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

Dr. Glenda Garvey

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?

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Sepsis Syndrome

- Definitions
- Pathophysiology
- Clinical Manifestations
- Therapy

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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
    - Dilated pupils
    - 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

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
          - Staphylococcus, Staphylococcus
          - Gram negative cocci
            - Neisseria meningitidis
      - Upper Bacteria
        - Mycobacteria tuberculosi
        - Viruses
          - Flavivirus
          - Coronavirus
          - Rickettsia
          - Rickettsia
            - Rickettsia
      - Fungi
        - Candida
        - Histoplasma
        - Aspergillus
    - Intoxication

ENDOTOXIN: A COMPONENT OF THE GRAM-NEGATIVE BACTERIAL CELL WALL
Systemic Activation of Inflammation in Sepsis

“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 beta3)
  - 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 signalling of inflammation is TLR
  - TLR4 for gram neg. bacteria
  - TLR2 for gram positive
- Translocation of NFkB
- Transcription of TNF

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
    - Lipoteichoic acids
- "Exotoxins"

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
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- Severe Sepsis
  - Sepsis
  - Organ dysfunction
    - Lactic acidosis
    - oliguria
    - Altered mental status
  - Septic shock
  - Severe Sepsis
  - Hypotension despite fluid resuscitation
    - SBP <90 mmHg or SBP decrease >40 mmHg
    - 1 vasopressor or inotropic agent
  - Multiple Organ Dysfunction Syndrome (MODS)
    - Altered organ function in an acutely ill patient
    - Homeostasis cannot be maintained without intervention

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.


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


Sepsis: More Than Just Inflammation

- Sepsis:
  - Known or suspected infection
  - Two or more SIRS criteria

- A significant link to disordered hemostasis

SHOCK SYNDROMES

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

Hemodynamic Profiles

<table>
<thead>
<tr>
<th></th>
<th>Peripheral 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>
</tbody>
</table>

Diagnosis

- Cultures
- Empiric Antibiotics
  - Likely site of infection “where?” (Source Control)
  - Likely Organisms
  - Specific Epidemiology from the environment
    - Antib gram
    - Early
- Clinical Response

Management

- Ventilatory Support (ABC’s)
- Antibiotics
  - Early
  - Appropriate
- Resuscitation
  - Fluid
    - Crystalloid
    - Colloid
  - Blood
  - Vasopressor 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/L/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 (14.9 vs. 4.9L), blood (18.5 vs. 64.1%), and Dobutamine (0.8 vs. 13.7%)
- The number needed to treat was 6

EARLY PHASE LATE PHASE

<table>
<thead>
<tr>
<th>Early Phase</th>
<th>Late Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vital Signs</td>
<td>Vital Signs</td>
</tr>
</tbody>
</table>
- BP: Modest ↓ |
- Temp ↑ ↑ |
- RR ↑ |
- Pulse ↑ “bounding” |
- Skin - warm, dry |
- CNS - may be altered, agitation |
- Urine output - usually ↓ |
- LAB DATA |
  - ABG |
  - pH ↓, pCO2 ↑ , pO2, mod ↓ |
  - Lactic acid may ↑ |
  - glucose may be ↑ or ↓ |
  - WBC ↑ ↓ |
  - Platelets ↓ |
- Vital Signs |
- BP very ↓ or <90 |
- Temp ↑ ↓ or ↓ |
- RR ↑ ↓ |
- Pulse ↑ “thready” |
- SKIN - cold, “clammy” |
- CNS - often confused |
- URINE output - usually ↓ ↓ |
- LAB DATA |
  - ABG |
  - pH ↓, pCO2 ↓ or ni , pO2, mod ↓ |
  - Lactic acid ↑ ↑ |
  - glucose may be ↑ or ↓ |
  - WBC ↑ ↓ |
  - Platelets ↓ |
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
- 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%
Future Directions

- Intensive Insulin Therapy
  - Van den Berghe et al. NEJM 2005;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

Intensive Insulin Therapy

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

- Prospective, randomized controlled study of 1548 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 ICU >5 days (20.2% vs. 15.6%)
- 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

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.
- 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 disability was reduced in patients treated for three or more days, these patients could not be identified before therapy.
Steroids and Septic Shock

Annan 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 ICUs 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 measured 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

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 joyful

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
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 (24hours)**
  - Stress steroids if still in shock and perform Cortrosyn stim test (d/c if >9 pre to post)
  - Consideration for Activated Protein C (Xigris)
  - [APACHE>25]
  - Insulin drip if glucose is >150

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