Support of Sepsis/MOSF: ECMO and Plasma Exchange

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Overwhelming Sepsis: Desperate Times…

Diseases desperate grown
By desperate appliance are relieved,
Or not at all.

-Claudius, King of Denmark
In Hamlet Act IV Scene 3
W. Shakespeare
Potential Extracorporeal Devices for Sepsis

- CRRT
- Extracorporeal Membrane Oxygenation (ECMO)
  - Potential benefits
  - Experience
  - Expert recommendations
- Plasma Exchange/Plasmapheresis
  - Use in TAMOF
  - Development of study network
  - Early results
ECMO in Sepsis-Why Use It?

- Temporary cardiovascular support
- Temporary lung support
- Temporary renal support
- Dilution of cytokines
- “Platform” for other therapies
ECMO in Sepsis

- Earlier view:
  - Sepsis a CONTRAINDICATION for use of ECMO in neonates and children
  - Concerns:
    - Cannula might perpetuate bacteremia
    - Foreign membranes might aggravate inflammatory response
    - Sepsis: pre-existing coagulopathy might increase bleeding complications

- Arensman, Extracorporeal Life Support, 1993 (1st ed.)
ECMO in Neonatal Sepsis: Clinical Experience

- Neonates: persistent pulmonary hypertension with Group B streptococcal sepsis
- ECMO used in this setting with good results
- Case series experience: 70-100% survival (McCune, J Ped Surg 1990; Hocker Peds 1992)
- ELSO registry review 1995: 1060 with sepsis (74% GBS): survival similar to nonseptic patients (Meyer, J Thorac Cardiovasc Surg, 1995)
ECMO in Neonatal Sepsis: Not A Contraindication

- “ECMO should not be withheld from neonates solely on the basis of sepsis”

ECMO in Neonatal Sepsis: Does It Improve Outcome?

- 1997 ECMO center survey
- 107 septic neonates on ECMO
- Gram positive infections (83%): 77% survival
- Gram negative infections (13%): 60% survival
ECMO in Neonatal Sepsis: Does It Improve Outcome?

- Neonates: ELSO Registry 2428 “sepsis” patients to present
- Mean run time: 138 hours
- 75% survival
- Difficult to know “how septic” from Registry
- Previous review: higher predicted risk of mortality than observed risk
- Similar to overall ECMO survival
ECMO in Neonatal Sepsis: Clinical Experience

- Septic neonates:
  - Higher incidence of intracranial hemorrhage
  - Higher incidence of VA support (89%)
  - Increasing use of VV ECMO could impact these outcomes

ECMO in Pediatric Sepsis: Clinical Experience

- More difficult to assess
- **Sepsis not listed** as a primary indication for ECMO in ELSO registry for pediatrics
- Coexisting sepsis in at least 12% of pediatric ARF ECMO
ECMO in Pediatric Sepsis: Clinical Experience

- 1997 ELSO registry pediatric review
- ECMO patients (univariate analysis)
  - With sepsis: 37% survival
  - Nonseptic 52% survival
- But multivariate → Sepsis NOT an independent predictor of ECMO survival
→ Don’t exclude from ECMO for sepsis

ECMO in Pediatric Sepsis: Clinical Experience

- Increased likelihood of seizures, CNS complications with sepsis
- Sepsis survival decreased with advancing age
- 83% of patients on VA ECMO (impact of increasing VV use)

ECMO in Pediatric Sepsis: Clinical Experience

- Our center:
  - Occasional use for refractory septic shock alone
    - 12 patients with primary or contributing indication (50% survival)
  - Sepsis a frequent coexisting diagnosis (40%)

- Pettignano, Fortenberry et al., Pediatr Crit Care Med 2003
ECMO in Pediatric Sepsis: Clinical Experience

• **35% of VV** respiratory failure (36% of VA) patients **on significant pressors** prior to cannulation

• Able to wean rapidly off pressors even on VV ECMO

ECMO in Pediatric Sepsis: Vasopressors in VV vs. VV ECMO

ELS For Intractable Cardiorespiratory Failure Due to Meningococcal Disease: Good News

- ECMO in 12 children with meningococcemia
- 7 for intractable shock within 36 hours (5 ARDS)
- 6/12 required CPR pre-ECMO
- 8/12 survived
  - 4/7 with shock
  - 4/5 with ARDS
- 6 functionally normal

- Goldman et al., Lancet 1997;349:466
ECMO for Meningococcal Sepsis: Not-So-Good News

- 11 children (prognostic scores 90% mortality) treated with ECMO
- Overall survival 55 percent
  - 5 with ARDS (4/5 VV, time to initiation 946 hours): **all survived**
  - 6 with refractory shock and organ failure (all VA, time to initiation 8.5 hours): **only 1/6 survived** (survivor cannulated at 74 hours)

- Luyt et al., Acta Pediatr 2004
Methicillin-Resistant Staphylococcus Aureus (MRSA)

- New scourge
  - Community acquired vs. hospital acquired
  - Marked increase
  - Immunocompetent
  - Adolescents
  - Associated with skin, soft tissue infections
  - Increased osteo, empyema, DVT
  - Profound sepsis
Panton Valentine Leukocidin (PVL) gene expression

- Risk factor for severity?
  - Local tissue invasion, DVT, severe systemic infection
- **75% mortality** in PVL+ patients presenting in septic shock
ECMO for MRSA Sepsis: ELSO Experience

- Review of ELSO experience 1986-2005
- 123 S. aureus patients
- 45 MRSA
- 20 in 2004-2005 alone
- Median age 2.4 years
- Overall S. aureus survival 43% (vs. 57.3 overall peds)
- VA ECMO in 53% of patients

-Creech et al., Ped Crit Care Med, 2007
ELSO Registry: Staph Aureus Runs

Prevalence of Staphylococcal infections

Number of cases (n)

- Staph
- MRSA

Year:
- 1995
- 1996
- 1997
- 1998
- 1999
- 2000
- 2001
- 2002
- 2003
- 2004
- 2005
ELSO Registry Data: S. Aureus Cases Are Increasing
MRSA and ECMO: Age and Mortality

% Survival

< 1 | 1-4 year | 5-9 year | 13-18 year

24
ELSO Registry Data: S. Aureus Mortality is Increasing

*p < .02
ECMO and Sepsis: Questions

- Current data difficult to assess
- When is ECMO used for “overwhelming” sepsis with C-R failure vs. respiratory failure alone?
- Need for more directed data collection (ELSO Registry)
ACCM Clinical Practice Parameters for Pediatric Septic Shock Support

- Recommendations for use of ECMO:
  - Newborns: Use for “refractory shock”
  - Pediatric: “Consider ECMO”
  - Both Level II = Reasonably justifiable by scientific evidence and strongly supported by expert critical care opinion

- Carcillo et al., CCM 2002; 30:1365
ACCM Clinical Practice Parameters for Neonatal Septic Shock Support

... persistent catecholamine-resistant shock

Refractory shock

Use ECMO

- Carcillo et al., CCM 2002; 30:1365
... persistent catecholamine-resistant shock

↓

Place PA catheter and direct therapies to attain normal MAP-CVP and CI . 3.3 and < 6.0 L/min/m²

↓

Refractory shock

↓

Consider ECMO

- Carcillo et al., CCM 2002; 30:1365
Benefits of ECMO in Sepsis:”Platform” for Immunomodulatory Therapies”?

- Allows for “easier” delivery of
  - Continuous renal replacement therapies (CRRT)
  - Plasmapheresis
  - Plasma exchange
Plasma Exchange on ECMO
Peak Concentration Model of Sepsis

Adapted from Ronco et al. Artificial Organs 27(9) 792-801, 2003
Peak Concentration Model of Sepsis

Adapted from Ronco et al. Artificial Organs 27(9) 792-801, 2003
Plasma Therapies

- **Plasmapheresis**: plasma removed → replaced with 5% albumin
- **Plasma exchange**: plasma removed → replaced with donor plasma
  - centrifugation
  - filtration
Plasmapheresis in Severe Sepsis and Septic Shock

- PRCT, Russian adult ICU
- 106 sepsis patients randomized to:
  - Standard therapy
  - Addition of plasmapheresis (1/2 FFP, 1/2 albumin)
- Decreased mortality with plasma exchange

- Busund et al., Intensive Care Medicine 2002
Plasma Exchange in Septic Shock

- Growing interest in use in children in sepsis
- TAMOF: particular subset
- Developed from interest in experience with TAMOF and plasma exchange at Children’s Hospital of Pittsburgh
- 10 institution pediatric multicenter TAMOF study network- plasma exchange in 6 centers
- Includes use in ECMO
Thrombocytopenia-Associated Multiple Organ Failure (TAMOF)

- TAMOF
  - MOF > 2 organs
  - Platelet count < 100K
- Variant of TTP
- Primarily secondary to sepsis
- High mortality in children
- Deficient ADAMTS-13 (vWf cleaving protease), increased vWf-CP antibodies, increased ulvWf multimers
- Potential therapy: plasma exchange
Thrombotic Microangiopathy: TAMOF

Endothelium → PAI-1 → TF → PAI-1

vWF → PAI-1

IL-8 → TF → TNF-α → IL-6

Platelet

ADAMTS13 Ab → IL-6

Platelet → Shear stress → Platelet

Plasminogen → Plasmin

TFPI

Platelet → Platelet

ADAMTS13 (vWF-CP)
Figure 3. Pediatric Logistic Organ Dysfunction Score, Mean with standard error for patients who received plasma exchange therapy (N = 5) and who did not receive plasma exchange therapy (N = 5) for each day x 28 days.
Children’s TAMOF Network

Active centers:
- Children’s of Atlanta at Egleston: coordinating center
- Children’s of Atlanta at Scottish Rite
- Children’s of Pittsburgh
- Cook Children’s-Fort Worth
- Vanderbilt Children’s
- Cincinnati Children’s
- Columbus Children’s
- LSU-Shreveport
- Arkansas Children’s
- University of Michigan
- 34 TAMOF patients registered to date-21 data complete
- Median age 12 years
- Median OFI: 4
- Similar PRISM, PELOD at admission

21 TAMOF patients

15 plasma exchange
- 11 lived (73%)
- 4 died

6 standard therapy
- 2 survived (33%)
- 4 died

2 survived
TAMOF Network Preliminary Data

Dying with standard therapy

Surviving with plasma exchange

PELOD Score

PELOD-D\_NTX

PELOD-S\_TX
Conclusions

- Outcome evidence is suggestive of benefit of ECMO for sepsis in neonates
- Less convincing results in children/adults
- ECMO is potential alternative of last resort in sepsis and a platform for adjuncts of CRRT and plasma exchange
- Plasma exchange in sepsis/TAMOF promising but needs study
Alexis-A Success Story
Plasma Therapies in Sepsis-Why Use Them?

- General: exchange “transfer factors”
- Specific: control thrombotic microangiopathy (TMA)
- Slow progression of TMA-induced organ failure
- Treat coagulation abnormalities
CRRT in Sepsis-Why Use It?

• Remove/modulate cytokines, pro- and anti-inflammatory factors
  ‣ Over 30 studies demonstrate removal by clearance/absorption
    – Most known mediators are water soluble
    – 500-60,000D “middle molecules”
• Manage septic ARF complications
• Manage fluid overload
• Multiple case reports, retrospective series: hemodynamic improvement, resolution of sepsis
### Pediatric Patients Receiving CVVH
Factors Associated with Mortality

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<th>Effect</th>
<th>β</th>
<th>SE</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
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<tr>
<td>PRISM III</td>
<td>0.107</td>
<td>0.049</td>
<td>1.24</td>
<td>1.02, 1.50</td>
<td>0.03</td>
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<tr>
<td>% FO</td>
<td>0.032</td>
<td>0.018</td>
<td>1.37</td>
<td>0.97, 1.94</td>
<td>0.07</td>
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</table>

- Foland, Fortenberry et al., CCM 2004
## MODS & ≥ 3 Organ Involvement

<table>
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<th>Effect</th>
<th>β</th>
<th>SE</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
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<tbody>
<tr>
<td>PRISM III</td>
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<td>1.10</td>
<td>0.88, 1.39</td>
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<td>% FO</td>
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<td>0.023</td>
<td>1.78</td>
<td>1.13, 2.82</td>
<td>0.01</td>
</tr>
</tbody>
</table>

- Foland, Fortenberry et al., CCM 2004
Extracorporeal Support in Sepsis

There would seem to be a consensus in the movements of fluids and vapours. Thus the stronger draws and the weaker is evacuated.

- Claudius Galen, ca. 170 AD
Back to “Bad Humours”

- Lots of interest in specific cytokine/factor control
- Animal experiments have not translated into human success
- Renewed interest in generalized control of immunologic stability-balancing inhibition of excessive inflammation with enhancement of anti-inflammatory and anti-thrombotic activity
Trends in Immune/Inflammatory Modulation Therapies for Sepsis

Specific: removal/blunting of proinflammatory factor

General: restoring immunologic stability → reduce both pro- and anti-inflammatory factors

-Kellum, Bellomo, Crit Care 2000
The Humours

Blood

Black Bile

Phlegm

Yellow Bile