Sepsis in the Hospital

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Objectives

• Review the new definitions of SIRS, sepsis, and septic shock and SOFA/qSOFA scoring
• Review updates from Sepsis-3 as well as updates on the Surviving Sepsis campaign with comparison to “old” guidelines
• Discuss use of lactic acid and procalcitonin levels in the management of septic patients
• What’s next?
• Take home points
Disclosures

• None
Why Sepsis?

PROTECT YOUR PATIENTS FROM SEPSIS.

Infections put your patients at risk for sepsis. Be alert to the signs and, if suspected, act fast.

Sepsis is the body’s extreme response to an infection. It is life-threatening, and without prompt treatment, often rapidly leads to tissue damage, organ failure, and death.

**SEPSIS STATS**

- More than 1.5 million people get sepsis each year in the U.S.
- At least 250,000 Americans die from sepsis each year.
- About 1 in 3 patients who die in a hospital have sepsis.

**WHAT CAUSES SEPSIS?**

The most frequently identified pathogens that cause infections that can develop into sepsis include *Staphylococcus aureus* (staphylococcus), *Escherichia coli* (E. coli), and some types of *Streptococcus* (strep).

Four types of infections that are often linked with sepsis:

- Lungs (e.g., pneumonia)
- Urinary tract (e.g., UTI)
- Skin
- Gut

Anyone can get an infection, and almost any infection can lead to sepsis. Certain patients are at increased risk for developing sepsis:

- **65+**
  - Adults 65 or older
- **Weakened immune systems**
  - People with weakened immune systems
- **Children younger than one**
  - Children younger than one
- **Underlying medical conditions**
  - Diseases, lung disease, cancer, and heart disease

WHO IS AT RISK?

www.cdc.gov/sepsis
Timeline Review...

- 1860s: Louis Pasteur gives scientific credence to the germ theory.
- 1890s: Robert Koch publishes Koch's Postulates which states a disease has a causative organism.
- 1990s: ProCESS, ProMISE, and ARSe demonstrate the importance of early recognition, fluid resuscitation, and antibiotics.
- 2001: Allen Jones and EMShockNet describes the utility of lactate clearance.
- 2004: Dellinger et al. delivers the first version of the Surviving Sepsis Campaign in CCM.
- 2008: Bernard et al. describes role for activated protein C.
- 2010: Alan Jones and EMTS shockNet demonstrates the limited utility of steroids in sepsis.
- 2016: "Sepsis-3" presented at the 48th annual SCCM Conference and published as a three article series in JAMA.
- What does the future hold?
“Early Goal Directed Therapy”

- EGDT was devised by Emanuel Rivers, et. al. in 2001 with the goal of intensive monitoring and aggressive management of hemodynamics in a septic patient with a high risk of morbidity and mortality
  - For a time, this formed the basis of the initial “Surviving Sepsis” campaign
- Subsequent to this – several studies have been published reporting that the concepts of EGDT should be abandoned
  - ProCESS, ARISE, ProMISE trials – large, multicenter studies demonstrated no benefit of expensive, invasive management in sepsis patients
What’s New?

- JAMA, Feb. 23, 2016: Sepsis-3, New criteria for defining sepsis
Sepsis-3

• Biggest change – no longer a “severe sepsis” definition
  • Redundant, as sepsis has a ~10% mortality rate and is already severe

• Potential for organ dysfunction is assessed via the Quick Sequential Organ Failure Assessment score (qSOFA)
  • Altered mental status (GCS <15)
  • Systolic BP <100mmHg
  • Respiration rate >22 breaths/min
  • If 2 of 3 met, patient at substantially greater risk for >3 night ICU stay, death
  • Poorly sensitive

## Sequential [Sepsis-Related] Organ Failure Assessment (SOFA) Score

<table>
<thead>
<tr>
<th>System</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiration PaO2/FlO2, mmHg (kPa)</td>
<td>2400 (53.3)</td>
<td>&lt;400 (53.3)</td>
<td>&lt;300 (40)</td>
<td>&lt;200 (26.7) with respiratory support</td>
<td>&lt;100 (13.3) with respiratory support</td>
</tr>
<tr>
<td>Coagulation Platelets, x10^3/μL</td>
<td>≥150</td>
<td>&lt;150</td>
<td>&lt;100</td>
<td>&lt;50</td>
<td>&lt;20</td>
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<tr>
<td>Liver Bilirubin, mg/dL (umol/L)</td>
<td>&lt;1.2 (20)</td>
<td>1.2 – 1.9 (20 – 32)</td>
<td>2.0 – 6.9 (33 – 101)</td>
<td>6.0 – 11.9 (102 – 204)</td>
<td>&gt;12.0 (204)</td>
</tr>
<tr>
<td>Cardiovascular MAP, mmHg</td>
<td>270 (≥70)</td>
<td>MAP ≤70mmHg</td>
<td>Dopamine &lt;6 or Dobutamine (any dose)</td>
<td>Dopamine 5.1 – 15 or Epinephrine ≤0.1 or Norepinephrine ≤0.1</td>
<td>Dopamine &gt;15 or Epinephrine &gt;0.1 or Norepinephrine &gt;0.1</td>
</tr>
<tr>
<td>CNS GCS Score</td>
<td>15</td>
<td>13 – 14</td>
<td>10 – 12</td>
<td>6 – 9</td>
<td>&lt;6</td>
</tr>
<tr>
<td>Renal Creatinine, mg/dL (umol/L)</td>
<td>&lt;1.2 (110)</td>
<td>1.2 – 1.9 (110 – 170)</td>
<td>2.0 – 3.4 (171 – 299)</td>
<td>3.5 – 4.9 (300 – 440)</td>
<td>&gt;5.0 (440)</td>
</tr>
<tr>
<td>Urine Output, mL/d</td>
<td>&lt;500</td>
<td>&lt;500</td>
<td>&lt;500</td>
<td>&lt;500</td>
<td>&lt;200</td>
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*Catecholamine Doses = μg/kg/min for at least 1hr*
Revised Definitions

- **Systemic Inflammatory Response Syndrome (SIRS)**
  - A systemic response to a nonspecific infectious or noninfectious insult with the presence of two or more of the following clinical criteria
    - Body temperature higher than 38°C (100.4°F) or lower than 36°C (96.8°F)
    - Hear rate >90 beats per minute
    - Respiratory rate >20 breaths per minute or hyperventilation with PaCO2 <32mmHg
    - Abnormal WBC count >12K or <4K or >10% bands

- **Sepsis (formerly severe sepsis)**
  - Life-threatening organ dysfunction due to a dysregulated host response to infection

- **Septic Shock**
  - A subset of sepsis with circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality
    - Vasopressors required to achieve MAP >65
    - Persisting blood lactate >2.0 mmol/L in spite of adequate fluids

Patient with Suspected Sepsis

• Best Practice Statement – Updated Surviving Sepsis Campaign:

  • “We recommend that a specific anatomic diagnosis of infection requiring emergent source control be identified or excluded as rapidly as possible in patients with sepsis or septic shock, and that any required source control intervention be implemented as soon as medically and logistically practical after the diagnosis is made.”
Patient with Suspected Sepsis

• Recommendations of Surviving Sepsis Campaign:
  • “We recommend that administration of IV antimicrobials be initiated as soon as possible after recognition and within 1 h for both sepsis and septic shock.”
    • Appropriate cultures (including 2 sets of blood cultures) should be obtained prior to first dose if no substantial delay in therapy
  • “We recommend empiric broad-spectrum therapy with one or more antimicrobials to cover all likely pathogens.”
  • “We recommend that in the resuscitation from sepsis-induced hypoperfusion, at least 30ml/kg of intravenous crystalloid fluid be given within the first 3 hours.”
    • Avoid starch containing solutions
Application of Fluid Resuscitation in Adult Septic Shock

Sepsis-induced hypotension or lactate > 4 mmol/L

- No high flow oxygen and No ESRD on dialysis or CHF
  - Rapid infusion of 30 ml/kg Crystalloid*

- Pneumonia or ALI with high flow oxygen requirements
  - Not intubated/mechanically ventilated
  - Consider intubation/mechanical ventilation to facilitate 30 ml/kg crystalloid*
  - Rapid infusion of 30 ml/kg crystalloid*

- ESRD on hemodialysis or CHF
  - Total of 30 ml/kg crystalloid* with frequent reassessment of oxygenation

Considerations post 30ml/kg crystalloid infusion

1. Continue to balance fluid resuscitation and vasopressor dose with attention to maintain tissue perfusion and minimize interstitial edema
2. Implement some combination of the list below to aid in further resuscitation choices that may include additional fluid or inotrope therapy
   - blood pressure/heart rate response,
   - urine output,
   - cardiothoracic ultrasound,
   - CVP, ScvO2,
   - pulse pressure variation
   - lactate clearance/normalization or
   - dynamic measurement such as response of flow to fluid bolus or passive leg raising
3. Consider albumin fluid resuscitation, when large volumes of crystalloid are required to maintain intravascular volume.
Empiric Antibiotic Selection

• Empiric antibiotic therapies should be initiated with combination therapy aimed at the most likely bacterial pathogens for the initial management of septic shock
  • Vancomycin + piperacillin-tazobactam

• Combination therapy should NOT be used for ongoing treatment of most other serious infections – including bacteremia and sepsis without septic shock
  • No more “double coverage” for pseudomonas/neutropenia

• Procalcitonin can be used for de-escalation of therapy
Antimicrobial Stewardship

• Antibiotics should be narrowed once pathogen is identified and sensitivities are established and/or patient has shown response to therapy
  • Daily consideration for de-escalation of therapies
• Duration of therapy for most serious cases of sepsis is 7-10 days
When Shock Does Not Improve

• Strong evidence to support norepinephrine as the first choice vasopressor
• Vasopressin or epinephrine can be added with a goal of achieving a MAP >65 or vasopressin can be used to decrease the norepinephrine dosage
• Consideration for initiation of high dose corticosteroids
• Assessment for other possible sources of shock (neuro, cardiac, etc.)
<table>
<thead>
<tr>
<th>SURVIVING SEPSIS CAMPAIGN RECOMMENDATION HIGHLIGHTS</th>
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<tr>
<td><strong>SEPSIS DEFINITION</strong></td>
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<tr>
<td>Systemic manifestation of infection + suspected</td>
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<tr>
<td>infection</td>
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<tr>
<td>Severe sepsis: sepsis + organ dysfunction</td>
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<tr>
<td><strong>INITIAL RESUSCITATION</strong></td>
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<td>at least 30 cc/kg in first 3 hours</td>
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<td>Crystalloid fluid (no recommendations on 0.9% NaCl</td>
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<td>vs balanced solution)</td>
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<td>Albumin if patients require “substantial” fluids</td>
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<td>(weak)</td>
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<td><strong>VASOPRESSORS</strong></td>
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<td><strong>STEROIDS</strong></td>
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<td><strong>ANTIBIOTICS</strong></td>
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<td><strong>SOURCE CONTROL</strong></td>
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Treating sepsis: the latest evidence

- **Antibiotics**: Early administration
  - Yes

- **Fluids**: Several liters initially
  - Yes
  - Colloids
  - Yes
  - Crystalloid
  - Yes
  - Starches
  - No
  - High chloride
  - No

- **Vasopressors**: 1–6 hours after onset
  - Yes
  - Norepinephrine
  - Yes
  - Epinephrine
  - Yes
  - Vasopressin
  - Yes
  - Dopamine
  - No
  - Phenylephrine
  - No

- **Enteral feeding**: Yes
- **Insulin therapy**: Yes
- **Deep sedation**: No
- **Molecular targeted therapies**: No
- **Lung protective ventilation**: Yes
- **Goal oriented therapy**: No
- **EGDT**: Early goal directed therapy
  - No
- **Urinary catheter**: Yes

Designed by: Will Stahl-Timmins
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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 >2mmol/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 < 65 mm Hg) or if initial lactate was >4 mmol/L, re-assess volume status and tissue perfusion and document findings according to Table 1.
7) Re-measure lactate if initial lactate elevated.

TABLE 1
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.
- Measure ScvO2.
- Perform bedside cardiovascular ultrasound.
- Perform dynamic assessment of fluid responsiveness with passive leg raise or fluid challenge.

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www.survivingsepsis.org
Lactic Acid, Procalcitonin

• When sepsis is suspected, lactic acid/serum lactate levels and procalcitonin levels can be drawn
  • Initial lactic acid levels should be trended until resuscitation has normalized lactate in patients with elevated levels as a marker of tissue hypoperfusion
• Procalcitonin is a peptide precursor of calcitonin and is usually below the level of detection in healthy persons
  • Procalcitonin rises in response to an inflammatory stimulus, especially of bacterial origin
  • 85% sensitive and 91% specific for differentiating patients between SIRS and sepsis
  • Low levels can be used to support de-escalation or shortening antibiotic duration in patients without obvious bacterial source of sepsis
Procalcitonin Algorithm

Procalcitonin guided antibiotic therapy

- **< 0.1 ug/L**
  - Bacterial infection very unlikely
  - **WITHHOLD AB!**
  - PCT control after 6-24 h
    - Consider antibiotics if
      - respiratory or hemodynamic instability
      - severest comorbidity
      - need for ICU admission

- **0.1 - 0.25 ug/L**
  - Bacterial infection unlikely
  - Withhold AB
  - PCT control after 6-24 h
    - Consider antibiotics if
      - severe comorbidity
      - localised infection (abscess, Empyema)
      - compromised host defense (e.g. immunosuppression, neutropenic fever)
      - Chronic a/o smouldering infection (e.g. endocarditis, Tuberculosis)

- **>0.25 – 0.5 ug/L**
  - Bacterial infection likely
  - Start or continue AB
  - Reevaluation after 3, 5 and 7 days
    - PCT measurement
    - Withhold antibiotics using above cut offs

- **>0.5 ug/L**
  - Bacterial infection Very likely
  - START or CONTINUE AB!
  - Reevaluation after 3, 5 and 7 days
    - PCT measurement
    - Withhold antibiotics using above cut offs
    - If Initial PCT levels are very high, then withhold when 80-90% decrease of peak PCT

The “Marik Protocol”

• Standard ICU treatment PLUS:

• Intravenous vitamin C 1.5g q6hr x4d or until ICU discharge

• Hydrocortisone 50mg q6hr x7d or until ICU discharge followed by a taper over 3d

• Intravenous thiamine 200mg q12hr x4 or until ICU discharge

Marik, PE et.al. Chest 2016
Vitamin C?

- Vitamin C has a role in mediating inflammation as an antioxidant
  - Also helps synthesize cortisol, catecholamines and vasopressin
- Some evidence to suggest using Vitamin C in addition to standard treatment to negate the effects of inflammation and improve hemodynamic stability in septic patients

*Vitamin C: The next step in sepsis management?*

Teng JI, Pourmand A, Mazer-Amirshahi M.

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Abstract

Sepsis is a life-threatening medical condition, affecting approximately 26 million people worldwide every year. The disease is a continuum, marked by dysregulated inflammation and hemodynamic instability leading to shock, multi-system organ dysfunction, and death. Over the past decades, there has been a focus on the early identification and treatment of sepsis primarily with bundled and goal directed therapy. Despite these advances, morbidity and mortality has remained high, prompting investigation into novel therapies. Vitamin C is a water-soluble vitamin that plays a role in mediating inflammation through antioxidant activities and is also important in the synthesis of cortisol, catecholamines, and vasopressin, which are key mediators in the disease process. Emerging evidence provides curative data in support of the administration of vitamin C in addition to standard therapy to ameliorate the effects of inflammation and improve hemodynamic stability in patients with sepsis and septic shock; however, further evidence is needed to support this practice. This review discusses the physiologic role of vitamin C as well as the recent literature and evidence for the use of vitamin C in patients presenting with sepsis.

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Some discussion...

- Small number of patients in the study (94)
  - NONE of the treatment patients died of sepsis, mortality was due to underlying disease
- Apparently inexpensive/safe protocol
- Concept of a synergistic effect of these 3 medications on many pathways in the management of sepsis
- Vitamin C dosing remains vague – risk of oxalate formation/renal deposition at high dose
- External validation required before any implementation
Take Home Points

• 3 Diagnostic categories – SIRS, sepsis, septic shock
• Antibiotics should be administered within 60min for all patients with suspected sepsis/septic shock
• Lactic acid trends can be monitored as a part of documenting response to treatment/therapies
• Procalcitonin levels can help foreshorten antibiotic courses when presentation of sepsis is unclear
• Protocols containing less expensive/relatively safe components ie Vitamin C/thiamine/steroids may be the all the rage moving forward
Questions?
mtaorminado@comcast.net