Sepsis

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Sepsis

- Epidemiology
- Definitions
  - Sepsis
  - SIRS
  - Severe sepsis
- Clinical, hematologic and immunologic manifestations
- Management
- Clinical example
  - Neisseria meningitides
Severe Sepsis:
A Significant Healthcare Challenge

- Major cause of morbidity and mortality worldwide
  - Leading cause of death in noncoronary ICU (US)*
  - 11th leading cause of death overall (US) †§

- More than 750,000 cases of severe sepsis in US annually‡

- In the US, more than 500 patients die of severe sepsis daily‡

Severe Sepsis: Comparison With Other Major Diseases

**Incidence of Severe Sepsis**

- AIDS*
- Colon Cancer
- Breast Cancer
- CHF
- Severe Sepsis

**Mortality of Severe Sepsis**

- AIDS*
- Breast Cancer
- AMI†
- Severe Sepsis‡

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Severe Sepsis: An alarming national trend

Today

>750,000 cases of severe sepsis/year in the US*

Future

2001 2025 2050

100,000 200,000 300,000 400,000 500,000 600,000

2001, 2025, 2050:

Sepsis Cases

US Population

Severe Sepsis Cases

US Population/1,000

ACCP/SCCM Consensus Definitions

• Infection
  – Inflammatory response to microorganisms, or
  – Invasion of normally sterile tissues

• Systemic Inflammatory Response Syndrome (SIRS)
  – Systemic response to a variety of processes

• Sepsis
  – Infection plus
  – ≥2 SIRS criteria

• Severe Sepsis
  – Sepsis
  – Organ dysfunction

• Septic shock
  – Sepsis
  – Hypotension despite fluid resuscitation

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

Sepsis: A Complex Disease

- 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: What are the clinical manifestations?

- Altered Consciousness
- Confusion
- Psychosis
- Delirium

- Tachypnea
  \( \text{PaO}_2 \ < 70 \text{ mm Hg} \)
  \( \text{SaO}_2 \ < 90\% \)
  \( \text{PaO}_2/\text{FiO}_2 \leq 300 \)

- Jaundice
  \( \uparrow \text{Enzymes} \)
  \( \downarrow \text{Albumin} \)
  \( \uparrow \text{PT} \)

- Tachycardia
- Hypotension
  \( \uparrow \text{CVP} \)
  \( \uparrow \text{PAOP} \)

- Oliguria
- Anuria
  \( \uparrow \text{Creatinine} \)

- \( \downarrow \text{Platelets} \)
  \( \uparrow \text{PT/APTT} \)
  \( \downarrow \text{Protein C} \)
  \( \uparrow \text{D-dimer} \)
Severe Sepsis: A Complex and Unpredictable Clinical Syndrome

- High mortality rate (28%-50%)
- Heterogeneous patient population
- Unpredictable disease progression
- Unclear etiology and pathogenesis

Systemic Inflammation and Disordered Homeostasis
Systemic Activation of Inflammation in Sepsis

Inflammation is Activated in Sepsis

Endotoxin (ng/L) vs. Minutes After LPS Infusion

0 60 120 180 240 300 360

TNF (ng/L)
IL-6 (U/mL)

Activation of Coagulation in Severe Sepsis


Percent of Patients

↓ Platelets  ↑ PTT  ↑ PT  Any One  Any Two  All Three  ↓ Protein C  ↑ D-Dimers

Impairment of Fibrinolysis in Severe Sepsis

Plasminogen/antiplasmin ratio

Time after hospital admission (day)

Survivors (n=23)  Nonsurvivors (n=25)  Normal Values

Homeostasis Is Unbalanced in Severe Sepsis

↑ Coagulation
↑ Inflammation
↓ Fibrinolysis

Homeostasis
Endogenous Modulators of Inflammation

- Antiinflammatory cytokines
- Activated Protein C
  - Inhibits thrombin-mediated inflammatory activities
  - Inhibits attachment of leukocytes to endothelium

Endogenous Modulators of Thrombosis

- Activated Protein C
- Antithrombin III-heparan sulfate
- Tissue factor pathway inhibitor (TFPI)

Prevent coagulation from becoming generalized

Endogenous Modulators of Fibrinolysis

- Tissue plasminogen activator (t-PA)
- Activated Protein C inhibits:
  - PAI-1
  - TAFI activation

Remove formed microthrombi and maintain blood fluidity

Endogenous Activated Protein C Modulates Coagulation, Fibrinolysis, and Inflammation in Severe Sepsis

Activated Protein C
\[ \downarrow \text{Coagulation} \quad \downarrow \text{Inflammation} \]

Activated Protein C
\[ \uparrow \text{Fibrinolysis} \]

Homeostasis

Severe Sepsis: The Final Common Pathway

*Endothelial Dysfunction and Microvascular Thrombosis*

- Hypoperfusion/Ischemia

- Acute Organ Dysfunction (Severe Sepsis)

- Death
Sepsis: Management
Severe Sepsis Therapy: Standard Care

- Source control
- Antibiotics
- Hemodynamic support
- Mechanical ventilation
- Renal replacement therapy
- Sedation/analgesia
- Ensure adequate nutrition
- Provide hematological support
- Other supportive measures

Severe Sepsis Therapy: Numerous Investigational Approaches

- **Bacterial modulators**
  - Antiendotoxin, BPI

- **Anticytokines**
  - IL-1ra, anti-TNF, sTNF-r

- **Antiinflammatory agents**
  - Glucocorticoids, leukocyte adhesion molecule inhibitors

- **Hemostatic agents**
  - Recombinant Human Activated Protein C, ATIII, TFPI, heparin

- **Other**
  - iNOS inhibition, antioxidants, thromboxane antagonists, bradykinin receptor antagonists

Role of Activated Protein C in Infection

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).
Figure 3. Changes in Median Plasma D-Dimer Levels in 770 Patients with Severe Sepsis in the Drotrecogin Alfa Activated Group and 729 Patients in the Placebo Group. Only patients with base-line values and at least one subsequent value were included in the analysis. The P values are for the comparison with the placebo group.
Meningococcal Disease

Inmate dies of meningitis

No other cases reported among other inmates, city jail staff

BY JIM MASON
TIMES-DISPATCH STAFF WRITER

A Richmond City Jail inmate diagnosed with bacterial meningitis died yesterday morning in Medical College of Virginia Hospitals.

The Richmond Sheriff's Office identified the inmate as Stephen Stevenson but provided no other details about him. A hospital spokesperson confirmed the death.

Sheriff Michelle B. Mitchell couldn't be reached last night, but a news release from her office yesterday afternoon said there had been no other reported cases among inmates or jail staff.

Doctors at MCV's Infectious Disease Clinic made the diagnosis and recommended treatment with an antibiotic for anyone who had had contact with the inmate, the release said.

The jail's night watch commander, asked last night whether any jail inmates or staff had been treated, said he wasn't authorized to give any information.

According to the news release, Stevenson entered the jail July 23. On Friday, he became ill with flu-like symptoms and was treated at the jail for pain and a fever.

A physician at the jail treated him Saturday morning for a viral infection and dehydration, the news release said.

Saturday evening, Stevenson's condition deteriorated, and he was taken to MCV.

Meningitis is an infection of the fluid of a person's spinal cord and fluid surrounding the brain. Viral meningitis is generally less severe, while bacterial meningitis may result in brain damage and is potentially fatal.

Infection is marked by high fever, headache and a stiff neck, symptoms that can develop within hours or a few days. Other symptoms may include nausea, vomiting and sleepiness.

Medical authorities say early diagnosis and treatment with antibiotics are critical.

Contact Jim Mason at (804) 649-6451 or jmason@timesdispatch.com

MONDAY, SEPTEMBER 10, 2001

Meningitis hits VUU student

Bacterial version strikes freshman

BY SHAWN COX
TIMES-DISPATCH STAFF WRITER

An 18-year-old freshman at Virginia Union University was in critical condition last night after contracting bacterial meningitis, a rare but contagious, and potentially fatal, infection.

The New York City native, whose identity is being withheld at the request of his family, was admitted to Virginia Commonwealth University's Medical College of Virginia Hospitals about 3 a.m. yesterday after experiencing vomiting and other flu-like symptoms.

"The doctor said, if he had a crystal ball and could look in it and tell us that everything was going to be all right, he certainly would want to be able to do that," VUU President Bernard W. Franklin said last night. "But at this point, the best that we can do is wait and pray.

"This has been a very sobering experience for our students, even though during our freshman orientation program we did emphasize the importance of getting a vaccination for meningitis. After the sobering effect, I
# Meningoccal Disease:
Recent Cases at MCVH

<table>
<thead>
<tr>
<th>Case #1</th>
<th>Case #2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admit date</td>
<td>August 11, 2001</td>
</tr>
<tr>
<td>Age/gender</td>
<td>24 year old male inmate</td>
</tr>
<tr>
<td>Residence</td>
<td>Richmond City Jail</td>
</tr>
<tr>
<td>Presentation</td>
<td>1 day h/o headache, fever, myalgias; found unconscious</td>
</tr>
<tr>
<td>PMH</td>
<td>GSW abdomen 1997→ asplenic</td>
</tr>
<tr>
<td>Outcome</td>
<td>Died on hospital day #3</td>
</tr>
</tbody>
</table>
**Meningococcal Disease:**
**Recent Cases at MCVH**

<table>
<thead>
<tr>
<th></th>
<th>Case #1</th>
<th>Case #2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cultures</td>
<td>Blood: <em>N. meningitidis</em></td>
<td>Blood, CSF: <em>N. meningitidis</em></td>
</tr>
<tr>
<td>Serogroup</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>PCN MIC</td>
<td>0.125 mg/L</td>
<td>0.25 mg/L</td>
</tr>
<tr>
<td>Ceftriaxone MIC</td>
<td>0.004 mg/L</td>
<td>0.004 mg/L</td>
</tr>
</tbody>
</table>
Microbiology

- Gram-negative, biscuit-shaped diplococci
- Usually found extracellularly & in PMNs
- Usually encapsulated & piliated
- Aerobic
- 13 serogroups based on capsular polysaccharide
- Capacity to exchange genes for capsule production → can switch serogroups
- Humans are the only natural reservoir
CSF Gram stain, patient #2
Virulence Factors

- Capsule: prevents desiccation & aids in evasion of host defenses
- Pili: promote adherence to epithelium
- Nutrient acquisition factors (e.g., iron)
- Endotoxin
- Autolysis: releases DNA & cell wall components which induce the inflammatory cascade

Epidemiology of Meningococcal Disease

- 2,400-3,000 cases/year in the US
- 500,000 cases/year in the world
- 2nd most common cause of meningitis in the US (10-35% of cases)
- >90% of cases occur in pts <45 years old
- Numerous outbreaks on college campuses
- Meningitis belt: intense serogroup A epidemics in broad savannah region in Africa from Gambia to Ethiopia

Source: WHO, 1998
Risk Factors for Meningococcal Disease in College Students
Matched (3:1) case control study; 96 cases; multivariate analysis

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freshman in dormitory</td>
<td>3.6 (1.6-8.5)</td>
<td>.003</td>
</tr>
<tr>
<td>White race</td>
<td>6.6 (1.2-38.0)</td>
<td>.03</td>
</tr>
<tr>
<td>Radiator heat</td>
<td>4.0 (1.4-11.0)</td>
<td>.008</td>
</tr>
<tr>
<td>URI in last month</td>
<td>2.3 (1.0-5.3)</td>
<td>.04</td>
</tr>
</tbody>
</table>

Bruce MG et al. JAMA 2001;286:688-693.
Meningococcal Disease, US Army, World Wars

<table>
<thead>
<tr>
<th></th>
<th>Number of cases</th>
<th>Number of deaths</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>World War I</td>
<td>5,839</td>
<td>1,836</td>
<td>31.4%</td>
</tr>
<tr>
<td>World War II</td>
<td>13,922</td>
<td>559</td>
<td>4.0%</td>
</tr>
</tbody>
</table>

Host Response to Respiratory Infection with *N. meningitidis*

- Complete eradication of the organism
- Nasopharyngeal carrier state without systemic invasion
- Nasopharyngeal carrier state leads to systemic disease
Transmission

- Person to person by respiratory droplets or direct contact with secretions
- Since respiratory droplet susceptible to drying, close contact (<3 feet) is necessary for transmission
- Most pts have not had contact with a case, thus asymptomatic carriers are the source of transmission
- 300-1000 fold increased risk for invasive disease in household contacts of an index case (attack rate 0.3-1%)
- 1/1000-1/5000 colonized persons develops invasive disease
Colonization

• Site of colonization is the nasopharynx
• 5-10% of adults are asymptomatic carriers
• Median duration of carriage = 9-10 months
• Carriage is an immunizing process
• Carriage rate increases under conditions where people from different regions are brought together (e.g., military recruits, pilgrims, colleges, jails)
Pathogenesis

1. Inhalation of infectious droplet
2. Organism passes the mucous barrier; produces ciliostasis via cytotoxic activity
3. Attachment to nonciliated epithelial mucosal cells via pili
4. Invasion via organism-directed endocytosis
5. Passage to submucosa
6. Bloodstream invasion

Pathology

- Primary lesion: diffuse vascular damage & intravascular coagulation
- Blood vessels blocked by fibrin thrombi with trapping of WBCs & bacteria → tissue ischemia
- Sites: skin, serosal & mucosal surfaces, mediastinum, epicardium, endocardium, lungs, liver, kidneys, adrenals, intestines, spleen
Clinical Syndromes Associated with *N. meningitidis*

- Transient benign bacteremia
- Acute meningococcemia without meningitis
- Meningitis ± meningococcemia
- Meningoencephalitis
- Respiratory tract infection: pneumonia, epiglottis, otitis media
- Focal infection: conjunctivitis, septic arthritis, urethritis, pericarditis
- Chronic meningococcemia
<table>
<thead>
<tr>
<th>Clinical Syndromes</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacteremia without sepsis</strong></td>
<td>Child presents with upper respiratory illness or viral exanthem; blood cultures surprisingly grow NM but repeat cultures negative; uncomplicated recovery without antibiotics</td>
</tr>
<tr>
<td>(transient benign bacteremia)</td>
<td></td>
</tr>
<tr>
<td><strong>Meningococcemia without meningitis</strong></td>
<td>Septic picture; headache, fever, rash, malaise, hypotension</td>
</tr>
<tr>
<td><strong>Meningitis + meningococcemia</strong></td>
<td>Headache, fever, meningeal signs, cloudy CSF; DTRs, superficial reflexes present; no pathologic reflexes</td>
</tr>
<tr>
<td><strong>Meningoencephalitis</strong></td>
<td>Profoundly obtunded, meningeal signs, septic CSF; DTRs, superficial reflexes altered; pathologic reflexes frequently present</td>
</tr>
</tbody>
</table>

Meningococcemia
Acute Meningococcemia without Meningitis

- Presents with sudden onset of fever, chills, myalgias, weakness, nausea, vomiting, headache
- Leukocytosis with left shift
- Rash present or develops over next few hours
- Some develop hypotension or shock
- In fulminant cases, death can occur within 12 hours of symptom onset
Acute Meningococcemia: Rash

• Erythematous maculopapular rash
  – Light pink
  – Indistinct borders
  – Transient (half hour to 2 days)
• Purpuric rash
  – Occurs in 40-90%
  – Always accompanied by DIC
  – Petechiae, ecchymoses or gross intracutaneous hemorrhages
  – Purpura usually appear within 12-36 hours of disease onset
  – May lead to purpura fulminans
Meningococcemia Complications

- Purpura fulminans
- Autoimmune-like complications:
  - Synovitis
  - Serositis
- Neurologic sequelae (0-15%)
  - Deafness (4-6%)
  - CN VI, VII palsies (5-10%)
Meningococcemia Complications

- Bilateral adrenal hemorrhage (Waterhouse-Friderichsen Syndrome)
  - Found in 30% of patients with shock secondary to meningococcal disease
  - Found in 70% of cases at autopsy

Laboratory Studies

- CSF: gram stain positive in 75-80%; culture positive in 90%
- CSF latex agglutination: 70-80% sensitive
- Peripheral blood smear: organisms may be seen indicating high-grade bacteremia; suspect asplenic state
- Blood culture: positive in 40-75%
Management

- Cannulation of large compressible vein (i.e., femoral)
- Early fluid resuscitation for patients in shock
- Inotropic support
- Alkalization for patients with rhabdomyolysis
- Maintain high suspicion for adrenal insufficiency
- Empiric corticosteroids for meningococcal meningitis controversial

Management: Antimicrobials

- Should not be delayed for diagnostic procedures
- Drug of choice: ceftriaxone 2 g IV q 12 hrs
Protein C

• Vitamin-K dependent glycoprotein
• Promotes fibrinolysis & inhibits thrombosis & inflammation
• Once activated, protein C requires protein S as a cofactor for its anticoagulant functions
• In severe meningococcal sepsis, protein C activation is impaired, leading to widespread thrombosis, DIC & purpura fulminans

Role of Activated Protein C in Infection

- **Antiinflammatory:**
  - inhibits production of inflammatory cytokines (TNF-α, IL-1, IL-6)
  - Limits rolling of monocytes & PMNs on injured endothelium

- **Antithrombotic:**
  - Inactivates factors Va & VIIIa, thereby limiting generation of thrombin

- **Fibrinolytic:**
  - Inhibits PAI-1

Management: Recombinant Activated Protein C for Severe Sepsis

- Randomized, double-blind, placebo-controlled, multicenter trial
- Severe sepsis, any organism
- N=1,690
- Reduced risk of death 19.4% (95% CI 6.6-30.5)
- Absolute reduction in risk of death 6.1% (P=0.005)
- Incidence of serious bleeding: 3.5% for APC vs. 2.0% for placebo (P=0.06)

Prognosis

• “No other infection so quickly slays…”
  Herrick WW. Arch Intern Med 1919;23:409-418.
• Almost all deaths from meningococcal meningitis are due to cerebral edema and brainstem herniation
• Little improvement in outcome over the past few decades despite significant advances in critical care
• Meningitis: 10-15% mortality
• Meningococcemia: up to 40% mortality
• Sequelae (hearing loss, neurologic disability, limb loss) in 11-19%
Conclusion

• **Sepsis:** Major cause of morbidity and mortality worldwide-Leading cause of death in noncoronary ICU (US)*

• **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
  – Respiration ≥20/min
  – WBC count ≥12,000/mL or ≤4,000/mL or >10% immature neutrophils

• **Sepsis:**
  
  – Known or suspected infection
  – Two or more SIRS criteria

• **Sepsis:** A significant link to disordered hemostasis

• The management of sepsis is largely supportive with the administration of IV fluids, vasopressors, antibiotics and for some cases, Activated Protein C.

• Meningococcemia is a classic example of gram negative sepsis