SEPSIS

I. Introduction:

Sepsis is defined as the body’s inflammatory response to an infectious precipitant. At first, it was thought that the profound inflammation seen with sepsis was due to the overwhelming bacterial load but patients continued to die despite the introduction of antibiotics. Therefore, it was determined that it was body’s response to the pathogen that drove the pathogenesis of sepsis.

In this session we will review the current concepts of pathogenesis of the systemic inflammatory response syndrome due to infection. We will also review the epidemiology, clinical manifestations, and an approach to diagnosis and treatment.

II. Definitions:

A. Systemic Inflammatory Response Syndrome (SIRS): Massive inflammatory reaction from systemic cytokine release. Defined as two or more of the following clinical manifestations present at the same time:
   1. Temperature of >38°C or <36°C
   2. Heart rate >90 beats per minute
   3. Respiratory rate > 20 breaths per minute or PaCO2 <32 mm Hg
   4. WBC count of >12,000/mm³ or <4,000/mm³ or >10% immature forms (bands)

B. Sepsis: SIRS plus a suspected or documented infection

C. Severe sepsis: Sepsis plus organ dysfunction (including but not limited to lactic acidosis (>2mmol/L), acute kidney injury (Cr >2mg/dL), oliguria, respiratory failure, altered mental status) or hypotension (SBP<90 or MAP<65)

D. Septic shock: Severe sepsis plus persistent hypotension (despite fluid resuscitation) or lactate ≥ 4mmol/L

III. SIRS.

A. First described in 1983 by a trauma surgeon

B. Reintroduced in 1991 by Dr. Roger Bone with the goal of aiding in the early detection of sepsis

C. Important to differentiate SIRS (body’s inflammatory response) from SIRS secondary to infection (sepsis)

D. Defined as cytokine release occurs in response to numerous insults. In addition to bacterial infection, SIRS is commonly seen in the following settings:
   1. Burn injury
   2. Trauma or hemorrhage
   3. Acute pancreatitis
   4. Acute adrenal insufficiency
   5. Ischemic tissue injury including liver or muscle
   6. Venous thrombosis/pulmonary emboli
7. Others: fat or amniotic fluid emboli, transfusion reaction, adverse drug reactions

IV. Septic shock

A. A type of distributive shock = severe peripheral vasodilation
   1. “Distributive” comes from the fact that blood flow is unevenly distributed to various tissues

B. Hyperdynamic shock, high cardiac output or "warm" shock
   1. MAP = CO x SVR
   2. Cardiac output will increase to compensate for low SVR leading to bounding pulses, warm, flushed skin, wide pulse pressure
   3. This is in contrast to low cardiac output or "cold" shock (cardiogenic, hypovolemic) which has cool extremities, thready pulses and narrow pulse pressure

V. Epidemiology of bacteremia and sepsis:

A. More than one million cases each year with up to a 45% mortality for septic shock
B. Incidence of sepsis is increasing:
   1. In 2000, there were 620,000 patient hospitalized with sepsis compared to over 1.1 million people in 2008
   2. Reason for rising incidence is likely due to more immunosuppression (organ transplant, bone marrow transplant, cancer patients), more indwelling catheters, artificial valves, joints, etc.
C. However, mortality from sepsis has been on the decline over the past 20-25 years
   1. 30-40% mortality in 1990s to around 20-25% in the last 2000s (similar to Loyola's mortality)
D. Published series disclose that about 1/3 of patients with sepsis have positive blood cultures.
E. A publication of 14,000 septic patients in 75 countries found Gram negative bacteria on 62%, Gram positive in 47% and fungi in 19% of positive blood cultures.
F. The lung is the most common site of infection with pneumonia causing about 50% of the cases of severe sepsis
   1. Intra-abdominal and genitourinary tract are other common sources of infection

VI. Pathophysiology

A. The body’s response to infection is characterized by both a proinflammatory response and an anti-inflammatory response
   1. The severity of these responses is determined by host factors (age, co-morbidities) and by pathogen (microbial load and virulence).

PROINFLAMMATORY:
B. There are 4 main classes of pattern-recognition receptors on surface of immune cells:
   1. Toll-like receptors (TLR) ← most important one
   2. C-type lectin receptors (CLR)
   3. Retinoic acid inducible gene 1-like receptors (RLR)
   4. Nucleotide-binding oligomerization domain-like receptors (NLR)

C. Pattern-recognition receptors recognize pathogen-associated molecular patterns (PAMPs).
   1. PAMPS are structures that are conserved among microbial species
   2. Examples of PAMPs include:
      a. Lipopolysaccharide (LPS)
         i. Outer membrane surface associated molecule
         ii. Gram negative bacteria
         iii. Recognized by TLR-4
      b. Peptidoglycan
         i. Cell wall fragment of gram positive bacteria
         ii. Recognized by TLR-2
      c. Beta-glucans of candida
         i. Recognized by TLR-2

D. When pattern-recognition receptors (such as TLR) bind to PAMPs, this activates the cytosolic transcription factor nuclear factor κB (NF-κB) which then moves from the cytoplasm to the nucleus and activates innate immunity:
   1. Upregulation of transcription of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6).
   2. Complement activation

E. Cell death caused by the inflammatory response releases damage-associated molecular patterns (DAMPs)
   1. DAMPs are also recognized by receptors such as TLR and can trigger further inflammation.
   2. DAMPs can also be released following burns or trauma which explains why a similar response (SIRS) can be seen without sepsis

F. Mechanism of organ failure in sepsis:
   1. Increased thrombosis of small vessels:
      a. Cytokines stimulate increased production of tissue factor → activates the coagulation system → increased thrombus formation
      b. Reduced activity of anti-coagulant factors (tissue factor pathway inhibitor, antithrombin and activated protein C)
      c. Fibrinolysis dampened
   2. Vasodilation → hypotension:
      a. Cytokines increase the activity of inducible nitric oxide synthase (iNOS), which increases the synthesis of nitric oxide (NO), a potent vasodilator.
   3. Increased fibrin-rich thrombi in the small vessels along with hypotension leads to hypoperfusion of tissues
   4. Loss of barrier function and capillary leak:
a. Pro-inflammatory cytokines loosen endothelial cell tight junctions leading to loss of barrier function
b. The loss of barrier function leads to capillary leak and third spacing of fluid with increased interstitial edema
i. Mechanism of ARDS
5. Mitochondrial dysfunction:
   a. Cytokines also cause the release of reactive oxygen species (ROS)
   b. Oxidative stress leads to mitochondrial dysfunction and decreased O2 consumption by tissues
6. The combination of tissue hypoperfusion (from small vessel thrombus and vasodilation/hypotension) + loss of barrier function + decreased O2 consumption due to mitochondrial dysfunction leads to tissue hypoxia and organ failure

ANTIINFLAMMATORY:
G. Roger Bone hypothesized that a powerful anti-inflammatory response already existed to balance the pro-inflammatory response and that anything that upset the balance too far in either direction (too much inflammation or failure to defend against invading organisms) led to death
H. The sepsis-induced proinflammatory state triggers counterregulatory immunosuppressive response which attenuates the proinflammatory response in order to limit the potential harmful effects
   1. As a result, septic patients may oscillate between hyperinflammatory and immunosuppressed states during their clinical course.
I. Proposed mechanisms for the immune suppression include:
   1. A shift from proinflammatory (T^H_1) to anti-inflammatory (T^H_2) cytokines
   2. Production of anti-inflammatory mediators (e.g., soluble TNF receptor, IL-1 receptor antagonist, and IL-10)
   3. Lymphocyte apoptosis
   4. Induction of cellular anergy
J. The combination of these anti-inflammatory responses leads to immunosuppression with increased susceptibility to secondary infection

K. Summary statement on pathogenesis:
   1. The host responses to infection with both proinflammatory and anti-inflammatory responses. The goal of the proinflammatory response is to eliminate invading pathogens and the goal of the anti-inflammatory response is to limit tissue injury. A disruption of the balance in either direction can lead to death.
## VII. Clinical Features of Sepsis

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<th>Mechanism</th>
<th>Effect in sepsis</th>
<th>Signs and symptoms</th>
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<tr>
<td>Lungs</td>
<td>• Capillary leak and edema</td>
<td>• Acute Respiratory Distress Syndrome (ARDS)</td>
<td>Tachypnea, Hypoxia, Respiratory failure</td>
</tr>
<tr>
<td>Cardiac</td>
<td>• Reduction in cardiac contractility</td>
<td>• Decreased cardiac output</td>
<td>Tachycardia, Mottled skin, Poor capillary refill, Troponin elevation</td>
</tr>
<tr>
<td>Renal</td>
<td>• Renal hypoperfusion, hypoxemia • Microcirculatory dysfunction</td>
<td>• Acute kidney Injury (both ATN and pre-renal)</td>
<td>Decreased urine output, Uremia, Hyperkalemia</td>
</tr>
<tr>
<td>Adrenals</td>
<td>• Decreased synthetic capacity</td>
<td>• Adrenal insufficiency</td>
<td>Hypotension not responsive to fluids</td>
</tr>
<tr>
<td>CNS</td>
<td>• Alterations in cell signaling • Dysfunction of blood brain barrier</td>
<td>• Encephalopathy</td>
<td>Confusion</td>
</tr>
<tr>
<td>Coagulation</td>
<td>• Thrombus formation • Consumption of clotting factors and platelets</td>
<td>• Disseminated intravascular coagulation (DIC)</td>
<td>Thrombocytopenia, Elevated INR, D-dimer, Decreased fibrinogen, Bleeding, petechiae, purpura</td>
</tr>
<tr>
<td>Liver</td>
<td>• Hypoperfusion</td>
<td>• Dysfunction of reticuloendothelial system • “Shock liver”</td>
<td>Hyperbilirubinemia → jaundice, Transaminitis, Elevated INR, Confusion</td>
</tr>
<tr>
<td>Pancreas</td>
<td>• Increased gluconeogenesis • Insulin release suppressed • Insulin resistance</td>
<td>• Poor glucose control • Neutrophil function suppressed</td>
<td>Hyperglycemia or hyoglycemia</td>
</tr>
<tr>
<td>GI tract</td>
<td>• Depression of gut barrier function</td>
<td>• Translocation of bacteria from gut into systemic circulation</td>
<td>Paralytic ileus</td>
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<td>Immune system</td>
<td>• Apoptosis of lymphocytes • Suppression of pro-inflammatory cytokines</td>
<td>• Increased susceptibility to secondary infection</td>
<td>New infection</td>
</tr>
</tbody>
</table>

### A. Acute Respiratory Distress Syndrome (ARDS)
1. Acute (within one week of inciting event)
2. Bilateral opacities on CXR
3. NOT due to pulmonary edema
4. Moderate to severe hypoxemia
   a. PaO2/FiO2 ratio <300mmHg
B. Warning Signs and Symptoms
1. Fever or hypothermia: >38°C or <36°C
2. Tachycardia
3. Tachypnea, dyspnea and/or hypoxia
4. Hypotension (Systolic BP <90, MAP <65)
5. Confusion, alteration in mental status
6. Initially, skin will be warm, well perfused, flushed with bounding pulses
7. As shock progresses, blood is shunted to core organs and skin becomes cool and mottled

C. Lab abnormalities:
1. Elevated (>12,000) or depressed (<4000) WBC count
2. Hyperglycemia or hypoglycemia in absence of diabetes
3. Transaminitis
   a. Ischemic hepatitis or “shock liver”: AST and ALT >1000 international unit/L
4. Hyperbilirubinemia
5. Acute renal failure
6. Thrombocytopenia
7. Elevated INR, D-dimer
8. Decreased fibrinogen
9. Elevated lactate
10. Positive cultures

VIII. Management of Sepsis

A. The most important management aspect of sepsis is the ability to recognize signs/symptoms of sepsis and also identify the deteriorating patient.

B. Stabilize airway and breathing:
1. Supplemental oxygen to help with O2 delivery to tissues
2. Many patient will require intubation due to:
   a. Increased work of breathing
      i. Lactic acidosis → metabolic acidosis → respiratory compensation (hyperventilation)
   b. Airway protection due to altered mental status

C. 3-hour bundle (needs to be completed with 3 hours of “time zero”)
1. Obtain cultures prior to administration of antibiotics
2. Administer broad spectrum antibiotics
3. Measure lactate level
4. Administer 30ml/kg crystalloid IV fluids for hypotension or lactate ≥4mmol/L

D. 6-hour bundle (needs to be completed with 6 hours of “time zero”)
1. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥65mmHg
2. Re-measure lactate if initial lactate elevated >2mmol/L
3. Reassessment note

E. Identification of source and eradication of infection
1. Cultures all potential sources (blood, urine, ascites, wounds)

F. Early antibiotics are KEY!
   1. Every hour from the onset of septic shock that antibiotics are delayed leads to an average decrease in survival of almost 8%.
   2. If antibiotics are delivered within the first hour, survival is 80%
   3. Empiric - choice based on patient assessment, hospital antimicrobial susceptibility patterns

G. Lactic acidosis:
   1. Shock leads to tissue hypoxia
   2. Intracellular aerobic respiration is replaced by anaerobic glycolysis with excessive production of lactic acid
   3. Lactate level is an independent predictor of mortality:
   4. Repeat lactate if elevated >2mmol/L to determine if your current management is adequate

H. IV fluid resuscitation:
   1. Only required if patient is hypotensive or lactate ≥ 4
   2. Crystalloid is preferred fluid (lactated ringers, 0.9% normal saline or plasmalyte)
   3. Recommended amount = 30cc/kg body weight
   4. Average patient in septic shock requires 4-6 liters of fluid in the first 24 hours

I. Vasopressors:
   1. Start vasopressors if the patient has received fluid resuscitation and MAP remains <65mmHg
   2. Vasopressors bind to alpha-receptors leading to vasoconstriction
      a. 1st choice = Norepinephrine
      b. 2nd choice = Vasopressin or Epinephrine

J. Reassessment
   1. It is important to go back and reassess your patient to determine volume status and whether organ perfusion is improving
   2. Assess for improvement in organ hypoperfusion:
      a. Improving mentation
      b. Improving blood pressure
      c. Improving urine output
      d. Improving lactate

K. Corticosteroids
   1. Studies support use of hydrocortisone 50mg IV every 6 hours in patients in whom hypotension persists despite adequate fluid resuscitation and vasopressor therapy
   2. Hastens recovery from shock and liberation from ventilator
      a. Of the three studies, one showed that in the sickest patients there was a slight improvement in survival