Septic Shock

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Sepsis = Infection + SIRS

Infection, documented or suspected, and some of the following:

General variables
- Fever (>38.3°C)
- Hypothermia (core temperature <36°C)
- Heart rate >90 min⁻¹ or >2 sd above the normal value for age
- Tachypnea

Inflammatory variables
- Leukocytosis (WBC count >12,000 μL⁻¹)
- Leukopenia (WBC count <4000 μL⁻¹)
- Normal WBC count with >10% immature forms

Bone RC et al. chest 1992; 101: 1644-55
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**Altered mental status**

**Significant edema or positive fluid balance (>20 mL/kg over 24 hrs)**

**Hyperglycemia (plasma glucose >140 mg/dL or 7.7 mmol/L) in the absence of diabetes**

**Inflammatory variables**
- Leukocytosis (WBC count >12,000 µL⁻¹)
- Leukopenia (WBC count <4000 µL⁻¹)
- Normal WBC count with >10% immature forms
- Plasma C-reactive protein >2 sd above the normal value
- Plasma procalcitonin >2 sd above the normal value

**Hemodynamic variables**
- Arterial hypotension (SBP <90 mm Hg; MAP <70 mm Hg; or an SBP decrease >40 mm Hg in adults or <2 sd below normal for age)

Levy MM et al. Crit Care Med 2003; 31: 1250-6
Sepsis = Infection + SIRS

- Infection (suspected or documented)
- Arterial hypotension
- SIRS
  - Altered consciousness
  - Positive fluid balance
  - Hyperglycemia; without DM
- Increased serum prolactin and CRP
Severe sepsis = Sepsis + organ dysfunction or hypotension

Cool or clammy skin, mottling, and elevated shock index (heart rate/systolic blood pressure > 0.9) may be signs of tissue hypoperfusion.

Urinary output is a marker for adequate renal perfusion and cardiac output.

Levy MM et al. Crit Care Med 2003; 31: 1250-6
Sepsis

Organ dysfunction

Tissue hypoperfusion

Sepsis syndrome/
Septic shock
Septic shock

- A subset of severe sepsis (SIRS) and defined as sepsis (SIRS) induced hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include lactic acidosis, oliguria, or an acute alteration in mental status.
<table>
<thead>
<tr>
<th>Microorganism &amp; its products</th>
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</thead>
<tbody>
<tr>
<td>Inflammation</td>
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<tr>
<td>Anti-inflammation</td>
</tr>
<tr>
<td>Multi-system involvement &amp; organ failure</td>
</tr>
</tbody>
</table>
Pathogenesis of septic shock

Infectious or noninfectious triggers

Cytokine and inflammatory mediator cascade

Cardiovascular dysfunction and microvascular injury

Hypotension and shock
Pathogenesis of septic shock

- Infectious or noninfectious triggers
- Cytokine and inflammatory mediator cascade
- Cardiovascular dysfunction and microvascular injury
- Hypotension and shock
**Bacterial-Mediated Sepsis**

**Bacteria**
- Gram(-)
  - death
- Gram(+)

**LPS + LBP**

**Macrophage**
- CD14
- TLR2
- TLR4

**Mediators of Inflammation**

“Key players”

**Definitions**
- LBP = LPS-Binding Protein
- LPS = Lipopolysaccharide
- LTA = Lipoteichoic acid
- TLR = Toll-like receptor
Severe Sepsis:
The Final Common Pathway

Endothelial Dysfunction and Microvascular Thrombosis

Mediators of inflammation

Hypoperfusion/Ischemia

Acute Organ Dysfunction (Severe Sepsis)

Death
The insights in pathogenesis of septic shock

• No single biological substance or mechanism is fully responsible for septic shock.

• Peripheral vasodilatation and vasopressor-poorly responded blood vessels are characteristics of septic shock. (Vasodilatory shock)
Septic shock

- Alternatively, **distributive shock** is caused by such conditions as direct arteriovenous shunting and is characterized by **decreased resistance or increased venous capacity** from the vasomotor dysfunction.
Circulatory and metabolic pathophysiology of septic shock

- The predominant hemodynamic feature of septic shock is **arterial vasodilatation**.
- Diminished peripheral arterial vascular tone causes vasodilatation to result in hypotension and shock if insufficiently compensated by a rise in cardiac output.
Circulatory and metabolic pathophysiology of septic shock

- Early in septic shock, the rise in cardiac output often is limited by hypovolemia and a fall in preload because of low cardiac filling pressures.

- When intravascular volume is augmented, the cardiac output usually is elevated (the hyperdynamic phase of sepsis and shock).
 prvornasanajing  

ก่อน shock  

2L  

ขณะ shock  

ก่อน shock  

 CPP  

ขณะ shock  

ก่อน shock
BP = CO \times TPR

Volume resuscitation

BP = CO \times TPR
Circulatory and metabolic pathophysiology of septic shock

- Even though the cardiac output is elevated, the performance of the heart, reflected by stroke work, usually is depressed.

- Factors responsible for myocardial depression of sepsis are myocardial depressant substances, coronary blood flow abnormalities, pulmonary hypertension, various cytokines, nitric oxide, and beta-receptor down-regulation.
Circulatory and metabolic pathophysiology of septic shock

- Hypotension is resulting from reduced arterial vascular tone, diminished venous return from venous dilation, and release of myocardial depressant substances.
Septic shock

- Vasodilatory mediators released
- Arteriolar dilatation
  - ↓ CVP, PcwP, SVR
  - ↑ C.O., ↓ BP
- Myocardial depressant substances
- Histamine, NO
What’s happening in the microcirculation of patients with septic shock?

- In the setting of sepsis and SIRS:
  A combination of decrease in CO, decreased systemic perfusion pressure, and a selective alteration in the perfusion of an individual organ system result in ischemia of that organ system.
Distribution of blood flow

- The peripheral blood flow: The balance between local regulation of arterial tone and the activity of central mechanisms (e.g., autonomic nervous system).

- The regional regulation, release of vasodilating substances (e.g., nitric oxide, prostacyclin), and vasoconstricting substances (e.g., endothelin) affect the regional blood flow.
What’s happening at the level of microcirculation?

- Significant derangement in the autoregulation of circulation is typical in patients with sepsis.

- **Nitric oxide** plays a central role in the vasodilatation of septic shock. Impaired secretion of vasopressin also may occur, which may permit the persistence of vasodilatation.

- Vasoactive mediators also cause an increase in the microvascular permeability at the site of infection.
What’s happening at the level of microcirculation?

- Maldistribution of blood flow, disturbances in the microcirculation, and, consequently, peripheral shunting of oxygen are responsible for diminished oxygen extraction and uptake, and lactate acidemia in patients experiencing septic shock.
What’s happening at the level of microcirculation?

- Development of increased systemic microvascular permeability also occurs, remote from the infectious focus, contributing to edema of various organs, particularly the lung microcirculation and development of ARDS.
The microcirculation is the key target organ for injury in patients with sepsis syndrome.

A decrease in the number of functional capillaries

- Intrinsic and extrinsic compression of capillaries
- Plugging of the capillary lumen by blood cells (DIC).

An inability to extract oxygen maximally

Increased endothelial permeability leads to widespread tissue edema of protein-rich fluid.
Characteristics of septic shock

• Systemic vasodilation and hypotension
• Tachycardia; depressed contractility
• Vascular leakage and edema; (relative) hypovolemia
• Compromised nutrient blood flow to organs
• Disseminated intravascular coagulation
• Abnormal blood gases and acidosis
• Respiratory distress and multiple organ failure
### Summary hemodynamic parameter in various type of shock

<table>
<thead>
<tr>
<th>Shock type</th>
<th>CVP</th>
<th>Pcwp</th>
<th>LVEF</th>
<th>SV, CO</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypovolemic</td>
<td>↓</td>
<td>↓</td>
<td>⇔</td>
<td>↓</td>
<td>↑</td>
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<tr>
<td>Cardiogenic</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
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<tr>
<td>Septic</td>
<td>↓ or ⇔</td>
<td>↓ or ⇔</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
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<tr>
<td>Obstructive</td>
<td>↑</td>
<td>↓ or ⇔</td>
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<td>↓</td>
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<tr>
<td>Organ System</td>
<td>Mild Criteria</td>
<td>Severe Criteria</td>
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<td>Hypoxia/hypercarbia requiring assisted ventilation for 3-5 d</td>
<td>ARDS requiring PEEP &gt;10 cm H₂O and FiO₂ &lt;0.5</td>
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Multiple Organ Dysfunction Syndrome (MODS)

• Sepsis is described as an autodestructive process that permits the extension of normal pathophysiologic response to infection (involving otherwise normal tissues), resulting in multiple organ dysfunction syndrome.
Multiple inflammatory pathways

↑ MODS/ MOF
risk for OIs or secondary infections
Multiple Organ Dysfunction Syndrome (MODS)

• Presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention.

• The imbalance among inflammation, coagulation, and fibrinolysis results in widespread coagulopathy and microvascular thrombosis and suppressed fibrinolysis, ultimately leading to MODS and death.
The major risk factors for developing of MODS/ MOF

- Sepsis and SIRS
- Shock and prolonged periods of hypotension
- Bowel infarction
- Hepatic dysfunction
- Increased age
- Alcohol abuse
Potential pathophysiologic mechanism(s) involved in the production of MODS/MOF

- Primary Cellular Injury
- Defective Red Blood Cells
- Inadequate Tissue/Organ Perfusion
- Circulating Immune/Inflammatory Mediators
- Adverse Effect of Directed Treatment or Medication
- Diffuse Endothelial Cell Injury
- Circulating Humoral Factors
- Bacterial - Toxin Translocation
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The principles in the management of septic shock

- Early recognition
- Proper initial management
- Corticosteroids (refractory vasopressor-dependent shock)
- Drotrecogin alpha (Severely ill if APACHE II > 25)
- Tight glycemic control
- Proper ventilator management with low tidal volume in patients with ARDS
The initial management of septic shock

Goal: maintenance of adequate tissue perfusion to prevent multiple organ dysfunction

• Initial resuscitation (the first 6 h.)
• Diagnosis of infection
• Appropriate empirical antimicrobial therapy
• Source identification and control
Early goal-directed therapy

- Hypotension persisting after initial fluid challenge or blood lactate concentration $> 4$ mmol/L

- Resuscitation should be initiated as soon as hypoperfusion is recognized and should not be delayed pending ICU admission.
Maintain adequate blood pressure during life-threatening hypotension and preserve perfusion pressure for optimizing flow in various organs (splanchnic and renal perfusion).

This treatment strategy resulted in a 16% improvement in mortality.

Early goal directed therapy

Fluid challenges require the definition of four components

- The type of fluid to be administered (e.g., natural or artificial colloids as well as crystalloids)
- The rate of fluid infusion (e.g., 500–1000 mL over 30 mins)
- The end points (e.g., mean arterial pressure of > 70 mmHg, heart rate of < 110 beats/min)
- The safety limits (e.g., development of pulmonary edema)
• Do not delay the beginning of fluid administration for placement of central access.
• Be prepared to deliver additional fluids. In order to reach the target CVP goal of $\geq 8$ mmHg in subsequent steps, volumes much $> \text{initial } 20 \text{ ml/kg or colloid equivalent may be required.}$
• If the patient is not responding to vigorous volume resuscitation, think of other causes of hypotension such as depressed myocardial function, adrenal insufficiency, tension pneumothorax, cardiac tamponade, etc.
• If using crystalloid, be sure to use isotonic fluids such as normal saline or lactated Ringer’s only.
Evaluation of regional perfusion in patients with septic shock

- Normalized blood pressure is inadequate.
- The evaluation includes evidence of myocardial ischemia, renal dysfunction manifested by decreased urine output or increased creatinine, CNS dysfunction indicated by a decreased level of consciousness, hepatic injury shown by increased levels of transaminases, splanchic hypoperfusion manifested by stress ulceration, ileus, or malabsorption.
Diagnosis of infection

- Obtain the most likely "clinical diagnosis": cause of septic shock
- Obtain appropriate cultures before starting antibiotics (1C) (if do not cause significant delay in antimicrobial admin.)
- Obtain two or more blood cultures
- One or more blood cultures should be percutaneous
Diagnosis of infection

- In CVC related infection, the hemoculture from vascular access device is positive much earlier than the peripheral blood culture (i.e. > 2 hrs earlier)
- One blood culture from each vascular access device in place > 48 hrs earlier
- Culture other sites as clinically indicated
- Perform imaging studies promptly to confirm and sample any source of infection

The clinical examination is unreliable for the detection of pneumonia; especially in elderly patients. Occult infiltrates can be detected by the routine use of chest radiography in patients who are febrile with neutropenia and without pulmonary symptoms.
Inappropriate cultures

• **Sputum culture** in the following conditions
  : absence of clinical signs/ symptoms of pneumonia
  : Culture from a patient without ET tube or tracheostomy and inability to cough effectively

• **Urine culture** in the following conditions
  : midstream collection in disable patients
  : no pyuria (except in neutropenic patients; adults who are febrile without localizing symptoms or signs have a 10-15% incidence of occult urinary tract infection. )
  : Urinary catheter tip culture

• **Swab culture** from an open wound
Is Gram stain helpful?

- Sputum: Definite diagnosis >>> Pulmonary norcardiosis (usually with a positive modified AFB stain)
  - Likely diagnosis >>> Pulmonary fungal infection (mostly, yeast form)
  - Gram positive diplococci (lancet shape): Pneumococci
  - Possible diagnosis >>> Gram negative rod with safety-pin: Melioidosis*
  - Gram negative diplococci: \textit{Acinetobacter} spp.
  - To exclude the diagnosis: Staphylococcal pneumonia
Is Gram stain helpful?

• Spunned urine: Definite diagnosis >>> Gram neg.
  intracellular diplococci: GC

• Bodily fluid: Likely diagnosis >>> Pleomorphism:
  anaerobic infection
Choice of empirical antimicrobial therapy

• Depends on: underlying disease, drug intolerances, the clinical syndrome (site and type of infection), and susceptibility patterns of pathogens in the community, in the hospital, and that previously have been documented to colonize or infect the patient.

• Recently used antibiotics should generally be avoided.

• Empirical antifungus might be necessary
Appropriate empirical antimicrobial therapy

- Begin IV antibiotics as early as possible (i.e. within the first hour of recognizing severe sepsis (1D) and septic shock (1B))
- Broad-spectrum: one or more agents active against likely pathogens and with good penetration into presumed source (1B)
- Reassess antimicrobial regimen daily (for optimization)(1C)
Appropriate empirical antimicrobial therapy

- Consider combination therapy in *Pseudomonas* infections and neutropenic patients
- Combination therapy 3–5 days and then de-escalation
- Duration of therapy typically limited to 7–10 days; longer if response is slow or there are undrainable foci of infection or immunologic deficiency (1D)
- Stop antimicrobial therapy if cause is found to be noninfectious (1D)
Tips

• Blood cultures will be negative in > 50% of cases of severe sepsis or septic shock, yet many of these cases are very likely caused by bacteria or fungi.

• The decisions to continue, narrow, or stop antimicrobial therapy must be made on the basis of clinician judgment and clinical information.
Source identification and control

- A specific anatomic site of infection should be established as rapidly as possible (1C) and within first 6 hrs of presentation (1D)

- Formally evaluate patient for a focus of infection amenable to source control measures (e.g. abscess drainage, tissue debridement) (1C)
Source identification and control

• Implement source control measures as soon as possible following successful initial resuscitation (1C) (exception: infected pancreatic necrosis, where surgical intervention is best delayed)

• Choose source control measure with maximum efficacy and minimal physiologic upset (1D)

• Remove intravascular access devices if potentially infected (1C)
Corticosteroid and septic shock

- Consider intravenous hydrocortisone for adult septic shock when hypotension responds poorly to adequate fluid resuscitation and vasopressors.

- ACTH stimulation test is not recommended to identify the subset of adults with septic shock who should receive hydrocortisone.
Corticosteroid and septic shock

- Hydrocortisone is preferred to dexamethasone.

- Fludrocortisone (50 g orally once a day) may be included if an alternative to hydrocortisone is being used that lacks significant mineralocorticoid activity.
Corticosteroid and septic shock

- Steroid therapy may be weaned once vasopressors are no longer required.
- Hydrocortisone dose should be ≤ 300 mg/day (1A)
- Do not use corticosteroids to treat sepsis in the absence of shock unless the patient’s endocrine or corticosteroid history warrants it (1D)
Recombinant human activated protein C and septic shock

- Consider rhAPC in adult patients with sepsis-induced organ dysfunction with clinical assessment of high risk of death (typically APACHE II ≥ 25 or multiple organ failure) if there are no contraindications

- Adult patients with severe sepsis and low risk of death (typically, APACHE II < 20 or one organ failure) should not receive rhAPC (1A)
Management of MODS/MOF

- The management of patients with MODS/MOF is predominantly supportive.
- The specific treatment is directed at identifying and treating the underlying disorder.
- Prevention of MODS/ MOF is plausible.
Thank You for Your Attention