Systemic Inflammatory Response Syndrome (SIRS) and ARDS in the PICU

Background and Definitions

Pathophysiology

Novel Approaches

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Case Presentation

- 4 y/o female
  - Former premature infant born at EGA 30 weeks
  - Developed NEC at age 2 mos requiring surgical bowel resection
  - Resultant short bowel syndrome/TPN dependent
  - Subsequently developed cholestatic liver disease requiring liver transplantation 7/02
Case Presentation (continued)

- Developed biliary stricture as complication of transplant
- Underwent ERCP with biliary sphincterotomy and placement of biliary endoprosthesis
- Post-procedure, developed pancreatitis
- Progressed to SIRS
  - Massive capillary leak
  - ARDS
  - Ascites
  - Pleural effusions
  - LFT’s
  - Thrombocytopenia
Case Presentation (continued)

- Required significant fluid therapy for circulatory support
- Required High Frequency Oscillatory Ventilation for nearly 3 weeks
- Successfully weaned off invasive mechanical ventilation after > 1 month
- Currently remains on non-invasive mechanical ventilation
- Pancreatitis resolved
- Liver function good though continues with increased bilirubin (stable)
The physiologic response to infection is central to the severity of illness associated with the infection itself.

- Different individuals infected with the same organism noted to have varying degrees of illness.
- Recognition by Bone, et al.
  - Formal definitions
  - Observation of “sepsis like syndrome” in patients without infection.
SRSA
- Slow releasing substance of anaphylaxis
- Now an archaic term

Era of attempts at “supranormal O₂ delivery”
- Belief that progression to multiple organ failure/dysfunction was due to increased metabolism of individual organs
- Liberal transfusion practice
- Use of inotropes despite “normal” cardiac output
- No improvement in outcome
Need for consensus definitions of sepsis continuum
- infection, SIRS, sepsis, severe sepsis, septic shock, MODS (multiple organ dysfunction syndrome)
- Aid in standardization of observational studies
- Aid in evaluation of therapeutic interventions
Definitions in children rely on age-specific norms of vital signs and laboratory data.

6 age groups proposed (preterm infants not included):
- Newborn - 0 days to 1 week
- Neonate - 1 week to 1 month
- Infant - 1 month to 1 year
- Toddler/pre-school – 2-5 years
- School age – 6-12 years
- Adolescent/young adult – 13 to < 18 years
SIRS

- A term used to describe the nonspecific inflammatory process that may occur after a variety of insults (NOT limited to infection)
- May occur as a result of:
  - Infection
  - Trauma
  - Burns
  - Pancreatitis
  - ARDS
  - malignancy
Definition of Infection

- A suspected or proven infection caused by any pathogen OR a clinical syndrome associated with a high probability of infection
- Evidence of infection may include positive findings on clinical exam, imaging, or laboratory tests
  - WBC’s in normally sterile body fluid, perforated viscus, CXR c/w pneumonia, petechial rash, purpura fulminans, etc…
SIRS

- The presence of at least 2 of the following 4 criteria
  - Core temperature > 38.5°C or < 36°C (may not be axillary or otic temperature)
  - Tachycardia – HR > 2 SD above normal for age in the absence of external stimuli, drug effect, or painful stimuli OR unexplained persistent elevation for > 30 minutes OR bradycardia for children < 1 y/o (<10th percentile for age) in the absence of vagal stimulus, medications, or CHD OR unexplained depression lasting > 30 min
  - Tachypnea – RR > 2 SD above normal for age or need for mechanical ventilation due to an acute process (i.e. not related to NM disease or anesthesia)
  - Leukocyte count increase or decreased for age NOT related to chemotherapy or >10% immature neutrophils
SIRS

- Major difference from adult definition of SIRS
  - Tachycardia/Tachypnea are common presenting symptoms of many pediatric diseases
  - To diagnose pediatric SIRS, 1 of the 2 criteria must be temperature or leukocyte abnormality
Sepsis, Severe Sepsis, and Septic Shock

- Sepsis
  - SIRS in the presence of or as a result of suspected or proven infection

- Severe Sepsis
  - Sepsis plus one of the following:
    - Cardiovascular organ dysfunction, ARDS, OR 2 or more other organ dysfunctions

- Septic Shock – sepsis and cardiovascular organ dysfunction (does NOT require presence of hypotension)

- Specific definitions for organ dysfunctions also delineated
Severe Sepsis: A Significant Healthcare Challenge

- Major cause of morbidity and mortality worldwide
  - Leading cause of death in noncoronary ICU (US)*
  - 11th leading cause of death overall (US) †§

- More than 750,000 cases of severe sepsis in US annually‡

- In the US, more than 500 patients die of severe sepsis daily‡

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*Sands KE et al. *JAMA*. 1997;278:234-40; †Based on data for septicemia. §Murphy SL. National Vital Statistics Reports. ‡Angus DC et al. *Crit Care Med*. 2001 (In Press); reflects hospital-wide cases of severe sepsis as defined by infection in the presence of organ failure.
Severe Sepsis: Comparison With Other Major Diseases

Incidence of Severe Sepsis

- AIDS*
- Colon Cancer
- Breast Cancer
- CHF†
- Severe Sepsis‡

Mortality of Severe Sepsis

- AIDS*
- Breast Cancer
- AMI†
- Severe Sepsis‡

Severe Sepsis: A Significant Healthcare Challenge

Mortality (%)

- 28%†
- 34%‡
- 50%§

Etiology of Septic Shock in Children

- N. meningitidis
- S. pneumoniae
- H. influenzae type B
- Group B Streptococcus
- S. aureus
- Gram negative enteric bacteria (enterobacter, E. coli)
- Immunocompromised pseudomonas, fungus/yeast
Sepsis Associated Mortality in Children

- In 1966, mortality rate reported to be 97%
- 1995 population-based study (Watson, et. al.) of U.S. children
  - >42,000 cases reviewed
  - Mortality rate 10.3%
  - Significant improvement, but:
    - Still > 4300 deaths annually
    - Represents 7% of all deaths among children
- Improvement in mortality due to improved antimicrobial therapy and supportive care, but specific therapy for SIRS still lacking
Pathogenesis of Sepsis

Microbes
(+/- Antibiotics)

Endotoxins, Exotoxins

Inflammatory Response:
Leukocyte Stimulation and Cytokine Release
Activation of Endothelium

Antigen Clearance
Host Autoinjury
A Network of Cascading Events

Infection

- Inhibits
- Stimulates
- Activates

T  Thrombin
TF  Tissue Factor
TM  Thrombomodulin
PAI-1  Plasminogen Activator Inhibitor 1
t-PA  Tissue-type Plasminogen Activator
TAFI  Thrombin Activatable Fibrinolysis Inhibitor
A Network of Cascading Events

- Infection
- Proinflammatory Mediators
- Anti-inflammatory Mediators
- Inflammation
- Coagulation
- Endothelial Injury
- T

Symbols:
- Inhibits
- Stimulates
- Activates

Acronyms:
- T: Thrombin
- TF: Tissue Factor
- TM: Thrombomodulin
- PAI-1: Plasminogen Activator Inhibitor 1
- t-PA: Tissue-type Plasminogen Activator
- TAFI: Thrombin Activatable Fibrinolysis Inhibitor
A Network of Cascading Events

- Inflammation
  - Proinflammatory Mediators
  - Anti-inflammatory Mediators
- Infection
- Coagulation
  - Thrombin (T)
  - Tissue Factor (TF)
  - Plasminogen Activator Inhibitor 1 (PAI-1)
  - Tissue-type Plasminogen Activator (t-PA)
  - Thrombin Activatable Fibrinolysis Inhibitor (TAFI)
- Endothelial Injury

Symbols:
- Inhibits
- Stimulates
- Activates
T Thrombin
TF Tissue Factor
TM Thrombomodulin
PAI-1 Plasminogen Activator Inhibitor 1
T-PA Tissue-type Plasminogen Activator
TAFI Thrombin Activatable Fibrinolysis Inhibitor
A Network of Cascading Events

Inflammation
- Proinflammatory Mediators
- Activated Protein C
- Anti-inflammatory Mediators

Coagulation
- T
- TM
- Protein C
- TAFI
- t-PA
- PAI-1

Fibrinolysis

Endothelial Injury
- TF

Infection

Inhibits
Stimulates
Activates
T
Thrombin
TF
Tissue Factor
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Thrombomodulin
PAI-1
Plasminogen Activator Inhibitor 1
t-PA
Tissue-type Plasminogen Activator
TAFI
Thrombin-Activatable Fibrinolysis Inhibitor
Early Biochemical Events in Sepsis

Intracellular Effect of Circulating Cytokines

Homeostasis Is Unbalanced in Severe Sepsis

↑ Coagulation
↑ Inflammation
↓ Fibrinolysis

Homeostasis

Effect of Unbalanced Homeostasis

- Thrombi form in microvasculature
- Prevent delivery of oxygen and nutrients to end organs despite seemingly adequate cardiac output and oxygen content of blood
- Damage to capillary bed – become “leaky”
- Results in progression of organ dysfunction
Severe Sepsis: The Final Common Pathway

Endothelial Dysfunction and Microvascular Thrombosis

Hypoperfusion/Ischemia of End Organ

Acute Organ Dysfunction (Severe Sepsis)

Death
Combined Cardiorespiratory support and antibiotics (N = 21)

Cardiorespiratory support alone (N = 8)

Antibiotics Alone (N = 8)

No Therapy (N = 11)

Endogenous Modulators of Inflammation

- Antiinflammatory cytokines
- Activated Protein C
  - Inhibits thrombin-mediated inflammatory activities
  - Inhibits attachment of leukocytes to endothelium

Decrease inflammatory response

Endogenous Modulators of Thrombosis

- Activated Protein C
- Antithrombin III-heparan sulfate
- Tissue factor pathway inhibitor (TFPI)

Prevent coagulation from becoming generalized

Endogenous Modulators of Fibrinolysis

- Tissue plasminogen activator (t-PA)
- Activated Protein C inhibits:
  - PAI-1
  - TAFI activation

Remove formed microthrombi and maintain blood fluidity

Severe Sepsis Therapy: Numerous Investigational Approaches

- **Bacterial modulators**
  - Antiendotoxin, BPI

- **Anticytokines**
  - IL-1ra, anti-TNF, sTNF-r

- **Antiinflammatory agents**
  - Glucocorticoids, leukocyte adhesion molecule inhibitors

- **Hemostatic agents**
  - Recombinant Human Activated Protein C, ATIII, TFPI, heparin

- **Other**
  - iNOS inhibition, antioxidants, thromboxane antagonists, bradykinin receptor antagonists

Endogenous Activated Protein C Modulates Coagulation, Fibrinolysis, and Inflammation in Severe Sepsis

- Activated Protein C
  - ↓ Coagulation
  - ↓ Inflammation
  - ↑ Fibrinolysis

Homeostasis

Activated Protein C
Xigris® (drotrecogin alfa)

- Recombinant Human activated protein C
- First “anti-inflammatory” agent to show clinical benefit in severe sepsis
- PROWESS Study Group
  - 164 centers in 11 countries
  - 1690 patients entered
  - Study stopped after 2nd planned interim analysis due to significant differences in mortality rates seen
PROWESS Study Group

● Results
  – Mortality rate 30.8% in placebo group compared to 24.7% in treatment group
  – Absolute reduction in risk of death 6.1% (P=0.005)
  – Means that 1 life saved for every 16 patients treated

● Only significant adverse effect seen was increase in serious bleeding
  – 3.5% vs. 2.0%, P=0.06
PROWESS Study Group
Additional Facts

- **Only** those with severe illness showed improvement
  - those with moderate illness showed no difference in outcome
  - those with mild illness showed slightly worsened outcome
- FDA was evenly divided on whether or not drug should be approved
- Significant exclusion criteria limit its use and evaluation in many clinical situations
Xigris in Pediatrics

- Recent Multicenter trial in Pediatric severe sepsis
- Study stopped at planned 2\textsuperscript{nd} interim analysis
- However, this study stopped due to unfavorable risk/benefit ratio
- Xigris currently NOT recommended for pediatric patients
Bactericidal/Permiability Increasing Protein (BPI)

- Lancet. 2000 Sep 16;356(9234):961-7
  - Randomized Trial of 393 pediatric patients with severe meningococcal sepsis
  - Trend toward decreased number of multiple severe amputations (p=.067)
  - Improved functional outcome (p=.019)
  - No significant difference in mortality (7.4% vs. 9.9%)

- Earlier smaller studies seemed to indicate a potential decrease in mortality of as much as 25%

- Submitted to FDA for approval - denied
Difficult to perform with mortality as end-point
- Current mortality rate ~ 10%
- Assume intervention will decrease mortality by 25%
- For alpha=.05 and power of 80%, would need 1,979 patients per group!!

As a result, alternate end-points often used
- Organ failure free days, mechanical ventilator free days, etc…
ARDS

- A clinical syndrome of acute lung injury with hypoxemic respiratory failure that develops following a primary, initiating, severe physiological insult.
- Pulmonary edema develops from increased permeability of the alveolar-capillary membrane.
1994 CONSENSUS

- Acute onset
  - may follow catastrophic event
- Bilateral infiltrates on chest radiograph
- PAWP < 18 mm Hg or no clinical suspicion of cardiac cause of lung disease
- Two categories:
  - Acute Lung Injury - PaO$_2$/FiO$_2$ ratio \( \leq 300 \)
  - ARDS - PaO$_2$/FiO$_2$ ratio \( \leq 200 \)
INCITING FACTORS

- Shock
- Aspiration of gastric contents
- Trauma
- Infections
- Inhalation of toxic gases and fumes
- Drugs and poisons
- Miscellaneous
Associated Disease

- Chemical Pneumonia
- Infectious Pneumonia
- Trauma
- Hemorrhagic Shock
- Arrest

Direct

Indirect

Sepsis
ARDS Pathogenesis

- **Triggers:**
  - \textit{infection, trauma, other}
- **Mediators:**
  - toxins, cytokines, complement, arachidonic acid metabolites
- **Effectors:**
  - activated neutrophil, stimulated endothelium
- **Lung Pathology**

Systemic Inflammation

ARDS
Frequency of Sites of Infection Giving Rise to Severe Sepsis

AS Headley. *Chest* 1997;111: 1306-1321
Non-survivors

Survivors

AS Headley. *Chest* 1997;111: 1306-1321
Mortality

- Incidence is approximately 10 cases/1000 PICU admissions
- Initial mortality rates 40 - 60%
- Respiratory failure accounts for only 16% of deaths
- MOSF and sepsis syndrome account for majority of deaths
- For survivors, long term outcome very good
Mortality may be decreasing in recent years
  – better ventilatory strategies
  – earlier diagnosis and treatment
  – More recent mortality rates around 30%
Protective-ventilation hypothesis in ARDS

Lung damage results from:
1) over-distention of lung units
   high ventilatory volumes and pressures
2) shear injury
   lung units to collapsing at end exhalation
   cyclic closing and reopening of alveoli

Protective - ventilation:
1) avoids regional over-distention
2) avoids alveolar collapse with each breath
3) will improve outcome and reduce mortality
Volutrauma vs. Barotrauma

- Large animal study
  - Group 1 with bound chest
    - High pressures/Low volumes
  - Group 2 with open chest
    - High volumes/Low pressures
- Group 1 with minimal inflammatory changes
- Group 2 with significant inflammatory changes
- Opposite of expected result
<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>GROUP RECEIVING LOWER TIDAL VOLUMES</th>
<th>GROUP RECEIVING TRADITIONAL TIDAL VOLUMES</th>
<th>P VALUE</th>
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</thead>
<tbody>
<tr>
<td>Death before discharge home and breathing without assistance (%)</td>
<td>31.0</td>
<td>39.8</td>
<td>0.007</td>
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<tr>
<td>Breathing without assistance by day 28 (%)</td>
<td>65.7</td>
<td>55.0</td>
<td>&lt;0.001</td>
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<tr>
<td>No. of ventilator-free days, days 1 to 28</td>
<td>12±11</td>
<td>10±11</td>
<td>0.007</td>
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<tr>
<td>Barotrauma, days 1 to 28 (%)</td>
<td>10</td>
<td>11</td>
<td>0.43</td>
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<tr>
<td>No. of days without failure of nonpulmonary organs or systems, days 1 to 28</td>
<td>15±11</td>
<td>12±11</td>
<td>0.006</td>
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</table>
28-Day Survival among 53 Patients with the ARDS Assigned to Protective vs Conventional Mechanical Ventilation

Mortality Rate in ARDS
Traditional Tidal Vol. (N = 257) vs Low Tidal Vol. (N= 260)

In patients with acute lung injury and the acute respiratory distress syndrome, mechanical ventilation with a lower tidal volume than is traditionally used results in decreased mortality and increases the number of days without ventilator use.
Inflammatory Mediators in BAL in ARDS Using Lung Protective Strategy

- Significant decrease in pro-inflammatory cytokine concentration in BAL fluid in patients receiving lung protective strategy

SIRS/Sepsis - Conclusions

- Sepsis is a significant healthcare challenge with major morbidity, mortality, and health economic implications.
- Patients with severe sepsis (acute organ dysfunction) are at high risk for mortality.
- Systemic inflammation, coagulation, and impaired fibrinolysis are key components of disordered homeostasis in patients with severe sepsis.
- With increased knowledge of sepsis pathophysiology, researchers have identified potential investigational agents that may interrupt the inflammatory cascade.
- The future may be brighter!!
ARDS in Pediatrics

Conclusions

- Nearly 40 years after initial description
- Better understanding of Pathology
- Improved insight into pathogenesis
- New trends in conventional treatment modalities
- Innovations occurring rapidly
- Expect outcome breakthrough soon
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of Patients</th>
<th>Mortality Rate</th>
<th>Predicted Mortality PRISM II</th>
<th>Predicted Mortality PIM2</th>
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<tbody>
<tr>
<td>ARDS</td>
<td>87</td>
<td>6.90%</td>
<td>2.61%</td>
<td>4.78%</td>
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<tr>
<td>Septic Shock</td>
<td>77</td>
<td>22.10%</td>
<td>18.83%</td>
<td>21.57%</td>
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<tr>
<td>Both</td>
<td>19</td>
<td>26.31%</td>
<td>33.31%</td>
<td>29.12%</td>
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