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)

Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Christopher Warren Seymour, MD, MSc; Manu Shankar-Hari, MSc, MD, FFICM; Djillali Annane, MD, PhD; Michael Bauer, MD; Rinaldo Bellomo, MD; Gordon R. Bernard, MD; Jean-Daniel Chiche, MD, PhD; Craig M. Coopersmith, MD; Richard S. Hotchkiss, MD; Mitchell M. Levy, MD; John C. Marshall, MD; Greg S. Martin, MD, MSc; Steven M. Opal, MD; Gordon D. Rubenfeld, MD, MS; Tom van der Poll, MD, PhD; Jean-Louis Vincent, MD, PhD; Derek C. Angus, MD, MPH

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

- **Organ Dysfunction:** Rise in SOFA of ≥ 2 points

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**Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score**

<table>
<thead>
<tr>
<th>System</th>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pao₂/Fio₂, mm Hg (kPa)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥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>
<td></td>
</tr>
<tr>
<td>Coagulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets, x10⁹/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</td>
<td></td>
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<tr>
<td>Bilirubin, mg/dL (µmol/L)</td>
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<tr>
<td>&lt;1.2 (20)</td>
<td>1.2-1.9 (20-32)</td>
<td>2.0-5.9 (33-101)</td>
<td>6.0-11.9 (102-204)</td>
<td>Dopamine &gt;5 or epinephrine &gt;0.1 or norepinephrine ≤0.1b</td>
<td></td>
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<tr>
<td>Cardiovascular</td>
<td></td>
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</tr>
<tr>
<td>MAP ≥70 mm Hg</td>
<td>MAP &lt;70 mm Hg</td>
<td>Dopamine &lt;5 or dobutamine (any dose)b</td>
<td>Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1b</td>
<td></td>
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<tr>
<td>Central nervous system</td>
<td></td>
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<td></td>
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<tr>
<td>Glasgow Coma Scale score</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>13-14</td>
<td>10-12</td>
<td>6-9</td>
<td>&lt;6</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Creatinine, mg/dL (µmol/L)</td>
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<td></td>
</tr>
<tr>
<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>
<td></td>
</tr>
<tr>
<td>Urine output, mL/d</td>
<td></td>
<td></td>
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<tr>
<td>&lt;500</td>
<td>&lt;200</td>
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</tr>
</tbody>
</table>

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**Abbreviations:**
- Fio₂, fraction of inspired oxygen
- MAP, mean arterial pressure
- Pao₂, partial pressure of oxygen

Adapted from Vincent et al.²⁷

b Catecholamine doses are given as µg/kg/min for at least 1 hour.

²⁷ 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 ≥2 SOFA points (a proxy for organ dysfunction)
- **Septic Shock:**
  - Sepsis and
  - Vasopressor therapy needed to elevate MAP ≥65 mm Hg and
  - Lactate >2 mmol/L (18 mg/dL) despite adequate fluid resuscitation
• 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?

Sepsis-3

- 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

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

Eamon P. Raith, MBBS, MACCP; Andrew A. Udy, MBChB, PhD, FCICM; Michael Bailey, PhD; Steven McGloughlin, BMed FRACP, FCICM, MPHTM; Christopher MacIsaac, MBBS, PhD, FRACP, FCICM; Rinaldo Bellomo, MD, FRACP, FCICM, FAHMS; David V. Pilcher, MBBS, FRACP, FCICM; for the Australian and New Zealand Intensive Care Society (ANZICS) Centre for Outcomes and Resource Evaluation (CORE)

<table>
<thead>
<tr>
<th></th>
<th>SIRS</th>
<th>qSOFA</th>
<th>SOFA</th>
<th>Between-Group Difference</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SOFA vs SIRS</td>
<td>SOFA vs qSOFA</td>
</tr>
<tr>
<td>In-Hospital Mortality (Primary Outcome)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude AUROC (99% CI)</td>
<td>0.589</td>
<td>0.607</td>
<td>0.753</td>
<td>0.164 (0.159-0.169)</td>
<td>0.146 (0.142-0.151)</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 (99% CI)</td>
<td>0.609</td>
<td>0.606</td>
<td>0.736</td>
<td>0.127 (0.123-0.131)</td>
<td>0.131 (0.127-0.134)</td>
</tr>
</tbody>
</table>

Conclusion: in the ICU, SOFA is better than SIRS or qSOFA
Prognostic Accuracy of Sepsis-3 Criteria for In-Hospital Mortality Among Patients With Suspected Infection Presenting to the Emergency Department

Yonathan Freund, MD, PhD; Najla Lemachatti, MD; Evguenia Krastinova, MD, PhD; Marie Van Laer, MD; Yann-Erick Claessens, MD, PhD; Aurélie Avondo, MD; Céline Occelli, MD; Anne-Laure Feral-Piessens, MD; Jennifer Truchot, MD; Mar Ortega, MD; Bruno Carneiro, MD; Julie Pernet, MD; Pierre-Géraud Claret, MD, PhD; Fabrice Dami, MD; Ben Bloom, MD; Bruno Riou, MD, PhD; Sébastien Beaune, MD, PhD; for the French Society of Emergency Medicine Collaborators Group

Table 3. Diagnostic Performances for the Prediction of In-Hospital Death

<table>
<thead>
<tr>
<th>For Prediction of Death</th>
<th>qSOFA</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>0.37 (0.26-0.53)</td>
<td>0.39 (0.27-0.56)</td>
<td>0.25 (0.11-0.58)</td>
<td>0.64 (0.51-0.79)</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>
How Good is qSOFA?

• Retrospective review of ED and ward patients with suspected infection
• Compared SIRS, qSOFA, MEWS, and NEWS
• Primary endpoint: in-hospital mortality, and combined endpoint of mortality or ICU admission

American Journal of Respiratory and Critical Care Medicine

Quick Sepsis-related Organ Failure Assessment, Systemic Inflammatory Response Syndrome, and Early Warning Scores for Detecting Clinical Deterioration in Infected Patients outside the Intensive Care Unit

Matthew M. Churpek, Ashley Snyder, Xuan Han, Sarah Sokol, Natasha Pettit, Michael D. Howell, and Dana P. Edelson

September 20, 2016
How Good is qSOFA?

**Modified Early Warning Score**

<table>
<thead>
<tr>
<th>Score</th>
<th>3</th>
<th>2</th>
<th>1</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory rate (min⁻¹)</td>
<td>≤8</td>
<td>9–14</td>
<td>15–20</td>
<td>21–29</td>
<td>&gt;29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (min⁻¹)</td>
<td>≤40</td>
<td>41–50</td>
<td>51–100</td>
<td>101–110</td>
<td>111–129</td>
<td>&gt;129</td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>≤70</td>
<td>71–80</td>
<td>81–100</td>
<td>101–199</td>
<td>≥200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine output (ml/kg/h)</td>
<td>Nil</td>
<td>&lt;0.5</td>
<td>3.1–3.6</td>
<td>3.6–19.9</td>
<td>≥3.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature (℃)</td>
<td>≤35</td>
<td>35.1–36</td>
<td>36.1–38</td>
<td>38.1–38.5</td>
<td>≥38.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurological</td>
<td>Alert</td>
<td>Reacting to voice</td>
<td>Reacting to pain</td>
<td>Unresponsive</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Physiological Parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>3</th>
<th>2</th>
<th>1</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiration Rate</td>
<td>≤8</td>
<td>9–11</td>
<td>12–20</td>
<td>21–24</td>
<td>≥25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen Saturations</td>
<td>≤91</td>
<td>92–95</td>
<td>94–95</td>
<td>≥96</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any Supplemental Oxygen</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature</td>
<td>≤35.0</td>
<td>35.1–36.0</td>
<td>36.1–38.0</td>
<td>38.1–39.0</td>
<td>≥39.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>≤90</td>
<td>91–100</td>
<td>101–110</td>
<td>111–219</td>
<td>≥220</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Rate</td>
<td>≤40</td>
<td>41–50</td>
<td>51–90</td>
<td>91–110</td>
<td>111–130</td>
<td>≥131</td>
<td></td>
</tr>
<tr>
<td>Level of Consciousness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>A</td>
<td>V, P, or U</td>
<td></td>
</tr>
</tbody>
</table>

**Select cutoffs to predict mortality or ICU transfer**

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIRS ≥ 2</td>
<td>91%</td>
<td>13%</td>
</tr>
<tr>
<td>qSOFA ≥ 2</td>
<td>54%</td>
<td>67%</td>
</tr>
<tr>
<td>NEWS ≥ 7</td>
<td>77%</td>
<td>53%</td>
</tr>
<tr>
<td>NEWS ≥ 8</td>
<td>67%</td>
<td>66%</td>
</tr>
<tr>
<td>NEWS ≥ 9</td>
<td>54%</td>
<td>78%</td>
</tr>
</tbody>
</table>
Conclusions:

• qSOFA has a poor sensitivity
• qSOFA is a late indicator of deterioration
• qSOFA is inferior to the NEWS score (despite the NEWS score being based on data which is equally easy to obtain at the bedside)
Sepsis: What Happened in 2016?

VANISH Trial

- Factorial 2 x 2 Design, DBRCT

<table>
<thead>
<tr>
<th>Vasopressin + Placebo +/- Norepinephrine PRN</th>
<th>Norepinephrine + Placebo +/- Vasopressin PRN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasopressin + Hydrocortisone +/- Norepinephrine PRN</td>
<td>Norepinephrine + Hydrocortisone +/- Vasopressin PRN</td>
</tr>
</tbody>
</table>

Outcome: No difference in renal failure-free days.
No difference in mortality
One-year outcomes of rosvastatin versus placebo in sepsis-associated acute respiratory distress syndrome: prospective follow-up of SAILS randomised trial.

Dinglas VD¹, Hopkins RO², Wozniak AW³, Hough CL⁴, Morris PE⁵, Jackson JC⁶, Mendez-Tellez PA⁷, Bienvenu OJ⁸, Fly EW⁹, Colantuoni E³, Needham DM¹⁰.

- Follow-up of patients from Statins for Acutely Injured Lungs from Sepsis (SAILS) Trial
- Compared rosvastatin 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.”
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

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

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
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 does not lead to a 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 PaO$_2$/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
• 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 $\geq$ 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
Marik Protocol: Mechanism?

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
Vitamin C is required to synthesize catecholamines

L-Tyrosine

Tyrosine hydroxylase

O₂ + Tetrahydrobiopterin

H₂O + Dihydrobiopterin

Ascorbic acid

L-DOPA

DOPA decarboxylase

Dopamine

O₂ + Ascorbic acid

Dopamine β-hydroxylase

H₂O + Dehydroascorbic acid

Norepinephrine

Phenylethanolamine N-methyltransferase

Epinephrine

Zipursky JS et al. BMJ Case Rep 2014; PMID 24859547

Vitamin C is required for catecholamine synthesis
Why add Hydrocortisone?

- Vitamin C needs help getting into cells
Marik Protocol: Mechanism?
Marik Protocol: Mechanism?

- **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)
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 CO$_2$ production.

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

**Steroids in Severe Sepsis (HYPRESS Trial)**

- Hyperglycemia ($\geq 150$ mg/dl)
  - ARI = 9.4%
  - NNTH 10.6 ($p=0.009$)
  - No statistically significant difference in total insulin administered

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

**Steroids in Septic Shock: CORTICUS Trial**

- Hyperglycemia ($\geq 150$ mg/dl)
  - ARI = 13%
  - NNTH 7.7

- Superinfection
  - ARI = 5%
  - NNTH 20

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

ARI = Absolute Risk Increase
Are there potential harms?

- Annane – Effect of Treatment with Low Doses of Hydrocortisone and Fludrocortisone on Mortality in Septic Shock (JAMA 2002)
  - Secondary Infection
    - ARR 1% (NNTB 100)
  - Vasopressor-associated harm
    - ARI 2% (NNTH 50)
  - Hyperglycemia – not reported

- 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)
### Patients with Refractory Septic Shock
- Already receiving steroids
- No/minimal predicted harm from adding Vitamin C and thiamine
- Reasonable to endorse use in this group

### Severe Sepsis and Non-Refractory Septic Shock
- These patients would not otherwise receive steroids per SSC Guidelines
- Inadequate Evidence-Based literature to justify endorsement
- Therefore, leave to individual practitioners to choose
Some bad news...

- IV Vitamin C has a single producer:

Still...
Thank you

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