Sepsis and the Clinical Laboratory

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Learning Objectives

• Outline the Pathogenesis of Sepsis

• Describe the Role of the Clinical Laboratory in the diagnosis and monitoring of sepsis

• Assess the clinical utility of sepsis biomarkers including: Lactate, Procalcitonin, and CRP

• Identify New Diagnostic Strategies for the Prediction of Sepsis
Sepsis Background and Significance

• Sepsis affects >750,000 American and >1.8 million patients worldwide per year.
• Sepsis accounts for >200,000 deaths each year in the United States.
• US hospital costs for sepsis are >$17 billion, with an uptrend of ~12%/year
• Severe forms of sepsis require ICU care – sepsis prevalence in medical ICUs is >20%
• Leading cause of death in non-cardiac ICUs
Pathophysiology of Sepsis

Systemic Inflammatory Response ➔ Coagulation Activation ➔ Impaired Fibrinolysis ➔ End organ dysfunction ➔ Hypotension
Systemic Inflammatory Response Syndrome (SIRS)

- Burns
- Trauma
- Pancreatitis
- Other

**SIRS**

- Temp >38 or <36°C
- WBC >12 or <4 x10^3 cells/μL (x10^9 cells/L)
- HR > 90 beats/min
- RR >20 breaths/min

American College of Chest Physicians/Society of Critical Care Medicine consensus panel definitions.
SIRS

Temp >38 or <36°C
WBC > 12 or <4 $\times 10^3$ cells/uL ($\times 10^9$ cells/L)
HR > 90 beats/min
RR > 20 breaths/min

Infection

Viral
Bacterial
Fungal
Parasitic

Sepsis = SIRS + Infection

American College of Chest Physicians/Society of Critical Care Medicine consensus panel definitions - 2002
Mortality Depends on Severity

- **Septic Shock**
  - Severe Sepsis + Hypotension
  - 40 – 70% Mortality

- **Severe Sepsis**
  - Sepsis + Organ Dysfunction
  - 25 – 30% Mortality

- **Sepsis**
  - SIRS + Infection
  - 15 – 20% Mortality
Early antimicrobial therapy is critical for survival in septic shock

Rapid initiation of treatment reduces mortality

Surviving Sepsis Campaign (SSC)

• Evidence based guidelines for Sepsis diagnosis and treatment of

• Introduced sepsis resuscitation bundles
  – Laboratory tests (lactate and blood cultures) and Radiology to rapidly identify sepsis and severity
  – Rapid/Targeted Therapy (i.e. antimicrobial and crystalloid for hypotension)
  – Two phased approach - **resuscitation and management**- with goals at 3, 6 and 24 hours
SSC Bundles Reduce Mortality

- 2 years
- 3 Countries
- >15,000 patients
- 165 hospitals

Compliance increase 10 – 31%

Reduced Mortality 37 – 30.8%

Biggest barrier is Recognition of sepsis

Intensive Care Medicine. 36:222-231; 2010
Diagnosis Sepsis is Complex

• Clinical Findings
  – SIRS Criteria
  – Clinical History
  – Physician assessment

• Laboratory findings
  – Bacterial Cultures = the “gold-standard”
    • Timely
    • Rate of false positive (~30%) and negatives (~50%)

  – Biomarkers - Diagnosis, Prognosis, and monitoring therapy
Sepsis Diagnostic Criteria

Infection, documented or suspected, and some of the following:

General variables

- Fever (> 38.3 °C)
- Hypothermia (core temperature < 36 °C)
- Heart rate > 90/min⁻¹ or more than two SD above the normal value for age
- Tachypnea
- Altered mental status
- Significant edema or positive fluid balance (> 20 mL/kg over 24 hr)

Hyperglycemia (plasma glucose > 140 mg/dL or 7.7 mmol/L) in the absence of diabetes

Inflammatory variables

- Leukocytosis (WBC count > 12,000 µL⁻¹)
- Leukopenia (WBC count < 4000 µL⁻¹)
- Normal WBC count with greater than 10% immature forms
- Plasma C-reactive protein more than two SD above the normal value
- Plasma procalcitonin more than two SD above the normal value
### Sepsis Diagnostic Criteria (Part II)

**Hemodynamic variables**
- Arterial hypotension (SBP < 90 mm Hg, MAP < 70 mm Hg, or an SBP decrease > 40 mm Hg in adults or less than two SD below normal for age)

**Organ dysfunction variables**
- Arterial hypoxemia (Pao₂/FiO₂ < 300)
- Acute oliguria (urine output < 0.5 mL/kg/hr for at least 2 hrs despite adequate fluid resuscitation)
- Creatinine increase > 0.5 mg/dL or 44.2 μmol/L
- Coagulation abnormalities (INR > 1.5 or aPTT > 60 s)
- Ileus (absent bowel sounds)
- Thrombocytopenia (platelet count < 100,000 μL⁻¹)
- Hyperbilirubinemia (plasma total bilirubin > 4 mg/dL or 70 μmol/L)

**Tissue perfusion variables**
- Hyperlactatemia (> 1 mmol/L)
- Decreased capillary refill or mottling

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WBC = white blood cell; SBP = systolic blood pressure; MAP = mean arterial pressure; INR = international normalized ratio; aPTT = activated partial thromboplastin time.

Diagnostic criteria for sepsis in the pediatric population are signs and symptoms of inflammation plus infection with hyper- or hypothermia (rectal temperature > 38.5°C or < 35°C), tachycardia (may be absent in hypothermic patients), and at least one of the following indications of altered organ function: altered mental status, hypoxemia, increased serum lactate level, or bounding pulses.

Lactate to Diagnose Sepsis?

- End-product of anaerobic glycolysis
- Increased in various settings:
  - Excessive energy demands
  - Tissue hypoperfusion (shock)
  - Low oxygen supply
  - Impaired cell metabolism
  - Impaired gluconeogenesis
- Severe sepsis = Lactate > ULN due to infection
- No role for lactate in diagnosis of early sepsis
Elevated Lactate Predicts Mortality

Lactate >4 mmol/L
OR=6 Acute-phase death
OR=3 In-hospital death

N=1,177

Mortality Rate

<table>
<thead>
<tr>
<th>Lactate</th>
<th>Mortality Rate</th>
</tr>
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<tbody>
<tr>
<td>0-2.4</td>
<td>1.5%</td>
</tr>
<tr>
<td>2.5-3.9</td>
<td>4.5%</td>
</tr>
<tr>
<td>&gt;4.0</td>
<td>22.4%</td>
</tr>
</tbody>
</table>

25d in-hospital mortality
Death within 3d
Lactate in Sepsis Management

- **The Surviving Sepsis Campaign** advocates measuring lactate within 6h of presentation.

- **Lactate >4 mmol/L** (36 mg/dL) within 6 hours – Prompts initiation of crystalloid therapy and measurement of Central Venous Pressure (CVP) and oxygen saturation (Scvo₂)

- **Lactate Clearance** can predict response to therapies and morality
  - Goal Clearance >10% in first 6hours
Lactate Clearance Rate for Prognosis

Lactate Clearance = \frac{(\text{Lactate}_{\text{ED Presentation}}) - (\text{Lactate}_{\text{Hour 6}})}{\text{Lactate}_{\text{ED Presentation}}} \times 100

Clearance goal = 10% in 6 hours

<table>
<thead>
<tr>
<th>Group</th>
<th>% mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance</td>
<td>19</td>
</tr>
<tr>
<td>Non-clearance</td>
<td>60</td>
</tr>
</tbody>
</table>

Is Procalcitonin an Ideal Biomarker?

Inflammation
- synthesis by non-thyroidal cells with no cleavage

Sepsis
- With increasing severity

Calcitonin precursor

Linscheid, P. et al. Endocrinology 2003;144:5578-5584
PCT to Identify Sepsis in SIRS Patients

Can PCT predict an Infectious cause of inflammation?

• Meta-Analysis: 18 studies, 2097 patients (ICU and ED)
• All patients with SIRS
• Specificity and Sensitivity ~70%

Summary ROC Curve
AUC = 0.78
OR = 7.79

Lancet Infect Dis 2007(7):210 - 217
PCT to Predict Prognosis

472 random ICU patients (n=3642)

Decreasing or low PCT 30.7% mortality rate

Increasing PCT 56.1%

Crit Care Med 2000; 34(10):2596-602
PCT Guided Antibiotic Therapy

- 3 RCTs PCT Guided Antibiotic Cessation in Ad ICU pts
  - N=378, PCT group and 380 Control group
  - Significant reduction in antibiotic duration with PCT

- 5 RCTs PCT Guided Antibiotic Therapy in Adult ICU and CAP
  - N=468 PCT group and 470 Control group
  - No change in mortality rate with PCT guided therapy

Metanalysis/Consensus Guidelines for PCT and Antibiotic Therapy

- Low PCT concentrations can be used to direct cessation of antibiotics in ICU Patients
- High PCT concentrations should NOT be used to intensify antibiotic therapy
- Utility of PCT is still unknown in Peds and neonates
- More research is needed to show that PCT reduces number of “superbugs”

C-Reactive Protein (CRP) Expression in Infection/Inflammation

- Acute Phase Reactant
- Up-regulated by cytokines
- Most commonly used inflammatory marker

*Nat. Rev. Rheumatol. 2011*
CRP to Identify Sepsis in SIRS Patients

- Metanalysis of 10 Studies
- Adult and Pediatric
- ICU and ED
- PCT better than CRP to predict infectious SIRS (Sens = 75%, Spec 67%)

“No recommendation can be given for the use of [PCT and CRP] to distinguish between Severe infection and other acute inflammatory states.”

CRP to Predict Prognosis

- N = 891 Adults with Sepsis
- Measured CRP post antibiotic administration
- Lower CRP >2 days on ABX = better prognosis

Not for Trauma or Surgical Patients!!!
Elevation of Inflammatory Markers After Insult (Pathogen or Trauma)

![Graph showing the elevation of inflammatory markers over time.](graph.png)
Inflammatory Biomarkers to Identify Sepsis in SIRS Patients

Crit Care. 2006;10(2)

Sepsis vs SIRS
n=194 patients, 1ry care or ED
Combination of Biomarkers has Superior Diagnostic Utility than Single Biomarkers

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>AUC</th>
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<tbody>
<tr>
<td>CRP</td>
<td>0.81</td>
</tr>
<tr>
<td>PCT</td>
<td>0.72</td>
</tr>
<tr>
<td>Neut Count</td>
<td>0.74</td>
</tr>
<tr>
<td>MIF</td>
<td>0.63</td>
</tr>
<tr>
<td>sTREM-1</td>
<td>0.61</td>
</tr>
<tr>
<td>suPAR</td>
<td>0.50</td>
</tr>
<tr>
<td>3-marker</td>
<td>0.84</td>
</tr>
<tr>
<td>6-marker</td>
<td>0.88</td>
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- **Prospective Study**
- **SIRS vs Sepsis**
- **N=151, 96 bacterial infection**
Multiple Marker Panel to Predict Sepsis in SIRS Patients

n=169 Adult ICU Patients
(67 Sepsis, 102 SIRS)

<table>
<thead>
<tr>
<th>Analyte</th>
<th>AUC</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>CRP</td>
<td>0.76</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TNFα</td>
<td>0.72</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IL-6</td>
<td>0.78</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IL-10</td>
<td>0.73</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LBP</td>
<td>0.74</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5-Marker Panel</td>
<td>0.85</td>
<td>&lt;0.001</td>
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Prognostic Utility of Marker Combinations

Unpublished Observation
### Sepsis Biomarker – Score Card
#### Which Biomarkers and When?

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Sepsis vs SIRS</th>
<th>Prognosis</th>
<th>Therapy</th>
<th>Standard of Care</th>
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<tbody>
<tr>
<td>lactate</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Procalcitonin</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>CRP</td>
<td>No</td>
<td>Yes</td>
<td>Yes/?</td>
<td>No</td>
</tr>
<tr>
<td>Cytokines</td>
<td>No</td>
<td>Yes</td>
<td>?</td>
<td>No</td>
</tr>
<tr>
<td>Multimarker</td>
<td>Yes</td>
<td>Yes</td>
<td>?</td>
<td>No</td>
</tr>
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Self Assessment Questions

1. What is the difference between Severe Sepsis and Septic Shock?
   a. Severe Sepsis is associated with higher mortality
   b. Severe Sepsis is associated with Hypotension
   c. Lactate is only elevated in septic shock.
   d. IL-6 and PCT concentrations are generally higher in septic shock.

2. Which laboratory test is not utilized in the routine work up of a septic patient?
   a. Calcitonin
   b. Glucose
   c. Lactate
   d. Blood Cultures

3. What is the clinical utility of calculating lactate clearance?
   a. To diagnose early sepsis
   b. To predict prognosis
   c. To detect a laboratory error
   d. To predict a positive bacterial culture

4. The Clinical Utility of Procalcitonin includes:
   a. Identification of infected patients among those with systemic inflammation
   b. Monitoring of therapy for patients with recent trauma or surgery
   c. Determine when antibiotics should be discontinued in adult ICU patients
   d. Monitoring of therapy in pediatric septic patients