Septic Shock and MOF in Newborns and Children

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Outcome from Severe Sepsis: Kids do Better than Adults

Mortality Rate

- 0-1 y
- 5-10 y
- 15-20 y
- 25-30 y
- 35-40 y
- 45-50 y
- 55-60 y
- 65-70 y
- 75-80 y

Mortality Rate
Improving Outcomes from Pediatric Shock with Continuous Innovation

- 1968 Univ Minn
- 1985 NCMC
- 1999 U.S.
- 2000 St Mary's U.K.

Mortality
Pediatric Mortality Absent If Normal MAP-CVP and Capillary Refill (< 3 sec) Attained in the First Hour

(Han et al, Pediatric Research, 108a, Volume 47(4)2000)

<table>
<thead>
<tr>
<th># Nonsurvivors/#Patients (Mortality%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>74 min</td>
</tr>
<tr>
<td>116 min</td>
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<tr>
<td>166 min</td>
</tr>
</tbody>
</table>

| Shock Present | 17/57 (30%) | 13/44 (30%) | 13/51 (25%) |
| Shock Absent  | 0/27 (0%)*  | 4/40 (10%)  | 4/33 (12%)  |

Less than 25% (13/57) of patients in shock at the time of team arrival had received appropriate therapy as
Adult Mortality Reduced by 50% when SVC O₂ sat maintained > 70% in the first 6 hours (Rivers et al. NEJM 2001)

Fluids/pressors used to maintain normal MAP-CVP in treatment and Control Groups
If SVC O₂ sat < 70% then treatment group given pRBCs if Hgb < 10 gm/dL and/or Dobutamine if Hgb > 10 gm/dL

What CI does SVC O₂ sat > 70% (Rivers et al NEJM, 2001) represent?

Oxygen consumption = CI (SaO₂-MVO₂) x 1.36 x %Hgb

\[135 = 3.3 \times (100-70) \times 1.36 \times 10\]
\[\text{to}\]
\[244 = 6.0 \times (100-70) \times 1.36 \times 10\]
Hemodynamics Predict Pediatric Septic Shock Outcomes!

• Pollack reported 57% mortality (CCM 1985)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Range</th>
<th>Percent Survival Within Range(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI</td>
<td>3.3–6.0(^b)</td>
<td>67</td>
</tr>
<tr>
<td>WP</td>
<td>&lt;11.3(^c)</td>
<td>69</td>
</tr>
<tr>
<td>Qsp/Qt</td>
<td>&lt;12(^c)</td>
<td>69</td>
</tr>
<tr>
<td>VO(_2)</td>
<td>&gt;200(^b)</td>
<td>75</td>
</tr>
<tr>
<td>C(a-(\bar{v}))(_O(_2))</td>
<td>&gt;5.50(^b)</td>
<td>71</td>
</tr>
<tr>
<td>O(_2) Extr</td>
<td>&gt;.28(^b)</td>
<td>59</td>
</tr>
<tr>
<td>pH</td>
<td>&gt;7.40(^c)</td>
<td>69</td>
</tr>
<tr>
<td>Core temp</td>
<td>≥37.0(^b)</td>
<td>58</td>
</tr>
</tbody>
</table>

\(^a\) Percent survival for all patients was 43%.

\(^b\) Range determined from distributions using normal values.

\(^c\) Range determined from distributions about survivor medians.
Fluid Resuscitation
Fluid Resuscitation Decreases Inflammation

• Mouse cecal ligation and puncture has attenuated TNFα and IL-1β mRNA expression with fluid bolus (crystalloid better than serum) (Wilson et al J Trauma 41, 1996).

• Septic shock patients given HES infusions have reduced levels of soluble adhesion molecules compared to albumin or pentoxifylline treated (Boldt et al Crit Car Med 24, 1996).
Fluid Increases CO and Survival in Experimental Sepsis

- Endotoxin and bacteria shock models only achieve a hyperdynamic state after 60 cc/kg volume bolus (Carrol et al Am J Physiol 243, 1982)
Fluid Resuscitation Decreases Inflammation

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Fluid Increases O$_2$ Consumption in Adult Septic Shock

**Figure 1.** Effect of increases in oxygen delivery (\(\dot{D}O_2\)) on oxygen consumption (\(\dot{V}O_2\)) in five patients with hypovolemic shock.

**Figure 2.** Effect of increases in oxygen delivery (\(\dot{D}O_2\)) on oxygen consumption (\(\dot{V}O_2\)) in eight patients with septic shock.
Historical Perspective

- In the past, 20 cc/kg recommended as maximum bolus in pediatric septic shock due to two concerns with potential harm from vigorous volume resuscitation:
  1) Fear of pulmonary edema
  2) Fear of SIADH in concomitant meningitis
Role of Early Fluid Resuscitation in Pediatric Septic Shock

(Carcillo et al JAMA 266, 1991)

• 34 patients in ED over 6 year period with septic shock and PAC at 6 hours.

• Evaluated amount of fluid resuscitation and relation to following outcome variables: cardiogenic pulmonary edema, non-cardiogenic pulmonary edema, persistent hypovolemic, and survival
Epidemiology

- Overall mortality rate was 47%
- 82% ventilator supported by 6 hrs
- 100% inotrope/vasopressor by 6 hrs
- 33 ml/kg volume (9 ml/kg colloid) at 1 hr
- 95 ml/kg volume (37 ml/kg colloid) at 6 hrs
## Fluid Resuscitation

### Table 2. Fluid Administration

<table>
<thead>
<tr>
<th></th>
<th>1 h (mean ± SD)</th>
<th>6 h (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 14; &lt;20 mL/kg in 1 h)</td>
<td>11 ± 6*</td>
<td>71 ± 29†</td>
</tr>
<tr>
<td><strong>Group 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 11; 20-40 mL/kg in 1 h)</td>
<td>32 ± 5*</td>
<td>108 ± 54</td>
</tr>
<tr>
<td><strong>Group 3</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 9; &gt;40 mL/kg in 1 h)</td>
<td>69 ± 19*</td>
<td>117 ± 29</td>
</tr>
<tr>
<td><strong>All patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 34)</td>
<td>33 ± 26</td>
<td>95 ± 42</td>
</tr>
<tr>
<td><strong>Survivors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 18)</td>
<td>42 ± 28‡</td>
<td>97 ± 49</td>
</tr>
<tr>
<td><strong>Nonsurvivors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 16)</td>
<td>23 ± 18</td>
<td>94 ± 37</td>
</tr>
</tbody>
</table>

*P<.05, comparing the mean volume administered at 1 hour in each group to the other groups.
†P<.05, comparing the mean volume administered at 6 hours in group 1 to group 2 or group 3.
‡P<.05, mean volume administered in first hour in survivors compared with nonsurvivors.
60 cc/kg Fluid Associated with 90% Survival!

- 0-20 cc/kg had increased hypovolemia and mortality of 68% (Similar to Pollack et al, 1987)
- > 40 cc/kg (mean 60 cc/kg) eliminated hypovolemia, improved survival and no increased incidence of pulmonary edema or herniation syndromes.
Outcomes

Fig 1.—The distribution of survivors and nonsurvivors within fluid resuscitation groups (see text for definition of groups). The asterisk indicates a significant difference in survival between group 3 and groups 1 and 2 individually and combined.
Outcomes

Table 3.—Occurrence of Persistent Hypovolemia by Fluid Resuscitation Group

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=14)</th>
<th>Group 2 (n=11)</th>
<th>Group 3 (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent hypovolemia at 6 h</td>
<td>6*</td>
<td>2*</td>
<td>0</td>
</tr>
<tr>
<td>Deaths in patients with persistent hypovolemia</td>
<td>6</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Not hypovolemic at 6 h</td>
<td>8</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Deaths in nonhypovolemic patients at 6 h</td>
<td>2</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Total deaths</td>
<td>8</td>
<td>7</td>
<td>1</td>
</tr>
</tbody>
</table>

*All patients with persistent hypovolemia died, but they did not succumb to refractory hypovolemia since all patients had a pulmonary capillary wedge pressure of more than 8 mm Hg after 6 hours.
Conclusions

• Repeated 20 ml/kg fluid boluses may be administered in excess of 60 ml/kg in the first hour and 120 ml/kg in the first 6 hours if BP, pulses, mental status, and urine output suggest that perfusion is decreased.

• Intravascular monitoring may be necessary to diagnose hypovolemia, NCPE, and CPE.
Pediatric Fluid Resuscitation After the First 6 Hours

• Feltes et al performed echocardiography on 5 children with hemodynamically stable sepsis and 10 children with shock (Crit Care Med 22, 1994).

• All 5 hemodynamically stable patients had normal performance, contractility, and preload. 3 of 5 had increased afterload.
Pediatric Fluid Resuscitation After the First 6 Hours

• Of the 10 patients with septic shock 4 had decreased contractility and increased afterload, 1 had decreased afterload, and 1 had a severe preload deficit.

• Despite aggressive volume resuscitation 6 of 10 had diminished preload. Ventricular loading abnormalities persisted in 5 of 10 patients for 3 to 6 days.
Inotrope, vasopressor, and vasodilator support for fluid refractory shock
Cardiovascular therapy improves outcome in experimental fluid refractory shock

- Inotropes and antibiotics improve outcome in experimental sepsis (Natanson et al, 1990)
- Inotropes and vasopressors increase IL-10 and reduce inflammation through cAMP effects. (Vincent et al, 1997)
Cardiovascular support improves experimental outcome

Percentage of survivors in all 4 treatment groups over time.

A MAP

- Cardiovascular Support Alone
- Combined Cardiovascular Support and Antibiotics
- Antibiotics Alone

B PCWP

Hours Post Surgery: Pre 0 2 8 14 20 26 30
Fluid Refractory Pediatric Septic Shock

- Volume resuscitated sepsis patients
  a) required inotropes/vasopressors by 6 hours (Carcillo et al JAMA 266, 1991)
  b) showed decreased contractility (4 of 10) (Feltes et al Crit Care Med 22, 1994)
- Volume resuscitated severe pediatric burn patients show inotrope-dependent reduced LVSWI (Reynolds et al J Pediatr Surg 30, 1995)
Fluid Refractory Pediatric Septic Shock

- Despite aggressive volume resuscitation, shock may persist secondary to cardiac and vascular dysfunction.
- Inotropes, vasopressors, and/or vasodilators are required in fluid refractory pediatric septic shock.
Hemodynamic Support in Fluid Refractory Pediatric Shock

- 50 children with septic shock refractory to > 60 cc/kg volume with PCWP > 8 and functioning PAC at 6 hr to 48 hr (3 centers, 4 year recruitment, 11 deaths) (Ceneviva et al Pediatrics 102:1998)

- Evaluated need of inotrope, vasopressor, and or vasodilator therapy to reverse shock at presentation and over the first 48 hours.
Goal directed therapies

- Reversal of clinical shock and maintenance of MAP-CVP appropriate for age.
- If unsuccessful then:
  - CI > 3.3 and < 6.0 L/min/m²
  - SVRI > 800 dyne-sec/cm⁵/m²
  - SVRI < 1600 and > 800 dyne-sec/cm⁵/m² if CI < 3.3 L/min/m²
Initial Therapies Needed to Overcome Fluid Refractory Shock at Presentation

• 18 % required a change in regimen from inotrope to vasopressor, or vasopressor to inotrope
• 24 % required catecholamines for dopamine or dobutamine refractory shock
• 16 % required the addition of vasodilator therapy
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Therapeutic changes guided by initial PAC variables

<table>
<thead>
<tr>
<th>Added Vasodilator</th>
<th>Added Catecholamines</th>
<th>Changed Therapy Regimen</th>
<th>Increased Class of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I: Nitroprusside</td>
<td>n = 3 Epinephrine</td>
<td>Changed from vasopressor to inotrope</td>
<td>n = 8 Increased or added new inotrope</td>
</tr>
<tr>
<td>Group II: Norepinephrine</td>
<td>n = 3</td>
<td>Changed from inotrope to vasopressor</td>
<td>n = 4 Increased or added new vasopressor</td>
</tr>
<tr>
<td>Group III: n = 4 Epinephrine</td>
<td>n = 2 Norepinephrine</td>
<td>Changed from inotrope alone or vasopressor alone to inotrope and vasopressor</td>
<td>n = 1 Increased inotrope</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>n = 2 Increased vasopressor</td>
</tr>
</tbody>
</table>
# Cardiovascular Agents

<table>
<thead>
<tr>
<th></th>
<th>Inotrope (µg/kg/min)</th>
<th>Vasopressor (µg/kg/min)</th>
<th>Vasodilator (µg/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dobutamine</td>
<td>11.2 ± 1.6 [5–40] (n = 26)</td>
<td>16 ± 1.2 [12–20] (n = 13)</td>
<td></td>
</tr>
<tr>
<td>Dopamine</td>
<td>4.9 ± .92 [4–8] (n = 11)</td>
<td>.48 ± .22 [0.3–2.0] (n = 9)</td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td>0.13 ± .04 [.05–.2] (n = 9)</td>
<td>.56 ± .35 [0.1–3.0] (n = 8)</td>
<td>2.2 ± .7 [0.1–5.0] (n = 8)</td>
</tr>
</tbody>
</table>

Mean ± SEM [range]; n = patients. Amrinone (n = 2), milrinone (n = 1), isoproterenol (n = 1), phenylephrine (n = 1), phentolamine (n = 1), and nitroglycerin (n = 1) were also used.

* Dopamine inotrope range, 5–10; vasopressor range, >10 µg/kg/min.

^ Epinephrine inotrope range, <0.3 µg/k/min or >0.3 µg/k/min in presence of vasodilator.
Low Cardiac Output Syndrome and High SVR is predominant in Fluid Refractory Shock

- 58% had a low CI (< 3.3 L/ min/m²) and high SVRI (> 1600 dyne-sec/cm⁵)
- Only 20% had a high CI and low SVRI.
- Kids are different from adults!
Effect of Therapy on Hemodynamics

<table>
<thead>
<tr>
<th></th>
<th>After Fluid Resuscitation</th>
<th>After Initial Therapy Adjustment</th>
<th>48 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group I (n = 29)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CI</td>
<td>3.06 ± .26</td>
<td>3.3 ± .16*</td>
<td>4.0 ± .2**</td>
</tr>
<tr>
<td>SVRI</td>
<td>1794 ± 176</td>
<td>1758 ± 158*</td>
<td>1178 ± 65**</td>
</tr>
<tr>
<td><strong>Group II (n = 10)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CI</td>
<td>8.51 ± 1.1</td>
<td>6.3 ± .75</td>
<td>5.06 ± .41**</td>
</tr>
<tr>
<td>SVRI</td>
<td>622 ± 184</td>
<td>919 ± 99</td>
<td>1090 ± 91**</td>
</tr>
<tr>
<td><strong>Group III (n = 11)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CI</td>
<td>3.93 ± .28</td>
<td>4.37 ± .26</td>
<td>5.07 ± .29**</td>
</tr>
<tr>
<td>SVRI</td>
<td>922 ± 87</td>
<td>904 ± 65</td>
<td>1089 ± 92</td>
</tr>
</tbody>
</table>

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).
Progressive Myocardial Dysfunction was the Predominant Cause of Persistent Shock

- Over 48 hours, the children with initial low CI required the addition of vasodilators and the children with initial high CI required inotropes to maintain CI > 3.3.
- Over 90% of children with persistent shock (n = 18) required inotrope and vasodilator therapy
Progressive myocardial dysfunction

Inotrope
Vasodilator
Vasopressor

Day 1  Day 3
Recurrent or Persistent Shock can also be caused by a complete change in hemodynamic state

• 10% of children showed a complete change in hemodynamic state from inotrope to vasopressor or vasopressor to inotrope therapy requirements.

• This observation is supported by experimental models (Hoban et al, 1991)
Changes in Cardiovascular Therapies Required over time

- **Group I Day 1**
- **Day 3**
- **Group II Day 1**
- **Day 3**
- **Group III Day 1**
- **Day 3**

- **inotrope**
- **inotrope + vasodilator**
- **vasopressor**
- **inotrope + vasopressor**
Catecholamine Refractory shock

• 20 % of patients were catecholamine and nitrosovasodilator refractory.
• These patients responded to the addition of a) hydrocortisone therapy (n = 5) b) PDE type III inhibitors (n = 4) c) vasopressin (n = 1)
• ECMO was used in two refractory shock patients.
Catecholamine Refractory Shock and Adrenal Insufficiency

- Risk Factors include a) Purpura Fulminans and b) History of Prior Chronic Steroid Use.
- 52% of 33 children (n =16 meningococcus) with septic shock had AI (Hatherill et al CCM 26,1998)
- 27% of 97 children with sepsis showed adrenal infarction/hemorrhage at autopsy (Amoo-Lamptey, unpublished)
Catecholamine Refractory Shock and Adrenal Insufficiency

• Adrenal shock is indistinguishable from septic shock ie low CI/ high SVR, or high CI/ low SVR state (Bouachor et al, Intens Care Med 20,1994) so should be diagnosed by ACTH stimulation or risk factors

• Hydrocortisone 50 mg/kg (AHFS 1998, Sumarmo et al Pediatr 69, 1982) or less?
Mechanism of Catecholamine Insensitivity

• LPS reduces β-receptor stimulated accumulation of cAMP. Forskolin bypasses this defect suggesting receptor, G-protein or PDE effects of LPS (Shepherd et al 1986, Campbell et al 1993)

• Increased catecholamine levels and need for doubling of catecholamine infusions in patients suggests receptor desensitization (Kovarik et al 1987, Reithman et al 1989)
Low CO syndrome reversible with PDE III inhibitors

• Children are less responsive to dopamine and dobutamine and may require epinephrine. (Perkin et al 1982)

• The inodilators milrinone (Barton et al 1996, Linsay et al 1998) and amrinone (Irazusta et al 2000) improve CI in catecholamine refractory, and catecholamine and nitrosovasodilator refractory shock (Ceneviva et al 1998)
Inotrope Therapies

Systole

Ca++

Diastole

Ca++

Gi

Gs

AC

β

cAMP

Phosphodiesterase (PDE)
ECMO is effective rescue for Low CO syndrome

- ECMO reduces mortality in refractory neonatal septic shock to 20%. (Meyer et al 1995)
- ECMO reduces mortality in refractory pediatric septic shock to 50%. (Goldman et al 1997, Beca et al 1994)
- ECMO rescues adult Hantavirus victims (Low CO/ high SVR syndrome) (Hallin et al 1996, Crowley et al 1998)
Mechanism of Vascular Catecholamine Insensitivity

• LPS reduces vascular α receptor numbers and phosphoinositide second messenger production. (Carcillo et al 1988, Deaciuc et al 1987)
• Norepinephrine reverses dopamine-resistant vascular failure
• Vasopressin reverses norepinephrine resistant vascular failure.
Vasoconstrictors and Dilators

**Inodilators**
- Prostacyclin

**Alpha agonists**
- Vasopressin
- Angiotensin

**Nitrosovasodilators**
- cGMP

**Second messengers**
- cAMP: (-)
- IP₃: (+)
- DAG: (+)
- Ca²⁺: ++
- cGMP: (-)
Reduced CO syndrome not vasoplegia was associated with mortality

• The overall survival rate was 80%, 72% in children with low CI and 90% in children with high CI.

• This survival rate compared favorably to that reported by Pollack et al when 60 cc/kg fluid resuscitation and goal directed therapy was not practiced.
Outcome of Fluid Refractory Shock with Goal Directed Hemodynamic Support

Graph showing survival rates for different groups:
- Group I
- Group II
- Group III
- Pollack et al. 1985

The y-axis represents survival rates ranging from 0 to 100, and the x-axis represents the groups.
Conclusions

• Unlike adults, children with fluid refractory shock are frequently hypodynamic and respond to inotrope and vasodilator therapy.

• Because hemodynamic states are heterogeneous and change with time, an incorrect cardiovascular therapeutic regimen should be suspected in any child with persistent shock.
Conclusions

• PAC indicated in a subgroup of children with fluid refractory septic shock (Zaritsky, Current Concepts in Pediatric Emergency and Critical Care)

• Outcomes can be improved when 60 cc/kg fluid resuscitation and goal-directed cardiovascular therapy is applied.
**Figure 1** Stepwise management of hemodynamic support with goals of normal perfusion and perfusion pressure (MAP-CVP) in infants and children with septic shock. Proceed to next step if shock persists.

0 min
- Recognize decreased mental status and perfusion.
- Maintain airway and establish access according to PALS guidelines.
- Push 20cc/kg isotonic saline or colloid boluses up to and over 60 cc/kg
- Correct hypoglycemia and hypocalcemia

5 min
- Fluid responsive
- Establish central venous access, begin dopamine therapy and establish arterial monitoring.

15 min
- Fluid refractory shock
- Fluid refractory-dopamine resistant shock
- Titrate epinephrine for cold shock, norepinephrine for warm shock to normal MAP-CVP and SVC O2 saturation > 70%

60 min
- At Risk of Adrenal Insufficiency? Catecholamine-resistant shock
- Not at Risk?
- Give hydrocortisone
- Do not give hydrocortisone

**Normal Blood Pressure**
- Cold Shock
- SVC O2 sat < 70%
- Add vasodilator or Type III PDE inhibitor
- Norepinephrine with volume loading

**Low Blood Pressure**
- Cold Shock
- SVC O2 sat < 70%
- Titrate Volume and Epinephrine

**Persistent Catecholamine-resistant shock**
- Place pulmonary artery catheter and direct fluid, inotrope, vasopressor, vasodilator, and hormonal therapies to attain normal MAP-CVP and CI > 3.3 and < 6.0 L/min/m²

**Refractory shock**
- Consider ECMO
Figure 2  Stepwise management of hemodynamic support with goals of normal perfusion and perfusion pressure (MAP-CVP) and pre and post-ductal oxygen saturation difference <5%, and central venous O₂ sat > 70% in near term-newborns with septic shock.

0 min
Recognize decreased perfusion, cyanosis, RDS.
Maintain airway and establish access according to NRP guidelines.

5 min
Push 10cc/kg isotonic crystalloid or colloid boluses to 60 cc/kg, correct hypoglycemia, and hypocalcemia. Begin prostaglandin infusion until echocardiogram shows no ductal-dependent lesion.

15 min
Fluid-responsive
Establish Central Venous and Arterial Access
Titrate dopamine and dobutamine

Fluid refractory-dopamine resistant shock
Titrate epinephrine. Systemic alkalinization if PPHN is present

Catecholamine-resistant shock

60 min
Cold shock
Normal blood pressure Poor LV function, CVC O₂ sat < 70%
Titrate vasodilator Type III PDE inhibitor with volume loading

Cold or Warm Shock Poor RV function PPHN, CVC O₂ sat < 70%
Inhaled nitric oxide

Refractory Shock
ECMO

Warm shock
Low blood pressure
Titrate volume and epinephrine (? Vasopressin or angiotensin)
Figure 3  Recommendation for stepwise management of hemodynamic support of shock in the first hour.

0 min
- Recognize shock, maintain airway, establish access.

5 min
- Liver up
  - Push 60 cc/kg fluid, consider hemorrhagic shock
- Liver Down
  - Push 10cc/kg isotonic crystalloid begin prostaglandin infusion (neonate only) and or dobutamine until echocardiogram r/o ductal-dependent lesion.

15 min
- Titrate epinephrine (if neonate with PPHN titrate NO)

60 min
- Cold shock
  - Normal blood pressure, SVC O$_2$ sat < 70%
  - Titrate vasodilator or Type III PDE inhibitor with volume loading
- Cold Shock with Low Blood Pressure, SVC O$_2$ sat < 70%
  - Titrated volume and epinephrine
- Warm shock
  - Low blood pressure
  - Titrated volume and norepinephrine (? Vasopressin or ? angiotensin)

Refractory Shock
- ECMO
What is the Pathophysiology of Sepsis Induced Multiple Organ Failure?

- No patients died from shock in the first 48 hours, instead all deaths occurred with MOF usually after 7 days.
- We performed a clinico-pathologic correlate study in two parts to determine the pathophysiology of sepsis-induced MOF in children admitted to the Children’s Hospital of Pittsburgh intensive care unit.
Methods Part I: Clinicopathologic Correlates

• One hundred children admitted to the PICU with sepsis and organ failure were enrolled with IRB and parental approval
• Plasma samples were attained on day 1 and 3 of sepsis
• Autopsies were performed on 11 of 13 children who died.

- A ten year search of the CHP pathology autopsy bank revealed 56 autopsies with a pre-mortem diagnosis of sepsis, 12 autopsies with a pre-mortem diagnosis of pneumonia without sepsis, and 21 autopsies with a pre-op diagnosis of organ failure without infection (lung failure n = 10, heart failure n = 4, liver failure n = 4, immune disease n = 2, metabolic disease n = 1)
Pro-inflammatory Cytokines and Nitric Oxide
White Cell Diapedesis
Thrombosis and Antifibrinolysis

Increased PAI-1

Decreased Thrombomodulin

Increased Tissue Factor
Inhibitory Anti-inflammatory Cytokine and WBC Apoptosis
Uncontrolled Infection

NO ONOO PARS Activation

Protein C ATIII IL-6 sFas
TF PAI-1 IL-10

APC

Unresolved Infection
Hypotheses

• Clinical correlates will show evidence of persistent inflammation and coagulation in children with persistent sepsis-induced MOF.

• Pathologic correlates will show increased evidence of persistent and unrecognized infection and thrombosis in children who die with sepsis-associated MOF.
Part I: Outcomes in sepsis-induced MOF at CHP-PICU

• < 3 organ failure - 96% survival
• Resolved ≥ 3 organ failure by day 3 - 88% survival
• Persistent ≥ 3 organ failure at day 3 - 65% survival
• Autopsy (11/13) showed that 10 children died of uncontrolled infection and 1 child died of thrombosis.
Day 1 of Sepsis
Day 3 of Sepsis
Uncontrolled Infection

NO  ONOO  PARS Activation

Protein C  ATIII  IL-6  sFas

IL-10

TF  PAI-1

APC

Unresolved Infection
Part II Autopsy Results (1988-1998)

* p < 0.05 sepsis vs pneumonia and organ failure without infection

<table>
<thead>
<tr>
<th>Pre-Mortem Diagnosis</th>
<th>Sepsis</th>
<th>Pneumonia</th>
<th>Organ Failure without Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-Mortem Infection</td>
<td>42/56 (75%)*</td>
<td>6/12 (50%)</td>
<td>1/21 (4.7%)</td>
</tr>
<tr>
<td>Systemic Thrombosis</td>
<td>46/56 (82%)*</td>
<td>4/12 (33%)</td>
<td>11/21 (52%)</td>
</tr>
<tr>
<td>Adrenal Pathology</td>
<td>17/56 (30%)*</td>
<td>0/12 (0%)</td>
<td>1/25 (2.5%)</td>
</tr>
</tbody>
</table>

- 60% persistent infection (pre-mortem = post-mortem)
- 40% unrecognized infection
- Gram (-) bacteria, candida, aspergillus, EBV, CMV.
- No gram positive bacteria
- Two meningococcus deaths (neither associated with infection at autopsy).
- Results similar in transplant and non-transplant patients.
- 10% (all groups) pulmonary embolus/thrombus
- 10% (all groups) myocardial infarction
- 10% (all groups) cerebral infarcts
- 5% (sepsis) DIC with fibrin microthrombi
- Adrenal pathology (sepsis) - hyperplasia (n = 2), atrophy (n = 5), infarcts/bleeding (n = 10)
Conclusion

• Pathologic correlates support persistent/unrecognized infection as the leading cause of death in children with sepsis-induced MOF in our PICU.
• Systemic thrombosis can contribute to mortality associated with organ failure with and without sepsis.
• Adrenal pathology is common only with sepsis-induced MOF.
Characterization of Pediatric MOF

- Thrombosis at autopsy
  Thrombocytopenia Associated MOF
- Infection at autopsy
  a) Unresolving MOF and prolonged monocyte deactivation
  b) Sequential MOF and EBV lymphoproliferative disease
  c) Prolonged Lymphopenia and Lymphoid Depletion Syndrome
Thrombocytopenia Associated MOF

• Platelet count less than 100,000 and 3 or greater organ failure

• Occurs with (20% of patients) and without (80% of patients) prolonged PT/PTT.
Homeostasis

Platelet

vWF

Platelet

vWF-CP

Platelet

vWF-CP

Endothelium

Platelet

vWF

tPA
Homeostasis

**TFPI**

**Heparin**

**ATIII**

**tPA**

**APC**

**Prot C**

**TFPI**

**Thrombomodulin**
vWF:Platelet Thrombus

- Platelet
- Fibrin
- Platelet
- Platelet
- Platelet
- Platelet
- vWF
- PAI-1
- tPA
- PAI-1
Endothelium

PAI-1

vWF

TF

PAI-1

vWF

PAI-1

vWF

TF

VII
Plasminogen → Plasmin

PAI-1

PAI-1

PAI-1

PAI-1
Specific Therapies

THROMBOSIS

Tissue Factor

(-)

TFPI

Prothrombin

(-)

Antithrombin III

Heparin

(-)

Thrombin

Fibrinogen

Fibrin

THROMBOSIS

Tissue Factor

(-)

TFPI

Prothrombin

(-)

Antithrombin III

Heparin

(-)

Thrombin

Fibrinogen

Fibrin

FIBRINOLYSIS

Plasminogen

TPA

Streptokinase

Urokinase

PAI-1

(-)

(+)

Plasmin

Aminocaproic Acid

Tranexamine

Aprotinin

FIBRINOLYSIS

Plasminogen

TPA

Streptokinase

Urokinase

PAI-1

(-)

(+)

Plasmin

Aminocaproic Acid

Tranexamine

Aprotinin

THROMBOSIS

Tissue Factor

(-)

TFPI

Prothrombin

(-)

Antithrombin III

Heparin

(-)

Thrombin

Fibrinogen

Fibrin

FIBRINOLYSIS

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TPA

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Urokinase

PAI-1

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(+)

Plasmin

Aminocaproic Acid

Tranexamine

Aprotinin

THROMBOSIS

Tissue Factor

(-)

TFPI

Prothrombin

(-)

Antithrombin III

Heparin

(-)

Thrombin

Fibrinogen

Fibrin

FIBRINOLYSIS

Plasminogen

TPA

Streptokinase

Urokinase

PAI-1

(-)

(+)

Plasmin

Aminocaproic Acid

Tranexamine

Aprotinin

THROMBOSIS

Tissue Factor

(-)

TFPI

Prothrombin

(-)

Antithrombin III

Heparin

(-)

Thrombin

Fibrinogen

Fibrin

FIBRINOLYSIS

Plasminogen

TPA

Streptokinase

Urokinase

PAI-1

(-)

(+)

Plasmin

Aminocaproic Acid

Tranexamine

Aprotinin
Non-specific therapies: Plasma infusion or exchange

- **Plasma Infusion**
  - Restores clotting factors (VII, VIII, X etc)
  - Restores vWF cleaving protease
  - Restores prostacyclin
  - Restores protein C and antithrombin III
  - Restores tPA

- **Plasma Exchange**
  - Removes Abs to vWF cleaving protease
  - Removes vWF
  - Removes PAI-1
  - Removes tissue factor
Recommended therapy for TTP

- Steroids for 24 hours.
- Plasma exchange 1 1/2 volumes then 1 volume per day (median 18 days) requires calcium infusion during therapy.
- If recalcitrant consider cryopreserved supernatant or SD plasma.
- Vincristine
Recommended therapy for DIC

- Treat shock and underlying disease
- Replace clotting factors with FFP, cryoprecipitate and platelets using infusion or plasma exchange.
- Anticoagulate with heparin, protein C, or antithrombin III
- Use fibrinolytics for life or limb threatening disease
- Use anti-fibrinolytics for life threatening bleeding
Our approach to Thrombotic Microangiopathy

- Remove source of thrombotic microangiopathy.
- Consider antithrombotic agents.
- If thromboctopenia associated MOF occurs then we use the TTP-based therapeutic protocol.
Therapeutic Trial of Plasma exchange for Thrombocytopenia Associated MOF

- Patients with platelet count < 100,000 and three or greater organ failure for 24 hours.
- Randomized to TTP-based plasma exchange protocol or usual therapy until resolution of MOF.
- Twenty patients met criteria; Only ten agreed to consent to randomization.
- Mean therapy 12 days, ranged 4 to 28 days.
PELOD decreased from 25.0 ± 2.0 to 0.8 ± 0.6 with plasma exchange at 28 d

PELOD increased from 25.4 ± 2.3 to 73.6 ± 18.4 without plasma exchange at 28 d

$p < 0.001$, power = 1.0, 2F-RM ANOVA
28-Day Survival in Study Patients

- Plasma exchange: 5/5 patients survived
- No plasma exchange: 1/5 patients survived

\( p < 0.05, \text{Fisher exact test} \)
Outcomes in children at the Children’s Hospital of Pittsburgh during the 2 years since study completion

- Plasma Exchange
  - 28 day mortality 10%
  - 1 year mortality 20%
  - n = 20 patients

- No Plasma Exchange
  - 28 day mortality 80%
  - 1 year mortality 85%
  - n = 10 patients
MOF Associated with Infection at Autopsy
Host Response to Inflammation

Antigen presentation; costimulatory signals

APC

IL-12

IFN-γ

IL-10

IL-4

TH0

TH1

TH2

Tc

NK cell

LAK cell

Macrophage

PMN leukocyte

TNF-α

IL-8

ROI RNI

IgG IgM IgA

Humoral immunity

Plasma cell

B cell

Cell-mediated immunity

IL-2 IFN-γ

IL-5 IL-6 IL-9 IL-10 IL-13

IL-4
The $T_{H1}$, $T_{H2}$ Paradigm

![Diagram showing a network of cytokines and chemokines related to $T_{H1}$ and $T_{H2}$ cells.](image-url)
Influence of Cytokines on Cell Mediated Response

CD4+ T Cell

- TCR/CD4
- CD2
- CD28
- CD40L

Expression of Cytokine Receptors (IL-2R, IL-12R, etc.)

Upregulation of CS, Secretion of Cytokines (IL-1, IL-6, IL-10, IL-12, IFN-\(\alpha\), etc.)

Effector Maturation
Strategies of Immunesuppression
Provocative Hypothesis and Speculation

• For the most part, children with BMT or solid organ transplantation who die of ARDS or MOF in PICUs do so as a result of fatal immunoparalysis caused by reversible iatrogenic immunosuppression.

• It has become acceptable to die from ARDS, MOF, sepsis, or PTLD; but not from rejection or GVHD.
Absent $T_H^1$ response in Fatal BMT-associated ARDS (Sparrelid et al. *Transplantation* 63(12):1782-9, 1997)

- Cryopreserved lung from 13 patients with BMT associated pneumonitis
- Increased AM, CD3+, CD4+, and CD40+B cells, IL-4, IL-10, IL-, TGF-beta producing cells.
- Absent IL-1, IFN$\gamma$, and TNF$\beta$ producers
- No perforin CD8+ T cells, but extensive IgA, IgG, and IgM.
- Fatal outcome with predominant Th2 response with minimal to absent T cell cytotoxicity.
Immunoparalysis in Adults with abdominal surgery associated sepsis (HD Volk Intens Care Med, 1996)

- Defined as HLA-DR+ monocytes < 30%
- Persists for at least 5 days associated with 19% (24/126) survival rate.
- Not detectable or only briefly associated with 80% (121/149) survival rate.
Outcome in adult transplant patients with sepsis (HD Volk et al *Intens Care Med* 1996)

<table>
<thead>
<tr>
<th>HLA-DR + monocytes</th>
<th>Rapid taper</th>
<th>Surviving patients</th>
<th>Surviving grafts</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 30%</td>
<td>No</td>
<td>1/12 (8%)</td>
<td>None</td>
</tr>
<tr>
<td>&lt; 30%</td>
<td>Yes</td>
<td>30/33 (90%)</td>
<td>29/30</td>
</tr>
<tr>
<td>&gt; 30%</td>
<td>No</td>
<td>28/28 (100%)</td>
<td>28/28</td>
</tr>
<tr>
<td>&gt; 30%</td>
<td>Yes</td>
<td>4/4 (100%)</td>
<td>0/4</td>
</tr>
</tbody>
</table>
Regulation of monocyte activation (HD Volk et al. 1996)

- Increases HLA-DR expression/cytokine secretion
  - IFN$\gamma$
  - GM-CSF

- Decreases HLA-DR expression/cytokine secretion
  - IL-10
  - TGF-beta
  - M-CSF
  - Immunesuppression
  - ROS
# Reversal of Immuneparalysis Using IFNγ

*(HD Volk *Intens Care Med* 1996)*

<table>
<thead>
<tr>
<th>Treatment (48 hour)</th>
<th>Patient group (n = 7)</th>
<th>% HLA-DR+ monocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Healthy donor</td>
<td>87 +/- 5</td>
</tr>
<tr>
<td>IFNγ</td>
<td>Healthy donor</td>
<td>93 +/- 11</td>
</tr>
<tr>
<td>Control</td>
<td>Patients</td>
<td>28 +/- 8</td>
</tr>
<tr>
<td>IFNγ</td>
<td>Patients</td>
<td>69 +/- 6*</td>
</tr>
</tbody>
</table>

- 13 children (9 with neutropenia, 10 with infection) received a mean of 15 days (4-49 days) of GM-CSF therapy.
- No attributable episodes of rejection
- Thought to have improved ability to fight infection.
Unresolving MOF and Prolonged Monocyte Deactivation

- Septic Shock patients receiving exogenous immunesuppression with $T_{H2}$ agents including tacrolimus, cyclosporine A who cannot clear infection.
- Children who recover from septic shock but then suffer secondary sepsis usually with gram negative bacteria or fungus, but also with Staphylococcus Aureus.
Immune Paralysis and HLA-DR

• HLA-DR is a class II MHC molecule which is expressed on the surfaces of antigen presenting cells, including monocytes.

• Its expression by monocytes is decreased in the anti-inflammatory state, as measured by flow cytometry.

• HLA-DR is strongly expressed on the surfaces of 90-100% of monocytes in healthy adults and neonates

• Expression of HLA-DR on less than 30% of circulating monocytes is considered to be a marker of Immune Paralysis in adults.

Janeway, Immunobiology 1997
The T-lymphocyte Contribution

- The importance of the CD4+ lymphocyte in the maintenance of immune function has been demonstrated in the HIV literature.

- CD4 counts of <750, 500, and 200 cells/mm\(^2\) in the first, second, and subsequent years of life have been associated with an increased risk for the development of infection and death. (CDC 1995)
CD4 Count
The T-lymphocyte Contribution

- The CD4 antigen serves as a co-receptor on certain T-lymphocytes, facilitating interaction with MHC class II molecules on antigen presenting cells.

- Role in Immune Paralysis?

*Janeway, Immunobiology 1997*
Hypothesis

• We hypothesize that prolonged monocyte HLA-DR expression of <30% and depression in CD4 count will be associated with an increased relative risk (RR) for the development of:
  – Gram negative and fungal superinfection
  – Chronic ARDS
  – Chronic MODS
  – Death.
Results to Date

• Total of 50 patients:
  – age 1 day to 22 years
  – 29 males
  – 21 females
  – 24 transplant, 26 non-transplant
Epidemiology
Transplant Patients

8  - Liver
6  - Liver / Small bowel
2  - Heart
2  - Lung
3  - Bone marrow
2  - Heart / Lung
1  - Kidney
Epidemiology
Immunosuppressive Medications

<table>
<thead>
<tr>
<th>Patients</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>Tacrolimus</td>
</tr>
<tr>
<td>12</td>
<td>Mycophenolate</td>
</tr>
<tr>
<td>3</td>
<td>Cyclosporin</td>
</tr>
<tr>
<td>1</td>
<td>Rapamycin</td>
</tr>
<tr>
<td>1</td>
<td>ATGAM</td>
</tr>
<tr>
<td>25</td>
<td>Methylprednisolone</td>
</tr>
</tbody>
</table>
Persistently Depressed Monocyte HLA-DR Expression Associated with Adverse Outcomes

Relative risks with 95%CI for low values after Day 3

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HLA-DR</th>
<th>CD4 Count</th>
<th>HLA-DR and CD4 Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superinfection</td>
<td>9.9 (3.3, 30)</td>
<td>1.6 (0.4, 3.2)</td>
<td>5.3 (2.3, 12)</td>
</tr>
<tr>
<td>Chronic ARDS</td>
<td>4.6 (2.2, 9.9)</td>
<td>1.6 (0.8, 3.3)</td>
<td>3.9 (2.0, 7.6)</td>
</tr>
<tr>
<td>Chronic MODS</td>
<td>12 (3.3, 50)</td>
<td>1.4 (0.5, 3.5)</td>
<td>5.6 (2.1, 14)</td>
</tr>
<tr>
<td>Death</td>
<td>8.5 (2.0, 35)</td>
<td>1.7 (0.5, 5.8)</td>
<td>5.5 (1.6, 18)</td>
</tr>
</tbody>
</table>
HLA-DR expression is decreased in the setting of superinfection.

P=0.003; two way ANOVA

* p<0.05; SNK test
**HLA-DR Expression and Outcome of Superinfection**  
\[ p=0.01; \text{two way ANOVA} \]

- **Persistent Infection**: \( n=5 \)
- **Resolved Infection**: \( n=12 \)
- **Controls**: \( n=12 \)

*\( p<0.05; \) SNK test*
Relative risk of superinfection with prolonged depression of HLA-DR:

Monocyte HLA-DR<30% after Day 3: 14/16 (88%)

Monocyte HLA-DR≥30% after Day 3: 3/34 (9%)

RR: 9.9 95%CI: 3.3, 30
HLA-DR expression is decreased in the setting of chronic ARDS.

p=0.001; two way ANOVA

* p<0.05; SNK test
Relative risk of chronic ARDS with prolonged depression of HLA-DR:

Monocyte HLA-DR<30% after Day 3: 13/16 (81%)

Monocyte HLA-DR≥30% after Day 3: 6/28 (21%)

RR: 4.6  95%CI: 2.2, 9.9
HLA-DR expression is decreased in the setting of chronic MODS.

P=0.002; two way ANOVA

* * * p<0.05; SNK test
Relative risk of chronic MODS with prolonged depression of HLA-DR:

**Monocyte HLA-DR<30% after Day 3:** 12/16 (75%)

**Monocyte HLA-DR≥30% after Day 3:** 2/34 (6%)

RR: 12 95%CI: 3.3, 50
HLA-DR expression is decreased in the setting of death.

\[
p=0.04; \text{two way ANOVA}
\]

*\[p<0.05; \text{SNK test}\]
Relative risk of death with prolonged depression of HLA-DR:

Monocyte HLA-DR<30% after Day 3:  8/16 (50%)

Monocyte HLA-DR≥30% after Day 3:  2/34 (6%)

RR: 8.5  95%CI: 2.0, 35
Relative risks for adverse outcomes with depressed HLA-DR in non-transplant patients:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superinfection</td>
<td>8.5</td>
<td>2.3, 31</td>
</tr>
<tr>
<td>Chronic ARDS</td>
<td>3.2</td>
<td>0.98, 10</td>
</tr>
<tr>
<td>Chronic MODS</td>
<td>12</td>
<td>1.5, 95</td>
</tr>
<tr>
<td>Death</td>
<td>11</td>
<td>1.4, 88</td>
</tr>
</tbody>
</table>
Reduction in FK506 increased DR expression without rejection, with 100% survival (n=7). Failure to decrease FK506 resulted in prolonged HLA-DR depression and 100% mortality (n=6). (p<0.002; two way ANOVA)

* p<0.05; SNK test
Tapering tacrolimus in patients with HLA-DR>30% resulted in 100% survival and no rejection. (n=6)
With no change in original immunosuppression, the addition of corticosteroids did not result in a difference in HLA-DR expression. \((n=6, \ p=0.66 ; \text{Student's t-test})\)
HLA-DR expression increased in response to GM-CSF therapy in one patient.

black bars = periods of treatment with
Inducible TNF-alpha production increased along with HLA-DR expression.

black bars = periods of treatment with GM-CSF
Unresolving MOF with persistent infection and too many or too few lymphocytes

- Too Many Lymphocytes
  Sequential MOF (liver and renal failure)
  a) Viral sepsis (Epstein Barr Virus)
  b) Lymphoproliferative disease (PTLD or x-linked)

- Too Few lymphocytes
  Unresolving MOF and prolonged lymphopenia (ALC < 1000 >7 days) Lymphoid depletion at autopsy
Fas, Fas ligand, and Liver Apoptosis/Necrosis

- Viral sepsis and lymphoproliferative disease associated with high circulating Fas Ligand and Fas and liver failure associated MOF.
- Autopsy shows lymphocyte infiltration of liver and hepatic destruction.
- Successful therapy B lymphocyte antibody now in compassionate clinical trial.
Lymphocyte Depletion Syndrome

- Prolactin prevents apoptosis of B and T lymphocytes.
- Prolonged lymphopenia (ALC < 1000) associated with secondary infection, unresolving MOF, and death.
- Lymphocyte depletion syndrome-absent lymphocytes in lymph nodes and spleen associated with prolonged lymphopenia and hypoprolactinemia (OR 10.8).
Planned Clinical Studies

- GM-CSF for prolonged monocyte deactivation.
- Prolactin for hypo-prolactinemic patients with prolonged lymphopenia.
- Protein C concentrate for patients at risk of bleeding (contraindication to activated protein C RCT)
Investigators

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Michael Whalen  Massdachussets General Hospital
Sandra Kaplan  University of Pittsburgh
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Yong Han  University of Pittsburgh
Mark Hall  Ohio State University
Trung Nguyen  University of Pittsburgh
Kate Felmet  University of Pittsburgh
Scott Watson  University of Pittsburgh
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Robert Clark  University of Pittsburgh
Derek Angus  University of Pittsburgh