



ACTUALITÉS EN RÉANIMATION  
Médecine intensive, Surveillance continue  
et Urgences Graves  
23 et 24 novembre 2017

# Sepsis 3.0: pourquoi une nouvelle définition?

**Jean-Daniel Chiche, MD PhD**

**MICU & Dept 'Infection, Immunity & Inflammation'  
Hôpital Cochin & Institut Cochin, Paris-F**

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-Hart, MSc, MD, FRCM, Dilek Anir, MD, PhD, Michael Bauer, MD, Rinaldo Bellomo, MD, Gordon R. Bernard, MD, Jean-Daniel Chiche, MD, PhD, Craig M. Cooksmith, MD, Richard S. Hinchey, MD, Mitchell M. Levy, MD, John C. Marshall, MD, Greg S. Martin, MD, MSc, Steven M. Opal, MD, Gordon D. Rubenstein, 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 pathobiology (changes in organ function, morphology, cell biology, biochemistry, immunology, and circulation), management, and epidemiology of sepsis, suggesting the need for reexamination.

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

**E** **Enthwurf** (page 253)

**Author Video Interview, Author Audio Interview, and JAMA Report Video at [jama.com](http://jama.com)**

 Related articles: pages 762 and 775

### Assessment of Clinical Criteria for For the Third International Consensus for Sepsis and Septic Shock (Sepsis

for Sepsis and Septic Shock

## ARTICLE #19 OF 100

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

SPECIAL COMMUNICATION IN JAMA

This Special Communication provides an updated definition of the symptoms of Sepsis and Septic Shock.

**MORE DETAILS**

**FREE TO READ**

Views **2,135,896** | Citations **703**

gSCFA (AUROC = 0.64) and LCOs (AUROC = 0.75,  $P = .009$ ) for both) or LCOs (AUROC = 0.75,  $P = .009$ ) encounters in the validation cohort (in non-ICU patients), gSCFA had predictive validity (88% [95% CI], gSCFA had predictive validity greater than SCFA (AUROC = 0.78; 95% CI, 0.75-0.79,  $P = .009$ ). Relative to gSCFA, LCOs 2 or higher had a 3- to 14-fold increase in risk, which was similar in external data sets and for the

**CONCLUSIONS AND RELEVANCE:** This study found predictive validity for in-hospital mortality across complex LOSIS but was statistically inferior to clinical criteria for sepsis. Among medical patients, LOSIS had predictive validity for in-hospital mortality, supporting its use as a prompt to

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.

[illegible]

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

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

Corresponding Author: Clifford S. Deutschman, MD, MS, Departments of Pediatrics and Molecular Medicine, Weill-Cornell School of Medicine, Feinstein Institute for Medical Research, 209-O1 25th Ave, New Hyde Park, NY 11040  
clifford@feinsteininstitute.org

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

**Corresponding Author:** Maria Shalloe, MD, MSc, Department of Critical Care Medicine, Guy's and Thomas NHS Foundation Trust, London SE1 2J4, United Kingdom  
m.shalloe@guytonline.com



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# WHY



# 1991 & 2001 Definitions: Any Issue?

- SIRS-based
- “Severe Sepsis”
- Different criteria yielding different results



## accp/sccm consensus conference

### Definitions for Sepsis and Organ Failure and Guidelines for the Use of Innovative Therapies in Sepsis

#### THE ACCP/SCCM CONSENSUS CONFERENCE COMMITTEE:

*Roger C. Bone, M.D., F.C.C.P., Chairman*

*Robert A. Balk, M.D., F.C.C.P.*

*Frank B. Cerra, M.D.*

*R. Phillip Dellinger, M.D., F.C.C.P.*

*Alan M. Fein, M.D., F.C.C.P.*

*William A. Knaus, M.D.*

*Roland M. H. Schein, M.D.*

*William J. Sibbald, M.D., F.C.C.P.*

### 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference

Mitchell M. Levy, MD, FCCP; Mitchell P. Fink, MD, FCCP; John C. Marshall, MD; Edward Abraham, MD; Derek Angus, MD, MPH, FCCP; Deborah Cook, MD, FCCP; Jonathan Cohen, MD; Steven M. Opal, MD; Jean-Louis Vincent, MD, FCCP, PhD; Graham Ramsay, MD; For the International Sepsis Definitions Conference



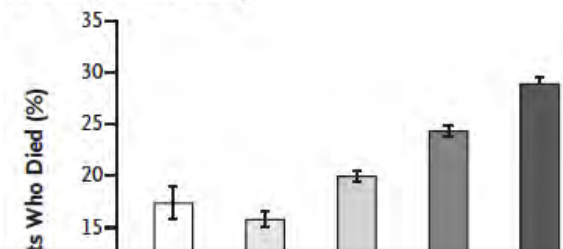
# SIRS: a Sensitive Issue?

## Systemic Inflammatory Response Syndrome Criteria in Defining Severe Sepsis

Kirsi-Maija Kaukonen, M.D., Ph.D., Michael Bailey, Ph.D., David Pilcher, F.C.I.C.M.,  
D. Jamie Cooper, M.D., Ph.D., and Rinaldo Bellomo, M.D., Ph.D.

N Engl J Med 2015;372:1629-38.

A Unadjusted Mortality



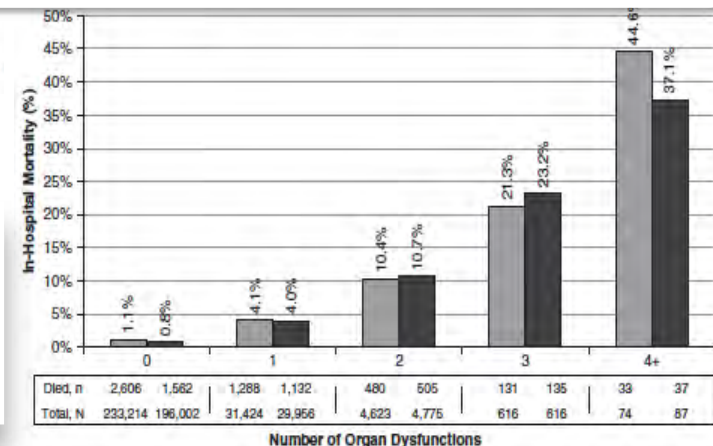
SIRS is an *appropriate* response to infection-  
or any other stimulus that activates inflammation

## Response Syndrome and Organ Dysfunctions in Ward Patients

Matthew M. Churpek<sup>1</sup>, Frank J. Zadavec<sup>1</sup>, Christopher Winslow<sup>2</sup>, Michael D. Howell<sup>1</sup>, and Dana P. Edelson<sup>1</sup>

Am J Respir Crit Care Med 2015; 192:958-964

**Conclusions:** Almost half of patients hospitalized on the wards developed SIRS at least once during their ward stay. Our findings suggest that screening ward patients using SIRS criteria for identifying those with sepsis would be impractical.



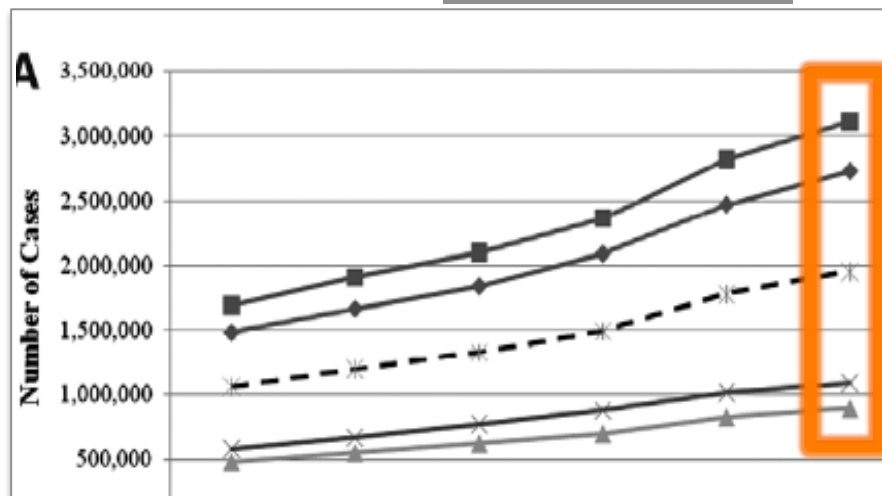
# Different Criteria → Different Results

## Benchmarking the Incidence and Mortality of Severe Sepsis in the United States\*

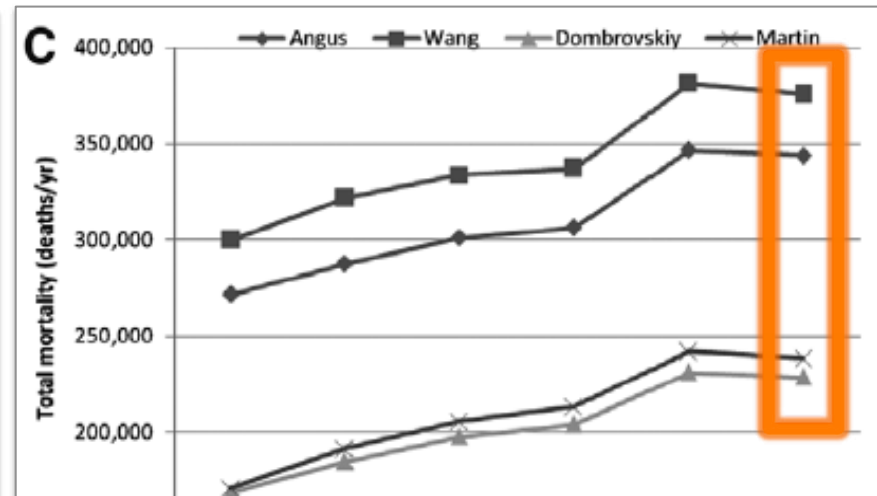
David F. Gaieski MD<sup>1</sup>; J. Matthew Edwards, MD<sup>1</sup>; Michael J. Kallan, MS<sup>2</sup>; Brendan G. Carr, MD, MA, MS<sup>1-3</sup>

*Crit Care Med* 2013; 41: 1167-1174

Number of cases **900K – 3.1 Mil**



**250K – 375K Total mortality**



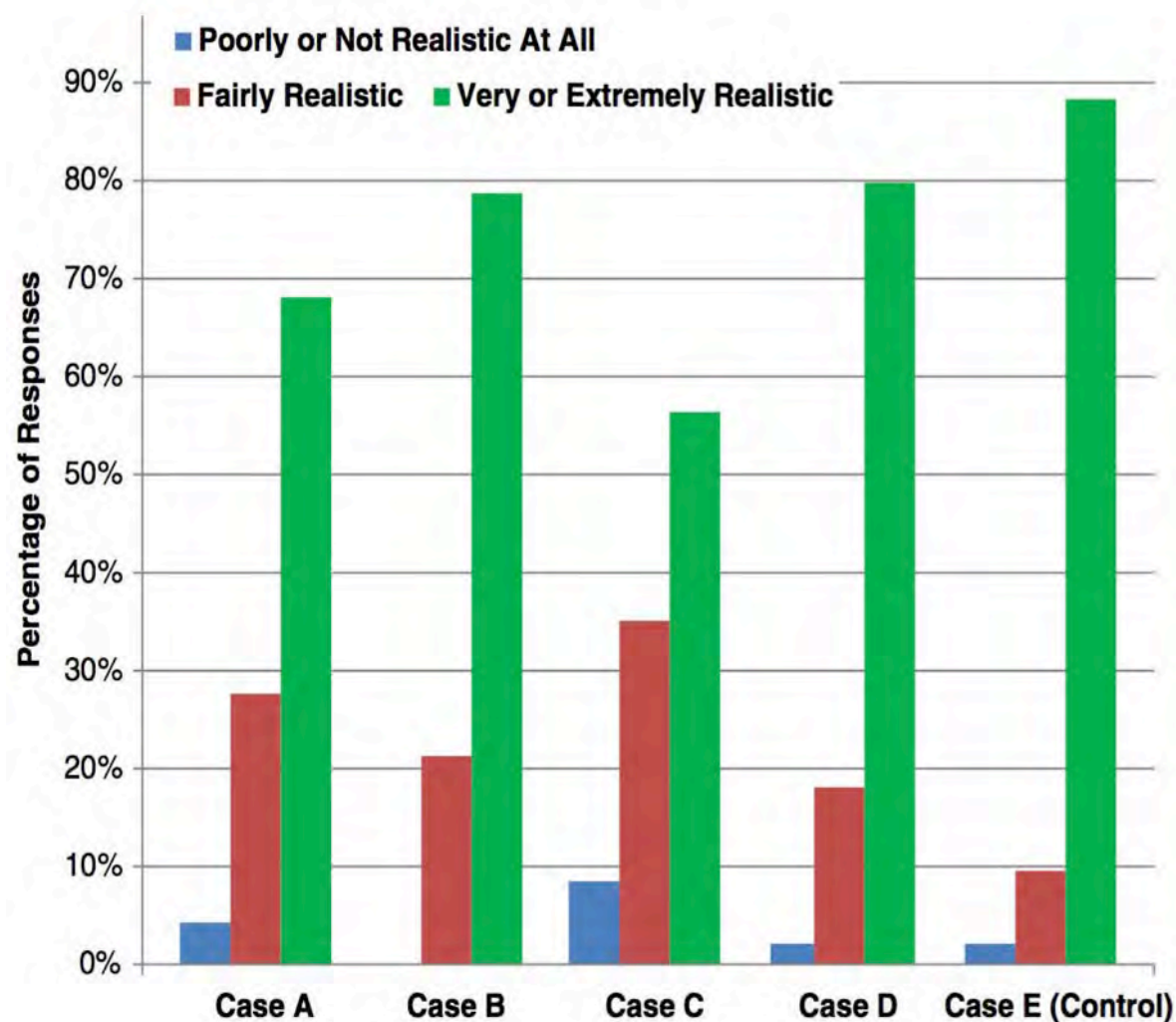
Four different ways to identify sepsis; four different sets of results

—◆— Angus —■— Wang —▲— Dombrovskiy —×— Martin —\*— Mean Weighted



# Diagnosing sepsis is subjective and highly variable: a survey of intensivists using case vignettes

Chanu Rhee<sup>1,2\*</sup>, Sameer S. Kadri<sup>3</sup>, Robert L. Danner<sup>3</sup>, Anthony F. Suffredini<sup>3</sup>, Anthony F. Massaro<sup>2</sup>, Barrett T. Kitch<sup>4</sup>, Grace Lee<sup>1</sup> and Michael Klompas<sup>1,2</sup>

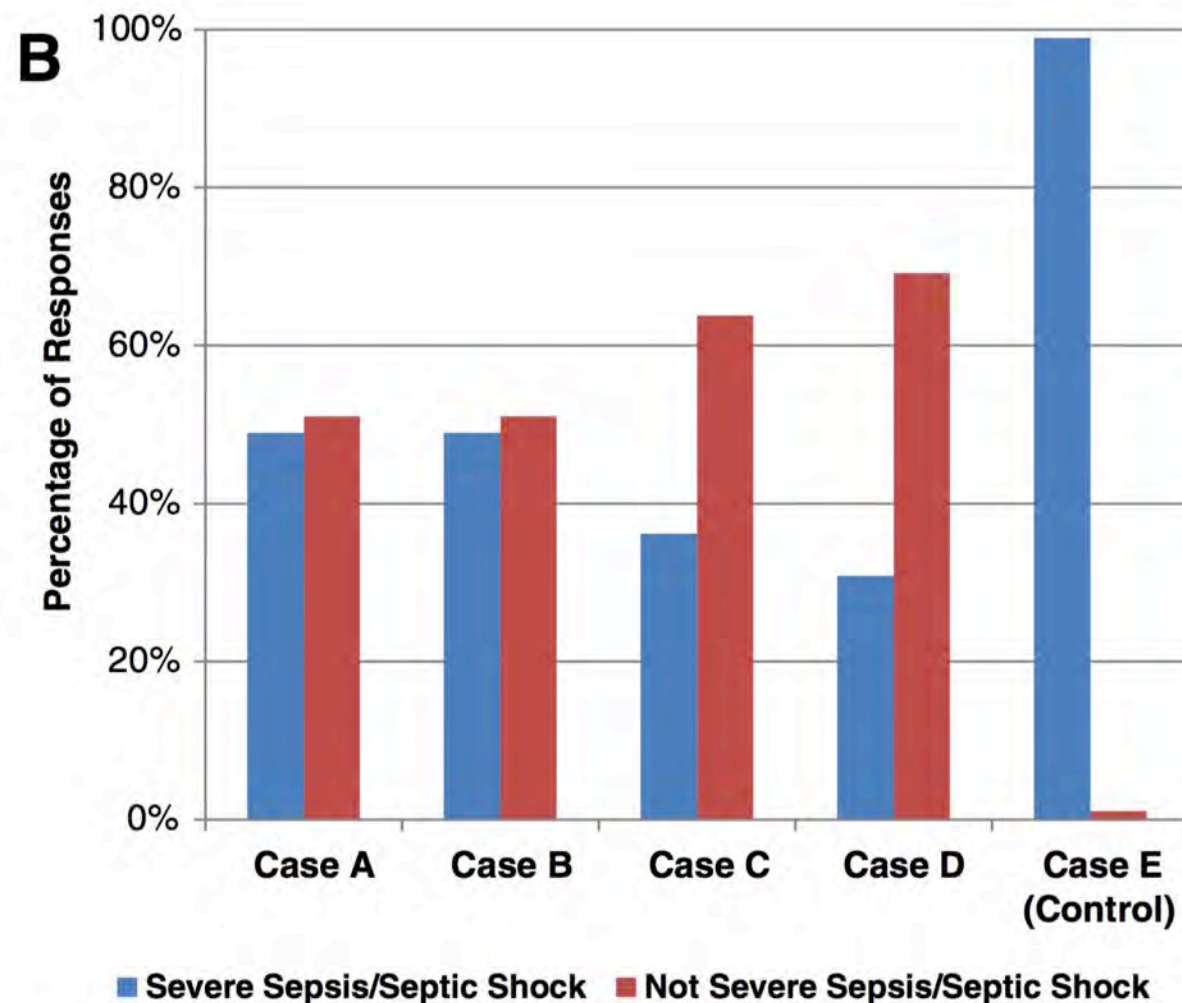


Respondent profile	Data
Subspecialties, <i>n</i> (%)	
Critical care	83 (88.3 %)
Pulmonary	37 (39.4 %)
Anesthesia	18 (19.1 %)
Surgery	8 (8.5 %)
Emergency medicine	8 (8.5 %)
Infectious diseases	4 (4.3 %)
Academic hospital , <i>n</i> (%)	85 (90.4 %)

# Diagnosing sepsis is subjective and highly variable: a survey of intensivists using case vignettes



Chanu Rhee<sup>1,2\*</sup>, Sameer S. Kadri<sup>3</sup>, Robert L. Danner<sup>3</sup>, Anthony F. Suffredini<sup>3</sup>, Anthony F. Massaro<sup>2</sup>, Barrett T. Kitch<sup>4</sup>, Grace Lee<sup>1</sup> and Michael Klompas<sup>1,2</sup>

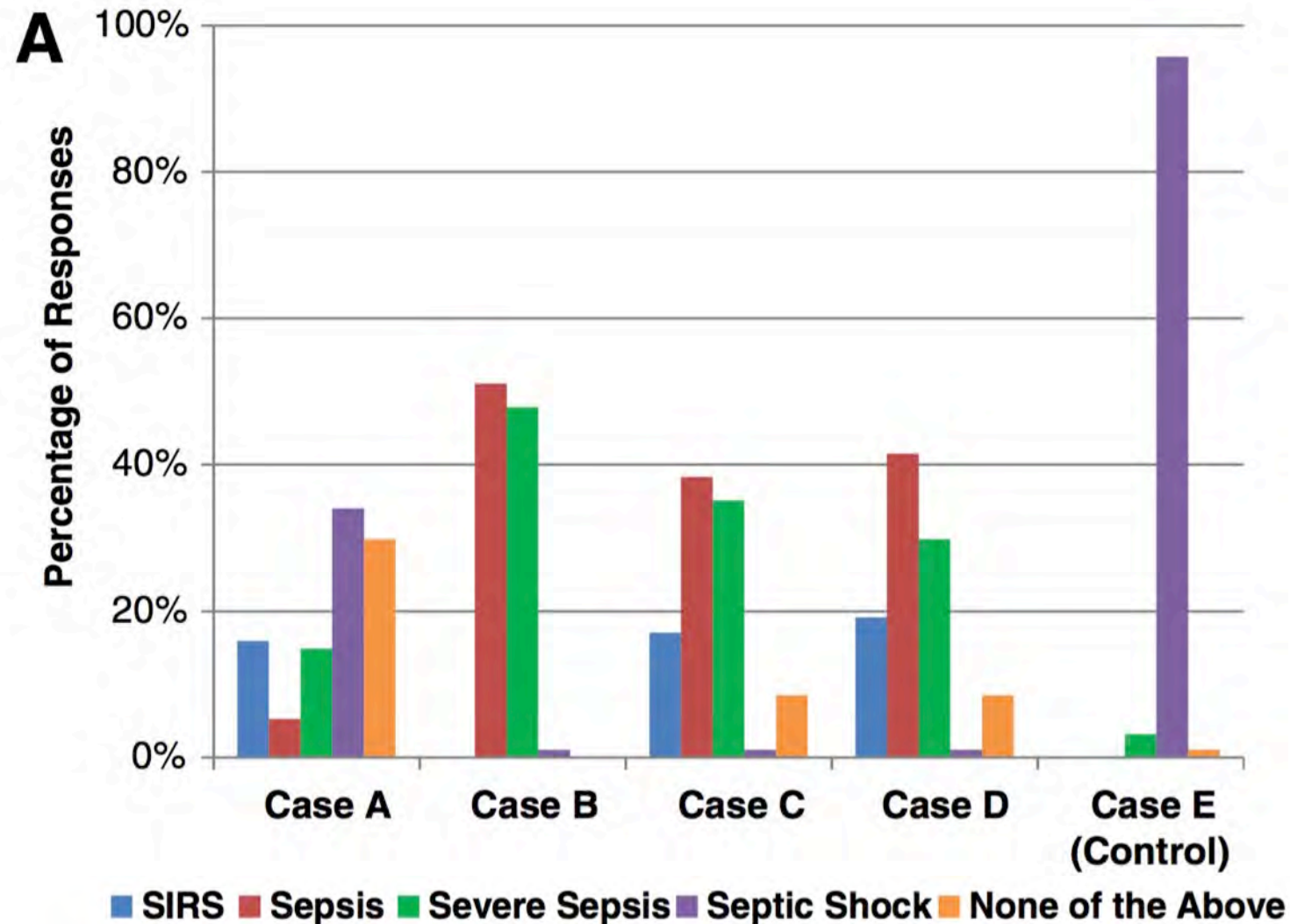




# Diagnosing sepsis is subjective and highly variable: a survey of intensivists using case vignettes

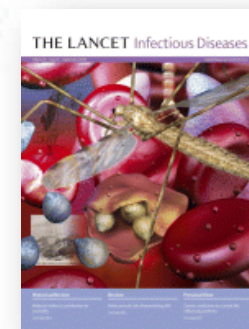


Chanu Rhee<sup>1,2\*</sup>, Sameer S. Kadri<sup>3</sup>, Robert L. Danner<sup>3</sup>, Anthony F. Suffredini<sup>3</sup>, Anthony F. Massaro<sup>2</sup>, Barrett T. Kitch<sup>4</sup>, Grace Lee<sup>1</sup> and Michael Klompas<sup>1,2</sup>



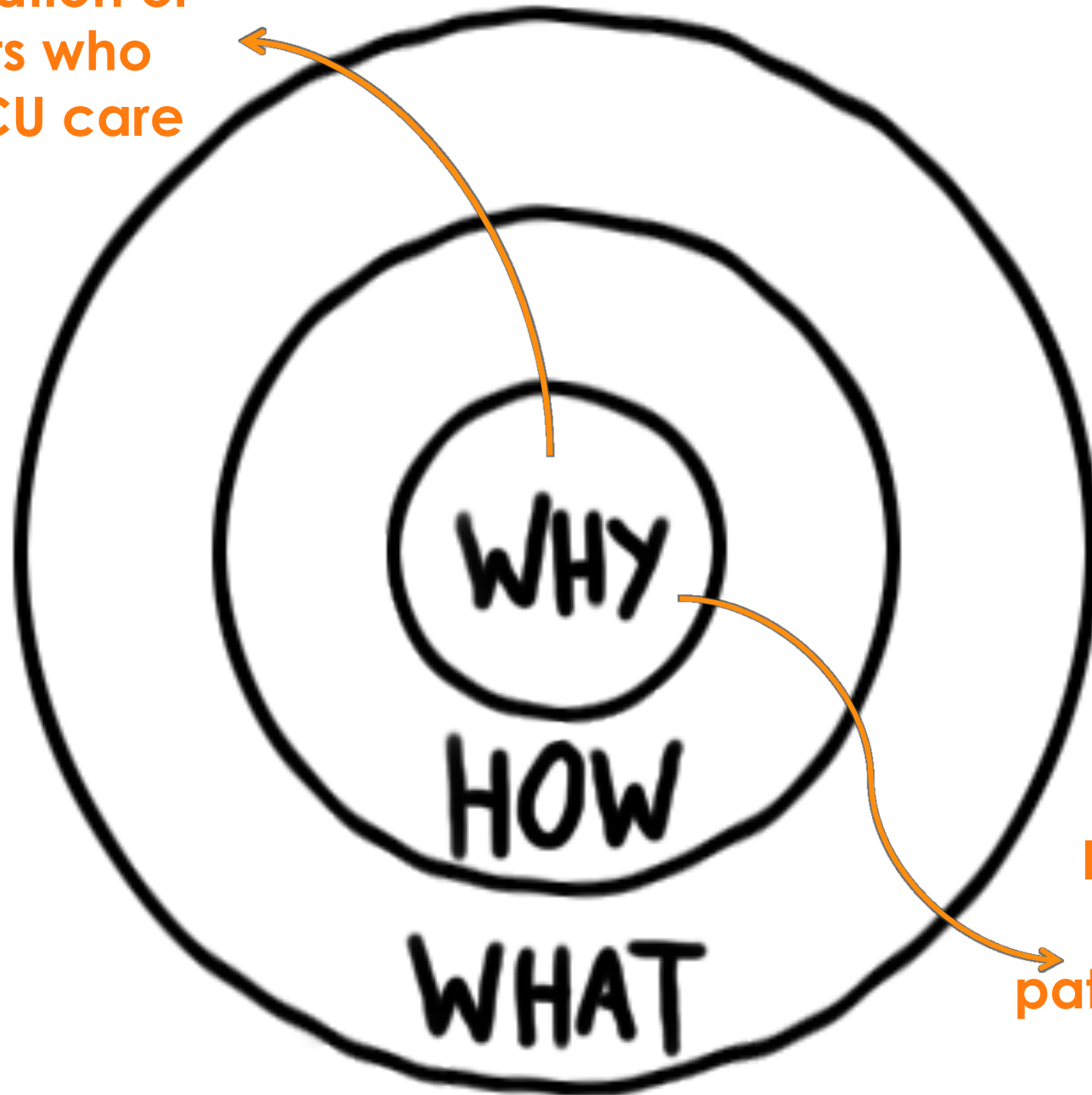
# Outcomes of the Surviving Sepsis Campaign in intensive care units in the USA and Europe: a prospective cohort study

Mitchell M Levy, Antonio Artigas, Gary S Phillips, Andrew Rhodes, Richard Beale, Tiffany Osborn, Jean-Louis Vincent, Sean Townsend, Stanley Lemeshow, R Phillip Dellinger



	USA	Europe	p value*
Count	18 766 (74.0%)	6609 (26.0%)	
Hospital mortality	5313 (28.3%)	2719 (41.1%)	<0.0001
Origin			<0.0001
Emergency department	12 218 (65.1%)	2159 (32.7%)	
Ward	4763 (25.4%)	3405 (51.5%)	
ICU	1785 (9.5%)	1045 (15.8%)	
Hospital mortality if origin is emergency department	3008 (24.6%)	736 (34.1%)	<0.0001
Hospital mortality if origin is ward	1661 (34.9%)	1481 (43.5%)	<0.0001
Hospital mortality if origin is ICU	644 (36.1%)	502 (48.0%)	<0.0001
Median ICU length of stay (days)	4.2 (2.2–8.9)	7.8 (3.4–17.2)	<0.0001

Identification of  
patients who  
need ICU care



Identify  
severe  
patients with  
high  
mortality

# HOW





# Sepsis Definitions Task force

**Co-chairs: Mervyn Singer & Cliff Deutschman**

**Derek Angus**

**Craig Coopersmith**

**Gordon Rubenfeld**

**Djilalli Annane**

**Richard Hotchkiss**

**Chris Seymour (co-opted)**

**Michael Bauer**

**Mitchell Levy**

**Manu Shankar Hari (co-opted)**

**Rinaldo Bellomo**

**John Marshall**

**Tom van der Poll**

**Gordon Bernard**

**Greg Martin**

**Jean-Louis Vincent**

**Jean-Daniel Chiche**

**Steve Opal**

Blend of:

- 21 continents (N America + Europe + Australasia)
- 21 specialties (ID, ICU with medical, respiratory, surgical, anaesthetic backgrounds)
- 21 clinician-scientists + clinician-epidemiologists + clinical trialists
- 21 specific organ expertise (immune, brain, heart, lung, kidney, liver, gut..)

*unrestricted funding from ESICM+ SCCM*

# Sepsis Definitions Process

- Face-to-face meetings
- Teleconferences
- Data-driven whenever possible
- Delphi-process
- Webster definition of « definition »
  - “a statement expressing the essential nature of something”  
or, more generically,
  - “a statement that describes what something is”

A definition therefore requires an understanding of the pathobiology of the disorder ..

.. which, for sepsis, is at best incomplete

# WHAT



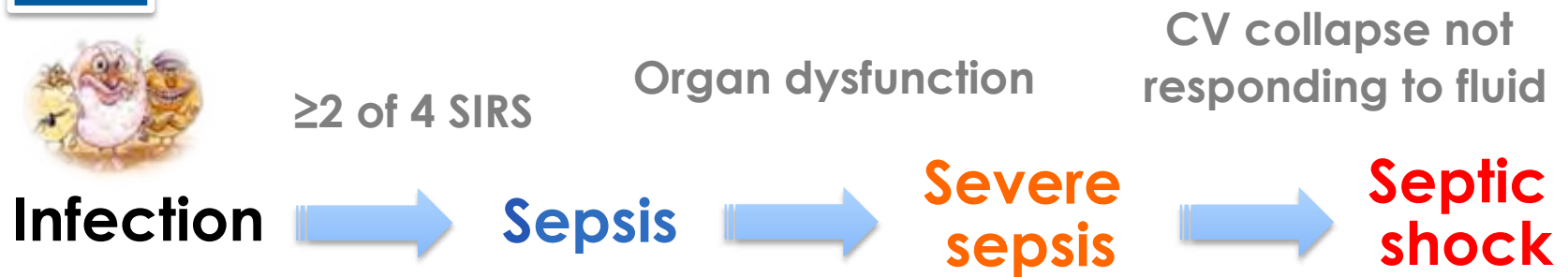
# Sepsis Definitions – The Consensus

- **No-one** liked current definition:
  - sepsis = infection +  $\geq 2$  SIRS criteria
    - ❖ too non-specific → over-diagnosis/over-Rx
    - ❖ not very sensitive in detecting those who go bad
- **Everyone** agreed that sepsis represents ‘bad’ infection
  - i.e. infection leading onto **organ dysfunction** → bad outcome (ICU admission for organ support ± death)
- **Everyone** agreed that [new] sepsis = [old] severe sepsis

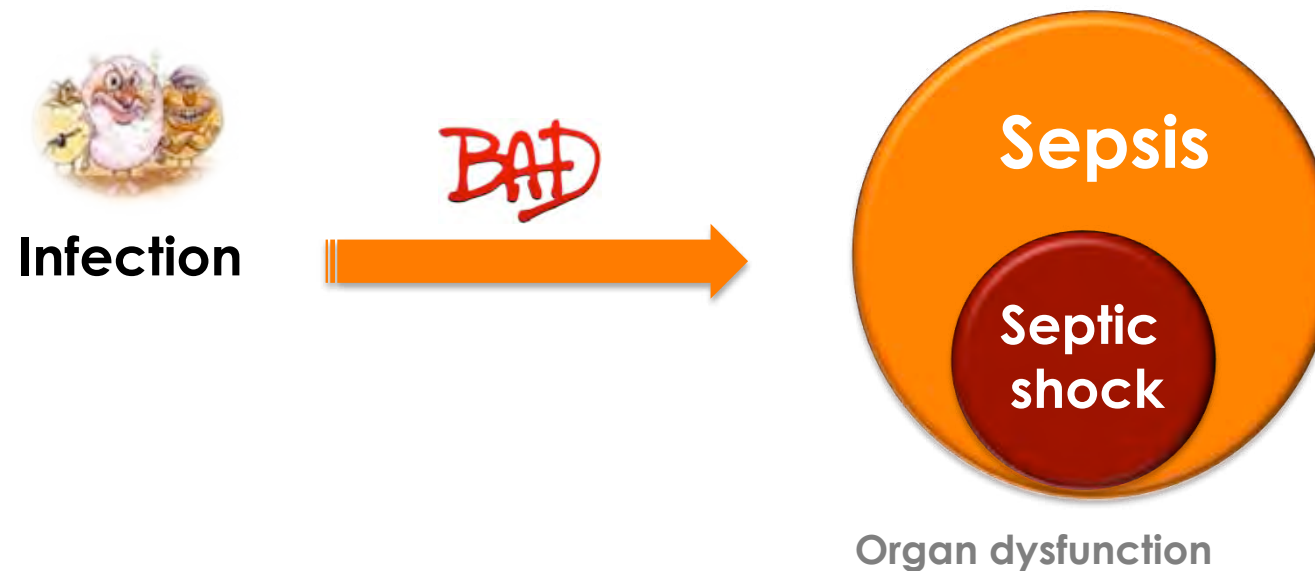


# The Conceptual Model

OLD



NEW



# **Better Understanding of Sepsis Pathobiology**

- **More than just rampant inflammation**
- **Key role of immunosuppression**
- **Contribution of non-immune mechanisms**
- **Possible adaptive nature of organ dysfunction - hibernation**
- **Re-appraisal of the nature of septic shock**

# Task Force Recommendations

**Sepsis should be defined as life-threatening organ dysfunction due to a dysregulated host response to infection**

# The Conceptual Model

- **Advantages**

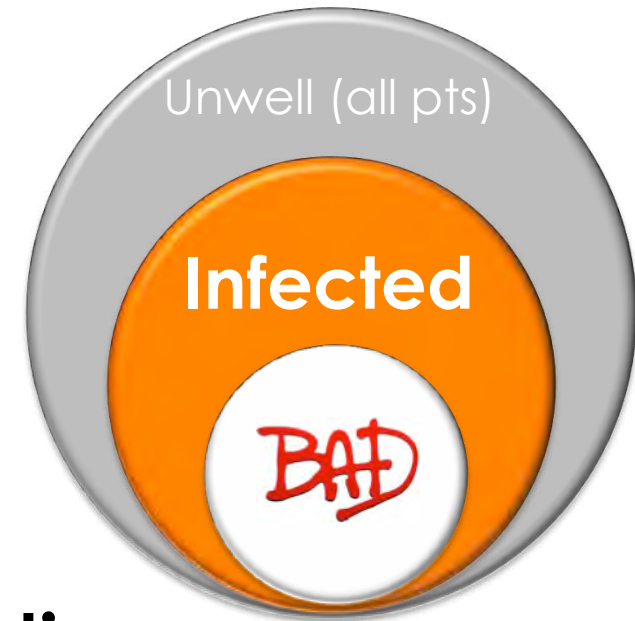
- Incorporates most up-to-date thinking on sepsis pathobiology
- Provides closest approximation possible to describing “what sepsis is”

- **Concerns**

- Of limited practical utility as they contain elements that cannot be clinically identified
- “organ dysfunction”
- “dysregulated host response”



# Sepsis Definitions – The Approach



- We did not try to define infection
- We wanted to recognize **BAD** = patients who do badly, i.e. needing long ICU stay, dying,...
- Can patients who go **BAD** be identified **early, simply & more accurately** than at present?

# Task Force Recommendations

Sepsis should be defined as life-threatening **organ dysfunction** due to a dysregulated host response to infection

- SOFA score to characterize organ dysfunction (OD)
  - Some limitations, but very familiar & multiple studies
- Rise in total SOFA  $\geq 2$  identifies OD within sepsis definition
- SOFA  $\geq 2$  identifies infected patients in ward/ED at significantly increased risk of death

Organ dysfunction is characterized by a rise in total SOFA  $\geq 2$

# Serial Evaluation of the SOFA Score to Predict Outcome in Critically Ill Patients

Flavio Lopes Ferreira, MD

Daliana Peres Bota, MD

Annette Bross, MD

Christian Mélot, MD, PhD,  
MSciBiostat

Jean-Louis Vincent, MD, PhD

# YES BUT...

**Table 1.** The Sequential Organ Failure Assessment (SOFA) Score\*

Variables	SOFA Score				
	0	1	2	3	4
Respiratory Pao <sub>2</sub> /Fio <sub>2</sub> mm Hg	≥100	<100	<80	<60†	<40†
Coagulation Platelet					
Liver Bilirubin					
Cardiovasc Hypoten					>0.1, >0.1§
Central ner Glasgow					
Renal Creatinine, mg/dL or urine output, mL/d					>0.6 or <200

\*Norepi indicates norepinephrine; Dob, dobutamine; Dop, dopamine; Epi, epinephrine; and Fio<sub>2</sub>, fraction of inspired oxygen.

†Values are with respiratory support.

‡To convert bilirubin from mg/dL to μmol/L, multiply by 17.1.

§Adrenergic agents administered for at least 1 hour (doses given are in μg/kg per minute).

||To convert creatinine from mg/dL to μmol/L, multiply by 88.4.

- ❖ Cumbersome (11 variables including blood tests)
- ❖ Will not be performed routinely on non-ICU patients
- ❖ Need simpler system to flag up at-risk patients on the ward

# 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; André 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



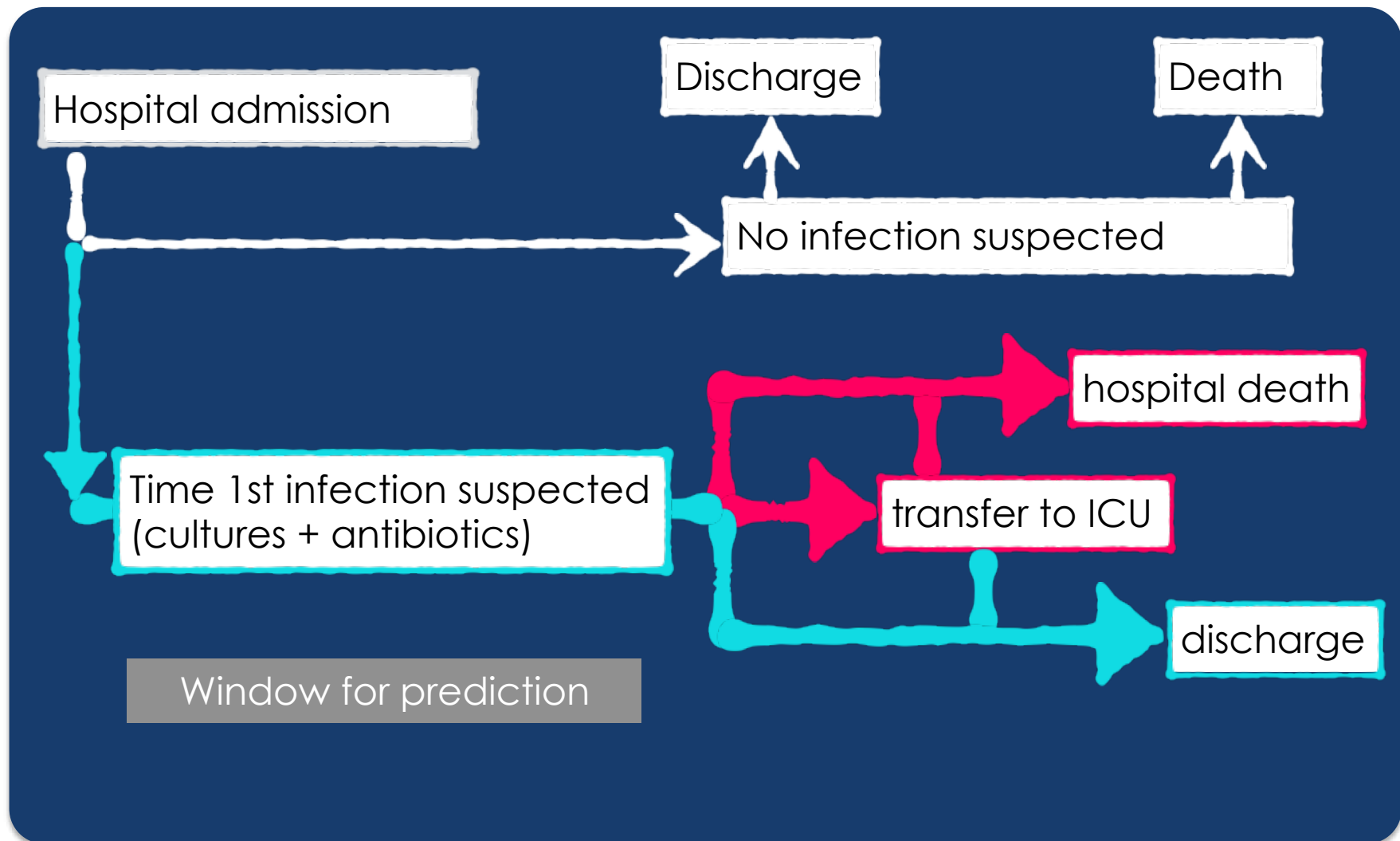
Chris Seymour, UPMC

Cohort	Years	Hospitals	Total no.
Univ Pittsburgh Med Center *	2010 - 2012	9	1,309,025
Kaiser Permanente N California *	2007 - 2013	20	1,847,165
Veterans' Administration Hospitals *	2007 - 2010	130	1,640,543
King County Emerg Med System	2009 - 2010	5	50,727
Jena Univ Hospital, Germany	2011 - 2012	1	38,098
<b>Totals</b>		<b>177</b>	<b>4,885,960</b>

\* Electronic health records

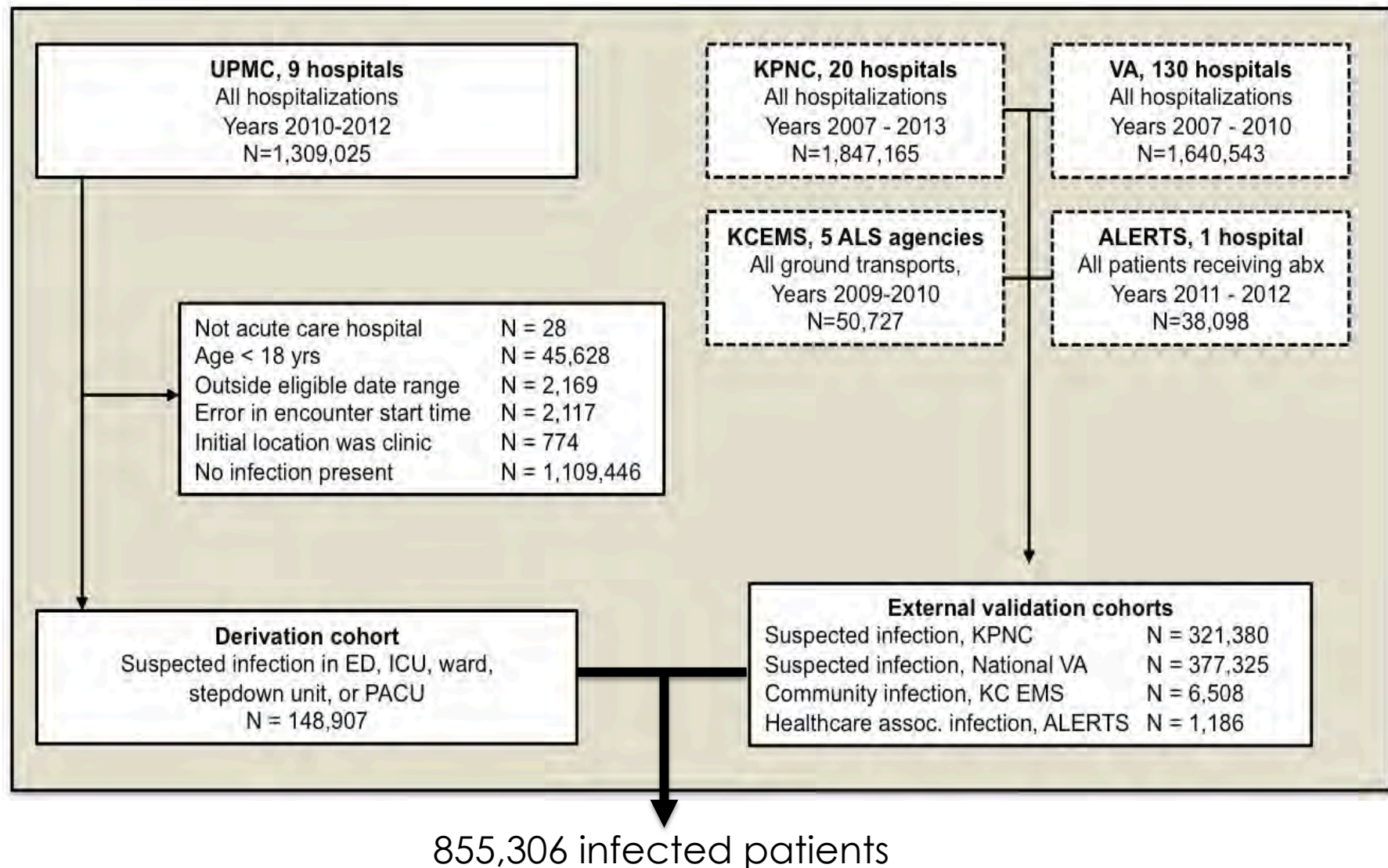
**JAMA. 2016;315(8):762-774.**

# An Empirical Evaluation of Criteria for Sepsis





# Derivation & validation cohorts



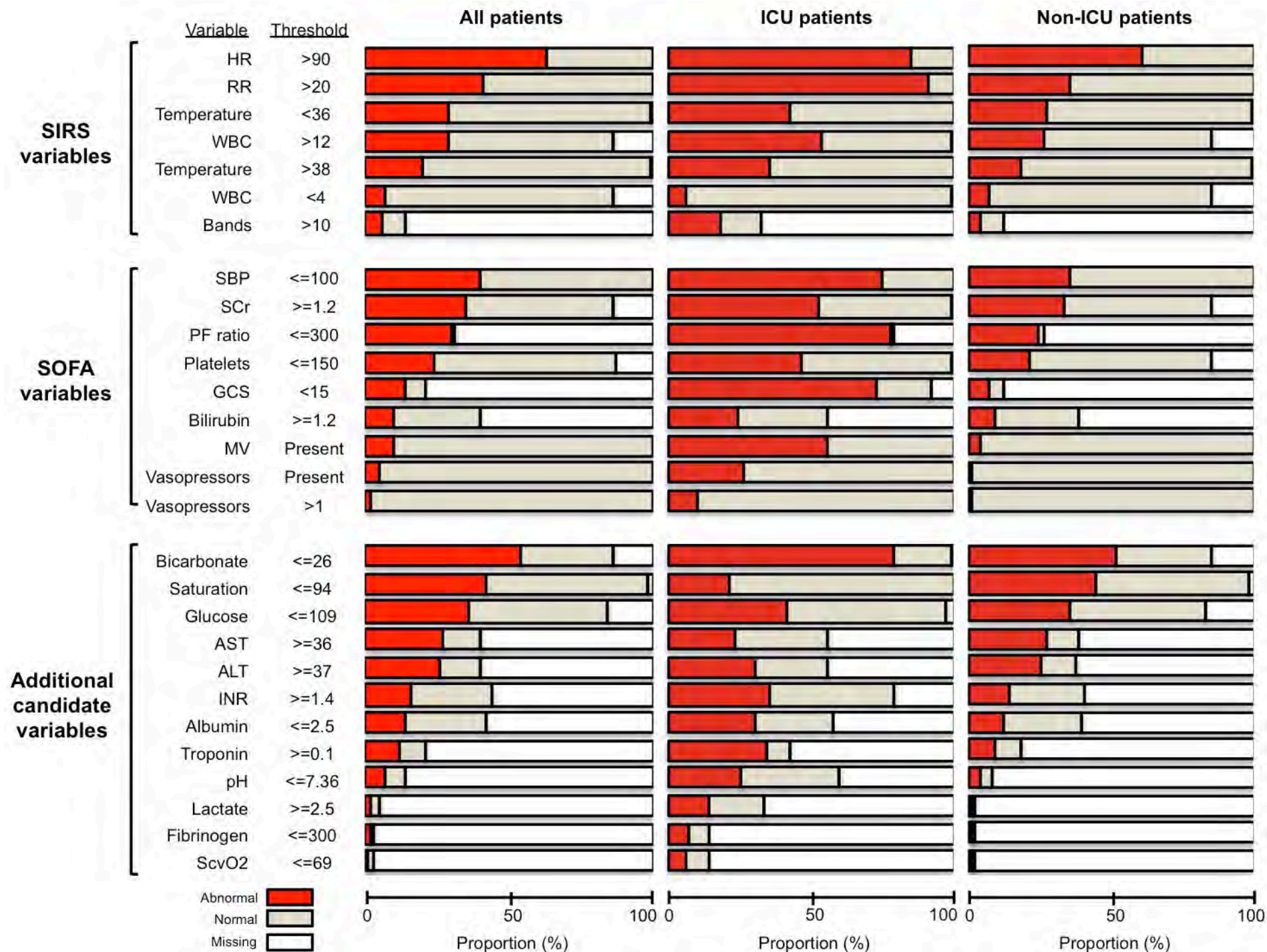
# Population characteristics & outcome

## Derivation cohort

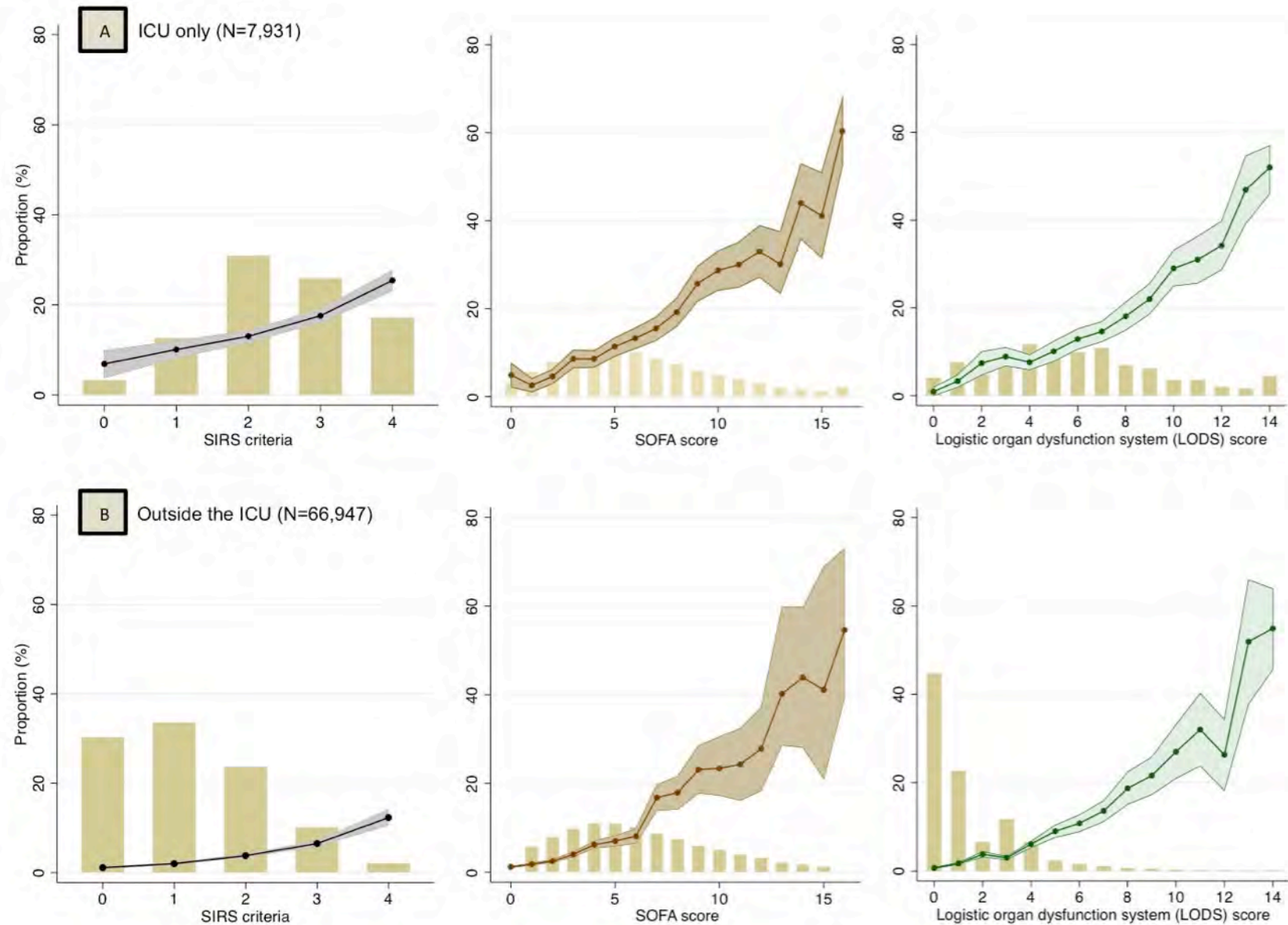
- N=148,907 pts; age 61 (19) y.o.; SOFA 1.8 (2.6)
- Suspected infection outside of ICU 77%
  - ED 44%
  - Ward 33%
  - ICU/PACU 12%
  - Stepdown 1%
- Suspected infection within 48h of admission 86%
- Lactate  $\geq 2.0$  mmol.L<sup>-1</sup> (% of measured) 46%
- ICU admission 25%
- Hospital mortality 4%

## Primary outcome

- Death
- Long ICU stay ( $\geq 3$  days)
- Influence of SOFA, SIRS, LODS variables...



# SIRS, SOFA & LODS scores: distribution & outcome





# Building novel, simplified criteria: the qSOFA

- Early, simple & accurate identification of 'badness'



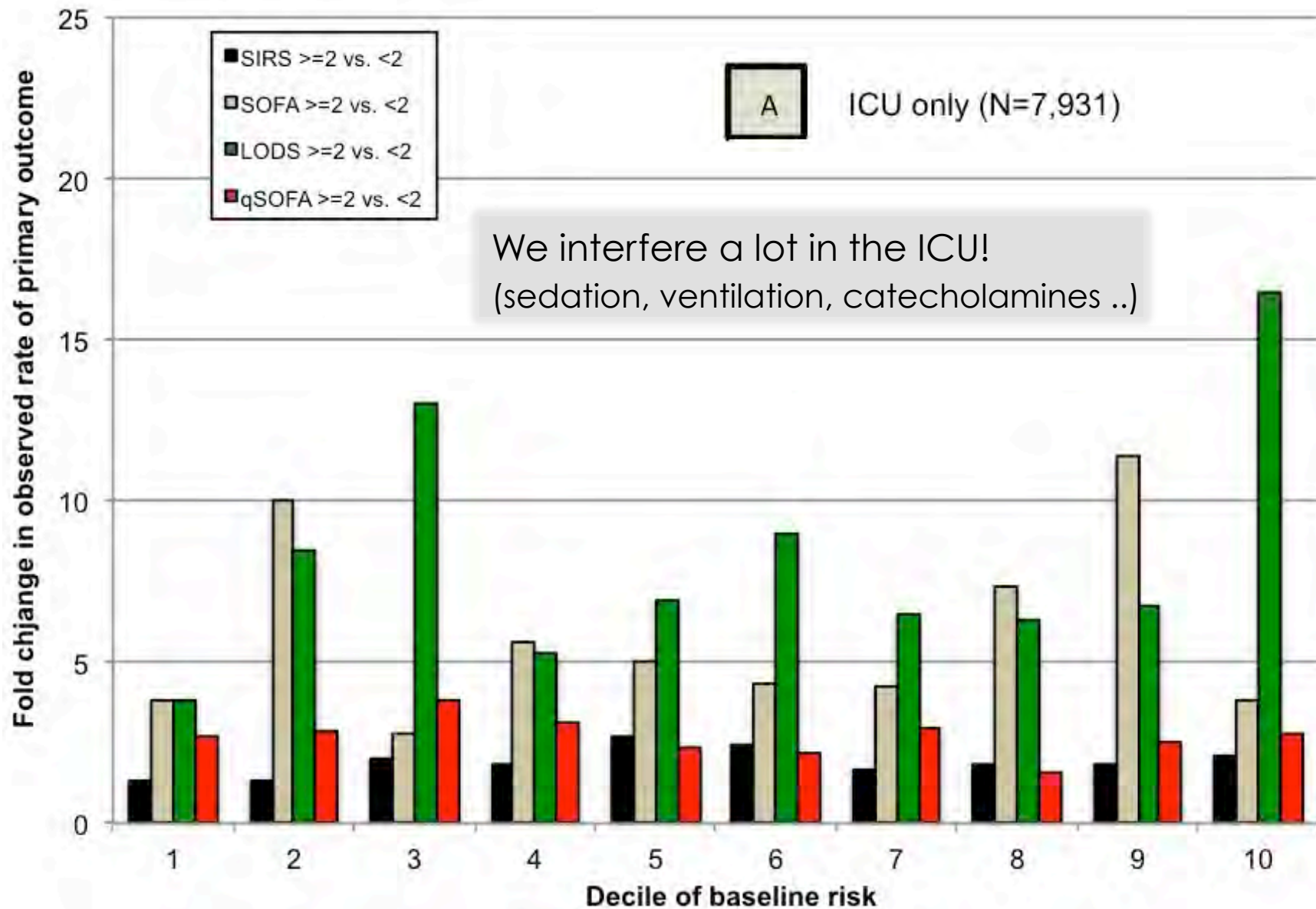
3 simple bedside clinical criteria



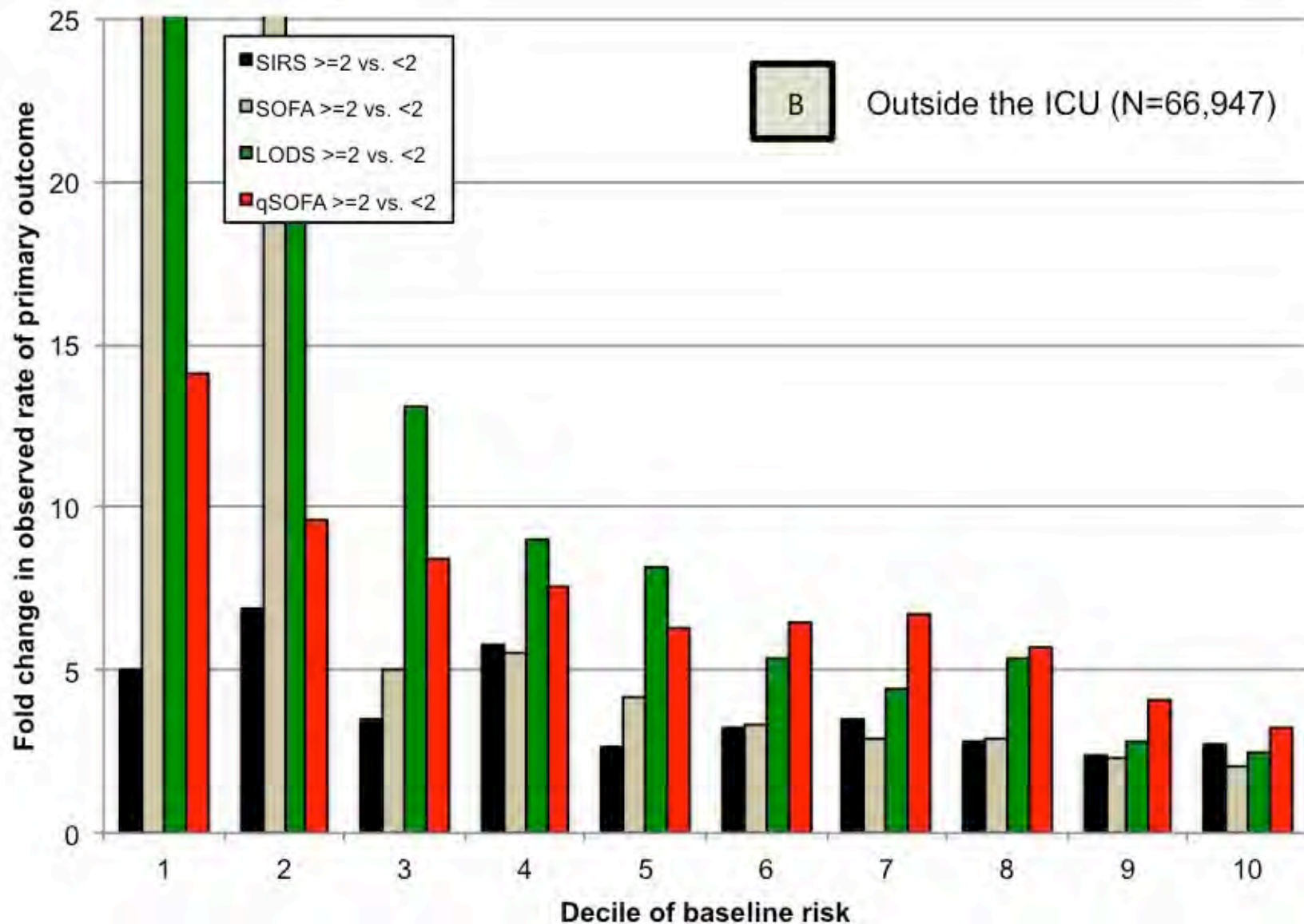
Baseline risk model variables		Odds ratios, 95% CI for primary outcome
Age, yrs *		4.03 (3.53, 4.59)
Charlson comorbidity		1.13 (1.11, 1.15)
Race/ Ethnicity	White	Ref
	Black	0.89 (0.79, 1.01)
	Other	1.37 (1.22, 1.53)
Male		1.54 (1.43, 1.66)
<b>qSOFA variables</b>		
Respiratory rate $\geq 22$ BPM		3.20 (2.90, 3.52)
Systolic blood pressure $\leq 100$ mmHg		2.60 (2.39, 2.84)
Altered mental status (GCS $\leq 13$ )		4.31 (3.96, 4.69)



# Scores & observed rates of primary putcome



# Scores & observed rates of primary outcome



## So...What is qSOFA?

- Not an absolute 'diagnostic' for sepsis, rather a simple, easily-performed bedside prompt to consider:
  - Need for blood tests (score SOFA and then formally diagnose 'sepsis')
  - Need for prompt interventions
  - Need for increased monitoring/surveillance & possible step-up to critical care



3 simple bedside  
clinical criteria



Low BP

Altered mental status

Tachypnoea

# How good is qSOFA?

ICU encounters N = 7,932 AUROC in-hospital mortality				
SIRS	0.64 (0.62, 0.66)			
SOFA	<0.01	0.74 (0.73, 0.76)		
LODS	<0.01	0.20	0.75 (0.73, 0.76)	
qSOFA	0.01	<0.01	<0.01	0.66 (0.64, 0.68)

**SOFA and LODS  
superior in the ICU**

Outside the ICU encounters N = 66,522 AUROC in-hospital mortality				
SIRS	0.76 (0.75, 0.77)			
SOFA	<0.01	0.79 (0.78, 0.80)		
LODS	<0.01	<0.01	0.81 (0.80, 0.82)	
qSOFA	<0.01	<0.01	0.72	0.81 (0.80, 0.82)

**qSOFA similar to  
complex scores  
outside the ICU**

**SEPSIS 3.0  
is not qSOFA!**





## EDITORIAL

# The new sepsis consensus definitions: the good, the bad and the ugly



Charles L. Sprung<sup>1,2,3\*</sup>, Roland M. H. Schein<sup>1,2,3</sup> and Robert A. Balk<sup>1,2,3</sup>

*Intensive Care Med (2016) 42:2024–2026*

OPENING THE DEBATE ON THE NEW SEPSIS DEFINITION

## Precision Medicine: An Opportunity to Improve Outcomes of Patients with Sepsis

American Journal of Respiratory and Critical Care Medicine Volume 194 Number 2 | July 15 2016

## Systemic Inflammatory Response Syndrome, Quick Sequential Organ Function Assessment, and Organ Dysfunction



Insights From a Prospective Database of ED Patients With Infection

Julian M. Williams, MBBS; Jaimi H. Greenslade, PhD; Juliet V. McKenzie, MBBS; Kevin Chu, MBBS, MS;

Anthony F. T. Brown, MBChB; and Jeffrey Lipman, MD (research)

CHEST 2017; 151(3):586-596

January 17, 2017

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

Yonathan Freund, MD, PhD<sup>1,2</sup>; Najla Lemachatti, MD<sup>2</sup>; Evguenia Krastinova, MD, PhD<sup>3</sup>; et al



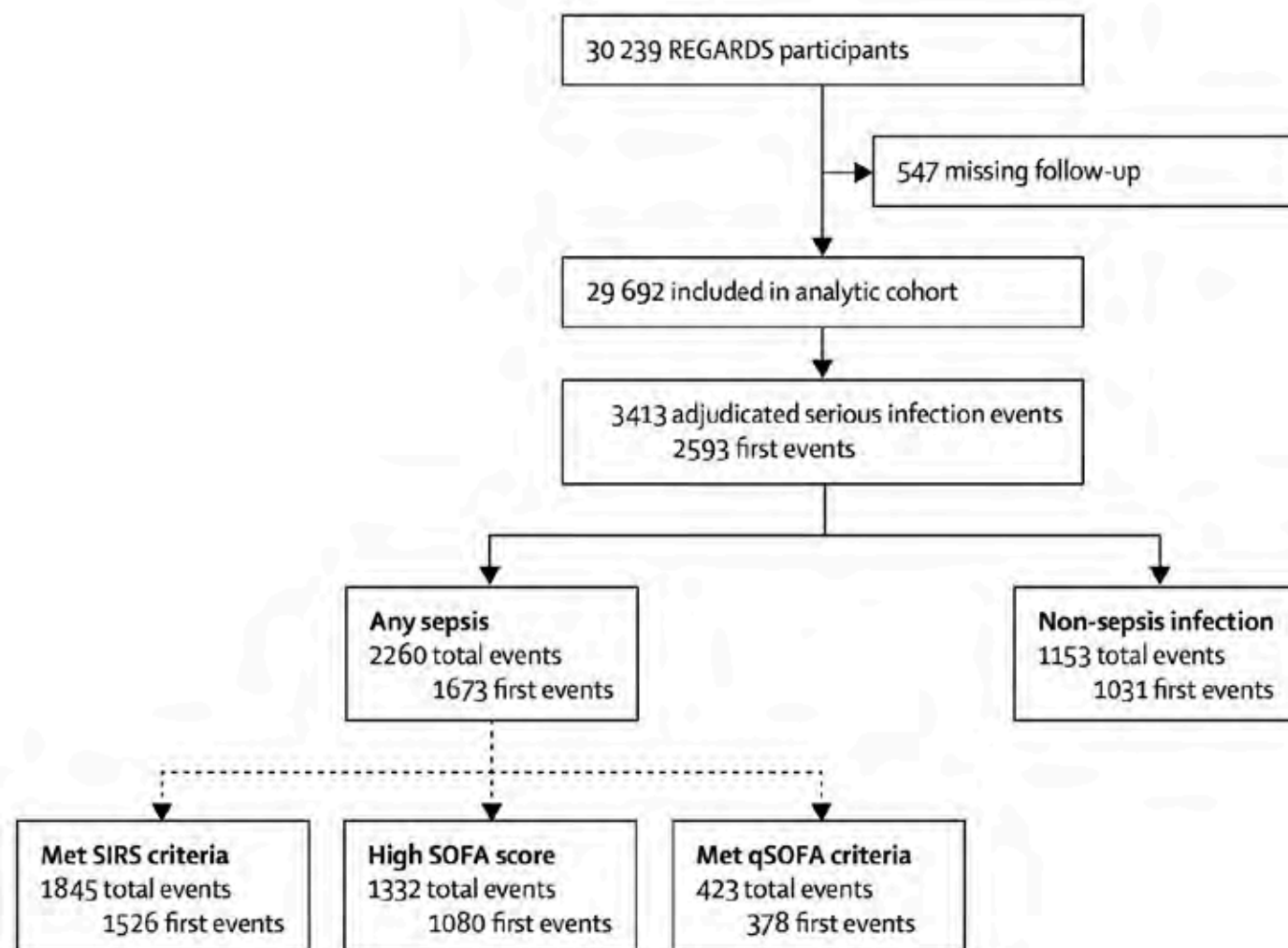
**Question** Does the quick Sequential Organ Failure Assessment (qSOFA) score more accurately predict in-hospital mortality than the systemic inflammatory response syndrome (SIRS) or severe sepsis criteria among emergency department patients with suspected infection?

**Findings** In this multicenter prospective cohort study involving 879 patients with suspected infection treated at the emergency department, the qSOFA was better at predicting in-hospital mortality with an area under the receiver operating curve (AUROC) of 0.80 than were SIRS (AUROC, 0.65) and severe sepsis (AUROC, 0.65).

**Meaning** Among patients presenting to the emergency department setting with suspected infection, the use of qSOFA resulted in greater prognostic accuracy for in-hospital mortality than either SIRS or severe sepsis.

# Application of the Third International Consensus Definitions for Sepsis (Sepsis-3) Classification: a retrospective population-based cohort study

John P Donnelly, Monika M Safford, Nathan I Shapiro, John W Baddley, Henry E Wang

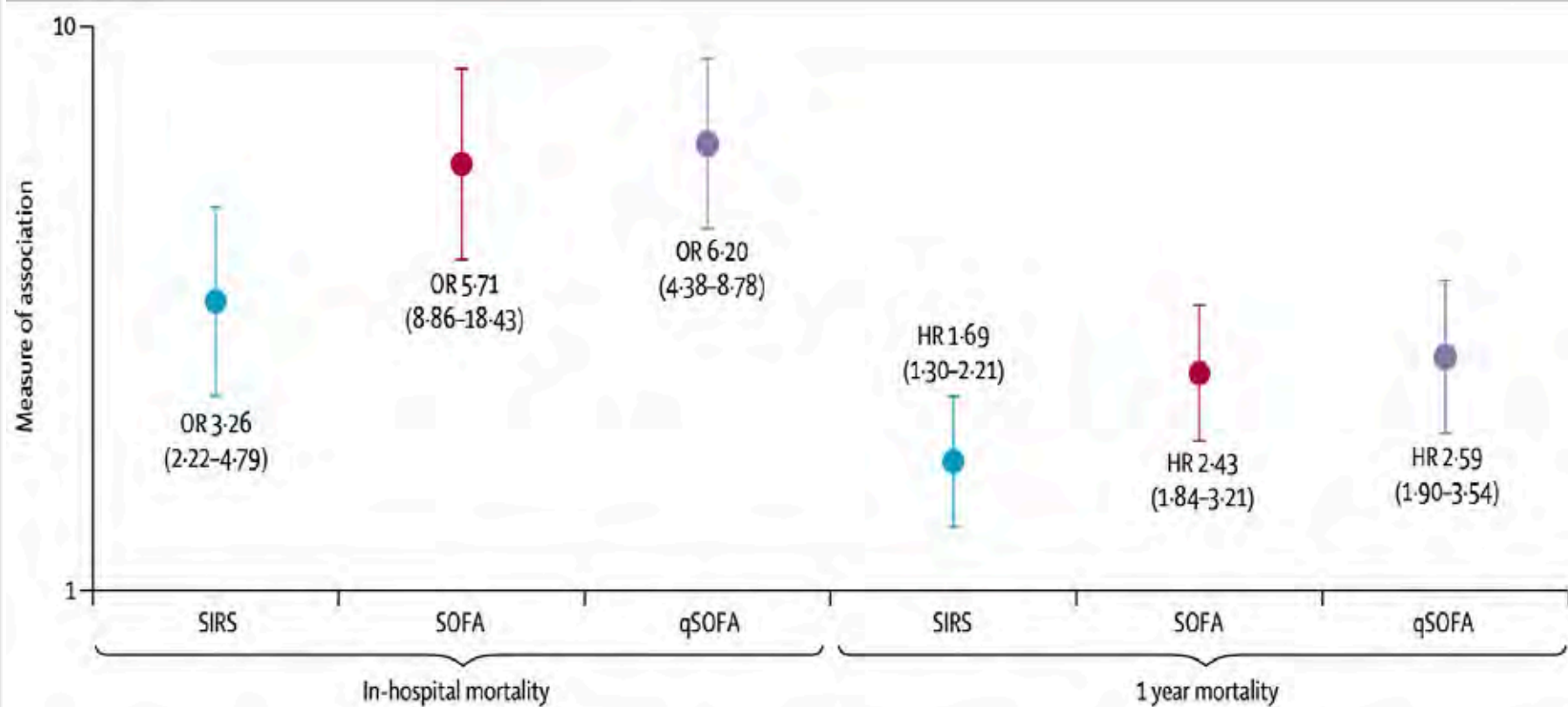


*Lancet Infect Dis 2017*



# Application of the Third International Consensus Definitions for Sepsis (Sepsis-3) Classification: a retrospective population-based cohort study

John P Donnelly, Monika M Safford, Nathan I Shapiro, John W Baddley, Henry E Wang



# Quick Sepsis-related Organ Failure Assessment, Systemic Inflammatory Response Syndrome, and Early Warning Scores for Detecting Clinical Deterioration in Infected Patients outside the Intensive Care Unit

Matthew M. Churpek<sup>1,2</sup>, Ashley Snyder<sup>1</sup>, Xuan Han<sup>1</sup>, Sarah Sokol<sup>3</sup>, Natasha Pettit<sup>3</sup>, Michael D. Howell<sup>1,2</sup>, and Dana P. Edelson<sup>1,2</sup>

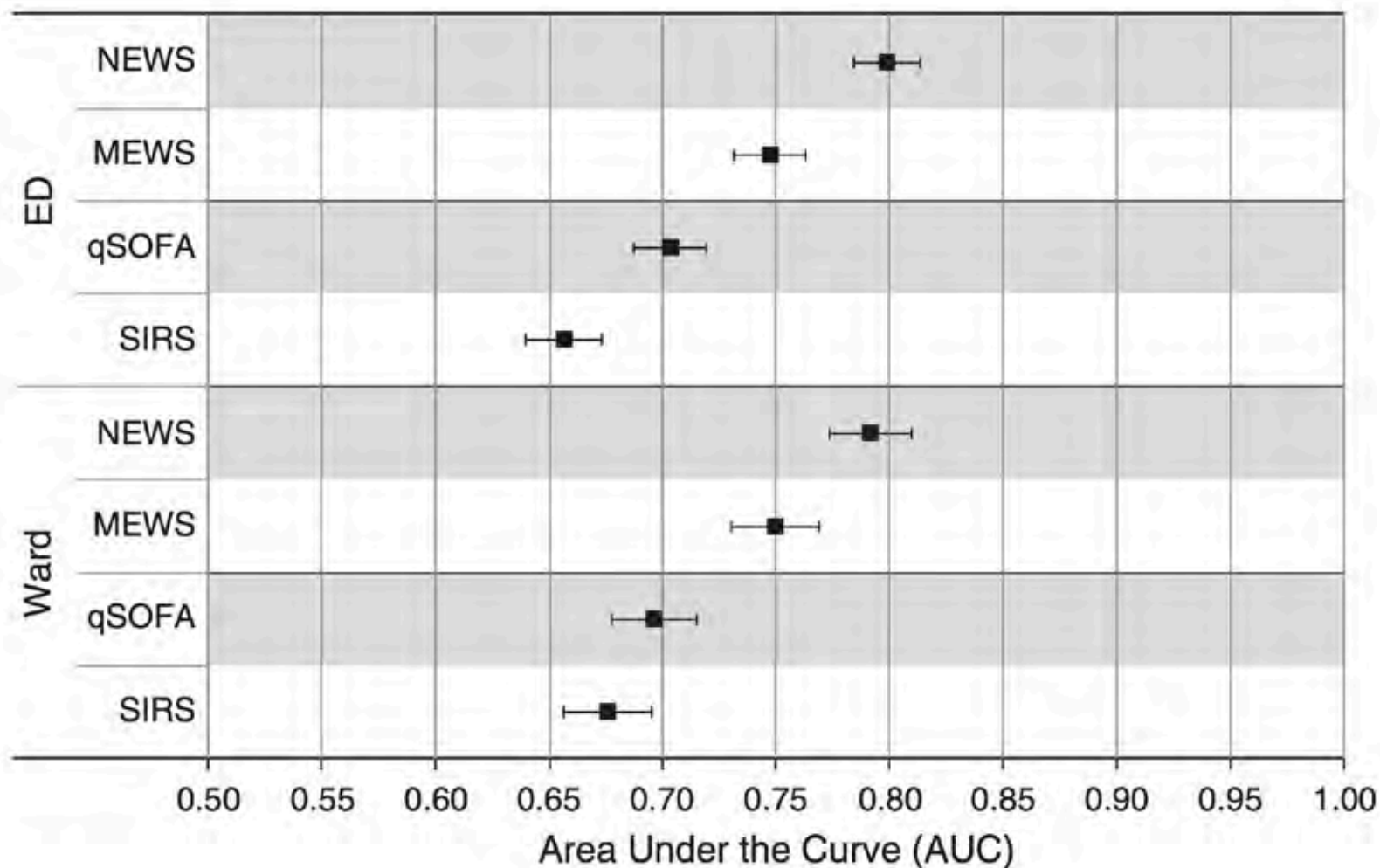


- **30,677 included patients**
- **Outcomes**
  - **Death 1649 pts (5.4%)**
  - **Death or ICU admission 7385 pts (24%)**
- **qSOFA, SIRS, Modified Early Warning Score (MEWS) & the National Early Warning Score (NEWS) compared for predicting death and ICU transfer.**



# Quick Sepsis-related Organ Failure Assessment, Systemic Inflammatory Response Syndrome, and Early Warning Scores for Detecting Clinical Deterioration in Infected Patients outside the Intensive Care Unit

Matthew M. Churpek<sup>1,2</sup>, Ashley Snyder<sup>1</sup>, Xuan Han<sup>1</sup>, Sarah Sokol<sup>3</sup>, Natasha Pettit<sup>3</sup>, Michael D. Howell<sup>1,2</sup>, and Dana P. Edelson<sup>1,2</sup>



# 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; André Scherag, PhD; Gordon Rubinfeld, 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

- **500,000 vs 30,677 patients**
- **Outcomes**
  - **Death  $\pm$  ICU stay > 3 days vs death  $\pm$  ICU admission**
- **A 3-boundary levels vs 13/19 boundaries**

## Quick Sepsis-related Organ Failure Assessment, Systemic Inflammatory Response Syndrome, and Early Warning Scores for Detecting Clinical Deterioration in Infected Patients outside the Intensive Care Unit

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## Sepsis-3: Syndromes and Empiricism in the Age of Big Data

Steve Harris, Ph.D.

*Department of Critical Care Medicine*

*University College Hospital London*

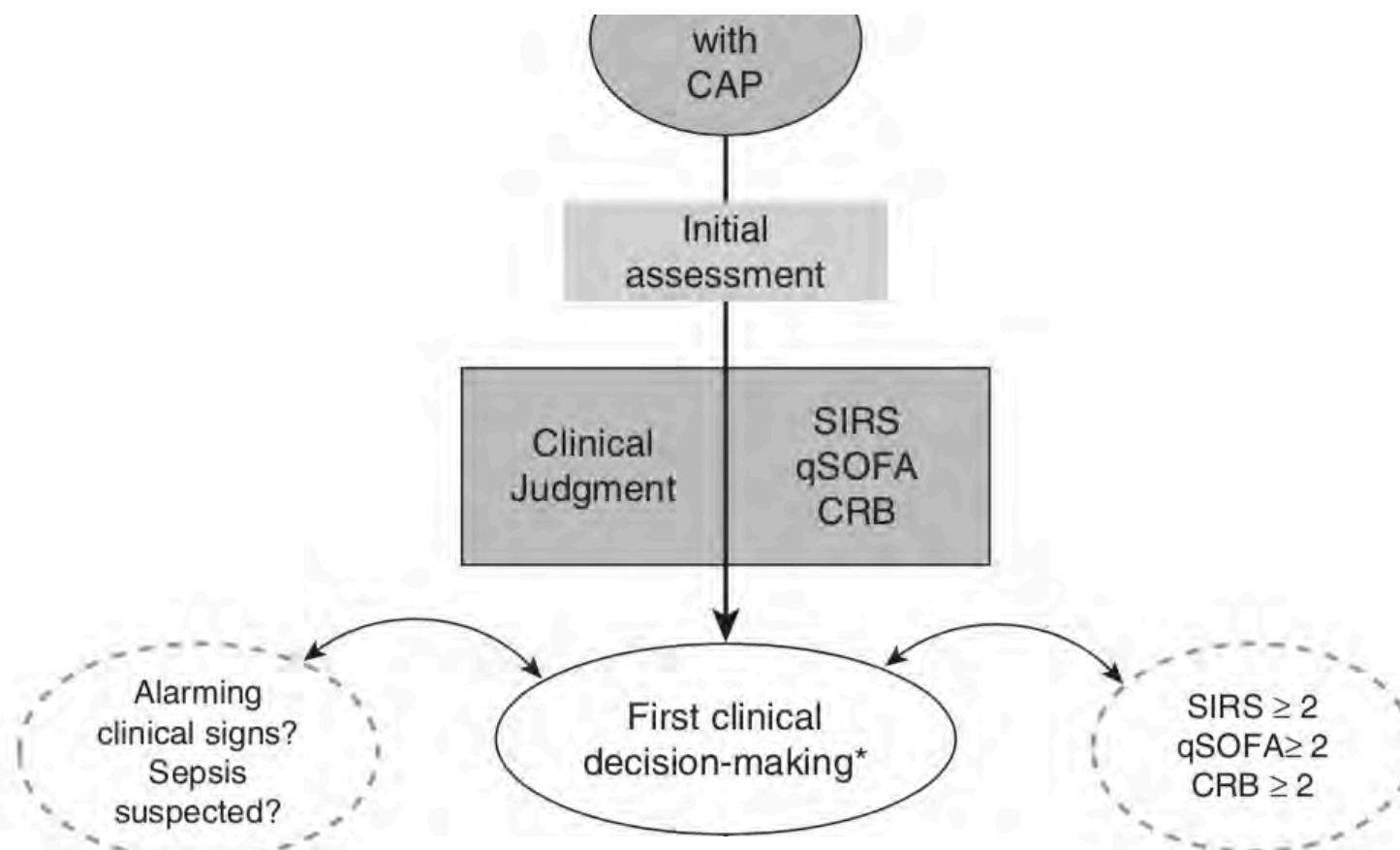
*London, United Kingdom*

...moving away from qSOFA, but this was never the intention. But neither should we wish for a Sepsis 3.1 revision with NEWS replacing qSOFA. Just as SIRS in the 1992 definition highlighted the systemic response to infection using a simple syndromic definition, qSOFA is highlighting that sepsis is a syndrome of “life-threatening organ dysfunction.” Where SIRS was sensitive, qSOFA is demonstrably more specific, but this should not be seen as putting patients at risk (12). Infection should be

# New Sepsis Definition (Sepsis-3) and Community-acquired Pneumonia Mortality

## A Validation and Clinical Decision-Making Study

Otavio T. Ranzani<sup>1,2</sup>, Elena Prina<sup>1</sup>, Rosario Menéndez<sup>3</sup>, Adrian Ceccato<sup>1,4</sup>, Catia Cilloniz<sup>1</sup>, Raul Méndez<sup>3</sup>, Albert Gabarrus<sup>1</sup>, Enric Barbeta<sup>1</sup>, Gianluigi Li Bassi<sup>1</sup>, Miquel Ferrer<sup>1</sup>, and Antoni Torres<sup>1</sup>

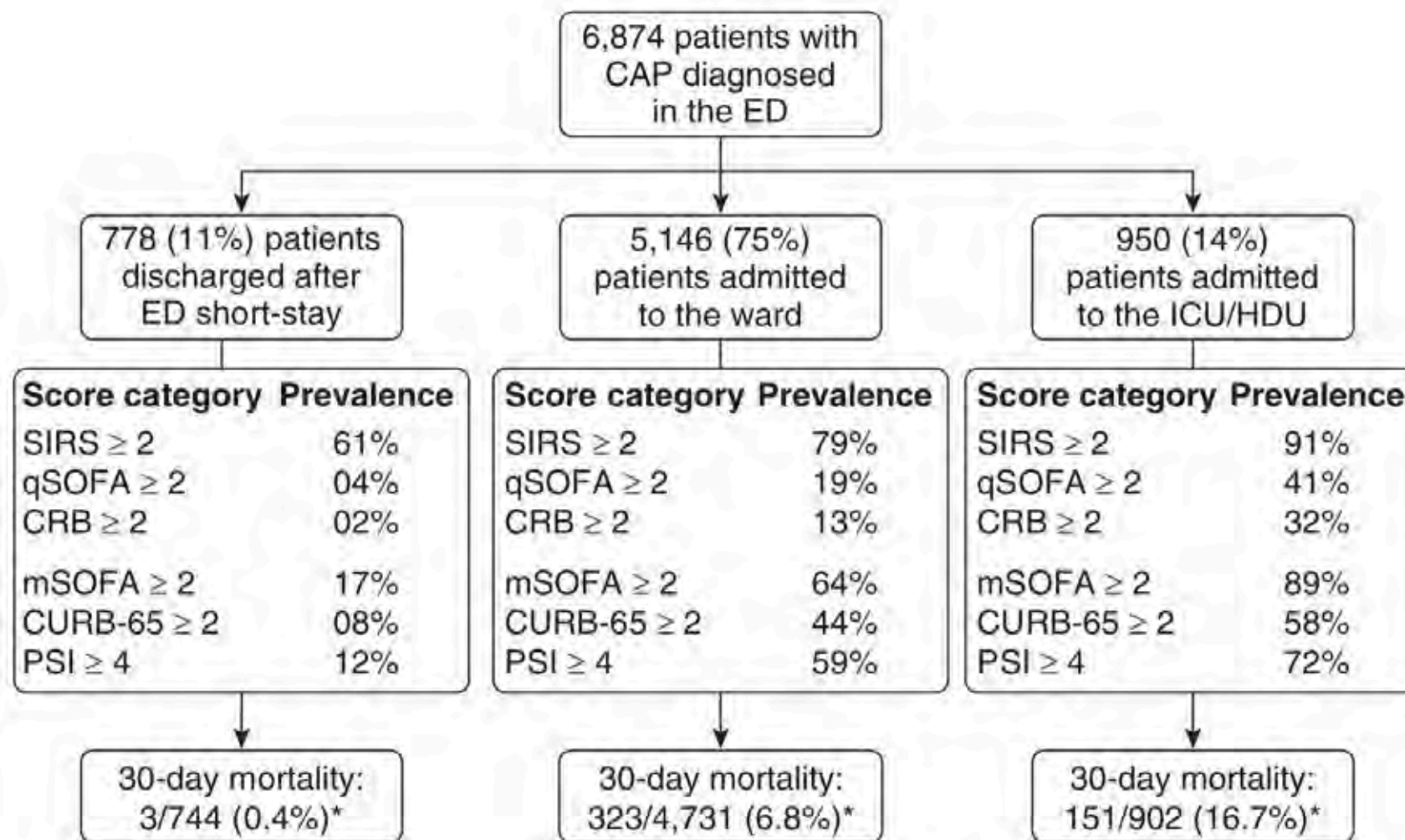




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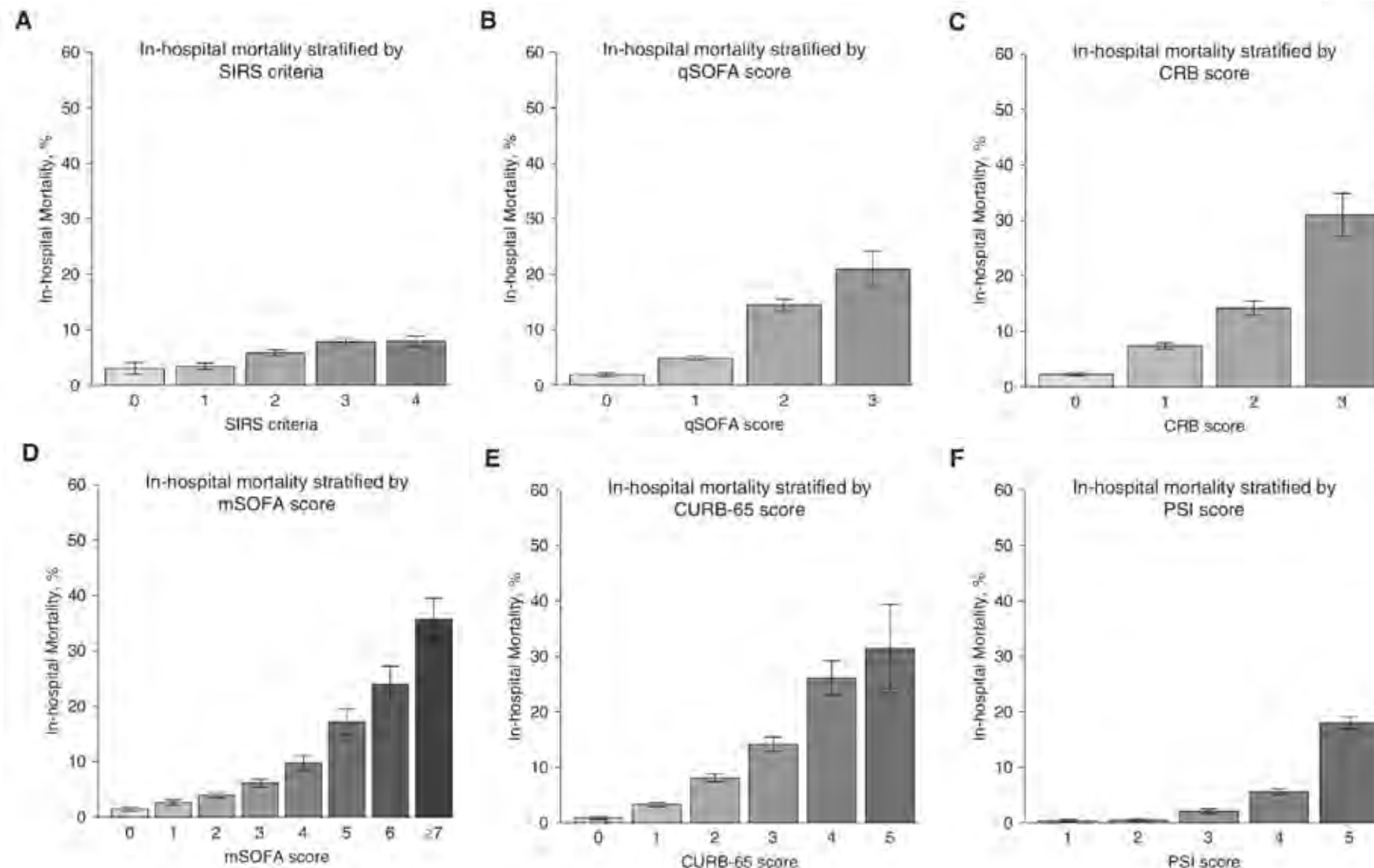




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# New Sepsis Definition (Sepsis-3) and Community-acquired Pneumonia Mortality

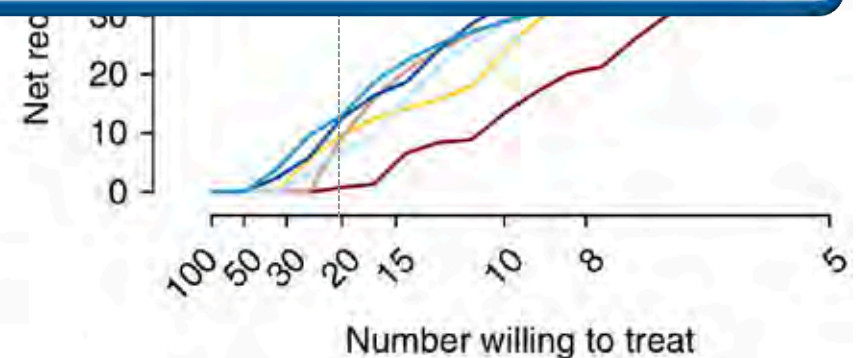
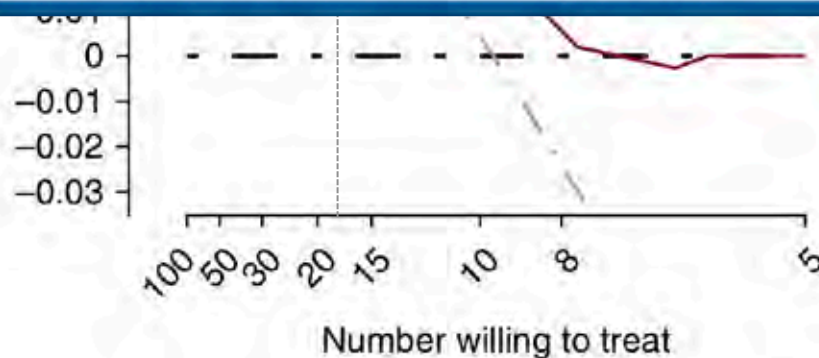
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Decision-curve analysis for in-hospital mortality/3 days of ICU stay

Interventions avoided for in-hospital mortality/3 days of ICU stay

**Conclusions:** qSOFA and CRB outperformed SIRS and presented better clinical usefulness as prompt tools for patients with community-acquired pneumonia in the emergency department. Among the tools for a comprehensive patient assessment, PSI had the best decision-aid tool profile.



**net benefit = benefit X true-positive classifications - harm/cost X false-positive classifications**

# Inside the Sepsis 3.0 Definitions

- **SIRS has disappeared**
- **Sepsis is old “severe sepsis”**
- **Clinical criteria for sepsis**
  - Infection plus 2 or more SOFA points (above baseline)
- **Prompt outside the ICU to consider sepsis**
  - Infection plus 2 or more qSOFA points

**What about septic shock?**

# Definition of Septic Shock

- **Everyone agreed** that septic shock is more than hypotension alone
- There are cellular & metabolic abnormalities

Sepsis can be defined as a subset of sepsis where underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality



## *Development plan*

- Systematic review of previous definitions
- Modified Delphi process to gain Task Force consensus
- Interrogation of large databases - SSC, UPMC, Kaiser

Manu Shankar-Hari, Guy's & St Thomas', London, UK

# Developing a New Definition and Assessing New Clinical Criteria for Septic Shock

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

Manu Shankar-Hari, MD, MSc; Gary S. Phillips, MAS; Mitchell L. Levy, MD; Christopher W. Seymour, MD, MSc; Vincent X. Liu, MD, MSc; Clifford S. Deutschman, MD; Derek C. Angus, MD, MPH; Gordon D. Rubenfeld, MD, MSc; Mervyn Singer, MD, FRCP; for the Sepsis Definitions Task Force

- **Circulatory dysfunction**
  - Hypotension after adequate fluid resuscitation
  - Vasopressors needed to maintain MAP  $\geq 65$  mmHg
- **Metabolic and cellular abnormalities**
  - Serum lactate
- **Outcome**
  - Acute hospital mortality



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	hypotension after fluids	vasopressor	lactate >2
Group 1			
Group 2			
Group 3			
Group 4			
Group 5			
Group 6			

# Highly variable mortality rates

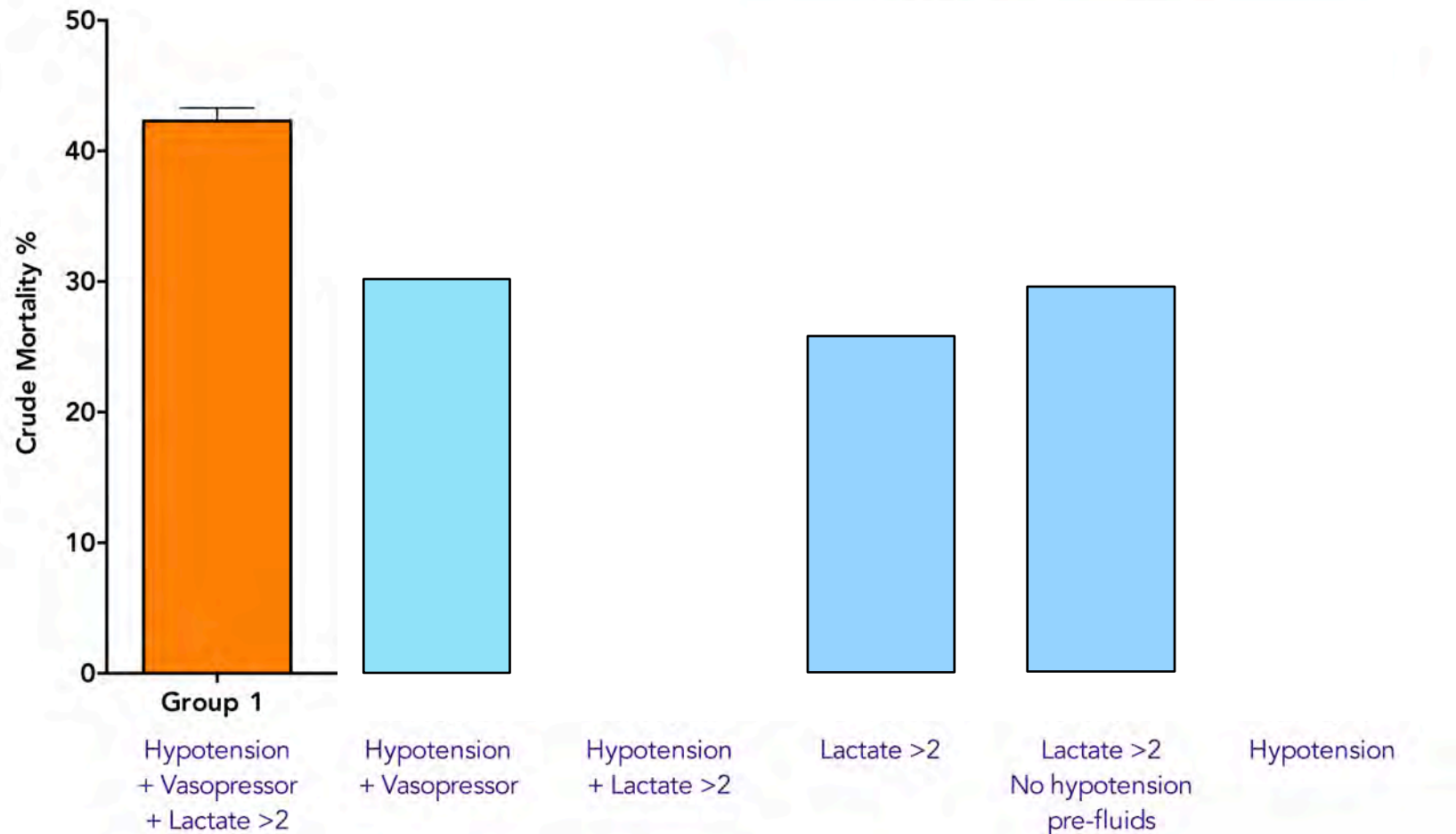


... heavily dependent  
upon definition!!

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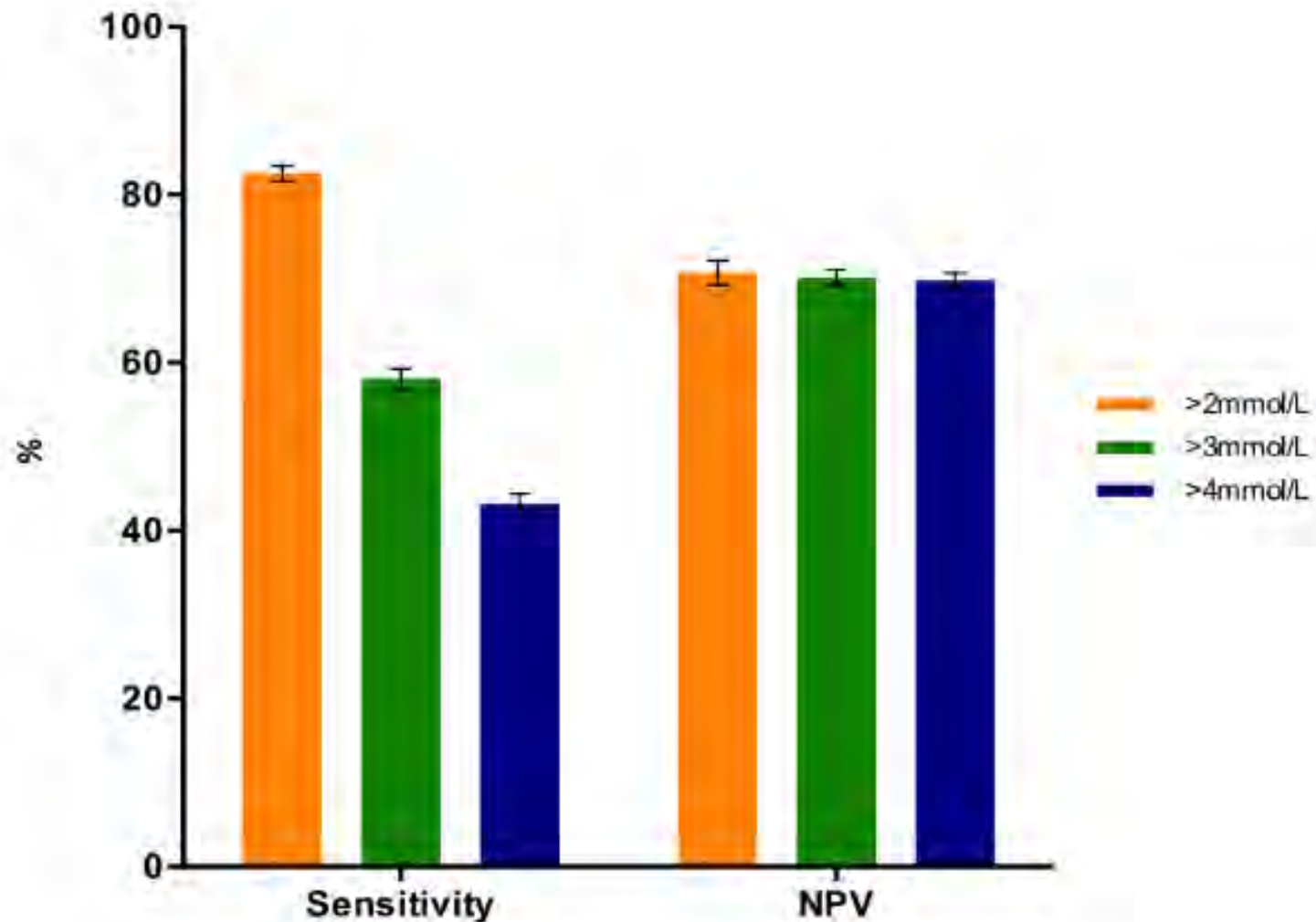


# Definition of Septic Shock – the Data

- **28,150 infected pts with  $\geq 2$  SIRS criteria +  $\geq 1$  organ dysfunction**
- **18,840 pts with persisting hypotension (MAP < 65 mmHg) and/or hyperlactatemia (> 2 mmol/L) after fluid resuscitation**
- **Hospital mortality**
  - **42.3% in patients having both hypotension + hyperlactatemia**
  - **25.7% with hyperlactatemia alone**
  - **30.1% with fluid-resistant hypotension alone**

# Rationale for the lactate cutoff

- Test performance (receiver operator characteristics)





# Definition of Septic Shock

- **Definition**

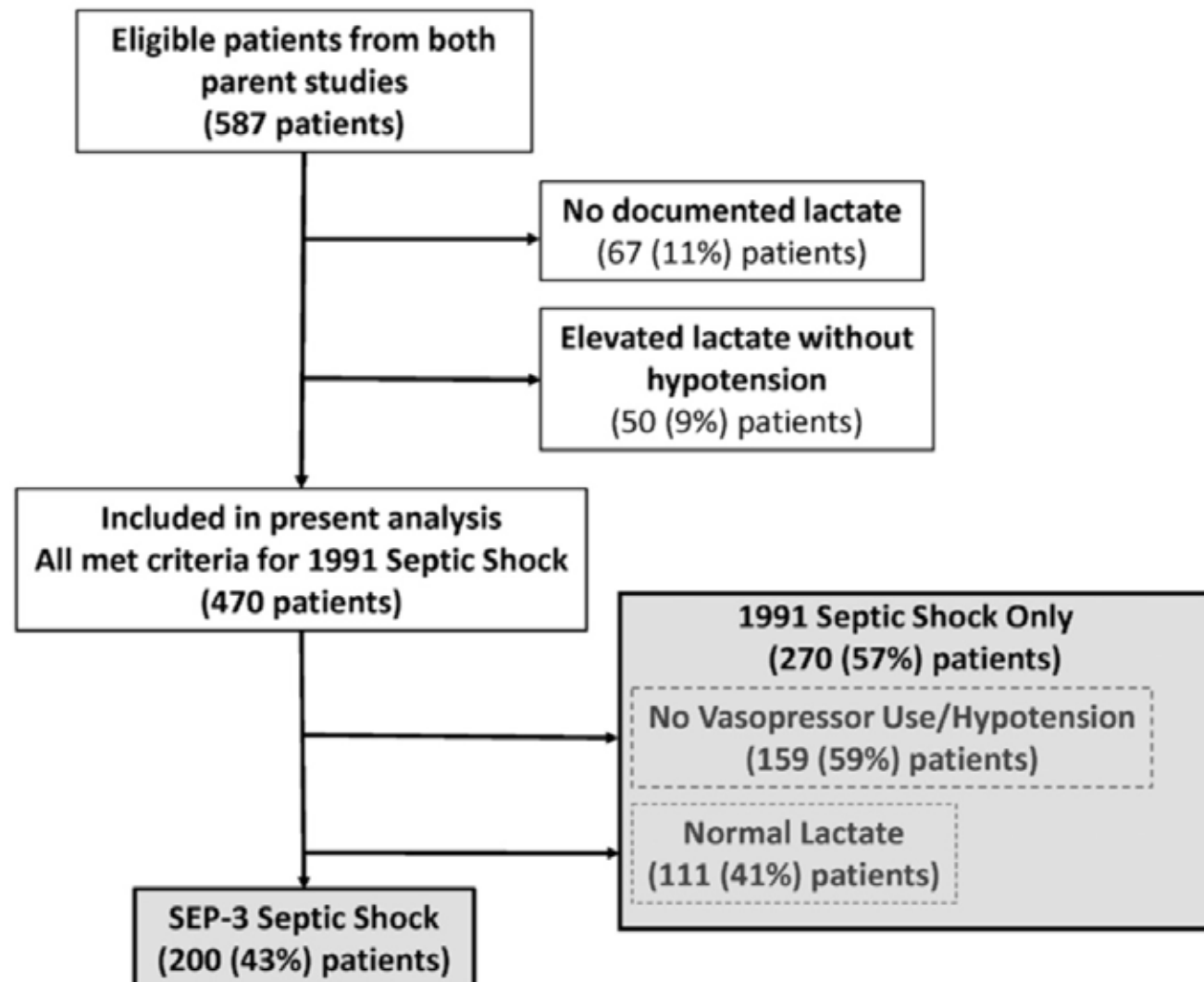
Sepsis can be defined as a subset of sepsis where underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality

- **Clinical criteria**

Despite adequate fluid resuscitation, lactate  $>2$  mmol/l and vasopressors are needed to elevate  $MAP \geq 65$  mmHg

# The Impact of the Sepsis-3 Septic Shock Definition on Previously Defined Septic Shock Patients\*

Sarah A. Sterling, MD<sup>1</sup>; Michael A. Puskarich, MD<sup>1</sup>; Andrew E. Glass, MD<sup>1</sup>;  
Faheem Guirgis, MD<sup>2</sup>; Alan E. Jones, MD<sup>1</sup>



# The Impact of the Sepsis-3 Septic Shock Definition on Previously Defined Septic Shock Patients\*

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Variable	"New" Septic Shock Criteria (Sepsis-3) (n = 200)	"Old" Septic Shock Criteria (1991 Only) (n = 270)	p
Mortality, n (%) <sup>a</sup>	57 (28.5); 95% CI, 22–35	39 (14.4); 95% CI, 10–19	< 0.001
Length of stay (IQR)			
Vasopressors days	1.3 (0.9–4); 95% CI, 2.3–4.2	1 (0–2); 95% CI, 0.9–1.4	< 0.001
Total hospital days	8 (5–16); 95% CI, 9.8–12.7	8 (4.5–12); 95% CI, 9.6–12.2	0.466
Total ICU days	3.2 (1.8–7); 95% CI, 4.9–7.1	2.5 (1–5); 95% CI, 3.6–5.1	0.006

**Conclusion:** In this analysis, 57% of patients meeting old definition for septic shock did not meet Sepsis-3 criteria. Although Sepsis-3 criteria identified a group of patients with increased organ failure and higher mortality, those patients who met the old criteria and not Sepsis-3 criteria still demonstrated significant organ failure and 14% mortality rate.

# Inside the Sepsis 3.0 Definitions

- SIRS has disappeared
- Sepsis is old “severe sepsis”
- Clinical criteria for sepsis
  - Infection + 2 or more SOFA points (above baseline)
- Prompt outside the ICU to consider sepsis
  - Infection + 2 or more qSOFA points
- Septic shock: after adequate fluid resuscitation
  - vasopressors needed to maintain MAP  $\geq 65$  mmHg

**AND**

  - lactate  $> 2$  mmol/l

# Sepsis Definition: Where Do We Stand?

- **New definitions and criteria aiming to :**
  - Help identify patients who need early ICU admission & patients with high mortality
  - Provide relevance to 2016 understanding of pathophysiology
  - Provide consistency
  - Facilitate implementation
- **Expect and encourage debate**
  - Iterative process
  - Sepsis-1 → Sepsis-2 → **Sepsis-3** → Sepsis-4



Thanks

