Sepsis: Evaluation and Management

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Introduction

- Sepsis is an inflammatory response to an infection or bacteremia, potentially leading to multiple organ dysfunction syndrome and death (Neviere, 2017).
- Common septic sites include respiratory, genitourinary, GI system, and skin and soft tissues (Gauer, 2013).
- Early detection of sepsis increases chances of survival.
  - Mortality rate:
    - Severe sepsis: 25% - 30%
    - Septic shock: 40% - 70%

Learning Objectives

At the end of the course, participants should be able to:

- Define sepsis and identify the etiology and risk factors of sepsis
- Identify diagnostic criteria of sepsis and recognize treatment options based on the patient’s presenting symptoms and outcomes

Quick Facts

- In the U.S., 1.5 million people are diagnosed with sepsis a year
- Over 62% of patients admitted to the hospital with sepsis were readmitted within 30 days
- Approximately 250,000 people die from sepsis each year
- One out of 3 people who die in the hospital has sepsis
- Sepsis survivors are left with life-changing effects
  - PTSD
  - Organ dysfunction
  - Fatigue
  - Chronic pain
  - Amputations

(CDC, n.d.)
### Stages of Sepsis

<table>
<thead>
<tr>
<th>Early Sepsis</th>
<th>Sepsis</th>
<th>Septic Shock</th>
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</thead>
<tbody>
<tr>
<td>- Infection and bacteremia</td>
<td>- Life threatening organ dysfunction</td>
<td>- Circulatory and metabolic abnormalities that increase the risk of mortality</td>
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<tr>
<td>- qSOFA score</td>
<td>- SOFA score</td>
<td>- Requires vasopressors to maintain MAP ≥ 65 mmHg</td>
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<td>- Respiratory rate ≥ 22 bpm</td>
<td>- qSOFA score</td>
<td>- Lactate &gt; 2 mmol/L (18 mg/dL)</td>
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<td>- Altered mental status</td>
<td>- Platelet concentration</td>
<td>- SOFA score ≥ 2 + Vasopressors = 40% mortality</td>
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<td>- Systolic blood pressure ≤ 100 mmHg</td>
<td>- Other organ dysfunction</td>
<td>- Can lead to MODS</td>
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<td>- Poor outcomes for scores of ≥2</td>
<td>- Scores of ≥ 2 indicate organ dysfunction</td>
<td>- Multiple Organ Dysfunction Syndrome: Progressive dysfunction in multiple organs that homeostasis cannot be maintained without intervention (Neviere, 2013).</td>
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### Why is Early Recognition Important?

**Untreated Septic Shock**
- Tissue hypoxia
- Tissue ischemia
- Untreated tissue ischemia
- Death

**Early recognition + Early, Aggressive Treatment Protocols = Improved Outcomes**

### Etiology

- Proinflammatory and anti-inflammatory mediators respond to pathogen invasion (Gauer, 2013)
- Endothelial damage, vascular permeability, microvascular dysfunction, activation of coagulation pathway, and impaired oxygenation of tissues leads to sepsis
- 80% of all cases of sepsis occur in the respiratory system, GU, GI, and skin and soft tissues
- Pneumonia is the most common condition leading to sepsis
- Most common cause are bacterial microbes (gram positive microbes account for 30% - 50% of all cases).
- Small numbers of fungal, viral, or parasitic infections

### Risk Factors

- Advanced age (>65 y/o)
  - 13 x more likely to develop sepsis
  - Two-folds higher risk of dying from sepsis
- Intensive Care Unit admission
- Immunosuppression (Diabetes, cancer)
- Community acquired pneumonia
- Recent hospitalization or surgery
- Indwelling catheters or other invasive devices (Neviere, 2013).
Pathophysiology

Normal Response to Infection

- Bacterial invasion is localized to the area of infection
- Circulating and fixed phagocytic cells are activated
- Both proinflammatory and antiinflammatory mediators are generated
- Infectious insult is overcome and homeostasis is restored

(Neviere, 2016)

Infection leads to sepsis when:

- The response to infection becomes generalized and involves normal tissues remote from the site of injury or infection
- Uncontrolled, unregulated, and self-sustaining inflammatory response

Pathophysiology Cont.

The mechanism of cellular injury associated with sepsis is not fully understood, but is thought to be caused by:

- Tissue ischemia - due to insufficient oxygen relative to oxygen need
  - Ineffective metabolic autoregulation
  - Microcirculatory & endothelial lesions
- Cytopathic injury - direct cell injury caused by proinflammatory mediators and/or other products of inflammation
  - Leads to sepsis-induced mitochondrial dysfunction and ultimately cytotoxicity
- Altered rate of apoptosis (programmed cell death)
  - Proinflammatory cytokines delay apoptosis in activated macrophages and neutrophils: prolongs/augments inflammatory response; contributes to MODS
  - Causes apoptosis in lymphocytes and dendritic cells: Alters immune response; results in decreased clearance of invading microorganisms

(Neviere, 2016)

Cellular injury accompanied by the release of proinflammatory and antiinflammatory mediators often progresses to organ dysfunction:

- Circulation - hypotension; unintended consequence of vasoactive mediators whose purpose is to improve metabolic autoregulation (e.g. nitric oxide)
- Lung - interstitial and alveolar pulmonary edema
- GI tract - translocation of bacteria and endotoxin from the gut into systemic circulation, possibly via lymphatics
- Kidney - ATN due to hypoperfusion and/or hypoxemia; exact cause of ARF unknown
- CNS - dysfunction attributed to changes in metabolism and alterations in cell signaling (e.g. inflammatory mediators)

(Neviere, 2016)
Diagnostic Criteria

Clinical presentation (Gauer, 2013):

- Vitals (hypotension, fever, hypoxia)
- Skin (ulcers, cellulitis, ecchymosis or petechiae)
- Pulmonary (cough, hyperventilation, tachypnea, hemoptysis, ronchi or rales)
- GI (abdominal pain, decreased bowel sounds, diarrhea)
- GU (suprapubic tenderness, costovertebral tenderness)
- Cardiovascular (tachycardia, murmur)
- Neurologic (altered mental status)

Diagnostic Criteria Cont.

- Shiver, fever, very cold
- Extreme pain or general discomfort (“worst ever”)
- Pale or discolored skin
- Sleepy, difficult to arouse, confused
- “I feel like I might die”
- Short of breath

Laboratory findings are nonspecific, but abnormalities may be due to underlying cause of sepsis (Neviere, 2013):

- Leukocytosis (WBC > 12,000 microL⁻¹), or leukopenia (WBC < 4,000 microL⁻¹)
- Hyperglycemia (>140 or 7.7 mmol) in absence of diabetes
- Acute oliguria (urine output <0.5mL/kg/hr for at least 2 hours)
- Creatinine increase >0.5mg/dL or 44.2micromol/L
- INR > 1.5 or aPTT >60 seconds
- Thrombocytopenia (platelets <100,000 microL⁻¹)
- Hyperbilirubinemia (total bilirubin >4mg/dL)
- Elevated serum lactate (>2mM/L)
What is severe sepsis?:
Sepsis + Acute Organ Dysfunction = Severe Sepsis
• Hypotension
  - Systolic BP < 90 mmHg or MAP < 65 mmHg
• Acute renal insufficiency
  - Creatinine > 1.2 mg/dl or Urine output < 0.5 ml/kg/hr
• Acute liver insufficiency
  - Bilirubin > 2 mg/dl, AST > 90 mg/dl, ALT > 90 mg/dl
  - Platelet count < 100,000/microL
• Lactic acid > 2mmol/L

What is septic shock?:
Sepsis + Refractory Arterial Hypotension = Septic Shock
• Refractory arterial hypotension
  - Hypotension that persists despite aggressive fluid replacement
• Perfusion abnormalities
• Altered mental status
• Delayed capillary refill
• Decreased urine output
• Lactic acidosis

Treatment:
Early Management of Sepsis

Therapeutic priorities: securing airway, correcting hypoxemia, and establishing vascular access
• Fluid bolus
  - To be given within first 3 hours
  - 30 ml/kg
• Crystalloid solutions (e.g. normal saline)
• Empiric broad spectrum antibiotics
  - To be given within first 3 hours
  - Should cover both gram-positive and negative bacteria (e.g. zosyn, carbapenem)
• Combination therapy – neutropenic patients, difficult-to-treat infections (e.g. Pseudomonas)

If blood cultures cannot be drawn in a timely manner, antibiotics should not be delayed!
(Schmidt & Mandel, 2017)

Treatment: Early Management of Sepsis Cont.
Therapeutic response should be assessed frequently after fluids and empiric antibiotics have been administered
• MAP (>65 mmHg)
• Urine output (>0.5 mL/kg/hr)
• Skin color
• Mental status
• Pulses
• Respiratory rate
• Temperature

Treatment: Management of Severe Sepsis and Septic Shock
• Hemodynamic support (Zwickler et al., 2013)
  - Fluid challenge with measurement of hemodynamic variables (i.e. pulse pressure, stroke volume) when fluid administration is continued
  - Albumin recommended when patients require large amounts of crystalloid solutions
  - Vasopressors (to achieve MAP of 65 mmHg):
    - Norepinephrine (NE) should be used first
    - Epinephrine - when additional agent is needed
    - Vasopressin - can be added to NE to raise MAP or decrease NE dose
    - Phenylephrine - not recommended for the treatment of septic shock unless:
      - Use of NE has caused serious arrhythmias
      - Cardiac output is high and BP is persistently low
    - Dobutamine can be used instead of NE in patients with low risk of tachyarrhythmias and absolute or relative bradycardia, should NOT be used for renal protection
  - Dopamine can be used instead of NE in patients with low risk of tachyarrhythmias and absolute or relative bradycardia, should NOT be used for renal protection

(Schmidt & Mandel, 2017)
Treatment: Management of Severe Sepsis and Septic Shock Cont.

- Supportive therapy (Dellinger et al., 2013):
  - Blood product administration
  - Mechanical ventilation
  - Renal replacement therapy
  - Deep vein thrombosis prophylaxis
  - Stress ulcer prophylaxis
  - Nutrition
  - Glucose control
  - Setting goals of care

- Blood product administration
  - Red blood cell transfusion – only if Hgb <7.0 g/dL
  - Platelets – indicated when counts are ≤30,000/mm³ (≥10 x 10⁹/L) or ≤80,000/mm³ (≥20 x 10⁹/L) if the patient has a significant risk of bleeding
  - Fresh Frozen Plasma – should not be used to correct clotting abnormalities in the absence of bleeding or planned invasive procedures
  - Immuneglobulins – not recommended for adult patients with severe sepsis or septic shock (Dellinger et al., 2013)

- Mechanical ventilation of sepsis-induced acute respiratory distress syndrome (ARDS)
  - Target tidal volume – 6mL/kg predicted body weight
  - Positive end-expiratory pressure (PEEP) – to avoid alveolar collapse at end-expiration
  - Maintain head of bed to 30 to 45 degrees to limit aspiration risk
  - Weaning protocol that encourages regular spontaneous breathing trials
  - Extubation indicated when the patient is:
    - Arousable
    - Hemodynamically stable
    - Has no new potentially serious conditions
    - Able to tolerate low PEEP/FiO2 and spontaneous breathing trial is successful
  (Dellinger et al., 2013)

- Renal replacement therapy
  - Continuous renal replacement therapies (CRRT) and intermittent hemodialysis are equivalent in patients with severe sepsis and acute renal failure
  - Continuous therapies are recommended to manage fluid balance in hemodynamically unstable septic patients
  - Continuous therapies are recommended to manage fluid balance in hemodynamically unstable septic patients

- Deep vein thrombosis prophylaxis
  - Daily venous thromboembolism prophylaxis with low-molecular weight heparin (LMWH)
  - If creatinine clearance is <30mL/min, enoxaparin or another form of LMWH that has a low degree of renal metabolism should be used
  - Patients with a contraindication for heparin use (e.g. thrombocytopenia, active bleeding, recent intracranial hemorrhage) should receive mechanical prophylaxis instead
  (Dellinger et al., 2013)
Treatment: Management of Severe Sepsis and Septic Shock Cont.

- Stress ulcer prophylaxis
  - H2 blocker or proton pump inhibitor (PPI)
  - Recommended for patients with severe sepsis/septic shock + bleeding risk factors
  - PPI > H2 blockers
  - Unnecessary for patients without risk factors

- Nutrition
  - Oral or enteral feedings should be started within 48 hours after diagnosis of severe sepsis/septic shock (as tolerated)
  - Start with low dose feeding (e.g. up to 500 calories per day) for the first week, advancing only as tolerated
  - If a patient requires parenteral nutrition, it should be given in conjunction with enteral feedings when possible (Dellinger et al., 2013)

- Glucose control
  - Insulin is recommended when two consecutive blood glucose levels are >180mg/dL.
  - Target glucose level = 180mg/dL.
  - Blood glucose values every 1 to 2 hours until glucose values and insulin infusion rates are stable, then every 4 hours
  - Use POC testing with caution (Dellinger et al., 2013)

Set goals of care

- Should be discussed with patients and families
- Should be incorporated into treatment and end-of-life care planning where appropriate
- Should be addressed as early as possible, but no later than within 72 hours of ICU admission

(Dellinger et al., 2013)

Factors Influencing Clinical Deterioration in Persons with Sepsis

- Study completed by Patiporn et al. (2017) recruited 172 participants from 11 different emergency departments. Participants presented with:
  - ≥ 2 criteria of SIRS without WBC and shock index ≥ 1 at triage
  - Diagnosed infectious disease

- Clinical deterioration was defined as worsening of any of the following parameters when compared at two different time points:
  - Respiratory system – respiratory rate and oxygen saturation
  - Circulatory system – SBP, pulse rate, urine output
  - Neurological system – Glasgow Coma Scale (GCS)

- 59.3% of participants showed symptoms of clinical deterioration
Factors Influencing Clinical Deterioration in Persons with Sepsis Cont.

- Factors influencing clinical deterioration included:
  - Higher severity of illness
  - Incomplete triage practices: initial VS, organ function assessments, inaccuracy of triage acuity level, non-achieved access time to care
  - Non-achieved performance of sepsis resuscitation bundle: fluid challenge, antibiotic administration, adequate MAP and urine output

- Implications for practice:
  - Provision of triage training
  - Development of sepsis fast track
  - Encourage use of triage assessment protocols and sepsis resuscitation bund[

Surviving Sepsis Campaign Bundle

The Surviving Sepsis Campaign Bundle is used to simplify a complex process in the care of patients with severe sepsis (SCC, 2015).

TO BE COMPLETED WITHIN 3 HOURS:
1) Measure lactate level
2) Obtain blood cultures prior to administration of antibiotics
3) Administer broad spectrum antibiotics
4) Administer 30 ml/kg crystalloid for hypotension or lactate ≥4mmol/L

"Time of presentation" is defined as the time of triage in the emergency department or, if presenting from another care venue, from the earliest chart annotation consistent with all elements of severe sepsis or septic shock ascertained through chart review.

TO BE COMPLETED WITHIN 6 HOURS:
5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥65 mm Hg.
6) In the event of persistent hypotension after initial fluid administration (MAP < 60 mm Hg) or if initial lactate was ≥4 mmol/L, reassess volume status and tissue perfusion and document findings according to Table 1.
7) Remeasure lactate if initial lactate elevated.

Treatment: Monitoring Response

Follow-Up Lab:
- Lactate clearance: serum lactate Q6H until value has clearly fallen
- ABGs: look for resolution of metabolic acidosis
- Routine lab: CBC, serum chemistries, and LFTs should be monitored until values have reached baseline
- Microbiology: additional cultures

(After 3 and 6 hour measures…..)

DOCUMENT REASSESSMENT OF VOLUME STATUS AND TISSUE PERFUSION WITH:

EITHER:

- Repeat focused exam (after initial fluid resuscitation) including vital signs, cardiopulmonary, capillary refill, pulse, and skin findings.

OR TWO OF THE FOLLOWING:

- Measure CVP (central venous pressure)
- Measure ScvO2 (central venous oxygen saturation)
- Bedside cardiovascular ultrasound
- Dynamic assessment of fluid responsiveness with passive leg raise or fluid challenge (SCC, 2015)

Figure 1. Surviving Sepsis Campaign Bundle, retrieved from http://www.survivingsepsis.org/Bundles/Pages/default.aspx

Figure 2. Surviving Sepsis Campaign Bundle, retrieved from http://www.survivingsepsis.org/Bundles/Pages/default.aspx

(After 3 and 6 hour measures…..)
Treatment: Monitoring Response Cont.

Once patients have demonstrated a response to therapy, the focus should shift towards de-escalation of fluids and antibiotics as appropriate.

- 7 to 10 days of pathogen- and susceptibility-directed antibiotics

Larger courses are indicated in the presence of: undrainable focus of infection, bacteremia with S. aureus, certain fungal or viral infections (such as herpes or cytomegalovirus), endocarditis, osteomyelitis, large abscesses, highly resistant gram-negative pathogens with limited sensitivities, neutropenia, or immunologic deficiencies

(Silmsdell & Mandel, 2017)

Life After Sepsis

- Physical limitations
- Limitations in activities of daily living (bathing, managing money)
- Neuropathy, myopathy, cognitive or respiratory impairments
- Cognitive impairment
- Memory, attention, decision making, speech fluency
- Mental health impairment
- Anxiety (20%), depression (39%), PTSD (44%)
- Recurrent infection and sepsis
- 45% readmitted within 90 days
- Exacerbation of chronic medical conditions
- Congestive heart failure, acute renal failure, exacerbation of COPD
- Impact on quality of life, work, and social relationships

(Prescott & Angus, 2018)

Sepsis Prevention

- Frequent and thorough handwashing
- Cough into the elbow
- Sterile technique
- Antibiotics
- Healthy diet, exercise, and rest
- Vaccinations
- Education

(Sepsis Alliance, n.d.)

Summary

- Complex inflammatory response
- Rate of mortality improving
- Most important:
  - Fluid resuscitation
  - Antibiotics
  - Timely recognition!
Implications for Practice

- Promotion of early goal directed therapy to reduce the risk of mortality rates
- Promotion of hospital order sets to provide efficient care with appropriate antibiotic therapy and fluid resuscitation
- Possibility of telemedicine in small rural hospitals in collaboration with tertiary medical hospitals for sepsis management

A 68-year-old woman is brought to the ED by her husband with symptoms of disorientation and weakness. She has a known history of frequent UTIs. Her husband states that she has had problems with urinary incontinence for years, and regularly uses briefs and pads to avoid accidents. Her first blood pressure reading is 80/45, and when a UA is obtained it appears cloudy and has a foul odor. You determine that she most likely has urosepsis. Along with fluid resuscitation, what antibiotic should be given within the first hour?

- a. Nitrofurantoin 100mg
- b. Amoxicillin/Clavulanate 875/125mg
- c. Zosyn 4.5g
- d. None of the above

Case Study # 1

Answer: C. Zosyn 4.5g

Rationale: An empiric broad spectrum antibiotic that covers both gram-positive and negative bacteria should be given in the first hour when sepsis is suspected. Pathogen- and susceptibility-directed antibiotics should be started once culture results are obtained.

Case Study # 2

A 92-year-old man presents to ED with symptoms of cough, persistent fevers, and weakness. He states that he has been battling cold symptoms for over a week now but woke up with a fever of 102.9°F this morning and became concerned. He has a productive, harsh cough with purulent sputum. His lactate is 3.2 mmol/L and current vital signs are as follows:

- Pulse – 98
- Respirations – 20
- BP – 110/54 (72)
- Temperature – 99.9°F

What should be done next based upon these findings?

- A. Obtain blood cultures prior to administration of antibiotics
- B. Administer broad-spectrum antibiotics
- C. Administer 30 ml/kg crystalloid solution
- D. All of the above
- E. Both A & B
Answer: E. Obtain blood cultures prior to administration of antibiotics & administer broad spectrum antibiotics

**Rationale:** A fluid bolus is not necessary at this time because the patient’s MAP is >65mmHg and his lactate is <4mmol/L. The patient does however rule in for sepsis due to an elevated lactate >2mmol/L, so blood cultures and broad spectrum antibiotics should be started within the first three hours of presentation.

**References**


