives were not attained after 40 cc/kg. If pulmonary edema or hepatomegaly were noted, fluids were stopped and intubation was performed. The central protocol used 20 cc/kg over 20 minutes with further 20 cc/hg aliquots up to 60 cc/kg administered if therapeutic goals were not attained. After 60 cc/kg of LR, dopamine was started but no further fluids were administered in the ED.

Intubation used ketamine, atropine, and succinylcholine. Hypoglycemia and asthma were treated according to standard protocols. For infants < 3 months old cefotaxime and ampicillin were used as antibiotics, whereas older children used cefotaxime. All patients were to be transferred to the ICU from the ED within one hour. Post-ED

care was stratified into no-vent required, mechanical ventilator available within six hours or extubated, or mechanical ventilator not available within six hours.

The primary outcome was hospital survival. Secondary outcomes included peripheral warmth, capillary refill time <2 seconds, age-appropriate normal BP, and urine output > 1mL/kg/hour. Investigators monitored for hypoxia, hepatomegaly and intubation while in ED at 20, 40 and 60 minutes for each protocol. Based on a (2-sided) α of 0.05, power 80%, and reduction in mortality from 50% to 25%, the study needed 60 subjects in each arm. Investigators increased this to 80 per arm to account for exclusion after enrollment.

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. "The children were randomly assigned to either goal-directed therapy (study) or to control therapy." (p. 651) "Random numbers were generated using randomization tables of blocks of eight." (p. 652)
2.	Was randomization concealed (blinded)?	Yes. "Sealed, opaque, randomly assorted envelopes were opened by a registered nurse who was not part of the study team." (p. 652)
3.	Were patients analyzed in the groups to which they were randomized?	Uncertain – no clear statement of intention to treat.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. "There were no differences in the baseline demographic or clinical characteristics between 74/147 study group and 73/147 control group patients." (p. 652)
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?	No. "Participants were unaware of the study group assignments." (p. 652)

2.	Were clinicians aware of group allocation?	Yes. "The nurse who administered fluids was aware of the study assignment but did not assess patients or influence therapeutic decisions. The PI was not blinded. The residents in the ED and the physicians in the wards were not aware that a study was in progress or the study-group assignments." (p. 652)
3.	Were outcome assessors aware of group allocation?	No. "The epidemiologist who performed the analysis was also blinded."
4.	Was follow-up complete?	No lost to follow-up is reported in the CONSORT diagram Figure 3. (p. 650)
II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect?	• 416 eligible but 256 excluded leaving 160 randomized, but the authors provide no demographics (age, illness severity) for these patients. • Volume of fluid significantly higher in study group than in control group (median 72.5 mL/kg vs. 60, p<0.01) • No difference in the intubation rates between the two groups (55% study group vs. 46.5%, p=0.28) • **Normalization of cap refill time, core peripheral temperature, urine output, and BP at 20, 40, and 60 minutes were not significantly different between groups** (see % with normalization below) Study / Control 20 minutes 12.1% 12.3% 40 minutes 51.4% 53.4% 60 minutes 83.8% 83.8% • Although both groups had similar pre-treatment hepatomegaly incidence (31% control group, 39.2% study group), at 20 minutes 35.6% of control group and 70% of study group (p<.01) had hepatomegaly. At 60 minutes hepatomegaly incidence was again the same in both groups (34.2% and 32.4%, respectively). • The incidence of hypoxia and intubations at 20, 40, and 60 minutes was the same in both groups. • **Overall mortality was 17.6% (95% CI 11.9-24.8%) which was far lower than the historical cohort mortality of 50%.** • Authors reported a 72-hour survival in control and study group as 72.5% and 77.6%, respectively (p=0.71 with unadjusted odds ratio for death in study group 0.94 (95% CI 0.77-1.15) and hazards ratio 0.81.

2.	How precise was the estimate of the treatment effect?	See 95% CI for mortality 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 status and nutritional health of India's children is likely more heterogeneous than in the United States. However, these children may be quite similar to the children in our vignette. In addition, a single clinician with a niche in pediatric resuscitation is difficult to replicate.
2.	Were all clinically important outcomes considered?	No. Mortality is important, but so is functional recovery but no morbidity-related outcomes are provided.
3.	Are the likely treatment benefits worth the potential harm and costs?	Yes, the "risks" appear to be transient hepatomegaly with no difference in mortality or primary outcomes of hypoxia or need for intubation.
4.	How will you communicate the findings of this study with your patients to facilitate shared decision-making?	In children with shock at a specialty hospital ED in India with limited access to a ventilator, treatment with a more aggressive fluid protocol and frequent "rapid cardiopulmonary assessments" by a single physician, there is no difference in 3-day mortality or intubation rates compared with standard care. Standard care still involves rapid and aggressive fluid therapy by IV and frequent re-assessment. The optimal volume of fluid and intensity of monitoring (frequency, expertise) remain unknown.

Limitations

1) **Detailed protocol and complex "rapid cardiopulmonary assessment" by one physician – uncertain reliability of transferred to large group practice. In general, 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. This represents a tremendous opportunity (i.e. unfilled niche) for diagnostic researchers to contribute to the *JAMA* Rational Clinical Exam and *Academic Emergency Medicine* Evidence Based Diagnostics series.**

2) **No assessment of inter-rater reliability between attending and resident, although methods report that this data was collected.**

3) **Failure to adjust for confounding variables in logistic regression analysis or Cox proportional hazards analysis.**

4) **Limited external validity to U.S. (and other developed nations) with ready access to ventilators.**

5) **Lack of blinding of clinician results in increased risk co-intervention bias.**

Bottom Line

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 hypoxia/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.