2016 Update in Sepsis

Hot Topics in Emergency Medicine
Hot Springs, VA
February 11, 2017

Christopher Hogan, MD, FACEP, FCCM*
Virginia Commonwealth University Medical Center
Departments of Emergency Medicine/Surgery
Richmond, VA

* I have no financial disclosures
Objectives

• Review the latest and greatest guideline changes to recognition, diagnosis and management of sepsis
• Review some core management strategies that will never change
• Go over some patient vignettes to reinforce the more salient points
Surviving Sepsis Campaign – What is it?

• “The Surviving Sepsis Campaign is a joint collaboration of the Society of Critical Care Medicine and the European Society of Intensive Care Medicine committed to reducing mortality from severe sepsis and septic shock worldwide.” [survivingsepsis.org]
• Was helped out by Eli Lilly and Xigris to raise awareness of sepsis, but survived the drug
• 2005 guidelines helped reduce mortality from sepsis, not from any one intervention, but by raising awareness and bundling a few common sense items (like antibiotics early)
Surviving Sepsis Campaign – What is it?

• The new 2016 guideline recommendations centered on 5 areas pertaining to sepsis:
  – Hemodynamics
  – Infections
  – Adjunctive therapies
  – Metabolic
  – Ventilation

• Various investigators then looked over existing data, using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) System, in which the strength of the study design and rigor of the research was taken into account.
For a point of reference, “sepsis” is life threatening organ dysfunction caused by a dysregulation host response to infection

<table>
<thead>
<tr>
<th>Strength</th>
<th>Level</th>
<th>Design</th>
<th>Randomization</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Level 1</td>
<td>Randomized control trial (RCT)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Meta-analysis of RCT with homogeneous results</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Level 2</td>
<td>Prospective comparative study (therapeutic)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Meta-analysis of Level 2 studies or Level 1 studies with inconsistent results</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Level 3</td>
<td>Retrospective Cohort Study</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Case-control Study</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Meta-analysis of Level 3 studies</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Level 4</td>
<td>Case Series</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Level 5</td>
<td>Case Report</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Expert Opinion</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Personal Observation</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
Surviving Sepsis 2016

SEPSIS STEPS

SIRS
T: >100.4 F
< 96.8 F
RR: >20
HR: >90
WBC: >12,000
<4,000
>10% bands
PCO2 < 32 mmHg

2 SIRS
Confirmed or suspected infection

SEVERE SEPSIS
Sepsis +
Signs of End Organ Damage
Hypotension (SBP <90)
Lactate >4 mmol

SEPTIC SHOCK
Severe Sepsis with persistent:
Signs of End Organ Damage
Hypotension (SBP <90)
Lactate >4 mmol

Slides Courtesy of Curtis Merritt, D.O.
Surviving Sepsis 2016: Resuscitation

- Sepsis and septic shock are medical emergencies – begin treatment and resuscitation immediately
- In the resuscitation from sepsis-induced hypo-perfusion, use 30 mL/kg of IV crystalloid fluid be given within the first 3 hours (strong rec., low quality of evidence)
- Following initial fluid resuscitation, additional fluids should be guided by frequent reassessment of hemodynamic status
  - Previous guidelines recommended a protocolized quantitative resuscitation, (EGDT), which included central venous pressure and central venous oxygen saturation measurement
  - Failed to show a mortality reduction in 3 multicenter RCTs (PROCESS)
  - Didn’t hurt but doesn’t help, so extra effort and risk not worth it
Surviving Sepsis 2016: Resuscitation

- After a thorough PE and RoS to look for root cause, use available physiologic variables like RR, HR, BP, O2 saturation, temperature and urine output (place a foley) if no TTE
- CVP alone to guide resuscitation no longer justified, but can do a passive leg raise if you are comfortable doing this
- Target MAP of 65 mm Hg has lower risk of atrial fibrillation and can use lower doses of vasopressors while having similar mortality when compared to high MAP goals
Surviving Sepsis 2016: Resuscitation

- Serum lactate is not a direct measure of tissue perfusion, but serves as a surrogate.
- May represent tissue hypoxia, accelerated aerobic glycolysis driven by excess beta adrenergic stimulation (think pressors).
- Better surrogate for tissue perfusion compared with PE or UO.
- A reduction in mortality was seen in lactate-guided resuscitation compared to resuscitation without lactate monitoring, but there was no evidence for difference in ICU length of stay (LOS).
Surviving Sepsis 2016: Diagnosis

- Send microbiologic cultures before starting antimicrobial therapy in suspected sepsis or septic shock if doing so results in no substantial delay in the start of antimicrobials
  - Helps down the road, especially when de-escalating abx
  - Always include at least two sets of blood cultures
  - If there is a PICC or HD line, check a set from that site
Surviving Sepsis 2016: Resuscitation

- If there is hypotension or evidence of hypo-perfusion (low UO, AMS), try a fluid challenge, continue as long as hemodynamic factors continue to improve
- Crystalloids are the fluid of choice for initial resuscitation and subsequent intravascular volume replacement in sepsis and septic shock (strong rec., moderate quality of evidence)
- Use either balanced crystalloids or saline for fluid resuscitation of patients with sepsis or septic shock
  - Use either NSS or LR, but remember NSS has a pH of 5.5 and hyperchloremic acidosis will develop if a patient gets multiple liters of NSS
Surviving Sepsis 2016: Resuscitation

• Use albumin for subsequent intravascular volume replacement in patients with sepsis and septic shock when patients require substantial amounts of crystalloids
  – The SAFE study showed that albumin was safe and equally effective as NSS in ICU patients requiring fluid administration
  – A mortality reduction trend was reported for albumin compared to crystalloids when given <6 h from identification (11 studies; n = 5515; OR, 0.94; 95% CI, 0.86–1.03)

• Avoid hydroxyethyl starches (HESs) or gelatins for intravascular volume replacement in patients with sepsis or septic shock (strong rec., high quality of evidence)
Surviving Sepsis 2016: Treatment

- Administration of IV antimicrobials should be initiated <1 h for both sepsis and septic shock (strong level of rec., moderate quality of evidence; grade applies to both conditions)
- Each hour delay in administration of antimicrobials is associated with a measurable increase in mortality and secondary end points such as LOS, AKI, ALI
- Drawing during fevers does not impact (+) Cx
Surviving Sepsis 2016: Treatment

• Remember source control is THE most important aspect, so use CXR, CT, UA or blood Cx to find out where the infection is
  – A target of no more than 6 to 12 hours after diagnosis appears to be sufficient for most cases to optimize outcomes, reduced survival beyond that point

• When choosing abx agents (note pleural here) remember:
  – Underlying diseases
  – Chronic organ failures
  – Indwelling devices
  – Immunosuppression or immunocompromised
  – Recent infections or colonization with known pathogens
  – Recent antimicrobials within the previous three months
  – Origin (community, SNF, acute rehab)
Surviving Sepsis 2016: Treatment

- Common pathogens: gram-negative bacteria, gram-positive and mixed
- Neutropenic patients at risk of resistant gram-negative bacilli and Candida species
- Patients with nosocomial acquisition of infections are prone to sepsis with MRSA and VRE
- Empiric use of micafungin is preferred in those with severe illness, who have recently been treated with other antifungal agents, or if Candida glabrata or Candida krusei infection
Surviving Sepsis 2016: Treatment

• Most patients with severe sepsis and septic shock are immunocompromised to some degree, so initial regimen should be broad enough to cover most pathogens isolated in healthcare-associated infections
• Should also add antifungal if they had recently been on antibiotics, had recent sepsis, are currently on antibiotics via PICC or TPN
Surviving Sepsis 2016: Treatment

- Broad-spectrum carbapenem (e.g., meropenem, imipenem/cilastatin) or extended-range penicillin/β-lactamase inhibitor combination (piperacillin/tazobactam or ticarcillin/clavulanate)
- 3rd or more generation cephalosporins as part of a multidrug regimen
- IM preparations are approved for β-lactams: mipenem/cilastatin, cefepime, ceftriaxone and ertapenem
Surviving Sepsis 2016: Treatment

- Consider whether fungi might be involved
- Risk factors for invasive *Candida* infections include:
  - Immunocompromised status (neutropenia, chemo, transplant, DM, chronic liver failure, ESRD)
  - Prolonged IV devices (HD, PICC or CV catheters)
  - TPN
  - Recent major surgery (particularly abdominal)
  - Prolonged broad-spectrum antibiotics
  - Prolonged hospital/ICU admission
  - Recent fungal infection
Surviving Sepsis 2016: Vasoactives

- Myocardial dysfunction occurs in a subset of septic patients
- Cardiac output is usually preserved by ventricular dilation, tachycardia, and reduced vascular resistance
- Norepinephrine is now the first-choice vasopressor (strong rec., moderate quality of evidence)
- Can add either vasopressin (up to 0.03 U/min) (weak rec., moderate quality of evidence) or epinephrine (weak rec., low quality of evidence) to norepinephrine to increase MAP
- Use after fluids have failed
Surviving Sepsis 2016: Vasoactives

- Dopamine is an alternative vasopressor but norepinephrine is more potent and may be more effective at reversing hypotension in patients with septic shock
- Use in selected patients, those at low risk of tachyarrhythmias, absolute or relative bradycardia) → May be particularly useful in patients with compromised systolic function but causes more tachycardia and may be more arrhythmogenic
- Titrate to an end point reflecting perfusion
- Reduce or discontinue if the patient develops worsening hypotension or arrhythmias
Surviving Sepsis 2016: Steroids

- SCCM guidelines recommends against using IV hydrocortisone to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability.
- If fluids, pressors and antibiotics fail, IV hydrocortisone at a dose of 200 mg per day (weak rec., low quality of evidence) should be considered in conjunction with ICU admitting team.
- Does not prevent progression of worsening shock per the HYPRESS trial just completed (JAMA 2016; 316(17): 1775).
Surviving Sepsis 2016: RBC’s

- Consider RBC transfusion when hgb < 7.0 g/dL except in extenuating circumstances such as MI, severe hypoxemia, or hemorrhage (strong rec., high quality of evidence)
- The PRoCESS (Protocol-Based Care for Early Septic Shock) trial looked at anemia in the goal directed treatment arms
  – The EGDT group received transfusion at a hgb 10 g/dL when the Scvo2 was < 70% after initial resuscitation interventions compared to the protocol-based standard care group that received blood transfusion only when the hgb was < 7.5 g/dL, but no significant differences were found between the two groups in 60-day in-hospital mortality or 90-day mortality
Surviving Sepsis 2016: Other blood Products

- Use FFP only to correct clotting abnormalities if there is bleeding or an invasive procedure (weak rec., very low quality of evidence)
- Use prophylactic platelet transfusion when counts <10,000/mm³ in the absence of apparent bleeding or when counts <20,000/mm³ if the patient has a significant risk of bleeding
- Higher platelet counts (≥ 50,000/mm³) are advised for active bleeding, surgery, or invasive procedures (weak rec., very low quality of evidence)
Surviving Sepsis 2016: Ventilation

- Sepsis uses up a lot of energy, so if the patient has a high work of breathing, consider NIPSV or intubation.
- If you intubate, watch plateau and peak airway pressures, as these may worsen with time as ARDS develops.
- There is data behind the use of neuromuscular blocking agents for ≤ 48 hours in adult patients with sepsis induced ARDS and a Pao2/Fio2 ratio < 150 mm Hg (weak rec., moderate quality of evidence), so if you have trouble ventilating, try paralysis.
- Remember that in mechanically ventilated sepsis patients, keep the head of the bed elevated between 30 and 45 degrees to limit aspiration and pneumonia risks.
Surviving Sepsis 2016: Ventilation

- Use a target tidal volume of 6 mL/kg predicted body weight (PBW) compared with 12 mL/kg in adult patients with sepsis-induced ARDS (strong rec., high quality of evidence)
- Use an upper limit goal for plateau pressures of 30 cm H2O over higher plateau pressures in adult patients with sepsis-induced severe ARDS (strong rec., mod quality of evidence)
- No single mode of ventilation has consistently been shown to be advantageous when compared with any other that respects the same principles of lung protection
Surviving Sepsis 2016: Glucose

• Need to intervene when 2 or more checks are >180 mg/dL (strong rec., high quality of evidence)
• Blood glucose values be monitored every 1 to 2 hours in the acute phase of illness
• Glucose levels obtained with point-of-care testing of capillary blood be interpreted with caution because such measurements may not accurately estimate arterial blood or plasma glucose values – back them up with a BMP
Surviving Sepsis 2016: Odds-n-Ends

- Bicarbonate is a bridge to somewhere – source control, increased RR on vent, emergent dialysis
- Sodium bicarbonate therapy should only be considered to improve hemodynamics or to reduce vasopressor requirements in patients with hypoperfusion-induced lactic acidemia when the pH ≥ 7.15 (weak rec., moderate quality of evidence)
Surviving Sepsis 2016: Odds-n-Ends

- All ICU patients are at risk for DVT (10%) and PE (2–4 %) but patients with sepsis and septic shock are at increased risk
- Use pharmacologic prophylaxis (unfractionated heparin [UFH] or LMWH] in the absence of contraindications (strong rec., moderate quality of evidence)
- Use weight based LMWH rather than UFH for VTE prophylaxis when you can (strong rec., moderate quality of evidence)
Surviving Sepsis 2016: Odds-n-Ends

- Start stress ulcer prophylaxis (PPI or H2 Blocker) in patients with sepsis or septic shock who have risk factors for gastrointestinal (GI) bleeding (strong rec., low quality of evidence)
- Especially true in freshly intubated patients
Surviving Sepsis 2016: What’s New

- Fluid resuscitation: 30 cc/kg IV crystalloids within 3 hours (strong rec., low quality evidence)
- MAP target 65 mm Hg (strong rec., low quality evidence)
- Norepinephrine 1st line (strong rec., moderate quality evidence), epinephrine (weak rec., low quality evidence) or up to 0.03 Units/min vasopressin (weak rec., moderate quality evidence) may be added
- Obtain blood cultures prior to administration, but do not delay antibiotics (best practice)
- Initiate empiric broad-spectrum antibiotics within 1 hour (strong rec., moderate quality evidence)
Surviving Sepsis 2016: What’s New

• Consider double gram-negative coverage in patients with septic shock at high risk of multidrug-resistant pathogen
• Risk factors for invasive Candida infection
  – immunocompromised state
  – TPN
  – necrotizing pancreatitis
  – recent major abdominal surgery
  – recent fungal infection
• IV loading dose of vancomycin of 25-30 mg/kg is favored
• Corticosteroids: IV hydrocortisone 200 mg per day if hemodynamic stability is not achieved through crystalloids and vasopressors (weak rec., low quality evidence)
Surviving Sepsis 2016: Cases

A 72 yo female presents to you after fever at SNF. H/O DM, CAD, recent cholecystectomy that started out laparoscopic and finished open with post-op leak. Now in SNF because too weak for acute rehab. Has a PICC in place for TPN and ceftriaxone for the next weeks. Vitals: HR 135, BP 92/48, RR 24, T 35.8 C. Chest clear but mildly tender abdomen EP signing out to you loaded with Zosyn and vancomycin now finishing. What should you add?
Surviving Sepsis 2016: Cases

- Consider adding an antifungal because she has multiple risk factors for fungal infection.
- Also remember blood cultures if not done.
- Do CXR and urine to make sure these aren’t in play.
- Passively rewarm if repeat temperature still hypothermic.
Surviving Sepsis 2016: Cases

- Despite adding antifungals and 2 liters of NSS, she continues to be hypotensive. Now awaiting an ICU bed but not ready for a while.

- Repeat vitals: HR 110, RR 20, T 36.0 (rectal), BP 90/50

- What are some options for the next step?
Surviving Sepsis 2016: Cases

-Albumin
-Pressors – which one?
-More crystalloid
-Steroids
Questions?