Controversies in Pediatric Resuscitation: 2015

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Conflicts of interest

Financial
- None

Academic/ Intellectual:
- Co-Chair, ILCOR Pediatric Task Force (2006-2015)
- Chair, AHA ‘PALS Guidelines’ Writing Group (2015)
- Member, SCCM/ ACCM Sepsis Guidelines Writing Group (2015)
- Heart and Stroke Foundation of Canada
Objectives

Dismantling dogma in resuscitation

● Fluid for pediatric septic shock
● Epinephrine for cardiac arrest
● Post-cardiac arrest care bundles
  ■ Temperature
  ■ Oxygenation
  ■ Ventilation
  ■ Blood pressure
● Prognostication post-cardiac arrest
Role of Early Fluid Resuscitation in Pediatric Septic Shock

Joseph A. Carcillo, MD; Alan L. Davis, MD; Arno Zaritsky, MD

N=34 patients
Early reversal of pediatric-neonatal septic shock by community physicians is associated with improved outcome
Han et al, Pediatrics, 2003

- Retrospective cohort study (1993–2001)
- 91 infants and children presenting to local community hospitals with septic shock and requiring transport to Children’s Hospital Pittsburgh
- When resuscitation was consistent with PALS guidelines, a lower mortality was observed
  - 8% vs. 38% mortality non-PALS based therapy
Children with severe febrile illness and impaired perfusion upon admission randomly assigned to receive:

- Boluses of 20 to 40 ml/kg of 5% albumin solution (albumin-bolus group)
- Boluses of 20 to 40 ml/kg of 0.9% saline solution
- No bolus (control group)

The primary end point was 48-hour mortality
The 48-hour mortality:

- 10.6% in albumin-bolus
- 10.5% in saline-bolus
- 7.3% in control

Relative mortality risk for any bolus vs. control: 1.45 (95% CI, 1.13 to 1.86; P = 0.003)
Criticisms of Extrapolating Matiland’s Data

Very poor specificity of inclusion criteria…

- The study was not specifically treating shock as currently defined by WHO
  - Cold hands
  - Capillary refill time (CFT) > 2 sec
  - A weak and fast pulse

- Maitland’s criteria were “One or more of”:
  - Severe tachycardia
  - CFT >2 sec
  - Lower limb T gradient
  - Weak radial pulse volume

- Likely inclusion of numerous patients with malaria and pneumonia, as opposed to true septic shock
A Prospective Randomized Controlled Study of Two Fluid Regimens in the Initial Management of Septic Shock in the Emergency Department

Santhanam, Ped Emerg Care, 2008

- Prospective RCT of pediatric septic shock in 147 children (older than 1 month of age), comparing:
  - 40 mL/kg of fluid over 15 minutes followed, by dopamine
  - 20 mL/kg over 20 minutes up to a maximum of 60 mL/kg over 1 hour, followed by dopamine (control protocol)
No difference in time to achieve **therapeutic goals**, or in **mortality rates** (~17%) between two groups.

No difference in **intubation rates** were the same (46.5% in control group; 55% in study group; \( P = 0.28 \)).

At 20 minutes, **hepatomegaly** in 35.6% of control group and 70% of study group \( (P < 0.01) \).
Paediatric community-acquired septic shock: the REPEM Network Study

*Van de Vourde, Eur J Pediatr, 2013*

- 270,461 (European) paediatric ED consultations screened over 1 year
- 176 cases of septic shock identified
- The median amount of fluid given in the first 6 hours was 30 ml/kg
- Overall mortality in this sample was 4.5%
- Mechanical ventilation needed in 25.9%
- Vasoactive medications needed in 42.9%
Retrospective single center study of 79 children admitted to a PICU with sepsis or septic shock

IV volume prior to inotropes was not independently associated with either PICU LOS or ventilator days

IV volume administered in the first 2 hours of resuscitation was an independent predictor of:

• PICU LOS: 0.22 (95%CI 0.05-0.38)
• Ventilator days: 0.09 (95%CI 0.02-0.15)
Fluid Bolus Therapy-Based Resuscitation for Severe Sepsis in Hospitalized Children: A Systematic Review

Ben Gelbart, FCIM\textsuperscript{1,2}; Neil J. Glassford, MRCP\textsuperscript{3,4}; Rinaldo Bellomo, MD\textsuperscript{3,4}

![Flow diagram of the study selection process for randomized studies and description of study exclusions.]

**Figure 3.** Flow diagram of the study selection process for randomized studies and description of study exclusions.
Still to Come....

SQUEEZE
Research Questions re: Fluid Resuscitation

- What are the appropriate clinical, hemodynamic and biochemical markers of adequate tissue perfusion?
- When is fluid unresponsiveness an appropriate goal?
- Is fluid resuscitation indicated when a clinical (eg. hypotension) or biochemical (eg. Lactate) problem co-exists with normal perfusion?
- What is the dose response relationship between fluid and outcomes, and what are the side effects/safety limits of different volumes?
- What are the appropriate outcome measures for fluid resuscitation trials?

Perner, ICM, 2015
Epinephrine and OHCA Care...

Olasveengen, JAMA, 2009

- % ROSC
- % Survived to Hospital
- % Survived to ICU Admission
- % Good CNS Outcome (CPC 1-2)
- % Alive 1 yr post-CPA

No ACLS Drugs (n=433)
PARAMEDIC2
The Adrenaline Trial
<table>
<thead>
<tr>
<th>Epinephrine average dosing period</th>
<th>No. of patients</th>
<th>Unadjusted survival to discharge No. (%)</th>
<th>Unadjusted Odds Ratio for Survival (95%CI)</th>
<th>Adjusted Odds Ratio for Survival (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9-10 min/dose</td>
<td>796</td>
<td>87(10.9)</td>
<td>1.27 (0.98, 1.65)</td>
<td>2.10 (1.50, 2.93)</td>
</tr>
<tr>
<td>8-9 min/dose</td>
<td>1052</td>
<td>119(11.3)</td>
<td>1.33 (1.04, 1.69)</td>
<td>1.96 (1.47, 2.62)</td>
</tr>
<tr>
<td>7-8 min/dose</td>
<td>1455</td>
<td>122(8.4)</td>
<td>0.96 (0.77, 1.20)</td>
<td>1.31 (1.01, 1.71)</td>
</tr>
<tr>
<td>6-7 min/dose</td>
<td>1987</td>
<td>178(9.0)</td>
<td>1.03 (0.83, 1.27)</td>
<td>1.37 (1.08, 1.74)</td>
</tr>
<tr>
<td>5-6 min/dose</td>
<td>2740</td>
<td>119(11.3)</td>
<td>0.86 (0.72, 1.03)</td>
<td>0.93 (0.75, 1.14)</td>
</tr>
<tr>
<td>4-5 min/dose</td>
<td>2665</td>
<td>233(8.7)</td>
<td>1(ref.)</td>
<td>1(ref.)</td>
</tr>
<tr>
<td>3-4 min/dose</td>
<td>1905</td>
<td>198(10.4)</td>
<td>1.20 (0.99, 1.45)</td>
<td>0.95 (0.76, 1.19)</td>
</tr>
<tr>
<td>1-3 min/dose</td>
<td>989</td>
<td>155(15.7)</td>
<td>1.91 (1.53, 2.38)</td>
<td>0.72 (0.55, 0.95)</td>
</tr>
<tr>
<td>Total</td>
<td>13,569</td>
<td>1,301(9.6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Ornato, Resuscitation, 2014*

Findings consistent for shockable and non-shockable rhythms
<table>
<thead>
<tr>
<th>Outcome</th>
<th>High-Dose Epinephrine (N=34)</th>
<th>Standard-Dose Epinephrine (N=34)</th>
<th>Unadjusted Odds Ratio (95% CI)*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Return of spontaneous circulation</td>
<td>20 (59)</td>
<td>21 (62)</td>
<td>1.1 (0.4–3.0)</td>
<td>0.80</td>
</tr>
<tr>
<td>For ≤20 min</td>
<td>4 (12)</td>
<td>6 (18)</td>
<td>1.6 (0.4–6.3)</td>
<td>0.49</td>
</tr>
<tr>
<td>For &gt;20 min but &lt;24 hr</td>
<td>15 (44)</td>
<td>8 (24)</td>
<td>0.4 (0.1–1.1)</td>
<td>0.07</td>
</tr>
<tr>
<td>Survival at 24 hr</td>
<td>1 (3)</td>
<td>7 (21)</td>
<td>8.6 (1.0–397.0)</td>
<td>0.05</td>
</tr>
<tr>
<td>Survival to hospital discharge</td>
<td>0</td>
<td>4 (12)</td>
<td></td>
<td>0.11</td>
</tr>
</tbody>
</table>

* CI denotes confidence interval.
Unadjusted analysis:

Adjusted* analysis:

* Multivariable logistic regression with generalized estimating equations. Odds ratio per minute delay in epinephrine administration. Adjusted for age, gender, illness category, mechanical ventilation, monitored status, witnessed status, location, time of the day/week, year of arrest, insertion of an airway, initial rhythm, time to initiation of chest compressions, hospital type and teaching status

Andersen, JAMA, 2015
Epinephrine and Cardiac Arrest

- Does the use of epinephrine during cardiac arrest lead to functional outcomes?
- Is demonstrating benefit dependent upon identifying the right:
  - Setting (IHCA vs. OHCA)?
  - Arrest etiology?
  - Timing of delivery?
  - Dose?
  - Frequency of dosing?
## Pediatric Post-Cardiac Arrest Syndrome

<table>
<thead>
<tr>
<th>% patients</th>
<th>IHCA Non-cv</th>
<th>IHCA CV-postop</th>
<th>IHCA CV-nonsurg</th>
<th>IHCA PICU CV-postop</th>
<th>OHCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=1109</td>
<td>N=640</td>
<td>N=306</td>
<td>N=91</td>
<td>N=624</td>
<td></td>
</tr>
<tr>
<td>(%) Return of spontaneous circulation (ROSC)</td>
<td>53</td>
<td>67</td>
<td>53</td>
<td>82</td>
<td>10</td>
</tr>
<tr>
<td>(%) 24 hr survival</td>
<td>37</td>
<td>60</td>
<td>42</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>(%) Survival to Hospital DC</td>
<td>23</td>
<td>37</td>
<td>28</td>
<td>25</td>
<td>6.4</td>
</tr>
</tbody>
</table>

Nadkarni, JAMA, 2006
De Mos, CCM, 2006
Ortmann, Circulation, 2011
Atkins, Circulation, 2009
Supportive Evidence for TTM (Temperature Targeted Management)

- Adult RCTs: controlling T(33-36°C) is better than not controlling temperature (37°C or higher)
  - High Quality Evidence

- Adult RCTs: outcomes (survival and CNS outcome) with 32°C-34°C, 33°C and 36°C are similar.
  - High Quality Evidence

![Graph showing percentage survival for Control and Intervention groups across different studies.](image)
Post-ROSC fever associated with worse outcomes (Bembea, 2010)
Post-ROSC oxygenation

Multiple animal studies have shown that ventilation with 100% oxygen during and following resuscitation contributes to free radical–mediated reperfusion injury to the brain, and may be associated with more neurologic deficit than ventilation with room air, especially when high PaO2 is experienced in the first hour post-ROSC.
Post-ROSC oxygenation

What about neonatal studies?

- Two LOE 5 meta-analyses of several randomized controlled trials comparing neonatal resuscitation initiated with room air versus 100% oxygen showed increased survival when resuscitation was initiated with room air.

  *Davis, Lancet, 2004; Rabi, Resuscitation, 2007*

Perinatal HIE is not Cardiac arrest
Pediatric Post-ROSC Oxygenation

- Pediatric and animal data “disconnect”

Hypoxemia post-ROSC is bad, but Hyperoxemia has less significant association with outcomes

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PaO2 &gt; 300</th>
<th>PaO2 60–300</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Del Castillo, 2012</td>
<td>10</td>
<td>19</td>
<td>1.29 [0.81, 2.07]</td>
<td>1.29 [0.81, 2.07]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>19</td>
<td>145</td>
<td>1.29 [0.81, 2.07]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>10</td>
<td>59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoxemia: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.07 (P = 0.28)</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
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</tr>
</thead>
<tbody>
<tr>
<td>Ferguson, 2012</td>
<td>91</td>
<td>207</td>
<td>1.12 [0.95, 1.33]</td>
<td>1.12 [0.95, 1.33]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>207</td>
<td>1220</td>
<td>1.12 [0.95, 1.33]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>91</td>
<td>478</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoxemia: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.34 (P = 0.18)</td>
<td></td>
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</tr>
</thead>
<tbody>
<tr>
<td>Guerra, 2013</td>
<td>10</td>
<td>34</td>
<td>1.26 [0.55, 2.90]</td>
<td>1.26 [0.55, 2.90]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>34</td>
<td>30</td>
<td>1.26 [0.55, 2.90]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>10</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoxemia: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.55 (P = 0.59)</td>
<td></td>
<td></td>
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<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bennett, 2013</td>
<td>57</td>
<td>87</td>
<td>1.17 [0.90, 1.52]</td>
<td>1.17 [0.90, 1.52]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>87</td>
<td>66</td>
<td>1.17 [0.90, 1.52]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>57</td>
<td>37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoxemia: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.16 (P = 0.24)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Ferguson, Circulation, 2012

Hypoxia (PaO2<60) - 24
Normoxia - 75
Hyperoxia (PaO2>300) - 11

Graph showing the probability of death in PICU for congenital heart disease and no congenital heart disease across different PO2 (mmHg) levels and age groups.
Bennett, CCM, 2013

P = 0.26

N = 195 patients
Cerebrovascular reactivity to changes in arterial carbon dioxide tension is preserved in comatose patients post-ROSC

Buunk Stroke 1997
Examples of TCD Profiles (n=18 patients)

Sundgreen, Stroke, 2001

Impaired CBF autoregulation
- Autoregulation with no identifiable lower limited
- Right-shifted autoregulation

“…should MAP be kept at a higher level than commonly accepted”; but how high and for how long?

Claus, Stroke 2001
PCAS: Myocardial Dysfunction

Animal models (VF)

- **Myocardial stunning**, with an onset within 30 min post-ROSC, and function returning to normal within 24-48 hours of the insult
- Systolic and diastolic dysfunction (biventricular)
- Recovery of systolic and diastolic function can be hastened by dobutamine, low dose epinephrine, milrinone or levodimendan

Kern, Circulation, 1997
Kern, J Am Coll Card, 1996
After controlling for patient and cardiopulmonary arrest characteristics, hypotension in the first 6 hours following ROSC was associated with:

- Significantly increased odds of in-hospital mortality (adjusted odds ratio = 1.71; \( p = 0.042 \))
- Increased odds of unfavorable outcome (adjusted odds ratio = 1.83; \( p = 0.032 \)).

- Marker of severity, or a Target for management?
- How best to treat, what best to target (BP vs. perfusion indices), post-ROSC mechanical support?
Timing of Prognostication Post ROSC

Fig. 2. Time to awakening after rewarming. Dashed lines indicate the 48 and 72 h timepoints.

Abend, Peds CCM, 2012
Thank You for your attention!

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