SEPSIS UPDATE

EARLY RECOGNITION THROUGH ADVANCED THERAPIES

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May 2016

OBJECTIVES

At the end of this presentation, the participant will be able to:
• Describe the rationale for the new definitions of sepsis and septic shock
• Define sepsis and septic shock according to the Sepsis-3 consensus statement
• Know one validated tool for the identification of patients at risk for sepsis and organ dysfunction
• List the steps for initial management of a patient with sepsis and septic shock
• Recognize advanced therapies utilized in sepsis and septic shock

WHY SEPSIS

• True incidence unknown
  • Multiple definitions of sepsis, organ dysfunction, and organ failure
  • Incidence rising in U.S.
• Pediatric Data
  • Worldwide
    • Annual mortality 1.6 million
  • U.S
    • 42,000 cases of severe sepsis per year
    • In-hospital mortality 10.3%
    • Average LOS 31 days, $40,000+
• Adult & Pediatric Data in U.S.
  • 2% of admissions, 10% of ICU admissions
  • 750,000+ cases per year
  • $20 billion

ORIGIN

4th Century BCE

8th Century BCE

2nd Century AD

DISCLOSURE

• I have no relevant relationships with financial or commercial companies to disclose

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SEPSIS HISTORY

In addition to incision and drainage of abscesses, Galen advocated for which of the following therapies?

A. Medicinal leeches  
B. Trepanation  
C. Children’s ‘soothing syrups’  
D. Bloodletting

GERM THEORY

1546  
“Contagium virum”

1674  
“Animacules”

FAST FORWARD

1991 – American College of Chest Physicians & Society of Critical Care Medicine defined sepsis

DEFINITIONS CIRCA 1991

A 16yo M presents to the emergency department for respiratory distress. Initial vital signs:
Temp 98.2°F (36.7°C)  HR 127  RR 36  BP 88/51  87% RA

This patient meets which of the following criteria?

A. Systemic inflammatory response syndrome (SIRS)  
B. Sepsis  
C. Severe sepsis  
D. Septic shock  
E. None of the above

1991 DEFINITIONS

SEPSIS STEPS

SEPTIC SHOCK

SIRS + Severe Sepsis

Septic Shock

SIRS + Sign of End Organ Damage

Hypotension

Lactate >4 mmol/L

Lactic acidosis
A host new information on the Pathobiology of Sepsis emerged...

**PATHOBIOLOGY IN FOCUS**

Pathophysiologic mechanisms in septic shock

- Cellular Dysfunction
  - Phagocytic & lymphocytic cells
  - Endothelial cells
- Soluble Inflammatory Mediators
  - Pathogen associated molecular patterns (PAMPs) and damage associated molecular patterns (DAMPs)
  - Innate immune response with or without infection
- Compensatory anti-inflammatory response (CARS)
  - No longer independent of PAMPs/DAMPs, nor “late effect” of sepsis response
- Disordered Coagulation
  - Tissue factor, anti-thrombin, Protein C system, & inhibition of fibrinolysis
- Dysregulation of glycemic control
  - Hyperglycemia and insulin resistance
PATHOBIOLOGY

DEFINITION LIMITATION RECAP

Limitations of 1991 Definitions:

1. Poor specificity of SIRS criteria
2. Misleading continuum model
3. Excessive focus on inflammation & broader understanding of pathobiology
4. Multiple definitions persist resulting in incidence and mortality discrepancies

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Which of the 1991 consensus committee identified an increased mortality risk to patients with which of the following?

A. SIRS
B. Sepsis
C. Severe sepsis
D. Septic shock

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SEPSIS REDEFINED

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

SEPSIS REDEFINED

- SIRS: Systemic Inflammatory Response Syndrome
- Sepsis: Suspected infection + at least 2 of the following:
  1. T temperature ≥ 38°C or ≤ 36°C
  2. R respiratory rate ≥ 20 breaths per minute
  3. S systolic blood pressure ≤ 90 mm Hg
  4. L laboratory evidence of infection (e.g., WBC ≥ 12,000 or ≤ 4,000 or > 10% bands)
NEW DEFINITIONS

- **Sepsis**: Life-threatening organ dysfunction caused by a dysregulated host response.
- **Septic shock**: Subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality.

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Which criteria do you use most often to assess organ dysfunction in your patients?

A. Clinical data: pupil exam, tachycardia, poor perfusion, jaundice, low urine output, edema
B. Organ specific laboratory data: elevated BNP, BUN, creatinine, AST/ALT, abnormal coag panel
C. Formal organ failure or mortality score: PeLOD, LODS, SOFA, P-MODS, PRISM-III
D. Biomarkers: CRP, PCT, α2-macroglobulin, ferritin, haptoglobin, serum amyloid-A, serum amyloid-P

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ORGAN DYSFUNCTION

- Multiple tools for pediatric patients
  - **PRISM-III**: Pediatric Risk of Mortality
    - Validated 1995
    - Derived from the Physiologic Stability Index
    - Predictive marker
  - **PELOD**: Pediatric Logistic Organ Dysfunction Score
    - Modeled after validated adult Logistic Organ Dysfunction Score
    - Validated 2003, re-investigated 2010
    - Outcome measure
  - **P-MODS**: Pediatric Multiple Organ Dysfunction Score
    - Developed 2005
    - Outcome measure

Table 1: Pediatric Multiple Organ Dysfunction Score (P-MODS)

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
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<tbody>
<tr>
<td>1.0</td>
<td>1.0</td>
<td>1.5</td>
<td>2.2</td>
<td>3.0</td>
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<tr>
<td>Lactate and venous, μmol/L</td>
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<td>Bilirubin, mg/dL</td>
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<td>Platelet count, G/L</td>
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<td>3.0</td>
</tr>
<tr>
<td>Packed cell volume</td>
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<td>2.2</td>
<td>3.0</td>
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<td>White blood cell count, G/L</td>
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<td>3.0</td>
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ORGAN DYSFUNCTION

- Sepsis-3 recommends Sequential Organ Failure Assessment (SOFA)

<table>
<thead>
<tr>
<th>Test</th>
<th>Score</th>
<th>Range</th>
<th>Range</th>
<th>95% CI</th>
<th>p value</th>
<th>AUC</th>
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<tbody>
<tr>
<td>SOFA</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

- SOFA – good performance in multiple small trials in pathology specific pediatric patients

SCREENING

- All organ dysfunction and mortality scores discussed require laboratory values
- First line providers need a tool... quick SOFA

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In children with suspected sepsis or septic shock, which of the following is true?

A. Early goal directed therapy (EGDT) is a standard of care
B. Biomarkers are useful in ruling out sepsis due to high negative predictive values
C. Corticosteroids are recommended for most children with suspected sepsis due to their immature HPA axes
D. Dopamine is the vasopressor of choice for fluid refractory shock

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**EARLY MANAGEMENT**

- Initial Resuscitation
  - Non-rebreather, CPAP
  - Volume resuscitation before intubation
  - Hs & Ts
  - Antibiotics in < 1 hr
  - Clindamycin & anti-toxin for refractory TSS
  - Fluids
    - 20cc/kg crystalloid or albumin until rales or hepatomegaly
- Vasoactive Agents
  - Start in PIV until CVL available
  - Corticosteroids
    - Fluid refractory, catecholamine resistant shock
    - Known adrenal insufficiency
- Blood Products
  - Hgb of 10 g/dL target (early / SvcO2 < 70%)

**MANAGEMENT ALGORITHM**

- Fluid Resuscitation
  - Adult Studies
    - 2001 – Rivers study on Early Goal Directed Therapy (EGDT)
    - 2015 – Angus, et. al. publish systematic review and meta-analysis of EGDT
      - ARISE, ProtekS6, and ProCESS Trials
        - Paul Marik, intensivist at Eastern Virginia
  - Data with low external validity in children
    - FEAST Trial – Fluid Expansion as Supportive Therapy
    - Bedside ultrasound on the rise
      - Allows clinicians to evaluate fluid responsiveness
      - Does not evaluate ‘volume status’
      - May reduce fluid overload, ARDS?

**CONTROVERSIES**

- Vasopressor Choice
  - Official PALS recommendation
    - Norepinephrine for warm shock
    - Epinephrine for cold shock
  - Adult data recommends norepinephrine for septic shock
    - 2010, De Backer and colleagues compared dopamine vs norepinephrine in RCT
      - No mortality difference
      - Higher rate adverse events with dopamine

- Fluid Resuscitation
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- Vasopressor Choice
  - 2015, Ventura – Pediatric RCT dopamine vs. epinephrine

- Vasoactive Agents
  - Fluid refractory, catecholamine resistant shock
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CONFUSING, BUT NOT CONTROVERSIAL

The 90s were full of biomarkers without a home

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ADVANCED THERAPIES

• Hemofiltration
  - Pediatric Patients
    - Prospective Pediatric Continuous Renal Replacement Therapy Registry Group (ppCRRT)
    - 2012 - Naran and colleagues retrospective study
      - 22 children with SIRS & MODS, all ventilated
      - No improvement in hemodynamic or respiratory parameters in 48 hrs
      - No control group, no analysis of ultrafiltration rates
  - Adult Patients
    - International CCM consensus statement 2010
      - Recommends against high volume hemofiltration in absence of AKI
    - IVOIRE Trial, 2013
      - High volume hemofiltration, adult RCT
      - No difference in 28 day mortality when compared to standard volume hemofiltration

• Extracorporeal Membrane Oxygenation (ECMO)
  - Melbourne, Australia - Royal Children’s Hospital
    - Beca and MacLaren’s studies reversed contraindication
    - Review in 2013 by Sivarajan

ADVANCED THERAPIES

• Extracorporeal Membrane Oxygenation (ECMO)
  - 2012, Skinner and colleagues report VV ECMO higher survival than VA ECMO

<table>
<thead>
<tr>
<th>Table 4: Summary of Extracorporeal Life Support Series for Septic Shock</th>
<th>Table 5: Multiple Variable Analysis for Mortality after ECMO for Noncardiac Pediatric Sepsis</th>
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</thead>
<tbody>
<tr>
<td>Variable</td>
<td>Reference</td>
</tr>
<tr>
<td>V A (ECMO) vs V V ECMO</td>
<td>0.40 (0.23-0.69)</td>
</tr>
<tr>
<td>N omal (9/23)</td>
<td>0.65 (0.38-1.10)</td>
</tr>
<tr>
<td>A dults (22/23)</td>
<td>0.76 (0.47-1.22)</td>
</tr>
<tr>
<td>V A ECMO vs V V ECMO</td>
<td>0.63 (0.39-1.02)</td>
</tr>
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<td>V A ECMO vs V V ECMO</td>
<td>0.67 (0.40-1.12)</td>
</tr>
<tr>
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FUTURE DIRECTIONS

• Universal Recognition
  - To date, American College of Emergency Physicians (ACEP) and American College of Chest Physicians (ACCP) have not endorsed new definitions
• SOFA Validation in children
• qSOFA Validation in pediatric patients
• Optimal volume administration in children with septic shock
• Ideal vasopressor choice for pediatric septic shock
• Stay tuned for expanding roles of gene array, plasmapheresis and ECMO

TAKE HOME POINTS

• Rationale for new definitions
  - Excessive focus on inflammation
  - Misleading continuum model
  - Poor specificity of SIRS criteria
  - Multiple definitions persist resulting in incidence and mortality discrepancies
• New definitions
  - Sepsis: Life threatening organ dysfunction caused by a dysregulated host response to infection
  - Septic Shock: A subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality
    - Clinically: Sepsis + vaspressors needed to keep MAP > 65mmHg, and lactate > 2mmol/L

TAKE HOME POINTS

• Clinical Tool
  - qSOFA – Identifies patients at risk for sepsis
    - Hypotension, tachypnea, altered mental status
  - SOFA score – Identifies life threatening organ dysfunction
    - Score ≥ 2 associated with 10% in-hospital mortality (adults)
• Management Principles
  - A, B, Cs
  - Fluids, antibiotics, and vaspressors
  - Watch for emerging data: ideal volume of IVF, best vasopressor, and new biomarkers
• Advanced Therapies
  - CVVH little utility outside of AKI
  - ECMO safe and effective to support patients through refractory septic shock

THANK YOU

HIGHLIGHTED ARTICLES