Advantages and Pitfalls of Sepsis 3.0 Definitions

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Sepsis remains a challenge

- Main cause of death in non-coronary ICUs
- Contributing factor in 30-50% of all hospital deaths in the US

August 2013

National Inpatient Hospital Costs: The Most Expensive Conditions by Payer, 2011

Celeste M. Torio, Ph.D., M.P.H. and Roxanne M. Andrews, Ph.D.

Table 1. Top 20 most expensive conditions treated in U.S. hospitals, all payers, 2011

<table>
<thead>
<tr>
<th>Rank</th>
<th>CCS principal diagnosis category and name</th>
<th>Aggregate hospital costs, U.S. $, in millions</th>
<th>National costs, %</th>
<th>Number of hospital discharges, in thousands</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Septicemia (except in labor)</td>
<td>20,298</td>
<td>5.2</td>
<td>1,094</td>
</tr>
<tr>
<td>2</td>
<td>Osteoarthritis</td>
<td>14,810</td>
<td>3.8</td>
<td>964</td>
</tr>
</tbody>
</table>
Sepsis 2.0
Some success...

Surviving Sepsis Campaign: Association Between Performance Metrics and Outcomes in a 7.5-Year Study

Confusing epidemiology


~16.5% / year
Finding Pure and Simple Truths With Administrative Data

Mary S. Vaughan Sarrazin, PhD
Gary E. Rosenthal, MD

The pure and simple truth is rarely pure and never simple. —Oscar Wilde

JAMA. 2012;307(13):1433-35

EUA - Reimbursement per diagnosis

Pneumonia: [0.73-1.43]
Sepsis: [1.15-5.83]
Confusing epidemiology

Comparison of Trends in Sepsis Incidence and Coding Using Administrative Claims Versus Objective Clinical Data
Confusing epidemiology

**Mortality Related to Severe Sepsis and Septic Shock Among Critically Ill Patients in Australia and New Zealand, 2000-2012**

Kaukonen KM et al. JAMA 2014;311(13):1308-16

- Jan 2000 - Dec 2012
- 1037115 pts admitted to 171 ICUs
- 9.7% - severe sepsis / septic shock

![Bar graph showing the proportion of admissions due to severe sepsis or septic shock from 2000 to 2012. The graph shows a significant increase from 2000 to 2012 with an odds ratio (OR) of 1.54 [1.47-1.61].]
Confusing epidemiology

sepsis
SEPSIS n.0?

~600 BC

Hugo Schottmüller [1867-1936]

"Sepsis is present if a focus has developed from which pathogenic bacteria, constantly or periodically, invade the blood stream in such a way that this causes subjective and objective symptoms ... therapy should not be directed against bacteria in the blood but against the released bacterial toxins (...)"

Mortality due to puerperal sepsis reduced from ~18% to <3% after introduction of hand hygiene procedures

Ignaz Semmelweiss [1818-1865]
Sepsis syndrome: A valid clinical entity.

Bone RC et al. Chest 1992;101;1644-55

2001 SCCM/ESICM/ACCP/ATS/SIS
International Sepsis Definitions Conference
Incidence and Prognostic Value of the Systemic Inflammatory Response Syndrome and Organ Dysfunctions in Ward Patients

Churpek MM et al. Am J Respir Crit Care Med 2015;192(8):958-64
The issue(s) with sepsis 2.0

The Association of Sepsis Syndrome and Organ Dysfunction With Mortality in Emergency Department Patients With Suspected Infection

SEPSIS had no prognostic relevance

Systemic Inflammatory Response Syndrome Criteria in Defining Severe Sepsis


109,663 patients with infection and acute OF

96,385 “SIRS +”

13,278 “SIRS -”

~12.1% of patients had no “sepsis”
The issue(s) with sepsis 2.0

Systemic Inflammatory Response Syndrome Criteria in Defining Severe Sepsis


<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients</th>
<th>Patients with SIRS-Positive Sepsis</th>
<th>Patients with SIRS-Negative Sepsis</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of patients with data</td>
<td>no. of patients with data</td>
<td>no. of patients with data</td>
<td></td>
</tr>
<tr>
<td>Age — yr</td>
<td>109,663</td>
<td>96,385</td>
<td>13,278</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>66.0</td>
<td>65.8</td>
<td>68.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>52.2–76.6</td>
<td>51.9–76.4</td>
<td>55.5–77.7</td>
<td></td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>109,663</td>
<td>60,484 (55.2)</td>
<td>52,932 (54.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>7552 (56.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical admission — no. (%)</td>
<td>109,663</td>
<td>23,630 (21.5)</td>
<td>18,441 (19.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>5189 (39.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APACHE III score†</td>
<td>105,674</td>
<td>71.7±30.1</td>
<td>73.7±30.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>12,208</td>
<td></td>
<td>56.7±26.1</td>
<td></td>
</tr>
<tr>
<td>Hospital outcome — no. (%)</td>
<td>109,663</td>
<td>96,385</td>
<td>13,278</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>25,713 (23.4)</td>
<td>23,577 (24.5)</td>
<td>2136 (16.1)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>60,292 (55.0)</td>
<td>52,000 (54.0)</td>
<td>8292 (62.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Discharge</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home</td>
<td>7,781 (7.1)</td>
<td>6,837 (7.1)</td>
<td>944 (7.1)</td>
<td>0.95</td>
</tr>
</tbody>
</table>
What is sepsis?
“New Sepsis” = suspected infection + \( \Delta \text{SOFA} > 1 \)

- Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.
- Organ dysfunction can be identified as an acute change in total.
Screening

Box 4. qSOFA (Quick SOFA) Criteria

- Respiratory rate $\geq 22$/min
- Altered mentation
- Systolic blood pressure $\leq 100$ mm Hg

Assess OF (ie - SOFA)

q-SOFA $> 1$

Search for occult infection
Advantages of Sepsis 3.0

- Data-driven > superior discriminative capacity when compared with SIRS
- Parsimonious (qSOFA) model derived from 21 available variables
- Focus attention more on OF than inflammation
- May turn out to be clearer
- Standardised assessment of organ failure (SOFA)
Advantages of Sepsis 3.0

Prognostic Accuracy of Sepsis-3 Criteria for In-Hospital Mortality Among Patients With Suspected Infection Presenting to the Emergency Department

Freund Y et al. JAMA. 2017;317(3):301-8

- International, prospective cohort
- 30 EDs; [May-June, 2016]
- All consecutive patients with suspected infection in the ED

1888 Patients admitted to emergency department with infection were assessed for eligibility

209 Excluded
149 Missing qSOFA score values
60 No infection

879 Patients included

661 qSOFA score <2
218 qSOFA score ≥2

22 In-hospital death
639 Alive and out of hospital
52 In-hospital death
166 Alive and out of hospital
Advantages of Sepsis 3.0

Receiver Operating Characteristic Curves for In-Hospital Mortality

<table>
<thead>
<tr>
<th></th>
<th>AUROC</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>qSOFA</td>
<td>0.8</td>
<td>[0.74-0.85]</td>
</tr>
<tr>
<td>SOFA</td>
<td>0.77</td>
<td>[0.71-0.82]</td>
</tr>
<tr>
<td>SIRS</td>
<td>0.65</td>
<td>[0.59-0.7]</td>
</tr>
<tr>
<td>Sev. sepsis</td>
<td>0.65</td>
<td>[0.59-0.7]</td>
</tr>
</tbody>
</table>

Freund Y et al. JAMA. 2017;317(3):301-8
Advantages of Sepsis 3.0

Use of CRB-65 and quick Sepsis-related Organ Failure Assessment to predict site of care and mortality in pneumonia patients in the emergency department: a retrospective study
Chen YX et al. Critical Care 2016
DOI 10.1186/s13054-016-1351-0

Conclusions: qSOFA is better than CRB-65 for identification of a high risk of mortality and requirement of ICU admission.
Advantages of Sepsis 3.0

- ~1000 beds
- ED and Intensive Medicine in the same department
- ~150 000 adult ED visits/year
Advantages of Sepsis 3.0

- Consecutive patients with activation of the iSFT and a concurrent diagnosis of malignant neoplasia (MN - ICD9 codes 140-239), who were admitted to the hospital
- Patients with MN, admitted for infection, *without* activation of the iSFT

1889 iSFT pts

- n=161
- 173 pts with active MN, included in the iSFT
- 97 pts admitted
### Advantages of Sepsis 3.0

#### SIRS vs qSOFA

<table>
<thead>
<tr>
<th>Risk Assessment</th>
<th>n</th>
<th>Mortality OR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIRS ≥2</td>
<td>217</td>
<td>1.261</td>
<td>0.552</td>
</tr>
<tr>
<td>qSOFA ≥2</td>
<td>70</td>
<td>2.29 [1.05-4.99]</td>
<td>0.037</td>
</tr>
</tbody>
</table>
Pitfalls

- qSOFA criteria appear to be a quick and effective tool to assess disease severity

**Box 4. qSOFA (Quick SOFA) Criteria**

- Respiratory rate $\geq 22$/min
- Altered mentation
- Systolic blood pressure $\leq 100$ mm Hg
Do textbooks of clinical examination contain information regarding the assessment of critically ill patients?

Caroline J. Cook\textsuperscript{a}, Gary B. Smith\textsuperscript{b,*}

Resuscitation 2004;60:129-36

Table 3
Numbers (%) of books containing information about clinical signs and measured parameters, important in the understanding, detection and investigation of critical illness

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>%</th>
<th>No</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breathing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the book mention the important role of RR in critical illness?</td>
<td>6</td>
<td>20</td>
<td>24</td>
<td>80</td>
</tr>
<tr>
<td>Does the book describe respiratory rate assessment?</td>
<td>16</td>
<td>53</td>
<td>14</td>
<td>46</td>
</tr>
<tr>
<td>Does the book quote a normal range for respiratory rate?</td>
<td>17</td>
<td>57</td>
<td>13</td>
<td>43</td>
</tr>
<tr>
<td>Does the book describe patterns of breathing, e.g. Cheyne stokes, periodic breathing?</td>
<td>20</td>
<td>66</td>
<td>10</td>
<td>33</td>
</tr>
<tr>
<td>Does the book describe how to assess the depth of breathing?</td>
<td>14</td>
<td>53</td>
<td>16</td>
<td>46</td>
</tr>
</tbody>
</table>

... One book discounted the usefulness of the respiratory rate with the following words: “... counting the respiratory rate is a traditional nursing observation, yet the precise rate is rarely of practical importance ...”
Patients admitted to the IMD from the ED during 2014

Proportion of pts missing RR records according to presence or absence of infection

- Infection: 31.84%
- No infection: 22.81%

P = 0.03
Some confusion is expected...

**COMMENTARY**

qSOFA does not replace SIRS in the definition of sepsis

Jean-Louis Vincent\(^1\)*, Greg S. Martin\(^2\) and Mitchell M. Levy
Pitfalls
“...A change in definition and diagnostic criteria could set back decades of work persuading providers at all levels to recognize sepsis early and to intervene aggressively....”
Decision Timing

qSOFA, SIRS, and early warning scores for detecting clinical deterioration in infected patients outside the ICU

Churpek MM et al. AJRCCM 2016; DOI: 10.1164/rccm.201604-0854OC

Cumulative percentage of patients meeting criteria prior to death or ICU admission
Decision Timing

qSOFA, SIRS, and early warning scores for detecting clinical deterioration in infected patients outside the ICU

Churpek MM et al. AJRCCM 2016; DOI: 10.1164/rccm.201604-0854OC

Time until >50% of patients meet criteria:
- qSOFA ≥2: 5 hrs
- NEWS ≥7: 17 hrs
- SIRS ≥2: 17 hrs
- SIRS ≥7: 12 hrs
- SIRS ≥5: 5 hrs
# SOFA Score

## 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>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( P_{aO_2}/F_{iO_2} ) (mm Hg (kPa))</td>
<td></td>
<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>
</tr>
<tr>
<td><strong>Coagulation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets, ( \times 10^3/\mu L )</td>
<td>≥150</td>
<td>&lt;150</td>
<td>&lt;100</td>
<td>&lt;50</td>
<td>&lt;20</td>
<td></td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin, mg/dL (( \mu mol/L ))</td>
<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>&gt;12.0 (204)</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP ( \geq 70 ) mm Hg</td>
<td></td>
<td>MAP &lt;70 mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Central nervous system</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glasgow Coma Scale score</td>
<td>15</td>
<td>13-14</td>
<td>10-12</td>
<td>6-9</td>
<td>&lt;6</td>
<td></td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine, mg/dL (( \mu mol/L ))</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)</td>
<td>&gt;5.0 (440)</td>
<td></td>
</tr>
<tr>
<td>Urine output, mL/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Scored items that are not normal include pH, lactate, glucose, mean arterial pressure, and 
organ-specific scores. Scored items that are not normal include pH, lactate, glucose, mean arterial pressure, and organ-specific scores.
Identification of infection
Identification of infection

qSOFA does not really address the key issue!
Identification of infection

Biomarkers

Interleukins

Procalcitonin

Methylglyoxal

Δ neutrophil

Real-time PCR

CR protein

Hgb sub-unit β

CD 64
Identification of infection

To whom should we order these tests???
“Try as hard as we may for perfection, the net result of our labors is an amazing variety of imperfectness...”

Samuel Crothers
The pursuit of perfection
Conclusion

- The new sepsis definitions have renewed the discussion about early identification.
- The qSOFA tool is a quick and effective way to select patients requiring more detailed assessment.
- …but has it’s limits!
- Attention should be drawn to recognised problem areas.
- Maybe SIRS retains some use?
Odds Ratio for Mortality - 0.49 over a 12 year period
Mar. 2019 - 24th Infection & Sepsis Symposium

OBRIGADO!

gis@gis.pt; www.gis.pt