Prehospital recognition of sepsis

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CRITICAL CARE MEDICINE

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Disclosures

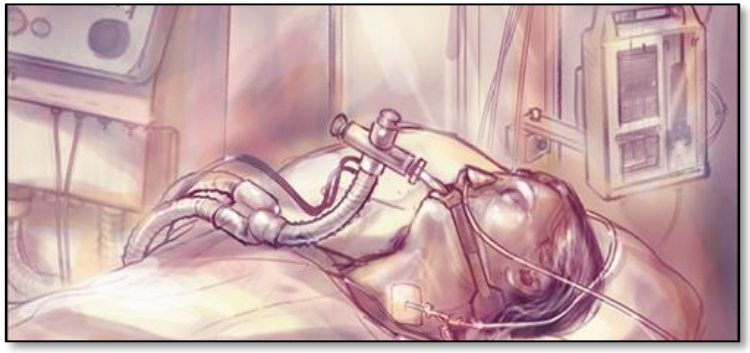
- Received funding from:
  NIH NIGMS, SCCM, AHA, MedicOne, SIS
- Consulting fees from Beckman Coulter, Edwards Inc.
- Member, Surviving Sepsis Campaign, ATS representative
- Member, 2016 Third International Sepsis Definitions Task Force

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

Death from a Cold?

The New York Times



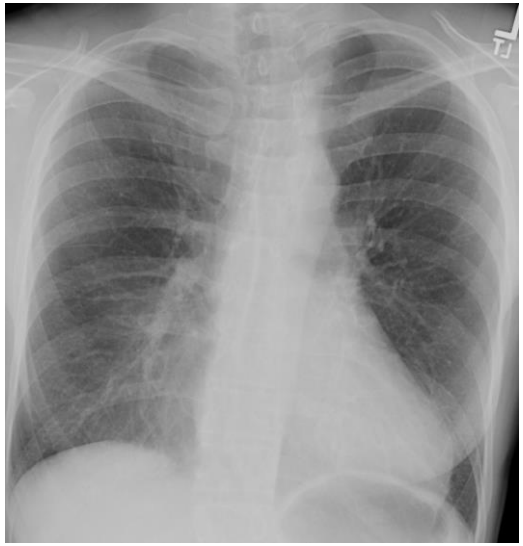
Can an otherwise healthy 58-year-old man die from a bad cold? He can, and he did. Through an unfortunate cascade of events, starting with a missed diagnosis of viral pneumonia, Tom Wilson, a systems analyst for Westinghouse, went from bad to worse until every major organ system -- kidneys, liver, lungs 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**.

New York Times, March 5, 2002

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

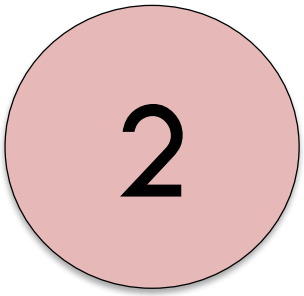
Deliver aggressive treatment without harm

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.



million US cases each year

percent of US healthcare spending

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

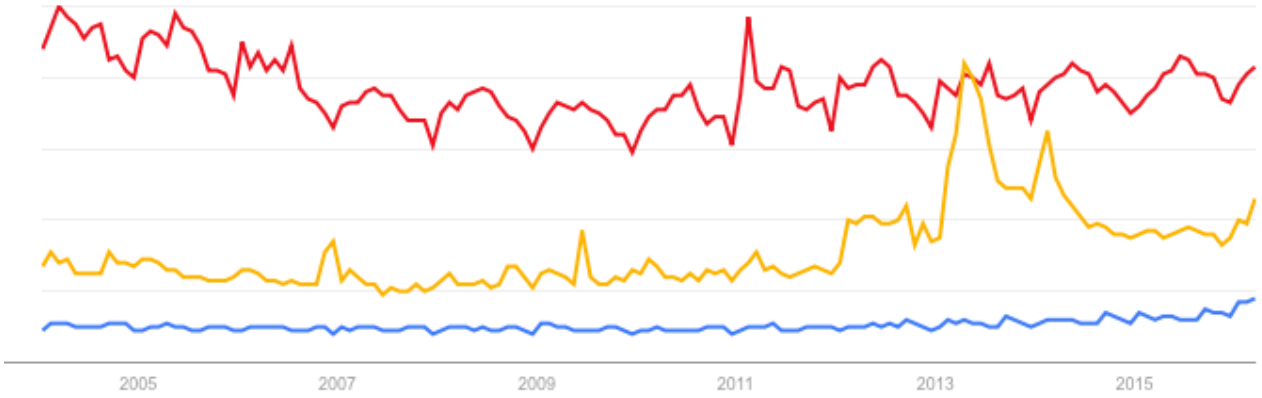
Sepsis is everywhere. (cont'd)

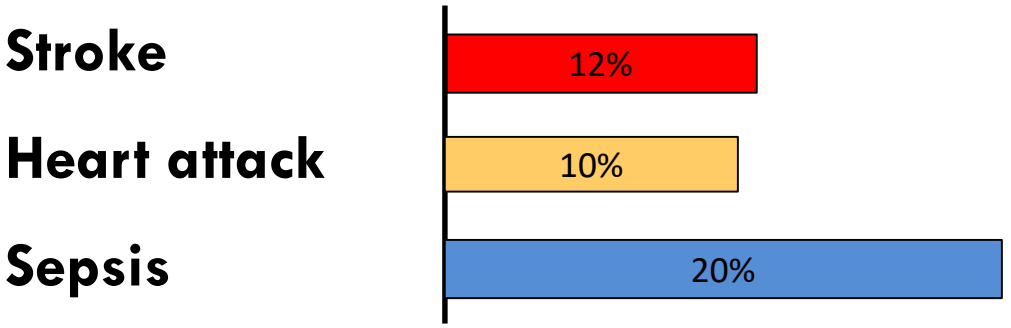
	Kaiser Permanente Northern California (2010-2012) (n = 21 Hospitals) (14 206 Deaths/482 828 Admissions)			
	Explicit	Explicit POA[c]	Implicit	Implicit POA[c]
Hospitalizations	55 008 (11.4) [11.3-11.5]	50 520 (10.5) [10.4-10.5]	80 678 (16.7) [16.6-16.8]	73 933 (15.3) [15.2-15.4]
Hospital mortality	6272 (11.4) [11.1-11.7]	5238 (10.4) [10.1-10.6]	7941 (9.8) [9.6-10.0]	7391 (10.0) [9.8-10.2]
% (95% CI) of all hospital deaths among patients with sepsis	44.2 (43.3-45.0)	36.9 (36.1-37.7)	55.9 (55.1-56.7)	52.0 (51.2-52.8)

1 out of every 2 to 3 hospital deaths

Liu et al., JAMA, 2014

We don’t talk about it.





Seymour et al., Am J Resp Crit Care Med, 2014

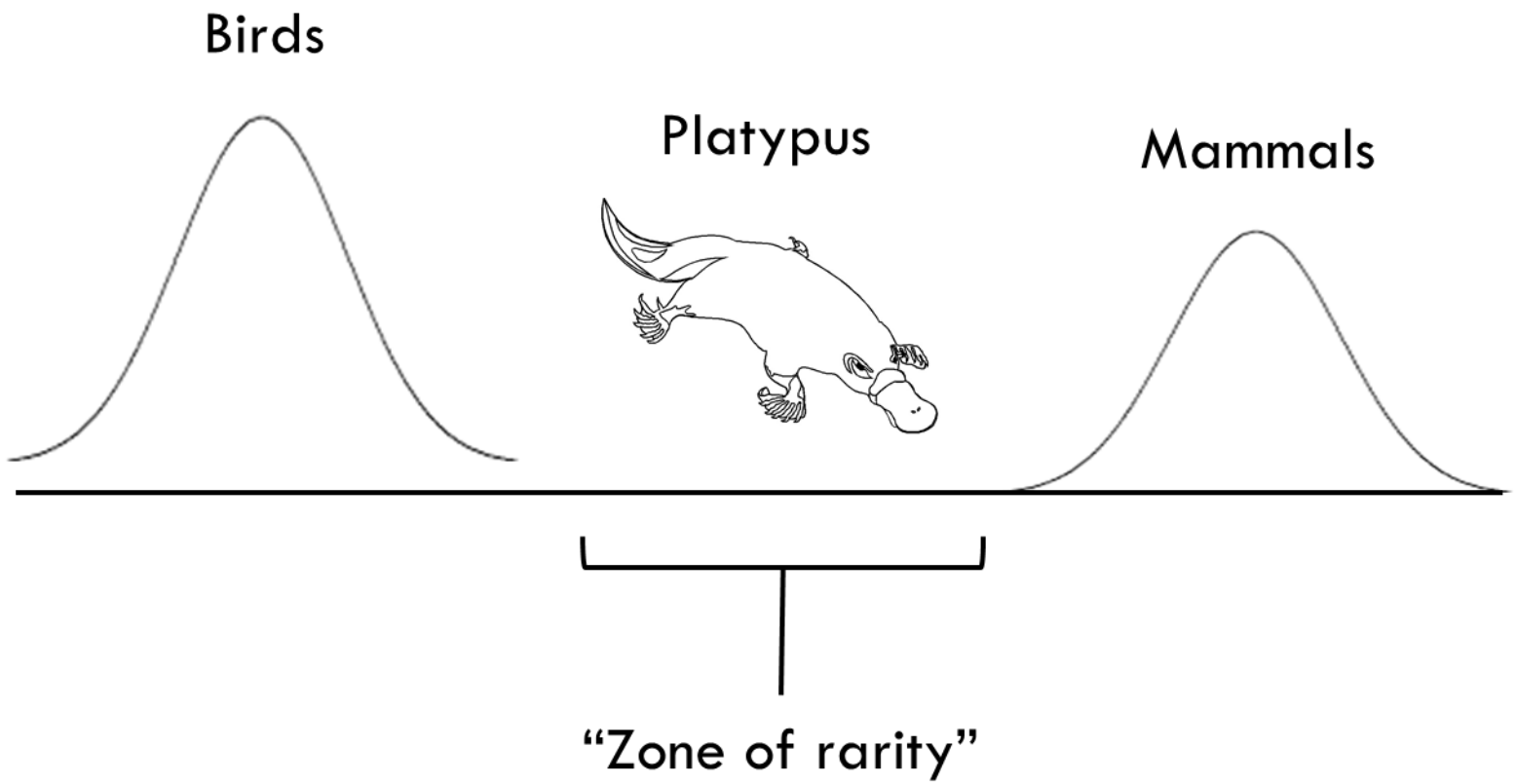
Why is defining sepsis difficult?

www.livescience.com

Why is defining sepsis difficult? (2)

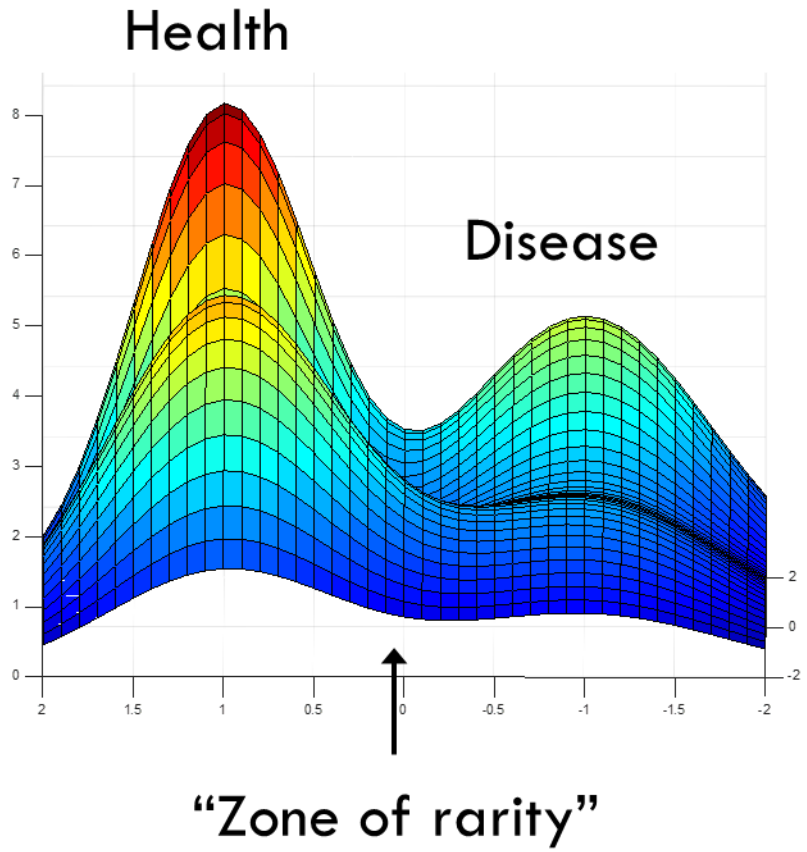
"He has a big beak and little webbed feet like Duck. He has a tail and fur coat like Beaver. And he is very shy, like Squirrel. And he came out of that roly-poly egg! "

Why is defining sepsis difficult? (3)



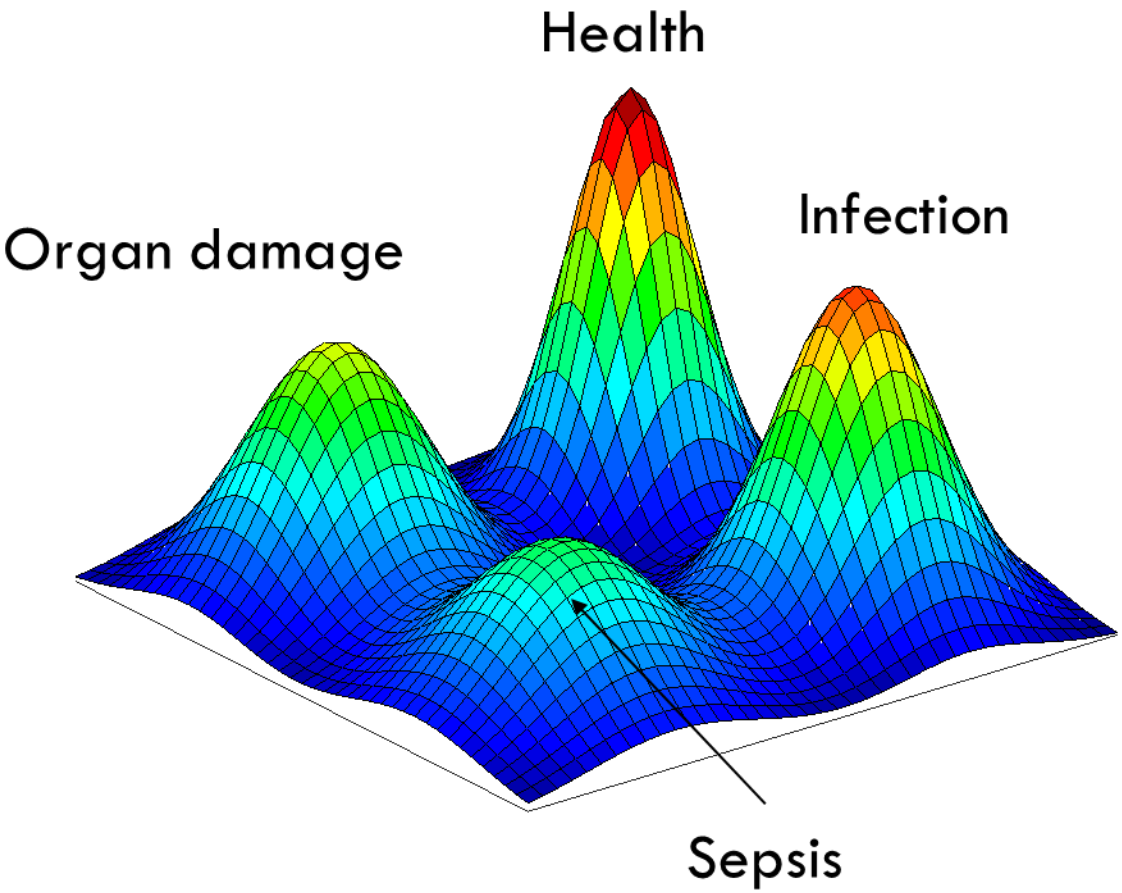
Guy Scadding, 1950s

Why is defining sepsis difficult? (4)



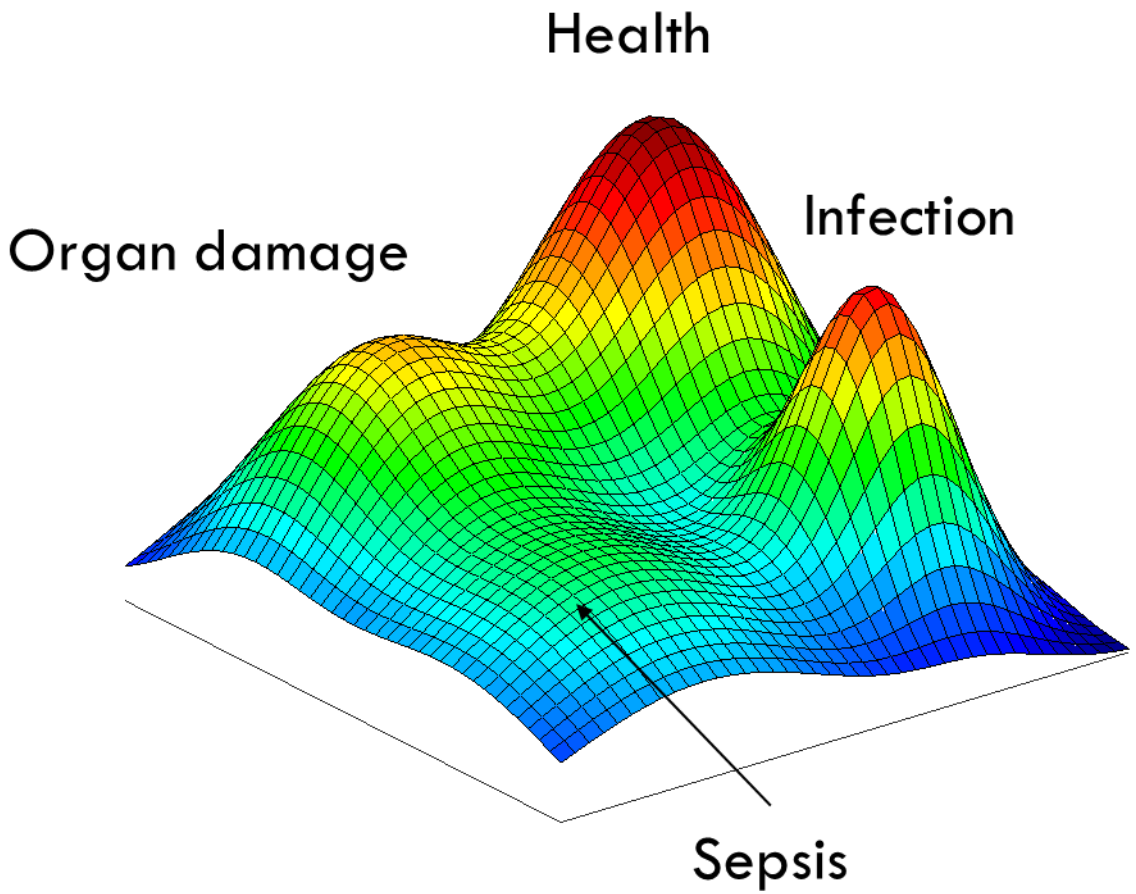
Seymour et al., Crit Care Med, 2016

Why is defining sepsis difficult? (5)



Seymour et al., Crit Care Med, 2016

Why is defining sepsis difficult? (6)



Seymour et al., Crit Care Med, 2016

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

Angus et al., Crit Care Med, 2016

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?

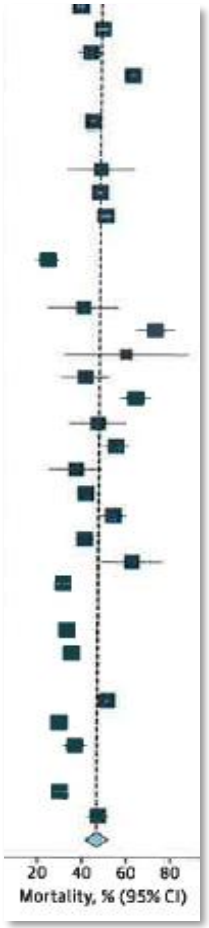
- Use expert consensus to develop a definition
- Use data to develop clinical criteria
- Focus is on the bedside clinician

What were we using “before” ?

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

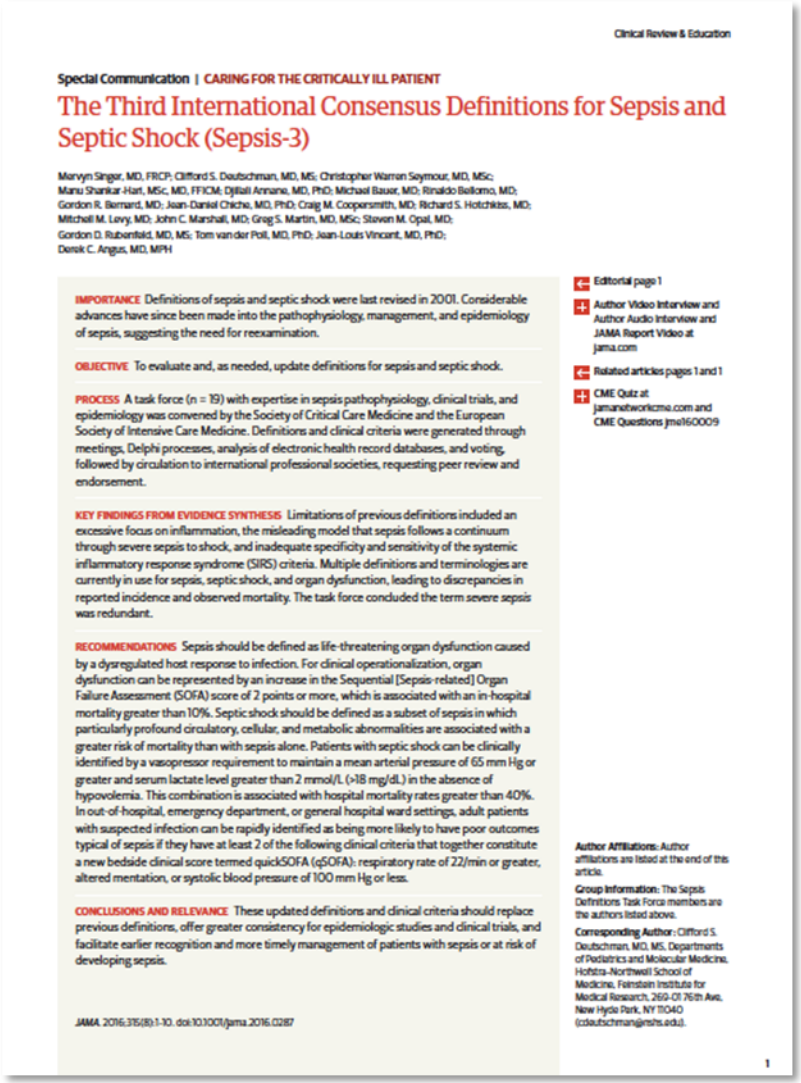
- 2 or more SIRS criteria to identify sepsis among those with suspected infection
- Organ dysfunction is key, but uncertain how to measure

- Multiple criteria for septic shock



Shankar-Hari et al., JAMA, 2016

Sepsis Defined



Clinical Review & Education

Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Christopher Warren Seymour, MD, MSc; Manu Shankar-Hari, MSc, MD, FFICM; Djillali Annane, MD, PhD; Michael Bauer, MD; Rinaldo Bellomo, MD; Gordon R. Bernard, MD; Jean-Daniel Chiche, MD, PhD; Craig M. Coopersmith, MD; Richard S. Hotchkiss, MD; Mitchell M. Levy, MD; John C. Marshall, MD; Greg S. Martin, MD, MSc; Steven M. Opal, MD; Gordon D. Rubenfeld, MD, MS; Tom van der Poll, MD, PhD; Jean-Louis Vincent, MD, PhD; Derek C. Angus, MD, MPH

IMPORTANCE Definitions of sepsis and septic shock were last revised in 2001. Considerable advances have since been made into the pathophysiology, management, and epidemiology of sepsis, suggesting the need for reexamination.

OBJECTIVE To evaluate and, as needed, update definitions for sepsis and septic shock.

PROCESS A task force (n = 19) with expertise in sepsis pathophysiology, clinical trials, and epidemiology was convened by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine. Definitions and clinical criteria were generated through meetings, Delphi processes, analysis of electronic health record databases, and voting, followed by circulation to international professional societies, requesting peer review and endorsement.

KEY FINDINGS FROM EVIDENCE SYNTHESIS Limitations of previous definitions included an excessive focus on inflammation, the misleading model that sepsis follows a continuum through severe sepsis to shock, and inadequate specificity and sensitivity of the systemic inflammatory response syndrome (SIRS) criteria. Multiple definitions and terminologies are currently in use for sepsis, septic shock, and organ dysfunction, leading to discrepancies in reported incidence and observed mortality. The task force concluded the term severe sepsis was redundant.

RECOMMENDATIONS Sepsis should be defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. For clinical operationalization, organ dysfunction can be represented by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more, which is associated with an in-hospital mortality greater than 10%. Septic shock should be defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia. This combination is associated with hospital mortality rates greater than 40%. In out-of-hospital, emergency department, or general hospital ward settings, adult patients with suspected infection can be rapidly identified as being more likely to have poor outcomes typical of sepsis if they have at least 2 of the following clinical criteria that together constitute a new bedside clinical score termed quickSOFA (qSOFA): respiratory rate of 22/min or greater, altered mentation, or systolic blood pressure of 100 mm Hg or less.

CONCLUSIONS AND RELEVANCE These updated definitions and clinical criteria should replace previous definitions, offer greater consistency for epidemiologic studies and clinical trials, and facilitate earlier recognition and more timely management of patients with sepsis or at risk of developing sepsis.

Editorial page 1

Author Video Interview and Author Audio Interview and JAMA Report Video at jama.com

Related articles pages 1 and 1

CME Quiz at jamanetworkcme.com and CME Questions jme160009

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The Sepsis Definitions Task Force members are the authors listed above.

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JAMA. 2016;315(8):1-10. doi:10.1001/jama.2016.0287

- 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.

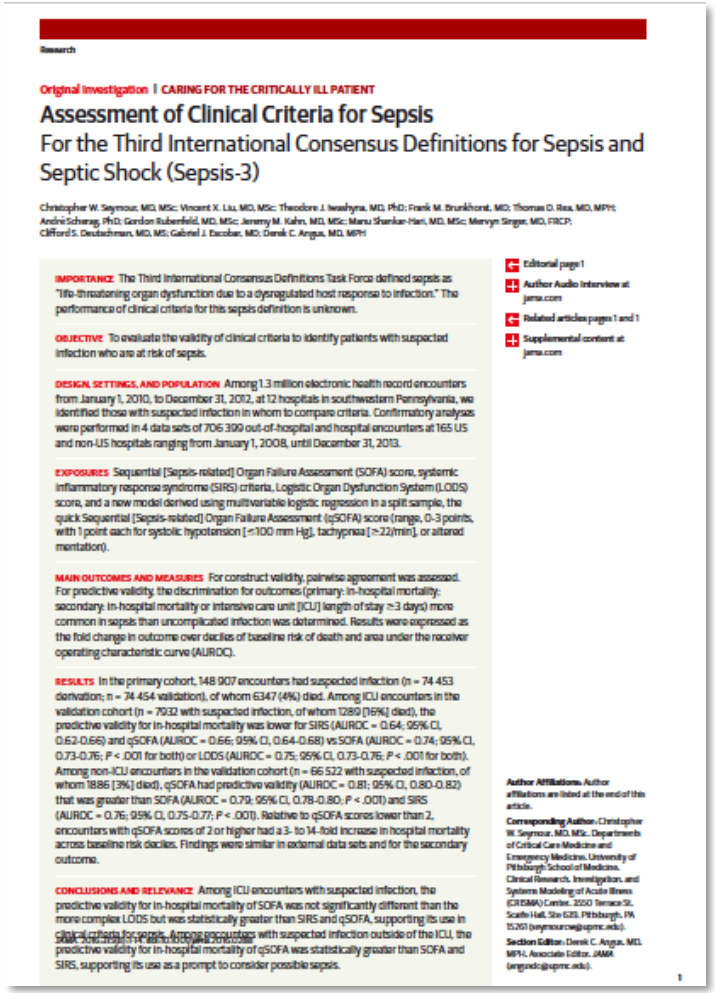
- Infection
- Organ dysfunction
- Life threatening
- Dysregulated host response

Singer et al., JAMA, 2016

We have a definition for sepsis.

Criteria for the bedside

Infection Defined



Research

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Assessment of Clinical Criteria for Sepsis

For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Christopher W. Seymour, MD, MSc; Vincent X. Liu, MD, MSc; Theodore J. Iwashyna, MD, PhD; Frank M. Brunkhorst, MD; Thomas D. Rea, MD, MPH; Andre Scherag, PhD; Gordon Rubenfeld, MD, MSc; Jeremy M. Kahn, MD, MSc; Manu Shankar-Hari, MD, MSc; Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Gabriel J. Escobar, MD; Derek C. Angus, MD, MPH

IMPORTANCE The Third International Consensus Definitions Task Force defined sepsis as "life-threatening organ dysfunction due to a dysregulated host response to infection." The performance of clinical criteria for this sepsis definition is unknown.

OBJECTIVE To evaluate the validity of clinical criteria to identify patients with suspected infection who are at risk of sepsis.

DESIGN, SETTINGS, AND POPULATION Among 1.3 million electronic health record encounters from January 1, 2010, to December 31, 2012, at 12 hospitals in southwestern Pennsylvania, we identified those with suspected infection in whom to compare criteria. Confirmatory analyses were performed in 4 data sets of 706 399 out-of-hospital and hospital encounters at 165 US and non-US hospitals ranging from January 1, 2008, until December 31, 2013.

EXPOSURES Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score, systemic inflammatory response syndrome (SIRS) criteria, Logistic Organ Dysfunction System (LODS) score, and a new model derived using multivariable logistic regression in a split sample, the quick Sequential [Sepsis-related] Organ Failure Assessment (qSOFA) score (range, 0-3 points, with 1 point each for systolic hypotension [≤100 mm Hg], tachypnea [≥22/min], or altered mentation).

MAIN OUTCOMES AND MEASURES For construct validity, pairwise agreement was assessed. For predictive validity, the discrimination for outcomes (primary: in-hospital mortality; secondary: in-hospital mortality or intensive care unit [ICU] length of stay ≥3 days) more common in sepsis than uncomplicated infection was determined. Results were expressed as the fold change in outcome over deciles of baseline risk of death and area under the receiver operating characteristic curve (AUROC).

RESULTS In the primary cohort, 148 907 encounters had suspected infection (n = 74 453 derivation; n = 74 454 validation), of whom 6347 (4%) died. Among ICU encounters in the validation cohort (n = 7932 with suspected infection, of whom 1289 [16%] died), the predictive validity for in-hospital mortality was lower for SIRS (AUROC = 0.64; 95% CI, 0.62-0.66) and qSOFA (AUROC = 0.66; 95% CI, 0.64-0.68) vs SOFA (AUROC = 0.74; 95% CI, 0.73-0.76; $P < .001$ for both) or LODS (AUROC = 0.75; 95% CI, 0.73-0.76; $P < .001$ for both). Among non-ICU encounters in the validation cohort (n = 66 522 with suspected infection, of whom 1886 [3%] died), qSOFA had predictive validity (AUROC = 0.81; 95% CI, 0.80-0.82) that was greater than SOFA (AUROC = 0.79; 95% CI, 0.78-0.80; $P < .001$) and SIRS (AUROC = 0.76; 95% CI, 0.75-0.77; $P < .001$). Relative to qSOFA scores lower than 2, encounters with qSOFA scores of 2 or higher had a 3- to 14-fold increase in hospital mortality across baseline risk deciles. Findings were similar in external data sets and for the secondary outcome.

CONCLUSIONS AND RELEVANCE Among ICU encounters with suspected infection, the predictive validity for in-hospital mortality of SOFA was not significantly different than the more complex LODS but was statistically greater than SIRS and qSOFA, supporting its use in clinical criteria for sepsis. Among encounters with suspected infection outside of the ICU, the predictive validity for in-hospital mortality of qSOFA was statistically greater than SOFA and SIRS, supporting its use as a prompt to consider possible sepsis.

Editorial page 1

Author Audio Interview at jama.com

Related articles pages 1 and 1

Supplemental content at jama.com

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- 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

	Infection[a]
	Documented or suspected *and* some of the following[b]:
	General parameters
	Fever (core temperature >38.3°C)
	Hypothermia (core temperature <36°C
	Heart rate >90 bpm or >2 SD above the normal value for age
	Tachypnea: >30 bpm
	Altered mental status
	Significant edema or positive fluid balance (>20 ml/kg over 24 h)
	Hyperglycemia (plasma glucose >110 mg/dl or 7.7 mM/l) in the absence of diabetes
	Inflammatory parameters
[a] Defined as a pathological process induced by a micro-organism	Leukocytosis (white blood cell count >12,000/μl)
[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	Leukopenia (white blood cell count <4,000/μl)
	Normal white blood cell count with >10% immature forms
	Plasma C reactive protein >2 SD above the normal value
	Plasma procalcitonin >2 SD above the normal value
	Hemodynamic parameters
[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	Arterial hypotension[b] (systolic blood pressure <90 mmHg, mean arterial pressure <70, or a systolic blood pressure decrease >40 mmHg in adults or <2 SD below normal for age)
	Mixed venous oxygen saturation >70%[b]
	Cardiac index >3.5 l min^{-1} m^{-2}[c]
[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	**Organ dysfunction parameters**
	Arterial hypoxemia ($PaO_2/FIO2$ <300)
	Acute oliguria (urine output <0.5 ml kg^{-1} hr^{-1} or 45 mM/l for at least 2 h)
	Creatinine increase ≥0.5 mg/dl
	Coagulation abnormalities (international normalized ratio >1.5 or activated partial thromboplastin time >60 s)
	Ileus (absent bowel sounds)
	Thrombocytopenia (platelet count <100,000/μl)
	Hyperbilirubinemia (plasma total bilirubin >4 mg/dl or 70 mmol/l)
	Tissue perfusion parameters
	Hyperlactatemia (>3 mmol/l)
	Decreased capillary refill or mottling

Levy et al., Crit Care Med, 2003

Criteria to evaluate

Table 1. Variables for Candidate Sepsis Criteria Among Encounters With Suspected Infection

Systemic Inflammatory Response Syndrome (SIRS) Criteria (Range, 0-4 Criteria)	Sequential [Sepsis-related] Organ Failure Assessment (SOFA) (Range, 0-24 Points)	Logistic Organ Dysfunction System (LODS)[a] (Range, 0-22 Points)	Quick Sequential [Sepsis-related] Organ Failure Assessment (qSOFA) (Range, 0-3 Points)
Respiratory rate, breaths per minute	$Pa0_2/Fi0_2$ ratio	$Pa0_2/Fi0_2$ ratio	Respiratory rate, breaths per minute
White blood cell count, 10^9/L	Glasgow Coma Scale score	Glasgow Coma Scale score	Glasgow Coma Scale score
Bands, %	Mean arterial pressure, mm Hg	Systolic blood pressure, mm Hg	Systolic blood pressure, mm Hg
Heart rate, beats per minute	Administration of vasopressors with type/dose/rate of infusion	Heart rate, beats per minute	
Temperature, °C	Serum creatinine, mg/dL, or urine output, mL/d	Serum creatinine, mg/dL	
Arterial carbon dioxide tension, mm Hg	Bilirubin, mg/dL	Bilirubin, mg/dL	
	Platelet count, 10^9/L	Platelet count, 10^9/L	
		White blood cell count, 10^9/L	
		Urine output, L/d	
		Serum urea, mmol/L	
		Prothrombin time, % of standard	

Patients

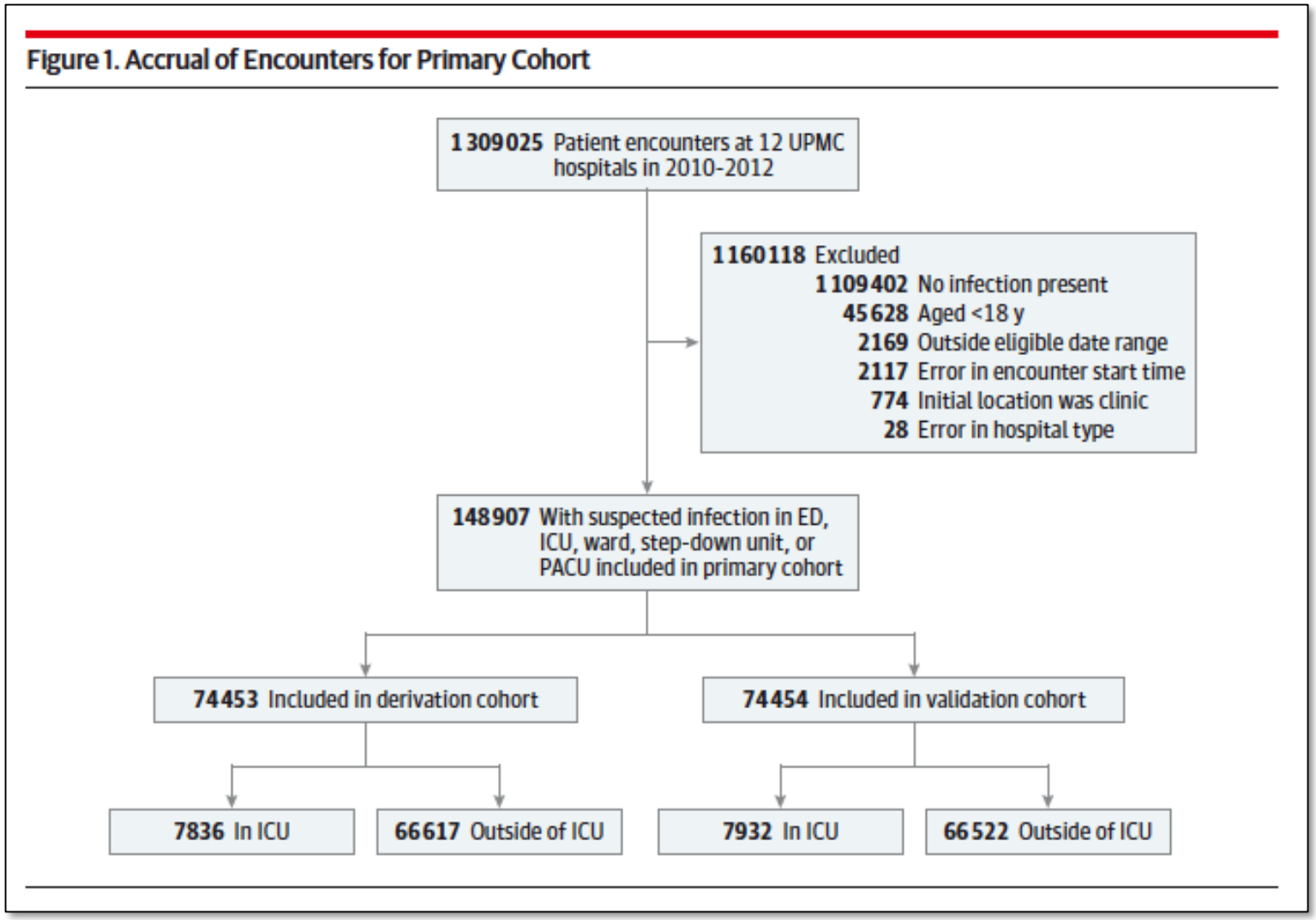


Figure 1. Accrual of Encounters for Primary Cohort
1 309 025 Patient encounters at 12 UPMC hospitals in 2010-2012
1 160 118 Excluded
1 109 402 No infection present
45 628 Aged <18 y
2169 Outside eligible date range
2117 Error in encounter start time
774 Initial location was clinic
28 Error in hospital type
148 907 With suspected infection in ED, ICU, ward, step-down unit, or PACU included in primary cohort
74 453 Included in derivation cohort
74 454 Included in validation cohort
7836 In ICU
66 617 Outside of ICU
7932 In ICU
66 522 Outside of ICU

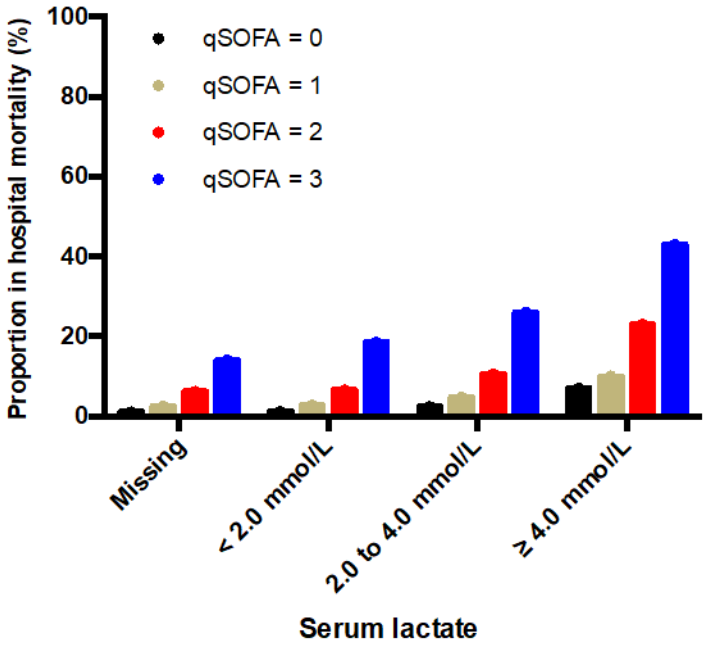
quick Sepsis - Related Organ Failure Assessment

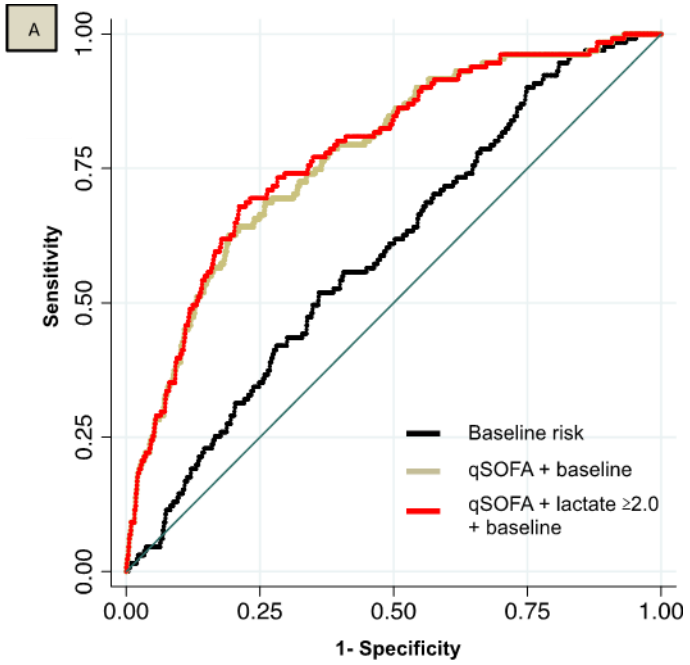
qSOFA is a clinical prompt

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

Why is qSOFA useful?

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

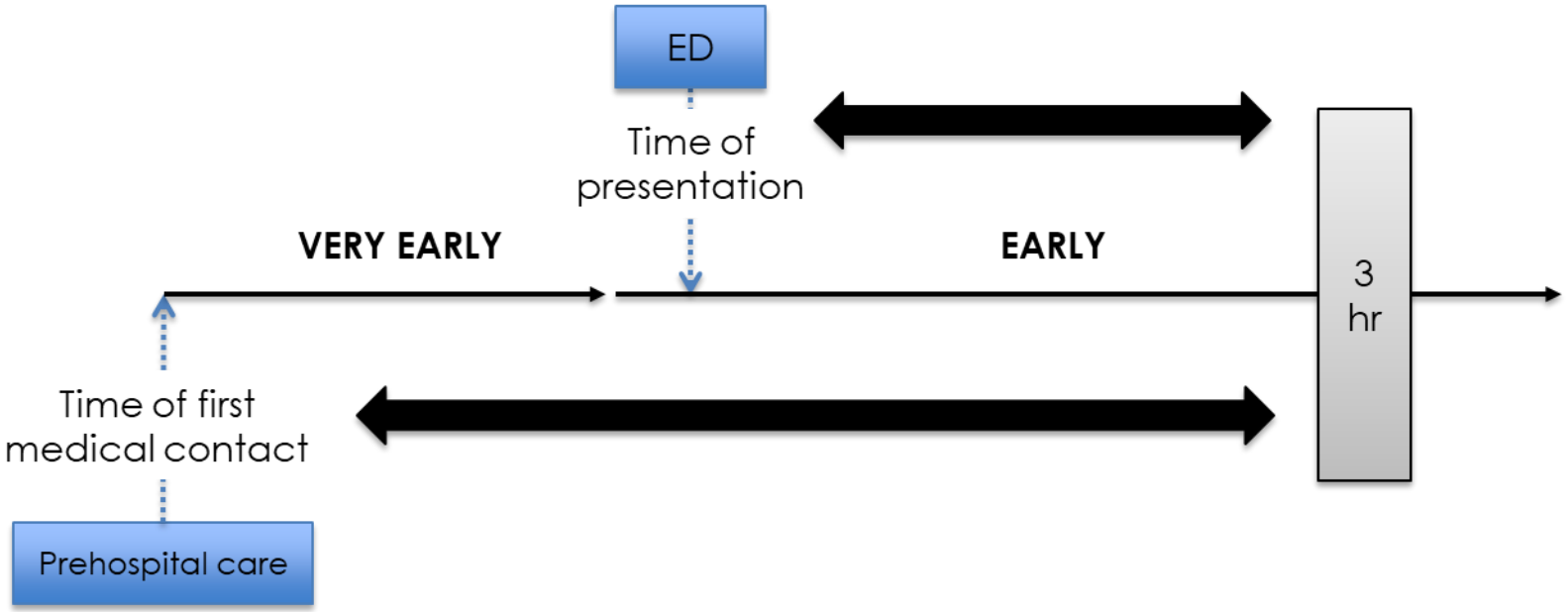
What's great about Sepsis-3?

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

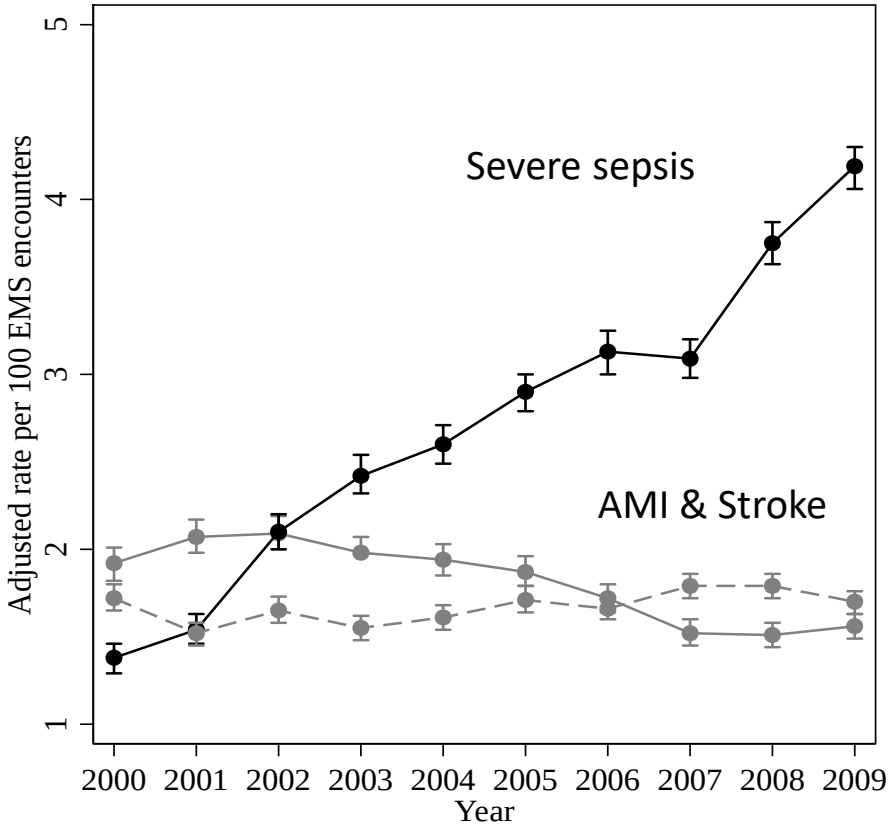
But could this lead to some confusion?

- Other criteria are available
  - CMS, CDC, inclusion into large randomized trials
- How would we identify suspected infection?
  - No check boxes proposed by Task Force

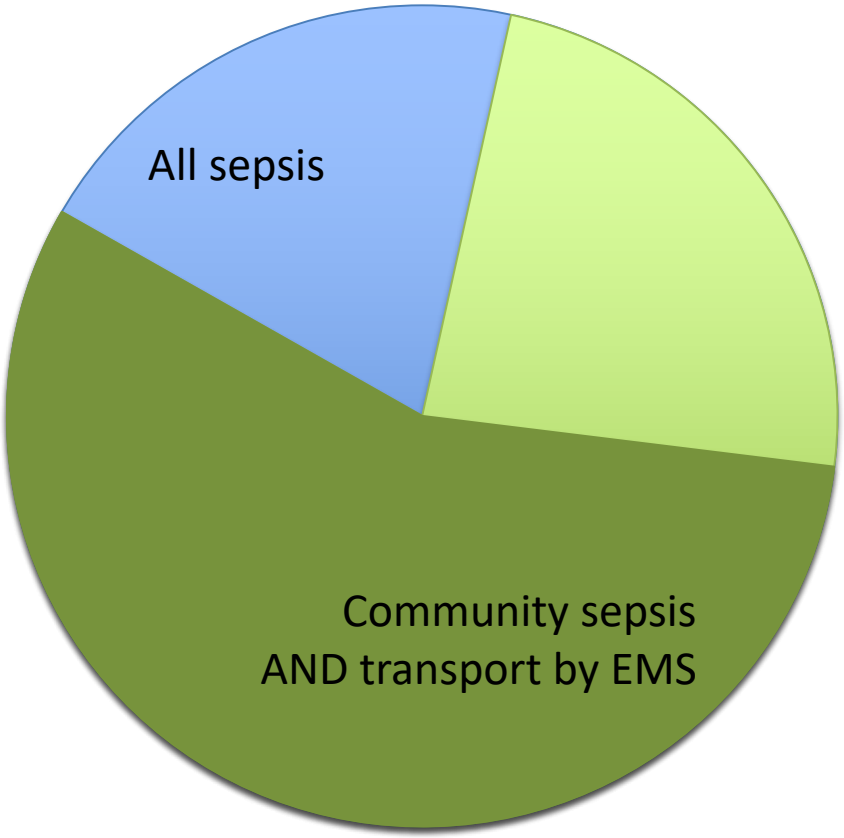
More importantly, what does this mean for EMS?



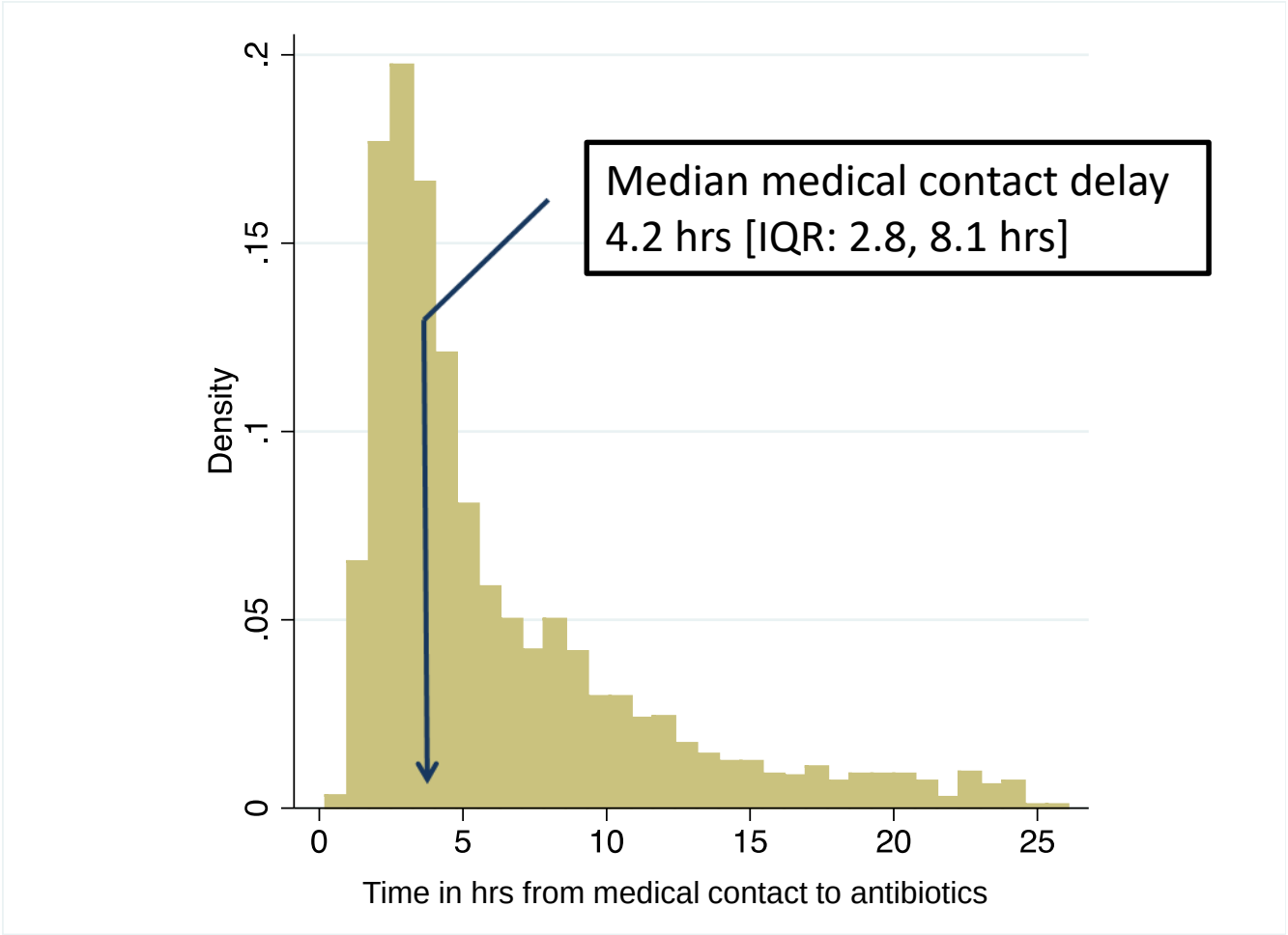
How often do EMS transport sepsis?



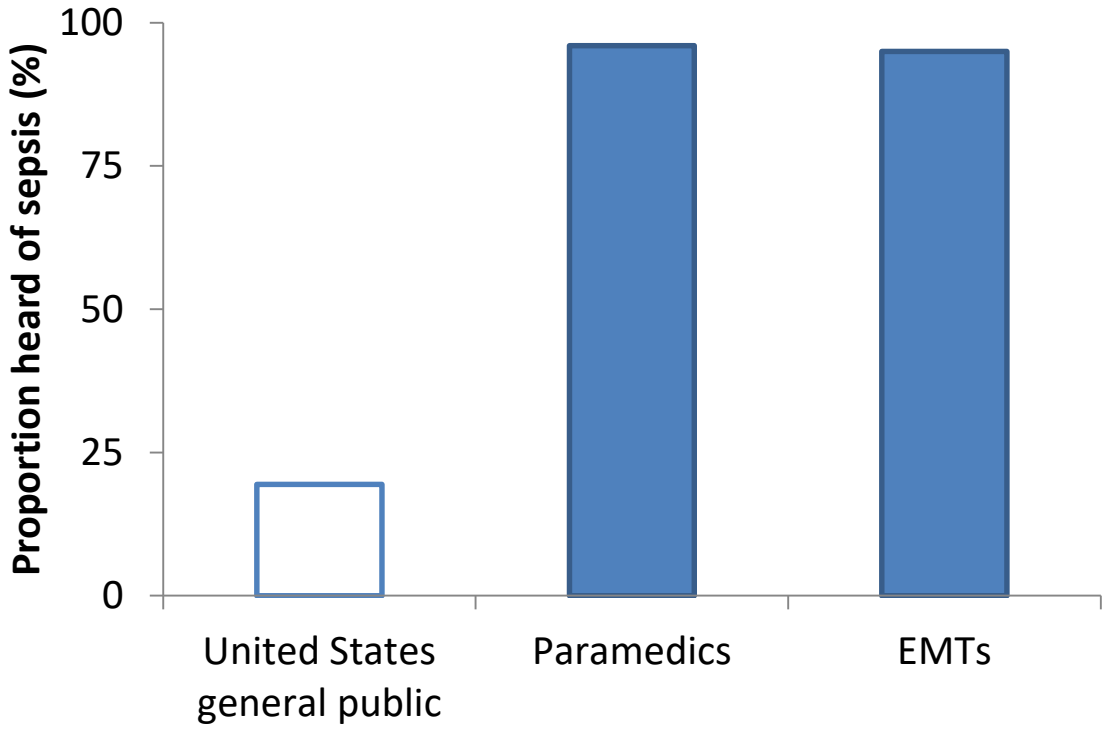
Among all sepsis cases



How much time with EMS?

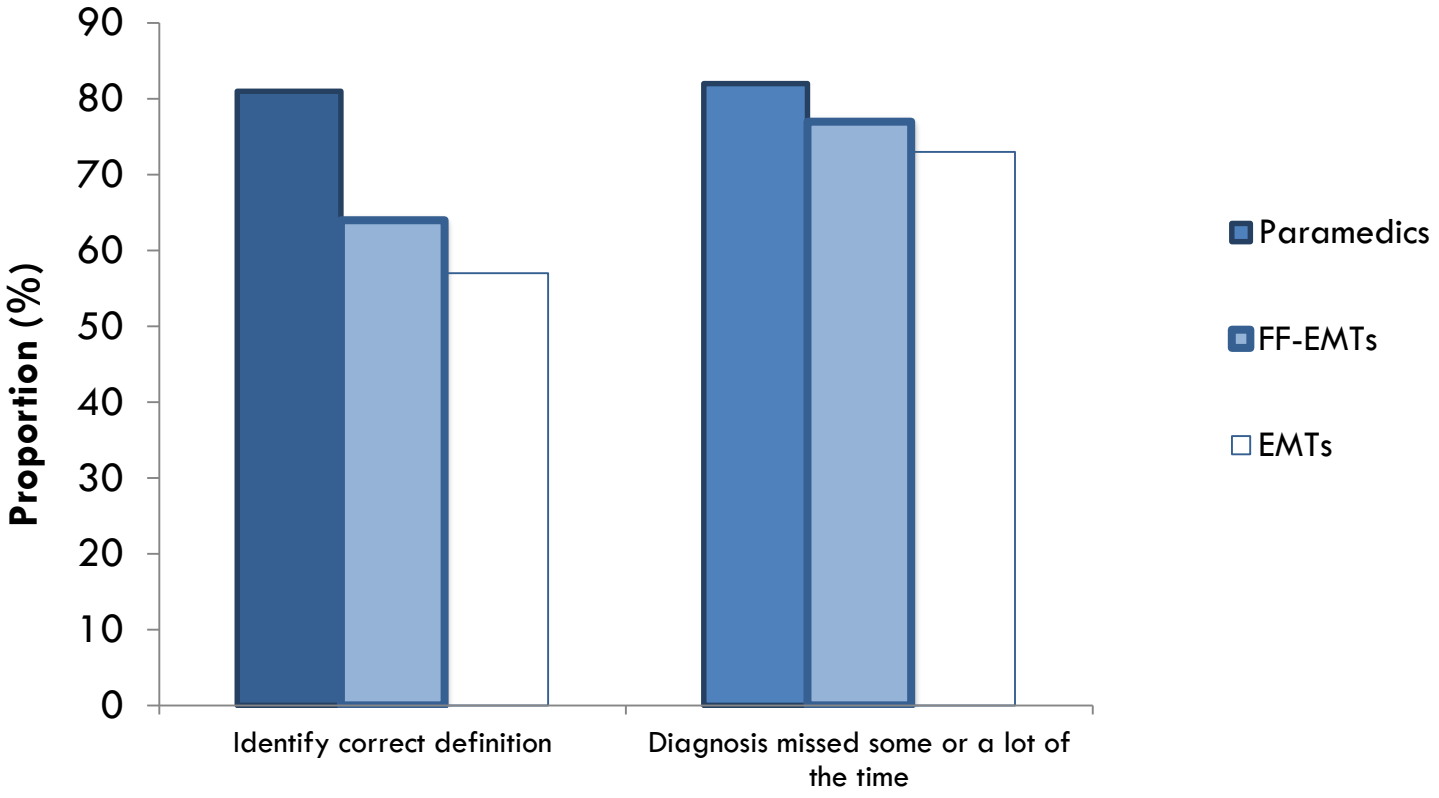


But is EMS aware of sepsis?



Seymour et al., 2012, J Emerg Med

But is EMS aware of sepsis? Cont'd



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, MS, 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

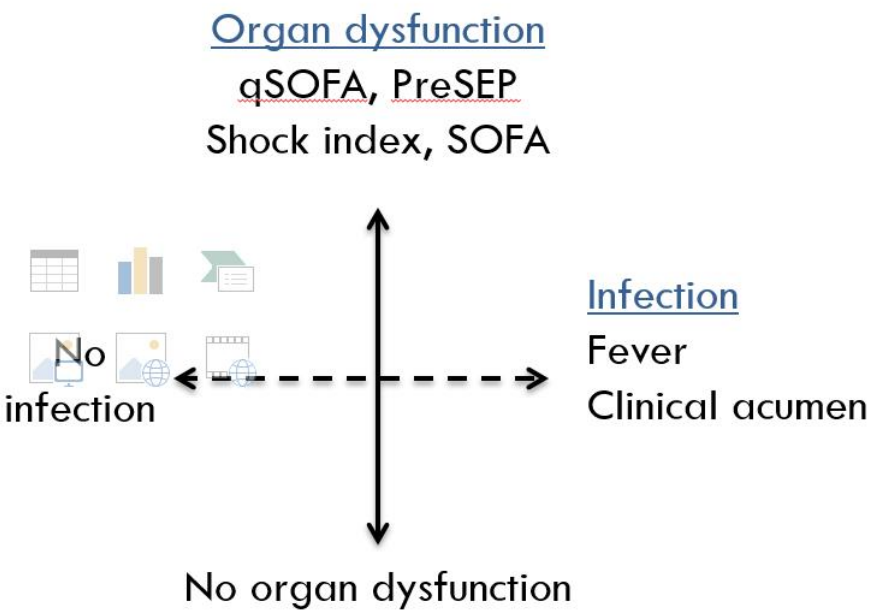
Acad Emerg Med. 2015 Jul;22(7):868-71. doi: 10.1111/acem.12707. Epub 2015 Jun 25.

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

Bayer O[1], Schwarzkopf D[2], Stumme C[1], Stacke A[1], Hartog CS[1,2], Hohenstein C[3], Kabisch B[1], Reichel J[1], Reinhart K[1,2], Winning J[1].

Author information

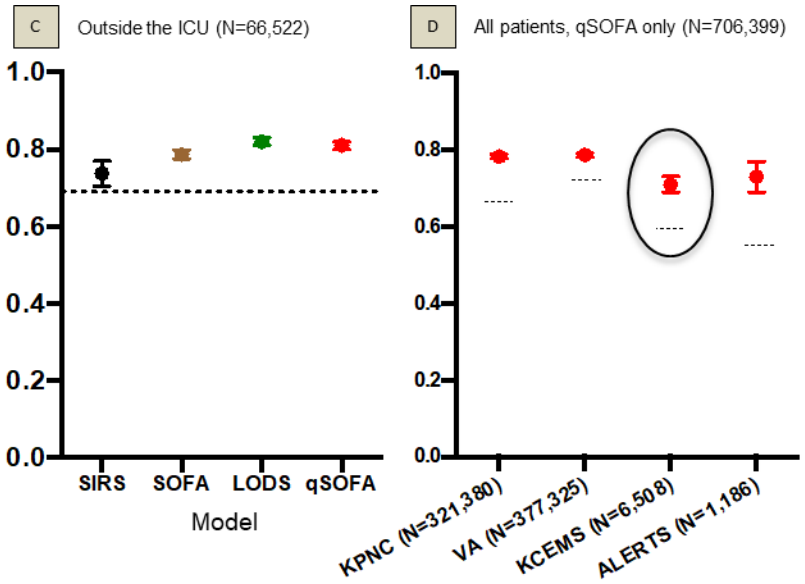
Finding sepsis in prehospital care, Cont'd



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
- >=2 points = 24% mortality

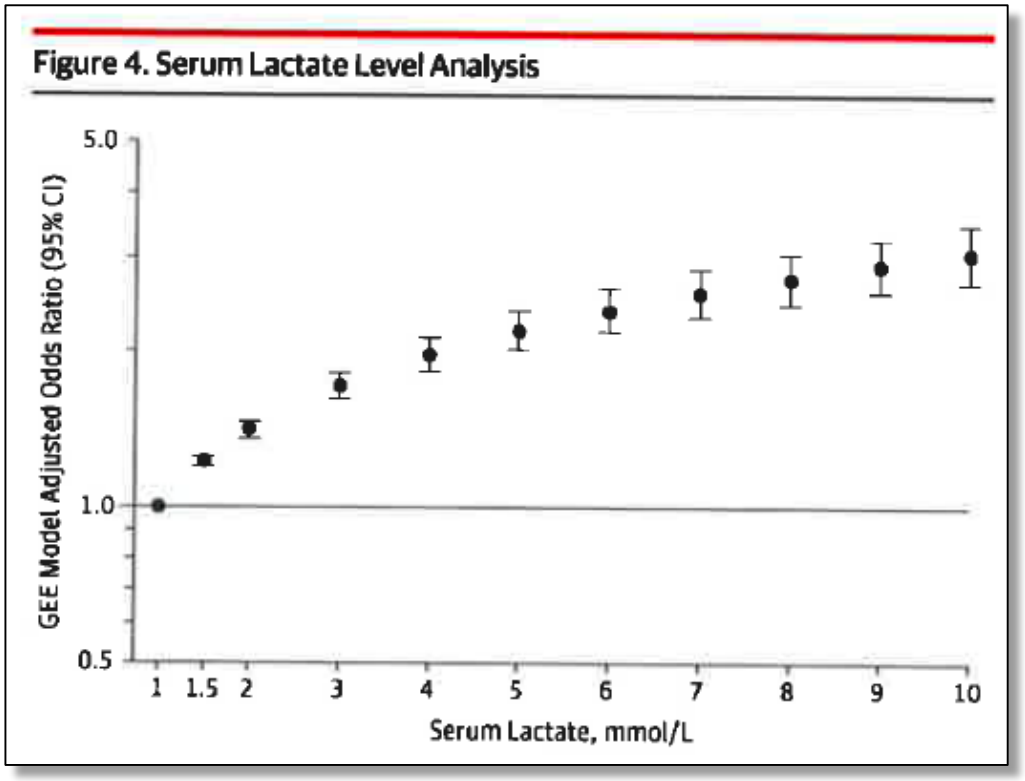
qSOFA was tested in EMS data



More than 3 million encounters, 5 cohorts
>10,000 EMS transport in King County, 30 agencies, 14 hospitals

Seymour et al., 2016, JAMA

Could serum lactate help?



Shankar Hari et al., 2016, JAMA

What about serum lactate?

PRO

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

CON

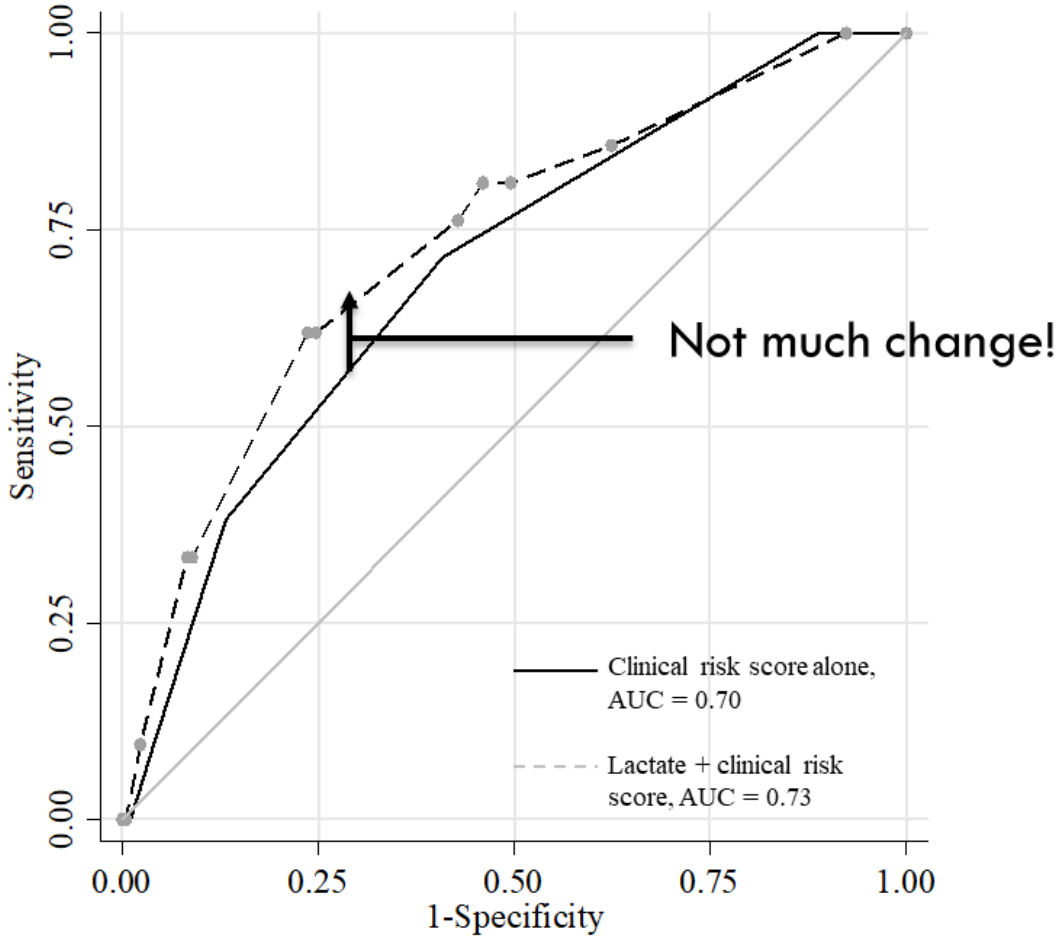
- Hard to find
- Not specific for infection
- Conflicting data

Shankar Hari et al., 2016, JAMA

What about serum lactate? 2

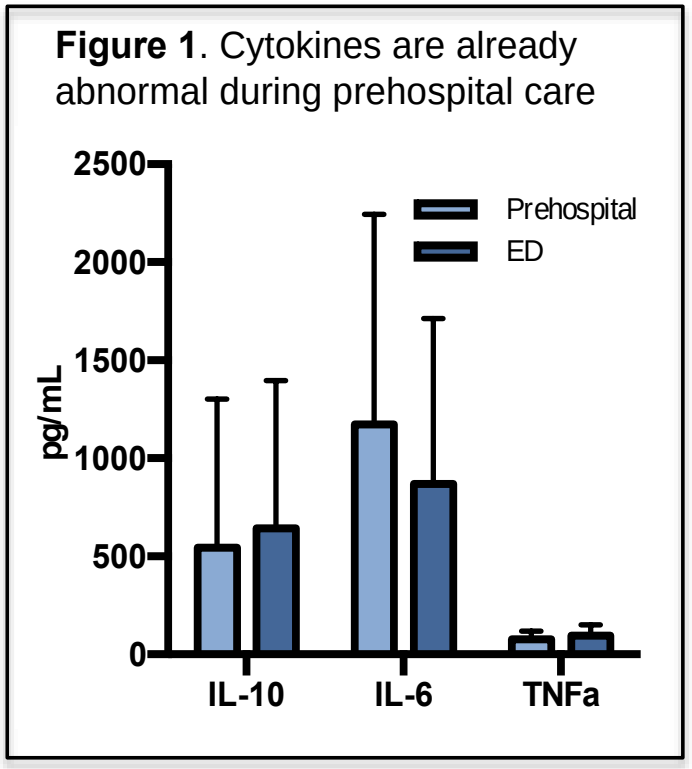
Study	Single biomarker?	Patients	Biomarker	Sample size
Shah et al.	Yes	Pediatric HEMS	Lactate	41
Guyette et al.	Yes	Adult trauma	Lactate	317
Mullen et al.	Yes	Adult HEMS	Lactate	20
Guyette et al.	Yes	Adult HEMS Trauma	Lactate	1,168
Van Beest et al.	Yes	Ground EMS	Lactate	135
Tobias et al.	Yes	Ground EMS	Lactate	673

What about serum lactate? 3



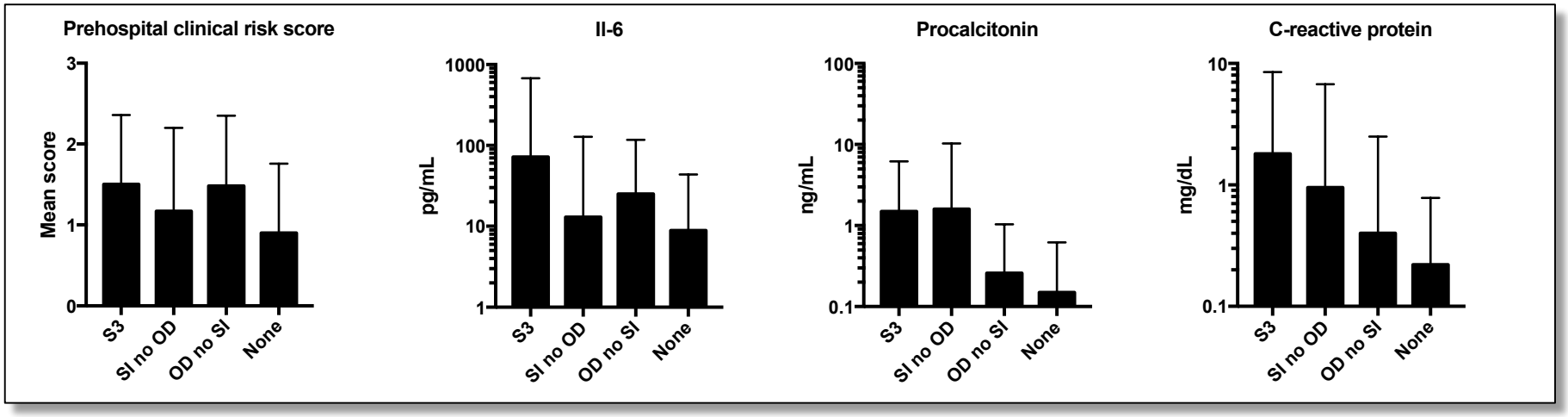
PIPeLINE

- 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



Seymour et al., in process

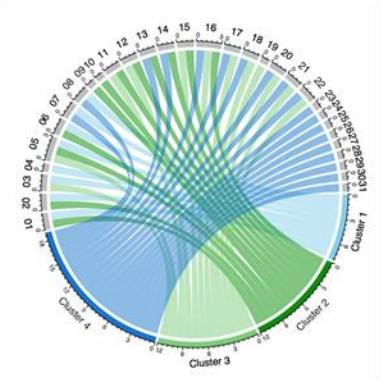
New tests coming?

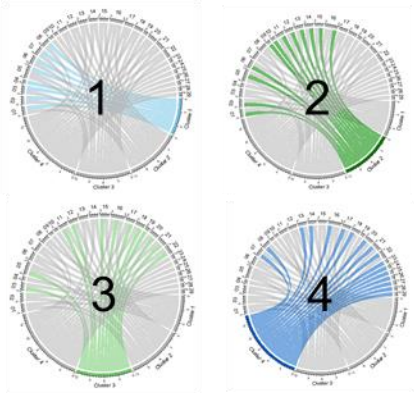


Certain biomarkers may help with infection (yes/no) but platforms not ready for prime time

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 pubic 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