Sepsis Syndrome

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Case

- 45 yo male Microbiology Course director with no sign 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 the Nobel Prize and is the new Dean of the Health Sciences Campus) and flushed with warm extremities
- His CXR shows dense, right sided, multi-lobar infiltrates
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
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) or < 36°C (96.8)
  - HR > 90
  - RR > 20 or pCO₂ < 32 mm 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 mmHg
  - Inotropic or vasopressor agents

- **Multiple Organ Dysfunction Syndrome (MODS)**
  - Altered organ function in an acutely ill patient
  - Homeostasis cannot be maintained without intervention


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Sepsis Syndrome

- Definitions
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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
    - Aerobes
      - Gram negative rods
        - Enterobacteriaceae-like Klebsiella, Serratia
        - Pseudomonas
      - Gram positive cocci
        - Streptococcus, Staphylococcus
      - Gram negative cocci
        - Neisseria Meningitidis
  - Upper Bacteria
    - Mycobacteria tuberculosis
  - Viruses
    - Flavivirus
    - Coronaviridae
  - Rickettsia
    - Rickettsia
  - Fungi
    - Candida
    - Histoplasma
    - Aspergillus

- Intoxication

Figure 3. Numbers of Cases of Sepsis in the United States, According to the Causative Organism, 1979-2000. Points represent the number of cases for the given year, and 1 bars the standard error.
ENDOTOXIN: A COMPONENT OF THE GRAM-NEGATIVE BACTERIAL CELL WALL
Systemic Activation of Inflammation in Sepsis


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 Beta1)
  - 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-sCD14 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 NFκB
- Transcription of TNF

**Figure 2. Early Biochemical Events in Sepsis**

An initial toxic stimulus (e.g., endotoxin) triggers the production of proinflammatory mediators (e.g., tumor necrosis factor and interleukin-1). These cytokines, in turn, result in neutrophil–endothelial cell adhesion, activation of clotting, and generation of numerous secondary inflammatory mediators, including other cytokines, prostaglandins, leukotrienes, and proteases. Anti-inflammatory compounds, such as interleukin-6 and interleukin-10, that may serve as negative feedback to the inflammatory process, are also released.
Vessel Endothelium

intracellular
arachidonic acid

clothing cascade

extracellular
activation of Hageman Factor (XII)
complement cascade

C5a
eicosanoids
monokines

Intrinsic pathway
Contact activation
Exposure of connective tissue or negatively charged surface
- XII → Xa → XII → Prekallikrein
- XI → Xa
- IX → IXa
- X → Xa

- Xa + VIIIa

- F + VIIIa

- Va + Xa

Extrinsic pathway
Tissue injury
Vessel damage
Subendothelial tissue exposed to blood
- Prothrombin
- Thrombin
- Fibrinogen
- Soluble fibrin
- Stable fibrin

- XII
- Thrombin
- fibrin
Homeostasis Is Lost in Sepsis

- Proinflammatory mediators
- Endothelial injury
- Tissue factor expression
- Thrombin production

↑ Coagulation
↑ Inflammation
↓ Fibrinolysis

PAI-1: plasminogen activator inhibitor-1, TAFI: thrombin activatable fibrinolysis inhibitor
A Network of Cascading Events

Inflammation

Pro-inflammatory Mediators

Anti-inflammatory Mediators

Endothelial Injury

TF

PAI-1

Infection

T

Coagulation

TF

T-PA

Fibrinolysis

TAFI

Activated Protein C

Infection

Pro-inflammatory Mediators

Anti-inflammatory Mediators

Inflammation

Activated Protein C

Endothelial Injury

TF

PAI-1

TAFI

T-PA

Fibrinolysis
SHOCK SYNDROMES

- Hypovolemic or Oligemic
- Cardiogenic
- Vascular Obstructive
- Distributive or Vasodilatory

Mechanisms of Vasodilatory Shock

- Activation of ATP-sensitive K channels
- Activation of the inducible form of NO synthase
- Deficiency of vasopressin
Figure 1. Regulation of Vascular Smooth-Muscle Tone.
The steps involved in vasoconstriction are shown in blue, and the steps involved in vasodilatation are shown in red. The phosphorylation (P) of myosin is the critical step in the contraction of vascular smooth muscle. By way of second messengers, vasoconstrictors such as angiotensin II and norepinephrine induce an increase in the cytosolic calcium concentration, which activates myosin kinase. Vasodilators such as atrial natriuretic peptide and nitric oxide activate myosin phosphatase and, by dephosphorylating myosin, cause vasoconstriction. The plasma membrane is shown at a resting potential (plus signs). The abbreviation cGMP denotes cyclic guanosine monophosphate.
**Hyperpolarization**

Vasodilatation

\[ \text{Ca}^{2+} \rightarrow K^{+} \]

\[ \text{ATP} \rightarrow \text{H}^{+} \rightarrow \text{Lactate} \]

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**Sepsis or Tissue Hypoxia with Lactic Acidosis**

- ↑ Nitric oxide synthase
- ↓ ATP, ↑ H⁺, ↑ lactate in vascular smooth muscle
- Vasopressin secretion
- Vasopressin stores
- ↓ Phosphorylated myosin
- ↓ Plasma vasopressin

**Figure 4.** Mechanisms of Vasodilatory Shock.

Septic shock and states of prolonged shock causing tissue hypoxia with lactic acidosis increase nitric oxide synthesis, activate ATP-sensitive and calcium-regulated potassium channels \( K_{Ca} \) and \( K_{ATP} \), respectively, in vascular smooth muscle, and lead to depletion of vasopressin. The abbreviation cGMP denotes cyclic guanosine monophosphate.
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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 nonspecific 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 in ≥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

Figure 4: Onset and Resolution of Organ Failure in Patients with Severe Sepsis.

The bars show the duration of organ failure, with the timing of the onset and resolution of organ failure shown at the left and right ends of the bars, respectively. Acute lung injury — or its more severe form, the acute respiratory distress syndrome (ARDS) — develops early and is long-lived, with a mean duration of nine days. Shock and oliguria are similar in the timing of their onset, and the duration of both is brief, averaging less than two days. In contrast, central nervous system (CNS) dysfunction has a delayed onset and an intermediate duration.
# Shock Syndromes

Hypovolemic or Oligemic
Cardiogenic
Vascular Obstructive
Distributive or Vasodilatory

## Hemodynamic Profiles

<table>
<thead>
<tr>
<th></th>
<th>Cardiac Output</th>
<th>Vascular Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>↑↑↑</td>
<td>↓↓</td>
</tr>
<tr>
<td>Late</td>
<td>↑↑</td>
<td>↓↓</td>
</tr>
<tr>
<td></td>
<td>(↓)</td>
<td>(↑)</td>
</tr>
</tbody>
</table>
EARLY PHASE LATE PHASE

**Vital Signs**
- BP: Modest ↓
- Temp: ↑/↓-
- RR: rapid↑
- Pulse: ↑ “bounding”

**Skin**: warm, dry

**CNS**: may be altered, agitation

**Urine output**: usually ↓

**LAB DATA**
- ABG
  - pH↑, pCO₂↓, pO₂ mod↓
  - Lactic acid maybe ↑
  - glucose may be ↑ or ↓
  - WBC ↑/↓
  - Protime prolonged
  - Platelets ↓

**Vital Signs**
- BP: very ↓ or < 90
- Temp: ↑/nl/↓
- RR: ↑/nl/↓
- Pulse: ↑ “thready”

**SKIN**: cold, “clammy”

**CNS**: often confused

**URINE output**: usually ↓

**LAB DATA**
- ABG
  - pH↓, pCO₂↓ or nl, pO₂ mod↓
  - Lactic acid↑↑
  - glucose may be ↑ or ↓
  - WBC ↑/↓
  - Protime prolonged
  - Platelets ↓

**Diagnosis**

- **Cultures**
- **Empiric Antibiotics**
  - Likely site of infection “where?” (Source Control)
  - Likely Organisms
  - Specific Epidemiology from the environment
    - Antibiogram
  - Early

- **Clinical Response**
Management

- Ventilatory Support (ABC’s)
- Antibiotics
  - Early
  - Appropriate
- Resuscitation
  - Fluid
    - Crystalloid
    - Colloid
  - Blood
  - 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
Rivers et al. NEJM 2001;345:1368-77

- 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%)
- The number needed to treat was 6
EFFICACY AND SAFETY OF RECOMBINANT HUMAN ACTIVATED PROTEIN C FOR SEVERE SEPSIS

GORDON R. BERNARD, M.D., JEAN-LOUIS VINCENT, M.D., PH.D., PIERRE-FRANCOIS LATERRE, M.D., STEVEN P. LAROSA, M.D., JEAN-FRANCOIS DHIANAUT, M.D., PH.D., ANGEL LOPEZ-Rodriguez, M.D., JAY S. STEINGRUB, M.D., GARY E. GABBER, M.D., JEFFREY D. HELTERBRAND, PH.D., E. WESLEY ELY, M.D., M.P.H., AND CHARLES J. FISHER, JR., M.D., FOR THE RECOMBINANT HUMAN ACTIVATED PROTEIN C WORLDWIDE EVALUATION IN SEVERE SEPSIS (PROWESS) STUDY GROUP*
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

Figure 2. Kaplan–Meier Estimates of Survival among 850 Patients with Severe Sepsis in the Drotrecogin Alfa Activated Group and 840 Patients with Severe Sepsis in the Placebo Group. Treatment with drotrecogin alfa activated was associated with a significantly higher rate of survival (P = 0.006 by the stratified log-rank test).
**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
Figure 3. Numbers of Cases of Septic in the United States, According to the Causative Organism, 1979–2000.
Points represent the number of cases for the given year, and 1 bars the standard error.

Figure 4. Overall In-Hospital Mortality Rate among Patients Hospitalized for Septic, 1979–2000. Mortality averaged 27.8 percent during the first six years of the study and 17.9 percent during the last six years. The 1 bars represent the standard error.
Future Directions

- **Intensive Insulin Therapy**
  - Van den Berghe et al. NEJM 2001;345:1359-67
  - Van den Berghe et al. NEJM 2006;454:449

- **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

- **New Process?**
  - Bundles

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### 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 were 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 prolong ventilation and intensive care
Intensive Insulin Therapy II

Intention-to-treat analysis of 1200 patients, intensive insulin therapy reduced blood glucose levels but did not significantly reduce in-hospital mortality (40.0 percent in the conventional-treatment group vs. 37.3 percent in the intensive-treatment group, P=0.33).

However, morbidity was significantly reduced by
- the prevention of newly acquired kidney injury,
- accelerated weaning from mechanical ventilation
- accelerated discharge from the ICU and the hospital.

Although length of stay in the ICU could not be predicted on admission.

Among 433 patients who stayed in the ICU for less than three days, mortality was greater among those receiving intensive insulin therapy.

In contrast, among 767 patients who stayed in the ICU for three or more days, in-hospital mortality in the 386 who received intensive insulin therapy was reduced from 52.5 to 43.0 percent (P=0.009) and morbidity was also reduced.

Conclusions

Intensive insulin therapy significantly reduced morbidity but not mortality among all patients in the medical ICU.

Although the risk of subsequent death and disease was reduced in patients treated for three or more days, these patients could not be identified before therapy.

Van den Berghe et al. NEJM 2006;454:449
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 po).
- 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 3-8 from the onset of shock.
- The patients were then given a 250 μg IV bolus and cortisol levels were measures at time 0, 30min, 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 was 63% and 53% in the steroid group.
- Vasopressors were withdrawn in the 57% in the steroid group vs. 40% in the placebo.

**Table 1. Investigational Treatments of Sepsis.**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Therapeutic Rationale</th>
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<tbody>
<tr>
<td>Antifibrosis antibodies</td>
<td>Neutralize endotoxin, a compound that triggers sepsis</td>
</tr>
<tr>
<td>Antioxidant compounds</td>
<td>Neutralize effects of oxidants-mediated toxic injury</td>
</tr>
<tr>
<td>Antibacterials</td>
<td>Kill bacteria and restore endogenous components</td>
</tr>
<tr>
<td>Anti-tumor necrosis factor</td>
<td>Block action of tumor necrosis factor at the tissue level</td>
</tr>
<tr>
<td>Anticytokine antibodies</td>
<td>Block action of tumor necrosis factor at the tissue level</td>
</tr>
<tr>
<td>Interleukin-1 receptor antagonists</td>
<td>Inhibit action of interleukin-1 on cellular receptors</td>
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<tr>
<td>Interleukin antibodies</td>
<td>Prevent interleukin-1 receptor interactions</td>
</tr>
<tr>
<td>Bradykinin receptor antagonists</td>
<td>Prevent vasoactive effects of bradykinin</td>
</tr>
<tr>
<td>Cyclooxygenase inhibitors</td>
<td>Block inappropriate pyrogens, thromboxane, and prostacyclin production</td>
</tr>
<tr>
<td>Thrombomodulin antagonists</td>
<td>Inhibit inappropriate vasoactive effects of thromboxane</td>
</tr>
<tr>
<td>Platelet activating factor</td>
<td>Block platelet activation and inflammatory lipid release</td>
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Germs NEJM 1972;287:553-5
Bundles

- All or nothing
- Changing our approach and processes
- Bundled together is profoundly better than any of the individual elements
- Decreasing hospital infection rates to 0
- Can be a wonderfully successful and joyous
Sepsis Bundle

- **Resuscitation**
  - Lactate if >4 mmol/L give at least 20mL/kg in the first 6 hours until the CVP > 8 mmHg or lactate < 4
  - Blood cultures prior to abx
  - Abx within 3 hours in ED or within 1 hour on the floor
  - Pressors if MAP > 65 if BP cannot be maintained with IVF (NE then Vasopressin)
  - Consider SvO2 sat (>65% is the goal)

- **Management (24 hours)**
  - Stress steroids if still in shock and perform Cortrosyn stim test (d/c if > 9 pre to post)
  - Consideration for Activated Protien C (Xigris) [APACHE > 25]
  - Insulin drip if glucose is > 150
When you are on the wards as a third year student and you have a patient with sepsis...