Sepsis Learning Collaborative: Sepsis New Definitions
Sepsis - 3, a New Definition

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Disclosures

- ACEP Sepsis Expert panel – Vice Chair
- ACEP CMMI TCPI SAN – Sepsis Project Manager
Objectives

- Brief History of the definitions
- Rationale for new definitions of Sepsis and Septic Shock
- Understanding Sepsis-3
Defintions

• 1991 Bone et al. published in CHEST the:
  • Definitions of Sepsis and Organ Failure and guidelines for the use of innovative therapies in Sepsis. The ACCP/SCCM Consensus Conference Committee

• SIRS Criteria
• Initial Definitions of Sepsis, Severe Sepsis and Septic Shock
Uncomplicated Sepsis

- Suspected infection *plus*

- Two out of Four SIRS criteria
  - Temp > 100.9 (38.3) or < 96.8 (36)
  - Heart Rate > 90
  - Respiratory rate > 20 or PaCO₂ < 32 mm HG
  - WBC > 12K or < 4K or > 10% bands
Severe Sepsis

- Uncomplicated Sepsis *plus*
- One or more organ dysfunction *or*
- Serum lactate > 4.0 mmol/L
Septic Shock

- Severe Sepsis *plus*
- Hypotension (SBP < 90 or MAP < 70) after fluid bolus
Definitions (Sepsis-2)

- 2001 ESICM/ESICM/ACCP/ATS/SIS International Sepsis Consensus Conference
  - Current concepts remain useful
  - SIRS is overly sensitive and non-specific
  - Expanded list of signs and symptoms
Sepsis Glory Days

• Intensive Insulin - Van den Gerge et al. NEJM, 2001
• Steroids - Annane et al. JAMA, 2002
• Surviving Sepsis Campaign - Dellinger et al. CCM, 2004
Refined

- Intensive insulin has a limited role - NICE SUGAR 2009
- Steroids in a limited population - CORTICUS 2008
- APC - gone - ADDRESS / PROWESS SHOCK 2005/2012
- Lactate clearance - Jones et al. JAMA, 2010
- Fluid choice... Colloid / Crystalloid - SPLIT Trial 2015
- Vasopressin use - VASST; BP target - SEPSISPAM 2014
- Restrictive transfusions - TRISS 2013
- ProCESS, ProMISE, ARISE - 2014 -2015
Importance of Sepsis Care

- Major public health concern
- $20 billion in costs on the US
- Increased incidence
  - Aging
  - Comorbidity
  - Increased recognition
  - Coding
- #1 cause for in-patient hospital mortality
The Third International Consensus Definitions for Sepsis and Septic Shock

Presented at the 45th annual SCCM Critical Care Congress in Orlando, FL on February 22, 2016

Published as a trio of papers in JAMA the same day
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

Assessment of Clinical Criteria for Sepsis
For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Christopher W. Seymour, MD, MSc; Vincent X. Liu, MD, MSc; Theodore J. Iwashyna, MD, PhD; Frank M. Bruninkhorst, MD; Thomas J. Scherag, PhD; Gordon Rubenfeld, MD, MSc; Jeremy M. Kahn, MD, MSc; Manu Shankar-Hari, MD, MSc; Mervyn Singer, MD; Clifford S. Deutschman, MD, MS; Gabriel J. Escobar, MD; Derek C. Angus, MD, MPH

Developing a New Definition and Assessing New Clinical Criteria for Septic Shock
For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Manu Shankar-Hari, MD, MSc; Gary S. Phillips, MAS; Mitchell L. Levy, MD; Christopher W. Seymour, MD, MSc; Vincent X. Liu, MD, MSc; Clifford S. Deutschman, MD; Derek C. Angus, MD, MPH; Gordon D. Rubenfeld, MD, MSc; Mervyn Singer, MD, FRCP; for the Sepsis Definitions Task Force
Why?

- SIRS is very non-specific
  - Kaukonen et al. NEJM 2015

- Improved understanding of pathobiology
  - SIRS just inflammatory
  - Need to consider anti-inflammatory, hormonal, metabolic, coagulation, bio-energetic, neuronal and autonomic

- Various terminology
  - Severe Sepsis vs. Sepsis (septicemia, sepsis syndrome)
How?

• 19 member task force of intensivists, infectious disease specialists, surgeons and pulmonologists

• Key Concepts:
  • Sepsis is the primary cause of death from infection
  • Dysregulated host response
  • Organ dysfunction may be occult
  • Phenotypes may be modified by comorbidities / interventions
  • Some infections cause local dysfunction w/o dysregulated systemic response
Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.
Some clarity about dysfunction

- Organ dysfunction can be identified as an acute change in total SOFA score $\geq 2$ points consequent to the infection.
- The baseline SOFA score can be assumed to be zero in patients not known to have preexisting organ dysfunction.
- A SOFA score $\geq 2$ reflects an overall mortality risk of approximately 10% in a general hospital population with suspected infection. Even patients presenting with modest dysfunction can deteriorate further, emphasizing the seriousness of this condition and the need for prompt and appropriate intervention, if not already being instituted.

Singer et al. JAMA, 2016
### Sequential (Sepsis-Related) Organ Function Assessment (SOFA) Score.\textsuperscript{a}

<table>
<thead>
<tr>
<th>System / Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiration: (\text{PaO}_2/\text{FiO}_2), mmHg (kPa)</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: Platelets x 10(^3)/(\mu)L</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: Bilirubin, mg/dL ((\mu)mol/L)</td>
<td>&lt;1.2 (20)</td>
<td>&lt;1.2-1.9 (20-32)</td>
<td>2.0-5.9 (33-101)</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 &lt;5 or dobutamine (any dose)\textsuperscript{b}</td>
<td>Dopamine 5.1-15 or epinephrine (\leq 0.1), or norepinephrine (\leq 0.1)\textsuperscript{b}</td>
<td>Dopamine &gt;15 or epinephrine, &gt;0.1, or norepinephrine &gt;0.1\textsuperscript{b}</td>
</tr>
<tr>
<td>Central nervous system: Glasgow coma scale score\textsuperscript{c}</td>
<td>15</td>
<td>13-14</td>
<td>10-12</td>
<td>6-9</td>
<td>&lt;6</td>
</tr>
<tr>
<td>Renal: Creatinine mg/dL ((\mu)mol/L); Urine output, mL/day</td>
<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); &lt;500</td>
<td>&gt;5.0 (440); &lt;200</td>
</tr>
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</table>

\textbf{Figure 2.} Abbreviations: \(\text{PaO}_2/\text{FiO}_2\), partial pressure of oxygen/fraction of inspired oxygen. a) Adapted from Vincent et al\textsuperscript{3}; b) Catecholamine dosing in \(\mu\)g/kg/min, >1 hour; c) Glasgow Coma Scale scores range from 3-15 (3 minimum, 15 normal).
Need for Public Definitions

- In lay terms, sepsis is a life-threatening condition that arises when the body’s response to an infection injures its own tissues and organs.
qSOFA - a new term

• Patients with suspected infection who are likely to have a prolonged ICU stay or to die in the hospital can be promptly identified at the bedside with qSOFA

• qSOFA criteria:
  • Alteration in mental status (GCS < 14)
  • Hypotension - SBP ≤100 mm Hg
  • Respiratory rate ≥22/min.
Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality.
Septic Shock

- Patients with septic shock can be identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain MAP $\geq$ 65 mm Hg and having a serum lactate level $>2$ mmol/L (18 mg/dL) despite adequate volume resuscitation.

- With these criteria, hospital mortality is in excess of 40%.

- *Note: Severe Sepsis no longer exists in these definitions*
Intent

• Definitions PLUS Clinical Criteria

• The purpose was to create the most scientifically valid description of sepsis possible while providing a definition that would be clinically useful.
  • Distinguish patients with sepsis—in whom organ damage increased the risk of mortality to greater than 10%
  • from patients with septic shock, whose mortality exceeded 40%

• Removed Severe Sepsis
The Science

- Needed 2 more papers

- Derivation Cohort
  - 1.3 million EMR encounters at 12 UPMC hospitals from 2010-2012

- Validation Cohort
  - 4 data sets (KPNC, VA, KCEMS, ALERTS)
  - 700K encounters at 165 hospitals from 2008-2013
The Science

- Very rigorous methods
  - 44% of patients from ED data
  - Many endorsements

- Concerns
  - Retrospective
  - Only 9% had initial lactate drawn
    - Lactate NOT used in screening, but only in definition of septic shock
## Sepsis definitions

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<tr>
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<th>Previous (1991-2016)</th>
<th>Sepsis 3 (2016-)</th>
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<tbody>
<tr>
<td><strong>Sepsis</strong></td>
<td>Systemic Inflammatory Response Syndrome (SIRS) + suspected infection.</td>
<td>Suspected or documented infection + [2] of qSOFA (systolic blood pressure &lt; 90 mmHg; GCS ≤ 13; respiratory rate ≥ 22 per minute) or Rise in SOFA score ≥ 2 points</td>
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<tr>
<td><strong>Severe Sepsis</strong></td>
<td>Sepsis + any of the following: Systolic blood pressure &lt; 90 mmHg or MAP &lt; 65; lactate &gt; 2.0 mmol/L; INR &gt; 1.5 or PTT &gt; 60s; bilirubin ≥ 2.0 mg/dL; creatinine 2.1 &gt; mg/dL urine output &lt; 0.5 mL/kg/hour (≥ 2 hours); platelets 100 x 10^9/L; spO2 &lt; 90% (room air).</td>
<td>Removed from official nomenclature</td>
</tr>
<tr>
<td><strong>Septic Shock</strong></td>
<td>Sepsis + hypotension after adequate fluid resuscitation</td>
<td>Sepsis + vasopressors required to maintain MAP &gt; 65 and lactate &gt; 2.0 mmol/L after adequate fluid resuscitation</td>
</tr>
</tbody>
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*Figure 1. Abbreviations: MAP, mean arterial pressure; INR, international normalized ratio; PTT, partial thromboplastin time; qSOFA, quick Sequential (sepsis-related) organ function assessment; GCS, Glasgow Coma Scale.*
Panel Discussion