

Sepsis – 3.0 CE Hours

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Course Objectives:

1. Define the Systemic Inflammatory Response Syndrome (SIRS).
2. Compare and contrast the conditions of sepsis, severe sepsis and septic shock.
3. Examine the process for early identification and management of sepsis.
4. Identify the signs of systemic hypoperfusion in septic shock.
5. Indicate the most common places for infections to start in the body.
6. List facts regarding the incidence of sepsis.
7. Identify people who are at high risk for developing sepsis.
8. Identify predisposing factors that contribute to developing sepsis.
9. Recite the correct order for the cascade for severe sepsis.
10. Relate how serum lactate is an indicator of tissue ischemia.

Overview

The following are the definitions from the American College of Chest Physicians and the Society of Critical Care Medicine.

Systemic Inflammatory Response Syndrome (SIRS)- Defined by the presence of two or more of the following findings:

- Body temperature < 36 °C (97 °F) or > 38 °C (100 °F) (hypothermia or fever).
- Heart rate > 90 beats per minute.
- Respiratory rate > 20 breaths per minute or, blood gas,

a P_aCO_2 less than 32 mm Hg (4.3 kPa) (tachypnea or hypocapnia due to hyperventilation).

- White blood cell (WBC) count $< 4,000$ cells/mm³ or $> 12,000$ cells/mm³ ($< 4 \times 10^9$ or $> 12 \times 10^9$ cells/L), or greater than 10% band forms (immature white blood cells, leukopenia, leukicytosis, or bandemia).

Sepsis- Defined as SIRS in response to a confirmed infectious process. Infection can be suspected or proven (by culture, stain, or polymerase chain reaction (PCR), or a clinical syndrome pathognomonic for infection. Specific evidence for infection includes WBCs in normally sterile fluid (such as urine or cerebrospinal fluid (CSF)); evidence of a perforated viscus (free air on abdominal x-ray or CT scan; signs of acute peritonitis); abnormal chest x-ray (CXR) consistent with pneumonia (with focal opacification); or petechiae, purpura, or purpura fulminans.

Severe sepsis- Defined as sepsis with organ dysfunction, hypoperfusion, or hypotension.

Septic shock- Defined as sepsis with refractory arterial hypotension or hypoperfusion abnormalities in spite of adequate fluid resuscitation. Signs of systemic hypoperfusion may be either end-organ dysfunction or serum lactate greater than 4 mmol/L. Other signs include oliguria and altered mental status. Patients are defined as having septic shock if they have sepsis plus hypotension after aggressive fluid resuscitation (typically upwards of 6 liters or 40 ml/kg of crystalloid solution).

Causes of Sepsis

Sepsis is caused by a bacterial infection that can begin anywhere in the body. Common places where an infection might start include: peritonitis (bowel), urinary tract or kidney infections (pyelonephritis), meningitis (lining of the brain), liver or gall bladder, lungs (bacterial pneumonia), skin

(cellulitis), heart, and bones (osteomyelitis). Hospitalized patients can acquire infections through their IV sites, surgical or injury wounds, drain sites and any area of skin breakdown.

Incidence and Facts

- Worldwide is the major cause of morbidity and mortality.
- Is the leading cause of death in the US in non-coronary ICUs.
- Overall is the tenth leading cause of death in the US.
- Annually in the US more than 750,000 cases of severe sepsis.
- 500 patients die every day in the US of severe sepsis.
- The number of people dying from sepsis has almost doubled in the past 20 years, mainly due to the increased usage of antibiotics.
- Because antibiotic use has increased, many strains of bacteria have become resistant to antibiotics, making the treatment of sepsis more difficult in some cases.

People at Risk for Sepsis

Although there are people at greater risk for developing sepsis, it is important to realize that anyone can develop it. People at risk for developing sepsis include:

- People with compromised immune systems. When the body's immune system is compromised the body can't fight against microbes that have entered the body. Infants are at a greater risk due to their immune system not being completely developed.
- The elderly and especially those with other medical conditions are at an increased risk due to a weak immune system.
- People who have had their spleen surgically removed (because the spleen helps fight certain infections).
- People who are being treated with chemotherapy drugs or

radiation.

- Anyone who is taking immunosuppressive medications (such as transplant recipients).
- People with long-standing diabetes, AIDS, or cirrhosis.
- People taking steroids (especially over the long term).
- Someone who has large burns or severe injuries.
- People with infections such as: pneumonia, meningitis, cellulitis.

Predisposing Factors for Developing Sepsis

1. Immunosuppression
2. Prior antibiotic therapy
3. Injury and inflammation
4. Surgery or invasive procedure
5. Malnutrition, alcohol abuse
6. Prolonged intubation
7. Ventilator associated pneumonia
8. Chronic illness

Pathophysiology of Sepsis

1. Tissue injury or pathogens
2. Trigger the release of pro-inflammatory mediators to clear the pathogen
3. An excessive response leads to a massive release of cytotoxic material
4. Direct damage to the endothelium
5. Triggers a cascade that is difficult to stop

Severe Sepsis Cascade

It is a complex physiologic process BUT it is also very simple: it is homeostasis out of balance.

1. Invasive Infection is when an antigen enters the bloodstream. This triggers the immune system to release pro-inflammatory mediators to clear the antigen, which is very toxic to normal tissue and cells. The

endothelium, the inner lining of the vessels, is damaged, causing capillary leakage syndrome and third spacing of fluid. There is an imbalance of these mediators. Malignant inflammatory processes are occurring.

2. The coagulation cascade is also triggered so that clots can form to engulf and isolate the antigen. Fibrinolysis is suppressed to allow the clots to form. But instead of this inflammatory/coagulation process being localized to the site of infection, this response is systemic. Clots are forming everywhere in the microcirculation, "slug in the capillaries," thus decreasing perfusion to the organs and the organs fail due to lack of adequate oxygenation and resulting in death.

Invasive Infection: foreign antigens from cell walls of bacteria and fungi, bacterial DNA, RNA from viruses, etc.

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Body's Immune Cells: Macrophages, neutrophils, endothelial cells, monocytes

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Cytokine Release: Interleukins, interferons, tumor necrosis factor, etc.

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Damage to Blood Vessel linings

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Increased inflammation (vasodilation, capillary leak), increased coagulation, decreased fibrinolysis

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Severe Sepsis/Septic Shock

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Multiple Organ Dysfunction Syndrome (lung, liver, kidney)

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Death (mortality 40-60% in severe sepsis/septic shock)

The initial inflammation of severe sepsis affects the

microvasculature through multiple pathways. The white blood cells become activated and release mediators, which in part activate systemic coagulation and the formation of clots in the microvasculature. Severe sepsis also leads to decreased fibrinolysis, thus reducing the body's innate ability to lyse clots. The clots accumulate, leading to hypoperfusion (the decreased blood flow through an organ) and cellular hypoxia. Additionally the white blood cells migrate through the endothelial walls, which contribute to the endothelial dysfunction of severe sepsis. Organ dysfunction may result from either global tissue hypoxia and/or direct damage to the organ cells/tissue.

The Importance of Early Recognition of Sepsis

Early identification can help improve survival. **Sepsis** is defined as a *suspected* or *confirmed* infection plus at least 2 SIRS criteria is a relatively benign condition with an average hospital mortality rate of 5-7%. In contrast **severe sepsis** is defined as sepsis plus acute dysfunction of at least 1 organ, is a highly lethal condition with a mortality rate of 20-80%.

Mortality rates increase as organ dysfunctions increase:

- 21.2% – 1 organ dysfunction
- 44.3% – 2 organ dysfunctions
 - 64.5% – 3 organ dysfunctions
 - 76.2% – 4 or more organ dysfunctions

Serum Lactate as Indicator of Tissue Ischemia

- Krebs Cycle: Aerobic metabolism/Anaerobic metabolism
- Lactate: normal 1-2 mmol/ > 4mmol with metabolic acidosis suggests tissue hypoxia
- Elevated lactate may not always be due to anaerobic metabolism. It may be elevated in reduced hepatic clearance, trauma, or profound dehydration. Regardless

of cause, elevation of lactate is associated with an increase in mortality.

Signs and Symptoms of Sepsis

Tachypnea is often the first detectable clinical sign of sepsis. The rapid breathing rates are due to the lung being the most common site of infection. Acute lung injury often results from non-pulmonary sources of infection. Tachypnea is the compensatory mechanism for metabolic acidosis.

Another early indicator is tachycardia. This is because it is an important compensatory mechanism to maintain perfusion in response to intravascular volume deficits, reduced cardiac contractility, and vasodilatation. The only time you will not see tachycardia is in patients that cannot be tachycardic due to a cardiac conduction defect or from the effects of pharmacotherapy.

Respiratory Dysfunction Signs and Symptoms

Signs: Tachypnea, $PaO_2/FiO_2 < 250$, abnormal chest x-ray, abnormal blood gases, respiratory alkalosis in early stage and metabolic acidosis with low perfusion in the late stage.

Symptoms: Restlessness, anxious, dyspnic, and cyanotic.

Cardiovascular Dysfunction Signs and Symptoms

Signs: Tachycardia, hypotension, increased CVP, poor capillary refill, arrhythmias, elevated CK, CKMB, and Troponin, and cardiac arrest.

Symptoms: Restlessness, palpitations, anxiety, chest pain, mottling, pale, cool to touch and diaphoretic.

GI and Hepatic Dysfunction Signs and Symptoms

Signs: Ileus elevated LFTs, AST, ALT, Bilirubin, Gamma-GT, decreased albumin, hypoglycemia

Symptoms: Nausea, vomiting, abdominal distension, change in bowel sounds, jaundice, and GI bleed.

Neurological Dysfunction Signs and Symptoms

Symptoms: Disoriented, confused, change in level of consciousness, agitated, restless

Renal Dysfunction Signs and Symptoms

Signs: Elevated BUN and Creatinine, GFR < 29, decreased urine output, oliguria <.4 ml/kg/hr, Anuria <50 ml/day, increased uric acid, increased electrolytes (K, MG, NA), metabolic acidosis.

Hematologic Dysfunction Signs and Symptoms

Signs: Abnormal WBC, left shift, thrombocytopenia, elevated PT, DIC

Symptoms: Bruising and bleeding

Skin Dysfunction Signs and Symptoms

Signs: Cellulitis, bullous lesions, phlebitis at intravenous sites, acrocyanosis and /or peripheral gangrene, ecchymotic or purpuric lesions, DIC, petechiae

Surviving Sepsis Campaign

A problem in the adequate management of septic patients has been the delay in administering therapy after sepsis has been recognized. Published studies have demonstrated that for every hour delay in the administration of appropriate antibiotic therapy there is an associated 7% rise in mortality. A large international collaboration was established to educate people about sepsis and to improve patient outcomes with sepsis, entitled the "Surviving Sepsis Campaign." The Campaign has published an evidence-based review of management strategies for severe sepsis. In 2004, the international group of experts

representing 11 organizations published the first set of internationally accepted guidelines that the bedside clinicians could use to improve outcomes in severe sepsis and septic shock. This was the second step in the surviving sepsis campaign SSC, an international effort to increase awareness and improve outcomes in severe sepsis. In 2006-2007 they were joined by several additional organizations to update the guidelines using evidence-based methodology.

Goal-directed therapy represents an attempt to predefine resuscitation end-points to help clinicians at the bedside to resuscitate patients in septic shock. The end-points used vary according to the clinical study but attempt to adjust cardiac preload, contractility, and afterload to balance systemic oxygen delivery with demand. Two essential features of the early goal directed therapy Include: maintaining an adequate central venous pressure (CVP) to carry out other hemodynamic adjustments and maximizing mixed or central venous oxygen saturation.

Sepsis Resuscitation Bundle:

1. Serum Lactate measured
2. Blood cultures obtained
3. Improved time to broad spectrum antibiotic
4. Treat hypotension and/or elevated lactate with fluids
5. Apply vasopressors for ongoing hypotension
6. Maintain adequate Central Venous Pressures (CVP)
7. Maintain adequate central venous oxygen saturation (ScV02, SV02)

Serum Lactate Measured

Obtaining serum lactate is essential to identifying tissue hypoperfusion in patients who are not yet hypotensive but who are at risk for septic shock. Given the high risk for septic shock, all patients with elevated lactate > 4 mmol/L (36 mg/dl) will enter the early goal-directed therapy portion of

the Severe Sepsis Resuscitation Bundle, regardless of blood pressure.

Following the Sepsis Resuscitation Bundle, once lactate is > 4 mmol/L (36 mg/dL), or hypotension has been demonstrated to be refractive to an initial fluid challenge with 20 mL/kg of crystalloid or colloid equivalent, patients should then have their CVP maintained > 8 mm Hg. Of note, in adhering to this strategy, patients receive the initial minimum 20 mL/Kg fluid challenge prior to placement of a central venous catheter and attempts to maximize CVP.

The resuscitation of severely septic individuals with lactate > 4 mmol (36 mg/dL) or in septic shock must start early. *The longer the resuscitation is delayed, the less likely a beneficial effect will be accrued.* This makes sense, as the purpose of resuscitating a patient is to prevent further organ dysfunction and failure. If the resuscitation is delayed until after cellular dysfunction and death is present, then strategies designed to provide the cells with more oxygen are unlikely to be helpful. It is unclear however when the transition from reversible cellular dysfunction to irreversible cellular dysfunction occurs. At present, the only strategy we can employ is to provide resuscitation at the earliest stage possible.

Blood Cultures Obtained

Obtain appropriate cultures before starting antibiotics providing this does not significantly delay antimicrobial administration. Obtain two or more blood cultures (one or more should be percutaneous), obtain one blood culture from each vascular access device in place >48 hours, and culture other sites as clinically indicated. Implement source control measures ASAP (i.e.: abscess drainage, tissue debridement, device removal). Look for maximum efficacy with the least physiological upset

Improve Time to Broad Spectrum Antibiotics

Begin as soon as possible. Treat the patient with a broad-spectrum antibiotic within three hours for emergency department admission and within one hour for non-emergency department ICU admissions.

The choice of antibiotics should be guided by the susceptibility of likely pathogens in the community and the hospital, as well as any specific knowledge about the patient, including drug intolerance, underlying disease, the clinical syndrome. The regimen should cover all likely pathogens since there is little margin for error in critically ill patients. Reassess daily based on culture results to prevent resistance, improve efficacy, avoid toxicity and superimposed or opportunistic infections (C-dif), and minimize costs. Stop antibiotic therapy if the cause is found to be non-infectious. Limit treatment to 7-10 days. All patients should receive a full loading dose of each antimicrobial. Those with renal or hepatic dysfunction will need dose adjustment and the pharmacy should be consulted to help with this.

Treat Hypotension and/or Elevated Lactate with Fluids

Patients with severe sepsis and septic shock may experience ineffective arterial circulation due to the vasodilatation associated with infection or impaired cardiac output. Poorly perfused tissue beds result in global tissue hypoxia, which is often found in association with an elevated serum lactate level. *A serum lactate value greater than 4 mmol/L (36 mg/dl) is correlated with increased severity of illness and poorer outcomes even if hypotension is not yet present.* As such, patients who are hypotensive or have a lactate greater than 4 mmol/L (36 g/dl) require intravenous fluids or colloid to expand their circulating volume and effectively restore perfusion pressure.

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 central venous pressure (CVP) goal of > 8 mmHg in subsequent steps, volumes much greater than the initial 20 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.

Apply Vasopressors for Ongoing Hypotension

In the event of hypotension and/or lactate > 4 mmol/L, apply vasopressors for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure (MAP) > 65 mm Hg. Norepinephrine or dopamine *centrally administered* are the initial vasopressors of choice. Epinephrine, phenylephrine, or vasopressin should not be the first choice. Use epinephrine as first alternative.

Adequate fluid resuscitation is a prerequisite for the successful and appropriate use of vasopressors in patients with septic shock. In general, the end points of fluid resuscitation are the same as those for the use of pharmacologic hemodynamic support, i.e. MAP > 65 mm Hg.

Sometimes, fluid resuscitation is enough on its own. When an appropriate fluid challenge fails to restore an adequate arterial pressure and organ perfusion, therapy with vasopressor agents should be started. Vasopressor therapy may also be required transiently to sustain life and maintain perfusion in the face of life-threatening hypotension, even when hypovolemia has not been resolved or when a fluid challenge is in progress.

Although all the vasopressor agents generally result in an increase in blood pressure, concerns remain in clinical practice about their potentially inappropriate or detrimental

use. The most obvious of these relates to the inadequately volume-resuscitated patient, in whom vasopressor use may worsen already inadequate organ perfusion. Even when volume resuscitation has been performed, discussion continues as to whether vasopressor agents may raise blood pressure at the expense of the perfusion of vulnerable organs, most particularly the kidneys and the abdomen. A further concern relates to the possibility that overenthusiastic use, especially if an unnecessarily high blood pressure is targeted, may increase left ventricular work to an unsustainable degree and so worsen cardiac output and end-organ perfusion. This may be especially harmful in patients with pre-existing heart disease.

Maintain Adequate ScV02/SV02

If the patient is both hypovolemic and the hematocrit is less than 30%, it is appropriate to transfuse packed red blood cells provided that the fluid resuscitation has achieved a CVP > 8. Once the decision to use blood products has been made, this may accomplish the dual purpose of increasing ScvO₂ due to increased oxygen delivery to ischemic tissue beds and keeping the central venous pressure > 8 mm Hg for longer periods than fluids alone.

Provided that the patient has been adequately resuscitated and the CVP is > 8 mmHg, it may be that cardiac output remains insufficient to meet metabolic needs of certain tissue beds despite an adequate circulating volume. In some cases, cardiac output itself may be diminished due to sepsis induced cardiac dysfunction. In these cases, dobutamine infusion (up to a maximum of 20 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) should be employed to increase oxygen delivery to the periphery and prevent further organ dysfunction due to hypoperfusion and ischemia. If dobutamine infusion results in hypotension, norepinephrine should be used to counteract the vasodilatory effects of dobutamine.

The maximum dose of dobutamine is 20 micrograms/kg/min.

The “2012 Surviving Sepsis Campaign Guidelines” suggest intravenous hydrocortisone be given only to adult septic shock patients after blood pressure is identified to be poorly responsive to fluid resuscitation and vasopressor therapy.

- **Administer low dose steroids:** The rationale for the use of glucocorticoids in sepsis trials has been the role they play in the stress response to infection and the anti-inflammatory effects they exert. Some newer research has proved that glucocorticoids activate specifically induced, anti-inflammatory monocyte subtypes that rapidly travel to the inflamed tissues. Consider hydrocortisone IV for adult septic shock when hypotension is poorly responsive to fluids and vasopressors. An ACTH stimulation test is not necessary. Steroid therapy should be weaned once vasopressors are no longer needed. Do not use corticosteroids in the absence of shock unless the patient’s endocrine or corticosteroid history warrants it.

Please note that the EMA stated that physicians should stop ongoing treatment of patients with activated drotrecogin alfa and should no longer start new patients on the agent – a warning repeated by the FDA on October 25, 2011.

Activated drotrecogin alfa is a recombinant form of human activated protein C. The drug’s efficacy has been questioned ever since the FDA authorized it for use here almost 10 years ago after a 20 to 20 vote by an agency advisory panel to recommend approval.

- **Maintain Adequate Glucose Control:** Use IV insulin to control hyperglycemia. Monitor blood glucose every 1-2 hours with the goal < 150 using a validated protocol. Provide a glucose calorie source. Low glucose levels from POC testing should be interpreted with caution as

that technique may overestimate arterial blood or plasma glucose levels.

- **Prevent Excessive Inspiratory Plateau Pressure:** Keep the head of the bed elevated 30- 45%, consider prone position, use a weaning protocol and a spontaneous breathing trial (SBT) regularly to evaluate potential for extubation.

The Nurse's Role

- Early Recognition of patients with signs of sepsis
- Early initiation of evidence based practice therapies appropriate for your area (lactate, cultures, antibiotics, & fluids)
- Swift transfer of patient where the rest of the bundle can be started
- Resuscitation Goals include: Central Venous Pressure (CVP) 8-12mm Hg, mean arterial pressure > 65 mmHg, urine output > .5 ml/kg/hour, and central venous (superior vena cava) oxygen saturation > 70% or mixed venous > 65%.

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