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.
Objectives

- Why is defining sepsis important?
- Why is defining sepsis difficult?
- Conceptual approach by the 2016 Sepsis Definitions Task Force
- Review of Sepsis-3
- Controversies post-release

Sepsis is everywhere.

2

5

million US cases each year

percent of US healthcare spending

Gawinski et al., Crit Care Med. 2014
Singer et al., JAMA. 2016

1 out of every 2 to 3 hospital deaths

Liu et al., JAMA. 2014
We don’t talk about it.

Stroke
Heart attack
Sepsis

Why is defining sepsis difficult?

- Sepsis is common
- We don’t agree on the terms
- Surface phenomena lead to small zone of rarity with lots of patients
- Time-sensitive diagnosis
- Knowledge is rapidly evolving
2016 Sepsis Definitions Task Force

- 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

Current state prior to Sepsis-3

- 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

- Infection
- Organ dysfunction
- Life threatening
- Dysregulated host response
We have a definition for sepsis.

Criteria for the bedside

- Criteria for Infection?
- Clinical diagnosis
- Not the province of the Task Force
- Criteria for organ dysfunction?

Developing sepsis criteria

- Use large electronic health record databases
- Identify those with suspected infection
- Study various existing OD criteria
  - SOFA score
  - LODS score
  - SIRS criteria

Seymour et al., JAMA, 2016

•

Levy et al., Crit Care Med, 2003

•
Use of predictive validity

- No gold standard for sepsis
- We can’t rely on tests like sensitivity, specificity etc
- Use outcome more common in septic patients than healthy patients

Candidate clinical criteria

Primary cohort
Patient characteristics

- CRISMA conducted primary analyses on UPMC data
- 2010 – 2012
- Suspected infection patients
- 12 hospitals
- 4% mortality rate
What do we already know at the bedside

- We built a baseline risk model using only age, demographics, race, co-morbidity
- Divide patients into deciles

- Compare validity within and across deciles

Predictive validity of criteria

Predictive validity of criteria
But SOFA is complex

- Sepsis criteria should be easy
- SOFA is complex, requires 12 variables, costly, range from 0 to 24 points
- Laboratory tests take time to result
- We need more simple parsimonious criteria for the bedside

qSOFA as a clinical prompt

- 3 variables
- Measured near onset of infection
- No laboratory tests
- Studied in 72 → 6 hr windows around infection

Quick Sepsis-Related Organ Failure Assessment
qSOFA as a clinical prompt

SOFA and LODS superior in the ICU

qSOFA similar to complex scores outside the ICU

Why is qSOFA useful?

While only 1 IN 4 infected patients have 2+ qSOFA points, they account for 3 OUT OF 4 deaths.

qSOFA in external datasets

<table>
<thead>
<tr>
<th>Data set and infection type</th>
<th>No. of patients with infection type</th>
<th>AUROC (95% CI)</th>
<th>qSOFA (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIRS hospital-acquired infections</td>
<td>1186</td>
<td>0.51 (0.51-0.60)</td>
<td>0.71 (0.68-0.74)</td>
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**Serum lactate as an adjunct**

![Graph showing serum lactate levels and in-hospital mortality.]

**Post hoc analyses**
- Addressed missing data
- Measurement windows for qSOFA and SOFA
  - 24 hrs after infection
  - 6 hr window around infection
- Agreement of SOFA and qSOFA exceeded 70%
- Delta of 2 SOFA points same predictive validity

**Conclusions**
- In the ICU, the SOFA and LODS have greater predictive validity than qSOFA or SIRS
- Outside the ICU, the qSOFA has similar predictive validity to more complex scores
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

Controversies

- Where did “severe sepsis” go?
  - Billing implications

- Was SIRS just left for dead?
  - Delays in treatment if infection not suspected

- Why isn’t lactate in the criteria?
  - Lacks face validity to not include

- Prospective evaluation?
  - No association of new definitions with better outcomes

Controversies

- Change in SOFA – from what baseline value?
  - Practical implementation is challenging

- Measure altered mentation?
  - Multiple different scales available

- What to do if intermediate risk?
  - qSOFA = 1

- Isn’t the AUROC a bad measure of clinical usefulness?
Why Sepsis-3 provides clarity

- Speak the same language
- Redundant terms like severe sepsis are removed
- Objective criteria for organ dysfunction recommended
- Data driven

Why Sepsis-3 may lead to confusion

- Other criteria are available
  - CMS, CDC surveillance criteria, RCT inclusion criteria
- Unclear how to choose time windows to measure criteria
  - Blessing and curse of EHR data
- Suspected infection is a clinical decision
  - No check boxes proposed by Task Force

My approach outside the ICU

[Image of a decision tree for sepsis diagnosis]
My approach outside the ICU

Pt arrives to ED

This looks like pneumonia!

Frequent re-assessment

Did qSOFA already occur?

Send lactate and SOFA labs

3-6 hr look back

Sepsis

My approach inside the ICU

Frequent re-assessment

Sepsis

Resources

www.jamasepsis.com
www.qSOFA.org
www.crisma.upmc.edu
Questions