Paediatric Septic Shock-
towards early goal directed therapy

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Paediatric Acute Care 2011 Conference
Outline

- Rivers Protocol (EGDT)
- ACCM Sepsis Protocol
  - Evidence
- Barriers to implementation
- Future considerations
EGDT

- **Rivers Protocol**
  - Adult study of 263 patients in septic shock
  - Compared “standard care” with targeted care (CVP, MAP, Hb, ScvO2) over first 6 hours
  - Reduction in mortality from 46.5% to 30.5%
  - EGDT group received more fluid in first 6 hours (no difference at 72 hours) more PRBC and more inotr
  - First study to show that EARLY and TARGETED therapy in septic shock improves outcome

Rivers et al NEJM Nov 2001
Concerns re:

- Adequacy of CVP as a marker of volume responsive low cardiac output

- Liberal fluid resuscitation a risk factor for ALI/ARDS?
  - No difference rate of early intubation between EGDT and control, fewer late intubation in EGDT

- High transfusion rate (64% vs 19% in control)- ? Risk for nosocomial infection, ALI, mortality

- Low ScvO2 (49%), high mortality (46.5%) in control group
Emergency Department

Schmidt Chest 2010
Insufficient validation reflected in current studies:

- ARISE- Australasian Resuscitation in Sepsis Evaluation n=1600
- ProCESS- Protocolized Care for Early Septic Shock n=1935
- ProMISE- Protocolised Management of Sepsis n=1260
Rivers protocol applicable to Paediatrics?

- Central line often not inserted during initial resuscitation- CVP, ScvO2 unknown
- Optimal Hb in paediatric septic shock unknown
- Pathophysiology of sepsis different in children- myocardial dysfunction more common than vasomotor dysfunction
- Showed early and goal directed resuscitation improved survival in adult septic shock- what goals should be targetted in paediatrics?
Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine*

- **Update 2002 practice parameter**
  - Based on “best clinical practice” and expert opinion

- **Incorporates evidence for**
  - Validity, efficacy of 2002 guideline
  - New treatment and outcome studies

* Brierly Crit Care Med 2009
Emphasis

First Hour (ED)
- Fluid/ inotrope therapy targeting HR, BP, CR, conscious state

Subsequent (ICU)
- Haemodynamic support targeting ScvO2 >70%, CI 3.3-6.0 L/Min/m²
Changes

- Advocate initiation of inotropes peripherally (not vasopressors)
- Ketamine for invasive procedures (etomidate discouraged)
- CO measurement with doppler echo, pulse index contour, FA thermodilution (vs PA catheter)
- Rescue therapies (levosimendan)
- Early fluid removal following resuscitation
Emergency Department

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

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

15 min
If 2nd PIV start inotrope.

60 min
Fluid refractory shock: Begin inotrope IV/IO. use atropine/ketamine IV/IO/IM to obtain central access & airway if needed. Reverse cold shock by titrating central dopamine or, if resistant, titrate central epinephrine. Reverse warm shock by titrating central norepinephrine.

Catecholamine resistant shock: Begin hydrocortisone if at risk for absolute adrenal insufficiency

Monitor CVP in PICU, attain normal MAP-CVP & ScvO₂ > 70%

Cold shock with
normal blood pressure:
1. Titrate fluid & epinephrine, ScvO₂ > 70%, Hgb > 10 g/dL
2. If ScvO₂ still < 70%
Add vasodilator with volume loading (nitrates, vasodilators, midriamprolone, imipramine, & others)
Consider levosimendan

Cold shock with
low blood pressure:
1. Titrate fluid & epinephrine, ScvO₂ > 70%, Hgb > 10 g/dL
2. If still hypotensive consider norepinephrine
3. If ScvO₂ still < 70%
Consider dobutamine, milrinone, enoximone or levosimendan

Warm shock with
low blood pressure:
1. Titrate fluid & norepinephrine, ScvO₂ > 70%
2. If still hypotensive
consider vasopressor, terlipressin or angiotensin
3. If ScvO₂ still < 70%
Consider low dose epinephrine

Persistent catecholamine resistant shock: Rule out and correct pericardial effusion, pneumothorax, & intra-abdominal pressure >12 mm Hg. Consider pulmonary artery, PICCO, or FAD catheter, &/or doppler ultrasound to guide fluid, inotrope, vasopressor, vasodilator and hormonal therapies.
Goal C.I. > 3.3 & < 6.0 L/min/m²

Refractory shock: ECMO
0 min

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

5 min

If 2nd PIV start inotrope.

Recognize decreased mental status and perfusion. Begin high flow O₂. Establish IV/IO access.
Evidence for early aggressive fluid resuscitation

- 34 patients correlating volume of fluid administered at 1 and 6 hours with survival
  - Group 1 (<20ml/kg) - 11ml/kg at 1 hour and 71ml/kg at 6 hours (43% survived)
  - Group 2 (20-40ml/kg) - 32ml/kg at 1 hour and 108ml/kg at 6 hours (36% survived)
  - Group 3 (>40ml/kg) - 69ml/kg at 1 hour and 117ml/kg at 6 hours (89% survived)
- No increased risk of ARDS with more volume

Carcillo JAMA 1991
Similar total volume of fluid administered at 6 hours in groups 2 and 3, suggesting that EARLY administration improves survival
Retrospective transport database review over 9 year period

91 paediatric patients with clinical septic shock

Shock reversal = normal SBP and CR

9-fold improved odds of survival with early shock reversal (PRISM adjusted)

Every hour of ongoing shock associated with 2x increased risk mortality (PRISM adjusted)

Initial resuscitation greatest impact on survival
Early aggressive fluid resuscitation improves survival
How much fluid to administer

- PALS/ ACCM- “until rales or hepatomegaly develop”
- Other methods of volume assessment
  - Clinical (HR, CR, LOC, u/o)
  - CVP
  - Passive leg raise / hepatic palpation
  - Arterial pulse pressure variation
  - IVC ultrasound
  - echo
What Fluid- crystalloid vs colloid

- 17 studies, 1977 participants
- Albumin reduced risk of mortality in sepsis

(pooled OR 0.82
95% CI 0.67-1.0 p=0.47)
Colloid may improve survival (but is more expensive)
Evidence for early antibiotic administration

- Retrospective adult cohort study, 2154 patients
- Survival 80% with adequate antimicrobial administration within 1 hour of hypotension
- Each hour delay associated with an increased risk of mortality of 7.6%

Kumar Crit Care Med 2006
Early antibiotics improve survival
**Fluid refractory shock:** Begin inotrope IV/IO.
use atropine/ketamine IV/IO/IM
*to obtain central access & airway if needed.*

*Reverse cold shock* by titrating central dopamine
or, if resistant, titrate central epinephrine

*Reverse warm shock* by titrating central norepinephrine.

**dose range:**
dopamine up to 10 mcg/kg/min,
epinephrine 0.05 to 0.3 mcg/kg/min.
<table>
<thead>
<tr>
<th>Hypovolemic Causes</th>
<th>MAP, SVR</th>
<th>Volume CVP, SSV</th>
<th>Flow CO, ScvO₂</th>
<th>Lactate</th>
<th>Treatment and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypovolemia</td>
<td>Variable</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>Volume</td>
</tr>
<tr>
<td>Compensated and vasodilatory</td>
<td>↓</td>
<td>Normal</td>
<td>↑</td>
<td>Variable</td>
<td>Vasopressors, Adrenal Dysf.</td>
</tr>
<tr>
<td>Myocardial Suppression</td>
<td>Variable</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>Correct anemia, Inotropic Therapy</td>
</tr>
<tr>
<td>Impairment of tissue O₂ utilization</td>
<td>Variable</td>
<td>Normal</td>
<td>↑</td>
<td>↑</td>
<td>Vasodilators, r-APC</td>
</tr>
</tbody>
</table>
Which inotrope to use

- Recommendations (grade 2C):
  - Initial: dopamine
  - For cold shock: epinephrine
  - For warm shock: norepinephrine

- Special circumstances:
  - Low CO/ high SVR: dobutamine / phosphodiesterase inhibitor
Catecholamine resistant shock: Begin hydrocortisone if at risk for absolute adrenal insufficiency.
Steroids in sepsis

- 300 adult patients in septic shock
- Randomised to long course (7 days) of low dose (50mg q6) hydrocortisone
- 28 day mortality in patients unresponsive to corticotropin stimulation test 63% placebo 53% steroid
- No mortality difference in responders

Annane JAMA 2002
CORTICUS

- Hydrocortisone therapy for adult patients in septic shock
- N = 499
- 47.6% had no response to corticotropin
- Hydrocortisone did not improve survival or reversal of shock (even in non-responders to corticotropin)

NEJM 2007
Corticosteroids for treating severe sepsis and septic shock (Review)

- No benefit overall
  - Mortality benefit from low dose long course steroid

- Problem - heterogeneity of dosing regimes

- Increased risk of hyperglycaemia

Annane 2010
Higher incidence of adrenal insufficiency in children?

- 78 children with vasopressor dependent shock
- Absolute adrenal insufficiency 56%
- Reduced inotrope requirement post steroid supplementation
- Impact on mortality unreported

Hebar Crit Care Med 2011
No evidence for survival benefit from steroids in septic shock

Potential benefit from low dose / long course steroids in corticotropin stimulation non-responders
Monitor CVP in PICU, attain normal MAP-CVP & ScvO₂ > 70%.

**Cold shock with normal blood pressure:**
1. Titrate fluid & epinephrine, ScvO₂ > 70%, Hgb > 10g/dL
2. If ScvO₂ still < 70%
Add vasodilator with volume loading (nitrosovasodilators, milrinone, imrinone, & others)
Consider levosimendan

**Cold shock with low blood pressure:**
1. Titrate fluid & epinephrine, ScvO₂ > 70%, Hgb > 10 g/dL
2. If still hypotensive consider norepinephrine
3. If ScvO₂ still < 70% consider dobutamine, milrinone, enoximone or levosimendan

**Warm shock with low blood pressure:**
1. Titrate fluid & norepinephrine, ScvO₂ > 70%,
2. If still hypotensive consider vasopressin, terlipressin or angiotensin
3. If ScvO₂ still < 70% consider low dose epinephrine
Therapeutic end points

- ScvO2 (SfvO2 adequate?)
- Lactate
- Lactate clearance
ScvO2 vs SfvO2

- N=39
- Mean ScvO2 73.1%
- Mean SfvO2 69.1
- > 50% diverged > 5%

- SfvO2 does NOT correlate well with ScvO2
Should ScvO2 > 70% be a target for resuscitation

- 102 children in septic shock randomised to ScvO2 directed therapy or not
- 28 day mortality 11.8% in directed group, 39.2% in control group
- More crystalloid, blood, inotropic support in ScvO2 directed group

Oliveira Int Care Med 2008
- Mortality difference more marked in ScvO2 <70% subgroup

Utility in discriminating high risk patients
Lactate clearance as a therapeutic target

- 300 adult patients with septic shock randomised to ScvO2 targeted care or lactate clearance targeted care
- Mortality targeting ScvO2 > 70%: 23%
- Mortality targeting lactate clearance >10%: 17%

Lactate clearance is a valid therapeutic end-point

Jones JAMA 2010
What is optimal Hb

- In stable patients resuscitated from septic shock:
  \[ \text{Hb} > 70 \]

- In unstable patients being actively resuscitated:
  \[ \text{Hb} > 100 \]
Persistent catecholamine resistant shock: Rule out and correct pericardial effusion, pneumothorax, & intra-abdominal pressure >12 mm/Hg. Consider pulmonary artery, PICCO, or FATD catheter, &/or doppler ultrasound to guide fluid, inotrope, vasopressor, vasodilator and hormonal therapies.

Goal C.I. > 3.3 & < 6.0 L/min/m²

shock not reversed?

Refractory shock: ECMO
Emergency Department

- Retrospective case series
- 45 patients on VA ECMO for septic shock (40% cardiac arrest prior to cannulation)
- 21 (47%) survived to hospital discharge
- Central cannulation associated with improved survival (73% vs 44%)
- None had severe disability on long term follow-up

Maclaren PCCM 2007
Summary of ACCM guideline

- Early, aggressive fluid resuscitation (consider colloid)
- Early antibiotics
- Therapeutic end-points: ScvO2 or lactate/ lactate clearance
- Hb >100
- ? benefit from low dose long course steroids
- Inotrope: dopamine then epinephrine for cold shock and norepinephrine for warm shock
Emergency management of children with severe sepsis in the United Kingdom: the results of the Paediatric Intensive Care Society sepsis audit

D P Inwald,1 R C Tasker,2 M J Peters,3 S Nadel,4 on behalf of the Paediatric Intensive Care Society Study Group (PICS-SG)

- Audit of 17 PICU’s
- 107 patients with septic shock
- 8% received care c/w ACCM guideline
  - 21% not given >60ml/kg despite ongoing shock
  - 15% not given dopa/ dobu despite fluid refractory shock
  - 23% not given catechol for dopa/ dobu refractory shock
  - 30% not given steroid despite catechol resistant shock

Inwald Arch Dis Child 2009
Why is implementation so poor?

- Cognitive barriers
  - Is severe sepsis seen as a problem
  - Has there been adequate dissemination of guideline
  - Are goals of ACCM guideline achievable
  - Are we practicing “informed skepticism”

- Process barriers
  - Shock recognition
  - Systems barriers
Lack of recognition of early shock

Lack of adequate vascular access

Shortage of health care providers
  • 2 nurses for 15 (25) patients in ED, 2 for 13 in PICU

Non-use of goals and treatment protocols
Future Directions

- Institutional audit
- Triage tool for early shock recognition
- Early senior staff review
- Tiered approach- non-invasive and invasive clinical pathways
- Collaboration / frequent review
Implementation of Goal-Directed Therapy for Children With Suspected Sepsis in the Emergency Department

- Implementation of sepsis protocol in ED
  - Triage sepsis recognition tool
  - Improved staffing of resuscitation area
  - Prioritisation of antibiotic
  - Improved graphic vital sign monitoring
- Decreased time to first bolus (56 to 22 min)
- Decreased time to antibiotic administration (130 to 38 min)
Questions?
Impact of FEAST

- Mortality after fluid bolus in African Children with severe infection (n=3141)
  - Mortality 10.5% with fluid bolus, 7.3% in standard maintenance fluid group
- Issues:
  - Patient selection
    - 57% malaria parasitaemia, 32% Hb <50
    - 83% respiratory distress, 25% SaO2 <90%
  - Diagnosis of shock
    - One of: severe tachycardia, CR > 3 sec, LL temp gradient, weak rad pulse volume

Maitland NEJM 2011
Treating the wrong children with fluid bolus’ will cause harm

Results of the FEAST Trial should not lead to a change in current practice of fluid bolus administration for septic shock