Sepsis, Severe Sepsis and Septic Shock
Evidence based approach
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Objectives
• Historical perspective
• Definition
• Epidemiology
• Protocol and Guidelines
• Evidence based approach
• Allegheny Health Network initiative

History of Sepsis
• Derived from a Greek word meaning PUTRID
• The Austrian obstetrician Ignaz Philipp Semmelweis and the English surgeon Joseph Lister in the 19th century
• Invasion of microorganisms or their toxins into the bloodstream together with the host response to this invasion

Definition
• Systemic, deleterious host response to infection
• Severe sepsis is acute organ dysfunction secondary to documented or suspected infection
• Septic Shock is severe sepsis plus hypotension not reversed with fluid resuscitation
• Hypotension is systolic BP < 90 mmHg or MAP < 70
• Hypoperfusion is defined as infection-induced hypotension, elevated lactate or oliguria

Severe Sepsis: A Significant Healthcare Challenge
• Major cause of morbidity and mortality worldwide
  - Leading cause of death in non-coronary ICU (US)*
  - 11th leading cause of death overall (US) 15
• More than 750,000 cases of severe sepsis in US annually8
• In the US, more than 500 patients die of severe sepsis daily7

Sepsis is the #1 Cause of Medicare Inpatient Deaths
2016 updates

- $20 billion spent in sepsis in 2011 (5.2% of total hospitals costs)
- Incidence is increasing
- Pathobiology is still not fully understood

New 2016 definition

- Defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection

Why a focus on Sepsis?

- The Network has recognized how sepsis impacts patients. AHN has made Sepsis an organization initiative to standardize best practices and improve patient outcomes
- Beginning October 1, 2015 Sepsis began as a CMS (Centers of Medicaid and Medicare Services) core measure. They will begin to look at how care is provided to these patients

Severe Sepsis Protocol

- Highmark initiative
- Started at St Vincent Hospital in 2013
- Very successful
- Over 3 years, mortality has been reduced to below the national average

Key Concepts of Sepsis (2016)

- Sepsis is the primary cause of death from infection, especially if not recognized and treated promptly. Its recognition mandates urgent attention.
- Sepsis is a syndrome shaped by pathogen factors and host factors (eg, sex, race and other genetic determinants, age, comorbidities, environment) with characteristics that evolve over time. What differentiates sepsis from infection is an aberrant or dysregulated host response and the presence of organ dysfunction.
- Sepsis-induced organ dysfunction may be occult; therefore, its presence should be considered in any patient presenting with infection. Conversely, unrecognized infection may be the cause of new-onset organ dysfunction. Any unexplained organ dysfunction should thus raise the possibility of underlying infection.
- The clinical and biological phenotype of sepsis can be modified by preexisting acute illness, long-standing comorbidities, medication, and interventions.
- Specific infections may result in local organ dysfunction without generating a dysregulated systemic host response.

<table>
<thead>
<tr>
<th>TABLE 1: Diagnostic Criteria for Sepsis</th>
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<tbody>
<tr>
<td>Infection, documented or suspected, and none of the following</td>
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<tr>
<td>General variables:</td>
</tr>
<tr>
<td>Fever $&gt;$38°C</td>
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<tr>
<td>Hypothermia (Core temperature $&lt;$36°C)</td>
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<tr>
<td>Heart rate $&gt;$95 b/min or more than two above the normal value for age</td>
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<tr>
<td>Tachypnea</td>
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<tr>
<td>Altered mental status</td>
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<tr>
<td>Significant change in blood pressure $&gt;$30 mm Hg, or $&lt;$90 mm Hg</td>
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<tr>
<td>Hypoglycemia (Glucose $&lt;$40 mg/dL or $&lt;$2.2 mmol/L) in the absence of diabetes</td>
</tr>
<tr>
<td>Inflammatory variables</td>
</tr>
<tr>
<td>Leukocytosis (WBC count $&gt;$15,000/cL)</td>
</tr>
<tr>
<td>Leukopenia (WBC count $&lt;$4,000/cL)</td>
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<tr>
<td>Normal WBC count with greater than 10% immature neutrophils</td>
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<tr>
<td>Plasma C reactive protein more than two above the normal value</td>
</tr>
<tr>
<td>Plasma procalcitonin more than two above the normal value</td>
</tr>
<tr>
<td>Hemodynamic variables</td>
</tr>
<tr>
<td>Arterial blood pressure (SBP) $&lt;$90 mm Hg, MAP $&lt;$60 mm Hg, or SBP decrease $&gt;$40 mm Hg in adults or less than two $&lt;$20 mm Hg below normal for age</td>
</tr>
</tbody>
</table>
Severe Sepsis

**Organ dysfunction variables**
- Arterial hypoxemia (PaO₂/FiO₂ < 300)
- Acute oliguria (urine output < 0.5 mL/kg/hr for at least 2 hrs despite adequate fluid resuscitation)
- Creatinine increase > 0.5 mg/dL or > 44.2 μmol/L
- Coagulation abnormalities (INR > 1.5 or aPTT > 60 s)
- Hypoalbuminemia (albumin < 3.0 g/dL)
- Hypothermia (rectal temperature < 35°C)
- Hypoglycemia (systolic blood pressure < 90 mm Hg for more than 3 hrs despite adequate fluid resuscitation)

**Tissue perfusion variables**
- Hyperlactatemia (> 4 mmol/L)
- Decreased capillary refill or mottling

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**Table 3: Severe Sepsis**

<table>
<thead>
<tr>
<th>Severe sepsis criteria</th>
<th>Severe sepsis-induced tissue hypoperfusion or organ dysfunction (any of the following thought to be due to the infection)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septic shock</td>
<td>Septic shock induced by a new source of infection (specifically due to the infection)</td>
</tr>
</tbody>
</table>

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**Initial resuscitation**

**A. Initial Resuscitation**

1. Resuscitation of patients with sepsis-induced hypoperfusion (defined in this document as hypotension persisting for 2 hours despite adequate fluid resuscitation and blood lactate concentration > 2 mmol/L). Goals during the first 6 hours of resuscitation:
   - Central venous pressure 10–15 mm Hg
   - Mean arterial pressure ≥ 65 mm Hg
   - Urine output ≥ 0.5 mL/kg/hr
   - Central venous oxygen saturation > 70% (or > 60% if < 70%)
   - In patients with elevated lactate levels targeting resuscitation to normalize lactate (grade 2C)

**B. Screening for Sepsis and Performance Improvement**

1. Routine screening of potentially infected adults to identify sepsis to allow earlier implementation of therapy (grade 1C)
2. Hospital-based performance improvement efforts in severe sepsis (3C)

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**Caveats**

- In mechanically ventilated patients, a higher target of CVP of 12 to 15 mm Hg is the goal

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**Screening**

1. Routine screening of potentially infected adults to identify sepsis to allow earlier implementation of therapy (grade 1C)
2. Hospital-based performance improvement efforts in severe sepsis (3C)
Diagnosis

C. Diagnosis
1. Cultures should be obtained before oropharyngeal and rectal swabs (CVC), blood culture (blood culture) (CVC), and sputum in septic patients (CVC) with at least 2 fever spikes and 1 neutrophilia, neutrophilia, and 1 hypotension and hypothermia, unless the source was recently CRBSI and is an abscess or tumor. 
2. Use of the 2-5 mg/kg dose of antibiotic prophylaxis (CVC, urinary, and anti-anesthetic antibiotic assay), if available and necessary, should be considered in patients with septic shock or severe sepsis.
3. Imaging studies performed promptly to confirm a potential source of infection (SSS)

Antibiotic Selection

Sepsis requires the correct antibiotic selection.

The SSVH Severe Sepsis Order set (found in both the ER and Hospital McKesson system), has specific recommendations depending upon infection source:
- Pneumonia
- Urinary Tract Infection
- Intra-abdominal Infection
- Central Line Related
- Neutropenic Sepsis
- Unclear or Undetermined Source

Clostridium difficile colitis

Antibiotics

A. Intravenous Therapy

B. Surgical Therapy

C. Antibiotic Therapy

D. Supportive Therapy

Source control

E. Source Control

1. A specific anatomic diagnosis of infection requiring consideration for emergent source control be sought and diagnosed or included as rapidly as possible, and identified as the source within 48 hours of antibiotic therapy.
2. When involved peritoneal sepsis is identified as a potential source of infection, definitive intervention should be delayed until adequate clearance of viable and nonviable tissue has occurred (grade 2A).
3. When source control in a severely infected patient is required, the effective intervention associated with the least physiologic insult should be used early, if failure to achieve any objective goal is observed (grade 2B).
4. If invasive source control is not possible, source of severe sepsis or septic shock, they should be removed promptly after other vascular access has been established (grade 2B).

Prevention of infection

F. Infection Prevention

1. Selective decontamination and selective digestive decontamination should be introduced and investigated as a method to reduce the incidence of ventilator-associated pneumonia. This infection control measure can be initiated in health care settings and regions where this methodology is found to be effective (grade 2B).
2. One chemotherapy-penicillin can be used as a form of prophylactic decontamination to reduce the risk of ventilator-associated pneumonia in ICU patients with severe sepsis (grade 2B).
### Surviving Sepsis Campaign Bundles

**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 ≥4 mmol/L

**To be completed within 6 hours:**
5. Apply vasopressors for hypotension that does not respond to initial fluid reabsorption
6. In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L (36 mg/dL), measure central venous pressure (CVP)
7. Rememeber lactate if initial lactate was elevated

*Targets for quantitative resuscitation included in the guidelines are CVP of 20 mm Hg, S<sub>vo2</sub>% of ≥70%, and normalization of lactate.

### Septic Shock Volume Status and Tissue Perfusion Assessment

Must be completed within 6 hours

- Focused exam- Physician, CRNP, or PA-C must document ALL 5 OF THE FOLLOWING:
  1. Vital Sign review
  2. Cardiopulmonary exam
  3. Capillary refill evaluation
  4. Peripheral Pulse Evaluation
  5. Skin Exam

<table>
<thead>
<tr>
<th>Vital Signs</th>
<th>Cardiopulmonary Exam</th>
<th>Capillary Refill Evaluation</th>
<th>Periperal Pulse Evaluation</th>
<th>Skin Exam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

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### Hemodynamic Support

**G. Fluid Therapy of Severe Sepsis**
1. Crystalloids as the initial fluid of choice in the resuscitation of severe sepsis and septic shock (grade 1C)
2. Against the use of hydrosoluble starches for fluid resuscitation of severe sepsis and septic shock (grade 1B)
3. Avoid in the fluid resuscitation of severe sepsis and septic shock when patients receive substantial amounts of crystalloids (grade 2C)
4. Initial fluid challenge is patients with sepsis-induced tissue hypoperfusion with resuscitation to achieve a mean arterial pressure (MAP) of 60 mm Hg or higher (grade 1C)
5. Fluid challenge technique should be applied whenever fluid administration is continued as long as there is a hemodynamic improvement (either based on dynamic or static changes in arterial pressure, urine output, or other variables) or stable (using arterial pressure, heart rate variables) (grade 2C)

### Hemodynamic Therapy

**H. Vasopressors**
1. Vasopressors therapy initially to be started a mean arterial pressure (MAP) of 60 mm Hg (grade 1C)
2. Norepinephrine as the first choice vasopressor (grade 1B)
3. Vasopressors are essential for patients who are not responding to vasopressors and require additional therapy (grade 1C)
4. Hemodynamic therapy should be adjusted to maintain MAP and CVP within the target range (grade 1C)
5. Therapy should be adjusted daily based on fluid balance and organ function (grade 1C)

**IV. Neuromuscular Blockade**
1. Neuronal muscle blockades are not recommended for the treatment of severe sepsis and septic shock (grade 1C)

### More Therapy?

**I. I. Cardioplegics**
1. Not using nonpolar cardioplegics in heart and severe septic shock patients (grade 1C)
2. Cardiac cineangiography should be performed at least every 48 hours (grade 1B)
3. Treatment should be adjusted to maintain MAP and CVP within the target range (grade 1C)
4. Patients with low cardiac output and/or vasopressor requirements (grade 1C)
Caveats

- Epinephrine is the second agent of choice
- Phenylephrine produces less tachycardia but it may decrease stroke volume and it is recommended only when norepinephrine caused arrhythmias, cardiac output is high or as a salvage therapy
- Vasopressin may be added to Norepinephrine

Other therapies

ARDS

- Mechanical ventilation should be performed with a PEEP of 5-10 cmH2O to maintain positive end-expiratory pressure (PEEP)
- Suctioning should be performed at regular intervals and no more than 4 times per hour
- Sedation and analgesia should be used to control agitation and pain
- Nutritional support is important to maintain adequate energy intake and protein levels during the critical period following ARDS
- Inotropic support may be necessary in some cases to maintain adequate cardiac output and perfusion
- Hemodynamic monitoring is crucial to guide therapy and monitor response to treatment
- Early recognition and intervention are essential to prevent complications and improve patient outcomes

Other therapies

- Vasopressor therapy should be individualized based on the patient's specific needs and response to treatment
- Fluid management should be tailored to the patient's hemodynamic status and goals of care
- Nutritional support should be optimized to meet the patient's energy requirements and prevent complications
- Early intervention and aggressive treatment of complications, such as infection, are critical to improve outcomes
- Regular monitoring and adjustment of therapies are necessary to ensure optimal management of the patient's condition.

Sedation and analgesia

- Sedation should be administered to maintain the patient's comfort and reduce stress and anxiety
- Analgesia should be provided to manage pain and prevent agitation
- Sedative and analgesic medications should be administered in a titrated manner to achieve the desired effect while avoiding oversedation and overanalgesia
- Regular monitoring of sedation and analgesia levels is necessary to ensure appropriate management of patient's condition
- Early mobilization and rehabilitation should be encouraged to promote functional recovery and reduce complications.
Glucose control

1. Hypoglycemic approach to blood glucose management in ICU patients with severe sepsis or septic shock is recommended for patients with 2 consecutive blood glucose levels at or below 100 mg/dL. This approach should be started at an upper limit of glucose of 140 mg/dL, then an upper limit of glucose of 180 mg/dL, then 200 mg/dL, then 220 mg/dL (grade 1C). 

2. Blood glucose values should be monitored every 1-2 hours until glucose values and insulin infusion rates are stable and then every 4 hours thereafter (grade 1C).

3. Glucose levels obtained with peripheral venous testing of capillary blood should be interpreted with caution, as such measurements may not accurately reflect arterial blood or plasma glucose values (A). 

Renal failure and HCO3

1. Renal replacement therapy in patients with severe renal failure and acute respiratory failure may be considered with any degree of respiratory failure, especially in patients with severe hypercapnia (grade 1C).

2. Use continuous therapies to facilitate management of fluid balance in hemodynamically unstable septic patients (grade 1B).

3. Sodium bicarbonate therapy for the purpose of improving hemodynamics or reducing vasopressor requirements in patients with hypokalemic metabolic acidosis with pH ≤7.10 (grade 1). 

Prophylaxis

1. Deep Venous Thrombus Prophylaxis

2. Patients with severe sepsis or septic shock should be treated with a combination of pharmacologic therapy and intermittent pneumatic compression devices whenever possible (grade 1C).

3. Use anticoagulation as an alternative for high-risk patients with severe sepsis or septic shock, but no mechanical prophylactic treatment such as pharmacologic thromboprophylaxis or intermittent compression devices (grade 2B).

4. Contraindicate anticoagulation for patients with severe sepsis or septic shock who have bleeding risk factors (grade 1C). 

Nutrition

1. Nutrition

2. Avoid mandatory full-caloric feeding in the first week and prefer low-calorie feeding (up to 50% calories per day), advancing intake as tolerated (grade 1).

3. Use intravenous glucose and enteral nutrition either alone or in combination with intravenous feeding in the first 7 days after a diagnosis of severe sepsis or septic shock (grade 1B). 

4. Use nutrition with no specific immunomodulating supplementation rather than nutrition providing specific immunomodulating supplementation in patients with severe sepsis (grade 2C).

Goals of care

1. Setting Goals of Care

2. Incorporate goals of care and support with patients and families (grade 1B).

3. Address goals of care as soon as feasible, but no later than within 72 hours of ICU admission (grade 2). 

New 2016 Score system

1. SOFA score system

2. Grades abnormality by organ system

3. Laboratory data is needed for completion
### qSOFA

- Quick assessment for Sepsis
- New/worsened altered mentation
- Respiratory rate >22
- Systolic BP <100

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### SOFA

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiration: (\text{P}_{a}O_2/\text{Fi}O_2)</td>
<td>1 (\leq) 300</td>
</tr>
</tbody>
</table>
| Renal: Creatinine (mg/dL) | \(\geq0.5\) | \(\geq1.0\) | \(\geq1.5\) | \(\geq2.0\)
| Lactic Acidosis | \(>2.0\) | \(>3.0\) | \(>4.0\) | \(>5.0\)
| Hemorrhagic: Platelet (platelets/\(\mu\)L) | \(\leq150\) | \(\leq100\) | \(\leq50\) | \(\leq20\)
| Neurologic: Glasgow coma scale score | \(<8\) | \(8-12\) | \(13-15\) | \(\geq15\)

Note: qSOFA indicates quick SOFA; MAP, mean arterial pressure; Pao2/Fio2, arterial oxygen partial pressure/inspired oxygen fraction; Systolic BP, systolic blood pressure.