Sepsis: What Happened in 2016?

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

Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

- Sepsis is redefined as: "life-threatening organ dysfunction caused by a dysregulated host response to infection."

- **Organ Dysfunction**: Rise in SOFA of $\geq 2$ points

<table>
<thead>
<tr>
<th>System</th>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td></td>
<td>$\geq 400$ (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</td>
<td>Platelet, $10^9$/μL</td>
<td>$\geq 150$</td>
<td>$&lt;150$</td>
<td>$&lt;100$</td>
<td>$&lt;50$</td>
<td>$&lt;20$</td>
</tr>
<tr>
<td>Liver</td>
<td>Bilirubin, mg/dL</td>
<td>$&lt;1.2$ (20)</td>
<td>$1.2-1.9$ (20-32)</td>
<td>$2.0-5.9$ (13-101)</td>
<td>$6.0-11.9$ (102-204)</td>
<td>$&gt;12.0$ (204)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>MAP $\geq 70$ mm Hg</td>
<td>MAP $&lt;70$ mm Hg</td>
<td>Dopamine $5$ or dopamine (any dose)$^a$</td>
<td>Dopamine $5.1-15$ or epinephrine $0.1$ or norepinephrine $&lt;0.1$</td>
<td>Dopamine $15$ or epinephrine $&gt;0.1$ or norepinephrine $&gt;0.1$</td>
<td></td>
</tr>
<tr>
<td>Central nervous</td>
<td>Glasgow Coma Scale score</td>
<td>15</td>
<td>13-14</td>
<td>10-12</td>
<td>6-9</td>
<td>6</td>
</tr>
<tr>
<td>System</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>Creatinine, mg/dL</td>
<td>$&lt;1.2$ (110)</td>
<td>$1.2-1.9$ (110-170)</td>
<td>$2.0-3.4$ (171-295)</td>
<td>$3.5-4.9$ (100-440)</td>
<td>$&gt;5.0$ (440)</td>
</tr>
</tbody>
</table>

**Abbreviations:** PaO$_2$, fraction of inspired oxygen; MAP, mean arterial pressure; PaO$_2$, partial pressure of oxygen; $^a$ Catecholamine doses are given as μg/kg/min for at least 1 hour. $^b$ Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.


- **Severe Sepsis**: No longer used
- **Sepsis**:  
  - Suspected or documented infection and  
  - Acute increase of $\geq 2$ SOFA points (a proxy for organ dysfunction)
- **Septic Shock**:  
  - Sepsis and  
  - Vasopressor therapy needed to elevate MAP $\geq 65$ mm Hg and  
  - Lactate $>2$ mmol/L (18 mg/dL) despite adequate fluid resuscitation
Sepsis: What Happened in 2016?

Sepsis-3

• qSOFA Score: A means of rapidly identifying ED and hospital ward (non-ICU) patients with suspected infection at increased risk

• At least 2 of 3 criteria:
  – RR ≥ 22/min
  – Altered mentation
  – SBP ≤ 100 mmHg

Sepsis: What Happened in 2016?

Sepsis-3

The U.S. response to the new definition:
Sepsis: What Happened in 2016?

- U.S. professional societies didn’t adopt Sepsis-3 (ACEP, ACCP)

  New Sepsis Criteria
  A Change We Should Not Make
  Steven Q. Simpson, MD, FCCP
  Kansas City, KS

  Podcast
  Chest May 2016

- CMS had already released SEP-1 Core Measure criteria based on Sepsis-2 definitions

How Good is SOFA?

Prognostic Accuracy of the SOFA Score, SIRS Criteria, and qSOFA Score for In-Hospital Mortality Among Adults With Suspected Infection Admitted to the Intensive Care Unit

<table>
<thead>
<tr>
<th></th>
<th>SIRS</th>
<th>qSOFA</th>
<th>SOFA</th>
<th>Between-Group Difference</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-Hospital Mortality (Primary Outcome)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude AUROC 0.589 (95% CI (0.585 - 0.593)</td>
<td>0.607 (603 - 611)</td>
<td>0.753 (675 - 0.777)</td>
<td>0.164</td>
<td>0.146</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>In-Hospital Mortality or ICU Stay ≥3 Days (Secondary Outcome)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude AUROC 0.609 (95% CI (0.606 - 0.612)</td>
<td>0.606 (602 - 609)</td>
<td>0.736 (673 - 0.739)</td>
<td>0.127</td>
<td>0.131</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Conclusion: in the ICU, SOFA is better than SIRS or qSOFA
How Good is SOFA?

Table 1. Diagnostic Performances for the Prediction of In-Hospital Death

<table>
<thead>
<tr>
<th>For Prediction of Death</th>
<th>gSOFa</th>
<th>SOFA</th>
<th>SIRS</th>
<th>Severe Sepsis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity, % (95% CI)</td>
<td>70 (59-80)</td>
<td>73 (61-83)</td>
<td>93 (85-98)</td>
<td>47 (36-59)</td>
</tr>
<tr>
<td>Specificity, % (95% CI)</td>
<td>79 (76-82)</td>
<td>70 (67-73)</td>
<td>27 (24-31)</td>
<td>82 (80-85)</td>
</tr>
<tr>
<td>Predictive value, % (95% CI)</td>
<td>24 (18-30)</td>
<td>18 (14-23)</td>
<td>11 (8-13)</td>
<td>20 (14-27)</td>
</tr>
<tr>
<td>Positive</td>
<td>97 (95-98)</td>
<td>97 (95-98)</td>
<td>98 (95-99)</td>
<td>94 (92-96)</td>
</tr>
<tr>
<td>Negative</td>
<td>3.40 (2.80-4.17)</td>
<td>2.40 (2.00-2.90)</td>
<td>1.29 (1.17-1.37)</td>
<td>2.70 (2.00-3.53)</td>
</tr>
<tr>
<td>AUROC, (95% CI)</td>
<td>0.80 (0.74-0.85)</td>
<td>0.77 (0.71-0.82)</td>
<td>0.65 (0.59-0.70)</td>
<td>0.65 (0.59-0.70)</td>
</tr>
</tbody>
</table>

Vasopressin + Placebo +/- Norepinephrine PRN
Norepinephrine + Placebo +/- Vasopressin PRN
Vasopressin + Hydrocortisone +/- Norepinephrine PRN
Norepinephrine + Hydrocortisone +/- Vasopressin PRN

Outcome: No difference in renal failure-free days. No difference in mortality.

Sepsis: What Happened in 2016?

VANISH Trial

Effect of Early Vasopressin vs Norepinephrine on Kidney Failure in Patients With Septic Shock The VANISH Randomized Clinical Trial

• Factorial 2 x 2 Design, DBRCT
Statins in Sepsis

One-year outcomes of rosuvastatin versus placebo in sepsis-associated acute respiratory distress syndrome: prospective follow-up of SAILS randomised trial.


- Follow-up of patients from Statins for Acutely Injured Lungs from Sepsis (SAILS) Trial
- Compared rosuvastatin vs. placebo in patients with sepsis-induced ARDS
- Evaluated SF-36 physical function and mental health domains at 6 months
- Findings:
  - No difference in 6-month survival
  - No difference in physical function
  - No difference in mental health
  - No difference in 6-minute walk test
  - “…survivors [demonstrated] substantial impairments in physical function and mental health.”

Statins in Sepsis

Rosuvastatin versus placebo for delirium in intensive care and subsequent cognitive impairment in patients with sepsis-associated acute respiratory distress syndrome: an ancillary study to a randomised controlled trial.


- Another subgroup study from the SAILS Trial
- Evaluated impact of rosuvastatin on delirium
- Findings:
  - Most patients had delirium – no between-group difference
  - About 1/3 patients had cognitive impairment at 6 months
Thiamine for Sepsis

Randomized, Double-Blind, Placebo-Controlled Trial of Thiamine as a Metabolic Resuscitator in Septic Shock: A Pilot Study

Michael W. Donnino, M.D., Lars W. Andersen, M.D., Maureen Chase, M.D., M.P.H., Katherine M. Berg, M.D., Mark Tidswell, M.D., Tyler Giberson, B.S., Richard Wolfe, M.D., Ari Moskowitz, M.D., Howard Smithlin, M.D., Long Ngo, Ph.D., and Michael N. Cocchi, M.D., for the Center of Resuscitation Science research group

- Thiamine 200 mg IV q12h vs. placebo x 7 days
- Endpoint: Lactate levels, time to shock reversal, SOI, mortality
- Findings:
  - No difference in overall groups
  - In patients with baseline thiamine deficiency (35% of total):
    - Lower lactate
    - Decreased mortality

EGDT and AKI

The Effects of Alternative Resuscitation Strategies on Acute Kidney Injury in Patients with Septic Shock

John A. Kellum, Lakhmir S. Chawla, Christopher Kaern, Paul M. Palevsky, Francis L. Pike, Donald M. Yealy, David T. Huang, and Derek C. Angus; for the ProCESS and ProGeSS-AKI Investigators

- Ancillary study to PROCESS Trial
- Evaluated impact of protocolized EGDT vs. standard care
- Finding: No difference in incidence/severity of AKI
Out with the Old, In with the New

Surviving Sepsis Campaign


Intensive Care Medicine
doi: 10.1007/s00134-017-4683-6
Published online: 18 Jan 2017

New Guideline:
Surviving Sepsis Campaign 2016

Focusing on the changes from 2012
• Adopted Sepsis-3 definitions of sepsis and septic shock
  – Sepsis: 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 a higher risk of mortality
• However, recognized that most of the studies forming the basis of guideline used traditional SIRS, sepsis, severe sepsis, septic shock
New Guideline: Surviving Sepsis Campaign 2016

• EGDT is gone as a specific recommendation
• Guide additional fluid by frequent reassessment of hemodynamic status
• If clinical examination dose not lead to clear diagnosis of volume status, use additional hemodynamic measures
• Use dynamic rather than static variables to predict fluid responsiveness, where available

New Guideline: Surviving Sepsis Campaign 2016

• Optimize antimicrobial dosing based on accepted pharmacokinetic/pharmacodynamics principles and particular drug properties in patients with sepsis/septic shock
  – Increased incidence of renal and hepatic impairment
  – Increased volume of distribution due to rapid expansion of ECV
  – Initiate therapy with full, high-end loading dose to avoid frequent subtherapeutic levels
New Guideline: Surviving Sepsis Campaign 2016

- 7-10 days of antimicrobial therapy for most serious infections, but shorter duration for some (rapid clinical resolution after intra-abdominal source control, urinary sepsis, uncomplicated pyelonephritis)
- Suggest use of procalcitonin to support shortening duration of antimicrobial therapy

New Guideline: Surviving Sepsis Campaign 2016

- Use prone positioning for ARDS with \( \text{PaO}_2/\text{FIO}_2 \) ratio < 150 (previously 100)
- No recommendation regarding use of Non-Invasive Ventilation (previously limited use based on risk/benefit assessment)
New Guideline: Surviving Sepsis Campaign 2016

Enteral feeding

• Use prokinetic agents for feeding intolerance

• Place post-pyloric feeding tubes for feeding intolerance or if high risk for aspiration

A Beacon of Light

The Marik Protocol
Marik Protocol

Paul Marik, MBBCh
Chief of Pulmonary and Critical Care Medicine

Endothelial Functions

NORMAL ENDOTHELIUM

DYSFUNCTIONAL ENDOTHELIUM
Marik Protocol

- Vitamin C 1.5 g IV q6h
- Thiamine 200 mg IV q12h
- Hydrocortisone 50 mg IV q6h
- For 4 days, or until patient is discharged from the ICU
Marik Protocol

- **Entry criteria**
  - Severe sepsis or septic shock
  - Procalcitonin ≥ 2 ng/ml

- **Exclusions:**
  - < 18 years old
  - Pregnant
  - Limitations of care

- Retrospective before-after clinical study
- 7 months, 47 patients in each group

Marik Protocol

- No differences between the two groups
- Study group mortality: 8.5%
- Control group mortality: 40.4%
- No deaths in the study group due to sepsis
- No patient in the study group developed progressive organ failure
- Mean time to vasopressor independence: 18 hours vs. 54 hours
Vitamin C

- Potent antioxidant/free radical scavenger
- Restores other cellular antioxidants
- Essential co-factor for iron and copper-containing enzymes
- Inhibits NF-κB activation

![Vitamin C and NF-κB Signalling](image)
Vitamin C

- Potent antioxidant/free radical scavenger
- Restores other cellular antioxidants
- Essential co-factor for iron and copper-containing enzymes
- Inhibits NF-κB activation
- Increases endothelial and epithelial tight junctions
- Preserves endothelial function and microcirculatory flow
- Catecholamine synthesis and vasopressor sensitivity

Why add Hydrocortisone?

- Vitamin C needs help getting into cells
• **SVCT2**
  - Expression is down-regulated by pro-inflammatory cytokines
  - Expression is up-regulated by corticosteroids

• Study of cultured endothelial cells + endotoxin

  Vitamin C alone: no help
  Steroids alone: no help

  Vitamin C + steroids:
  Restored function
Marik Protocol: Mechanism?

Why do we need extra vitamin C?
• Levels are very low or undetectable in critical illness
• Intestinal receptor is saturable, so can’t restore levels with oral dosing

Why does thiamine help?
• Shunts metabolism of vitamin C away from oxalate (potential for renal crystallization)

Marik Protocol: Application

What are the ethics of implementing this protocol?

“Hardcore evidence-based medicine disciples may be aghast at using a therapy without a large multi-center RCT, whereas more integrative, theoretically-minded clinicians may be willing to consider it.”

-- Josh Farkas, MD
Bioethical Principles

• Non-maleficence (“First, do no harm”)
  – Harms of commission
  – Harms of omission

• Beneficence
• Autonomy
• Justice

Are there potential harms?

• Vitamin C: Oxaluria with potential for renal deposition and crystallization in patients with impaired renal function – but renal function improved more in the protocol group than in controls, and thiamine shunts vitamin C metabolism away from oxalate to CO₂ production

• Thiamine: Rare reports of hypersensitivity or anaphylaxis, especially with repeated injections
Are there potential harms?

### Steroids in Severe Sepsis (HYPRESS Trial)

- **Hyperglycemia**  
  - ARI = 9.4%  
  - NNTH 10.6 (p=0.009)  
  - No statistically sig. difference in total insulin administered

- **Secondary Infections**  
  - ARI = 4.6%  
  - NNTH 21.7 (NS)

**ARI = Absolute Risk Increase**

### Steroids in Septic Shock: CORTICUS Trial

- **Hyperglycemia**  
  - ARI = 13%  
  - NNTH 7.7 Superinfection  
  - ARI = 5%  
  - NNTH 20

- **New Septic Shock**  
  - ARI = 4%  
  - NNTH 25

**NB: All 3 studies, plus VANISH Trial, showed no mortality increase with steroids**
Costs

• IV Vitamin C: $88 - 260 for 4-day course (drug only)

• IV Thiamine: $45 for 4-day course (drug only)

• Hydrocortisone: ~ $80 (drug only)

Implementation Options: A Proposal

<table>
<thead>
<tr>
<th>Patients with Refractory Septic Shock</th>
<th>Severe Sepsis and Non-Refractory Septic Shock</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Already receiving steroids</td>
<td>• These patients would not otherwise receive steroids per SSC Guidelines</td>
</tr>
<tr>
<td>• No predicted harm from adding Vitamin C and thiamine</td>
<td>• Inadequate Evidence-Based literature to justify endorsement</td>
</tr>
<tr>
<td>• Reasonable to endorse use in this group</td>
<td>• Therefore, leave to individual practitioners to choose</td>
</tr>
</tbody>
</table>
Some bad news...

- IV Vitamin C has a single producer:

Still...

Sepsis Update 2017

BRIGHT FUTURE
Thank you

Jim Leo, MD
jleo@memorialcare.org