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
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

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

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

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 MD¹; J. Matthew Edwards, MD¹; Michael J. Kallan, MS²; Brendan G. Carr, MD, MA, MS¹-³

Crit Care Med 2013; 41: 1167-1174

Number of cases

- 900K – 3.1 Mil

Total mortality

- 250K – 375K

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

<table>
<thead>
<tr>
<th>Derek Angus</th>
<th>Richard Hotchkiss</th>
<th>Greg Martin</th>
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<tr>
<td>Djilali Annane</td>
<td>Mitchell Levy</td>
<td>Manu Shankar-Hari</td>
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<td>Michael Bauer</td>
<td>John Marshall</td>
<td>Chris Seymour</td>
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<td>Rinaldo Bellomo</td>
<td>Steve Opal</td>
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<td>Gordon Bernard</td>
<td>Gordon Rubenfeld</td>
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<td>Jean-Daniel Chiche</td>
<td>Tom van der Poll</td>
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<td>Craig Coopersmith</td>
<td>Jean-Louis Vincent</td>
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</tbody>
</table>
The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Mervyn Singer, MD; Frédéric C. Couture, MD; Daniel E. Cook, MD; Cyril Krangle, MD; Robert S. Hotchkiss, MD; Michael V. Levy, MD; John C. Marshall, MD; Greg M. Martin, MD, MSc; Steven M. Opal, MD; Gordan D. Rubertides, MD; Tom van der Poll, MD, PhD; Jean Louis Vincent, MD, PhD; Derek C. Angus, MD, MPH

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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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.
What is sepsis?

A life threatening organ dysfunction caused by a dysregulated host response to infection.
What is sepsis?

A life threatening organ dysfunction caused by a dysregulated host response to infection.
What is sepsis?

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

1. Among encounters with suspected infection,
2. who is really sick?
What is sepsis?

All the patients you see..
We did not..

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

We did..

![Diagram showing the relationship between infected, really sick, cohort, and cases.]

- Infected
  - Really sick
    - Cohort
    - Cases
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?

1309025 Patient encounters at 12 UPMC hospitals in 2010-2012

1160118 Excluded
1109402 No infection present
45628 Aged <18 y
2169 Outside eligible date range
2117 Error in encounter start time
774 Initial location was clinic
28 Error in hospital type

148907 With suspected infection in ED, ICU, ward, step-down unit, or PACU included in primary cohort

74453 Included in derivation cohort
7836 In ICU
66617 Outside of ICU

74454 Included in validation cohort
7932 In ICU
66522 Outside of ICU
### External datasets

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

- >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?

<table>
<thead>
<tr>
<th>Systemic Inflammatory Response Syndrome (SIRS) Criteria (Range, 0-4 Criteria)</th>
<th>Sequential [Sepsis-related] Organ Failure Assessment (SOFA) (Range, 0-24 Points)</th>
<th>Logistic Organ Dysfunction System (LODS) (Range, 0-22 Points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory rate, breaths per minute</td>
<td>( Pao_2/Fio_2 ) ratio</td>
<td>( Pao_2/Fio_2 ) ratio</td>
</tr>
<tr>
<td>White blood cell count, ( 10^9/L )</td>
<td>Glasgow Coma Scale score</td>
<td>Glasgow Coma Scale score</td>
</tr>
<tr>
<td>Bands, %</td>
<td>Mean arterial pressure, mm Hg</td>
<td>Systolic blood pressure, mm Hg</td>
</tr>
<tr>
<td>Heart rate, beats per minute</td>
<td>Administration of vasopressors with type/dose/rate of infusion</td>
<td>Heart rate, beats per minute</td>
</tr>
<tr>
<td>Temperature, °C</td>
<td>Serum creatinine, mg/dL, or urine output, mL/d</td>
<td>Serum creatinine, mg/dL</td>
</tr>
<tr>
<td>Arterial carbon dioxide tension, mm Hg</td>
<td>Bilirubin, mg/dL</td>
<td>Bilirubin, mg/dL</td>
</tr>
<tr>
<td>Platelet count, ( 10^9/L )</td>
<td>Platelet count, ( 10^9/L )</td>
<td>White blood cell count, ( 10^9/L )</td>
</tr>
<tr>
<td>Urine output, L/d</td>
<td>Serum urea, mmol/L</td>
<td>Prothrombin time, % of standard</td>
</tr>
</tbody>
</table>
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

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

- Respiratory rate ≥ 22 bpm
- Altered mentation
- Systolic blood pressure ≤ 100 mmHg
Assessment of criteria

<table>
<thead>
<tr>
<th></th>
<th>SIRS</th>
<th>SOFA</th>
<th>LODS</th>
<th>qSOFA</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU encounters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUROC in-hospital mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 7,932</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>0.64 (0.62, 0.66)</td>
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<tr>
<td>&lt;0.01</td>
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<tr>
<td>0.74 (0.73, 0.76)</td>
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<tr>
<td>&lt;0.01</td>
<td></td>
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<tr>
<td>0.75 (0.73, 0.76)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>0.66 (0.64, 0.68)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>SIRS</th>
<th>SOFA</th>
<th>LODS</th>
<th>qSOFA</th>
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</thead>
<tbody>
<tr>
<td>Outside the ICU encounters</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>AUROC in-hospital mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 66,522</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.76 (0.75, 0.77)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.79 (0.78, 0.80)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&lt;0.01</td>
<td></td>
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<tr>
<td>0.81 (0.80, 0.82)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.01</td>
<td></td>
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SOFA and LODS superior in the ICU

qSOFA similar to complex scores outside the ICU
Assessment of criteria

SOFA and LODS superior in the ICU
Assessment of criteria

Outside the ICU encounters
N = 66,522

Decile of baseline risk of in-hospital mortality

Fold change, in-hospital mortality

- SIRS 2 vs. SIRS <2
- SOFA 2 vs. SOFA <2
- LODS 2 vs. LODS <2
- qSOFA 2 vs. qSOFA <2

qSOFA similar to complex scores outside the ICU
qSOFA in external datasets

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

- 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

<table>
<thead>
<tr>
<th>Decile of baseline risk of in-hospital mortality</th>
<th>All KPNC encounters N = 321,380</th>
</tr>
</thead>
<tbody>
<tr>
<td>(qSOFA + serum lactate) &lt; 2</td>
<td>vs. (qSOFA + lactate) &lt; 2</td>
</tr>
</tbody>
</table>

- Specificity
- Sensitivity

All KPNC encounters
N = 321,380
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

Manu Shankar-Hari, MD MSc, FFICM
Guy’s and St Thomas’ Hospitals NHS Trust, London, UK
King’s College London, 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)

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
1017 Records identified and screened
  982 MEDLINE
  35 Other sources\textsuperscript{a}

915 Excluded
  894 Did not meet screening criteria
  21 Duplicate

102 Met full-text review criteria

36 Excluded\textsuperscript{b}
  16 Specific population
  10 Included all age groups
  10 Interventional study

26 New records included from reference search of full-text articles

92 Included for qualitative synthesis of definitions and criteria

44 Reported septic shock-specific mortality for quantitative synthesis\textsuperscript{c}
Systematic review

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

<table>
<thead>
<tr>
<th>Group</th>
<th>hypotension after fluids</th>
<th>vasopressor</th>
<th>lactate &gt;2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Group 2</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Group 3</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Group 4</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Group 5</td>
<td>No</td>
<td>hypotension pre-fluids</td>
<td>No</td>
</tr>
<tr>
<td>Group 6</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
Derivation of clinical criteria - SSC
Lactate cutoff rationale

↑ lactate → ↑ mortality

GEE Model Adjusted Odds Ratio (95% CI)

Serum Lactate, mmol/L
Lactate cutoff rationale

- Test performance (receiver operator characteristics)
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?’ …
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

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

<table>
<thead>
<tr>
<th></th>
<th>Hospital mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension + lactate &gt;2</td>
<td>42.3</td>
</tr>
<tr>
<td>Hypotension alone</td>
<td>30.1</td>
</tr>
<tr>
<td>Lactate &gt;2 alone</td>
<td>25.7</td>
</tr>
<tr>
<td>No hypotension and lactate &lt;2</td>
<td>18.7</td>
</tr>
</tbody>
</table>

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.
<table>
<thead>
<tr>
<th>Current Guidelines and Terminology</th>
<th>Sepsis</th>
<th>Septic Shock</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991 and 2001 consensus terminology^9,10</td>
<td>Severe sepsis, Sepsis-induced hypoperfusion</td>
<td>Septic shock^13</td>
</tr>
<tr>
<td>2015 Definition</td>
<td>Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection</td>
<td>Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality</td>
</tr>
<tr>
<td>2015 Clinical criteria</td>
<td>Suspected or documented infection and an acute increase of ≥2 SOFA points (a proxy for organ dysfunction)</td>
<td>Sepsis^a and vasopressor therapy needed to elevate MAP ≥65 mm Hg and lactate &gt;2 mmol/L (18 mg/dL) despite adequate fluid resuscitation^13</td>
</tr>
</tbody>
</table>

Recommended primary ICD codes^a

<table>
<thead>
<tr>
<th>ICD-9</th>
<th>ICD-10^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>995.92</td>
<td>R65.20</td>
</tr>
<tr>
<td>785.52</td>
<td>R65.21</td>
</tr>
</tbody>
</table>
The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

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 (e.g., 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, i.e., 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 vasoressors 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.
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