Sepsis Update 2018

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• No disclosures
Overview

• Review sepsis definitions
• 2018 Surviving Sepsis Bundle
• Steroids? Steroids! (Probably) Steroids.
• The state of fluid resuscitation in 2018
• Vitamin C
• Take home points
What is sepsis anyway?

“We therefore propose the phrase *systemic inflammatory response syndrome* (SIRS) to describe this inflammatory process…”

SIRS when 2 or more of the following criteria met:
1. Temperature > 38°C or < 36 °C
2. Heart rate >90
3. Respiratory rate >20 or PaCO2 <32

SIRS + Infection = Sepsis
Sepsis-3: Out with SIRS, in with SOFA

1992; 1st Definition of Sepsis Published in CHEST

2001: International Sepsis Consensus Conference; "Sepsis-2"

2016: International Sepsis Consensus Conference; "Sepsis-3"
SOFA Scoring

The Sepsis-3 definitions recommend using a change in the total SOFA score of two or more points from the baseline score to represent organ dysfunction.
Quick SOFA criteria (qSOFA)

- Respiratory rate ≥22/min
- Altered mentation
- Systolic blood pressure ≤100 mm Hg

- Non-ICU patients with qSOFA = 2-3 are at increased risk of death or prolonged ICU stay (> 3 days)

Singer et al. JAMA (2016)
Limitations of SOFA + qSOFA

- SOFA and qSOFA scores were designed as research tools at a population level to predict which patients with sepsis were likely to die…they do not define sepsis

- Clinical deterioration in patients with a positive qSOFA score may be due to causes other than sepsis

- New organ dysfunction should prompt you to consider occult infection

- *** The addition of serum lactate to qSOFA did not significantly change the ability of qSOFA to predict mortality.

Singer et al. JAMA (2016)
“…qSOFA was poorly sensitive (60.8%) and moderately (72%) specific for prediction of mortality. Whereas SIRS were more sensitive but much less specific.”

qSOFA had better sensitivity in ICU population. Better specificity in non-ICU patients.
National Early Warning Score (NEWS)?

qSOFA, SIRS and NEWS for predicting inhospital mortality and ICU admission.

Robert Goulden
Nsutebu

Quick Sepsis-related Organ Failure Assessment, Systemic Inflammatory Response Syndrome, and Early Warning Scores for Detecting C Intensive Care

Matthew M. Churp
Dana P. Edelson

A Comparison of the Quick Sequential (Sepsis-Related) Organ Failure Assessment Score and the National Early Warning Score in Non-ICU Patients With/Without Infection

Oliver C. Redfern, PhD; Gary B. Smith, FRCA; David R. Prytherch, PhD; Paul Meredith, PhD; Matthew Inada-Kim, FRCP; Paul E. Schmidt, MRCP
“Sepsis-4”: What does the future hold?

*Sepsis* is life-threatening organ dysfunction caused by a dysregulated host response to infection

*Septic Shock*: Subset of sepsis with circulatory and cellular/metabolic dysfunction associated with higher risk of mortality
Surviving Sepsis Campaign 2018

Initially Proposed:
“The most important change in the revision of the SSC bundles is that the 3-h and 6-h bundles have been combined into a single “1-hour bundle” with the explicit intention of beginning resuscitation and management immediately.”

The Society of Critical Care Medicine (SCCM) and the American College of Emergency Physicians (ACEP) acknowledge concerns expressed about the recently released Surviving Sepsis Campaign (SSC) Hour-1 bundle.

SCCM and ACEP along with other involved international experts are organizing a meeting ASAP to carefully review the recommendations, and provide guidance on bundle implementation and care of potentially septic patients who present to emergency departments in the United States.

We recommend that hospitals not implement the Hour-1 bundle in its present form in the United States at this time.
Summary thus far

• Sepsis is a life threatening organ dysfunction caused by overwhelming host response to infection

• Carry a high index of suspicion, evaluate early, re-evaluate often

• Give antibiotics early!
Time to antibiotics

Fraction of total patients vs. time from hypotension onset (hrs)

- Survival fraction
- Cumulative effective antimicrobial initiation

Summary thus far

• Sepsis is a life threatening organ dysfunction caused by dysregulated host response to infection
• Carry a high index of suspicion, evaluate early, re-evaluate often
• Give antibiotics early!
• Fluid resuscitate appropriately
  – 30 mL/kg initial bolus recommended
• Common Sense is still important
  – Consider transfer to the ICU if not clinically improving
  – Guideline concordant care improves patient outcomes but there is still room for clinical judgement
2018: What’s new in sepsis literature?
Steroids in sepsis: A tale as old as time

- 1987: “A controlled clinical trial of high dose methylprednisolone in the treatment of severe sepsis and septic shock” NEJM → no mortality benefit

- 2002: Annane et al. JAMA
  - Hydrocortisone 50 mg q6h + fludrocortisone 50 mcg/d for 7 days
  - 28 day mortality benefit in those with “inadequate adrenal reserve”

- 2008: CORTICUS trial (Sprung et al, NEJM)
  - Hydrocortisone 50 mg q6h x5 days + 6 day taper
  - No mortality benefit in any group but more rapid reversal of shock seen in all groups
  - Possible increased super-infections in steroid group

- 2016 Surviving Sepsis: consider giving hydrocortisone in septic shock after adequate fluid resuscitation and use of vasopressors in patients who have not achieved hemodynamic stability. -- Weak evidence (Level 2C).
Steroids: The ADRENAL Trial

• RCT, 3800 patients

• Hydrocortisone 200 mg continuous infusion x 7 days

• Primary endpoint: 90 day mortality

Conclusion: “Among patients with septic shock undergoing mechanical ventilation, a continuous infusion of hydrocortisone did not result in lower 90-day mortality than placebo.”
Steroids: The ADRENAL Trial

• But Wait!
• There were some improved secondary outcomes:
  – More rapid shock reversal
  – Increased ventilator free days
  – Decreased ICU length of stay
  – Fewer blood transfusions required
• Possible increase risk in adverse effects in steroid group
Steroids: APROCCHSS

**ORIGINAL ARTICLE**

Hydrocortisone plus Fludrocortisone for Adults with Septic Shock

Djillali Annane, M.D., Ph.D., Alain Renault, M.Sc., Christian Brun-Buisson, M.D., Bruno Megarbane, M.D., Jean-Pierre Quenot, M.D., Shidasp Siami, M.D., Alain Cariou, M.D., Xavier Forceville, M.D., Ph.D., Carole Schwebel, M.D., Claude Martin, M.D., Jean-François Timo, M.D., Benoît Misset, M.D., et al., for the CRICS-TRIGGERSEP Network

- Hydrocortisone 50mg q6h + fludrocortisone 50 mcg NG daily for 7 days

- 90-day all-cause mortality was lower among those who received hydrocortisone plus fludrocortisone than among those who received placebo

- Slight increase in risk of hyperglycemia and viral infections
Steroids: Meta-analysis

Low-dose corticosteroids for adult patients with septic shock: a systematic review with meta-analysis and trial sequential analysis

Sofie Louise Rygård, Ethan Butler, Anders Granholm, Morten Hylander Møller, Jeremy Cohen, Simon Finfer, Anders Perner, John Myburgh, Balasubramanian Venkatesh, and Anthony Delaney

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“Conclusions: In adults with septic shock treated with low dose corticosteroids, short- and longer-term mortality are unaffected, adverse events increase, but duration of shock, mechanical ventilation and ICU stay are reduced.”
Steroids: In real life practice

• Even if steroids do not confer mortality benefit, improvements in secondary endpoints may be meaningful

• There is no clear evidence of harm

• If I was ventilated with vasopressor-dependent shock:
  – I would probably want steroids
  – But if you don’t give me steroids, that’s ok too
New in IV Fluid Resuscitation

• Balanced Crystalloids Versus Saline in Noncritically Ill Adults (SALT-ED)
  – Self, et al. NEJM 2018

• Balanced Crystalloids versus Saline in Critically Ill Adults. (SMART)
  – Semler, et al. NEJM 2018
SALT-ED and SMART

**ED → Non-ICU Bed**
- Balanced IVF
- Saline
- Median 1079 mL
- Primary Outcome: Days alive + out of hospital
  - No difference
- Secondary Outcome: MAKE 30
  - Composite p = 0.02; ↓ MAKE 30

**ICU**
- 3 MICU + 2 SICU
- Balanced IVF
- Saline
  - Median: Saline 1020 mL, Balanced 1000 mL
- Primary Outcome: MAKE 30
  - Composite p = 0.04
- Difference driven by mortality! (11.1% vs. 10.3%, p = 0.06)
SALT-ED & SMART Conclusions

Use of balanced crystalloids significantly reduced MAKE30 (Composite of Death from any cause, new RRT, or persistent renal dysfunction) in both trials.

Clinical Practice:
Recommend use of balanced solutions for fluid resuscitation unless significant metabolic alkalosis or primary neurologic diagnosis.
Angiotensin II, the new vasopressor

- Non-catecholamine vasopressor that preferentially causes vasoconstriction

- Shown to increase blood pressure in vasodilatory shock that did not respond to high doses of conventional vasopressors
  - Carries significant risk of thrombosis
  - Cost $1000-1500/1 mL

- When would I consider using?
  - Mostly as a “Hail Mary”

ATHOS-3 Trial. Khanna et al., NEJM (2017)
Cocktail of Vitamin C, thiamine and steroids was shown to reduce death from sepsis

8.5% mortality in treatment group vs 40% in “control” group

N = 47 patients

Retrospective before/after study ≠ RCT
Stay Tuned!

- Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS)
- Likely revised Surviving Sepsis Campaign bundle
- Vitamin C, Thiamine and Steroids in Sepsis (VICTAS) and many others…
Sepsis, beyond the ICU

Pre-sepsis care

Post-sepsis care

Common symptoms after sepsis
- Muscle weakness
- Fatigue
- Difficulty swallowing
- Cloudy thinking
- Difficulty concentrating
- Poor memory
- Difficulty sleeping
- Sadness
- Anxiety

Liu et al., Crit Care Med (2018)
Take Home Points

• Sepsis is a life threatening organ dysfunction caused by dysregulated host response to infection

• Surviving Sepsis 2018 bundle (1-3 hours)
  – Measure lactate, re-measure if elevated
  – Give antibiotics as early as possible
  – Fluid resuscitate for hypotension or lactate > 4; balanced crystalloids are probably preferred
  – Start vasopressors for hypotension refractory to fluids; adjunct steroids are reasonable for vasopressor dependent shock

• Consider transfer to the ICU and/or “Intensivist consult” if not clinically improving
Thank you

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