**Sepsis Syndrome**

David Chong M.D.
Assistant Professor of Medicine
Medical Director of Critical Care
Mountainside Hospital, Montclair New Jersey
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**Case**

- 45 yo male Microbiology Course director with no prior medical history comes in cough, shortness of breath, and chills for 5 days
- He is febrile to 103 and with RR of 35-40, HR of 115, and a BP of 85/60
- On Exam he has diffuse coarse right sided crackles with mild diffuse rhonchi
- He is a little confused (He believes he has won a Nobel Prize recently) and flushed with warm extremities
- His CXR shows dense, right sided, multi-lobar infiltrates

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**Labs**

- His ABG 7.49/31/105 on 100% Oxygen
- WBC 25k with 25 bands, PLT 80k
- Lactate is elevated at 5, Cr. 2.5, INR 3
- D-Dimer is elevated 8, and fibrinogen is low at 120

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**Assessment & Management**

- Diagnosis?
- Differential?
- Therapy?
- Complications?
- Outcome?
Sepsis Syndrome

- Definitions
- Pathophysiology
- Clinical Manifestations
- Therapy

ACCP/SCCM Consensus

Definitions

- Infection
  - Inflammatory response to microorganisms, or
  - Invasion of normally sterile tissues
- Systemic Inflammatory Response Syndrome (SIRS)
  - T >38°C (100.4°F) or <36°C (96.8°F)
  - HR >90
  - RR >20 or pCO2 <32mm Hg
  - WBC >12K or <4K or >10% Bands
- Sepsis
  - Infection plus ≥2 SIRS criteria
- Severe Sepsis
  - Sepsis
  - Organ dysfunction
  - Hypoperfusion
    - Lactic acidosis
    - Oliguria
    - Altered mental status
  - Septic shock
    - Severe Sepsis
    - Hypotension despite fluid resuscitation
      - BP <90 or SBP decrease >40
      - Inotropic or vasopressor agents
  - Multiple Organ Dysfunction Syndrome (MODS)
    - Altered organ function in an acutely ill patient
    - Homeostasis cannot be maintained without intervention

Lewis Thomas

“the microorganisms that seem to have it in for us . . . turn out . . . to be rather more like bystanders. . . . It is our response to their presence that makes the disease. Our arsenals for fighting off bacteria are so powerful . . . that we are more in danger from them than the invaders.”

Germs NEJM 1972;287:553-5
### Determinants of the Sepsis Syndrome

- Virulence of the organism
- Inoculum of the organism
- Site of Infection
- Host response
  - Inflammatory
  - Anti-inflammatory
  - “Balance”
- Genetic factors
  - Susceptibility
  - Regulation

### Organisms

- **Direct Invasion**
  - Bacteria
    - Aerobic
      - Gram-negative rods
        - Enterobacteriaceae-like: Klebsiella, Serratia
        - Pseudomonas
        - Gram-positive rods
          - Staphylococcus, Streptococcus
          - Neisseria meningitides
    - Upper Bacteria
      - Mycobacteria tuberculosis
      - Viruses
        - Flavivirus
        - Coronaviridae
      - Rickettsia
      - Fungi
        - Candida
        - Histoplasma
        - Aspergillus
      - Intoxication
  - Direct Invasion
    - Mycobacteria tuberculosis
    - Viruses
      - Flavivirus
      - Coronaviridae
    - Rickettsia
    - Fungi
      - Candida
      - Histoplasma
      - Aspergillus
    - Intoxication

![Diagram 1](image1.png)

**Figure 1.** Numbers of Cases of Sepsis in the United States, According to the Exposing Organism, 1995-2005.

- 25,000
- 20,000
- 15,000
- 10,000
- 5,000
- 0

![Diagram 2](image2.png)

![Diagram 3](image3.png)

**ENDOTOXIN: A COMPONENT OF THE GRAM-NEGATIVE BACTERIAL CELL WALL**

- Protein
- Cytoplasm
- Lipid A
- Core polysaccharide
- Disaccharide diphosphate
- Fatty acids
- O-antigen repeat 40 units

**Structure of Lipopolysaccharide**
Systemic Activation of Inflammation in Sepsis

Inflammation is Activated in Sepsis


LPS “Endotoxin” Interaction

- Growth phases of the bacteria
- Cell lysis by host clearance mechanisms
  - Complement fixation
  - Antibiotic action
- Direct interaction with host tissue
- Similar mechanism for gram positive organisms
  - Peptidoglycan layer
  - Non-peptidoglycan polymers
    - Teichoic acids
    - TNF and IL1

“Exotoxins”

- Toxic shock syndrome toxins
  - Strains of S. Aureus
  - Group A Strep. (S. Pyogenes)
- Superantigens
  - Unconventional binding
    - Antigen presenting cells
      - “outside” the antigen presenting groove of the MHC II molecule of the macrophage
    - T Lymphocytes
      - Bind uniquely to specific family of T lymphocytes with identical V beta regions of the T-cell receptor (for example V Beta11)
    - Small amounts resulting in a large T-cell and cytokine response

Pathophysiology of Sepsis

- LPS initiates the stereotypic inflammatory response
- Initial targets are the macrophage and vascular endothelial cell
- Endothelial cell
  - LPS-CD14 complex receptor
  - Macrophage
    - LPS-LPS binding protein CD14 receptor
- Another transmembrane signaling of inflammation is TLR
  - TLR4 for gram neg. bacteria
  - TLR2 for gram positive
- Translocation of NFkB
- Transcription of TNF

Mechanisms of Vasodilatory Shock

- Activation of ATP-sensitive K channels
- Activation of the inducible form of NO synthase
- Deficiency of vasopressin

SHOCK SYNDROMES

- Hypovolemic or Oligemic
- Cardiogenic
- Vascular Obstructive
- Distributive or Vasodilatory
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- Clinical Manifestations
- Therapy

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Sepsis: A Complex Disease

- This Venn diagram provides a conceptual framework to view the relationships between various components of sepsis.
- The inflammatory changes of sepsis are tightly linked to disturbed hemostasis.

**SIRS: More Than Just a Systemic Inflammatory Response**

- SIRS: A clinical response arising from a non-specific insult manifested by ≥2 of the following:
  - Temperature: ≥38°C or ≤36°C
  - HR: ≥90 beats/min
  - Respirations: ≥20/min
  - WBC count: ≥12,000/µL or ≤4,000/µL, or >10% immature neutrophils
- Recent evidence indicates that hemostatic changes are also involved.


**Sepsis: More Than Just Inflammation**

- Sepsis:
  - Known or suspected infection
  - Two or more SIRS criteria
- A significant link to disordered hemostasis


**Severe Sepsis: Acute Organ Dysfunction and Disordered Hemostasis**

- Severe Sepsis: Sepsis with signs of organ dysfunction ≥1 of the following systems:
  - Cardiovascular
  - Renal
  - Respiratory
  - Hepatic
  - Hemostasis
  - CNS
  - Unexplained metabolic acidosis


**Identifying Acute Organ Dysfunction as a Marker of Severe Sepsis**

- Tachycardia
- Hypotension
- Jaundice
- ↑ Enzymes
- ↓ Albumin
- ↑ PT
- Altered Consciousness
- Confusion
- Psychosis
- Tachypnea
- PaO2 <70 mm Hg
- SaO2 <90%
- PaO2/FiO2 ≤300
- Oliguria
- Anuria
- ↑ Creatinine
- ↓ Platelets
- ↑ PT/APTT
- ↓ Protein C
- ↑ D-dimer

**SHOCK SYNDROMES**

- Hypovolemic or Oligemic
- Cardiogenic
- Vascular Obstructive
- Distributive or Vasodilatory
### Hemodynamic Profiles

<table>
<thead>
<tr>
<th></th>
<th>Peripheral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Output</td>
<td>Early ↑↑</td>
</tr>
<tr>
<td></td>
<td>Late ↑↑</td>
</tr>
<tr>
<td>Vascular Resistance</td>
<td>↓↓</td>
</tr>
</tbody>
</table>

### Early Phase Late Phase

<table>
<thead>
<tr>
<th></th>
<th>Vital Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BP Modest ↓</td>
</tr>
<tr>
<td></td>
<td>Temp ↑ / ↓</td>
</tr>
<tr>
<td></td>
<td>RR ↑ / ↓</td>
</tr>
<tr>
<td></td>
<td>Pulse ↑ / ↓</td>
</tr>
<tr>
<td>Skin - warm, dry</td>
<td>CNS - may be altered, agitation</td>
</tr>
<tr>
<td>Urine output - usually ↓</td>
<td></td>
</tr>
<tr>
<td>Lab Data</td>
<td>ABG: pH ↑, pCO₂ ↓, pO₂ mod ↓</td>
</tr>
<tr>
<td></td>
<td>Lactic acid: ↑ or ↓</td>
</tr>
<tr>
<td></td>
<td>WBC: ↑ / ↓</td>
</tr>
<tr>
<td></td>
<td>Protime: prolonged</td>
</tr>
<tr>
<td></td>
<td>Platelets ↓</td>
</tr>
</tbody>
</table>

### Diagnosis

- Cultures
- Empiric Antibiotics
  - Likely site of infection “where?”
  - Likely Organisms
  - Specific Epidemiology from the environment
  - Antibigram
  - Early
- Clinical Response

### Management

- Ventilatory Support (ABC’s)
- Antibiotics
  - Early
  - Appropriate
- Resuscitation
  - Fluid
  - Crystalloid
  - Colloid
  - Vasoactive agents
- Intensive Monitoring
- Assess for cause
- Modulate the host response (restore balance)
- Minimize complications

### Early Goal-Directed Therapy In The Treatment of Severe Sepsis and Septic Shock

- Patients with severe sepsis or septic shock were randomly assigned to get early goal directed therapy vs. standard therapy for the first 6 hours; the physicians were "blinded"
- EGDT and standard therapy included CVP (8-12 mmHg), MAP (>65 mmHg), and UO (>0.5/hr) but EGDT added ScvO₂ >70, Hct 30 and DBA to increase CI to achieve the saturation goal
- There was a 16% absolute mortality reduction (46.5% vs. 30.5%)
- In the EGDT group O₂ saturation was higher, lactate was lower, base deficit was lower, pH higher, APACHE II lower and there was less severe organ dysfunction
- The EGDT got more fluid (3.49 vs. 4.98L), blood (18.5 vs. 64.1%), and Dobutamine (0.8 vs. 13.7%)
Results

- The study was halted at the 2nd interim eval.
- Reduction in the relative risk of death by 19.4%
- Absolute reduction was 6.1% (30.8 vs. 24.7)
- Incidence of serious bleeding was higher in the treatment group
- 3.5% vs. 2%
- The mortality difference was greatest in the sickest patients
- 1 additional life saved for every 16 treated
- 1 additional serious bleed for every 66 treated

Epidemiology

- Accounts for about 2% of admissions but 59% require intensive care
- $17 billion dollars in the US alone
- Mortality is 20-50%
- 2nd leading cause of death in noncoronary ICU’s
- 10th leading cause of overall death
- More common in men and in non-whites
- Patients are now older (57 to 60)
- Incidence has increased from 1979 (164,000 cases) to 2000 (660,000)-Annualized increase of 8.7%
- Deaths have increased from 43,579 to 120,491
- Gram positive organism are the predominant pathogens since 1987
- Mortality has decreased from 27% to 17%
- But only 56% go home vs. 78%

NEJM 2003;346:1546-54
Future Directions

- Intensive Insulin Therapy
  - Van den Berghe et al. NEJM 2001;345:1359-67

- Stress Dose Steroids
  - Annane et al. JAMA 2002;288:862-871

- New Immunomodulators?
  - Abraham et al. OPTIMIST Trial JAMA 2003;290:238-247

- New Paradigm?
  - Hotchkiss NEJM 2003;348:138-150

Intensive Insulin Therapy

Van den Berghe et al. NEJM 2001;345:1359-67

- Prospective, randomized controlled study of SICU patients on mechanical ventilation
- Intensive insulin therapy
  - Maintenance of blood glucose at a level between 80 and 110 mg per deciliter
- Conventional treatment
  - Infusion of insulin only if the blood glucose level exceeded 215 mg per deciliter and maintenance of glucose at a level between 180 and 200 mg per deciliter
- 1548 patients over 12 months
  - Reduced mortality from 8% to 4.6%
  - Benefit was due to its effect on patients who stayed in the SICU >5 days (20.2% vs. 10.6%)
  - The greatest reduction in mortality was in those patients that had MODS from a septic focus
  - Reduced in-hospital mortality by 34%
  - Blood stream infections by 46%
  - ARF requiring HD or CVVH by 41%
  - Median number of RBC transfusions by 50%
  - CIPN by 44%
  - Less likely to require prolonged ventilation and intensive care

Steroids and Septic Shock

Annane et al. JAMA 2002;288:862-871

- Septic shock may be associated with relative adrenal insufficiency; replacement therapy with low doses has been proposed (50 mg of hydrocortisone q6h plus 50 µg of fludrocortisone per day)
- Placebo-controlled, randomized, double-blind, parallel group trial in 19 ICU’s in France from 1995-1999
- Replacement steroids (n=151) or matching placebo (n=149) were given for 7 days; 28 day mortality in the nonresponders was the main outcome measure
- All the patients had to be septic and in shock and were randomized from the onset of shock
- The patients were then given a 250 µg IV bolus and cortisol levels were measured at time 0, 30 min, and 60 min
- Relative adrenal insufficiency was defined as a response of 9 µg/dL or less
- There were 229 nonresponders (115 placebo and 114 steroid) and 70 responders
- The mortality in the placebo group was 63% and 53% in the steroid group
- Vasopressors were withdrawn in the 57% in the steroid group vs. 40% in the placebo
Lewis Thomas

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Germs. NEJM 1972;287:553-5

When you are on the wards as a third year student and you have a patient with sepsis...