Society of Critical Care Medicine

The Intensive Care Professionals

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

The Sepsis Definitions Task Force

The new definitions: Why, how and what
Clifford S. Deutschman

Clinical criteria for sepsis
Christopher W Seymour

Clinical criteria for septic shock
Manu Shankar-Hari

Controversies, concerns and FAQs
Mervyn Singer

Society of Critical Care Medicine
The Intensive Care Professionals

The New Definitions: Why, How and What

Clifford S. Deutschman

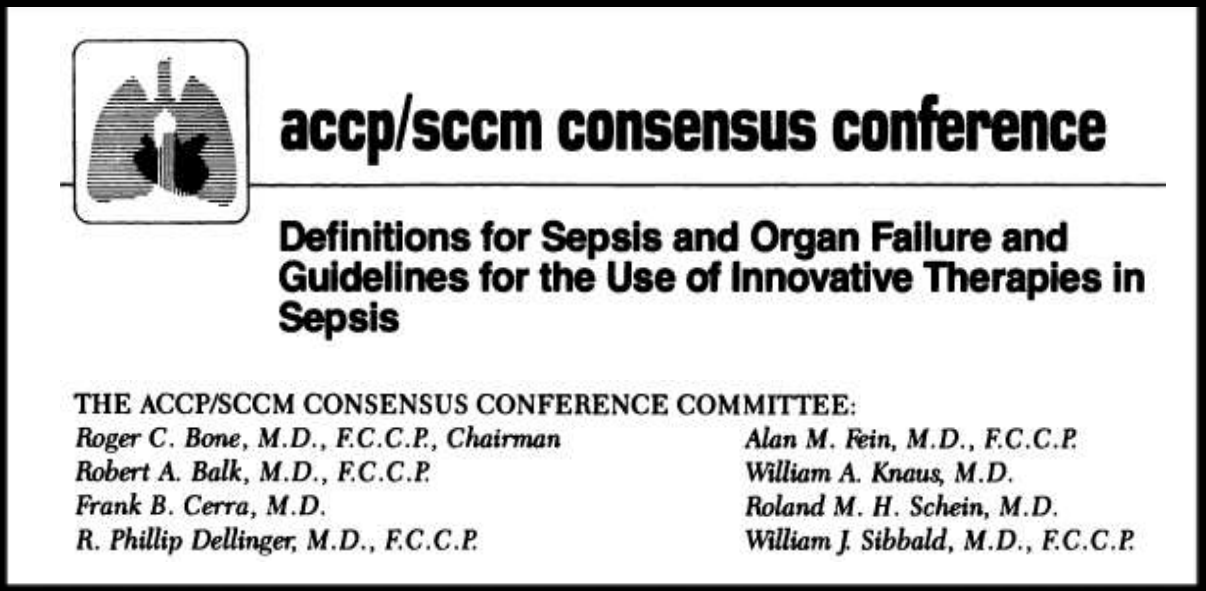
Cohen Children's Medical Center

The Feinstein Institute for Medical Research

Task Force Co-Chair

1. Why

Issues with the 1991 and 2001 Definitions

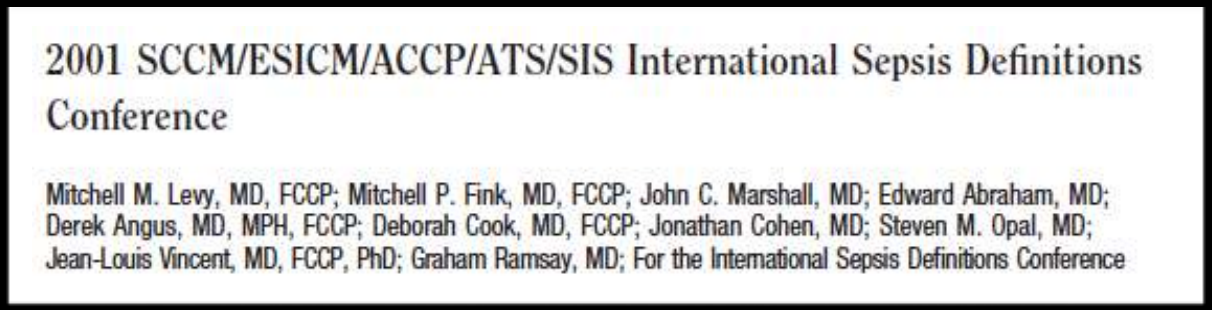


accp/sccm consensus conference

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

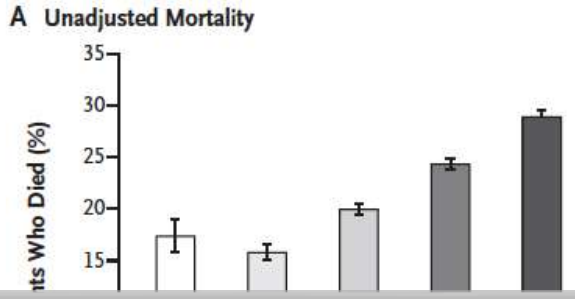
- SIRS – based
- "Severe Sepsis"
- Different criteria yielding different results

SIRS Sensitivity

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.

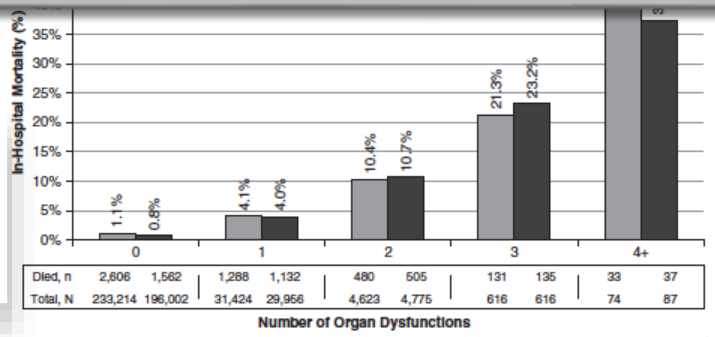
N Engl J Med 2015;372:1629-38.



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

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.



Severe Sepsis

- Confusing
  - Most people say “sepsis” when they mean “severe sepsis”
  - Is “severe sepsis” really needed ?

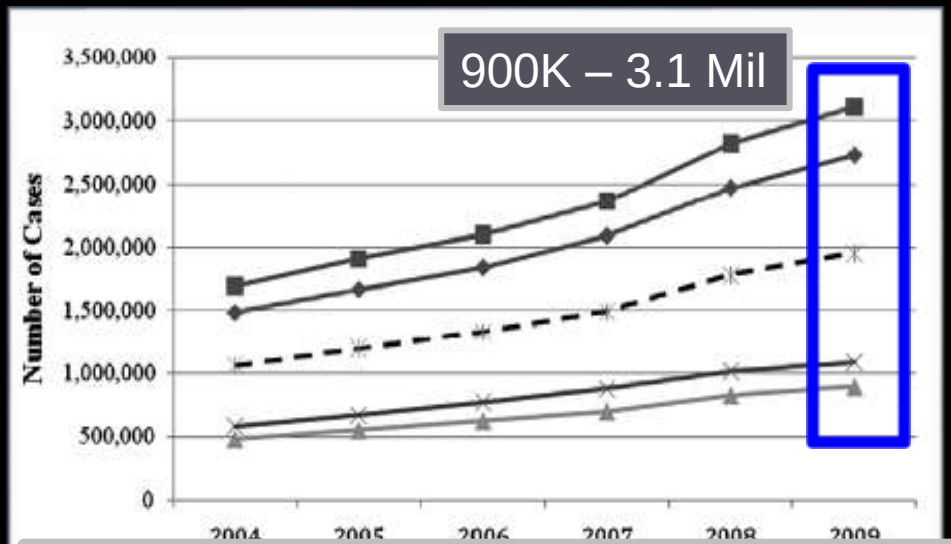
Different Criteria, Different Results

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

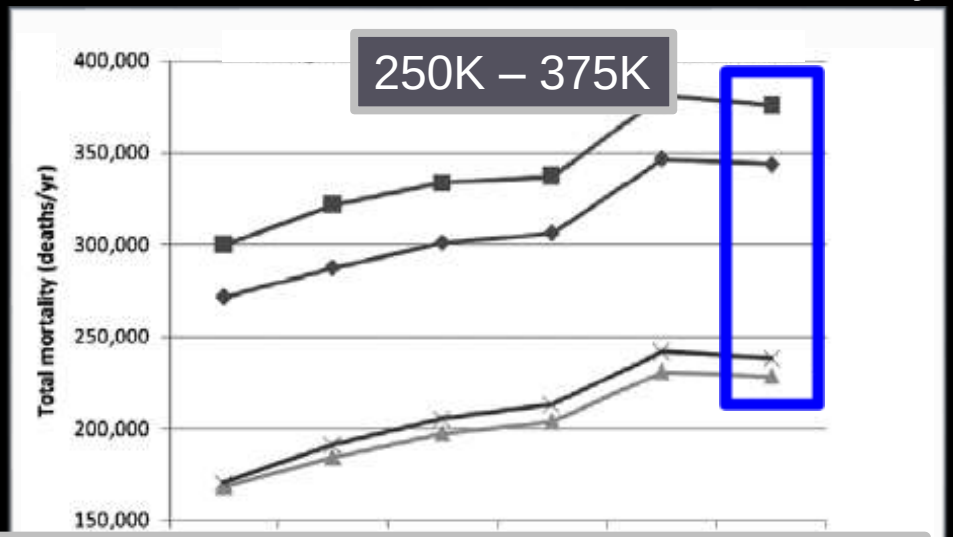
David F. Gaieski MD[1]; J. Matthew Edwards, MD[1]; Michael J. Kallan, MS[2]; Brendan G. Carr, MD, MA, MS[1–3]

Crit Care Med 2013; 41: 1167-1174

Number of cases



Total mortality



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

Different Criteria, Different Results

Mortality from septic shock

- Australia – 22%
  - Kaukonen et al, 2014
- Germany – 60.5%
  - Heublein et al, In press
- The Netherlands – 60%
  - Klein-Klouwenberg et al, 2012

Variable Variables

hypotension (SAP <90, MAP <60 or <70, fall in SAP >40)

AND/OR

.. that persists despite adequate fluid resuscitation (either unspecified or after challenges of either 20 ml/kg OR 1000 ml)

AND/OR

biochemical variables (e.g. lactate >2 or >4, or base deficit >5)

AND/OR

use of inotropes and/or vasopressors [±dose specified]

AND/OR

new onset organ dysfunction (defined variably using APACHE II, APACHE III, or SOFA cardiovascular component

Increased 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

2. How

SCCM/ESICM Task Force to Re-Define Sepsis

- Co-Chairs – Mervyn Singer, Cliff Deutschman

Derek Angus
Djilalli Annane
Michael Bauer
Rinaldo Bellomo
Gordon Bernard
Jean-Daniel Chiche
Craig Coopersmith
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Greg Martin
Manu Shankar-Hari
Chris Seymour

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 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.

PROCESS A task force (n = 19) with expertise in sepsis pathobiology, 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 (by 31 societies listed in the Acknowledgment).

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 757

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

Related articles pages 762 and 775

CME Quiz at jamanetworkcme.com and CME Questions page 816

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):801-810. doi:10.1001/jama.2016.0287

The Document

Singer M, Deutschman CS, Seymour CW, Shankar-Hari M et al.

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

JAMA 2016; 315: 801-10

3. What

Task Force Decisions

CONSENSUS

1. Beyond the remit of the task force to define infection
2. Sepsis is not simply infection + two or more SIRS criteria
3. The host response is of key importance
4. Sepsis represents bad infection where

   bad = infection leading to organ dysfunction
5. “Severe sepsis” is not helpful and should be eliminated

Definitions

Per the Merriam – Webster English Dictionary:

- 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

The Definition of Sepsis

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

The Definition of Sepsis

Key Distinctions

Sepsis is life-threatening ***organ dysfunction*** caused by a dysregulated host response to infection

So … “sepsis” now = the old “severe sepsis”

The Definition of Sepsis

Key Distinctions

Sepsis is life-threatening organ dysfunction caused by a ***dysregulated host response*** to infection

As opposed to the
“regulated host response”
that characterizes the non-septic response to infection

The Definition of Septic Shock

More problematic

- Is septic shock sepsis where the dysfunctional organ is the cardiovascular system ?
  - Task force opinion - NO
    - Also involves cellular/metabolic abnormalities
- What distinguishes septic shock from sepsis ?
  - Treatment ?
    - NO. Management is the same
  - Pathobiology ?
    - Maybe … but at this time not known

The Definition of Septic Shock

- What tangibly differentiates septic shock from sepsis ?
  - MORTALITY
    - Septic shock is “really bad” sepsis

Septic shock is a subset of sepsis in which profound circulatory, cellular and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone

Sepsis Definitions

- 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”

The Need for Something Additional

- Practitioners require something of value at the bedside
  - Preferably data-driven
- Clinical criteria
  - Existing
  - Newly derived and validated

Clinical criteria for sepsis

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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; 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

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.

JAMA. 2016;315(8):762-774. doi:10.1001/jama.2016.0288

Editorial page 757

Author Audio Interview at jama.com

Related articles pages 775 and 801

Supplemental content at jama.com

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Seymour CW, Liu VX, Iwashyna TJ et al.

Assessment of Clinical Criteria for Sepsis

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

JAMA 2016; 315: 762-774

What is sepsis?

A life threatening organ dysfunction caused by a dysregulated host response to infection.

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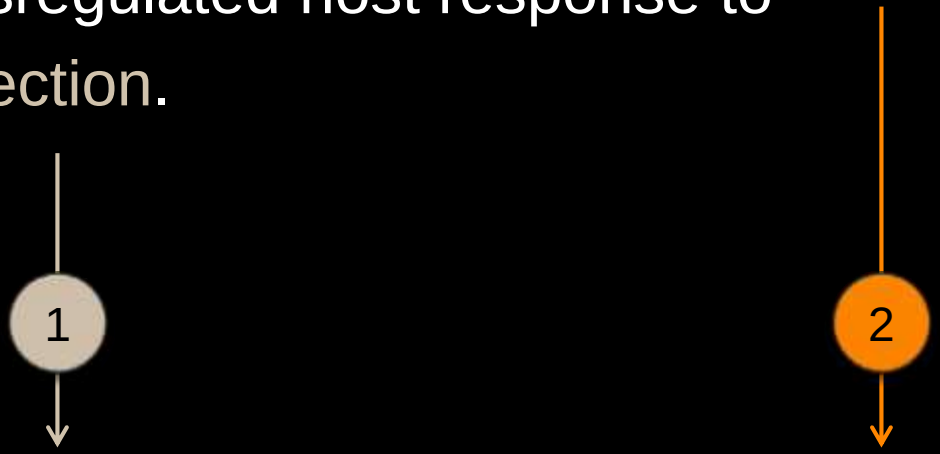
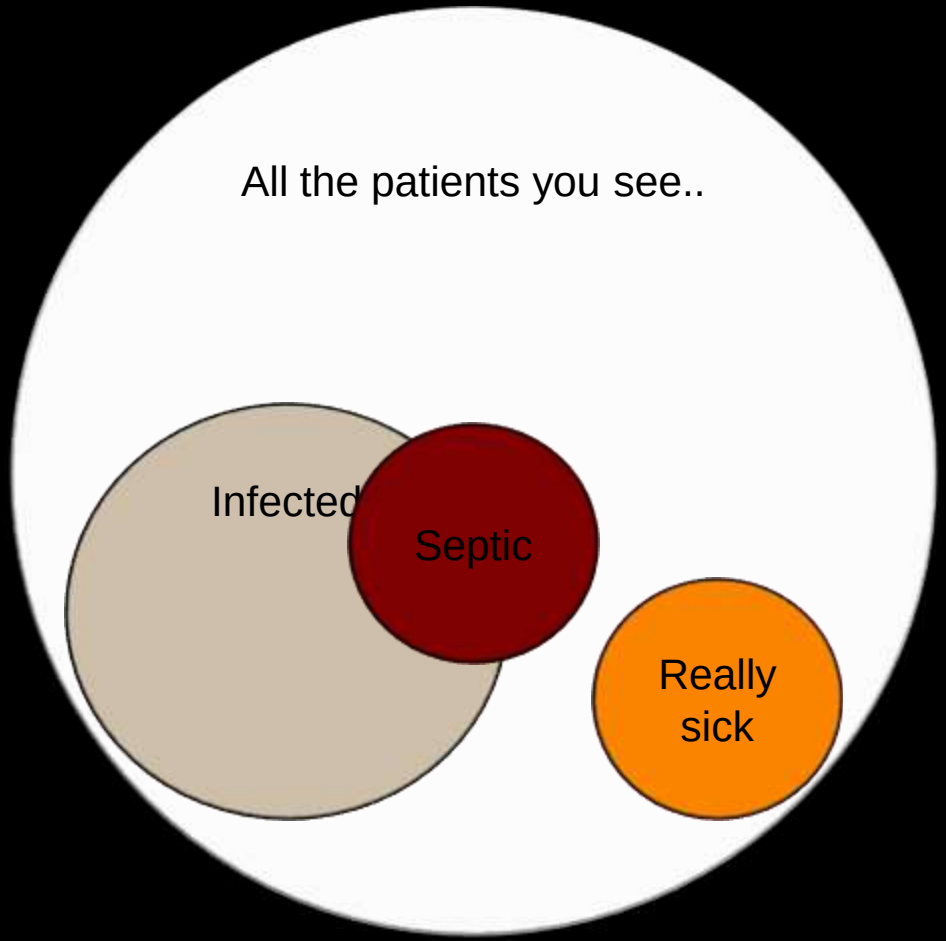
A life threatening organ dysfunction caused by a dysregulated host response to infection.



Among encounters with suspected infection,

who is really sick?

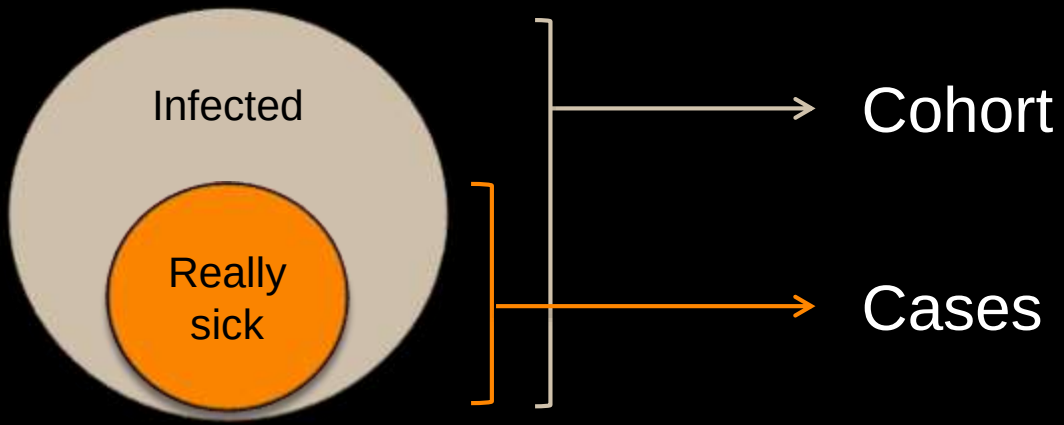
What is sepsis?



We did not..

- Study criteria for infection
- Build an alert or sniffer among non-infected patients

We did..

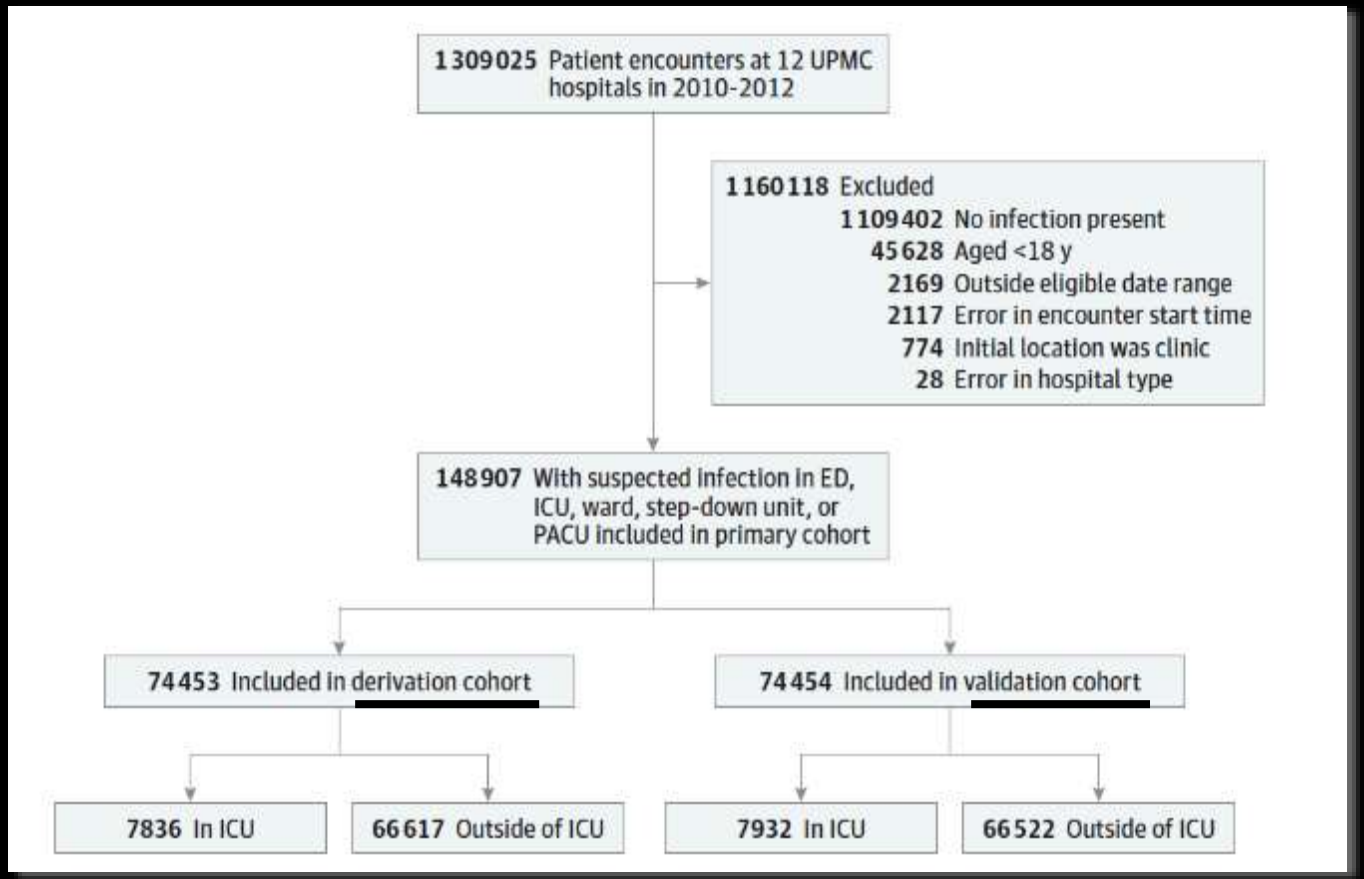


Our challenges

- What data to use?
- How to identify infection?
- What clinical criteria to study?
- How to define really sick?




What data source to use?



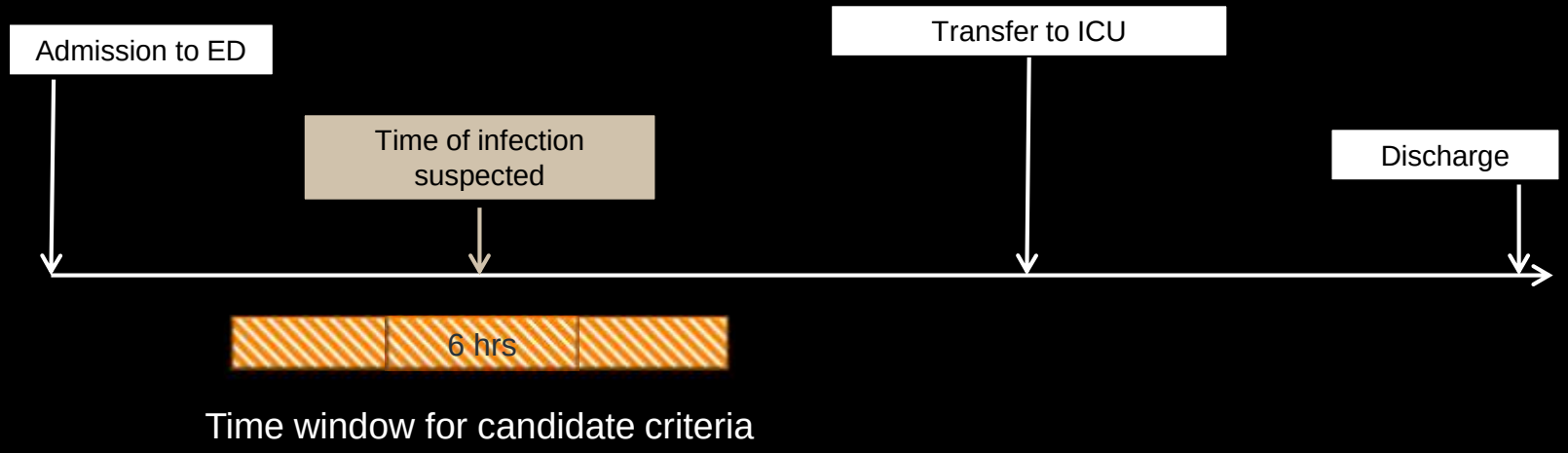
External datasets

Characteristics	KPNC	VA	ALERTS	KCEMS
Years of cohort	2009-2013	2008-2010	2011-2012	2009-2010
No. of hospitals	20	130	1	14
Total No. of encounters	1 847 165	1 640 543	38 098	50 727
Data source and study design	Retrospective study of EHRs	Retrospective study of EHRs	Prospective cohort study	Retrospective study of administrative records
Setting	Integrated health system in northern California	All hospitals in the US VA system	Single university hospital, Jena, Germany	Out-of-hospital records from integrated emergency medical services system in King County, Washington

- >700,000 encounters
- 170 academic, community hospitals in rural-urban locale
- Prehospital, ED, ward
- Community and hospital-acquired infections

How to identify infection?

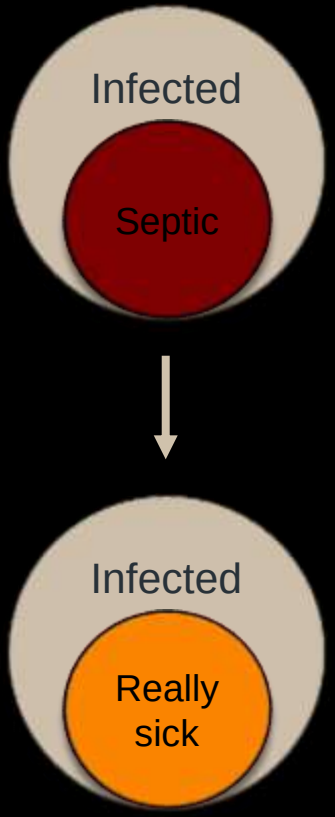
- Used electronic health records
- First episode of cultures and antibiotics
  - Excluded prophylactic antibiotics, intra-operative
- Determined when infection first suspected



What clinical criteria to study?

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)
Respiratory rate, breaths per minute	Pao_2/Fio_2 ratio	Pao_2/Fio_2 ratio
White blood cell count, $10^9/L$	Glasgow Coma Scale score	Glasgow Coma Scale score
Bands, %	Mean arterial 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

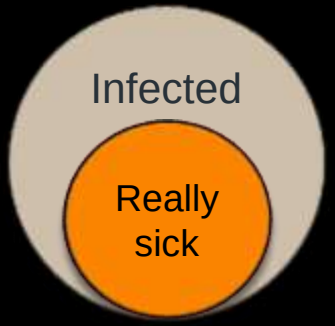
How to define really sick?



- There is no gold standard for sepsis

- "Really sick" is a proxy
- More common among infected patients who are septic than those who are not

How to define really sick?

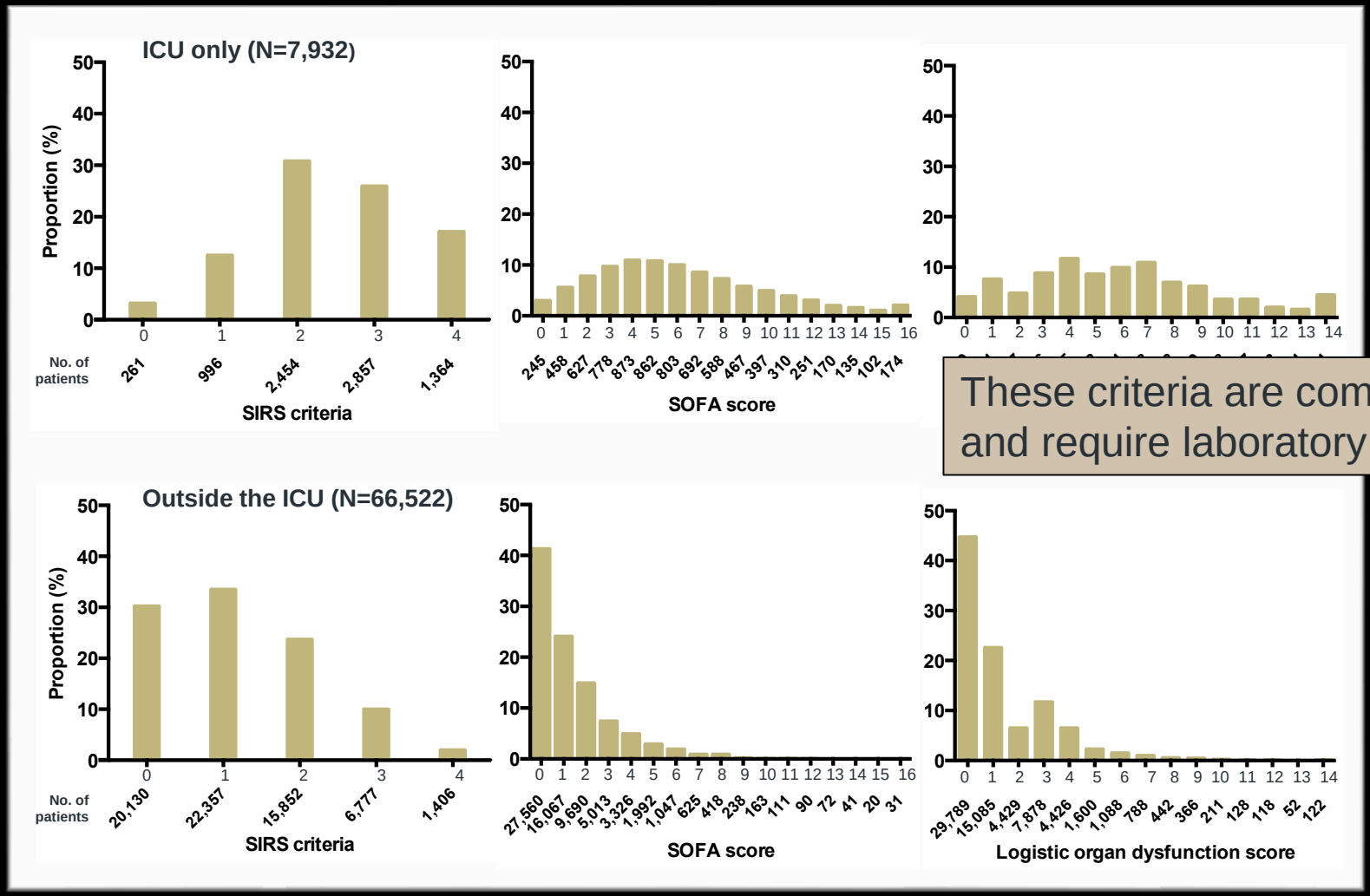


- Clinical review committees
- Death in the hospital
- Prolonged stay in the ICU
- Discharge diagnosis of sepsis
- Positive microbiologic cultures

Patients in primary cohort

Variables	Statistic
Total encounters	148,907
Confirmed bacteremia	6,875 (5)
Age, mean (SD)	61 (19)
Male, no. (%)	63,311 (43)
Onset of infection within 48 hrs, no. (%)	128,358 (86)
Location when infection suspected, no. (%)	
Emergency department	65,934 (44)
Ward	49354 (33)
Intensive care	15,768 (11)

Distribution of existing criteria

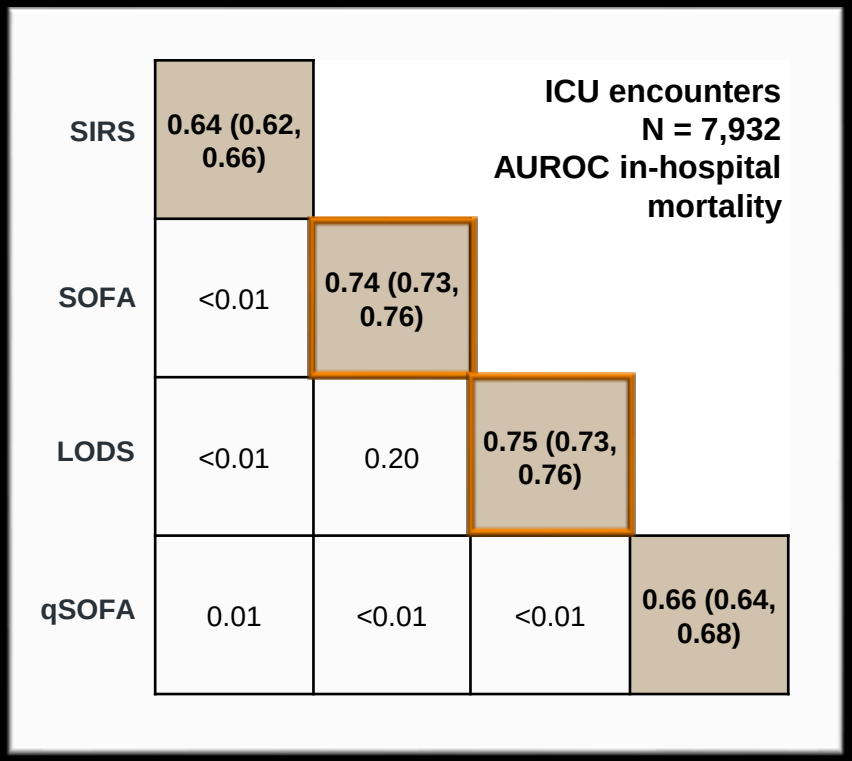


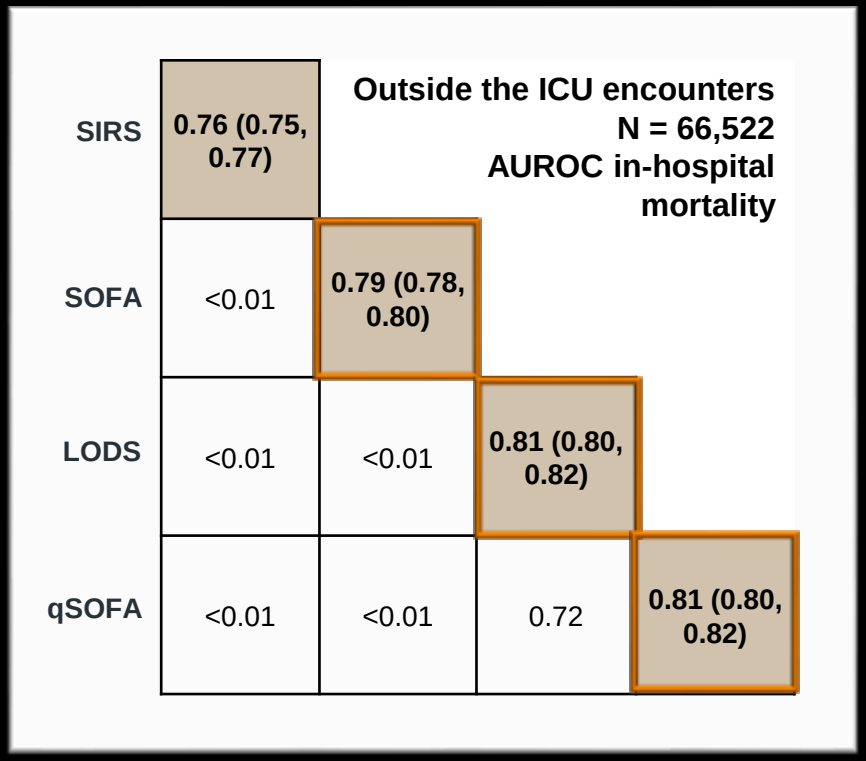
These criteria are complex and require laboratory tests

Developing new criteria

- Focus on timeliness, ease of use
- Studied 21 variables from Sepsis-2
- Multivariable logistic regression for in-hospital mortality

Assessment of criteria

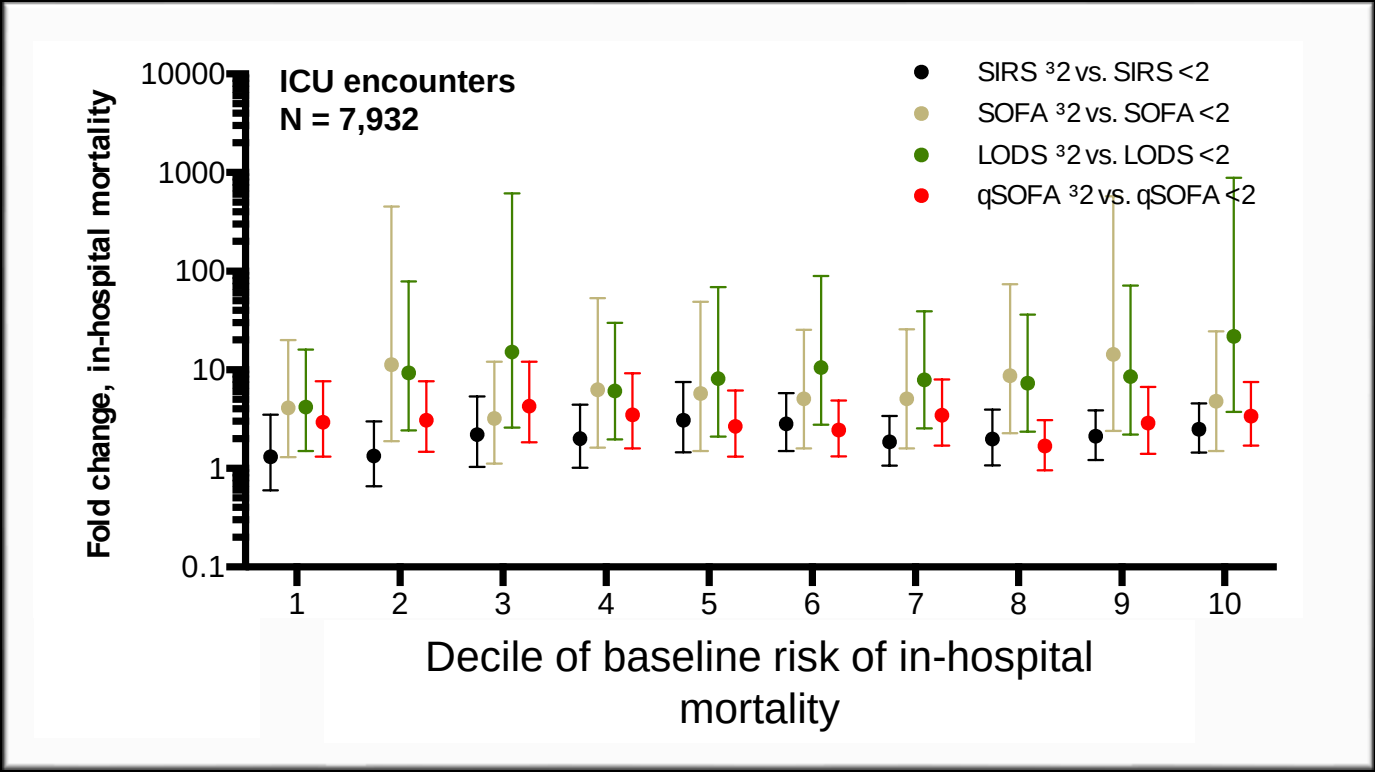




SOFA and LODS superior in the ICU

qSOFA similar to complex scores outside the ICU

Assessment of criteria



SOFA and LODS superior
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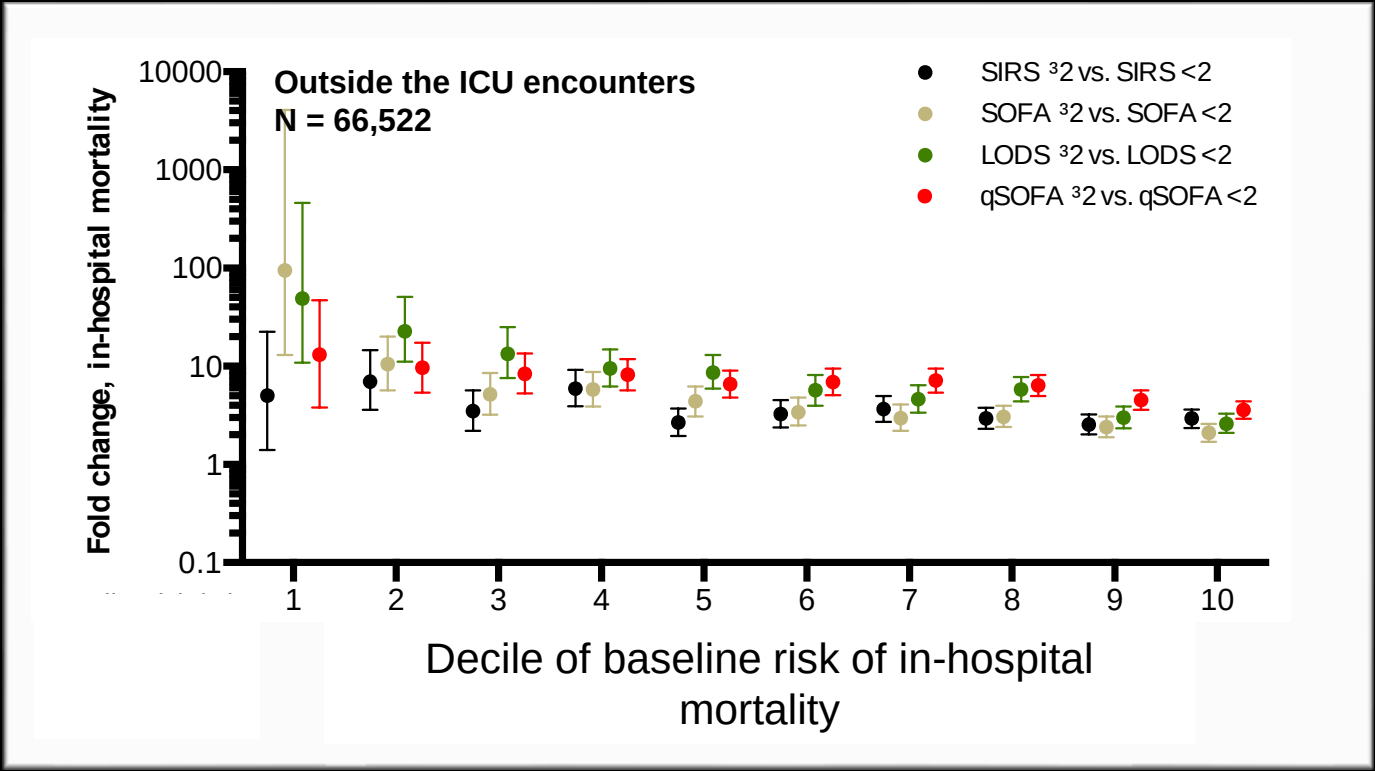
Assessment of criteria



qSOFA similar to complex scores outside the ICU

qSOFA in external datasets

Data Set and Infection Type	No. of Patients With Suspected Infection	AUROC (95% CI)	
		Baseline Model	Baseline Model + qSOFA
KPNC (all suspected infections)	321 380	0.67 (0.67-0.67)	0.78 (0.78-0.78)
ICU patients	7031	0.64 (0.62-0.66)	0.72 (0.70-0.73)
Non-ICU patients	314 349	0.68 (0.67-0.68)	0.78 (0.78-0.79)
VA (all suspected infections)[a]	377 325	0.73 (0.73-0.74)	0.78 (0.78-0.79)
ALERTS (hospital-acquired infections)	1186	0.55 (0.51-0.60)	0.73 (0.69-0.77)
KCEMS (community-acquired infections)	6508	0.59 (0.57-0.62)	0.71 (0.69-0.73)

- Adequate predictive validity (AUC range 0.7 to 0.8)
  - Hospital acquired infections
  - Ward and ICU encounters
  - Prehospital records

Post hoc analyses requested by TF

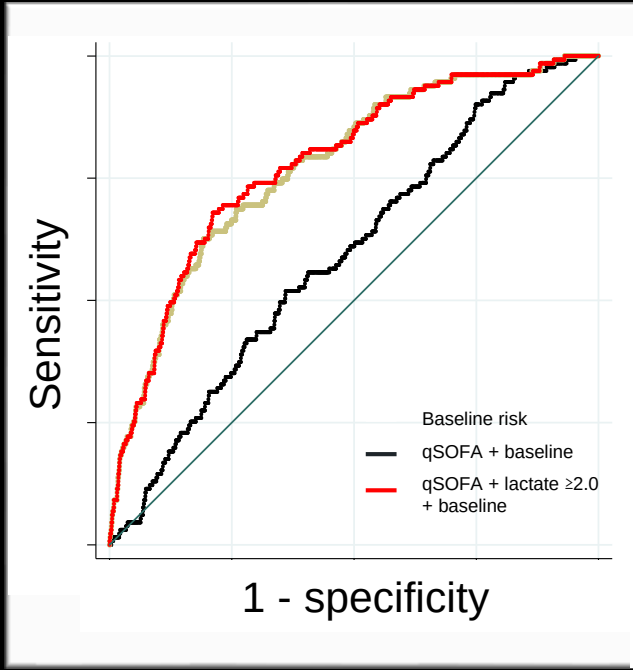
- Alternate time windows around infection
- Altered mentation using GCS < 15
- Multiple imputation of missing data

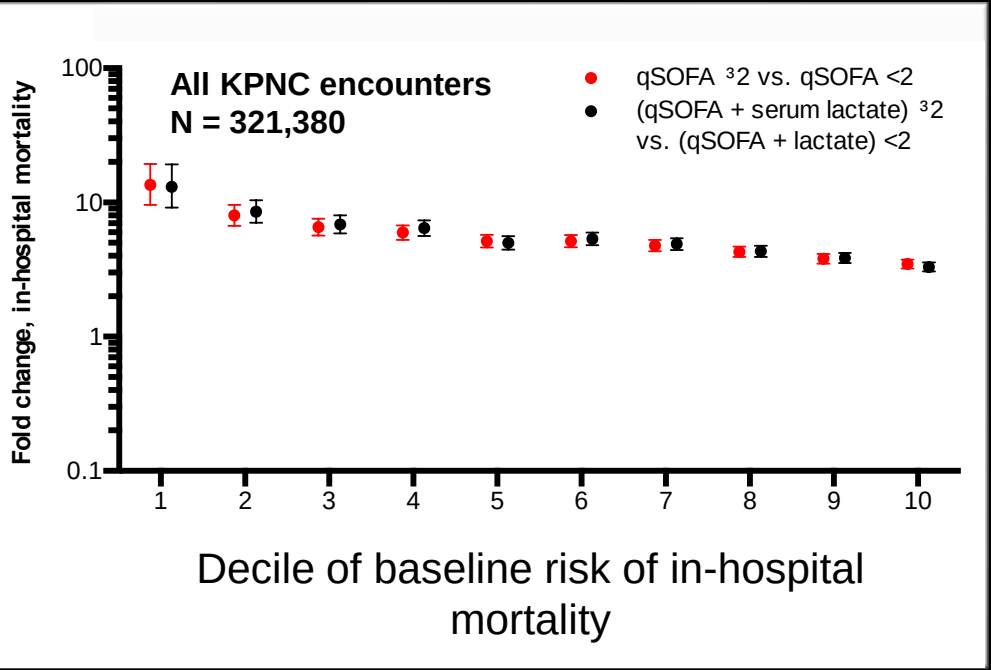
Change in SOFA

- Increase by 2 or SOFA points from baseline
  - Greater predictive validity than SIRS criteria
  - Similar to SOFA alone

Serum lactate

- Not retained during qSOFA model build
- Serum lactate at various thresholds added to qSOFA





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

Please visit www.qsofa.org

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

Please visit www.qsofa.org

Clinical criteria for septic shock

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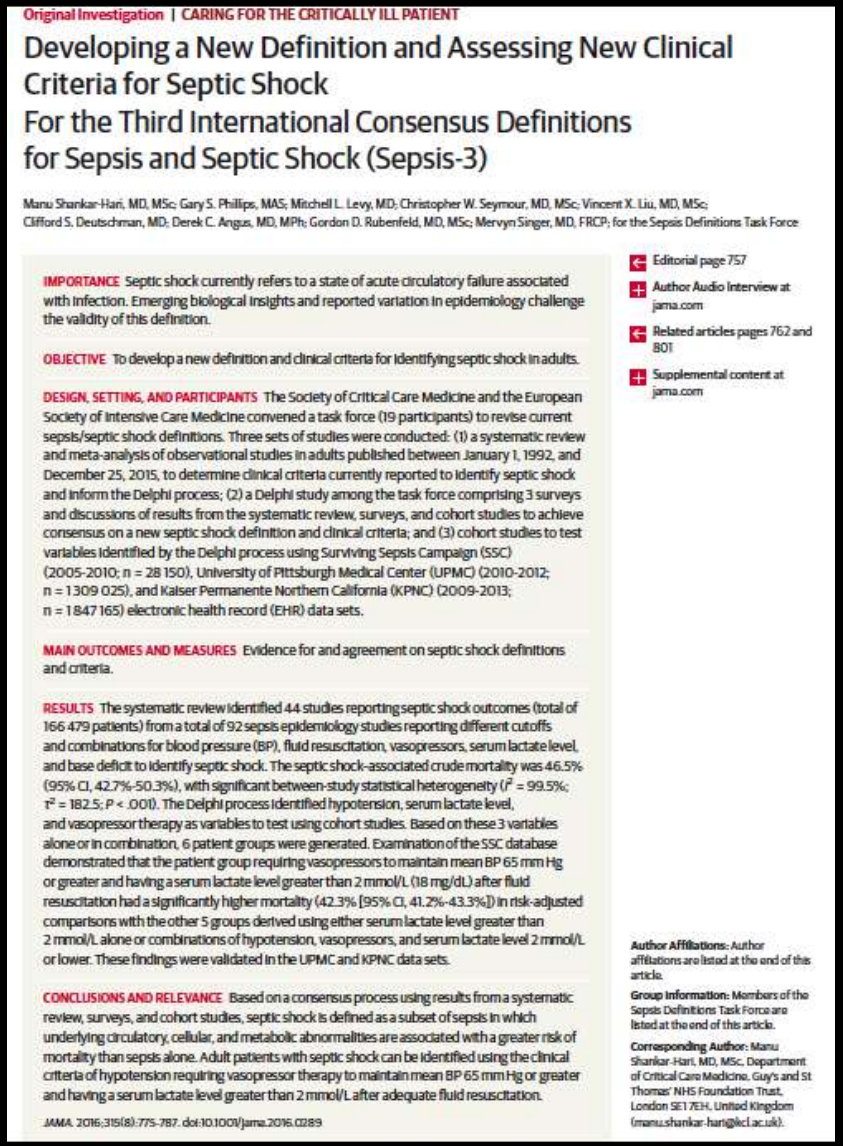

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

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

IMPORTANCE Septic shock currently refers to a state of acute circulatory failure associated with infection. Emerging biological insights and reported variation in epidemiology challenge the validity of this definition.

OBJECTIVE To develop a new definition and clinical criteria for identifying septic shock in adults.

DESIGN, SETTING, AND PARTICIPANTS The Society of Critical Care Medicine and the European Society of Intensive Care Medicine convened a task force (19 participants) to revise current sepsis/septic shock definitions. Three sets of studies were conducted: (1) a systematic review and meta-analysis of observational studies in adults published between January 1, 1992, and December 25, 2015, to determine clinical criteria currently reported to identify septic shock and inform the Delphi process; (2) a Delphi study among the task force comprising 3 surveys and discussions of results from the systematic review, surveys, and cohort studies to achieve consensus on a new septic shock definition and clinical criteria; and (3) cohort studies to test variables identified by the Delphi process using Surviving Sepsis Campaign (SSC) (2005-2010; n = 28 150), University of Pittsburgh Medical Center (UPMC) (2010-2012; n = 1 309 025), and Kaiser Permanente Northern California (KPNC) (2009-2013; n = 1 847 165) electronic health record (EHR) data sets.

MAIN OUTCOMES AND MEASURES Evidence for and agreement on septic shock definitions and criteria.

RESULTS The systematic review identified 44 studies reporting septic shock outcomes (total of 166 479 patients) from a total of 92 sepsis epidemiology studies reporting different cutoffs and combinations for blood pressure (BP), fluid resuscitation, vasopressors, serum lactate level, and base deficit to identify septic shock. The septic shock–associated crude mortality was 46.5% (95% CI, 42.7%-50.3%), with significant between-study statistical heterogeneity (I^2 = 99.5%; τ^2 = 182.5; P < .001). The Delphi process identified hypotension, serum lactate level, and vasopressor therapy as variables to test using cohort studies. Based on these 3 variables alone or in combination, 6 patient groups were generated. Examination of the SSC database demonstrated that the patient group requiring vasopressors to maintain mean BP 65 mm Hg or greater and having a serum lactate level greater than 2 mmol/L (18 mg/dL) after fluid resuscitation had a significantly higher mortality (42.3% [95% CI, 41.2%-43.3%]) in risk-adjusted comparisons with the other 5 groups derived using either serum lactate level greater than 2 mmol/L alone or combinations of hypotension, vasopressors, and serum lactate level 2 mmol/L or lower. These findings were validated in the UPMC and KPNC data sets.

CONCLUSIONS AND RELEVANCE Based on a consensus process using results from a systematic review, surveys, and cohort studies, septic shock is defined as a subset of sepsis in which underlying circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than sepsis alone. Adult patients with septic shock can be identified using the clinical criteria of hypotension requiring vasopressor therapy to maintain mean BP 65 mm Hg or greater and having a serum lactate level greater than 2 mmol/L after adequate fluid resuscitation.

JAMA. 2016;315(8):775-787. doi:10.1001/jama.2016.0289

Editorial page 757

Author Audio Interview at jama.com

Related articles pages 762 and 801

Supplemental content at jama.com

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

Group Information: Members of the Sepsis Definitions Task Force are listed at the end of this article.

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Shankar-Hari M, Phillips GS, Levy ML et al.

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

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JAMA 2016; 315: 775-787

1991 & 2001 Septic Shock definitions

1991

- *Sepsis-induced hypotension, persisting despite adequate fluid resuscitation, along with the presence of hypoperfusion abnormalities or organ dysfunction*

2001

- *State of acute circulatory failure characterized by persistent arterial hypotension unexplained by other causes*

Neither definition proposed explicit criteria

2016 Septic Shock Definition

Subset of sepsis in which **underlying circulatory, cellular and metabolic abnormalities** are associated with a **greater risk of mortality** than sepsis alone

How do we operationalize this definition at the bedside, i.e. what clinical criteria describe septic shock?

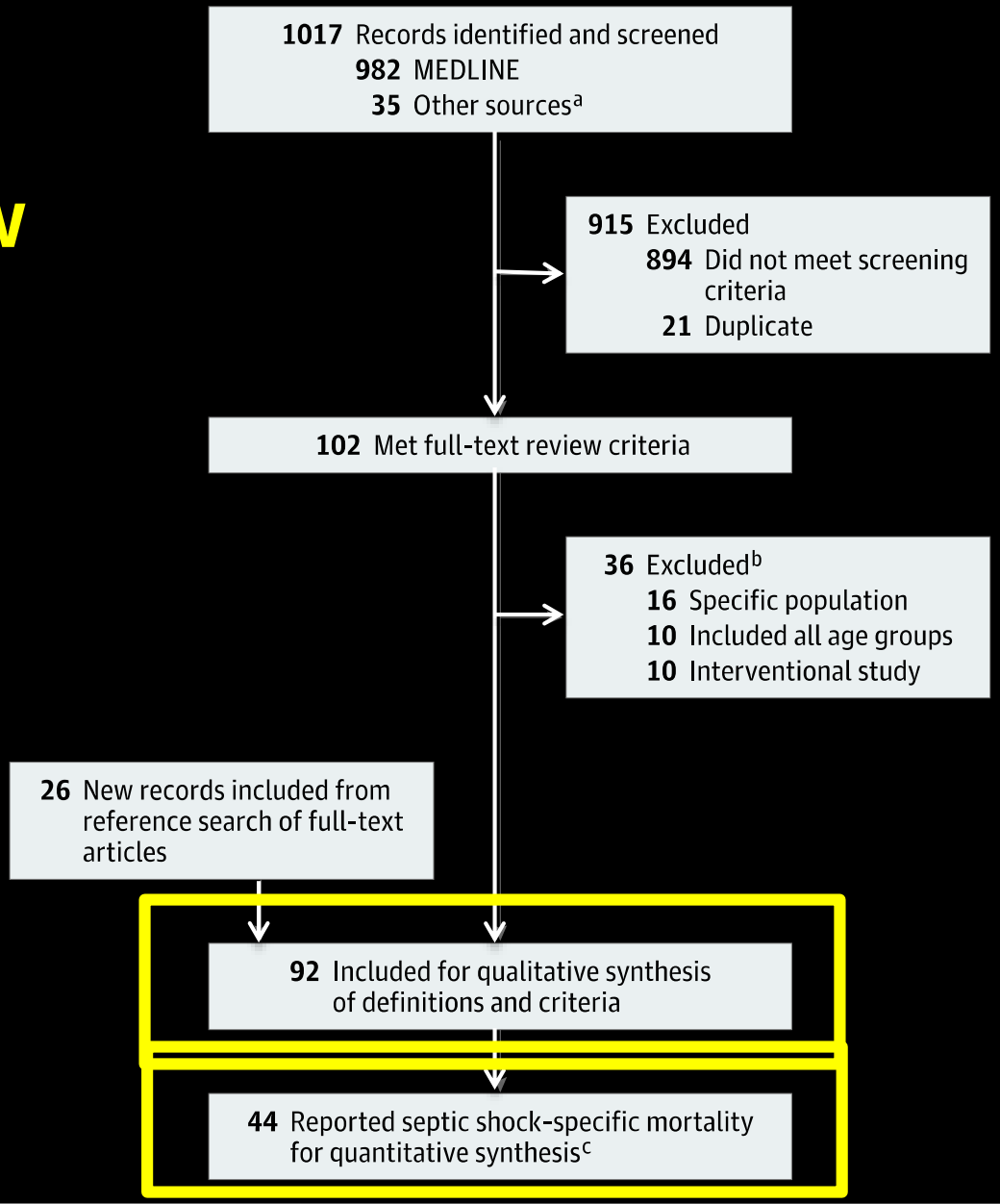
Development plan

- Systematic review of observational studies
  - Criteria reported to identify septic shock
- Delphi (3 surveys + face-to-face discussions)
  - Develop definition
  - Agree analysis plan
  - Agree clinical criteria

Data analysis

- Derivation cohort
  - Surviving Sepsis Campaign Database (SSC)
    - 2005-2010; n = 28,150
- Validation cohort
  - 12 hospitals in Pennsylvania (UPMC)
    - 2010-2012; n = 1,309,025
  - 20 Hospitals (Kaiser Permanente Northern California, KPNC)
    - 2009-2013; n = 1,847,165

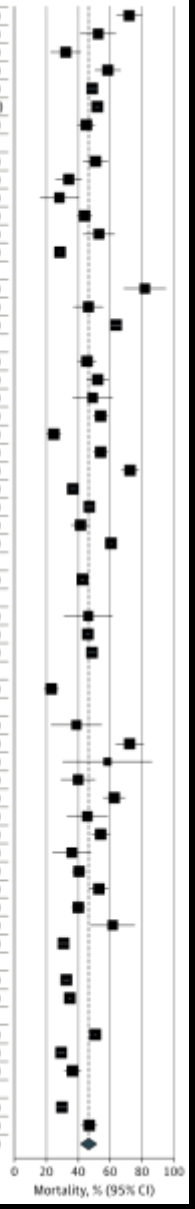
Systematic review



Systematic review

- Multiple criteria used to identify septic shock
- Wide heterogeneity
  - 4-fold variation in mortality

Source	Septic Shock Deaths, No.	Patients With Septic Shock, No.	Mortality, % (95% CI)
Consensus Definition			
Degoricija et al,[46] 2006	90	125	72.0 (64.1-79.9)
Angkasekwinai et al,[38] 2007	41	78	52.6 (41.5-63.6)
Nesseler et al,[27] 2013	30	93	32.3 (22.8-41.8)
Sakr et al,[25] 2013	85	145	58.6 (50.6-66.6)
Goncalves-Pereira et al,[23] 2014	418	856	48.8 (45.5-52.2)
Leligdowicz et al,[5] 2014	4146	7974	52.0 (50.9 -53.1)
Ortiz et al,[19] 2014	144	319	45.1 (39.7-50.6)
Hypotension			
Laupland et al,[47] 2004	81	159	50.9 (43.2-58.7)
Gaspraovic et al,[45] 2006	44	129	34.1 (25.9-42.3)
Shapiro et al,[44] 2006	15	53	28.3 (16.2-40.4)
Povoa et al,[35] 2009	202	458	44.1 (39.6-48.7)
Klein Klowenberg et al,[7] 2012	52	98	53.1 (43.2-62.9)
Kaukonen et al,[22] 2014	14609	51079	28.6 (28.2-29.0)
Hypotension + Perfusion Abnormalities and/or Vasopressor Therapy			
Rangel-Frausto et al,[56] 1995	51	110	46.4 (37.0-55.7)
Salvo et al,[55] 1995	27	33	81.8 (68.7-95.0)
Alberti et al,[52] 2002	752	1180	63.8 (60.7-67.0)
Hypotension + Vasopressor Therapy			
Rodriguez et al,[31] 2001	129	283	45.6 (39.8-51.4)
Silva et al,[48] 2004	106	203	52.2 (45.3-59.1)
Laupland et al,[49] 2005	28	57	49.1 (36.5-61.8)
Vincent et al,[43] 2006	250	462	54.1 (49.6-58.7)
Karlsson et al,[40] 2007	90	363	24.8 (20.4-29.2)
Sakr et al,[39] 2007	250	462	54.1 (49.6-58.7)
Kauss et al,[34] 2010	185	255	72.5 (67.1-78.0)
Levy et al,[6] 2010	915	2494	36.7 (34.8-38.6)
Phua et al,[32] 2011	441	939	47.0 (44.3-49.7)
Ogura et al,[20] 2014	117	282	41.5 (35.7-47.2)
GiViTI database, 2015[a]	15935	26295	60.6 (60.0-61.2)
Hypotension + Vasopressor Therapy + Serum Lactate Level >2 mmol/L			
Group 1[b]	3602	8520	42.3 (41.2-43.3)
Hypotension + Perfusion Abnormalities + Vasopressor Therapy			
Lundberg et al,[54] 1998	19	41	46.3 (31.1-61.6)
Levy et al,[6] 2010	3428	7436	46.1 (45.0-47.2)
Quenot et al,[26] 2013	728	1495	48.7 (46.2-51.2)
Hypotension ± Vasopressor Therapy or Metabolic Abnormalities			
Peake et al,[36] 2009	75	324	23.1 (18.6-27.7)
Hypotension or Vasopressor Therapy			
Dahnash et al,[59] 1993	14	36	38.9 (23.0-54.8)
McLauchlan et al,[58] 1995	73	101	72.3 (63.5-81.0)
Pittet et al,[57] 1995	7	12	58.3 (30.4-86.2)
Schoenberg et al,[53] 1998	32	80	40.0 (29.3-50.7)
Engel et al,[42] 2007	119	190	62.6 (55.8-69.5)
Esteban et al,[41] 2007	27	59	45.8 (33.1-58.5)
Khwannimit and Bhuayanontachai,[37] 2009	164	303	54.1 (48.5-59.7)
Moore et al,[33] 2011	22	61	36.1 (24.0-48.1)
Zahar et al,[30] 2011 (community)	215	530	40.6 (36.3-44.8)
Zahar et al,[30] 2011 (ICU)	123	232	53.0 (47.1-59.0)
Zahar et al,[30] 2011 (nosocomial)	233	580	40.2 (36.1-44.2)
Klein Klowenberg et al,[7] 2012	29	47	61.7 (47.8-75.6)
Park et al,[28] 2012	228	740	30.8 (27.5-34.1)
Hypotension or Serum Lactate Any Value or Vasopressor Therapy			
Liu et al,[21] 2014	827	2536	32.6 (30.8-34.4)
SSC database,[16] 2016[b]	6556	18840	34.8 (34.1-35.5)
International Classification of Diseases Codes			
Annane et al,[51] 2003	13269	26172	50.7 (50.1-51.3)
Flaatten,[50] 2004	457	1562	29.3 (27.1-31.6)
Whittaker et al,[24] 2013	117	321	36.4 (31.2-41.7)
Serum Lactate Level >4 mmol/L			
Levy et al,[6] 2010	242	811	29.8 (26.7-33.0)
Phua et al,[32] 2011	219	466	47.0 (42.0-52.0)
Overall (I^2 = 99.5%; P = .000)			46.5 (42.7-50.3)



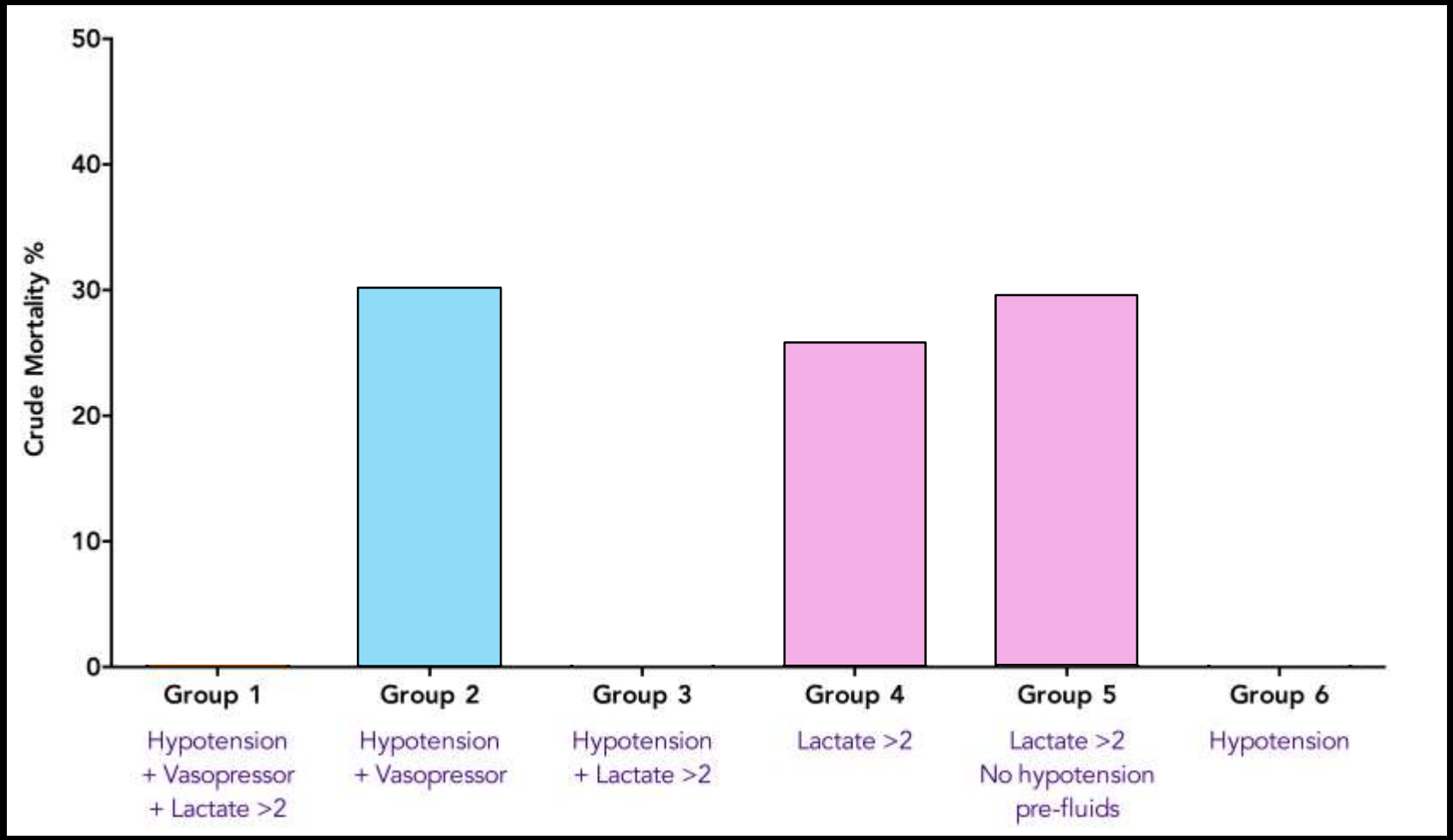
Delphi process

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

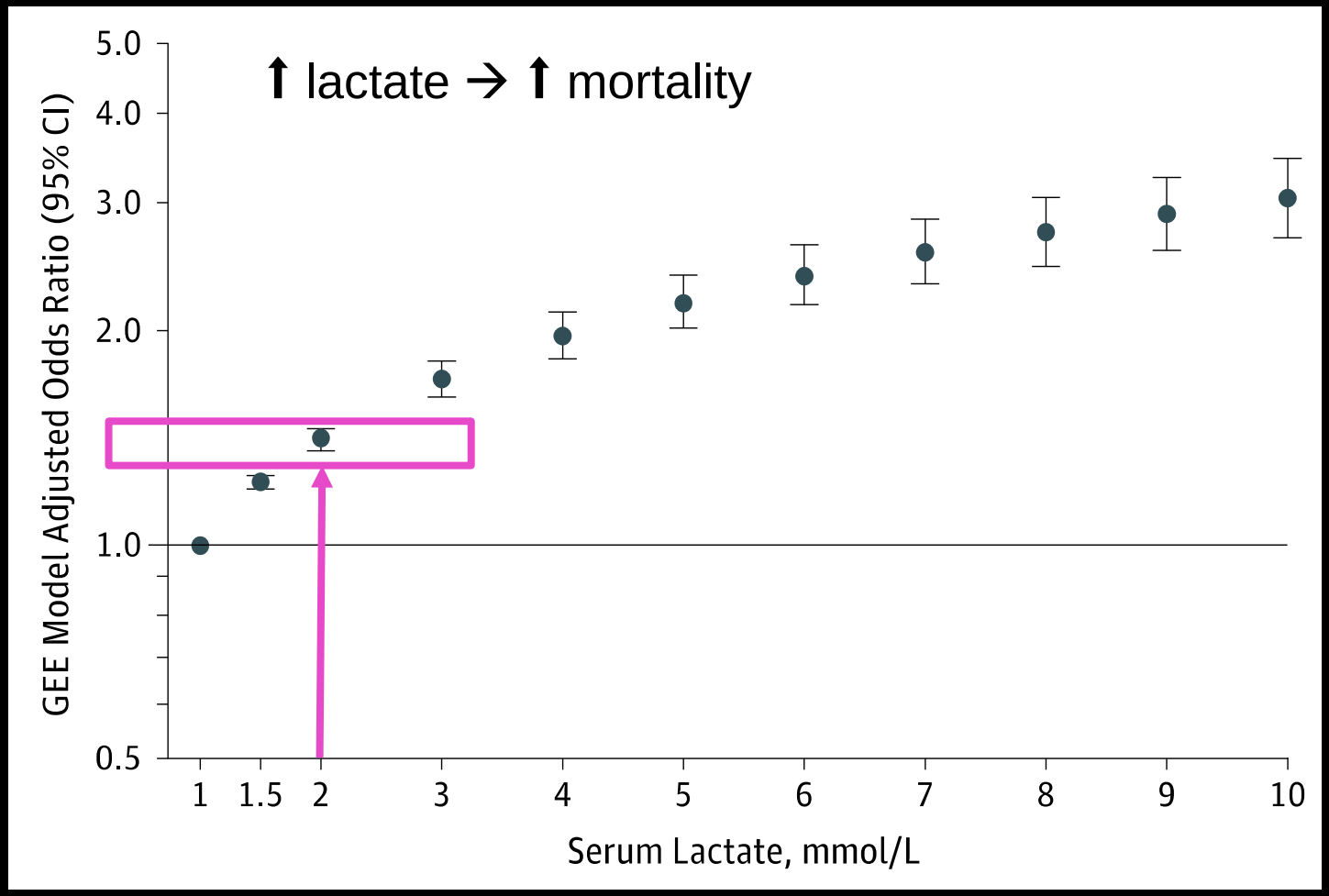
6 patient groups based on 3 variables

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

Derivation of clinical criteria - SSC

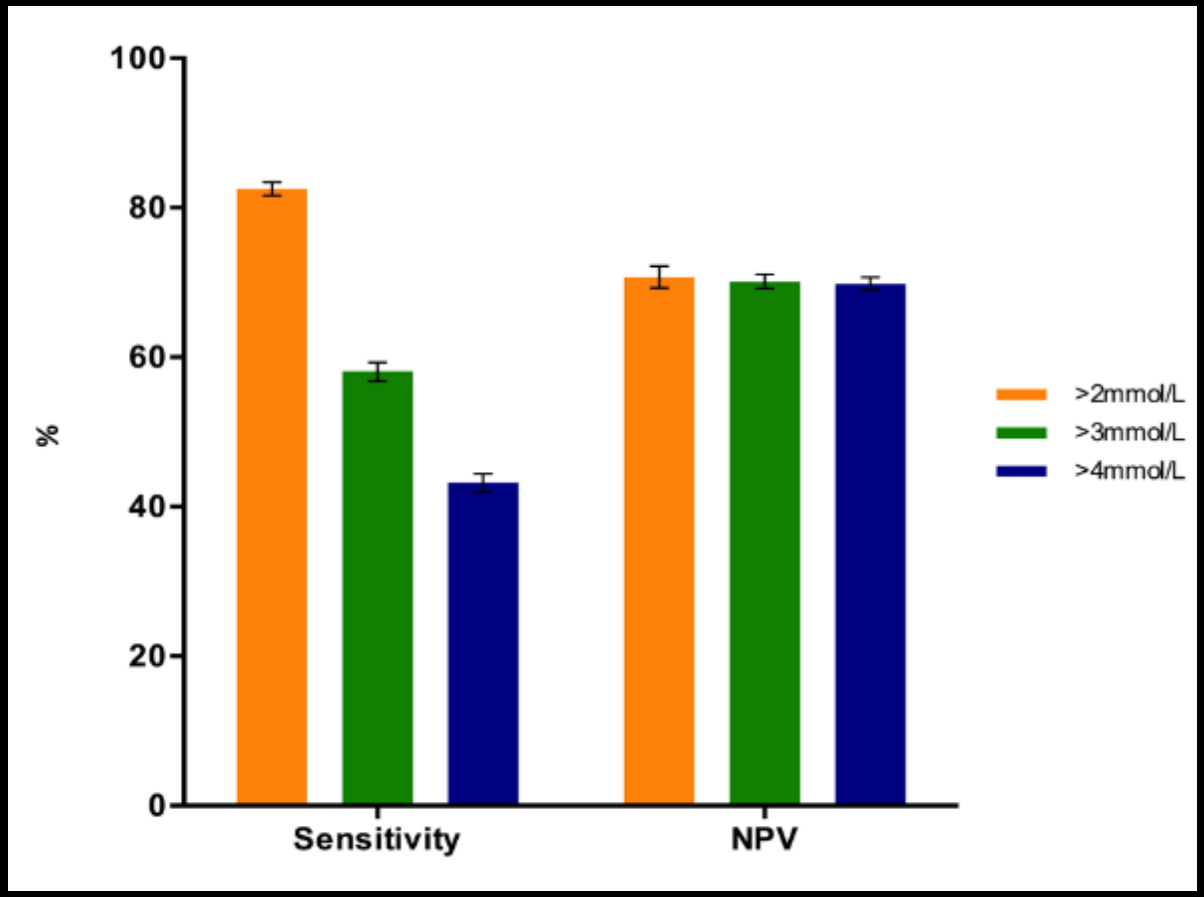


Lactate cutoff rationale



Lactate cutoff rationale

- Test performance (receiver operator characteristics)



2016 Septic Shock Criteria

Despite adequate fluid resuscitation

- vasopressors needed to maintain MAP ≥65 mmHg

  AND

- lactate >2 mmol/l

Conclusions

- Definition
  - Septic shock is defined as a subset of sepsis in which underlying circulatory, cellular and metabolic abnormalities are associated with a greater risk of mortality than sepsis alone

- Clinical criteria
  - Hypotension requiring use of vasopressors to maintain MAP ≥65 mmHg and having a serum lactate >2 mmol/l persisting despite adequate fluid resuscitation

Controversies, Concerns and FAQs

Mervyn Singer
University College London, London, UK
Task Force Co-chair

Soft launch

- talking publicly for >1 year – really useful feedback
- extensive informal peer review
- formal peer review by >30 (inter)national societies

  (developed and developing world) + JAMA process
- heard/considered most (all ?) of the arguments

Some of the concerns raised …

- *'SIRS is vital to diagnose sepsis and to treat patients early'*
- *'SOFA won't be measured daily on every patient'*
- *'do I need to measure SOFA twice to measure change'*
- *'lactate should be in the sepsis criteria'*
- *'lactate should go from the septic shock criteria'*
- *'80% of the world cannot measure lactate'*
- *'why not shock = hyperlactatemia OR hypotension?'*
- *'patients will die if we wait until qSOFA hits ≥2 before treating'*
- *'why don't we just use qSOFA to diagnose sepsis?'*
- *'the coders won't like it'*
- *'what about children?' …*

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

Controversies and Limitations

There are inherent challenges in defining sepsis and septic shock. First and foremost, *sepsis* is a broad term applied to an incompletely understood process. There are, as yet, no simple and unambiguous clinical criteria or biological, imaging, or laboratory features that uniquely identify a septic patient. The task force recognized

A pragmatic offering

- there is no absolute biomarker (yet) for sepsis or septic shock
- generalizability - readily measurable identifiers that best capture conceptualisation of ‘sepsis’
- objectivity, reproducibility – speak same language
- ease of use
  - qSOFA - rapid bedside measure
  - SOFA - clinical measures and lab tests performed routinely in any sick patient

SIRS has its place
.. though not for diagnosing sepsis

- white count, temperature etc.. still useful in helping to form a provisional diagnosis of infection
- SIRS is an appropriate - but not necessarily dysregulated - host response to infection

Sepsis is (often) diagnosed in retrospect …

- infection usually confirmed belatedly (or not in ~30-50%) … yet still often treated if suspected
- same with sepsis .. start treating patient and modify as more data become available ..
- identifying patient as being ‘septic’ should not affect treatment other than prompting/confirming that the patient is at high risk for a poor outcome

What does qSOFA mean?

- tool derived retrospectively on large, mainly US, datasets
- uses different time windows before/after consideration of infection (cultures, starting antibiotics)
- new onset vs. ‘established’ qSOFA points unknown
- needs prospective validation in different healthcare settings
- .. thus current recommendation as a prompt to consider possibility of sepsis (i.e. change in SOFA ≥2 related to infection)
- if confirmed prospectively, qSOFA may be a useful rapid diagnostic tool (e.g. in resource-poor settings)

SOFA Score

Variables/points	1	2	3	4
Neurological (GCS)	13-14	10-12	6-9	<6
Respiratory (P:F ratio)	<400	<300	<200 (+ resp support)	<100 (+ resp support)
Cardiovascular (systolic BP)	<70	dopamine ≤5 or dobutamine (any dose)	dopamine >5 or EPI ≤0.1 or NOREPI ≤0.1	dopamine >15 or EPI >0.1 or NOREPI >0.1
Renal (creatinine or UO)	110-170	171-299	300-440 (or <500 ml/day)	>440 (or <200 ml/day)
Haematological (platelets)	<150	<100	<50	<20
Liver (bilirubin)	20-32	33-101	102-204	>204

Why use SOFA for the Sepsis Clinical Criteria?

- familiarity (at least in ICU)
- predictive validity
- uses routinely measured variables
- can be measured by automated systems
- not perfect … Sepsis-4 will improve on it
- .. but SOFA ≥2 relates to 10% chance of dying in hospital

Why a change of ≥2 from baseline SOFA?

- many patients have existing (new/old) comorbidities pre-onset of possible sepsis – thus already score SOFA points at baseline
- most of these 'SOFA-scorers' will already be known
- … so look for change in SOFA ≥2 related to pre-infection baseline
- assume 0 SOFA score if previously healthy

Treat the patient in front of you

- NOT suggesting that infected patients shouldn't be actively managed until qSOFA≥2 or ΔSOFA ≥2
- so treat infection, oliguria, hypoxaemia etc as indicated
- .. do not wait until criteria met

What does hyperlactatemia mean?

- marker of cellular/metabolic stress
- .. not necessarily tissue hypoperfusion
- can also occur with liver disease, catecholamine Rx, other drugs ..
- independent predictor of mortality

Lactate and qSOFA

- lactate added only small improvement to predictive validity compared with qSOFA alone ..
- may have some utility in intermediate risk patients (qSOFA = 1)
- not discouraging its use as a management tool as a guide to therapeutic response nor an indicator of severity

Lactate and septic shock

- septic shock is more than hypotension alone
- wanted to reflect a sicker subset at higher risk of dying
- needed a readily available marker of cellular/metabolic abnormality
- lactate is best current measure that fits this role

Why hypotension AND hyperlactatemia for septic shock?

	hospital mortality (%)
hypotension + lactate >2	42.3
hypotension alone	30.1
lactate >2 alone	25.7
no hypotension and lactate <2	18.7

Shankar-Hari et al. JAMA 2016

What about children?

- definitions still hold true
- Task Force lacked expertise to derive clinical criteria for children at differing age ranges
- pediatric initiatives underway

Developing world

- many lack ability to measure lactate or SOFA criteria
- ? use qSOFA as surrogate for sepsis (post-validation)
- for septic shock, use clinical marker of tissue perfusion if lactate not available (e.g. capillary refill)
- PoC testing increasingly available and cheap

Coding

Table 2. Terminology and *International Classification of Diseases* Coding

Current Guidelines and Terminology	Sepsis	Septic Shock
1991 and 2001 consensus terminology[9,10]	Severe sepsis Sepsis-induced hypoperfusion	Septic shock[13]
2015 Definition	Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection	Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality
2015 Clinical criteria	Suspected or documented infection and an acute increase of ≥2 SOFA points (a proxy for organ dysfunction)	Sepsis[a] and vasopressor therapy needed to elevate MAP ≥65 mm Hg and lactate >2 mmol/L (18 mg/dL) despite adequate fluid resuscitation[13]
Recommended primary *ICD* codes[a]		
ICD-9	995.92	785.52
ICD-10[a]	R65.20	R65.21

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Box 2. Key Concepts of Sepsis

- Sepsis is the primary cause of death from infection, especially if not recognized and treated promptly. Its recognition mandates urgent attention.
- Sepsis is a syndrome shaped by pathogen factors and host factors (eg, sex, race and other genetic determinants, age, comorbidities, environment) with characteristics that evolve over time. What differentiates sepsis from infection is an aberrant or dysregulated host response and the presence of organ dysfunction.
- Sepsis-induced organ dysfunction may be occult; therefore, its presence should be considered in any patient presenting with infection. Conversely, unrecognized infection may be the cause of new-onset organ dysfunction. Any unexplained organ dysfunction should thus raise the possibility of underlying infection.
- The clinical and biological phenotype of sepsis can be modified by preexisting acute illness, long-standing comorbidities, medication, and interventions.
- Specific infections may result in local organ dysfunction without generating a dysregulated systemic host response.

Box 3. New Terms and Definitions

- 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 SOFA score ≥2 points consequent to the infection.
  - The baseline SOFA score can be assumed to be zero in patients not known to have preexisting organ dysfunction.
  - A SOFA score ≥2 reflects an overall mortality risk of approximately 10% in a general hospital population with suspected infection. Even patients presenting with modest dysfunction can deteriorate further, emphasizing the seriousness of this condition and the need for prompt and appropriate intervention, if not already being instituted.
- 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.
- Patients with suspected infection who are likely to have a prolonged ICU stay or to die in the hospital can be promptly identified at the bedside with qSOFA, ie, alteration in mental status, systolic blood pressure ≤100 mm Hg, or respiratory rate ≥22/min.
- Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality.
- Patients with septic shock can be identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain MAP ≥65 mm Hg and having a blood lactate level >2 mmol/L (18 mg/dL) despite adequate volume resuscitation. With these criteria, hospital mortality is in excess of 40%.

Abbreviations: MAP, mean arterial pressure; qSOFA, quick SOFA; SOFA: Sequential [Sepsis-related] Organ Failure Assessment.

Acknowledgements

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- ESICM - Daniel de Backer, Maurizio Cecconi, Jean-Daniel Chiche
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