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 his name is Barack Obama and is the presumptive Democratic nominee for president) and flushed with warm extremities
- His CXR shows dense, right sided, multi-lobar infiltrates
Labs

- His ABG is 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 < 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 mmHg
    - Inotropic or vasopressor agents
- **Multiple Organ Dysfunction Syndrome (MODS)**
  - Altered organ function in an acutely ill patient
  - Homeostasis cannot be maintained without intervention

Sepsis Syndrome

- Definitions
- **Pathophysiology**
- Clinical Manifestations
- Therapy

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
    - Coronavirus
  - 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

Protein

Cytoplasm

Protein

Lipid A

Structure of Lipopolysaccharide

O-antigen
repeat 40 units

Core polysaccharide

Disaccharide diphosphate

Fatty acids

man

rha

abe

gal

P

qln

qln

P

O HN

O HN
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 NFkB
- Transcription of TNF

Representative Agonists for Toll-like Receptors

- Bacterial Lipoprotein
- Mycoplasmal Lipoprotein
- Lipopolysaccharide
- Viral RNA
- Enzyme-modified LPS
- Bacterial Flagellin
- Bacterial DNA

Activation of Innate Immune Response
Figure 2: Early Biochemical Events in Sepsis
An initial toxic stimulus (e.g., endotoxin) triggers the production of proinflammatory monokines (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. Antiinflammatory compounds, such as interleukin-6 and interleukin-10, that may serve as negative feedback to the inflammatory process, are also released.
SHOCK SYNDROMES

- Hypovolemic or Oligemic
- Cardiogenic
- Vascular Obstrucive
- 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 vasorelaxation. The plasma membrane is shown at a resting potential (plus signs). The abbreviation cGMP denotes cyclic guanosine monophosphate.
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 $K_{ATP}$ and $K_{Ca}$ 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**

- Altered Consciousness
- Confusion
- Psychosis
- Tachypnea
- PaO₂ < 70 mm Hg
- SaO₂ < 90%
- PaO₂/FiO₂ ≤ 300
- Jaundice
- ↑ Enzymes
- ↓ Albumin
- ↑ PT
- Tachycardia
- Hypotension
- 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>Peripheral</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

- 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 ↓

LATE PHASE

- 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
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
**Figure 1.** Population-Adjusted Incidence of Septic, According to Sex, 1979–2000.
Points represent the annual incidence rate, and 1 bars the standard error.

**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.
Future Directions

- Intensive Insulin Therapy?
- Stress Dose Steroids?
- New Immunomodulators?
- New Paradigm?
- New Process?
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

Van den berghe et al. NEJM 2006;454:449

- 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.
- Length of stay >3 days 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.
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 hours from the onset of shock
- The patients were then given a 250 μg IV bolus and cortisol levels were measured at time 0, 30min, and 60 min after
- 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
- However, the analysis was done correcting for baseline cortisol, cortisol response, McCabe Classification, LOD score, arterial lactate, and P/F ratio

Corticus

- Multicenter, randomized, double-blind, placebo-controlled trial
- 251 patients received 50 mg of intravenous hydrocortisone and 248 patients received placebo every 6 hours for 5 days; then the dose was then tapered during a 6-day period.
- At 28 days, the primary outcome was death among patients who did not have a response to a corticotropin test.
- Of the 499 patients in the study, 233 (46.7%) did not have a response to corticotropin (123 in the hydrocortisone group and 108 in the placebo group).
- At 28 days, there was no significant difference in mortality between patients in the two study groups who did not have a response to corticotropin (39.2% in the hydrocortisone group and 36.1% in the placebo group, P = 0.69)
- No difference in patients who had a response to corticotropin (28.8% in the hydrocortisone group and 28.7% in the placebo group, P = 1.00).
- At 28 days, 86 of 251 patients in the hydrocortisone group (34.3%) and 78 of 248 patients in the placebo group (31.5%) had died (P = 0.51).
- In the hydrocortisone group, shock was reversed more quickly than in the placebo group.
- However, there were more episodes of superinfection, including new sepsis and septic shock.
- Of note the original plan was to recruit 800 patients but had to stop at 500; however it is still the largest study to date.
- Recruitment from 52 centers over 44 months, on average each center took approx 5 months to recruit each patient. The question of clinical equipoise was raised.
In this multicenter, randomized, double-blind trial, patients who had septic shock and were receiving a minimum of 5 μg of norepinephrine per minute to receive either low-dose vasopressin (0.01 to 0.03 U per minute) or only norepinephrine (6 to 15 μg per minute) in addition to open-label vasopressors.

The primary end point was the mortality rate 28 days after the start of infusions.

A total of 778 patients underwent randomization (396 patients received vasopressin, and 382 norepinephrine), and were included in the analysis.

There was no significant difference between the vasopressin and norepinephrine groups in the 28-day mortality rate (35.4% and 39.3%, respectively; P = 0.26) or in 90-day mortality (43.9% and 49.6%, respectively; P = 0.11).

There were no significant differences in the overall rates of serious adverse events (10.3% and 10.5%, respectively; P = 1.00).

In the prospectively defined stratum of less severe septic shock, the mortality rate was lower in the vasopressin group than in the norepinephrine group at 28 days (26.5% vs. 35.7%, P = 0.05).

In the stratum of more severe septic shock, there was no significant difference in 28-day mortality (44.0% and 42.5%, respectively; P = 0.76). A test for heterogeneity between these two study strata was not significant (P = 0.10).

Low-dose vasopressin did not reduce mortality rates as compared with norepinephrine among patients with septic shock who were treated with catecholamine vasopressors.

*This was not a primary vasopressor trial*

*These patients were not refractory to vasopressors.*

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**Table 1. Investigational Treatments of Sepsis**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Therapeutic Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimicrobial antibodies</td>
<td>Neutralize endotoxin, a compound that elicits sepsis</td>
</tr>
<tr>
<td>Antioxidant compounds</td>
<td>Neutralize effects of oxidant-mediated tissue injury</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>Inhibit formation of microthrombi and injury due to tissue ischemia and reperfusion</td>
</tr>
<tr>
<td>Tumor necrosis factor 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>
</tr>
<tr>
<td>Interleukin-1 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 inappropriately prolonged, thromboxane, and prostacyclin production</td>
</tr>
<tr>
<td>Thrombomodulin antagonists</td>
<td>Inhibit inappropriately von Willebrand factor and platelet aggregation</td>
</tr>
<tr>
<td>Platelet activating factor analogues</td>
<td>Block platelet activation and inflammatory lipid release</td>
</tr>
<tr>
<td>Inhibitors of leukocyte adhesion molecule</td>
<td>Prevent endothelial-leukocyte interaction</td>
</tr>
<tr>
<td>Nitric oxide antagonists</td>
<td>Restore appropriate vasoregulation</td>
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Germs NEJM 1972;287:553-5
A new approach?

A new process of care?

Central Line Bundle

- Hand Hygiene
- Maximal Barrier Precautions Upon Insertion
- Chlorhexidine Skin Antisepsis
- Optimal Catheter Site Selection
- Daily Review of Line Necessity with Prompt Removal of Unnecessary Lines
Ventilator Associated Pneumonia (VAP) Bundle

- Elevation of the Head of the Bed
- Daily "Sedation Vacations" and Assessment of Readiness to Extubate
- Peptic Ulcer Disease Prophylaxis
- Deep Venous Thrombosis Prophylaxis

BELLEVUE MICU

VAP

CRBSI
Sepsis Bundle

- **Resuscitation**
  - Lactate if >4 mmol/L give at least 20 ml/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 (24hours)**
  - Stress steroids if the patient is “poorly responsive to fluid and vasopressor therapy”
  - Documentation of the consideration for Activated protein C (APACHE>25)
  - Insulin drip if glucose is >150
  - Plateau Pressure <30 cmH2O

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**Improvement in Process of Care and Outcome After a Multicenter Severe Sepsis Educational Program in Spain**

- **Objectives**
  - To determine whether a educational program based on the Severe Sepsis Campaign guidelines improved process or outcomes in severe sepsis.
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- **Methods**
  - A multicenter before-after study in 24 hospitals from Madrid, Barcelona, and Malaga.
  - The study was conducted over 2 years (2010-2011).
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- **Results**
  - Significant improvements in process of care were observed in all centers.
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- **Conclusions**
  - A national educational effort to improve outcomes of severe sepsis patients was associated with improved process of care and lower mortality.
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When you are on the wards as a third year student and you have a patient with sepsis...