Sepsis
Mechanisms of Human Disease
November 29, 2018
Emily Gilbert, MD

Outline
- History of sepsis
- Definitions
- Epidemiology
- Pathophysiology
- Signs and symptoms
- Diagnosis and Management
- Case

History
Systemic Inflammatory Response Syndrome (SIRS)

- **Temperature:**
  - > 38°C or
  - < 36°C
- **Respiratory rate:**
  - > 20 breaths per minute or
  - pCO2 < 32 mmHg
- **Heart rate:**
  - > 90 beats per minute
- **White blood cell count:**
  - > 12,000 or
  - < 4,000 or
  - > 10% bands
Systemic Inflammatory Response Syndrome

Pancreatitis

Burn Injury

Trauma

PE

SIRS
Need ≥ 2

Sepsis

Severe Sepsis

Septic Shock

- T > 38°C or < 36°C
- RR > 20 bpm or pCO2 > 32 mmHg
- HR > 90 bpm
- WBC > 12,000 or < 4,000 or > 10% bands

Two or more SIRS plus suspected infection

Inadequate blood or plasma volume

Peripheral vasodilatation and pooling of blood
Endothelial activation and injury
Leukocyte induced damage
Disseminated Intravascular Coagulation
Activation of cytokine cascade

Type of Shock

Clinical Examples

Principle Pathogenic Mechanism

Cardiogenic

Myocardial Infarction
Ventricular Rupture
Arhythmia
Cardiac Tamponade
Pulmonary Embolism

Failure of myocardial pump due to intrinsic myocardial damage, extrinsic pressure or obstruction to flow

Hypovolemic

Hemorrhage
Fluid loss (vomiting, diarrhea, burns, trauma)

Inadequate blood or plasma volume

Septic

Overwhelming microbial infection
Gram negative or gram positive septicaemia
Fungal septis
Superantigens (e.g. toxic shock syndrome)

Peripheral vasodilatation and pooling of blood
Endothelial activation and injury
Leukocyte induced damage
Disseminated Intravascular Coagulation
Activation of cytokine cascade

Notes (Last updated): Venkatesh Vaddadi, MD, MHI, FACP, Critical care, Dec 3, 2019
Septic shock

- Distributive shock
  - severe peripheral vasodilation
- Hyperdynamic “warm” shock
  - MAP = CO x SVR

<table>
<thead>
<tr>
<th>Type of shock</th>
<th>Warm Shock</th>
<th>Cold Shock</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse Pressure</td>
<td>Wide (&gt;30mmHg)</td>
<td>Narrow (&lt;30mmHg)</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>Decreased</td>
<td>Normal or Increased</td>
</tr>
<tr>
<td>Distal Pulses</td>
<td>Bounding</td>
<td>Weak or thready</td>
</tr>
<tr>
<td>Extremities</td>
<td>Warm (early)</td>
<td>Cool</td>
</tr>
</tbody>
</table>

Mortality

<table>
<thead>
<tr>
<th>Disease</th>
<th>Cases/Year</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>591,966</td>
<td>6-7</td>
</tr>
<tr>
<td>AMI</td>
<td>540,891</td>
<td>10</td>
</tr>
<tr>
<td>Trauma</td>
<td>697,025</td>
<td>5-16</td>
</tr>
<tr>
<td>Sepsis</td>
<td>859,858</td>
<td>15-20</td>
</tr>
<tr>
<td>Septic Shock</td>
<td>200,000</td>
<td>36-47</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1,187,180</td>
<td>5-9</td>
</tr>
</tbody>
</table>

* AHQR, Healthcare Cost and Utilization Project Brief Statistics
Epidemiology

• Over one million cases of severe sepsis or septic shock per year in the United States
• Sepsis incidence increasing

Kaukonen MK et al. JAMA 2014

Loyola Mortality Rates

Mortality Rates - 2017

Mortality Rate - 2018
**Epidemiology**

- Over one million cases of severe sepsis or septic shock per year in the United States
- Sepsis incidence increasing
- Blood cultures + in only 1/3 of cases

<table>
<thead>
<tr>
<th>Organism</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram negative</td>
<td>62</td>
</tr>
<tr>
<td>Gram positive</td>
<td>47</td>
</tr>
<tr>
<td>Fungi</td>
<td>19</td>
</tr>
</tbody>
</table>

*Escherichia coli*
*Klebsiella*
*Pseudomonas*
*Streptococcus pneumoniae*
*Staphylococcus aureus*

*Streptococcus pneumoniae* (most common)

Intraabdominal
Urinary Tract Infection

**Pathophysiology**
Pathogen-associated molecular patterns (PAMPs)
- Lipopolysaccharide (LPS)
- Outer membrane surface associated molecule
- Gram negative bacteria
- Recognized by TLR-4
- Peptidoglycan
- Cell wall fragment of gram positive bacteria
- Recognized by TLR-2

Pathophysiology

<table>
<thead>
<tr>
<th>TLR</th>
<th>Toll-like receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAMP</td>
<td>Pathogen-associated molecular pattern</td>
</tr>
<tr>
<td>DAMP</td>
<td>Damage associated molecular patterns</td>
</tr>
<tr>
<td>Cytokines</td>
<td>Proinflammatory cytokines: TNF-α, IL-1, and IL-6</td>
</tr>
</tbody>
</table>
- Shift from Th1 to Th2 cytokines
- Increased production of anti-inflammatory mediators
- Induction of cellular anergy
- Lymphocyte apoptosis
Pathophysiology

• The host responds to sepsis with both pro-inflammatory and anti-inflammatory responses
  • Pro-inflammatory:
    o Goal = eliminate invading pathogens
    o Thrombus formation
    o Hypotension
    o Capillary leak, edema
    o Mitochondrial dysfunction
    o Tissue hypoperfusion, hypoxia
    o Organ failure
  • Anti-inflammatory:
    o Goal = limit tissue injury
    o Increased susceptibility to secondary infection

Clinical features of sepsis
### SEPSIS

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Effect in sepsis</th>
<th>Signs and symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capillary leak and edema</td>
<td>Acute Respiratory Distress Syndrome (ARDS)</td>
<td>Tachypnea, Hypoxia, Respiratory failure</td>
</tr>
</tbody>
</table>

### Acute Respiratory Distress Syndrome (ARDS)

- Acute
- Bilateral opacities on CXR
- NOT due to cardiogenic pulmonary edema
- Moderate to severe hypoxemia
  - \( \text{PaO}_2/\text{FiO}_2 \) ratio <300mmHg
  - Example:
    - \( \text{PaO}_2 \) of 100mmHg on 0.50 \( \text{FiO}_2 \)
    - \( \text{P/F} \) ratio = 200

### SEPSIS

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Effect in sepsis</th>
<th>Signs and symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokine-induced myocardial depression</td>
<td>Decreased cardiac output</td>
<td>Tachycardia, Mottled skin, Poor capillary refill, Troponin elevation</td>
</tr>
</tbody>
</table>
### Signs and Symptoms of Sepsis

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Effect in sepsis</th>
<th>Signs and symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal hypoperfusion, hyposmia</td>
<td>Acute kidney injury:</td>
<td>Decreased urine output</td>
</tr>
<tr>
<td>Microcirculatory dysfunction</td>
<td>Acute tubular necrosis (FeNa &gt;2%)</td>
<td>Uremia</td>
</tr>
<tr>
<td></td>
<td>Pre-renal (FeNa&lt;1%)</td>
<td>Hyperkalemia</td>
</tr>
<tr>
<td>Decreased synthetic capacity</td>
<td>Adrenal insufficiency</td>
<td>Hyptension not responsive to fluids</td>
</tr>
<tr>
<td>Altered cell signaling</td>
<td>Encephalopathy</td>
<td></td>
</tr>
<tr>
<td>Dysfunction of blood brain barrier</td>
<td>Confusion</td>
<td></td>
</tr>
</tbody>
</table>
### SEPSIS Mechanism Effect in sepsis Signs and symptoms

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Effect in sepsis</th>
<th>Signs and symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Thrombus formation in microcirculation</td>
<td>Disseminated intravascular coagulation (DIC)</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>• Consumption of clotting factors and platelets</td>
<td></td>
<td>Petechiae, purpura</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ INR, D-dimer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fibrinogen, bleeding</td>
</tr>
<tr>
<td>• Hypoperfusion</td>
<td>• Dysfunction of reticuloendothelial</td>
<td>Hyperbilirubinemia</td>
</tr>
<tr>
<td></td>
<td>system</td>
<td>• jaundice</td>
</tr>
<tr>
<td></td>
<td>• “Shock liver” or ischemia</td>
<td>Transaminitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Elevated INR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Confusion</td>
</tr>
<tr>
<td>• Increased gluconeogenesis</td>
<td>Poor glucose control</td>
<td>Hyperglycemia or hypoglycemia</td>
</tr>
<tr>
<td>• Insulin release suppressed</td>
<td>Neutrophil function suppressed</td>
<td></td>
</tr>
<tr>
<td>• Insulin resistance</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**SEPSIS**

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**SEPSIS**

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<thead>
<tr>
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<th>Effect in sepsis</th>
<th>Signs and symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression of gut barrier function</td>
<td>Translocation of bacteria from gut into systemic circulation</td>
<td>Paralytic ileus</td>
</tr>
</tbody>
</table>

**Signs and symptoms**

- Fever or hypothermia
- Tachycardia
- Tachypnea, dyspnea, hypoxia
- Hypotension
- Mental status changes
- Early skin findings:
  - Warm, flushed
  - Bounding pulses
- Late skin findings:
  - Cool, mottled

**Clinical features of Sepsis**

<table>
<thead>
<tr>
<th>Signs and symptoms</th>
<th>Lab abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased susceptibility to secondary infection</td>
<td>Increased susceptibility to secondary infection</td>
</tr>
</tbody>
</table>
Diagnosis and Management of Sepsis

**Diagnosis of Sepsis**

1. Recognize signs and symptoms of sepsis and impending deterioration

**Modified Early Warning Score (MEWS)**

<table>
<thead>
<tr>
<th>MEWS</th>
<th>2</th>
<th>2</th>
<th>1</th>
<th>1</th>
<th>0</th>
<th>0</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temp.</td>
<td>35.0</td>
<td>35.1</td>
<td>35.2</td>
<td>35.3</td>
<td>35.4</td>
<td>35.5</td>
<td>35.6</td>
</tr>
<tr>
<td>Pulse</td>
<td>40</td>
<td>41</td>
<td>42</td>
<td>43</td>
<td>44</td>
<td>45</td>
<td>46</td>
</tr>
<tr>
<td>Resp.</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td>11</td>
<td>12</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>SBP</td>
<td>70</td>
<td>71</td>
<td>72</td>
<td>73</td>
<td>74</td>
<td>75</td>
<td>76</td>
</tr>
<tr>
<td>LOC</td>
<td>Confused</td>
<td>Agitated</td>
<td>Alert</td>
<td>Confusion</td>
<td>Restless</td>
<td>Unconscious</td>
<td>Lethargic</td>
</tr>
<tr>
<td></td>
<td>Awake</td>
<td>Awake</td>
<td>Awake</td>
<td>Awake</td>
<td>Awake</td>
<td>Awake</td>
<td>Awake</td>
</tr>
</tbody>
</table>

Positive MEWS ≠ Sepsis
**Diagnosis of Sepsis**
1. Recognize signs and symptoms of sepsis and impending deterioration
2. Support airway and breathing

\[ \text{↑ Lactate} \rightarrow \text{Metabolic Acidosis (↓ Bicarbonate)} \]

\[ \text{Respiratory compensation = Tachypnea} \rightarrow \text{↓ pCO}_2 \]

**Management of Sepsis**
1. Recognize and diagnose sepsis EARLY!!
2. Support airway and breathing
3. Cultures (blood, urine)
4. Serum lactate
5. Broad spectrum antibiotics
6. IVF if hypotensive or ↑ lactate
7. Vasopressors if patient remains hypotensive despite fluids
8. Repeat lactate if elevated
9. Patient reassessment

\[ \text{3-hour bundle} \]
\[ \text{6-hour bundle} \]

**Source Control**
- Cultures all potential sources (blood, urine, ascites, wounds)
- Remove chronic IV lines (PICC line, portacath)
- Drain abscesses
- Debride, amputate soft tissue sources
Antibiotics

- Broad spectrum antibiotics as soon as possible!
- Every hour delay in antibiotics increases mortality from sepsis

**Lactate**

**SHOCK**

Tissue Hypoxia

Anaerobic glycolysis

↑ Lactate production
**Lactate**

<table>
<thead>
<tr>
<th>Lactate &gt;4mmol/L</th>
<th>Hypotensive</th>
<th>N</th>
<th>Unadj Hosp Mortality % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>No</td>
<td>3,004</td>
<td>23.3 (21.8-24.8)</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>996</td>
<td>29.0 (26.2-31.8)</td>
</tr>
</tbody>
</table>

**IV fluids**

- Only required if patient is hypotensive or lactate ≥ 4
- Crystalloid is preferred fluid
- Recommended amount = **30cc/kg body weight**
- Average patient in septic shock requires 4-6 liters of fluid in the first 24 hours

**Vasopressors**

- Goal mean arterial pressure (MAP) ≥ 65mmHg to maintain organ perfusion

<table>
<thead>
<tr>
<th>Choice</th>
<th>Vasopressor</th>
<th>Receptors activated</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td>Norepinephrine</td>
<td>α1 and β1</td>
</tr>
<tr>
<td>V2a</td>
<td>Vasopressin</td>
<td>Vasculat (V-3), renal (V-2)</td>
</tr>
<tr>
<td>E2</td>
<td>Epinephrine</td>
<td>α1, β1 and β2</td>
</tr>
</tbody>
</table>
Reassessment
- Assess for improvement in organ hypoperfusion:
  - Improving blood pressure
  - Improving mentation
  - Improving urine output
  - Improving lactate
- Does my patient need more fluid?
- Document reassessment in epic:
  “SEPSIS EXAM DONE”

Management of Shock
Management of Sepsis

- Recognize sepsis
- Support airway and breathing

<table>
<thead>
<tr>
<th>3 hour bundle</th>
<th>6 hour bundle</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cultures</td>
<td>• Vasopressors if patient remains hypotensive despite fluids</td>
</tr>
<tr>
<td>• Serum lactate</td>
<td>• Repeat lactate if elevated</td>
</tr>
<tr>
<td>• Broad spectrum antibiotics</td>
<td>• Patient reassessment</td>
</tr>
<tr>
<td>• IV fluids if hypotensive or lactate ≥ 4mmol/L</td>
<td>• Consider steroids if hypotensive despite fluids and pressors</td>
</tr>
</tbody>
</table>

Case #1

- 65 year old male with a history of end stage renal disease on hemodialysis presents to the emergency room with lethargy.
- On exam, temp is 39°C Celsius, BP 90/30, HR 120, RR 24, O2 94% on room air. Weight is 70kg.
- He is only oriented to person. Heart is regular without murmurs, lungs are clear, abdomen is nontender. His hemodialysis line is erythematous with purulent drainage noted.
- Labs reveal a WBC of 18,000 with 12% bands. Cr of 3.2mg/dL (baseline 3.0). Lactate is 5.2 mmol/L.
- He is given 2.1L of 0.9% normal saline
- Blood pressure after the fluid bolus is 85/35
Question 1

Which of the following does the patient have?

A. Systemic Inflammatory Response Syndrome (SIRS)
B. Sepsis
C. Severe sepsis
D. Septic shock

Case #1

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- He is given 2.1L of 0.9% normal saline
- Blood pressure after the fluid bolus is 85/35

Case #2

45 year old male with history of alcohol abuse presents to the emergency room with 8/10 abdominal pain, nausea, vomiting.

- He also reports cough productive of yellow sputum and dyspnea
- On exam, temp is 38.1, BP 145/90, HR 120, RR 28, O2 93% on room air.
- He appears uncomfortable. Lung exam is significant for rhonchi at the right base. Abdomen is tender to palpation in epigastric area without rebound.
- Labs reveal a WBC of 13.0, Cr of 0.3. AST 90, ALT 40, amylase and lipase are elevated. The remainder of his labs are within normal limits
- CXR shows an consolidation at the right base
- CT of the abdomen/pelvis is consistent with chronic pancreatitis
Question 2

- Which of the following does the patient have?
  A. Systemic Inflammatory Response Syndrome (SIRS)
  B. Sepsis
  C. Severe sepsis
  D. Septic shock

Case #2

- 45 year old male with history of alcohol abuse presents to the emergency room with 8/10 abdominal pain, nausea, vomiting.
- He also reports cough productive of yellow sputum and dyspnea.
- On exam, temp is 38.1, BP 145/90, HR 120, RR 28, O2 93% on room air.
- He appears uncomfortable. Lung exam is significant for rhonchi at the right base. Abdomen is tender to palpation in epigastric area without rebound.
- Labs reveal a WBC of 13.0, Cr of 0.3, AST 90, ALT 40, amylase and lipase are elevated. The remainder of his labs are within normal limits.
- CXR shows a consolidation at the right base.
- CT of the abdomen/pelvis is consistent with chronic pancreatitis.

Case #2

- The patient is started on antibiotics and admitted to the hospital.
- Overnight, the patient becomes progressively more confused and the nurse thinks his urine output is dropping.
- Blood cultures from admission are growing gram negative rods.
Question 3

Which of the following will recognize LPS on gram negative bacteria and activate the immune response?

A. PAMPs
B. Toll-like receptors
C. Damage-associated molecular patterns
D. Nuclear factor κB (NF-κB)

Question 4

Which of the following would suggest that the patient has progressed from sepsis to severe sepsis:

A. Serum creatinine has increased to 2.5mg/dL
B. The patient’s heart rate has increased from 85 to 105
C. Serum bicarbonate has dropped from 24 to 14
D. Serum amylase has doubled

Case #2

The patient’s creatinine is elevated to 2.5mg/dL (admit Cr 0.3mg/dL).

Given his deterioration, repeat vital signs are taken: T 38.2, BP 110/65 (MAP 80), HR 100, RR 22, O2 sat 90% on RA

He had blood cultures drawn the day prior and was already started on broad spectrum antibiotics.
Question 5

Which of the following should be ordered to complete the 3-hour bundle for severe sepsis/septic shock?

A. Crystalloid (0.9% normal saline) IVF bolus
B. Vasopressors
C. Serum lactate
D. Oxygen by nasal cannula

Case #2

Lactate returns at 4.2mmol/L
Vital signs are unchanged

Question 6

Which of the following does the patient have?

A. Systemic Inflammatory Response Syndrome (SIRS)
B. Sepsis
C. Severe sepsis
D. Septic shock
Objectives

- Define the systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis and septic shock
- Identify the cellular receptors of the innate immune system that interact with microbial components and initiate the inflammatory response
- Understand why septic patients are at increased risk for infection
- Understand the mechanism of organ failure in sepsis
- Recognize the signs and symptoms of a septic patient
- Know the components of the 3-hour and 6-hour bundle for management of severe sepsis and septic shock