SEPSIS-3: THE NEW DEFINITIONS
WHAT THEY SHOULD MEAN TO YOU
THE THIRD INTERNATIONAL CONSENSUS DEFINITIONS FOR SEPSIS AND SEPTIC SHOCK (SEPSIS-3)

JAMA

https://www.youtube.com/watch?v=1S8I5D2xr6w
IN THE BEGINNING
THERE WAS "SEPSIS-1"

Focusing on the left portion of the image, the text reads:

accp/sccm consensus conference

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

THE ACCP/SOCCM 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. Rein, 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.

(Chest 1992; 101:1644-55)

Sepsis = the systemic response to infection, manifested by two or more of the following conditions as a result of infection: (1) temperature >38°C or <36°C; (2) heart rate >90 beats per minute; (3) respiratory rate >20 breaths per minute or PaCO₂ <32 mm Hg; and white blood cell count >12,000/cu mm, <4,000/cu mm, or >10% immature (band) forms.

Severe sepsis = sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to lactic acidosis, oliguria, or an acute alteration in mental status.

Septic shock = sepsis-induced with hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status. Patients who are receiving inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured.
AND "SEPSIS-2" COULDN'T REALLY ADD TO IT
WE’VE COME TO RECOGNISE MANY ISSUES WITH “OLD” SEPSIS

- ‘Sepsis’ means different things to different people
- It’s a syndrome with no perfect diagnostic test
- .. though the science has moved on since 2001
- Is SIRS still fit for purpose to define ‘sepsis’?
- No specified criteria to describe ‘organ dysfunction’ or ‘shock’
- .. so the epidemiology is a complete mess
- Sepsis is a killer .. but is it a mass murderer? Hype ++++++
SEPSIS-3

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

Morryn Singer, MD, FRCPC; Clifford D. Deutscher, MD, MSc; Christopher W. Seymour, MD, MSc; Vincent X. Liu, MD, MSc; Theodore J. Nwachukwu, MD, PhD; Frank Andriech, PhD; Gordon Rubenfeld, MD, MSc; Jeremy M. Kehin, MD, MSc; Manu Shankar-Hari, MD, MSc; Clifford S. Deutscher, MD, MSc; Gabriel J. Escobar, MD; Derek C. Angus, MD, MPH

Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

REASSESSMENT OF CLINICAL CRITERIA FOR SEPSIS

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

Christopher W. Seymour, MD, MSc; Vincent X. Liu, MD, MSc; Theodore J. Nwachukwu, MD, PhD; Frank Andriech, PhD; Gordon Rubenfeld, MD, MSc; Jeremy M. Kehin, MD, MSc; Manu Shankar-Hari, MD, MSc; Clifford S. Deutscher, MD, MSc; Gabriel J. Escobar, MD; Derek C. Angus, MD, MPH

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

DEVELOPING A NEW DEFINITION AND ASSESSING NEW CLINICAL CRITERIA FOR SEPTIC SHOCK

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, MSc; Mitchell C. Levy, MD; Christopher W. Seymour, MD, MSc; Vincent X. Liu, MD, MSc; Derek C. Angus, MD, MPH; Gordon D. Rubenfeld, MD, MSc; Mervyn Singer, MD, FRCPC, for the Sepsis Definitions Task Force

There is no right answer …

.. so we tried to develop - as best we could - new definitions based on science, driven by data, and which could be easily and consistently applied .. and with the ED/ward patient in mind
PLEASE DO READ THE PAPERS FOR YOURSELVES

.. SOME EDITORIALISTS/TWEETERS HAVE CLEARLY NOT

... AND GOT IT BADLY WRONG!
Sepsis isn’t just a systemic pro-inflammatory response.
≥2 of 4 SIRS
organ dysfunction
CV collapse not responding to fluid.
severe sepsis
septic shock

Does SIRS really fit within the sepsis construct??

What does ‘organ dysfunction’ mean?

What does ‘shock’ mean?

Too much overlap between ‘infection’ and ‘sepsis’
Sepsis isn’t just a systemic pro-inflammatory response.

- Infection
- Sepsis
- Organ dysfunction
- Severe sepsis
- CV collapse not responding to fluid
- Septic shock

≥2 of 4 SIRS (Systemic Inflammatory Response Syndrome)
pro-inflammatory

anti-inflammatory

bioenergetic

immune

metabolic

hormonal

cardiovascular

neural

endothelial

coagulation
infection

1991/2002

≥2 of 4 SIRS

organ dysfunction

sepsis

severe sepsis

CV collapse not responding to fluid

septic shock

too much overlap between ‘infection’ and ‘sepsis’
"BIG DATA" USED TO UNDERPIN RECOMMENDATIONS

- predominantly taken from large US hospital EHR databases
- ~ 5 million patient encounters in wide range of hospitals
- ~ 850,000 patients with suspected infection (cultures/Abx)
- ~ 90% outside the ICU
12 Pittsburgh/W Pennsylvania hospitals (big + small)
1.3M patient encounters
11% (149K) suspected infection (89% ED/ward)
... of these, only 4% (6347) died
... ?? from or with infection (e.g. COPD, cancer)
... how many of these suspected cases were truly infected??
i.e. at most, only 1 in 200 of the entire population died of/with sepsis (infection + organ dysfunction)
1991/2002

≥2 of 4 SIRS

sepsis

organ dysfunction

severe sepsis

CV collapse not responding to fluid

septic shock

does SIRS really fit within the sepsis construct??

infection

sepsis

organ dysfunction

severe sepsis

CV collapse not responding to fluid

septic shock
• SIRS usually represents an **appropriate** body response to infection .. even a bad cold

• .. but does this make the infection “sepsis” ????

• Need to clearly differentiate straightforward infection from a life-threatening “**bad**” infection

• SIRS has both sensitivity and specificity issues
SIRS —> SENSITIVE (-ISH) BUT POOR SPECIFICITY

Systemic Inflammatory Response Syndrome Criteria in Defining Severe Sepsis

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

Unadjusted Mortality

![Graph showing mortality rates for patients with varying numbers of SIRS criteria met.]

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.

Incidence and Prognostic Value of the Systemic Inflammatory Response Syndrome and Organ Dysfunctions in Ward Patients

Matthew M. Churpek, Frank J. Zadravec, Christopher Winslow, Michael D. Howell, and Dana P. Edelson

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.

n.b. SIRS still has a place when considering possibility of infection but NOT ‘sepsis’
1991/2002

- infection
  - ≥2 of 4 SIRS
    - sepsis
      - organ dysfunction
        - severe sepsis
          - CV collapse not responding to fluid
            - septic shock

what does ‘organ dysfunction’ mean?
what does ‘shock’ mean?
Conclusions: An increasing number of admissions for severe sepsis combined with declining mortality rates contribute to more individuals surviving to hospital discharge.
Conclusions: An increasing number of admissions for severe sepsis combined with declining mortality rates contribute to more individuals surviving to hospital discharge.
WHAT IS ‘SEPSIS’?

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

Conclusions: Diagnosing sepsis is extremely subjective and variable. Objective criteria and standardized methodology are needed to enhance consistency and comparability in sepsis research, surveillance, benchmarking, and reporting.

Electronic questionnaire:
94 experienced clinicians (most ICU)

‘unequivocal’ septic shock + MOF due to Gm- bacteraemia

Critical Care (2016) 20:89
What is ‘sepsis’?

Diagnosing sepsis is subjective and unstable: a survey of intensivists using vignettes

Conclusions: Diagnosing sepsis is extremely subjective and unstable. Methodology are needed to enhance consistency and comparability in diagnosing sepsis.

Key messages:

- Interobserver agreement among intensivists in diagnosing sepsis is poor.
- When diagnosing sepsis, there is a substantial amount of subjectivity in deciding whether infection is present, whether acute organ dysfunction is present, and whether acute organ dysfunction is attributable to infection.
- Subjectivity in diagnosing sepsis must be taken into account when interpreting the results of sepsis quality improvement initiatives and public reporting for sepsis bundle adherence, as well as for epidemiologic studies and clinical trials.
- Objective criteria and standardized methodology are needed to enhance consistency and comparability in sepsis research, surveillance, and quality reporting.
SYSTEMATIC REVIEW OF CRITERIA USED 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)
SEPTIC SHOCK
VARIABLY DEFINED —>
4-FOLD VARIATION IN MORTALITY
10-FOLD VARIATION IN INCIDENCE

Truth

NEXT EXIT
A DEFINITION —> WHAT SOMETHING ‘IS’, THE ‘ESSENCE’ OF SOMETHING ..

Sepsis is defined as life–threatening organ dysfunction due to a dysregulated host response to infection.

Septic shock is defined as a subset of sepsis where underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality.
Organ dysfunction is characterized by a rise in total SOFA ≥2

- assume SOFA = 0 unless patient known to have abnormal score prior
- SOFA ≥2 associated with >10% chance of dying in hospital
- For formal characterisation of ‘sepsis’ SOFA can be scored retrospectively ...
  … but actively treat patient in interim
Shock is characterised by lactate >2 mmol/l and vasopressors needed to elevate MAP≥65 mmHg despite adequate fluid resuscitation.

Septic shock is defined as a subset of sepsis where underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality.

why didn’t we use lactataemia OR hypotension???
SURVIVING SEPSIS CAMPAIGN (SSC) REGISTRY

- 28,150 infected patients with ≥2 SIRS criteria + ≥1 organ dysfunction after fluid resuscitation

- Hospital mortality
  - 42.3% in patients having both hypotension + hyperlactataemia
  - 25.7% with hyperlactataemia alone
  - 30.1% with fluid-resistant hypotension alone
  - 25% with organ dysfunction but lactate ≤2 and MAP ≥65
IS ICU LACTATE THE SAME AS ED LACTATE??

90 day mortality (%) vs lactate (mmol/l)

- ED enrolled
- ICU enrolled
- ARISE
- ProCESS
- SEPSISPAM
- TRISS

Questions and discussion points:
8.3.13 Evidence statements

2 Clinical

3 The evidence from the seventeen studies included in the review was of very low quality for all the indicators found in one study with a blood lactate threshold of 1 mmol/l. Quality of evidence was generally very low. One reason was high levels of imprecision or the lack of any measures of precision. Another reason was very serious risk of bias, principally due to lack of evidence that physicians treating patients were blinded to the lactate status. The assumed lack of blinding means that lactate levels could affect treatment, which would possibly affect outcome. In some of the studies the description of selection of participants was limited. The GDG agreed therefore that they could not be confident in the evidence due to poor quality.

Other considerations

The GDG were interested in whether lactate could be used a discriminating factor to indicate which patients required more urgent and aggressive treatment. The GDG discussed the relative importance of sensitivity and specificity, mainly the risk of missing people with sepsis against the harm to the population of treating people unnecessarily. However the evidence indicated a high sensitivity occurred mainly with lower lactate levels. Information on how many people this would identify is not available, but the GDG considered that a lactate of 2 mmol/l would pick up many people with less serious infections. The GDG concluded that the evidence was not strong enough to justify determining a particular lactate threshold on a rule in or rule out basis.
QSOFA = QUICK BEDSIDE STRATIFICATION TOOL
.. NOT A DIAGNOSTIC FOR SEPSIS

- tachypnoea (≥22/min)
- low systolic BP (≤100 mmHg)
- altered mentation

QSOFA = cardiovascular dysfunction?

neurological dysfunction?

respiratory ± metabolic dysfunction?

<table>
<thead>
<tr>
<th>qSOFA</th>
<th>mortality (%)</th>
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<tbody>
<tr>
<td>0</td>
<td>~1</td>
</tr>
<tr>
<td>1</td>
<td>~3</td>
</tr>
<tr>
<td>2</td>
<td>~8-10</td>
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<tr>
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Dr currently called at NEWS 5 (or 4)
SUMMARY

- SEPSIS-3 offers (we hope) objectivity, reproducibility and generalizability for research, for coding, for epidemiology..
- qSOFA may be a useful bedside prompt to highlight at-risk patients
  - needs prospective validation
  - embedded within NEWS (standard-of-care EWS in UK)
- NOT the final word - it’s an iterative process..
  - ... Sepsis-4 will improve on Sepsis-3
  - .. but I do hope it is progress!!!