Le sepsis en 2016 c'est quoi ?

Et le choc septique ?

srlf
SOCIÉTÉ DE RÉANIMATION DE LANGUE FRANÇAISE

SPILF
SOCIETE DE PATHOLOGIE INFECTIEUSE DE LANGUE FRANÇAISE

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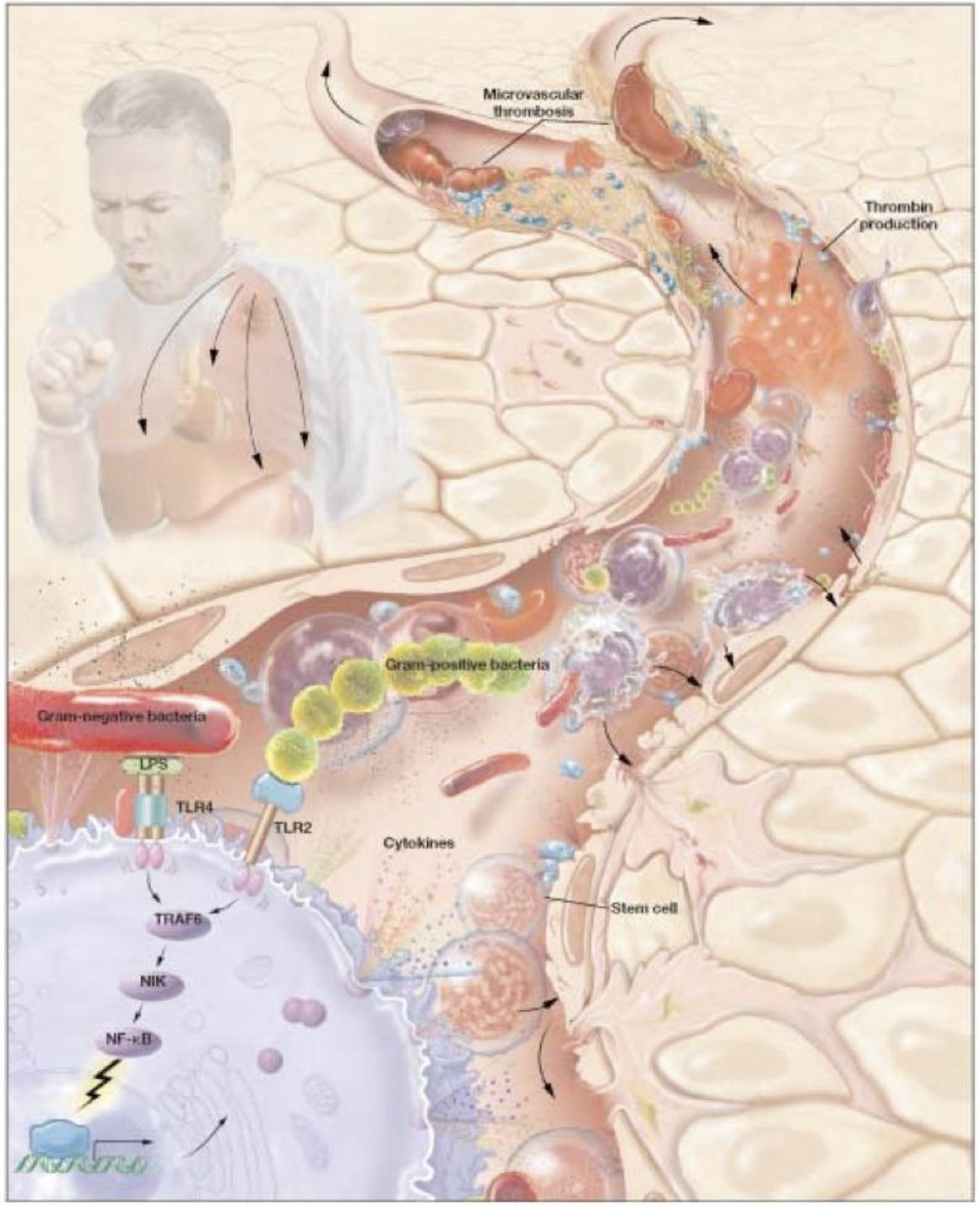
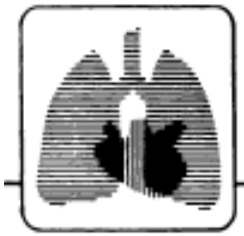
Aucun conflit d’intérêt


Microvascular thrombosis
Thrombin production
Gram-positive bacteria
Gram-negative bacteria
LPS
TLR4
TLR2
Cytokines
Stem cell
TRAF6
NIK
NF-κB

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

WHY

Dear SIRS, I'm sorry to say that I don't like you.

Vincent, Jean-Louis; MD, PhD

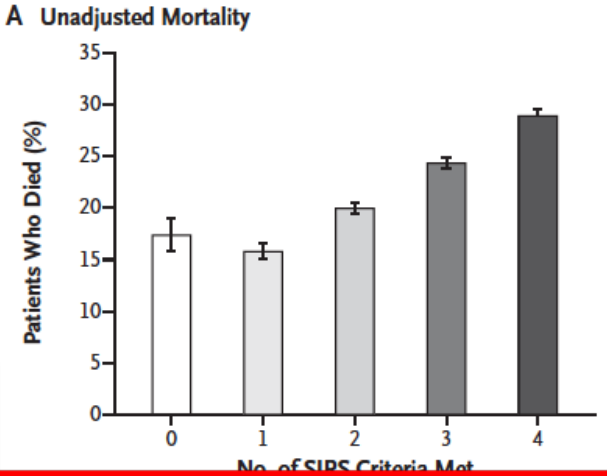
Critical Care Medicine 1997; 25(2):372-374.

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.

The need for two or more SIRS criteria to define severe sepsis excluded one in eight otherwise similar patients with infection, organ failure, and substantial mortality

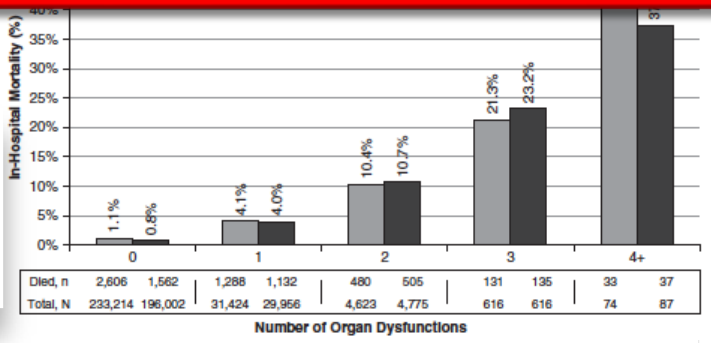


SIRS is an *appropriate* response to infection –

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

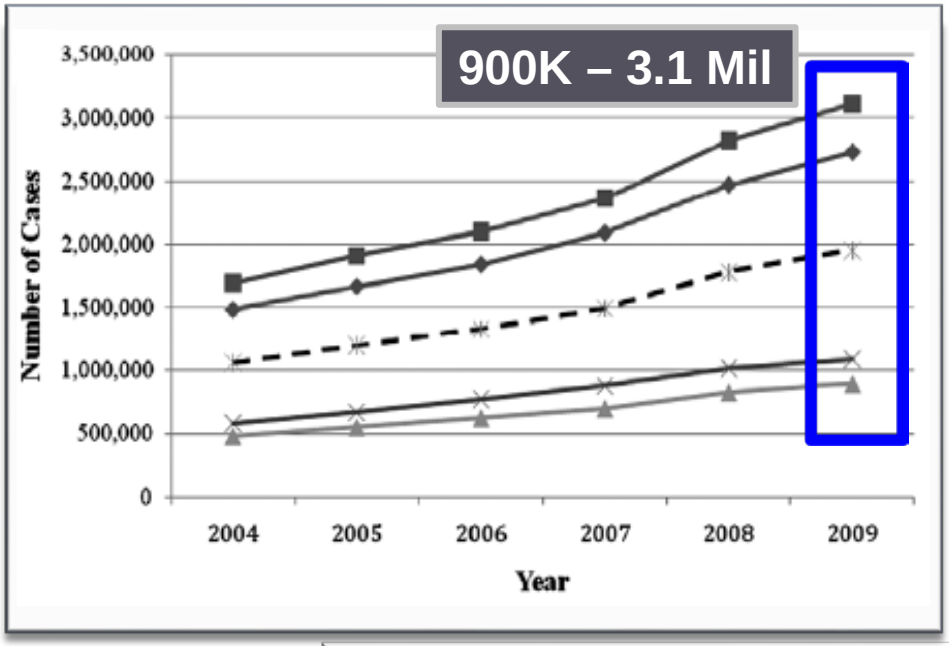
- Most people say “sepsis” when they mean “severe sepsis”
- Is “severe sepsis” really needed ?

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

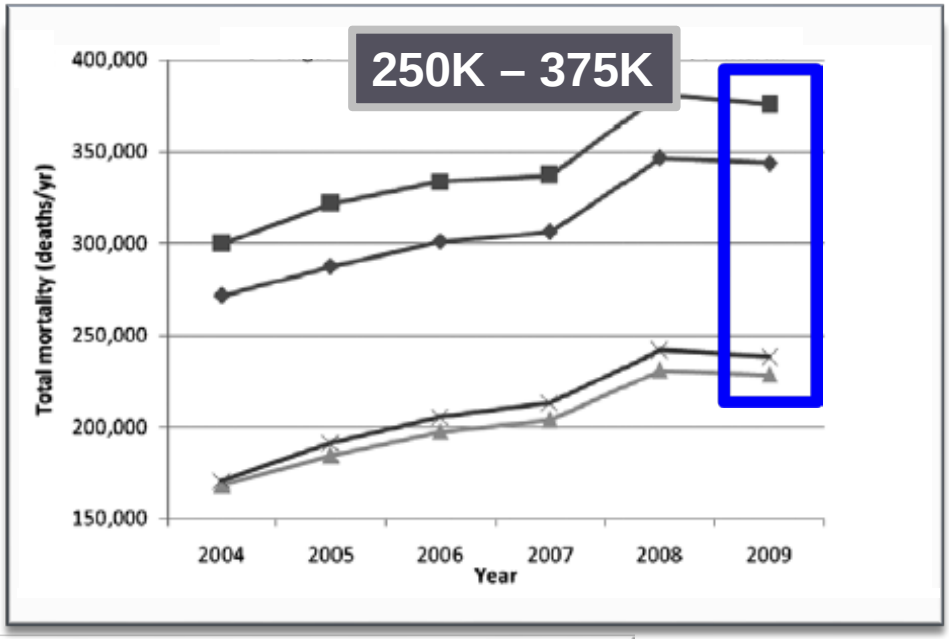
David F. Gaieski MD[1]; J. Matthew Edwards, MD[1]; Michael J. Kallan, MS[2]; Brendan G. Carr, MD, MA, MS[1–3]

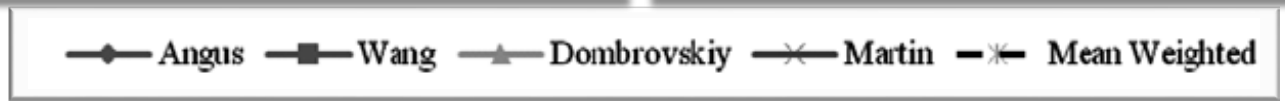
Four different ways to identify sepsis
Four different sets of results

Number of cases



Total mortality





Crit Care Med 2013; 41: 1167-1174

Variable Variables for Septic shock

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

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


START

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

The Sepsis Definitions Task Force

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), m... epidemiology of sepsis, suggesting the need for reexamination.

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

PROCESS A task force (n = 19) with expertise in sepsis pathobiology, clin... epidemiology was convened by the Society of Critical Care Medicine and... Society of Intensive Care Medicine. Definitions and clinical criteria were... meetings, Delphi processes, analysis of electronic health record databas... followed by circulation to international professional societies, requestin... endorsement (by 31 societies listed in the Acknowledgment).

KEY FINDINGS FROM EVIDENCE SYNTHESIS Limitations of previous defini... excessive focus on inflammation, the misleading model that sepsis follo... through severe sepsis to shock, and inadequate specificity and sensitivi... inflammatory response syndrome (SIRS) criteria. Multiple definitions an... currently in use for sepsis, septic shock, and organ dysfunction, leading... reported incidence and observed mortality. The task force concluded th... was redundant.

RECOMMENDATIONS Sepsis should be defined as life-threatening organ... by a dysregulated host response to infection. For clinical operationalizat... dysfunction can be represented by an increase in the Sequential [Sepsis... Failure Assessment (SOFA) score of 2 points or more, which is associate... mortality greater than 10%. Septic shock should be defined as a subset... particularly profound circulatory, cellular, and metabolic abnormalities a... a greater risk of mortality than with sepsis alone. Patients with septic sh... identified by a vasopressor requirement to maintain a mean arterial pres... or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in... hypovolemia. This combination is associated with hospital mortality rat... In out-of-hospital, emergency department, or general hospital ward sett... with suspected infection can be rapidly identified as being more likely t... typical of sepsis if they have at least 2 of the following clinical criteria tha... a new bedside clinical score termed quickSOFA (qSOFA): respiratory rat... altered mentation, or systolic blood pressure of 100 mm Hg or less.

CONCLUSIONS AND RELEVANCE These updated definitions and clinical c... previous definitions, offer greater consistency for epidemiologic studies... facilitate earlier recognition and more timely management of patients w... developing sepsis.

JAMA. 2016;315(8):801-810. doi:10.1001/jama.2016.0287

Editorial page 757

Author Video Interview, Author Audio Interview, and

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Assessment of Clinical Criteria for Sepsis For the Third International Consensus Definiti... for Sepsis and Septic Shock (Sepsis-3)

Christopher W. Seymour, MD, MSc; Vincent X. Liu, MD, MSc; Theodore J. Iwashyna, MD, PhD; Frank M. Brunkl... André Scherag, PhD; Gordon Rubenfeld, MD, MSc; Jeremy M. Kahn, MD, MSc; Manu Shankar-Hari, MD, MSc; ... 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, w... identified those with suspected infection in whom to compare criteria. Confirmatory analyse... 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

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

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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 = 1309 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 ($I^2 = 99.5\%$; $\tau^2 = 182.5$; $P < .001$). 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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Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

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

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Task Force Decisions

CONSENSUS

1. **Sepsis is not simply infection + two or more SIRS criteria**
2. **The host response is of key importance**
3. **Sepsis represents bad infection leading to organ dysfunction**
4. **“Severe sepsis” is not helpful and should be eliminated**

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

Assessment of Clinical Criteria for Sepsis
For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

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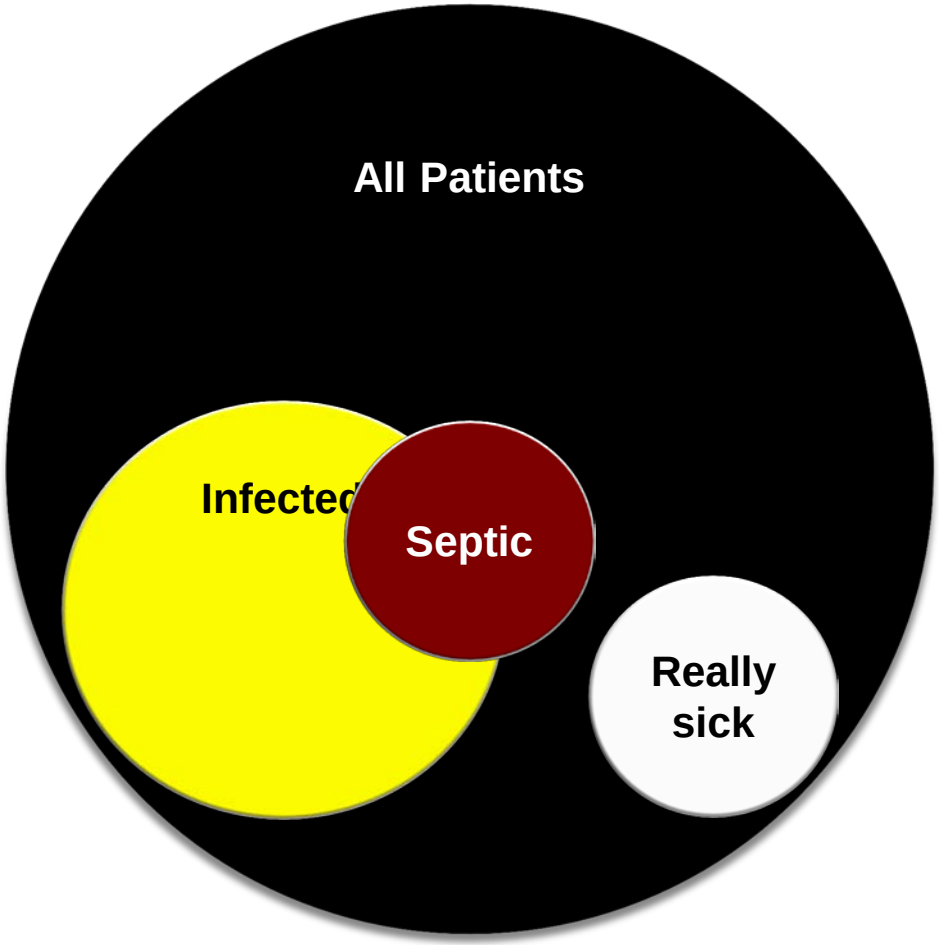
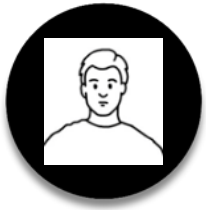
How to define sepsis?



The challenge

What data to use?

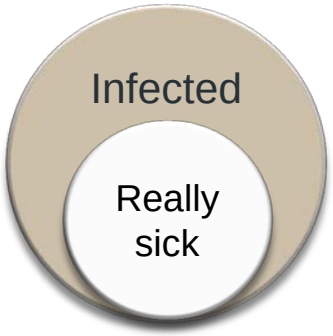


How to identify infection?

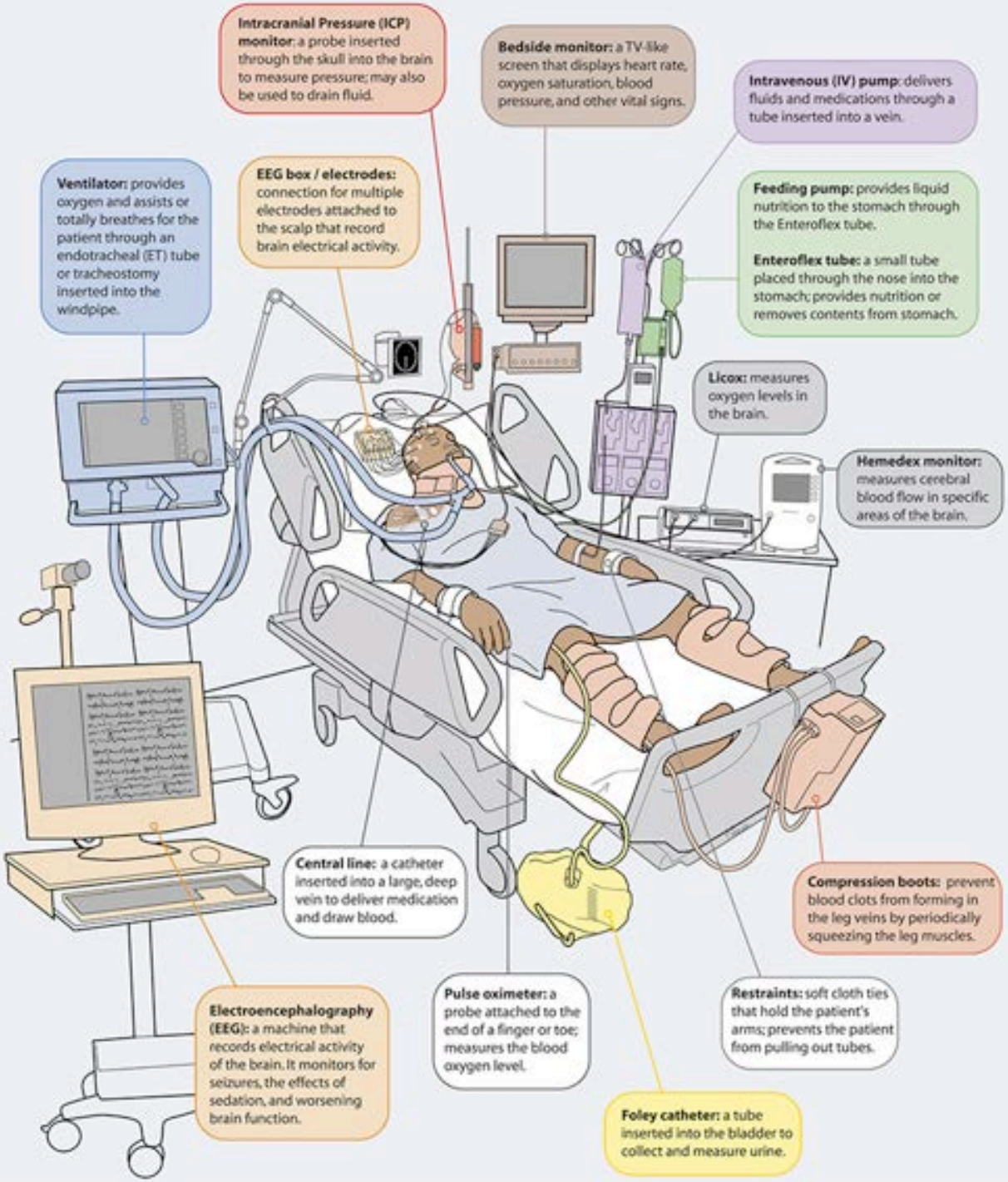
What clinical criteria to study?
SIRS, SOFA, LODS…

How to define really sick?

Definition of really sick patients ?



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


Intracranial Pressure (ICP) monitor: a probe inserted through the skull into the brain to measure pressure; may also be used to drain fluid.
Bedside monitor: a TV-like screen that displays heart rate, oxygen saturation, blood pressure, and other vital signs.
Intravenous (IV) pump: delivers fluids and medications through a tube inserted into a vein.
Ventilator: provides oxygen and assists or totally breathes for the patient through an endotracheal (ET) tube or tracheostomy inserted into the windpipe.
EEG box / electrodes: connection for multiple electrodes attached to the scalp that record brain electrical activity.
Feeding pump: provides liquid nutrition to the stomach through the Enteroflex tube.
Enteroflex tube: a small tube placed through the nose into the stomach; provides nutrition or removes contents from stomach.
Licox: measures oxygen levels in the brain.
Hemedex monitor: measures cerebral blood flow in specific areas of the brain.
Central line: a catheter inserted into a large, deep vein to deliver medication and draw blood.
Compression boots: prevent blood clots from forming in the leg veins by periodically squeezing the leg muscles.
Electroencephalography (EEG): a machine that records electrical activity of the brain. It monitors for seizures, the effects of sedation, and worsening brain function.
Pulse oximeter: a probe attached to the end of a finger or toe; measures the blood oxygen level.
Restraints: soft cloth ties that hold the patient's arms; prevents the patient from pulling out tubes.
Foley catheter: a tube inserted into the bladder to collect and measure urine.

SOFA Score

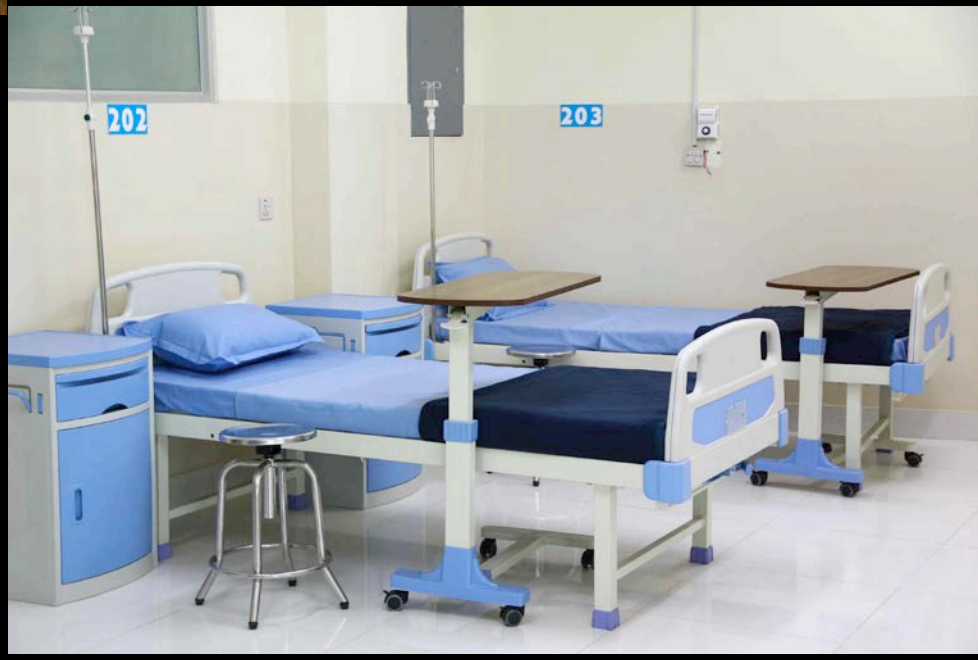
Variables/points	1	2	3	4
Neurological (GCS)	13-14	10-12	6-9	<6
Respiratory (P:F ratio)	<400	<300	<200 (+ resp support)	<100 (+ resp support)
Cardiovascular (systolic BP)	<70	dopamine ≤5 or dobutamine (any dose)	dopamine >5 or EPI ≤0.1 or NOREPI ≤0.1	dopamine >15 or EPI >0.1 or NOREPI >0.1
Renal (creatinine 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

- 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.

Why a change of ≥2 from baseline SOFA?

- many patients have existing 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


Emergency


202
203

Developing new criteria

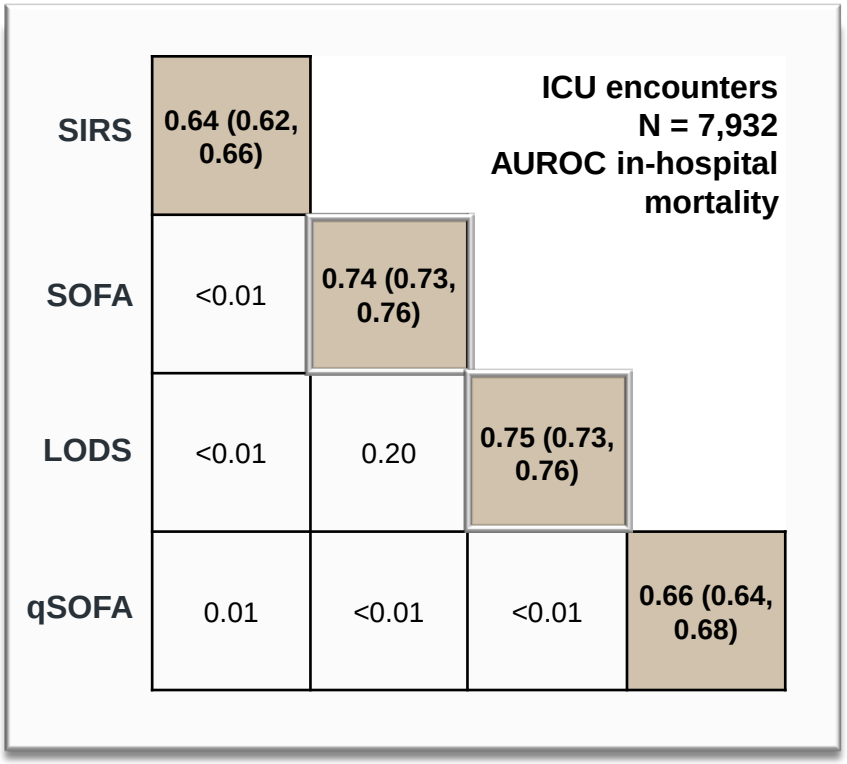
Focus on timeliness, ease of use

Studied 21 variables from Sepsis-2

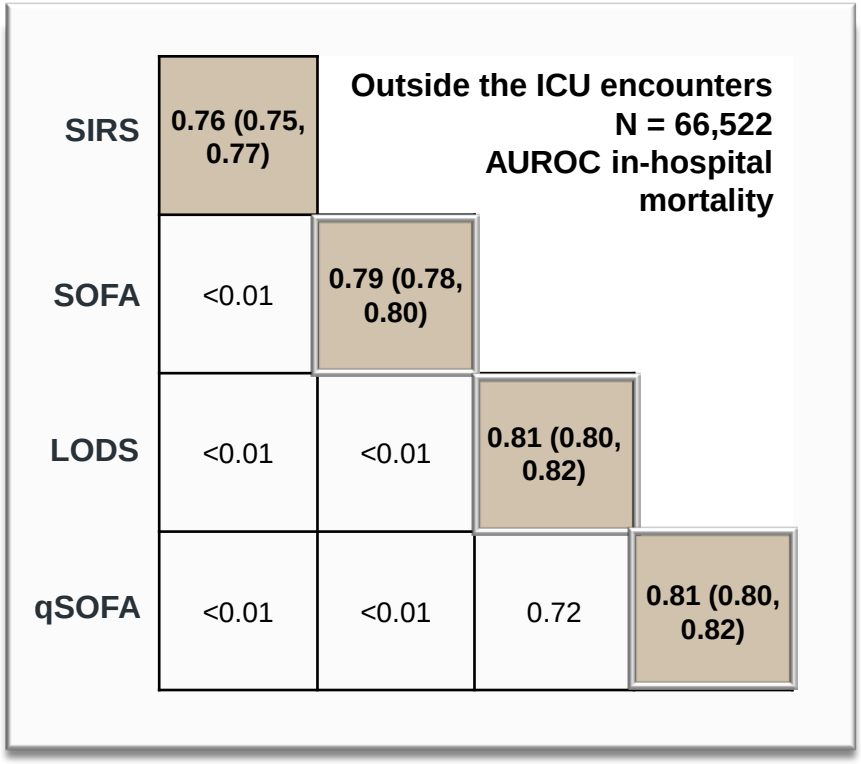
Multivariable logistic regression for in-hospital mortality

www.qsofa.org

Assessment of criteria



SOFA and LODS superior in the ICU



qSOFA similar to complex scores outside the ICU

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

www.qsofa.org

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

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

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

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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?

Data analysis

Derivation cohort

Surviving Sepsis Campaign Database (SSC)

2005-2010; n = 28,150

Validation cohort

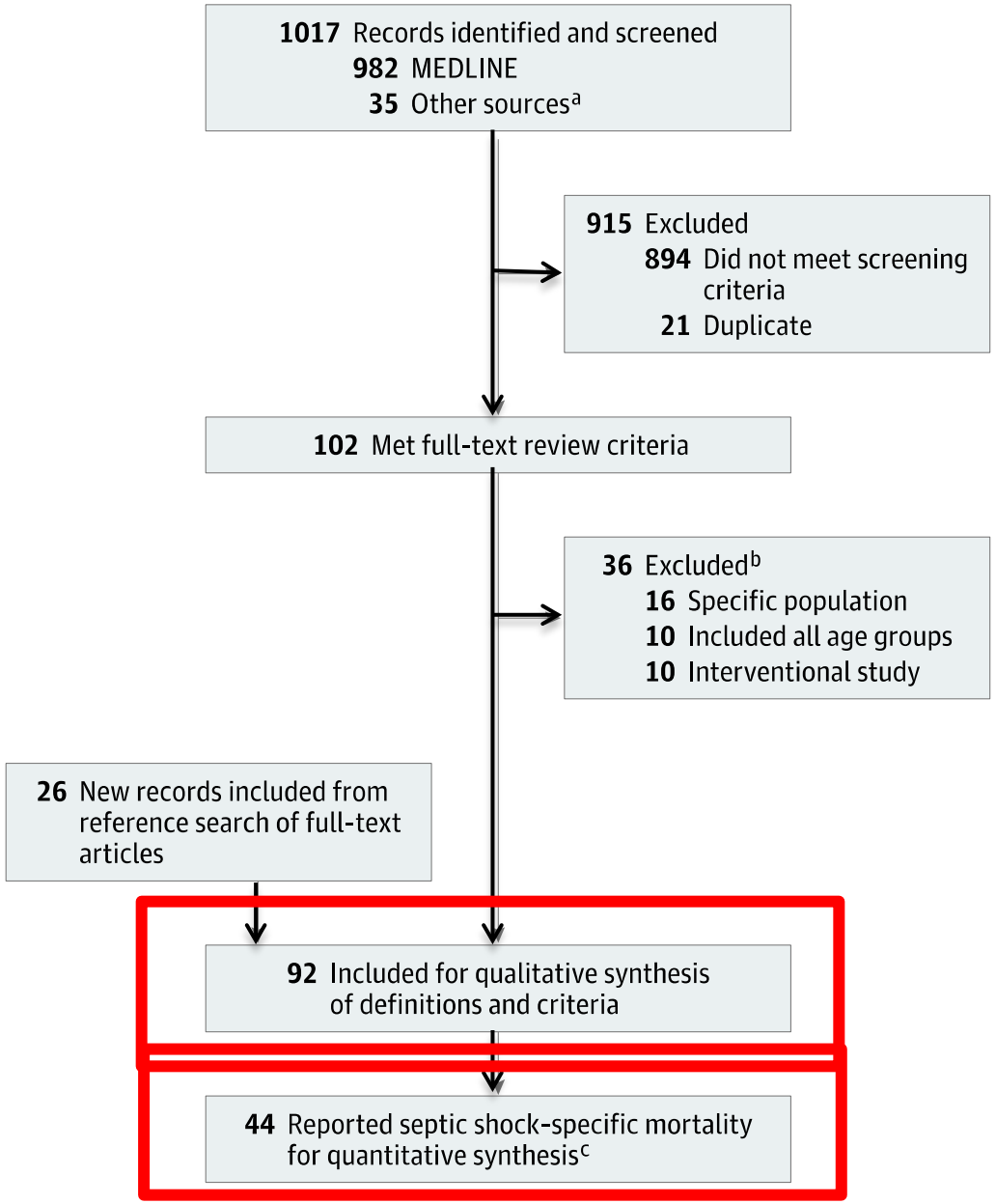
12 hospitals in Pennsylvania (UPMC)

2010-2012; n = 1,309,025

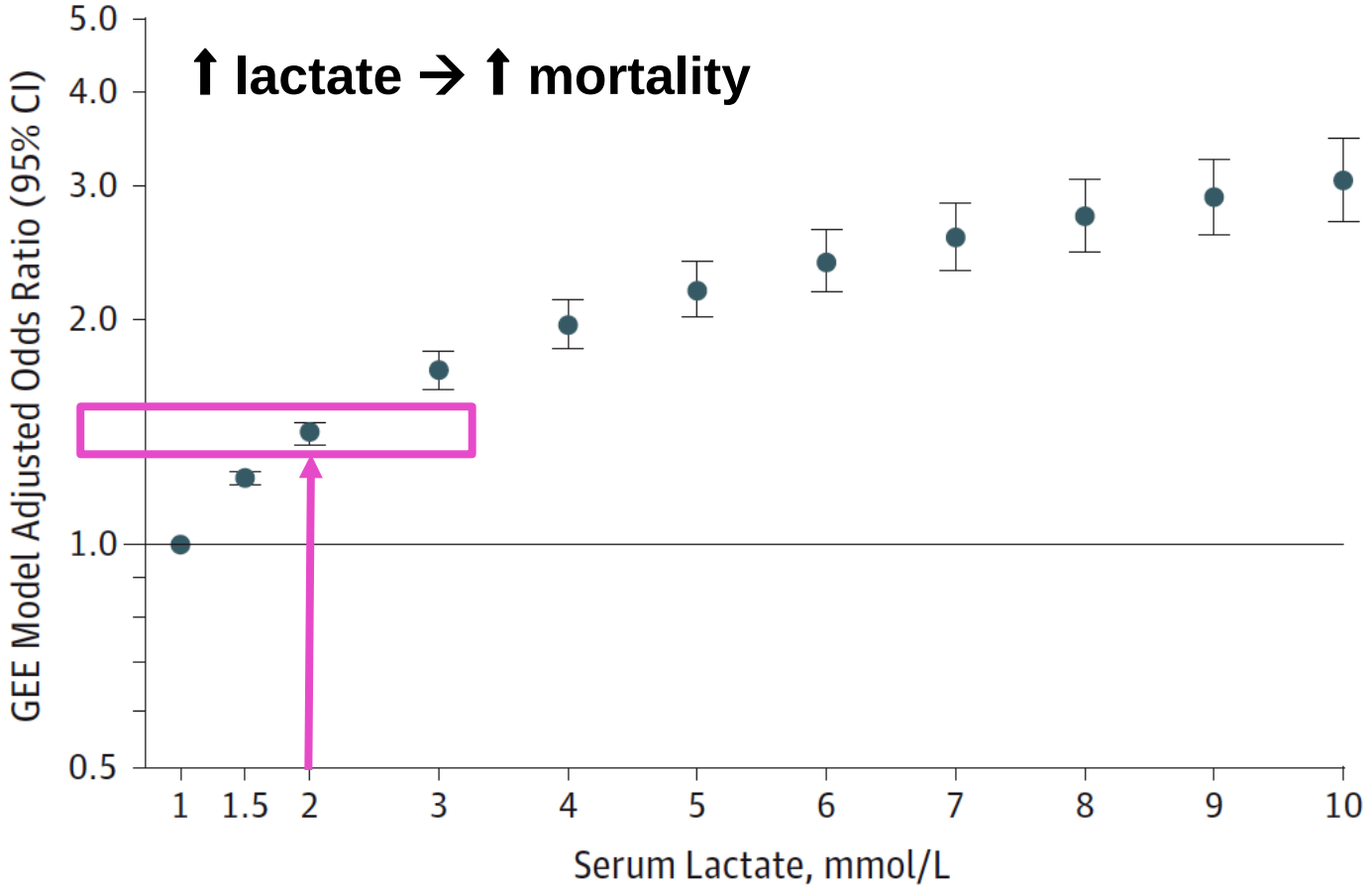
20 Hospitals (Kaiser Permanente Northern California, KPNC)

2009-2013; n = 1,847,165

Systematic review



Lactate cutoff rationale



Hypotension AND hyperlactatemia in 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

2016 Septic Shock Criteria

Despite adequate fluid resuscitation

- **vasopressors needed to maintain MAP ≥65 mmHg**

  AND

- **lactate >2 mmol/l**

Septic shock

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

Conclusion on new definitions

- **Pragmatic**
  - **There is no absolute biomarker (yet) for sepsis or septic shock**
  - **Generalizability - readily measurable identifiers that best capture conceptualisation of ‘sepsis’**
- **Ease of use**
  - **qSOFA - rapid bedside measure**
  - **SOFA - clinical measures and lab tests performed routinely in any sick patient**

qSOFA

- 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)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Sepsis: older and newer concepts

Jean-Louis Vincent, Jean-Paul Mira, Massimo Antonelli

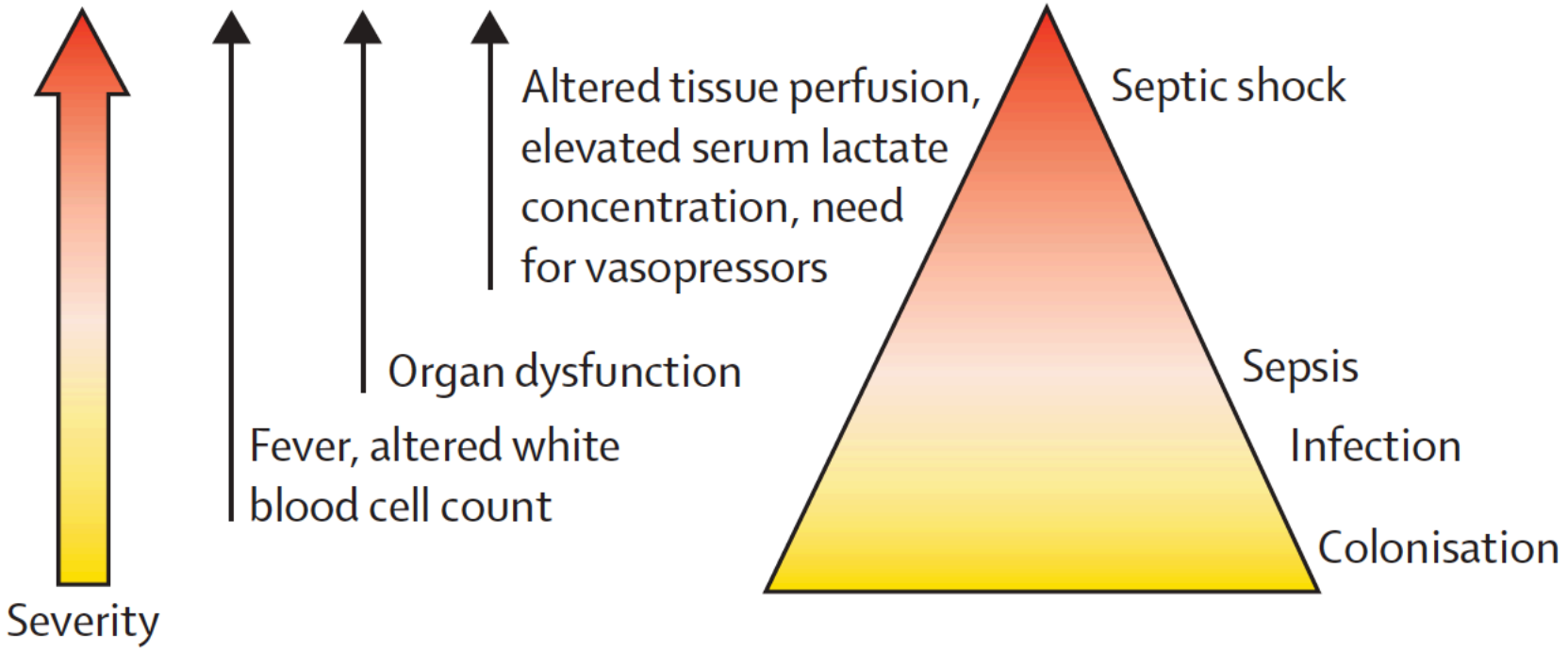
Sepsis is a common complication in patients in intensive care units and a frequent reason for intensive care unit admission. Sepsis is a major cause of morbidity and mortality and, without specific antisepsis therapies, management relies on infection control and organ support. For these interventions to be most effective, they must be started early, which highlights the need for all health-care workers to be aware of sepsis so that diagnosis can be made as early as possible. In this Viewpoint, we discuss some of the earlier terms used to characterise and define sepsis, and point out some of their limitations. We then introduce some aspects of new consensus definitions, proposed by an expert panel, which highlight in particular the importance of organ dysfunction. These definitions should help provide a more standardised approach to the identification of patients with suspected sepsis in both clinical practice and clinical research.

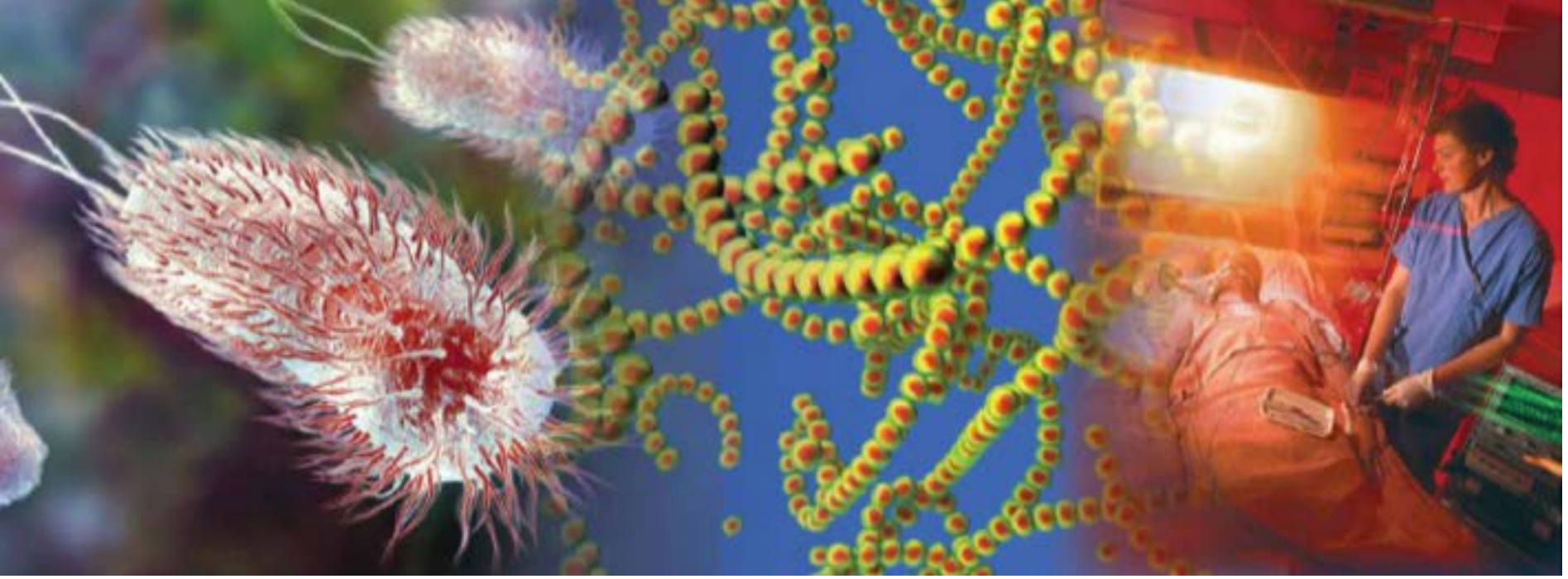
Lancet Respir Med 2016; 4: 237–40

Published Online February 22, 2016 http://dx.doi.org/10.1016/S2213-2600(15)00522-6

See Online for podcast interview with Jean-Louis Vincent

Department of Intensive Care,



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THANK YOU!
FRAPAR.