Pediatric Sepsis Treatment: (treat) Early & (reevaluate) Often

Disclosures

• None
Agenda

- **Sepsis: pathophysiology at-a-glance**
  - Pediatric differences impact treatment
- **Treatment guidelines & evidence**
  - Guideline-based treatment works!
  - Early antibiotics
  - Pathway care
  - Vasoactive support
- **Late mortality**
Sepsis, shock & septic shock

**Sepsis: infection + inflammation**
- Fever, tachycardia, tachypnea, abnormal WBC, abnormal MS

**Shock: oxygen delivery does not meet demand**

Updated Sepsis 3 definitions (in adults) - SOFA
- qSOFA: **Hypotension** | **altered MS** | **↑ RR**
  
  Martin Minerva Pediatr 2015 qsofa.org

Septic shock: 3 kinds of shock in one

- **Distributive shock**
  - vasodilation
  - endothelial dysfunction

- **Hypovolemic shock**
  - vascular resistance

- **Cardiogenic shock**
Septic shock: 3 kinds of shock in one

- **Distributive shock**
  - fluid & vasopressors
  - vasodilation + endothelial dysfunction

- **Hypovolemic shock**
  - IV fluid

- **Cardiogenic shock**
  - ionotropes

How are children different?

- **Presentation:** varies widely!
  - Common features: tachycardia, low urine output, lethargy
  - 80% **cold shock**: low cardiac output, ± low vascular tone
    - Diminished pulses, delayed cap refill, narrow pulse pressure
  - 20% **warm shock**: normal/high cardiac output, + low vascular tone
    - Bounding pulses, brisk cap refill, wide pulse pressure

- **Why?**
  - Young infants cannot increase stroke volume; only heart rate
  - Children can generate profound tachycardia (HR > 200)
  - This comes at a cost (↓ diastole = ↓ cardiac filling = ↓ cardiac output)
  - Tachypnea: robust compensatory efforts for acidosis
  - Hypoglycemia more common
TREATMENT GUIDELINES

Treat early:

Improved survival with guideline-directed therapy

Han Pediatrics 2003
The role of healthcare delivery in the outcome of meningococcal disease in children: case-control study of fatal and non-fatal cases


Nini BMJ 2005

Multivariable model: odds of death increased w/ each missed treatment goal

<table>
<thead>
<tr>
<th>#</th>
<th>OR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
<td>-</td>
</tr>
<tr>
<td>1</td>
<td>8.7</td>
<td>0.001</td>
</tr>
<tr>
<td>2</td>
<td>34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3+</td>
<td>113</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Treatment Guidelines

**Pediatric Septic Shock Algorithm**

**Recognition**
- Altered mental status (irritability or decreased level of consciousness)
- Altered heart rate (tachycardia or, less commonly, bradycardia)
- Altered temperature (fever or hypothermia)
- Altered perfusion (prolonged or "flash" capillary refill, cool or very warm extremities, mottled color or pallor; possible ecchymosis or purpura; decreased urine output)
- Hypotension: May or may not be present

**Immediate (10-15 min)**

- Establish vascular access (IV or IO): draw blood for culture and additional laboratory studies, including glucose and delayed antibiotic or fluid therapy
- Antibiotics: Give broad-spectrum antibiotics
- Fluid bolus: Give 20 mL/kg isotonic crystalloid bolus for neonates and those with pre-existing cardiovascular compromise
- Avoid heparin
- If needed
  - Goals of therapy: Improved mental status; normalization of heart rate and temperature; adequate systolic and diastolic blood pressure, improved perfusion (see box above)

**IV Access**

- Antimicrobials:
  - Rapid IV fluid boluses
Timing of antibiotics impacts mortality

Empiric Antibiotic Treatment Reduces Mortality in Severe Sepsis and Septic Shock From the First Hour: Results From a Guideline-Based Performance Improvement

Ferrer CCM 2014

True in children too

Delayed Antimicrobial Therapy Increases Mortality and Organ Dysfunction Duration in Pediatric Sepsis

Scott L. Weiss, MD; Julie C. Fitzgerald, MD, Ph; Elizabeth R. Alpern, MD, MDCE; Irene Lavelle, J; Robert Grandmonte, MD; Vicky M. Nadkarni.
Rapid IV fluid resuscitation

Role of Early Fluid Resuscitation in Pediatric Septic Shock

- N=14 <20 ml/kg
- N=11 20-40 ml/kg
- N=9 >40 ml/kg

Carcillo JAMA 1991

Pathways improve recognition & 1st hour therapy

Implementation of Goal-Directed Therapy for Children With Suspected Sepsis in the Emergency Department
Cruz Pediatrics 2011

- Computerized triage system & vital sign alert
- Standardized orderset
- Bedside presence of additional RN, RT, pharmacy
Time to first bolus
72 → 22 min

Time to third bolus
280 → 61 min

Time to antibiotics
143 → 38 min

State-wide pathway implementation & outcomes

- 12-year-old Rory Staunton’s death from septic shock prompted NY state to mandate hospitals adopt sepsis screening & treatment protocols (2013)
State-wide pathway implementation & outcomes

State Sepsis Mandates — A New Era for Regulation of Hospital Quality
Tina B. Hershey, J.D., M.P.H., and Jeren

A. Adult Patients with Sepsis

- Protocol Initiation
- 3-hr Bundle Compliance
- Mortality

Quarter and Year

B. Pediatric Patients with Sepsis

- Protocol Initiation
- 3-hr Bundle Compliance
- Mortality

Quarter and Year
Treatment Guidelines

Vasoactive drugs

Agent | α1 | β1 | β2 | other
--- | --- | --- | --- | ---
Dopamine | vasoconstriction (high dose) | ionotropy | vasodilation | dopamine receptors \( \rightarrow \) adrenalin, noradrenalin
Norepinephrine | vasoconstriction | warm shock | cold shock
Epinephrine | vasoconstriction (high dose) | ionotropy | vasodilation (low dose) | 
Dobutamine | ionotropy | chronotropy | vasodilation |

First hour!

Vasopressors & ionotropes: many choices

Remember IV fluid (dehydration, losses, capillary leak)
Why not dopamine? Is a peripheral vasopressor OK?

Double-Blind Prospective Randomized Controlled Trial of Dopamine Versus Epinephrine as First-Line Vasoactive Drugs in Pediatric Septic Shock

Andréa M. C. Ventura, MD; Huei Hsin Shieh, MD; Albert Reusso, MD; Patricia F. Góes, MD; Ircarina de Cássia F. O. Fernandes, MD; Daniela C. da Souza, MD; Rodrigo Locatelli-Pedro Paulo, MD; Fabiana Chagas, RN; Alfredo E. Gillio, MD

Start peripheral epinephrine early

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**TABLE 2. Treatment Administered**

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Dopamine (n = 60)</th>
<th>Epinephrine (n = 67)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to fluids, h*</td>
<td>0.4 (0.6)</td>
<td>0.4 (0.9)</td>
<td>0.344</td>
</tr>
<tr>
<td>Fluids 1st h, mL/kg</td>
<td>467 (18.1)</td>
<td>967 (109)</td>
<td>0.114</td>
</tr>
<tr>
<td>Fluids 1st h, mL/kg</td>
<td>903 (33.9)</td>
<td>866 (20.4)</td>
<td>0.183</td>
</tr>
<tr>
<td>Antibiotics 1st h, yes, n (%)</td>
<td>59 (81.7)</td>
<td>40 (59.7)</td>
<td>0.162</td>
</tr>
<tr>
<td>Time to start epinephrine, h*</td>
<td>3.2 (1.1)</td>
<td>2.4 (1.5)</td>
<td>0.442</td>
</tr>
<tr>
<td>Duration of resuscitation, h*</td>
<td>51 (5.07)</td>
<td>16.1 (25.6)</td>
<td>0.004</td>
</tr>
<tr>
<td>MAP, yes, n (%)</td>
<td>62 (84)</td>
<td>51 (76.5)</td>
<td>0.052</td>
</tr>
<tr>
<td>MAP-free days*</td>
<td>14.3 (10.6)</td>
<td>18.6 (10.9)</td>
<td>0.178</td>
</tr>
<tr>
<td>Hydrocortisone, yes, n (%)</td>
<td>21 (33.3)</td>
<td>17 (25.4)</td>
<td>0.069</td>
</tr>
<tr>
<td>Renal replacement therapy, yes, n (%)</td>
<td>11 (17.4)</td>
<td>6 (10.5)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Epinephrine: Shorter resuscitation, less renal failure

Ventura CCM 2015
Epinephrine:
Lower mortality, fewer HAI

Similar to adult data

- Lower mortality with norepinephrine vs. dopamine → Fewer adverse events & arrhythmias
- Similar mortality with norepinephrine vs. epinephrine

TABLE 6. Multiple Logistic Regression Analyses: Outcomes Odds Ratios or Relative Risk With 95% CI

<table>
<thead>
<tr>
<th>Variable</th>
<th>Death at 23 D</th>
<th>Healthcare-Acquired Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td>6.51 (1.82–27.69); 0.007</td>
<td>0.77 (0.44–1.36); 0.021</td>
</tr>
</tbody>
</table>

Ventura CCM 2015
Hydrocortisone

- History of chronic steroid therapy
- History of panhypopituitarism
- Consider if poor response to high-dose pressors

Therapies intended for the critical care environment and expertise

move to critical care

Critical care goals of therapy: Svo2 >70%, adequate SVR, normalized IFR, adequate cardiac output/inotrop support

Pediatric Septic Shock Algorithm (continued)

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Reassess & Titrate therapies to exam

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What about Early Goal-Directed Therapy?

Since then...

Early, Goal-Directed Therapy for Septic Shock — A Patient-Level Meta-Analysis

Table 1. (Continued.)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>EGDT (N=1857)</th>
<th>Usual Care (N=1880)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from ED presentation to first IV antimicrobial agents — min*</td>
<td>75</td>
<td>72</td>
</tr>
<tr>
<td>IQR</td>
<td>42-120</td>
<td>42-120</td>
</tr>
<tr>
<td>IV fluids administered before hospital presentation until randomization — no./total no. (%)</td>
<td>1801/1846 (97.6)</td>
<td>1818/1871 (97.2)</td>
</tr>
<tr>
<td>Volume administered — ml</td>
<td>2000</td>
<td>2000</td>
</tr>
<tr>
<td>IQR</td>
<td>1250-3000</td>
<td>1200-3000</td>
</tr>
<tr>
<td>Volume administered per kilogram of body weight — ml</td>
<td>27.5</td>
<td>27.2</td>
</tr>
<tr>
<td>IQR</td>
<td>16.5-42.3</td>
<td>16.2-41.7</td>
</tr>
</tbody>
</table>
Since then…

Early, Goal-Directed Therapy for Septic Shock — A Patient-Level Meta-Analysis

Figure 1. Patient Survival over a Period of 1 Year.
Pediatric mortality after septic shock

The Epidemiology of Hospital Death Following Pediatric Severe Sepsis: When, Why, and How Children With Sepsis Die*

Weiss PCCM 2017

<table>
<thead>
<tr>
<th>Days 0-1</th>
<th>Days 2-3</th>
<th>Days 4-7</th>
<th>&gt;7 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not related to sepsis</td>
<td>Resp/other</td>
<td>Neuro</td>
<td>MODS</td>
</tr>
</tbody>
</table>

Post-sepsis immune suppression

Multiorgan failure in critical illness

“Immune paralysis”, lymphopenia

ALC < 1000 x 7 days predicted mortality; deaths from HAI

Feinert J Imm 2005

Secondary infection & late mortality

Low TNFα associated with increased & persistent HAI, mortality

Hall ICM 2011
In summary…

- Focus on **early identification** of the septic patient & **early resuscitation**
  - Early IV access (IO)
  - IV fluid (20 ml/kg x 3) + antibiotics **within 1 hour**
  - Peripheral epinephrine (norepinephrine) next
  - A protocol might help
- **Reevaluate frequently!**
- Children recovering from septic shock are not out of the woods
  - Multiorgan failure & **immune suppression**

Thank you!
References


