Pediatric Septic Shock

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Case

- 4 year old male with a history of gastroschisis repaired in infancy with a history of short gut syndrome from necrotizing enterocolitis.
- He has had fever and decreased po intake for 24 hours. No urine output in 12 hours. He is sleepy and hard to arouse
- He presents with the following vitals:
  - BP 78/50, HR 185, RR 32 T 40 C
Case

- Exam:
  - CR 5-6 seconds
  - Palpable but not strong pulses
  - Port-a-Cath site is unremarkable
  - Clear lungs with tachypnea and retractions
  - Tachycardiac without murmur
  - Opens eyes with exam but not following commands
Shock

• Adults:
• “Inadequate organ perfusion and cellular hypoxia.”
• “...a reduction in effective perfusion of tissues with decreased oxygen delivery to the capillary bed”
Shock

• Children:
  “..acutely inadequate or deranged circulatory function, with inadequate substrate (O2, glucose) delivery to and energy production by the tissues.”

• “..an acute, complex state of circulatory dysfunction that results in failure to deliver sufficient amounts of oxygen and other nutrients to meet tissue metabolic demands.”
Shock

- Children:

Also contrary to adults, a reduction in oxygen delivery rather than a defect in oxygen extraction, can be the major determinant of oxygen consumption in children (22). Attainment of the thera-

(Crit Care Med 2009; 37:666–688)
OXYGEN CONSUMPTION/DELIVERY AND SHOCK

DO₂/VO₂ Ratio: 2  3  4  5
O₂ Extraction Ratio: .5  .33  .25  .2
V Sat: 50  66  75  80
(If Sa = 100)

VO₂ cc m³

Gas volumes STPD

DO₂ cc C

Slide courtesy of RH Bartlett M.D
Hemodynamics of Pediatric Shock

- Shock refractory to > 60ml/kg Fluid therapy.
- Categorized pediatric shock by hemodynamics.
  - SVR (800-1600 dyne-sec/cm²/m²)
  - CI (3.3-5.5 L/min/m²)
- Also looked at response to therapy
  - Inotrope
  - Vasopressor
Hemodynamic Support in Fluid-refractory Pediatric Septic Shock

Gary Ceneviva, MD‡; J. Alan Paschall, MD||; Frank Maffei, MD‡; and Joseph A. Carcillo, MD, FAAP*‡§

<table>
<thead>
<tr>
<th>Group</th>
<th>CI (L/min/m²)</th>
<th>SVRI (dyne/sec/cm²)</th>
<th>After Fluid Resuscitation</th>
<th>After Initial Therapy Adjustment</th>
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<tr>
<td>Group I (n = 29)</td>
<td>3.06 ± .26</td>
<td>1794 ± 176</td>
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Values = mean ± SEM.
* P < .05 difference group I versus group II and group III after fluid-resuscitation and initial therapy adjustment (Kruskal–Wallis with Dunn’s tests).
** P < .05 difference in hemodynamic variables over time within group compared with baseline after fluid resuscitation (repeated-measures ANOVA with Student Neuman–Keuls test).

- **Group I** Low CI High SVR
  - Inotrope (Isolated contractility) = 58%
- **Group II** Low SVRI Normal CI
  - Vasopressor (Isolated vasomotor tone) = 20%
- **Group III** Low CI + Lowish SVRI
  - Inotrope + Vasopressor (Combination) = 22%
- 78% required an inotrope
- Overall 80% survival to 28 days
Etiology of Septic Shock

- Gram Positive Organisms
  - S. Pnemoniae
  - S. Aureus
  - Group B Strep
  - Enterococcus
- Gram Negative Organisms
  - Neisseria
  - E. Coli
Diagnostic Definition

- Most adult definitions are driven by hypotension with SBP < 90mm Hg
  - Surviving sepsis campaign also included (for septic shock)
    - Mean BP < 70 mmHg
    - SBP decrease by > 40 mmHg
    - lactate ≥ 4mmol/L
Diagnostic Definition Pediatrics

Table 2. American College of Critical Care Medicine hemodynamic definitions of shock

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<th>Definition</th>
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<td>Cold or warm shock</td>
<td>Decreased perfusion manifested by altered decreased mental status, capillary refill &gt;2 secs (cold shock) or flash capillary refill (warm shock), diminished (cold shock) or bounding (warm shock) peripheral pulses, mottled cool extremities (cold shock), or decreased urine output &lt;1 mL/kg/h</td>
</tr>
<tr>
<td>Fluid-refractory/</td>
<td>Shock persists despite ≥60 mL/kg fluid resuscitation (when appropriate) and dopamine infusion to 10 μg/kg/min</td>
</tr>
<tr>
<td>dopamine-resistant shock</td>
<td></td>
</tr>
<tr>
<td>Catecholamine-resistant shock</td>
<td>Shock persists despite use of the direct-acting catecholamines; epinephrine or norepinephrine</td>
</tr>
<tr>
<td>Refractory shock</td>
<td>Shock persists despite goal-directed use of inotropic agents, vasopressors, vasodilators, and maintenance of metabolic (glucose and calcium) and hormonal (thyroid, hydrocortisone, insulin) homeostasis</td>
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Table 3. Threshold heart rates and perfusion pressure mean arterial pressure-central venous pressure or mean arterial pressure-intra-abdominal pressure for age

<table>
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<tr>
<th>Threshold Rates</th>
<th>Heart Rate (bpm)</th>
<th>Mean Arterial Pressure-Central Venous Pressure (mm Hg)</th>
</tr>
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<tbody>
<tr>
<td>Term newborn</td>
<td>120–180</td>
<td>55</td>
</tr>
<tr>
<td>Up to 1 yr</td>
<td>120–180</td>
<td>60</td>
</tr>
<tr>
<td>Up to 2 yrs</td>
<td>120–160</td>
<td>65</td>
</tr>
<tr>
<td>Up to 7 yrs</td>
<td>100–140</td>
<td>65</td>
</tr>
<tr>
<td>Up to 15 yrs</td>
<td>90–140</td>
<td>65</td>
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bpm, beats per minute.
Management Adults

Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008

R. Phillip Dellinger, MD; Mitchell M. Levy, MD; Jean M. Carlet, MD; Julian Bion, MD; Margaret M. Parker, MD; Roman Jaeschke, MD; Konrad Reinhart, MD; Derek C. Angus, MD, MPH; Christian Brun-Buisson, MD; Richard Beale, MD; Thierry Calandra, MD, PhD; Jean-Francois Dhainaut, MD; Herwig Gerlach, MD; Maureen Harvey, RN; John J. Marini, MD; John Marshall, MD; Marco Ranieri, MD; Graham Ramsay, MD; Jonathan Sevransky, MD; B. Taylor Thompson, MD; Sean Townsend, MD; Jeffrey S. Vender, MD; Janice L. Zimmerman, MD; Jean-Louis Vincent, MD, PhD; for the International Surviving Sepsis Campaign Guidelines Committee

Objective: To provide an update to the original Surviving Sepsis Campaign clinical management guidelines, "Surviving Sepsis Campaign Guidelines for Management of Severe Sepsis and Septic Shock," published in 2004.

Design: Modified Delphi method with a consensus conference of 55 international experts, several subsequent meetings of subgroups and key individuals, teleconferences, and electronic-based discussion among subgroups and among the entire committee. This process was conducted independently of any industry funding.

Methods: We used the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system to guide assessment of quality of evidence from high (A) to very low (D) and to determine the strength of recommendations. A strong recommendation (1) indicates that an intervention's desirable effects clearly outweigh its undesirable effects (risk, burden, cost) or clearly do not. Weak recommendations (2) indicate that the tradeoff between desirable and undesirable effects is less clear. The grade of strong or weak is considered of greater clinical pressure is identified to be poorly responsive to fluid and vasopressor therapy (2C); recombinant activated protein C in patients with severe sepsis and clinical assessment of high risk for death (2B except 2C for postoperative patients). In the absence of tissue hypoperfusion, coronary artery disease, or acute hemorrhage, target a hemoglobin of 7–9 g/dl (1B); a low tidal volume (1B) and limitation of inspiratory plateau pressure strategy (1C) for acute lung injury (ALI)/acute respiratory distress syndrome (ARDS); application of at least a minimal amount of positive end-expiratory pressure in acute lung injury (1C); head of bed elevation in mechanically ventilated patients unless contraindicated (1B); avoiding routine use of pulmonary artery catheters in ALI/ARDS (1A); to decrease days of mechanical ventilation and ICU length of stay, a conservative fluid strategy for patients with established ALI/ARDS who are not in shock (1C); protocols for weaning and sedation/analgesia (1B); using either intermittent bolus sedation or continuous infusion sedation with daily interruptions or lightening (1B); avoidance of neuromuscular blockers. If at all possible (1B); institution of alveolar control (1B).

- Crit Care Med 2008;36:296-327
Management Pediatrics

Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine*

Joe Brierley, MD; Joseph A. Carcillo, MD; Karen Choong, MD; Tim Cornell, MD; Allan DeCaen, MD; Andreas Deymann, MD; Allan Doctor, MD; Alan Davis, MD; John Duff, MD; Marc-Andre Dugas, MD; Alan Duncan, MD; Barry Evans, MD; Jonathan Feldman, MD; Kathryn Felmot, MD; Gene Fisher, MD; Lorry Frankel, MD; Howard Jeffries, MD; Bruce Greenwald, MD; Juan Gutierrez, MD; Mark Hall, MD; Yong Y. Han, MD; James Hanson, MD; Jan Hazelzet, MD; Lynn Herman, MD; Jane Kiff, MD; Niranjan Kissoon, MD; Alexander Kon, MD; Jose Irazusta, MD; John Lin, MD; Angie Lorts, MD; Michelle Mariscalco, MD; Renuka Mehta, MD; Simon Nadel, MD; Trung Nguyen, MD; Carol Nicholson, MD; Mark Peters, MD; Regina Okhuysen-Cawley, MD; Tom Poulton, MD; Monica Reives, MD; Agustin Rodriguez, MD; Ranna Rozenfeld, MD; Eduardo Schnitzler, MD; Tom Shanley, MD; Sara Skache, MD; Peter Skippen, MD; Adalberto Torres, MD; Bettina von Dessauer, MD; Jacki Weingarten, MD; Timothy Yeh, MD; Amo Zaitsky, MD; Bonnie Stojadinovic, MD; Jerry Zimmerman, MD; Aaron Zuckerberg, MD

*Background: The Institute of Medicine calls for the use of clinical guidelines and practice parameters to promote “best practices” and to improve patient outcomes.

Objective: 2007 update of the 2002 American College of Critical Care Medicine guidelines. Early use of the 2002 guidelines was associated with improved outcome in the community hospital setting.

• Crit Care Med 2009;37(2):666-88
Management Pediatrics

R. Phillip Dellinger, MD¹; Mitchell M. Levy, MD²; Andrew Rhodes, MB BS³; Djillali Annane, MD⁴; Herwig Gerlach, MD, PhD⁵; Steven M. Opal, MD⁶; Jonathan E. Sevransky, MD⁷; Charles L. Sprung, MD⁸; Ivor S. Douglas, MD⁹; Roman Jaeschke, MD¹⁰; Tiffany M. Osborn, MD, MPH¹¹; Mark E. Nunnally, MD¹²; Sean R. Townsend, MD¹³; Konrad Reinhart, MD¹⁴; Ruth M. Kleinpell, PhD, RN-CS¹⁵; Derek C. Angus, MD, MPH¹⁶; Clifford S. Deutschman, MD, MS¹⁷; Flavia R. Machado, MD, PhD¹⁸; Gordon D. Rubenfeld, MD¹⁹; Steven A. Webb, MB BS, PhD²⁰; Richard J. Beale, MB BS²¹; Jean-Louis Vincent, MD, PhD²²; Rui Moreno, MD, PhD²³; and the Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup‡

practices" and to improve patient outcomes. Objective: 2007 update of the 2003 American College of Critical
10% in chronically ill children). Early use of 2002 guidelines was

• (Crit Care Med 2013; 41:580–637)
Pediatric Algorithm

- Major difference from adults is not using SVO₂ to titrate initial therapy.
- Also the separation of warm and cold shock is also different.
- ECMO is not included in the algorithm for adults.
Pediatric Algorithm

**Therapeutic End Points:** (Level III)
- Capillary refill ≤2 secs, threshold HRs, normal pulses with no differential between the quality of the peripheral and central pulses, warm extremities, urine output >1 mL/kg/h, normal mental status, CI >3.3 and <6.0 L/min/m² with normal perfusion pressure (MAP—central venous pressure, or MAP—IAP) for age, ScvO₂ >70%; maximize preload to maximize CI, MAP — central venous pressure; normal INR, anion gap, and lactate.

### Initial resuscitation:
- Push boluses of 20 cc/kg isotonic saline or colloid up to 60 cc/kg until perfusion improves or unless rules of hepatomegaly develop.
- Correct hypoglycemia & hypocalcemia. Begin antibiotics.

**0 min**
- Recognize decreased mental status and perfusion.
- Begin high flow O₂. Establish IV/I0 access.

**5 min**
- If 2nd PIV start inotrope.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac</td>
<td>0.05 to 0.3 mg/kg/min</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>10 mg/kg/min</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>10 μg/kg/min</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>1 μg/kg/min</td>
</tr>
</tbody>
</table>

**Sepsis**
- Septic shock with low blood pressure:
  1. Titrate fluid & norepinephrine, SevO₂ >70%.
  2. If still hypotensive consider vasopressin, terlipressin or angiotensin.
  3. If SevO₂ still <70% consider low dose epinephrine

**Hypovolemia**
- Precordial effusion, pneumothorax, Hg.
- Doppler ultrasound to guide normal therapies.
A Normal Capillary Refill Time of ≤ 2 Seconds is Associated with Superior Vena Cava Oxygen Saturations of ≥ 70%

Patricia L. Raimer, MD, Yong Y. Han, MD, Monica S. Weber, RN, Gail M. Annich, MD, and Joseph R. Custer, MD

Conclusions A normal CRT ≤ 2 seconds can be predictive of ScvO₂ ≥ 70%. Our study corroborates the recommendations of the Pediatric Advanced Life Support curricula targeting a normal CRT ≤ 2 seconds as a therapeutic endpoint for goal-directed shock resuscitation. This clinical target remains particularly relevant in community hospitals when the ability to obtain central venous catheter access may be limited and ScvO₂ data unavailable. (J Pediatr 2011;158:968-72).
Early Goal-Directed Therapy in Pediatric Septic Shock: Comparison of Outcomes “With” and “Without” Intermittent Superior Venacaval Oxygen Saturation Monitoring: A Prospective Cohort Study*

Jhuma Sankar, MD¹; M. Jeeva Sankar, DM²; C. P. Suresh, MD¹; Nandkishore K. Dubey, MD¹; Archana Singh, MD¹

**Conclusion:** Early goal-directed therapy using intermittent Scvo₂ monitoring seemed to reduce the mortality rates and improved organ dysfunction in children with septic shock as compared with those without such monitoring. (*Pediatr Crit Care Med 2014; 15:e157–e167*)
Initial Therapy

- Do they need Fluid?
  - Many have not taken PO in the preceding 24-48 hours
  - Children have up to 3-4 times the metabolic rate of adults
    - Remember 1ml H2O used per kcal burned
Initial Therapy

C. Fluid Resuscitation

1. In the industrialized world with access to inotropes and mechanical ventilation, we suggest that initial resuscitation of hypovolemic shock begin with infusion of isotonic crystalloids or albumin, with boluses of up to 20 mL/kg for crystalloids (or albumin equivalent) over 5 to 10 mins. These should be titrated to reversing hypotension, increasing urine output, and attaining normal capillary refill, peripheral pulses and level of consciousness without inducing hepatomegaly or rales. If hepatomegaly or rales develop, inotropic support should be implemented, not fluid resuscitation. In children with severe hemolytic anemia (severe malaria or sickle cell crises) who are not hypotensive, blood transfusion is considered superior to crystalloid or albumin bolusing (grade 2C).

resuscitation can require 40 to 60 mL/kg or more; however, if these signs are present, then fluid administration should be ceased and diuretics should be given. Inotrope infusions and
Initial Therapy

- Adherence to PALS fluid resuscitation guidelines improves outcomes.

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**Early Reversal of Pediatric-Neonatal Septic Shock by Community Physicians Is Associated With Improved Outcome**

Yong Y. Han, MD*:§; Joseph A. Carcillo, MD*:‡§; Michelle A. Dragotta, RN§; Debra M. Bills, RN§;
R. Scott Watson, MD, MPH*:‡§; Mark E. Westerman, RT§; and Richard A. Orr, MD*:‡§

**ABSTRACT.** Objective. Experimental and clinical studies of septic shock support the concept that early resuscitation with fluid and inotropic therapies improves survival in a time-dependent manner. The new American College of Critical Care Medicine-Pediatric Advanced Life

mote ACCM-PALS recommended rapid, stepwise escalations in fluid as well as inotropic therapies may have value in improving outcomes in these children. *Pediatrics* 2003;112:793–799; fluid resuscitation, inotropes, interfacility transport, hydrocortisone.
Can I Give Too Much Fluid? You most certainly can!

- Check for Hepatomegaly
- Check for Rales
- Evaluate MAP – CVP
- Evaluate SVV, or SBP variation

- You can definitely do harm if you do not attend to this! Some children need no 0 mLs / kg of fluid while others need up to 60 mL/kg of fluid during resuscitation.

Slide Courtesy of J. Carcillo M.D
Too much crystalloid in a group who need vasopressors and Blood

>50% with Malarial Sepsis
Fluid Refractory Shock

- Add inotropes or vasopressors if shock persists.
- Dopamine is standard/usual.
- Epinephrine for cold shock
  - $\beta_2$ activity reduces DBP (afterload) but MAP goes up due to increased inotropy.
  - $\alpha$ activity at higher doses, some suggest $> 0.3\text{mcg/kg/min}$
Fluid Refractory Shock Adults

- Only adult studies could compare Dopamine and NE.
  - Pediatric shock has different physiology usually.
Catecholamine Resistant Shock

• In practice we often add vasopressin to Dopa + Epi
• Steroids
  – Just as murky as the adult data.
  – Most define risk
    • Azole use
    • Recent steroids
    • Etomidate use
Steroids

Absolute adrenal insufficiency (group 1): baseline cortisol <20 μg/dL and increment ≤9 μg/dL

Relative adrenal insufficiency (group 2): baseline cortisol ≥20 μg/dL and an increment ≤9 μg/dL

Adequate adrenal response with an elevated baseline cortisol (group 3): baseline cortisol ≥20 μg/dL and an increment >9 μg/dL

Adequate adrenal response without an elevated baseline cortisol (group 4): baseline cortisol <20 μg/dL and an increment >9 μg/dL

• 18% Absolute Insufficiency, 26% Relative Insufficiency
  – High catecholamine resistance
• Adrenal function predicted response to inotropetic therapy.

Objective: Corticosteroid replacement improves outcome in adults with relative adrenal insufficiency and catecholamine-resistant septic shock. We evaluated the relationship of absolute and relative adrenal insufficiency to catecholamine-resistant septic shock in children.

Design: Prospective cohort study.

Setting: University hospital pediatric intensive care unit in Brazil.

Patients: Fifty-seven children with septic shock. Children with HIV infection, those with a history of adrenal insufficiency, and those submitted to any steroid therapy or etomidate within the week before diagnosis of septic shock were excluded.

Interventions: None.

Measurements and Main Results: A short corticotropin test (250 μg) was performed, and cortisol levels were measured at baseline and 30 and 60 mins posttest. Adrenal insufficiency was defined by a response ≤9 μg/dL. Absolute adrenal insufficiency was further defined by a baseline cortisol <20 μg/dL and relative adrenal insufficiency by a baseline cortisol >20 μg/dL. Absolute adrenal insufficiency was observed in 18% of children, all of whom had catecholamine-resistant shock. Relative adrenal insufficiency was observed in 26% of children, of whom 80% had catecholamine-resistant and 20% had dopamine/dobutamine-responsive shock. All children with fluid-responsive shock had a cortisol response >9 μg/dL. Children with adrenal insufficiency had an increased risk of catecholamine-resistant shock (relative risk, 1.88; 95% confidence interval, 1.26–2.79). However, mortality was independently predicted by chronic illness or multiple organ failure (p < 0.05), not adrenal insufficiency.

Conclusions: Absolute and relative adrenal insufficiency is common in children with catecholamine-resistant shock and absent in children with fluid-responsive shock. Studies are warranted to determine whether corticosteroid therapy has a survival benefit in children with relative adrenal insufficiency and catecholamine-resistant septic shock. (Crit Care Med 2005; 33:855-859)

Key Words: septic shock; sepsis; adrenal insufficiency; shock; corticosteroids; cortisol.
Adrenal function is associated with therapy response but not with outcome.
CONCLUSIONS

Absolute and relative adrenal insufficiency is common in children with septic shock and may contribute to the development of catecholamine-resistant shock; in other words, it is associated with an increased vasopressor requirement. However, doubts still persist regarding the efficacy of replacement therapy with low-dose steroids in children with catecholamine-resistant septic shock, and further studies are needed to determine whether treatment of such patients changes morbidity and/or mortality (28, 29).

- Adrenal response
Steroid Resistant Shock

- Milrinone in pediatric sepsis.
- Vasopressin
  - In practice we add this often before steroids.
- Levosimendan
Steroid Resistant Shock

- Milrinone in pediatric sepsis.

Pharmacokinetics and pharmacodynamics of milrinone lactate in pediatric patients with septic shock

Christine A. Lindsay, PharmD, Phil Barton, MD, Stephen Lawless, MD, Louann Kitchen, RN, MS, Amy Zorka, MBA, Jorge Garcia, MD, Amjad Kouatli, MD, and Brett Giroir, MD

(J Pediatr 1998;132:329-34)
Milrinone in pediatric sepsis.

Vasopressin – In practice we add this often before steroids.

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**Hemodynamic Support in Fluid-refractory Pediatric Septic Shock**

Gary Ceneviva, MD*‡; J. Alan Paschall, MD∥; Frank Maffei, MD‡; and Joseph A. Carcillo, MD, FAAP*‡∥

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**TABLE 3. CI (L/min/m²) and SVRI (dyne/sec/cm²) in Groups I, II, and III After Fluid Resuscitation, Initial Therapy Adjustment, and 48 Hours**

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* P < .05 difference group I versus group II and group III after fluid-resuscitation and initial therapy adjustment (Kruskal–Wallis with Dunn’s tests).

** P < .05 difference in hemodynamic variables over time within group compared with baseline after fluid resuscitation (repeated-measures ANOVA with Student Neuman–Keuls test).
Conclusions: Diastolic dysfunction is common in children with fluid refractory septic shock, and immediate outcomes may be poorer in such patients.
Steroid Resistant Shock

- Levosimendan
- Not FDA approved in U.S.
- Ca Channel sensitizer.
Steroid Resistant Shock

- Levosimendan
- Not FDA approved in U.S.
- Ca sensitizer via Troponin C.

Early experience with Levosimendan in children with ventricular dysfunction*

Poongundran Namachivayam, MRCPCH; David S. Crossland, MRCPCH; Warwick W. Butt, FRACP; Lara S. Shekerdemian, MD, FRACP

Objective: To describe our preliminary experience with Levosimendan, a new calcium-sensitizing agent in critically unwell infants and children with severe heart failure.

Design: Retrospective cohort analysis.

Setting: Pediatric intensive care unit.

Patients: Fifteen children aged 7 days to 18 yrs (median age 38 months) with severe myocardial dysfunction secondary to end-stage heart failure, or acute heart failure, who were inotropic-dependent (requiring at least one catecholamine).

Interventions: A single dose (bolus and intravenous infusion over 24–48 hrs) of Levosimendan was given under continuous hemodynamic monitoring in our intensive care unit. Eleven children received a single dose, three children received two doses, and one child received four doses. Echocardiographic assessments of ventricular function were made before and 3–5 days after Levosimendan infusion.

Measurements and Main Results: Heart rate, systolic pressure, diastolic pressure, mean blood pressure, and central venous pressure were unchanged during and after Levosimendan. Levosimendan allowed for discontinuation of catecholamines in ten patients and a dose reduction in three. The dose of dobutamine was reduced from 6.4 μg/kg/min pre-Levosimendan to 1.8 μg/kg/min on day 5 (p < .01). Ejection fraction for the group as a whole improved from 29.8% to 40.5% (p = .015); this did not increase significantly in patients with end-stage heart failure but increased by 63% in the children with acute heart failure.

Conclusions: Levosimendan can be safely administered to infants and children with severe heart failure. Levosimendan allowed for substantial reduction in catecholamine infusions in children with end-stage or acute heart failure and also produced an objective improvement in myocardial performance in children with acute heart failure. (Pediatr Crit Care Med 2006; 7:445–448)

Key Words: Levosimendan; children; heart failure; infants; pediatric intensive care; congenital heart disease.
Vasopressin Levels Adults

- Vasopressin levels in adults are high initially, but then decline.

- Administration however does not improve outcome.
Vasopressin Levels in Pediatrics

- Levels are high and remain high during sepsis
  - Limited studies
  - This contradicts the anecdotal use of Vasopressin

Serial circulating vasopressin levels in children with septic shock

Rakesh Lodha, MD; Subbiah Vivekanandhan, PhD; Manjunatha Sarthi, MD; Sushil K. Kabra, MD

**Background:** Septic shock is an important cause of death in pediatric intensive care units. Initial evaluations have shown that vasopressin may have a role in catecholamine refractory shock in adults. It is important to determine whether children with septic shock have deficiency of vasopressin. This will help in defining the role of vasopressin in septic shock.

**Design:** Prospective cohort study.

**Setting:** Pediatric intensive care unit of a tertiary care hospital in north India.

**Patients:** Patients were children with septic shock, and controls were children with sepsis but no shock.

**Study Design:** Vasopressin levels in plasma were determined by enzyme-linked immunosorbent assay for children with septic shock at diagnosis (baseline) and thereafter at 24, 48, and 96 hrs to determine the time trends. The baseline vasopressin values for children with septic shock were compared with those for children without shock.

**Results:** The median (95% confidence interval) vasopressin level at baseline in children with septic shock was 116 (63.3–130.7) pg/mL, and in children with sepsis but no shock it was 106 (61.7–131.77) pg/mL. The median value for survivors was 76 (44.6–130.3) pg/mL, and for nonsurvivors, 118 (81.7–258) pg/mL. The serial values also did not show any significant changes; the values at 24 hrs (n = 17), 48 hrs (n = 16), and 96 hrs (n = 15) were 105 (76.1–125.9), 105 (41.4–155.5), and 109.5 (54.9–154.8) pg/mL, respectively.

**Conclusions:** The results of our study suggest that vasopressin levels are elevated in children with septic shock and that serial values up to 96 hrs do not show any decline. (Pediatr Crit Care Med 2006; 7:220–224)
Vasopressin infusion in children with catecholamine-resistant septic shock

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Conclusions: Although terlipressin infusion had no effect on mortality, it significantly increases mean arterial pressure, PaO₂/FIO₂, and survival time in nonsurvivors. Terlipressin seems to cause no adverse effect but warrants further evaluation as a rescue therapy in refractory septic shock.
Then What?

- Get an ECHO
- Source Control
  - Remove the Broviac
  - Abdominal Sepsis
- ECMO
- Activated Protein C
Then What?

ECMO

Extracorporeal membrane oxygenation for refractory septic shock in children: One institution’s experience*

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**Objective:** To report our institutional experience of venoarterial extracorporeal membrane oxygenation (ECMO) in children with septic shock and circulatory collapse.

**Design:** Retrospective case series.

**Setting:** Intensive care unit of a tertiary pediatric referral center.

**Patients:** Forty-five children with refractory septic shock who received venoarterial ECMO for hemodynamic support.

**Interventions:** Venoarterial ECMO.

**Measurements and Main Results:** We measured mean arterial pressure and inotropes before cannulation, ventilator settings, oxygenation, site and cause of infection, time on ECMO, complications of ECMO relating to the circuit or anticoagulation, survival to hospital discharge, and functional outcome assessment. Between July 1988 and October 2006, 441 children at our institution received extracorporeal life support for a variety of indications. Forty-five (10%) with septic shock received venoarterial ECMO specifically for hemodynamic support. Eighteen (40%) of these had suffered cardiac arrest and were receiving chest compressions immediately before cannulation. The median time spent on ECMO was 84 hrs (range, 32–135). There were mechanical problems with the ECMO circuit requiring intervention in 17 (38%) patients, such as oxygenator or pump head failure, clots in the circuit, or cannulae malposition. This caused no long-term harm in any but one of the patients, who died during a circuit change. Eleven patients (24%) had clinically apparent episodes of bleeding that required surgical intervention or blood transfusion. Twenty-one (47%) patients survived to hospital discharge. Atrioaortic cannulation through a sternotomy incision was associated with an improvement in survival to hospital discharge (73% of those with central cannulation survived vs. 44% without, p = .05). No survivors had severe disability at long-term follow-up.

**Conclusions:** Extracorporeal membrane oxygenation can be safely used to resuscitate and support children with sepsis and refractory shock. Sepsis and multiorgan failure should not be considered a contraindication to ECMO. This study adds support to existing guidelines. (Pediatr Crit Care Med 2007; 8:447–451)

**Key Words:** sepsis; septic shock; pediatric; extracorporeal membrane oxygenation; cardiac arrest
Then What?

- ECMO
- Activated Protein C
Then What?

Eprosteregon alfa (activated) in children with severe sepsis: a multicentre phase III randomised controlled trial

Simon Nadel, Brahima Baistein, Mark D Williams, Hadil Wolfsion, Mark Peters, William L Macias, Shamel A Abd-Allah, Howard Levy, Robinette Angle, Dazhe Wang, David P Sundin, Principal for the REsearching severe Sepsis and Organ dysfunction in children: a gLobal perspective (RESOLVE) study group

Summary

Background Eprosteregon alfa (activated) (DrotAA) is used for the treatment of adults with severe sepsis who have a high risk of dying in a phase l open-label study has indicated that the pharmacokinetics and pharmacodynamics of DrotAA are similar in children and adults. We initiated the RESOLVE (REsearching severe Sepsis and Organ dysfunction in children: a gLobal perspective) trial to investigate the efficacy and safety of the drug in children.

Methods Children aged between 38 weeks’ corrected gestational age and 17 years with sepsis-induced cardiovascular and respiratory failure were randomly assigned to receive placebo or DrotAA (24 μg/kg/h) for 96 h. We used a prospectively defined, novel primary endpoint of Composite Time to Complete Organ Failure Resolution (CTCOFR) score. Secondary endpoints were 28-day mortality, major amputation, and safety. Analysis was by intention-to-treat. This trial is registered with clinicaltrials.gov, number NCT00497064.

Findings 477 patients were enrolled; 237 received placebo, and 240 DrotAA. Our results showed no significant difference between groups in CTCOFR score (p=0.72) or in 28-day mortality (placebo 10%, DrotAA, 17; p=0.93). Although there was no difference in overall serious bleeding events during the 28-day study period (placebo 6.8%; DrotAA 6.7%; p=0.97), there were numerically more instances of CNS bleeding in the DrotAA group (11 [4.6%], vs 5 [2.1%] in placebo, p=0.13), particularly in children younger than 60 days. For CTCOFR score ≤1—14, correlation coefficient was −0.016 (95% CI −0.106 to 0.74); relative risk for 28-day mortality was 1.06 (95% CI 0.76 to 1.46) for DrotAA compared with placebo.

Interpretation Although we did not record any efficacy of DrotAA in children with severe sepsis, serious bleeding events were similar between groups and the overall safety profile acceptable, except in children younger than 60 days. However, we gained important insights into clinical and laboratory characteristics of childhood severe sepsis, and have identified issues that need to be addressed in future trials in critically ill children.
Other Measures

• Antibiotics
  – No data about survival with antibiotics in the first hours
  – BUT, easy to extrapolate

Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department*

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*Objective: To study the association between time to antibiotic administration and survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department.


Setting: The emergency department of an academic tertiary care center from 2005 through 2006.

Patients: Two hundred sixty-one patients undergoing early goal-directed therapy.

Interventions: None.

Measurements and Main Results: Effects of different time cutoffs from triage to antibiotic administration, qualification for early goal-directed therapy to antibiotic administration, triage to appropriate antibiotic administration, and qualification for early goal-directed therapy to appropriate antibiotic administration on in-hospital mortality were examined. The mean age of the 261 patients was 59 ± 16 yrs; 41% were female. In-hospital mortality was 31%. Median time from triage to antibiotics was 119 mins (interquartile range, 76–192 mins) and from qualification to antibiotics was 42 mins (interquartile range, 0–93 mins). There was no significant association between time from triage or time from qualification for early goal-directed therapy to antibiotics and mortality when assessed at different hourly cutoffs. When analyzed for time from triage to appropriate antibiotics, there was a significant association at the ≤1 hr (mortality 19.5 vs. 33.2%; odds ratio, 0.30 [95% confidence interval, 0.11–0.83]; p = .02) time cutoff; similarly, for time from qualification for early goal-directed therapy to appropriate antibiotics, a significant association was seen at the ≤1 hr (mortality 25.0 vs. 38.5%; odds ratio, 0.50 [95% confidence interval, 0.27–0.92]; p = .03) time cutoff.

Conclusions: Elapsed times from triage and qualification for early goal-directed therapy to administration of appropriate antimicrobials are primary determinants of mortality in patients with severe sepsis and septic shock treated with early goal-directed therapy. (Crit Care Med 2010; 38:1045–1053)

Key Words: sepsis; early goal-directed therapy; antimicrobial timing; appropriateness; outcomes; resuscitation
• CRRT
  – Recommend 35 ml/kg/hr Clearance
  – Not well reproduced
  – Probably > 20ml/kg/hr is the threshold
Mortality

- Mortality rates 2-10% overall (2012 Surviving Sepsis Update)
- Low compared to adults
- MODS develops early (first 7 days)
• Fluid Resuscitation
• Inotrope
• CRRT
• ICU Care

Reduction in case fatality rate from meningococcal disease associated with improved healthcare delivery

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**Figure 1** Number of yearly admissions of children with MD to the PICU at St Mary’s Hospital, shown by the bars. Annual case fatality rates predicted by PRISM and actual annual case fatality rates are superimposed as line graphs.