Redefining Sepsis, The End of a SIRS-Era

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PGY-2 Critical Care Resident
Objective

• Review presently accepted definitions for sepsis and septic shock as set forth by the Surviving Sepsis Campaign

• Identify the limitations of current criteria for identification and diagnosis of sepsis and septic shock

• Describe the literature surrounding the newly released definitions for sepsis and septic shock
1991 Sepsis Definition (Sepsis-1)

# 2001 Sepsis Definition (Sepsis-2)

<table>
<thead>
<tr>
<th>Category</th>
<th>Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>Documented or suspected and <strong>some</strong> of the following</td>
</tr>
<tr>
<td>General</td>
<td>Fever, Hypothermia</td>
</tr>
<tr>
<td></td>
<td>Tachycardia, Tachypnea</td>
</tr>
<tr>
<td></td>
<td>Altered mental status</td>
</tr>
<tr>
<td></td>
<td>Edema, positive fluid balance</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Leukocytosis, leukopenia, Bandemia</td>
</tr>
<tr>
<td></td>
<td>Elevated CRP, procalcitonin</td>
</tr>
<tr>
<td>Hemodynamic</td>
<td>Hypotension</td>
</tr>
<tr>
<td></td>
<td>Increased mixed venous oxygen saturation</td>
</tr>
<tr>
<td>Organ dysfunction</td>
<td>Hypoxemia</td>
</tr>
<tr>
<td></td>
<td>Oliguria, increased SCr</td>
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<tr>
<td></td>
<td>Coagulopathy</td>
</tr>
<tr>
<td></td>
<td>Ileus</td>
</tr>
<tr>
<td>Tissue perfusion</td>
<td>Hyperlactatemia</td>
</tr>
<tr>
<td></td>
<td>Decreased capillary refill</td>
</tr>
</tbody>
</table>

47 y/o F s/p MVA
WBC 20 cells/mm³
RR 31 breaths/min
T 35°C
HR 112 bpm
= 4/4 SIRS

69 y/o M with AMS
WBC 9 cells/mm³
RR 12 breaths/min
T 38.1°C
HR 86 bpm
= 0/4 SIRS
SIRS, Poor Performance

• Kaukonen et al. 172 ICUs in Australia and New Zealand
  • 1 in 8 people (12%) with severe sepsis met <2 SIRS criteria
  • SIRS positive/negative patients, no mortality difference

• Churpek et al. 5 hospital wards in the United States
  • 47% of patients met ≥2 SIRS criteria at least once during ward admission

47 y/o F s/p MVA
WBC 20 cells/mm³
RR 31 breaths/min
T 35ºC
HR 112 bpm
= 4/4 SIRS

Inflammatory response to trauma

69 y/o M w/ AMS
WBC 9 cells/mm³
RR 12 breaths/min
T 38.1ºC
HR 86 bpm
= 0/4 SIRS

HSV meningitis
Hypotensive requiring pressors, died
Sepsis-3 Task Force, Identified Issues

- No gold standard for sepsis diagnosis
- Previous definitions not evidenced-based
- SIRS is an *appropriate* response to infection, inflammatory stimulus
- Severe sepsis terminology misused
- Different variables for sepsis identification, divergence in mortality results
Marbles = infected population
Infection

Sepsis

Septic Shock

Increasing Mortality
Third time’s a charm with Sepsis-3?

Sepsis and Septic Shock
“Sepsis is **life-threatening organ dysfunction** caused by a **dysregulated host response** to infection”
Sepsis

• Multicenter, retrospective cohort study
  • University of Pennsylvania Medical Center (UPMC) health care system
  • Kaiser Permanente Northern California (KPMC)
  • Veterans Administration Ann Arbor (VA)
  • Washington State Department of Health
  • King County Emergency Medical Services (KCEMS)

• Derivation cohort followed by validation

Determining Clinical Criteria for Sepsis

1. Existing Criteria
2. Novel Criteria
Determining Clinical Criteria for Sepsis

1. Existing Criteria
2. Novel Criteria
# Existing Criteria

<table>
<thead>
<tr>
<th>Systemic Inflammatory Response Syndrome (SIRS, 0-4 criteria)</th>
<th>Sequential Organ Failure Assessment (SOFA, 0-24 points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory rate</td>
<td>PaO2/FiO2 ratio</td>
</tr>
<tr>
<td>White blood cell count</td>
<td>Glasgow Coma Scale</td>
</tr>
<tr>
<td>Heart rate</td>
<td>MAP</td>
</tr>
<tr>
<td>Temperature</td>
<td>Vasopressor data</td>
</tr>
<tr>
<td></td>
<td>Serum creatinine, UOP</td>
</tr>
<tr>
<td></td>
<td>Bilirubin</td>
</tr>
<tr>
<td></td>
<td>Platelet count</td>
</tr>
</tbody>
</table>

Determining Clinical Criteria for Sepsis

1. Existing Criteria
2. Novel Criteria
Development of Novel Criteria

- Readily available, easy to interpret
- Variables listed in 2001 Sepsis-2 definition
- Multivariable logistic regression in-hospital mortality

qSOFA = crude marker of organ dysfunction

- Altered Mentation
- SBP ≤100 mmHg
- RR ≥22/minute

72h Window for Evaluation

Infection Onset
Antibiotics
Body fluid cultures

12 UPMC Hospitals

1,309,025 Patient encounters

148,907 With suspected infection

74,453 Derivation cohort

7,836 ICU

66,617 non-ICU

74,454 Validation cohort

7,932 ICU

66,522 non-ICU

## Baseline Demographics

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Encounters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total, suspected infection, No.</td>
<td>148,907</td>
</tr>
<tr>
<td>Confirmed bacteremia, No. (%)</td>
<td>6875 (5)</td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
<td>61 ± 19</td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>63,311 (43)</td>
</tr>
<tr>
<td>Onset of infection within 48h admission, No. (%)</td>
<td>128,358 (86)</td>
</tr>
<tr>
<td>Location at infection onset, No. (%)</td>
<td></td>
</tr>
<tr>
<td>Emergency department</td>
<td>65,934 (44)</td>
</tr>
<tr>
<td>Floor</td>
<td>49,354 (33)</td>
</tr>
<tr>
<td>ICU</td>
<td>15,768 (11)</td>
</tr>
</tbody>
</table>

ICU Encounters, AUROC for In-Hospital Mortality

SIRS

SOFA

qSOFA

SIRS 0.64

<0.001 0.74

0.01 <0.001 0.66

Predictive validity
SOFA > both qSOFA, SIRS

Non-ICU Encounters, AUROC for In-Hospital Mortality

- SIRS: 0.76
- SOFA: <0.001 0.79
- qSOFA: <0.001 <0.001 0.81

Predictive validity: qSOFA > SIRS

Taking it One Step Further

• Post hoc analysis requested by task force

• Increase in SOFA score ≥2 points from baseline
  • Greater predictive validity than SIRS (P <0.001)
  • Similar to max SOFA score, previously reported

Additional Conclusions

• qSOFA performed similarly in remaining 4 validation cohorts

• qSOFA not meant to diagnose, but signal further work-up

• Addition of lactate did not increase the performance of qSOFA in mortality analysis
Sepsis Definition

Infection Suspected

- Continue to assess

ICU status?

- Yes: Evaluate SOFA
- No: qSOFA ≥2

qSOFA ≥2

- No: Sepsis
- Yes: Δ 2 points from baseline?

Δ 2 points from baseline?

- Yes: Sepsis
- No: Sepsis

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”
Clinical Criteria + Clinical Outcomes

• Systematic review of criteria used to define septic shock in observational studies
  • Mortality range 23.1% to 81.8%
  • 4-fold difference in 44 studies evaluated

• Delphi Method (3 surveys, meetings to develop a consensus)
  1. Develop a definition from above
  2. Determine a plan for analysis
  3. Finalize clinical criteria

Step #1: Definition, 3 Variables Identified

- Circulatory collapse
  - Hypotension despite adequate fluid resuscitation
  - Vasopressor support for MAP ≥65 mmHg

- Cellular, metabolic aberration
  - Serum lactate

- Bottom line, identify subset of sepsis patients with a uniquely high mortality relative to the rest

Step #2: Analysis

• Derivation cohort:
  • Surviving Sepsis Campaign Database, 18 countries
  • 2005-2010; N = 28,150 patients evaluated for inclusion

• Validation cohort
  • UPMC
  • KPNC

## Clinical Presentation

<table>
<thead>
<tr>
<th>Group</th>
<th>Hypotension post-fluids</th>
<th>Vasopressors</th>
<th>Lactate (&gt;2 mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Group 2</td>
<td>✔</td>
<td>✔</td>
<td>✗</td>
</tr>
<tr>
<td>Group 3</td>
<td>✔</td>
<td>✗</td>
<td>✔</td>
</tr>
<tr>
<td>Group 4</td>
<td>✔</td>
<td>✗</td>
<td>✔</td>
</tr>
<tr>
<td>Group 5</td>
<td>✗</td>
<td>✗</td>
<td>✔</td>
</tr>
<tr>
<td>Group 6</td>
<td>✔</td>
<td>✗</td>
<td>✗</td>
</tr>
</tbody>
</table>

Mortality Distribution, Derivation Cohort

Hypotension
Vasopressors
Lactate >2 mmol/L

42.3

Group 1

30.1

Group 2

28.7

Group 3

25.7

Group 4

29.7

Group 5

18.7

Group 6

Hypotension
No vasopressors
Lactate ≤2 mmol/L

Mortality Distribution, Validation Cohort

• **UPMC**
  - 148,907 patients with suspected infection
  - 7,892 patients met group 1 criteria

• **KPNC**
  - 321,380 patients with suspected infection
  - 47,885 patients met group 1 criteria

Step #3: Septic Shock Definition

Sepsis

Hypotension? (Check lactate)

Yes

Fluid resuscitate

No

Continue to assess

Vasopressors for MAP >65 mmHg AND Lactate >2 mmol/L

Yes

Septic Shock
Missing Pieces, Sepsis and Septic Shock

• Practical application, complexity of SOFA scoring system

• Performance in non-traditional patient populations
  • i.e., immunocompromised

• Is MAP <65 mmHg appropriate hypotension definition for all patients?

• Assumptions regarding patients without baseline data

• What is ‘adequate’ fluid resuscitation?
Conclusions

• Sepsis-1 and Sepsis-2 definitions
  • Developed according to expert opinion
  • Dependent upon SIRS, subjective data
  • Failed to identify, misclassified many patients
  • No connection to mortality

• Sepsis-3 definition
  • Sepsis = $\Delta$SOFA
  • Septic shock = vasopressors + lactate
  • Definitions directly linked to mortality
  • Future iterations of SSC likely to reflect this research
RE is a 64 y/o M presenting to the ED with SOB, found to have a CXR concerning for pneumonia. While in the ED, RE becomes altered and is found to have a SBP 90 mmHg and RR 20. What is RE’s qSOFA score?

A. 1
B. 2
C. 3
D. Not enough information to calculate
A qSOFA score of ≥2 in a patient outside of the ICU meets criteria for a sepsis diagnosis?

A. True
B. False
JM is a 59 y/o M admitted to the ICU due to concern for infection. In calculating JM’s SOFA score you note that it is 4 points higher than his baseline. Further, JM has a baseline lactate of 4 mmol/L, remains hypotensive after adequate fluid resuscitation, and is now requiring norepinephrine for support. What is JM’s diagnosis according to the new definitions for sepsis, septic shock?

A. Sepsis
B. Severe sepsis
C. Septic shock
D. JM does not meet criteria for any of the above
E. Both A and C
Questions & Discussion