Conceptual framework for sepsis definitions

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A Framework for the Development and Interpretation of Different Sepsis Definitions and Clinical Criteria

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ABSTRACT: Although sepsis was described more than 2,000 years ago, and clinicians still struggle to define it, there is no “gold standard” and multiple varying approaches and terms exist. Challenges include the ever-changing knowledge base that informs our understanding of sepsis, competing views on which aspects of any potential definition are most important, and the tendency of most potential criteria to be distributed in all-risk populations in such a way as to hinder separation into discrete sets of patients. We propose that the development and evaluation of any definition or diagnostic criteria should follow four steps: 1) define the epidemiologically underlying disease, 2) agree on all relevant terms used to frame the question, 3) state the intended purpose for any proposed set of criteria, and 4) adopt a scientific approach to inform their usefulness with regard to the intended purpose. Usefulness can be measured across six domains: 1) reliability, (ability of criteria during retesting, between raters, over time, and across settings); 2) content validity (similar to face validity); 3) construct validity (whether criteria measure what they purport to measure); 4) criterion validity (how new criteria compare to standards); 5) measurement burden (cost, safety, and acceptability); and 6) timelessness (whether criteria are applicable concurrent with care decisions). The relative importance of these domains of usefulness depends on the intended purpose, of which there are four broad categories: 1) clinical care, 2) research, 3) surveillance, and 4) quality improvement and audit. This proposed methodological framework is intended to aid understanding of the strengths and weaknesses of different approaches, provide a mechanism for explaining differences in epidemiologic estimates generated by different approaches, and guide the development of future definitions and diagnostic criteria. [Crit Care Med 2016; 44:e1106–e1113]

Keywords: definitions, diagnosis, diagnostic criteria, measurement, reliability, sepsis, validity

Although sepsis was first described more than 2,000 years ago, clinicians and researchers still struggle to define it (1). While the identification of clinical manifestations of sepsis may present little difficulty, such classic cases are unusual, and even in these, the diagnosis may not be obvious until the patient has progressed toward the optimal time for intervention. With advances in our understanding of the physiology of sepsis and heightened awareness of its public health importance, there is increasing pressure to have widely deployable, consistent, and accurate diagnostic criteria, which in turn spur a desire for a so-called “gold” definition. However, there are competing definitions and criteria by which sepsis is measured. These different approaches identify different patients and produce different estimates of incidence and outcomes, generating frustration and confusion. The problem in that defining sepsis, like any other diagnosis or syndrome, is more complex than might initially be apparent. But complexity necessitates neither opacity nor futility. With transparency and rigor, approaches can be developed to define and measure sepsis. And, there can be room for more than one...
Sepsis is difficult to define

- Described more than 2000 years ago
- Clinicians struggle to recognize promptly
- Increasing pressure for widely deployable, consistent definition
- Complex pathophysiology, rapidly evolving knowledge base

Angus et al., Crit Care Med, 2016
Classification of sepsis

- The goal: the convenience of assigning a label

- The problems:
  - **Knowledge**  Do we know what sepsis is?
  - **Purpose**  For what purpose will definitions be used?
  - **Statistical**  To what degree can we identify discrete sets?

No sepsis

Sepsis

Angus et al., *Crit Care Med*, 2016
Sepsis: the knowledge problem

Process by which flesh rots, wounds fester, swamps foul air

Bacteria or microbes lead putrefaction

Subjective / objective symptoms resulting from pathogens

Address therapy to body’s response
Sepsis: the knowledge problem

“Sepsis is life threatening organ dysfunction due to a dysregulated host response to infection”

But do we know?

• Organ dysfunction
• Dysregulated
• Host response

Our knowledge of sepsis not static, future definitions will change
Knowledge problem

We’re not alone

[Graph showing the number of disorders over time from 1920 to 2000, with points labeled DSM-1 to DSM-4.]
Sepsis: the purpose problem

• Not one purpose for classifying sepsis patients
  • Clinical care of patients
  • Epidemiology and sepsis surveillance
  • Quality improvement / performance audit
• Research
  • Clinical trials
  • Basic research

Which definition/criteria to use when? Can there be more than one?
Ideal disease classification there are discrete sets and very few in between (platypus)
Sepsis: the statistical problem

Ideal classification in sepsis

Actual classification sepsis

Leads to missed cases, overdiagnosis, frustration
Conceptual framework for a definition

- Philosophic underpinning
  - Agree that sepsis exists

- Consideration of the words we use
  - Severe sepsis vs. sepsis vs. not

- Plan a scientific method for evaluating classification scheme

- Consideration of different purposes and their priorities

Right  ×  Useful  ✔
How do we measure usefulness?

- Propose 6 domains
- Can be used to judge a definition or classification scheme
- Each purpose may value domains differently

**Domains of usefulness for disease classification**

- **Reliability**
  - Inter-rater
  - Test-retest
  - Meta-reliability

- **Criterion validity**
  - Concurrent
  - Predictive
  - Convergent

- **Construct validity**
  - Discriminant
  - Multi-trait, multi-method

- **Content validity**
  - Face validity

- **Burden**
  - Cost
  - Safety
  - Complexity

- **Timeliness**

Angus et al., *Crit Care Med*, 2016
Example of different priorities

- Reliability

High priority for surveillance criteria and clinical research

Hospital A → Hospital B

Lower priority for a single center phase 2 trial
Example of different priorities

- **Timeliness**

  High priority for clinical care where prompt classification is recommended

Low(er) priority for quality improvement / audit
Framework for sepsis definitions

• Starts with a collective philosophy
• Talk about sepsis using the same terms
• Acknowledge there are different purposes for sepsis

• Each purpose has different priorities
• Consider that no single criteria can / will perform well in all areas
The Usefulness of Alternative Sepsis Criteria

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Disclosures

• None
Application of a Framework to Assess the Usefulness of Alternative Sepsis Criteria

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• Definitions of sepsis
  • 3rd International consensus definitions
  • CMS
  • Clinical Trials
  • CDC
  • ......

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
Domains of Usefulness for Potential Sepsis Criteria

• Reliability
• Content Validity
• Construct validity
• Criterion validity
• Measurement burden
• Timeliness
<table>
<thead>
<tr>
<th>Objective</th>
<th>Example</th>
<th>Criteria</th>
<th>Caveats</th>
</tr>
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<tbody>
<tr>
<td>To inform the direct clinical care of sepsis at the bedside</td>
<td>ESICM/SCCM 3rd International Consensus definitions for sepsis and septic shock Task Force</td>
<td>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</td>
<td>• No criteria proposed for infection; left to clinician • Still have to screen for infection • SOFA baseline may not be always available</td>
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## Research: Clinical

<table>
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<tr>
<td>Guide the conduct of clinical research in sepsis</td>
<td>Enrollment criteria for ACCESS trial</td>
<td>Among patients with evidence of infection, all of: • 3 or more SIRS criteria • 1 major organ dysfunction • High risk of death (APACHE II)</td>
<td>• Broad variety in clinical research criteria • Enrollment in clinical trials rely on objective criteria for reliability • Subsets chosen to reduce heterogeneity</td>
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### Research: Basic

<table>
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<tbody>
<tr>
<td>Guide the study of fundamental principles of sepsis, often animal models</td>
<td>Murine sepsis score after fecal-induced peritonitis</td>
<td>Score ranging from 0-28, 4 points for:</td>
<td>• Reported with high inter-rater and test-retest reliability</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Appearance</td>
<td>• May be species specific</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• LOC</td>
<td>• Alternative models under study</td>
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<tr>
<td></td>
<td></td>
<td>• Activity</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Response to stimulus</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Eyes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Respiratory rate</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Respiration quality</td>
<td></td>
</tr>
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<tr>
<td>To track local and national burden, incidence and outcomes of sepsis across hospitals over time</td>
<td>Center for Disease Control (CDC) and Prevention Epicenters Preliminary Criteria</td>
<td>Among patients with infection, ≥ 1 of: • Vasopressor use • ≥ 2 days of mechanical ventilation • Rise in serum creatinine by ≥ 0.5</td>
<td>• Avoids data elements not readily available in the EHR (vital signs) • Feasibility • For similar patients, clinicians may provide organ support differently</td>
</tr>
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<tr>
<td>To inform quality improvement initiatives and audit performance across hospitals</td>
<td>Centers for Medicare and Medicaid Services (SEP-1)</td>
<td>• ICD-10 claims based identification to find denominator of sepsis patients&lt;br&gt;• Manual chart review for SIRS criteria and organ dysfunction criteria</td>
<td>• Restricts to cohort of patients identified with administrative data&lt;br&gt;• Some hospitals using EHR algorithm&lt;br&gt;• <em>May result in smaller, sicker subset of patients</em></td>
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## Case Identification by Different Criteria

- **Case study of EHRs of 396,241 patients**

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<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>
</tr>
<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>
</tr>
<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>
</tr>
<tr>
<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>
</tr>
<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>
</tr>
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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