Prehospital recognition of sepsis

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• Consulting fees from Beckman Coulter, Edwards Inc.

• Member, Surviving Sepsis Campaign, ATS representative

• Member, 2016 Third International Sepsis Definitions Task Force
Caveats

• I am not an EMS clinician

• Involved in prehospital sepsis trial (CIHR, PI: Scales, PITSTOP) planning to enroll in 2018

• Intensivist at UPMC-Mercy in Pittsburgh, PA
Can an otherwise healthy 58-year-old man die from a bad cold? He can, and he did. Through an unfortunate cascade of events, starting with a missed diagnosis of viral pneumonia, Tom Wilson, a systems analyst for Westinghouse, went from bad to worse until every major organ system -- kidneys, liver, lungs and finally his heart -- stopped working.

After 10 days in intensive care during which doctors struggled in vain to get ahead of the rampaging disorder, Mr. Wilson died. Cause of death: **septic shock**.
What happened?

- Delay in diagnosis
- Case characterized by the class of organism and primary organ involved
- Treatment without practice guidelines?

For the next Mr. Wilson, how can we:
- Find his septic shock sooner
- Deliver aggressive treatment without harm
- Deliver care that’s right for him, not necessarily for everyone
Objectives

- What is sepsis?
- Why is defining sepsis difficult?
- What is the new definition and criteria for sepsis?
- Can we identify sepsis during prehospital care?
- Are new tools coming down the pipeline?
Sepsis is everywhere.

2 million US cases each year

5 percent of US healthcare spending

Singer et al., JAMA, 2016
### Kaiser Permanente Northern California (2010-2012) (n = 21 Hospitals) (14 206 Deaths/482 828 Admissions)

<table>
<thead>
<tr>
<th></th>
<th>Explicit</th>
<th>Explicit POA&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Implicit</th>
<th>Implicit POA&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalizations</td>
<td>55 008 (11.4) [11.3-11.5]</td>
<td>50 520 (10.5) [10.4-10.5]</td>
<td>80 678 (16.7) [16.6-16.8]</td>
<td>73 933 (15.3) [15.2-15.4]</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>6272 (11.4) [11.1-11.7]</td>
<td>5238 (10.4) [10.1-10.6]</td>
<td>7941 (9.8) [9.6-10.0]</td>
<td>7391 (10.0) [9.8-10.2]</td>
</tr>
<tr>
<td>% (95% CI) of all hospital deaths among patients with sepsis</td>
<td>44.2 (43.3-45.0)</td>
<td>36.9 (36.1-37.7)</td>
<td>55.9 (55.1-56.7)</td>
<td>52.0 (51.2-52.8)</td>
</tr>
</tbody>
</table>

1 out of every 2 to 3 hospital deaths
We don’t talk about it.

Seymour et al., Am J Resp Crit Care Med, 2014
Why is defining sepsis difficult?
Why is defining sepsis difficult? (2)

“He has a big beak and little webbed feet like Duck. He has a tail and fur coat like Beaver. And he is very shy, like Squirrel. And he came out of that roly-poly egg!“
Why is defining sepsis difficult? (3)

Birds

Platypus

Mammals

“Zone of rarity”
Why is defining sepsis difficult? (4)

“Zone of rarity”
Why is defining sepsis difficult? (5)
Why is defining sepsis difficult? (6)
Why is recognizing sepsis difficult?

- Sepsis is incredibly common
- We don’t agree on the terms / words
- Vague signs and symptoms lead to small “zone of rarity”
- Important to make the diagnosis rapidly
- Definitions and criteria are changing
There is a new definition of sepsis

- Goal: to re-examine existing criteria for sepsis and septic shock
  - Does current pathophysiology, epidemiology mandate an update?
- Use expert consensus to develop a definition
- Use data to develop clinical criteria
- Focus is on the bedside clinician
What were we using “before”?

- Variety of terms
  - Septicaemia, septic, severe sepsis, septic shock, sepsis

- 2 or more SIRS criteria to identify sepsis among those with suspected infection

- Organ dysfunction is key, but uncertain how to measure

- Multiple criteria for septic shock

Shankar-Hari et al., JAMA, 2016
Infection
Organ dysfunction
Life threatening
Dysregulated host response

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

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.
We have a definition for sepsis.

Criteria for the bedside
Infection Defined

• Criteria for Infection?
• Clinical diagnosis
• Not the prevue of the Task Force

• Criteria for organ dysfunction?

Seymour et al., JAMA, 2016
What criteria for organ dysfunction?

Table 1 Diagnostic criteria for sepsis

<table>
<thead>
<tr>
<th>Infection$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Documented or suspected and some of the following$^b$:</td>
</tr>
<tr>
<td>General parameters</td>
</tr>
<tr>
<td>Fever (core temperature &gt;38.3°C)</td>
</tr>
<tr>
<td>Hypothermia (core temperature &lt;36°C)</td>
</tr>
<tr>
<td>Heart rate &gt;90 bpm or &gt;2 SD above the normal value for age</td>
</tr>
<tr>
<td>Tachypnea: &gt;30 bpm</td>
</tr>
<tr>
<td>Altered mental status</td>
</tr>
<tr>
<td>Significant edema or positive fluid balance (&gt;20 ml/kg over 24 h)</td>
</tr>
<tr>
<td>Hyperglycemia (plasma glucose &gt;110 mg/dl or 7.7 mM/l) in the absence of diabetes</td>
</tr>
<tr>
<td>Inflammatory parameters</td>
</tr>
<tr>
<td>Leukocytosis (white blood cell count &gt;12,000/µl)</td>
</tr>
<tr>
<td>Leukopenia (white blood cell count &lt;4,000/µl)</td>
</tr>
<tr>
<td>Normal white blood cell count with &gt;10% immature forms</td>
</tr>
<tr>
<td>Plasma C reactive protein &gt;2 SD above the normal value</td>
</tr>
<tr>
<td>Plasma procalcitonin &gt;2 SD above the normal value</td>
</tr>
<tr>
<td>Hemodynamic parameters</td>
</tr>
<tr>
<td>Arterial hypotension$^b$ (systolic blood pressure &lt;90 mmHg, mean arterial pressure &lt;70, or a systolic blood pressure decrease &gt;40 mmHg in adults or &lt;2 SD below normal for age)</td>
</tr>
<tr>
<td>Mixed venous oxygen saturation &gt;70%$^b$</td>
</tr>
<tr>
<td>Cardiac index &gt;3.5 l/min·m$^{-2}$</td>
</tr>
<tr>
<td>Organ dysfunction parameters</td>
</tr>
<tr>
<td>Acute oliguria (urine output &lt;0.5 ml kg$^{-1}$ hr$^{-1}$ or 45 ml/min for at least 2 h)</td>
</tr>
<tr>
<td>Creatinine increase ≥0.5 mg/dl</td>
</tr>
<tr>
<td>Coagulation abnormalities (international normalized ratio &gt;1.5 or activated partial thromboplastin time &gt;60 s)</td>
</tr>
<tr>
<td>Ileus (absent bowel sounds)</td>
</tr>
<tr>
<td>Thrombocytopenia (platelet count &lt;100,000/µl)</td>
</tr>
<tr>
<td>Hyperbilirubinemia (plasma total bilirubin &gt;4 mg/dl or 70 mmol/l)</td>
</tr>
<tr>
<td>Tissue perfusion parameters</td>
</tr>
<tr>
<td>Hyperlactatemia (&gt;3 mmol/l)</td>
</tr>
<tr>
<td>Decreased capillary refill or mottling</td>
</tr>
</tbody>
</table>

$^a$ Defined as a pathological process induced by a micro-organism
$^b$ Values above 70% are normal in children (normally 75–80%) and should therefore not be used as a sign of sepsis in newborns or children
$^c$ Values of 3.5–5.5 are normal in children and should therefore not be used as a sign of sepsis in newborns or children
$^d$ Diagnostic criteria for sepsis in the pediatric population is signs and symptoms of inflammation plus infection with hyper- or hypothermia (rectal temperature >38.5°C or <35°C), tachycardia (may be absent in hypothermic patients) and at least one of the following indications of altered organ function: altered mental status, hypoxemia, elevated serum lactate level, and bounding pulses

Levy et al., Crit Care Med, 2003
## Criteria to evaluate

<table>
<thead>
<tr>
<th>Systemic Inflammatory Response Syndrome (SIRS) Criteria (Range, 0-4 Criteria)</th>
<th>Sequential [Sepsis-related] Organ Failure Assessment (SOFA) (Range, 0-24 Points)</th>
<th>Logistic Organ Dysfunction System (LODS) $^a$ (Range, 0-22 Points)</th>
<th>Quick Sequential [Sepsis-related] Organ Failure Assessment (qSOFA) (Range, 0-3 Points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory rate, breaths per minute</td>
<td>$\text{PaO}_2/\text{FiO}_2$ ratio</td>
<td>$\text{PaO}_2/\text{FiO}_2$ ratio</td>
<td>Respiratory rate, breaths per minute</td>
</tr>
<tr>
<td>White blood cell count, $10^9/L$</td>
<td>Glasgow Coma Scale score</td>
<td>Glasgow Coma Scale score</td>
<td>Glasgow Coma Scale score</td>
</tr>
<tr>
<td>Bands, %</td>
<td>Mean arterial pressure, mm Hg</td>
<td>Systolic blood pressure, mm Hg</td>
<td>Systolic blood pressure, mm Hg</td>
</tr>
<tr>
<td>Heart rate, beats per minute</td>
<td>Administration of vasopressors with type/dose/rate of infusion</td>
<td>Heart rate, beats per minute</td>
<td></td>
</tr>
<tr>
<td>Temperature, $^\circ\text{C}$</td>
<td>Serum creatinine, mg/dL, or urine output, mL/d</td>
<td>Serum creatinine, mg/dL</td>
<td></td>
</tr>
<tr>
<td>Arterial carbon dioxide tension, mm Hg</td>
<td>Bilirubin, mg/dL</td>
<td>Bilirubin, mg/dL</td>
<td></td>
</tr>
<tr>
<td>Platelet count, $10^9/L$</td>
<td>Platelet count, $10^9/L$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood cell count, $10^9/L$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine output, L/d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum urea, mmol/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prothrombin time, % of standard</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>
quick Sepsis - Related Organ Failure Assessment
qSOFA is a clinical prompt

- 3 variables
- Measured when infection is suspected
- No laboratory tests
- Studied in 72 → 6 hr windows around infection
Why is qSOFA useful?

While only 1 IN 4 infected patients have 2+ qSOFA POINTS, they account for 3 OUT OF 4 deaths.
Does lactate add to qSOFA?
Clinical criteria for sepsis

- Infection plus 2 or more SOFA points above baseline

Prompt to consider sepsis outside the ICU

- Infection plus 2 or more qSOFA points
What’s great about Sepsis-3?

• Speak the same language

• Redundant terms like “severe sepsis” are removed

• Objective criteria for organ dysfunction recommended

• Data driven
But could this lead to some confusion?

• Other criteria are available
  • CMS, CDC, inclusion into large randomized trials

• How would we identify suspected infection?
  • No check boxes proposed by Task Force
More importantly, what does this mean for EMS?
How often do EMS transport sepsis?
Among all sepsis cases

- Community sepsis
- Community sepsis AND transport by EMS
How much time with EMS?

Median medical contact delay
4.2 hrs [IQR: 2.8, 8.1 hrs]
But is EMS aware of sepsis?

![Bar chart showing proportion heard of sepsis among United States general public, Paramedics, and EMTs.](image-url)
But is EMS aware of sepsis? Cont’d

<table>
<thead>
<tr>
<th>Proportion (%)</th>
<th>Paramedics</th>
<th>FF-EMTs</th>
<th>EMTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identify correct definition</td>
<td>80%</td>
<td>60%</td>
<td>50%</td>
</tr>
<tr>
<td>Diagnosis missed some or a lot of the time</td>
<td>80%</td>
<td>70%</td>
<td>60%</td>
</tr>
</tbody>
</table>

Seymour et al., 2012, J Emerg Med
Finding sepsis in prehospital care

Simple, cheap, fast
Augment clinical suspicion for infection
Consistent with guidelines
Embrace uncertainty

Prehospital recognition of severe sepsis: development and validation of a novel EMS screening tool

Carmen C. Polito, MD, MSE, Alex Isakov, MD, MPH, Arthur H. Yancey II, MD, MPH, Duncan K. Wilson, MD, Blake A. Anderson, MD, Ingrid Bloom, MD, Greg S. Martin, MD, MS, Jonathan E. Sevransky, MD, MS

An Early Warning Scoring System to Identify Septic Patients in the Prehospital Setting: The PRESEP Score.


© Author information
Finding sepsis in prehospital care, Cont’d

Organ dysfunction
qSOFA, PreSEP
Shock index, SOFA

Infection
Fever
Clinical acumen

No organ dysfunction

No infection
Could qSOFA work on the ambulance?

- Cheap
- Easy to remember
- But doesn’t get at infection
- May not find all patients, but those at higher risk
- \( \geq 2 \) points = 24% mortality
qSOFA was tested in EMS data

More than 3 million encounters, 5 cohorts
>10,000 EMS transport in King County, 30 agencies, 14 hospitals
Could serum lactate help?
What about serum lactate?

**PRO**

- Relatively cheap
- Associated with organ dysfunction
- Well validated in the ED and hospital

**CON**

- Hard to find
- Not specific for infection
- Conflicting data
What about serum lactate?

<table>
<thead>
<tr>
<th>Study</th>
<th>Single biomarker?</th>
<th>Patients</th>
<th>Biomarker</th>
<th>Sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shah et al.</td>
<td>Yes</td>
<td>Pediatric HEMS</td>
<td>Lactate</td>
<td>41</td>
</tr>
<tr>
<td>Guyette et al.</td>
<td>Yes</td>
<td>Adult trauma</td>
<td>Lactate</td>
<td>317</td>
</tr>
<tr>
<td>Mullen et al.</td>
<td>Yes</td>
<td>Adult HEMS</td>
<td>Lactate</td>
<td>20</td>
</tr>
<tr>
<td>Guyette et al.</td>
<td>Yes</td>
<td>Adult HEMS Trauma</td>
<td>Lactate</td>
<td>1,168</td>
</tr>
<tr>
<td>Van Beest et al.</td>
<td>Yes</td>
<td>Ground EMS</td>
<td>Lactate</td>
<td>135</td>
</tr>
<tr>
<td>Tobias et al.</td>
<td>Yes</td>
<td>Ground EMS</td>
<td>Lactate</td>
<td>673</td>
</tr>
</tbody>
</table>
What about serum lactate?
• Prospective cohort study of prehospital biomarkers
• N=432 patients, >20,000 samples
• 2013-2014, 2 hospitals, Pittsburgh City EMS
• Cytokines, lactate, procalcitonin, troponin, robust clinical data

Figure 1. Cytokines are already abnormal during prehospital care
New tests coming?

Certain biomarkers may help with infection (yes/no) but platforms not ready for prime time.
So what is next?

- Not all sepsis is the same
- There may be phenotypes or groups of septic patients that deserve greater attention
Finding sepsis

• Sepsis is an enormous public health problem

• New sepsis definitions released in 2016

• Clinical suspicion for infection remains a challenge

• New tools such as qSOFA may be prompts but are not adequately sensitive

• New and old biomarkers — good for research — not yet ready for prime time
Questions