Surviving Sepsis Campaign Updates: What's New?

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Disclosures

- Nothing to disclose

Pharmacist Objectives

- Explain the new definitions of sepsis and septic shock
- Evaluate the new trials regarding early goal directed therapy
- Determine the appropriate use of albumin in severe sepsis and septic shock
- Understand the current literature regarding hemoglobin threshold in severe sepsis and septic shock

Technician Objectives

- Describe the signs and symptoms of septic shock
- Demonstrate knowledge of importance of time to antibiotics based on the new core measure
- Understand use of vasopressors after fluid resuscitation

Outline

- Background
- New definitions
- New articles discussing Early Goal Directed Therapy
- Unchanged recommendations
- Other guideline changes
- Patient Case
- Assessment questions

Sepsis Epidemiology

- Kills 1 in 4 patients worldwide
  - Estimated to cost the U.S. healthcare system over $20 billion in 2011
- Eleventh most common cause of death in the US
- Leading cause of mortality and critical illness worldwide

JAMA. 2016;315(8):801-810.

What is the Surviving Sepsis Campaign?

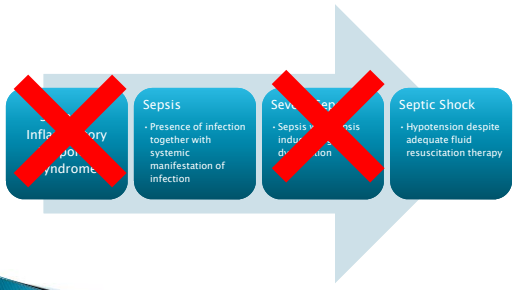
- Collaboration between the Society of Critical Care Medicine and European Society of Intensive Care Medicine
- Utilize evidence-based guidelines for the management of sepsis and septic shock
- Most recent update in 2016

Surviving Sepsis Campaign

Society of Critical Care Medicine
The Intensive Care Professionals

ESICM

SIRS TO SEPTIC SHOCK



Sepsis-3 Definitions

- Sepsis
  - Life-threatening organ dysfunction caused by a dysregulated host response to infection
    - Organ dysfunction represented by an increase in the Sequential Organ Failure Assessment (SOFA) score of $\geq$2 points

JAMA. 2016;315(8):801-810.

Sepsis-3 Definitions

- qSOFA score: Use outside the hospital, ED, or general hospital floor
  - -Suspected infection and the 2 of the following:

Q-Sofa Score	
RR	>22
GCS	<13
SBP	<100

  - Allows for rapid identification of being more likely to have poor outcomes

JAMA. 2016;315(8):801-810

Sepsis-3 Definitions

- Septic Shock
  - Subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than sepsis alone
  - Clinical features:
    - Vasopressor requirement to maintain MAP >65 mmHg and serum lactate >2 mmol/L in the absence of hypovolemia

JAMA. 2016;315(8):801-810.

Impact of Sepsis-3 Septic Shock Definition

- Recent secondary analysis of two early clinical trials with septic shock resuscitation
- Compared in-hospital mortality of the "old" definition of septic shock from 1991 to the Sepsis-3 definition
- 473 patients were included
  - 42.5% met Sepsis-3 v. 57.4% met old definition
  - Sepsis-3 criteria patients demonstrated higher SOFA scores and mortality of 29%
  - Old criteria patients still had significant organ failure and mortality of 14%

Crit Care Med 2017; 45:1436-1442

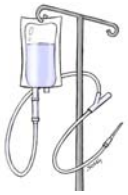
Septic Shock Pathophysiology

- Features of multiple shock types
- Distributive (hypoperfusion) shock
  - Failure of the vascular smooth muscle to vasoconstrict
- Cardiogenic shock
  - Decreased cardiac contractility
- Hypovolemic shock
  - Loss of cardiac filling
- Cytotoxic shock
  - Inability to utilize oxygen at the cellular level

JAMA. 2016;315(8):801-810.

2012 Initial Resuscitation Recommendations

- Protocolized, quantitative resuscitation (early goal directed therapy) with specific goals related to
  - CVP
  - MAP
  - UOP
  - $ScVO_2$



Crit Care Med. 2017; 45 (3) : 486-552

2016 Initial Resuscitation Recommendations

- Resuscitation from sepsis-induced hypoperfusion = at least 30 mL/kg of IV crystalloid be given within the first 3 hours
- Additional fluids guided by frequent reassessment of hemodynamic status
- Initial target MAP >65 mmHg in patients requiring vasopressors
- Guiding resuscitation to normalize lactate as a marker of tissue hypoperfusion

Crit Care Med. 2017; 45 (3) : 486-552

EGDT Criticisms

- Unknown which part of the protocol made the most significant impact on mortality
  - Goal directed protocol
  - Addition of $ScvO_2$ monitoring
  - Both?
- Use of CVP as a resuscitation goal
  - Poor surrogate of blood volume in the critically ill
- Lactate was not included in the protocol in directing care
- To address controversies: PROCESS Trial

JAMA 2010;303:739-46

ProCESS Trial

- Hypothesis:
  - Protocol-based therapy superior to standard care?
  - All aspects of the trial necessary?
    - Central hemodynamic monitoring
- Primary Outcome:
  - All cause in hospital mortality at 60 days

NEJM 2014; 370 (18) 1683-1693

ProCESS Trial: Inclusion Criteria

- For research sites:
  - Academic hospital with >40,000 ED visits annually
  - Use of serum lactate as a method for screening for cryptogenic shock
  - No routine use of $ScvO_2$
- For patients:
  - Similar to the Rivers trial
  - $\geq$ 2 SIRS criteria
  - Refractory Hypotension
  - Enroll within 12 hours of ED arrival

NEJM 2014; 370 (18) 1683-1693

ProCESS Trial: Design

Protocol-based EGDT	Protocol-based Standard	Usual Care
• Oximetric CVC • CVP: 8-12 mmHg • Map >65 mmHg • $ScvO_2$ >70%	• 2 large bore IV • Fluids • Vasopressors • Transfusion goal (7.5 g/dL)	• All decisions based on resuscitation team

NEJM 2014; 370 (18) 1683-1693

ProCESS Trial: Outcomes

- Primary outcome: No difference in 60 day in-hospital mortality between the 3 groups
- Secondary outcomes:
  - Reaching MAP goal: lowest in the usual care group
  - ICU admission: lowest in the protocol based group
  - AKI: lowest in the usual care group

NEJM 2014; 370 (18) 1683-1693

ProCESS Trial: Conclusions

- Early identification of those in septic shock is crucial
- No mortality difference observed when comparing protocolized resuscitation to usual care
- Modernization of care may have reduced importance of strict hemodynamic monitoring and resuscitation goals

NEJM 2014; 370 (18) 1683-1693

ARISE Trial

- Randomized 1600 patients with severe sepsis/shock
- 2 treatment arms- EGDT and usual care
- Protocol was very similar to PROCESS Trial
  - Antibiotic initiation was mandated prior to randomization

NEJM 2014; 371 (16) 1496-1506

ARISE Trial: Outcomes

- No difference in primary outcome of all-cause mortality at 90 days
- Trial was limited by lower than expected mortality rate
  - Lead to underpowering
- Confirmed the results of the PROCESS Trial
  - Support moving away from EGDT as the default therapy for severe sepsis and septic shock

NEJM 2014; 371 (16) 1496-1506

SSC Response

- October 2014
- "Results of the ProCESS and ARISE trials did NOT demonstrate any adverse outcomes in groups that utilized CVP and $ScvO_2$ as end points for resuscitation. Therefore no harm exists in keeping the current SSC bundles."

PROMISE Trial

- 1260 patients assigned to EGDT or usual care
- Primary Outcome: 90 day mortality
  - No difference between the treatment groups
- Increased use of fluids, vasoactive drugs, and transfusions in the EGDT group
  - Significantly worse organ-failure scores, longer ICU LOS, increased costs
- Again, EGDT didn't lead to improved outcomes

NEJM 2015; 372 (14) 1301-1311)

PRISM Meta Analysis

- All 3 trials failed to show that EGDT reduced mortality
  - 24.9% EGDT vs 25.4% usual care (P=0.68)
- EGDT was associated with greater mean use of intensive care days and cardiovascular support compared to usual care
  - 5.3 days vs 4.9 days; P=0.04
- Subgroup analysis showed no benefit in patients with "worse shock"

NEJM 2017; 376;23 2223-2234

Unchanged recommendations

- Sepsis screening or performance improvement
- Diagnosis/Source Control
- Fluid Therapy
- Vasoactive medications
- Corticosteroids
- Blood products/Immunoglobulins
- Glucose Control
- Renal Replacement Therapy
- Venous Thromboembolism Prophylaxis
- Nutrition

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Antibiotic Therapy

- Empiric broad spectrum therapy with one or more antimicrobials should be started to cover all likely pathogens
- Defined empiric therapy, targeted/definitive therapy, broad-spectrum therapy, multi-drug therapy, and combination therapy
- De-escalation with discontinuation of combination therapy within the first few days with evidence of clinical improvement

Crit Care Med. 2017; 45 (3): 486-552

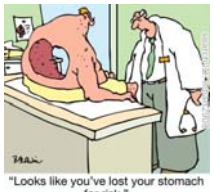
Mechanical Ventilation

- Use NMBAs for <48 hours in adults with sepsis induced ARDS
- No change in recommendation against use of B-2 agonists for sepsis-induced ARDS without bronchospasm

Crit Care Med. 2017; 45 (3): 486-552

Stress Ulcer Prophylaxis

- Either proton pump inhibitor or a histamine-2 receptor antagonist be used when stress ulcer prophylaxis is indicated



"Looks like you've lost your stomach for risk."

Crit Care Med. 2017; 45 (3) : 486-552

Patient case

- MJ 65 year old woman
- PMH: HTN
- ED Presentation: 3 day history of chills, dysuria, dizziness, and dry mucous membranes
- Home medications: Amlodipine 10mg daily
- Vitals: 38.6^{0}C, HR 125 BPM, BP 85/55 (MAP 65), RR 28 BPM, O_2 saturation 94% on room air

NEJM 2017; 376 (23) 2282–2285

Patient Case

- Laboratory findings
- SCr 1.8 mg/dL, BUN 76 mg/dL, lactate 5.0 mmol/L, anion gap 25 mmol/L
- WBC 20.0 mm^3, Hgb 9.0 g/dL
- Urinalysis: 3+ leukocyte esterase, >100 white cells/hpf, many bacteria

NEJM 2017;376 (23) 2282–2285

Patient Case

- Based on the previous case the patient meets what definition of sepsis or septic shock?
- A. Sepsis
- B. Patient does not meet the definition of sepsis or septic shock
- C. Severe sepsis
- D. Septic shock

Assessment questions

- Based on the case, what is the most appropriate initial fluid resuscitation strategy?
- A. Administer 2100 mL (30 mL/kg) of crystalloid fluid
- B. Administer crystalloid fluids to target a MAP >65, CVP 8–12, UOP >0.5 mL/kg/hr
- C. Administer 2100 mL of albumin
- Give no fluids and start norepinephrine

Patient Case

- The Surviving Sepsis Campaign recommends antibiotic administration within 1 hour of diagnosis. How much time does CMS allow in their sepsis bundle?
- A. 1 hour
- B. 3 hours
- C. 24 hours
- D. No time specified

Conclusions

- Sepsis and Septic shock definitions changed to be more broad and removing SIRS criteria
- 3 new clinical trials disproving the mortality benefit of early goal directed therapy
- New trials on the horizon regarding thrombomodulin and its use

- Questions?


NEWS ITEM: AVERAGE EMERGENCY ROOM WAIT NEARS ONE HOUR, CDC SAYS.
YOUR CASE IS QUITE ADVANCED. IT'S BETTER TO CATCH THESE THINGS IN THE EARLY STAGES.
IT WAS ONLY A SMALL PATCH ON MY ARM WHEN I ARRIVED HERE...