Sepsis Redefined

March 29, 2016
Moderator

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Conflicts of interest to disclose: none
Today’s Presenters

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Professor of Medicine, Warren Alpert Medical School of Brown University
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Rhode Island Hospital
Providence, Rhode Island, USA
Learning Objectives

• Understand *The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)* and related clinical assessment tools

• Recognize the rationale behind the new definitions for sepsis and septic shock

• Understand the relationship of the new sepsis definitions to bedside screening and treatment of sepsis patients

*This webcast is supported by the Gordon and Betty Moore Foundation.*

CE/CME Credits are not available for this event
Audience Participation

Your Participation

Submit questions throughout the presentation using the Question box located on your control panel.

Note: Today’s presentation is being recorded and will be provided within 3 business days.

https://www.facebook.com/SCCM1

#SepsisRedefined
Sepsis Redefined Resources

SCCM Website: [http://www.sccm.org/sepsisredefined](http://www.sccm.org/sepsisredefined)
- Slides for today’s presentations will be available shortly at the link above

European Society of Intensive Care Medicine Website: [http://www.esicm.org/webinars/sepsis](http://www.esicm.org/webinars/sepsis)

Surviving Sepsis Campaign Website: [http://www.survivingsepsis.org](http://www.survivingsepsis.org)
Clifford S. Deutschman

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

The Sepsis Definitions Task Force
Why do we need a new definition?
Issues with the 1991 and 2001 Definitions

- SIRS – based
- “Severe Sepsis” is problematic
- Different assessment criteria yield different results
SIRS Sensitivity

**Conclusions:** Almost half of patients hospitalized on the wards developed SIRS at least once during their ward stay. Our findings suggest that screening ward patients using SIRS criteria for identifying those with sepsis would be impractical.
Sepsis/Severe Sepsis

- Confusing
  - Most people say “sepsis” when they mean “severe sepsis”
  - What the initial two task forces called “sepsis” is what most people call “infection”
Different Criteria, Different Results

Benchmarking the Incidence and Mortality of Severe Sepsis in the United States*

David F. Gaieski MD; J. Matthew Edwards, MD; Michael J. Kallan, MS; Brendan G. Carr, MD, MA, MS

Crit Care Med 2013; 41: 1167-1174

900K – 3.1 Mil

250K – 375K

Four different ways to code for sepsis; four different sets of results
Different Criteria, Different Results

Mortality from septic shock

- Australia – 22%
  - Kaukonen et al, 2014
- Germany – 60.5%
  - Heublein et al, In press
- The Netherlands – 60%
  - Klein-Klouwenberg et al, 2012
Increased Understanding of Sepsis Pathobiology

- More than just unimpeded inflammation
- Key role of immunosuppression
- Contribution of non-immune mechanisms
- Possible adaptive nature of organ dysfunction – hibernation
- Re-appraisal of the nature of septic shock
SCCM/ESICM Task Force to Re-Define Sepsis

- Co-Chairs – Mervyn Singer, Cliff Deutschman
  - Derek Angus
  - Djilalli Annane
  - Michael Bauer
  - Rinaldo Bellomo
  - Gordon Bernard
  - Jean-Daniel Chiche
  - Craig Coopersmith
  - Richard Hotchkiss
  - Mitchell Levy
  - John Marshall
  - Steve Opal
  - Gordon Rubenfeld
  - Tom van der Poll
  - Jean-Louis Vincent
  - Greg Martin
  - Manu Shankar-Hari
  - Chris Seymour
The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Singer M, Deutschman CS, Seymour CW, Shankar-Hari M et al.

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

JAMA 2016; 315: 801-10
What are the new definitions?
Definitions

Per the Merriam – Webster English Dictionary:

- **Definition**
  - “a statement expressing the *essential nature of something*”
  - or, more generically,
  - “a statement that describes *what something is*”

A definition therefore requires an understanding of the pathobiology of the disorder..

.. which, for sepsis, is at best incomplete
Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection.
More problematic

- Is septic shock sepsis where the dysfunctional organ is the cardiovascular system?
  - Task force opinion - NO
    - Also involves cellular/metabolic abnormalities

- What distinguishes septic shock from sepsis?
  - Treatment?
    - NO. Management is the same
  - Pathobiology?
    - Maybe … but at this time not known
The Definition of Septic Shock

- What tangibly differentiates septic shock from sepsis?
  - MORTALITY
  - Septic shock is “really, really, really bad” sepsis

Septic shock is a subset of sepsis in which profound circulatory, cellular and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone.
Advantages

- Incorporates most up-to-date thinking on sepsis pathobiology
- Provides closest approximation possible to describing “what sepsis is”

Concerns

- Of limited practical utility as they contain elements that cannot be clinically identified
  - “organ dysfunction”
  - “dysregulated host response”
What is qSOFA?
Christopher W. Seymour, MD MSc
The CRISMA Center
University of Pittsburgh
Departments of Critical Care and Emergency Medicine

Seymour CW, Liu VX, Iwashyna TJ et al.
Assessment of Clinical Criteria for Sepsis
For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

JAMA 2016; 315: 762-774
What is sepsis?

Life threatening organ dysfunction caused by a dysregulated host response to infection.
What is sepsis?

A life threatening organ dysfunction caused by a dysregulated host response to infection.

Among patients with suspected infection, who is really sick?
What is sepsis?

All the patients you see...

- Infected
- Septic
- Really sick
Our challenges

- What data sources to use?
- How do we identify infection?
- What clinical criteria to study?
- How to identify who is “really sick”?
What data sources to use?

- **Derivation** - 1.3 million EHR records from UPMC
- **Validation** – almost 6 million records
  - KPNC
  - VA
  - “ALERTS” database from Germany
  - Kings County (Seattle) EMS
How do we identify infection?

- First episode of cultures, antibiotics
- Derivation - 1.3 million EHR records from UPMC
  - 148,000 with suspected infection
- Validation – almost 6 million records
  - KPNC
  - VA
  - “ALERTS” database from Germany
  - Kings County (Seattle) EMS
  - > 700,000 with suspected infection
What clinical criteria to study?

- SIRS
  - 0-4 points
  - Temp, HR, RR, WBC count

- SOFA
  - 0-24 points
  - 13 variables, clinical labs, therapeutic data

- LODS
  - 0-22 points
  - Similar to SOFA
How to identify who is “really sick”?

- Sepsis is “life threatening organ dysfunction caused by a dysregulated host response to infection”
  But that can’t be measured clinically

- “Really sick” is a proxy
- More common among infected patients who are septic than those who are not
How to identify who is “really sick”? 

- Possible Proxies
  - Clinical review committees
  - Death in the hospital
  - Prolonged stay in the ICU
  - Discharge diagnosis of sepsis
  - Positive microbiologic cultures
Distribution of existing criteria

- **ICU only (N=7,932)**
  - SIRS criteria
  - SOFA score
  - Logistic organ dysfunction score

- **Outside the ICU (N=66,522)**
  - SIRS criteria
  - SOFA score
  - Logistic organ dysfunction score

SOFA and LODS criteria are complex and require laboratory tests

No. of patients

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
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<td>SIRS criteria</td>
<td>261</td>
<td>996</td>
<td>2,454</td>
<td>2,857</td>
<td>1,406</td>
<td>1,047</td>
<td>625</td>
<td>418</td>
<td>381</td>
<td>163</td>
<td>111</td>
<td>90</td>
<td>72</td>
<td>41</td>
<td>20</td>
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<tr>
<td>SOFA score</td>
<td>27,560</td>
<td>16,067</td>
<td>9,690</td>
<td>5,013</td>
<td>3,326</td>
<td>1,992</td>
<td>1,047</td>
<td>625</td>
<td>418</td>
<td>381</td>
<td>163</td>
<td>111</td>
<td>90</td>
<td>72</td>
<td>41</td>
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<tr>
<td>Logistic organ dysfunction score</td>
<td>29,789</td>
<td>15,085</td>
<td>4,429</td>
<td>7,878</td>
<td>4,426</td>
<td>1,600</td>
<td>1,088</td>
<td>788</td>
<td>442</td>
<td>366</td>
<td>211</td>
<td>128</td>
<td>118</td>
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<td>20,129</td>
<td>22,357</td>
<td>15,852</td>
<td>6,777</td>
<td>1,406</td>
<td>0</td>
<td>10</td>
<td>20</td>
<td>30</td>
<td>40</td>
<td>50</td>
<td>60</td>
<td>70</td>
<td>80</td>
<td>90</td>
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<tr>
<td>SOFA score</td>
<td>529</td>
<td>677</td>
<td>809</td>
<td>925</td>
<td>1,063</td>
<td>1,194</td>
<td>1,326</td>
<td>1,457</td>
<td>1,588</td>
<td>1,720</td>
<td>1,851</td>
<td>1,982</td>
<td>2,113</td>
<td>2,244</td>
<td>2,375</td>
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<tr>
<td>Logistic organ dysfunction score</td>
<td>329</td>
<td>604</td>
<td>377</td>
<td>696</td>
<td>925</td>
<td>682</td>
<td>774</td>
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<td>552</td>
<td>549</td>
<td>488</td>
<td>287</td>
<td>283</td>
<td>164</td>
<td>354</td>
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</table>
Developing new criteria

- Focus on timeliness, ease of use
- Studied 21 variables from Sepsis-2
- Multivariable logistic regression for in-hospital mortality
  - UPMC EHR as derivation dataset

- Validated with EHR data - KPNC, VA, KC (Seattle) EMS, “ALERTS” (Germany)

- Respiratory rate ≥ 22 bpm
- Altered mentation
- Systolic blood pressure ≤ 100 mmHg
Assessment of criteria

SOFA and LODS superior in the ICU

qSOFA similar to complex scores outside the ICU
Serum lactate

- Not retained during qSOFA model building
- Serum lactate at various thresholds added to qSOFA
New Definition of Sepsis

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

Among patients with suspected infection
- SOFA ≥ 2 (or a change ≥ 2, ΔSOFA)
- in ED/on wards, qSOFA
What clinical criteria identify patients with septic shock?
Septic shock is a subset of sepsis in which profound circulatory, cellular and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone.

- Arrived at via by use of Delphi method among members of task force
- As with sepsis, elements are difficult to identify clinically
What is septic shock?

A subset of sepsis in which profound circulatory, cellular and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone.

So these are patients with sepsis who are especially sick.
**What is septic shock?**

A subset of sepsis in which profound circulatory, cellular and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone.

Among patients with sepsis (that is, who have suspected infection and are really sick):

Who is really, really, really sick? (eg, has a 50:50 chance of dying)
How to identify who is really, really, really sick?

- Septic shock is a subset of sepsis
- It is characterized by "profound circulatory, cellular and metabolic abnormalities"
- Once again, these elements cannot really be measured clinically

- This time, need a proxy for "really, really, really sick"
- What proxies can be used?
Data analysis

- **Derivation cohort**
  - Surviving Sepsis Campaign Database (SSC)
    - 28,150 patients with severe sepsis or septic shock

- **Validation cohort**
  - UPMC
  - KPNC

- **Criteria** – identified by modified Delphi process – task force
  - After fluids
    - Hypotension, vasopressor dependence, elevated lactate
# 6 patient groups based on 3 variables

<table>
<thead>
<tr>
<th></th>
<th>hypotension after fluids</th>
<th>vasopressors</th>
<th>lactate &gt;2</th>
<th>Prevalence (SSC)</th>
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<tr>
<td><strong>Group 1</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>45.2%</td>
</tr>
<tr>
<td><strong>Group 2</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>21.2%</td>
</tr>
<tr>
<td><strong>Group 3</strong></td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>1.2%</td>
</tr>
<tr>
<td><strong>Group 4</strong></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>17.3%</td>
</tr>
<tr>
<td><strong>Group 5</strong></td>
<td>No hypotension pre-fluid</td>
<td>No</td>
<td>Yes</td>
<td>14.3%</td>
</tr>
<tr>
<td><strong>Group 6</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>0.8%</td>
</tr>
</tbody>
</table>
# 6 patient groups based on 3 variables

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<th>Group</th>
<th>Hypotension after fluids</th>
<th>Vasopressors</th>
<th>Lactate &gt;2</th>
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<td>No</td>
<td>No</td>
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<td>No</td>
<td>Yes</td>
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Septic shock is a subset of sepsis in which profound circulatory, cellular and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone.
New Clinical Criteria for Septic Shock

Septic shock is a subset of sepsis in which profound circulatory, cellular and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone.

Despite adequate fluid resuscitation:

- vasopressors needed to maintain MAP ≥65 mmHg

  AND

- lactate >2 mmol/l
Summary (I)

- Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.
- Septic shock is defined as a subset of sepsis in which profound circulatory, cellular and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone.
Summary (II)

- Outside the ICU, patients with suspected or presumed infection who are highly likely to have poor outcomes can be clinically identified using qSOFA
  - SBP < 100mm Hg
  - RR > 22 breath/min
  - Altered mental status
- In the ICU, patients with suspected or presumed infection who are highly likely to have poor outcomes can be clinically identified by the presence of 2 or more SOFA points
Summary (III)

- Patients with septic shock can be clinically identified if, despite adequate resuscitation,
- They require vasopressors to maintain MAP $\geq 65$ mmHg
  
  AND

- Their serum lactate level is $> 2$ mmol/l
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Conflicts of interest to disclose: none
The Usefulness of Alternative Sepsis Criteria
Application of a Framework to Assess the Usefulness of Alternative Sepsis Criteria

Christopher W. Seymour, MD¹; Craig M. Coopersmith, MD²; Clifford S. Deutschman, MD³; Foster Gesten, MD⁴; Michael Klompas, MD⁵; Mitchell Levy, MD⁶; Gregory S. Martin, MD⁷; Tiffany M. Osborn, MD⁸; Chanu Rhee, MD⁵; David k. Warren, MD⁹; R. Scott Watson, MD¹⁰; Derek C. Angus, MD¹

• Definitions of sepsis
  – 3rd International consensus definitions
  – CDC
  – CMS
  – ……

Crit Care Med 2016; 44:e122–e130
What’s the Problem?

• There is no perfect method to unambiguously categorize patients as having sepsis or not
• Multiple initiatives for sepsis with different goals
• **Four** broad purposes for sepsis criteria:
  – Clinical Care
  – Research
  – Surveillance
  – QI and audit
# Clinical Care

<table>
<thead>
<tr>
<th>Objective</th>
<th>Example</th>
<th>Criteria</th>
<th>Caveats</th>
</tr>
</thead>
</table>
| To inform the direct clinical care of sepsis at the bedside               | ESICM/SCCM 3rd International Consensus Definitions for Sepsis and Septic Shock Task Force | Among patients in whom the clinician suspects infection:  
  • Acute change in SOFA score ≥ 2 points  
  For clinical prompt in infected patients:  
  • ≥ 2 qSOFA points outside the ICU | • Sepsis not restricted to confirmed infection  
• No criteria proposed for infection; left to clinician  
• SOFA baseline may not be always available |
<table>
<thead>
<tr>
<th>Objective</th>
<th>Example</th>
<th>Criteria</th>
<th>Caveats</th>
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</thead>
</table>
| Guide the conduct of clinical research in sepsis | Enrollment criteria for ACCESS trial | Among patients with evidence of infection, all of:  
- 3 or more SIRS criteria  
- 1 major organ dysfunction  
- High risk of death (APACHE II) |  
- Sepsis not restricted to confirmed infection  
- No criteria proposed for infection; left to clinician  
- SOFA baseline may not be always available |
## Research: Basic

<table>
<thead>
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<th>Objective</th>
<th>Example</th>
<th>Criteria</th>
<th>Caveats</th>
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</table>
| Guide the study of fundamental principles of sepsis, often animal models | Murine sepsis score after fecal-induced peritonitis                                            | Score ranging from 0-28, 4 points for:  
  - Appearance  
  - LOC  
  - Activity  
  - Response to stimulus  
  - Eyes  
  - Respiratory rate  
  - Respiration quality                                      | • Reported with high inter-rater and test-retest reliability  
• May be species specific  
• Alternative models under study                                      |
## Surveillance and Epidemiology

<table>
<thead>
<tr>
<th>Objective</th>
<th>Example</th>
<th>Criteria</th>
<th>Caveats</th>
</tr>
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</table>
| To track local and national burden, incidence and outcomes of sepsis across hospitals over time | Center for Disease Control (CDC) and Prevention Epicenters Preliminary Criteria | Among patients with infection, $\geq 1$ of:  
- Vasopressor use  
- $\geq 2$ days of mechanical ventilation  
- Rise in serum creatinine by $\geq 0.5$                                                                 |  
- Avoids data elements not readily available in the EHR (vital signs)  
- Feasibility  
- For similar patients, clinicians may provide organ support differently |
## QI and Audit

<table>
<thead>
<tr>
<th>Objective</th>
<th>Example</th>
<th>Criteria</th>
<th>Caveats</th>
</tr>
</thead>
</table>
| To inform quality improvement initiatives and audit performance across hospitals | Centers for Medicare and Medicaid Services (SEP-1) | • ICD-10 claims based identification to find denominator of sepsis patients  
• Manual chart review for SIRS criteria and organ dysfunction criteria | • Restricts to cohort of patients identified with administrative data  
• Some hospitals using EHR algorithm  
• *May result in smaller, sicker subset of patients* |
### Case Identification by Different Criteria

**Case study of EHRs of 396,241 patients** – 12 academic and community hospitals – Southwestern Pennsylvania

- **2012**

**Cases identified using**
- 2016 Consensus Definitions
- CDC epicenter surveillance criteria
- CMS SEP-1 criteria

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<tbody>
<tr>
<td>Total no.</td>
<td>11,011</td>
<td>9,823</td>
<td>9,176</td>
<td>12,041</td>
<td>2,709</td>
</tr>
<tr>
<td>Positive blood cultures, no. (%)</td>
<td>854 (8)</td>
<td>786 (8)</td>
<td>824 (9)</td>
<td>1,034 (9)</td>
<td>N/A</td>
</tr>
<tr>
<td>Maximum day 1 SOFA score, mean (sd)</td>
<td>2.9 (3.0)</td>
<td>2.9 (3.5)</td>
<td>3.1 (3.6)</td>
<td>2.6 (3.4)</td>
<td>4.2 (4.2)</td>
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<tr>
<td>≥ 2 SIRS criteria, no. (%)</td>
<td>7,003 (64)</td>
<td>7,487 (76)</td>
<td>5,903 (64)</td>
<td>7,166 (60)</td>
<td>2,709 (100)</td>
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<tr>
<td>ICU admission, no. (%)</td>
<td>5,402 (49)</td>
<td>6,808 (69)</td>
<td>6,658 (73)</td>
<td>7,288 (61)</td>
<td>2,239 (83)</td>
</tr>
<tr>
<td>ICU length of stay, median days (IQR)</td>
<td>5 (3–10)</td>
<td>5 (3–10)</td>
<td>6 (4–12)</td>
<td>6 (4–11)</td>
<td>7 (3–13)</td>
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<td>Hospital length of stay, median days (IQR)</td>
<td>8 (5–13)</td>
<td>9 (6–16)</td>
<td>12 (7–19)</td>
<td>11 (7–18)</td>
<td>12 (7–20)</td>
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<tr>
<td>In-hospital mortality, no. (%)</td>
<td>977 (8.9)</td>
<td>1,072 (11)</td>
<td>1,256 (14)</td>
<td>1,319 (11)</td>
<td>663 (24)</td>
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</tbody>
</table>
Conclusions

• Unrealistic goal to have a single gold-standard definition of sepsis
  – Different populations, goals, purpose
• Possible to develop methodologic framework to develop and assess different definitions and criteria
• Each set of criteria valuable for different purpose
• Harmonization and standardization may be possible over time as new technologies and markers develop
Thank You
Questions/Comments/Discussion

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