Sepsis and Shock States

INFECTION
- Inflammatory response to microorganisms, or
- Invasion of normally sterile tissues

SYSTEMIC INFLAMMATORY RESPONSE SYNDROME (SIRS)
Systemic response to inflammation
May or may not be due to infection
Two or more of the following:
- Core temp > 100.4 F (38C) or < 96.8 F (36C)
- Elevated heart rate (>90 to 100 BMP)
- Respiratory rate > 20 breaths/min or PaCO2 <32 mm Hg or mechanical ventilation for acute respiratory process
- WBC count > 10,000 – 12,000/mm³ or <4000/mm³ or >10% immature neutrophils
<table>
<thead>
<tr>
<th>SEPSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Known or suspected infection, plus</td>
</tr>
<tr>
<td>- ≥ 2 SIRS Criteria</td>
</tr>
<tr>
<td>- Evidence of hypoperfusion</td>
</tr>
<tr>
<td>- Altered mental state, hypoxemia, increased plasma lactate, oliguria</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SEVERE SEPSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Sepsis plus</td>
</tr>
<tr>
<td>- ≥ 1 organ dysfunction</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SEPTIC SHOCK</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Sepsis with</td>
</tr>
<tr>
<td>- Hypotension despite fluid resuscitation, and</td>
</tr>
<tr>
<td>- Perfusion abnormalities</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MULTIPLE ORGAN DYSFUNCTION (MODS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention</td>
</tr>
</tbody>
</table>
Sepsis and Severe Sepsis

- Sepsis
- Severe Sepsis

SIRS + Infection

Sepsis + Organ Dysfunction

Hypotension
Hypo perfusion
Lactic Acidosis
Change in Mental Status
Oliguria

Common Sources of Infection

- Lungs
  - Most common site of infection
- Blood
  - Intravascular devices common cause of nosocomial infection
- Abdomen
- Urinary Tract
- Skin
- Most common organisms
  - Gram negative and gram positive bacteria, fungi and viruses
  - Gram negative bacteria play a key role (Endotoxin in cell wall)
Severe Sepsis

- 750,000 cases per year
- High mortality rate - 30-40% (Marini & Wheeler, 2006)
- Leading cause of death in noncardiac ICU’s
- Unpredictable disease progression
- Unclear etiology and disease pathogenesis

Pathophysiology of Sepsis

Disturbances in

- Inflammation
- Coagulation
- Fibrinolysis

Proinflammatory and procoagulation response
Pathophysiology of Sepsis

**THREE PROBLEM AREAS**

↑ INFLAMMATION

↑ COAGULATION

↓ FIBRINOLYSIS

---

Homeostasis Is Lost In Sepsis

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

Increase in PAI-1
Increase in TAFI
Reduced Protein C
(Activated Protein C inhibits PAI-1)

Source: Adv Neonatal Care © 2004 W. B. Saunders
Pathophysiology of Sepsis
Infectious Process (due to microorganism, ischemia, trauma, reperfusion, multisystem injury, damage to endothelium)
⇒ Immune response initiated
  ⇒ Monocytes and macrophages release cytokines (mediators of inflammation)
  ⇒ Tumor necrosis factor (TNF), interleukin 1 (IL-1)
  ⇒ Platelet activating factor, promote nitric oxide production, promote neutrophil activity, release IL-6 and IL-8
  ⇒ Release of Tissue Factor
  ⇒ Stimulation of Extrinsic coagulation path
    ⇒ Formation of thrombin (pro-inflammatory, promotes leukocyte adhesion to vessel walls - damage
    ⇒ Thrombin converts fibrinogen to fibrin
    ⇒ Formation of clots in microvasculature
Pathophysiology of Sepsis

Additionally

- Plasminogen Activator Inhibitor – 1 (PAI-1) and thrombin activatable fibrinolysis inhibitor (TAFI) are released (TNF, IL-1)
- Suppress fibrinolysis and allow the clot to remain

The Endothelium

- Control of vasomotor tone
- Promotion of movement of cells and nutrients
- Maintenance of blood fluidity
- Key role inflammatory, prothrombotic and impaired fibrinolytic components of sepsis
- The largest organ in the body

Response to Damaged Endothelium in Sepsis

- Alterations in vasomotor tone
  - Increased production of nitric oxide
  - Abnormal endothelium-dependent vascular relaxation
  - Vasodilatation
  - Refractory hypotension and impaired microcirculatory blood flow
Response of the Damaged Endothelium

- Increased vascular permeability
  - Inflammatory fluids and cells move from the blood into interstitial spaces
  - Increased endothelial dysfunction, inflammation and formation of edema
- Impaired vasoregulation
- Impaired gas exchange
- Cellular hypoxia
- Decreased production of thrombomodulin
- Decrease protein C receptor
- Decrease level of activated protein C
- Increase thrombin production and plasminogen activator inhibitor-1
- Increased clot production with decreased fibrinolysis

More on Activated Protein C

- There are reduced Activated Protein C levels in Sepsis
- Activated Protein C has many functions including:
  - Inhibiting thrombin production
  - Inhibiting thrombin mediated inflammation
What are risks for Sepsis?

- Malignancy
- Diabetes Mellitus
- Chronic Liver Disease
- Chronic Kidney Disease
- Immunosuppressed State
- Surgery
- Trauma
- Burns

Diagnosis

- Tachypnea – early warning sign
- >90% develop hypoxemia
- 75% require mechanical ventilation (Marini & Wheeler, 2006)
- Leukocytosis
- Fever
- Hypothermia
  - elderly, chronic renal failure, patients on steroids or anti-inflammatory medications
  - Poor prognosis
- Determine site of infection

Biomarkers for Sepsis

- C-reactive protein.
- Procalcitonin.
- sTREM-I (new potential biomarker to replace C-reactive protein and procalcitonin).
### Possible Signs of Sepsis

<table>
<thead>
<tr>
<th>Category</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General</strong></td>
<td>Fever, chills</td>
</tr>
<tr>
<td><strong>Hemodynamic</strong></td>
<td>↑ HR, ↑ CO (early), ↓ SVR (early), ↓ BP, widened pulse pressure, bounding pulse, ↓ RAP, ↓ PAOP, ↓ LVSWI, ↑ RR early, ↑ SVO2</td>
</tr>
<tr>
<td><strong>Metabolic</strong></td>
<td>↑ insulin requirements</td>
</tr>
<tr>
<td><strong>Tissue Perfusion</strong></td>
<td>Altered mental state, altered skin perfusion, pink, warm, flushed (early)</td>
</tr>
<tr>
<td></td>
<td>↓ urine output</td>
</tr>
<tr>
<td><strong>Inflammatory</strong></td>
<td>Altered WBCs (↑immature neutrophils – shift to the left), ↑ C-reactive protein</td>
</tr>
<tr>
<td><strong>Coagulopathy</strong></td>
<td>↑ d-dimers, ↓ protein C, ↑ PT, aPTT</td>
</tr>
<tr>
<td><strong>Organ Dysfunction</strong></td>
<td>↑ BUN / creatinine, ↓ platelet count, Hyperbilirubinemia</td>
</tr>
</tbody>
</table>

### Organ Dysfunction

- **Pulmonary Dysfunction**
  - Usually first organ to fail
  - Receives 100% of cardiac output
  - Greatest exposure to toxins in an extensive capillary system
  - Compensates for metabolic acidosis
  - 50% develop lung injury or ARDS

- **Cardiac Dysfunction**
  - Hypotension
  - Decreased cardiac output due to vasodilation

- **Kidney Dysfunction**
  - Due to hypotension and shock
Lactic Acidosis

- Late septic shock
- Due to decrease in delivery of oxygen to tissues
  - Misdistribution of oxygen to tissues
  - System attempts to provide oxygen to vital organs
  - Decreased oxygen extraction in some areas
- Elevated lactate levels
  - Oxygen consumption is no longer independent of oxygen delivery

Septic Shock (Distributive – Early)

- Sepsis with hypotension despite fluid resuscitation, and perfusion abnormalities
- Three key processes involved in sepsis
  - Inflammation
  - Coagulation
  - Impaired fibrinolysis

Presentation

- Tachypnea
- Hypoxia
- Tachycardia
- Profound hypotension
Septic Shock

Hemodynamic Profile

Early Septic Shock
- ___ HR
- ___ Preload (RA, PAOP)
- ___ Afterload (SVR)
- ___ Contractility
- ___ Stroke Volume
- ___ CO / CI
- ___ Blood Pressure
- ___ $S VO_2$

Late Septic Shock
- ___ HR
- ___ Preload (RA, PAOP)
- ___ Afterload (SVR)
- ___ Contractility
- ___ Stroke Volume
- ___ CO / CI
- ___ Blood Pressure
- ___ $S VO_2$

Septic Shock Treatment

- **Treatment Goal:** Maximize the delivery of oxygen to the tissue
  - Remember: CI, Hemoglobin, SaO2
  - Prevention – hand hygiene
  - Treat the cause - antibiotics

- **CI**
  - Volume replacement
    - Crystalloids 4-8 liters
  - Vasopressors
  - May need inotropes

- **Hemoglobin**
  - Transfuse as necessary

- **SaO2**
  - Oxygen
  - Intubation and Mechanical Ventilation

---

Early Goal Directed Therapy
- CVP 8-12 mm Hg
- PAOP 12-18 mm Hg
- MAP > 65 mm Hg
- U.O. > 0.5 cc/kg/hr
- SaO2 > 90%
- Central venous oxygen saturation > 70%
Early Goal-Directed Therapy (EGDT)

Attempts to adjust cardiac preload, afterload and contractility to balance systemic oxygen delivery with oxygen demand.

Six hour window

Early Goal Directed Therapy (EGDT)

<table>
<thead>
<tr>
<th>Standard Therapy</th>
<th>EGDT</th>
</tr>
</thead>
<tbody>
<tr>
<td>• CVP 8-12 mmHg</td>
<td>• CVP 8-12 mm Hg</td>
</tr>
<tr>
<td>• MAP &gt; 65 mmHg</td>
<td>• PAOP 12-18 mm Hg</td>
</tr>
<tr>
<td>• U.O. &gt; 0.5 cc/kg/hr</td>
<td>• MAP &gt; 65 mm Hg</td>
</tr>
<tr>
<td></td>
<td>• U.O. &gt; 0.5 cc/kg/hr</td>
</tr>
<tr>
<td></td>
<td>• SaO₂ &gt; 90%</td>
</tr>
<tr>
<td></td>
<td>• Central venous oxygen saturation &gt; 70%</td>
</tr>
</tbody>
</table>
Early Goal Directed Therapy (EGDT)

- EGDT involves giving:
  - More fluid
    - Fluid administered until end points are met
  - Blood transfusions
  - Inotropes
  - Vasopressors if not responsive to fluids
    - Norepinephrine preferred

- Mortality impact:
  - *In hospital, 28 day and 60 day mortality improved by 40%*

Antibiotic Therapy

- Timing
  - Mortality rates increase after the first hour of presentation
  - Antibiotics should be initiated within first 30-60 minutes of presentation

- Appropriate coverage
  - Broad spectrum antibiotic
    - Covers gram-positive, gram-negative and anaerobic bacteria
  - Antipseudomonal coverage
    - Neutropenia
    - Most hospital-acquired sepsis
  - Immunocompromised critically ill patients require 2 antibiotics with overlapping coverage
Drotrecogin Alfa (Activated) Xigris

**Actions:**
- Anticoagulation Effect
- Profibrinolytic Effect
- Anti-Inflammatory Effect

*Reduced mortality by 6% in all patients and by 12.8% in severely ill patients.*

---

Drotrecogin Alfa (Activated) Xigris

- **Contraindications**
  - Recent CVA (3 months)
  - Recent GIB (6 weeks)
  - Recent surgery (12 hours)
  - Thrombocytopenia (< 80,000)

- Can be used with ASA
- Should not be used with anticoagulants or glycoprotein IIb / IIIa inhibitors
- Not used in
  - Pediatric patients
  - Patients with low risk of death
  - Surgical sepsis with only single organ dysfunction
Corticosteroids

- May improve outcomes in patients with adrenal insufficiency
- If vasopressor dependent shock with adrenal insufficiency
- No documented benefit to patients with adequate adrenal function

Modifying Mediators in Sepsis

- Antihistamines: Modify / block histamine
- Naloxone (Narcan): Modify / block endorphins
- Ibuprofen / Indomethacin: Modify / Block prostaglandin
- Corticosteroids: Modify / block several mediators (stabilize cell membrane) (modest doses only in well defined subsets)
- ACE Inhibitors: Inhibits production of Angiotensin II
- Activated Protein C: Modulates coagulation, fibrinolysis, and inflammation
- Anticoagulants (Heparin): Modify the clotting cascade
  * Blocking mediators is controversial / mediators are important
Other Treatment Considerations

- Enteral feedings
- Jejunal feedings preferred
- Help to decrease stress ulcers and translocation of bacteria
- High metabolic requirements

- CEBT
  - Possible benefit in removal of substances responsible for inflammation
  - Not currently recommended unless accompanying kidney injury.

QUESTIONS??

Thanks for Attending Cardiovascular Boot Camp

You may contact us at www.cardionursing.com