“Water Under the Bridge”: Controversies in Pediatric Sepsis
Fluid Management

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MCEP Critical Care Conference
March 21, 2019

Disclosures and Conflicts of Interest

• I have no conflicts of interest in relation to this presentation
• Frances Balamuth, MD, PhD
  – PROMT BOLUS Study
  – Children’s Hospital of Philadelphia
Learning Objectives

• Describe current guidelines for fluid resuscitation in pediatric sepsis
• Review evidence for colloids in hypovolemia
• Compare different types of crystalloid fluid
• Identify areas of future research

“...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.” (Thomas Latta, Letter to Lancet, June 2, 1832)
Intravenous Fluids

• Cornerstone of management for septic (and other) shock states
• Most common intervention in critical care (besides O₂)
• One of the least well-studied interventions, relative to its frequency of use

Questions in Pediatric Resuscitation

1. How much IV fluid?
2. What kind of IV fluid?
   – Hypotonic vs. Isotonic
   – Colloid vs. Crystalloid
3. Balanced crystalloid fluid better?
   – Balanced vs. Unbalanced
Fluid Volume?

American College of Critical Care Medicine
2017 Guidelines

Clinical Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock

0 min
Recognize decreased mental status and perfusion. Begin high flow O₂ and establish IO/IV access according to PALS.

5 min
If no hepatomegaly or rales / crackles then push 20 mL/kg isotonic saline boluses and reassess after each bolus up to 60 mL/kg until improved perfusion. Stop for rales, crackles or hepatomegaly. Correct hypoglycemia and hypocalcemia. Begin antibiotics.

15 min
Fluid refractory shock?

20 mL/kg Isotonic Saline Boluses x 3


Improved Outcomes with Higher Fluid Volumes in 1st Hour

Carcillo et al, JAMA 1991

Oliveira et al, Peds Emerg Care 2008

Fig. The distribution of survivor and non-survivors within fluid resuscitation groups.

Fig. Patients with septic shock: mortality vs. first hour resuscitation volume

Adherence to PALS Sepsis Guidelines and Hospital Length of Stay

- 19% Overall Adherence Rate
  - Recognition, Vascular Access, Fluids, Antibiotics, Inotropes
- Fluid adherence (60 mL/kg) = Shorter LOS

Table 3: Association of Total Algorithm Adherence With LOS

<table>
<thead>
<tr>
<th></th>
<th>Algorithm Bundle Adherence, n = 24, Mean No. Days</th>
<th>Algorithm Bundle Nonadherence, n = 102, Mean No. Days</th>
<th>Decrease, %</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital LOS</td>
<td>6.8</td>
<td>10.9</td>
<td>57</td>
<td>0.09</td>
</tr>
<tr>
<td>ICU LOS</td>
<td>5.5</td>
<td>6.8</td>
<td>59</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Adherence to PALS Sepsis Guidelines and Hospital Length of Stay


<table>
<thead>
<tr>
<th>Fluid Adherence, n = 46</th>
<th>Fluid Nonadherence, n = 80</th>
<th>Decrease, %</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital LOS</td>
<td>8</td>
<td>11.2</td>
<td>.57</td>
</tr>
<tr>
<td>ICU LOS</td>
<td>5.5</td>
<td>7.2</td>
<td>.42</td>
</tr>
</tbody>
</table>

*Unadjusted means.

Fluid Causes Death???


Mortality Rates
Albumin 10.6%
Saline 10.5%
Control 7.3%

FEAST Subgroup Analysis

Higher prevalence of malaria and anemia

Not just in Africa...

**Increased mortality with continuous renal replacement**

![Graph showing increased mortality with continuous renal replacement. Sutherland et al, AJKD, 2010.]


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**PALS Fluids Recommendations 2015**

**Evidence for restrictive fluid resuscitation in pediatrics**

![Chart showing evidence for restrictive fluid resuscitation.]

- Initial fluid bolus of **20 mL/kg** to infants and children with shock is reasonable (Class IIa, LOE C-LD)

- Children with severe febrile illness with limited access to critical care resource, administration of bolus IV fluids should be undertaken with extreme caution (Class IIb, LOE B-R)

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PALS Fluids Recommendations 2015

• Continued emphasis on fluid resuscitation for shock
  – 20 mL/kg isotonic saline bolus x 3 (Goal 15 min!)

• Increased emphasis on
  – Individual patient assessment and reassessment
  – Consideration of vulnerability to fluid
    • Nutrition status
    • Diseases (i.e. anemia, malaria)
    • Critical care resources


Fluid Type?
Hypotonic vs. Isotonic
Holliday & Segar (1957)

**The Maintenance Need for Water in Parenteral Fluid Therapy**

By Malcolm A. Holliday, M.D., and William E. Segar, M.D.

Department of Pediatrics, Indiana University Medical Center

<table>
<thead>
<tr>
<th>Weight in kg (kilogram)</th>
<th>Holliday Segar method (mL/kg/day)</th>
<th>Holliday Segar estimate (mL/kg/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First 10 kg</td>
<td>100</td>
<td>4</td>
</tr>
<tr>
<td>Second 10 kg</td>
<td>50</td>
<td>2</td>
</tr>
<tr>
<td>Every kg thereafter</td>
<td>20</td>
<td>1</td>
</tr>
</tbody>
</table>

4-2-1 Rule


Holliday & Segar

- Electrolyte Requirements
  - Na⁺ 3 mEq/100 ml
  - Cl⁻ mEq/100 ml
  - K⁺ mEq/100 ml
- ¼ and ½ normal saline for younger children
- Risk of hyponatremia???
  - Overestimated energy & water requirements
  - ADH stimulation

Risk of Hyponatremia

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Isotonic n/N</th>
<th>Hypotonic n/N</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil 1994</td>
<td>3/6</td>
<td>3/7</td>
<td>38%</td>
<td>0.27</td>
<td>0.07</td>
</tr>
<tr>
<td>Cheong 2011</td>
<td>5/100</td>
<td>47/112</td>
<td>27.1%</td>
<td>0.58</td>
<td>0.39</td>
</tr>
<tr>
<td>Gauthard 2012</td>
<td>0/39</td>
<td>7/40</td>
<td>44%</td>
<td>0.07</td>
<td>0.00</td>
</tr>
<tr>
<td>Cuelo 2012</td>
<td>0/20</td>
<td>8/26</td>
<td>44%</td>
<td>0.04</td>
<td>0.00</td>
</tr>
<tr>
<td>Kanan 2010</td>
<td>5/58</td>
<td>18/109</td>
<td>7.4%</td>
<td>0.51</td>
<td>0.20</td>
</tr>
<tr>
<td>Monta 2008</td>
<td>15/51</td>
<td>20/52</td>
<td>11.7%</td>
<td>0.76</td>
<td>0.04</td>
</tr>
<tr>
<td>Neville 2010</td>
<td>9/62</td>
<td>23/62</td>
<td>13.6%</td>
<td>0.39</td>
<td>0.09</td>
</tr>
<tr>
<td>Rey 2011</td>
<td>17/68</td>
<td>29/66</td>
<td>23.4%</td>
<td>0.42</td>
<td>0.02</td>
</tr>
<tr>
<td>Saba 2011</td>
<td>0/16</td>
<td>1/21</td>
<td>0.8%</td>
<td>0.04</td>
<td>0.00</td>
</tr>
<tr>
<td>Tung 2009</td>
<td>3/24</td>
<td>6/26</td>
<td>34%</td>
<td>0.54</td>
<td>0.15</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>449</td>
<td>521</td>
<td>100.0%</td>
<td>0.48</td>
<td>0.38, 0.60</td>
</tr>
</tbody>
</table>

Favors Isotonic  Favors Hypotonic


AAP Guidelines 2018

Clinical Practice Guideline: Maintenance Intravenous Fluids in Children

Leonard G. Feld, MD, PhD, MMM, FAAP, a Daniel R. Neuspiel, MD, MPH, FAAP, b Byron A. Foster, MD, MPH, FAAP, c Michael G. Leu, MD, MS, MHS, FAAP, d Matthew D. Garber, MD, FHM, FAAP, e Kelly Austin, MD, MS, FAAP, FACS, f Rajit K. Basu, MD, MS, FCCM, g,h Edward E. Conway Jr, MD, MS, FAAP, i James J. Fehr, MD, FAAP j

- Patients requiring maintenance IVFs should receive isotonic solutions with appropriate potassium chloride and dextrose because they significantly decrease the risk of developing hyponatremia (LOE: A; recommendation strength: strong)

Fluid Type?
Colloids vs. Crystalloid

Figure 1. Kaplan–Meier Estimates of the Probability of Survival. p = 0.96

A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit
The SAFE Study, NEJM 2004

Figure 1. Kaplan–Meier Estimates of the Probability of Survival. p = 0.96

Albumin May Benefit Sepsis

<table>
<thead>
<tr>
<th>Patients</th>
<th>Albumin Group</th>
<th>Saline Group</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>726/3473</td>
<td>729/3460</td>
<td>0.99 (0.91–1.09)</td>
</tr>
<tr>
<td>Trauma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>81/596</td>
<td>59/590</td>
<td>1.36 (0.99–1.86)</td>
</tr>
<tr>
<td>No</td>
<td>643/2831</td>
<td>666/2810</td>
<td>0.96 (0.88–1.06)</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>185/603</td>
<td>217/615</td>
<td>0.87 (0.74–1.02)</td>
</tr>
<tr>
<td>No</td>
<td>518/2734</td>
<td>492/2720</td>
<td>1.05 (0.94–1.17)</td>
</tr>
<tr>
<td>ARDS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>24/61</td>
<td>28/66</td>
<td>0.93 (0.61–1.41)</td>
</tr>
<tr>
<td>No</td>
<td>697/3365</td>
<td>697/3354</td>
<td>1.00 (0.91–1.09)</td>
</tr>
</tbody>
</table>


**CONFERECE REPORTS AND EXPERT PANEL**


2. **We recommend that, in the resuscitation from sepsis-induced hypoperfusion, at least 30 mL/kg of IV crystalloid fluid be given within the first 3 hours (strong recommendation, low quality of evidence).**

4. **We suggest using albumin in addition to crystalloids for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock when patients require substantial amounts of crystalloids (weak recommendation, low quality of evidence).**

Crystalloid Fluid Type?
Balanced vs. Unbalanced

Crystalloid Fluids

- **0.9% Normal Saline**: 1880’s Hartog Joakob Hamburger
  - Erythrocytes did not lyse when placed in NS and concluded that “the blood of man was isotonic with NaCl solution of 0.9%”
  - Human plasma is actually closer to 0.6% sodium chloride

- **Ringer’s**: 1880’s Sydney Ringer
  - Added calcium and potassium to saline after observing that inorganic constituents of pipe water better preserved frog heart muscle ex vivo than just salt dissolved in distilled water

- **Hartmann’s solution (LR)**: 1932 Alexis Hartmann (pediatrician)
  - Modified Ringer’s original formula in order to reduce the acidosis observed in infants with diarrhea by adding lactate

- **Plasma-Lyte**
  - Developed to address the slight hypotonicity and presence of calcium in LR and Hartmann’s solutions
  - Physiochemical properties similar to human plasma
Crystalloid Fluid Composition

<table>
<thead>
<tr>
<th></th>
<th>Blood</th>
<th>NS</th>
<th>LR</th>
<th>Plasma-Lyte</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na (mEq/L)</td>
<td>140</td>
<td>154</td>
<td>130</td>
<td>140</td>
</tr>
<tr>
<td>Cl (mEq/L)</td>
<td>100</td>
<td>154</td>
<td>109</td>
<td>98</td>
</tr>
<tr>
<td>K (mEq/L)</td>
<td>4</td>
<td>0</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Ca (mEq/L)</td>
<td>5</td>
<td>0</td>
<td>2-3</td>
<td>0</td>
</tr>
<tr>
<td>Lactate (mEq/L)</td>
<td>2</td>
<td>0</td>
<td>28</td>
<td>(Acetate)</td>
</tr>
<tr>
<td>pH</td>
<td>7.4</td>
<td>4-5</td>
<td>6.5</td>
<td>7.4</td>
</tr>
<tr>
<td>SID</td>
<td>+40</td>
<td>0</td>
<td>+28</td>
<td>+25</td>
</tr>
<tr>
<td>Osmolality</td>
<td>290</td>
<td>308</td>
<td>273</td>
<td>295</td>
</tr>
<tr>
<td>Cost (per 500 mL)</td>
<td>$1</td>
<td>$1-2</td>
<td>$3-6</td>
<td></td>
</tr>
</tbody>
</table>

SID = Strong Ion Difference

Clinical Effects of Crystalloid

<table>
<thead>
<tr>
<th></th>
<th>NS</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperchloremia</td>
<td>++++</td>
<td>+</td>
</tr>
<tr>
<td>Acidosis</td>
<td>++++</td>
<td></td>
</tr>
<tr>
<td>Acute Kidney Injury</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>Rare</td>
<td>Rare-er</td>
</tr>
<tr>
<td>Coagulation</td>
<td>Coagulopathy</td>
<td>Hypercoagulability (?)</td>
</tr>
<tr>
<td>Lactic Acidosis</td>
<td>Only with fulminant liver failure</td>
<td></td>
</tr>
<tr>
<td>Fluid Overload</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Cerebral Edema</td>
<td>ICP↑ 4 cm H₂O</td>
<td></td>
</tr>
</tbody>
</table>

Saline Is the Solution for Crystalloid Resuscitation

Paul Young, MBChB

“Saline is the first-choice crystalloid fluid and is supported by 150 years of experience. I submit that the current level of evidence falls far below the threshold [practice change]. Our options are to stick with what is tried and tested or change to more expensive fluids on the basis of inductive physiologic reasoning and observational data that are subject to bias and confounding.”

Saline Is Not the First Choice for Crystalloid Resuscitation Fluids

Matthew W. Semler, MD, MSc; Todd W. Rice, MD, MSc

“The similar availability and cost of each crystalloid, established safety of balanced crystalloids, and mounting concerns about acidosis, AKI, and mortality with saline argue that saline should not be the first choice fluid for crystalloid resuscitation.”

Balanced Crystalloids versus Saline in Noncritically Ill Adults


Balanced Crystalloids versus Saline in Critically Ill Adults


<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical</td>
<td>0.87 (0.77-0.99)</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td>1.10 (0.89-1.36)</td>
<td>0.38</td>
<td></td>
</tr>
<tr>
<td>Neurologic</td>
<td>0.77 (0.59-0.99)</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>0.95 (0.74-1.21)</td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td>Surgical</td>
<td>0.93 (0.66-1.30)</td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>0.96 (0.86-1.07)</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.80 (0.67-0.94)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Traumatic brain injury</td>
<td>0.89 (0.81-0.98)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.09 (0.81-1.47)</td>
<td>0.58</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>0.91 (0.83-0.99)</td>
<td>0.04</td>
<td></td>
</tr>
</tbody>
</table>

What evidence is there for use of specific crystalloid fluids in pediatrics?

Current Crystalloid Practice

- ICU: 10-20% use of LR for crystalloid fluid resuscitation¹
  - Drift toward increased LR use in ICUs²
- ED: Limited data
  - AAP/PERC/Australia: 2-3% PEM attendings used LR as initial fluid³,⁴

Opportunity for a minor shift in clinical practice to substantially alter outcomes if LR superior to NS

Pediatric Evidence for Balanced Fluid Resuscitation

<table>
<thead>
<tr>
<th></th>
<th>Premier(^1)</th>
<th>PHIS(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>4,234</td>
<td>10,724</td>
</tr>
<tr>
<td>Design</td>
<td>Retrospective</td>
<td>Retrospective</td>
</tr>
<tr>
<td>Comparison</td>
<td>All NS vs. Any LR</td>
<td>All NS vs. All LR</td>
</tr>
<tr>
<td>Match</td>
<td>Integer + fine balance; 1:1</td>
<td>Propensity Score; 1:6</td>
</tr>
<tr>
<td>Mortality</td>
<td>7.9% NS vs. 7.2% LR (p = 0.20)</td>
<td>15% NS vs. 13% LR (p = 0.046)</td>
</tr>
</tbody>
</table>


MAKE30 in Pediatric Sepsis

1,685 children primarily treated in a PHIS+ hospital (85% ED)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PHIS+</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAKE30</td>
<td>9.6% (95% CI 8.2, 11.1%)</td>
</tr>
<tr>
<td>Mortality</td>
<td>4.5%</td>
</tr>
<tr>
<td>Renal replacement therapy</td>
<td>1.7%</td>
</tr>
<tr>
<td>Persistent kidney dysfunction</td>
<td>5.8%</td>
</tr>
</tbody>
</table>

MAKE30 associated with hospital mortality, costs, and CKD

Weiss/Balamuth, submitted
Future Research?

PRoMPT BOLUS
PRagMatic Pediatric Trial of Balanced vs nOrmaL Saline FIUid in Sepsis
Feasibility Pilot Study
ClinicalTrials.gov/NCT03340805

- Collaborative effort with Trial Innovation Network
- FDA IND (#13698)
- **Feasibility Aims:**
  1. Estimate proportion of eligible patients enrolled
  2. Determine adherence with study fluid administration
  3. Demonstrate acceptability of EFIC

Funding: NICHD K12 HL109009

Planned/Ongoing Pediatric Trials

**Optimal type?**
Normal saline vs. lactated ringer’s
United States (Dr. F Balamuth, S. Weiss)

**Optimal volume?**
10 mL/kg vs. 20 mL/kg boluses
United Kingdom (Dr. David Inwald)

**Optimal duration?**
Usual care vs. early norepinephrine
Canada (Dr. Melissa Parker)
Take Home Points

1. How much IV fluid?
   - 20 cc/kg bolus x3 (Goal 15 minutes!!)

2. What kind of IV fluid?
   - Isotonic Saline > Hypotonic Saline
     - Bolus: 0.9% NS
     - Maintenance: D5 0.9%NS
     - No mortality benefit for colloids (sepsis?)

3. Balanced crystalloid fluid better?
   - ↑ chloride load → ↑MAKE30
   - Consider balanced fluids in severe shock states

References

References

• Inwald, DP., et al on behalf of PERU4 and PICS SG. “Restricted fluid bolus volume in early septic shock: Results of the fluids in shock pilot trial.” Archives of Disease in Childhood. Published Online First: 07 August 2018.

Questions/Evaluation

https://survey.az1.qualtrics.com/jfe/form/SV_bPF4PxKfOWhFK1T