A BRIEF HISTORY OF SEPSIS

Euan Mackay
Aims

• History of sepsis definition
• Validity of new definition
Hippocrates – 4\textsuperscript{th} century BC

- Hippocrates introduced the term "σήψις"
  - the process of decay or decomposition of organic matter.
Avicenna – 11th century AD

- Avicenna used the term "blood rot" for diseases linked to a severe purulent process.
19th century

• Though severe systemic toxicity had already been observed, it was only in the 19th century that the specific term – sepsis – was used for this condition.
• By the end of the 19th century it was widely believed that microbes released toxins during infection which could injure the host.
“Advances in the treatment of fever… have not kept pace with the rapid progress in our knowledge of the etiology. In the present condition of bacteriology we may expect great things in the near future, but meanwhile we jog along without any fixed aim, too often carried away by winds of doctrines and wild theories.”
Early 20\textsuperscript{th} century

- The term endotoxin was coined at the beginning of the 20\textsuperscript{th} century to denote the pathophysiology of cholera disease.
- It was soon realised that endotoxins were expressed by most gram-negative bacteria.
'ware Hitler's Greatest Ally

Herr Septicaemia (Alias Bloodpoisoning)

Uses Blitz Methods

Only waiting for the slightest scratch to inject his poison.
Has more victims to his discredit than the whole of the German fighting forces put together.
Is usually defeated by immediate First Aid treatment.
To neglect yourself is to play into the enemy's hands.

Don't Help Hitler!

Issued by the Ministry of Labour and National Service and produced by the Industrial Accident Prevention Department of the M.I.P.A.
Consensus definitions


• 2001 - Society of Critical Care Medicine, the European Society of Intensive Care Medicine, The American College of Chest Physicians, the American Thoracic Society and the Surgical Infection Society.

• 2016 - Society of Critical Care Medicine and the European Society of Intensive Care Medicine Redefinitions Task Force.
Sepsis 1

• Introduced the term “systemic inflammatory response syndrome” (SIRS).

• SIRS is considered to be present when patients have more than one of the following clinical findings:
  • Body temperature higher than 38°C or lower than 36°C
  • Heart rate higher than 90/min
  • Hyperventilation evidenced by respiratory rate higher than 20/min or PaCO2 lower than 32 mmHg
  • White blood cell count higher than 12,000 cells/ μl or lower than 4,000/ μl
Sepsis 1

• Sepsis
  • SIRS plus infection

• Severe sepsis
  • sepsis associated with organ dysfunction, hypoperfusion or hypotension

• Septic shock
  • sepsis with arterial hypotension despite “adequate” fluid resuscitation
SIRS limitations

- SIRS lacks sensitivity for defining sepsis
  - 1 in 8 ICU patients with infection and organ dysfunction do not have 2 or more SIRS criteria
- SIRS not specific
  - 4 in 5 ICU patients without infection have ‘SIRS’ criteria
- Different sources of infection are associated with different mortality rates
- SIRS criteria do not account for the dynamic time-course of sepsis (e.g. rise and fall in white cell count over time, fluctuations in vital signs)
Sepsis 2

• Unchanged concepts of sepsis, severe sepsis, and septic shock

• Original SIRS overly sensitive and nonspecific -> increased complexity of scoring system.
Expanded SIRS criteria

**Table 1** Diagnostic criteria for sepsis

<table>
<thead>
<tr>
<th>Infection<strong>a</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Documented or suspected <em>and</em> some of the following<strong>b</strong>:</td>
</tr>
</tbody>
</table>

**General parameters**
- Fever (core temperature >38.3°C)
- Hypothermia (core temperature <36°C)
- Heart rate >90 bpm or >2 SD above the normal value for age
- Tachypnea: >30 bpm
- Altered mental status
- Significant edema or positive fluid balance (>20 ml/kg over 24 h)
- Hyperglycemia (plasma glucose >110 mg/dl or 7.7 mM/l) in the absence of diabetes

**Inflammatory parameters**
- Leukocytosis (white blood cell count >12,000/μl)
- Leukopenia (white blood cell count <4,000/μl)
- Normal white blood cell count with >10% immature forms
- Plasma C reactive protein >2 SD above the normal value
- Plasma procalcitonin >2 SD above the normal value

**Hemodynamic parameters**
- Arterial hypotension**b** (systolic blood pressure <90 mmHg, mean arterial pressure <70, or a systolic blood pressure decrease >40 mmHg in adults or <2 SD below normal for age)
- Mixed venous oxygen saturation >70%
- Cardiac index >3.5 l min⁻¹ m⁻²
- Organ dysfunction parameters
- Arterial hypoxemia (PaO₂/FIO2 <300)
- Acute oliguria (urine output <0.5 ml kg⁻¹ h⁻¹ or 45 mM/l for at least 2 h)
- Creatinine increase ≥0.5 mg/dl
- Coagulation abnormalities (international normalized ratio >1.5 or activated partial thromboplastin time >60 s)
- Ileus (absent bowel sounds)
- Thrombocytopenia (platelet count <100,000/μl)
- Hyperbilirubinemia (plasma total bilirubin >4 mg/dl or 70 mmol/l)

**Tissue perfusion parameters**
- Hyperlactatemia (>3 mmol/l)
- Decreased capillary refill or mottling

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**a** Defined as a pathological process induced by a micro-organism

**b** Values above 70% are normal in children (normally 75–80%) and should therefore not be used as a sign of sepsis in newborns or children

**c** Values of 3.5–5.5 are normal in children and should therefore not be used as a sign of sepsis in newborns or children

**d** Diagnostic criteria for sepsis in the pediatric population is signs and symptoms of inflammation plus infection with hyper- or hypothermia (rectal temperature >38.5°C or <35°C), tachycardia (may be absent in hypothermic patients) and at least one of the following indications of altered organ function: altered mental status, hypoxemia, elevated serum lactate level, and bounding pulses.
Sepsis 3

• Sepsis is 'life-threatening organ dysfunction due to a dysregulated host response to infection.'

• Layperson definition ‘a life-threatening condition that arises when the body’s response to infection injures its own tissue.’

• ‘Severe sepsis’ no longer exists as a concept, there is simply ‘sepsis’ and ‘septic shock.’
Sepsis

• Sepsis clinical criteria: organ dysfunction is defined as an increase of 2 points or more in the Sequential Organ Failure Assessment (SOFA) score
  • for patients with infections, an increase of 2 SOFA points gives an overall mortality rate of 10%

• 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 (“HAT”); i.e. 2 or more of:
  • Hypotension: SBP less than or equal to 100 mmHg
  • Altered mental status (any GCS less than 15)
  • Tachypnoea: RR greater than or equal to 22
Septic Shock

• Septic shock is ‘a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality.’

• Septic shock clinical criteria: Sepsis and (despite adequate volume resuscitation) both of:
  • Persistent hypotension requiring vasopressors to maintain MAP greater than or equal to 65 mm Hg, and
  • Lactate greater than or equal to 2 mmol/L

• With these criteria, hospital mortality is in excess of 40%
Figure. Operationalization of Clinical Criteria Identifying Patients With Sepsis and Septic Shock

Patient with suspected infection

qSOFA ≥2? (see A)

Yes

Assess for evidence of organ dysfunction

SOFA ≥2? (see B)

Yes

Sepsis

Despite adequate fluid resuscitation, 1. vasopressors required to maintain MAP ≥65 mm Hg AND 2. serum lactate level >2 mmol/L?

Yes

Septic shock

No

Sepsis still suspected?

No

Monitor clinical condition; reevaluate for possible sepsis if clinically indicated

Yes

Monitor clinical condition; reevaluate for possible sepsis if clinically indicated
qSOFA

- Definition was developed from a data set of 148,907 patients (USA/Germany) with suspected infection who had body fluids sampled for culture and received antibiotics
- Internally validated (AUROC = 0.81)
- Significance of ‘new onset’ versus ‘established’ qSOFA points is unknown
- Addition of lactate did not meaningfully improve predictive validity of qSOFA but ‘may’ help identify patients at intermediate risk
External Validation

• Churpek 2016: qSOFA, SIRS, and early warning scores for detecting clinical deterioration in infected patients outside the ICU.
• 30,677 patients in the emergency department and ward at the University of Chicago who were suspected of having infection (defined as any anyone cultured and started on IV antibiotics).
• Electronic records were retrospectively analysed to calculate SIRS, qSOFA, MEWS and NEWS.
• These scores were compared to a primary outcome of in-hospital mortality and a combined outcome of mortality or ICU admission.
## Scoring systems

<table>
<thead>
<tr>
<th>Components of SIRS, qSOFA, MEWS, and NEWS</th>
<th>SIRS</th>
<th>qSOFA</th>
<th>MEWS</th>
<th>NEWS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Heart rate</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Oxygen saturation</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Use of supplemental oxygen</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Mental status</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Leukocyte count</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine Output</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>
**qSOFA = simplified NEWS score?**

**Chart 1: National Early Warning Score (NEWS)**

<table>
<thead>
<tr>
<th>PHYSIOLOGICAL PARAMETERS</th>
<th>3</th>
<th>2</th>
<th>1</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiration Rate</td>
<td>≤8</td>
<td>9 - 11</td>
<td>12 - 20</td>
<td></td>
<td>21 - 24</td>
<td>≥25</td>
<td></td>
</tr>
<tr>
<td>Oxygen Satuations</td>
<td>≤91</td>
<td>92 - 93</td>
<td>94 - 95</td>
<td>≥96</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any Supplemental Oxygen</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature</td>
<td>≤35.0</td>
<td>35.1 - 36.0</td>
<td>36.1 - 38.0</td>
<td>38.1 - 39.0</td>
<td>≥39.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>≤90</td>
<td>91 - 100</td>
<td>101 - 110</td>
<td>111 - 219</td>
<td></td>
<td>≥220</td>
<td></td>
</tr>
<tr>
<td>Heart Rate</td>
<td>≤40</td>
<td>41 - 50</td>
<td>51 - 90</td>
<td>91 - 110</td>
<td>111 - 130</td>
<td>≥131</td>
<td></td>
</tr>
<tr>
<td>Level of Consciousness</td>
<td></td>
<td>A</td>
<td></td>
<td></td>
<td></td>
<td>V, P, or U</td>
<td></td>
</tr>
</tbody>
</table>

*The NEWS initiative flowed from the Royal College of Physicians’ NEWSDIG, and was jointly developed and funded in collaboration with the Royal College of Physicians, Royal College of Nursing, National Outreach Forum and NHS Training for Innovation.*

**qSOFA score:**

- Altered mental status
- Respiratory rate ≥ 22
- Systolic blood pressure ≤ 100
• NEWS superior at predicting mortality or ICU transfer, qSOFA and SIRS were similar:
Time to death or ICU admission

Cumulative percentage of patients meeting ≥2 qSOFA criteria, ≥7 NEWS criteria, or ≥2 SIRS criteria in the 48 hours prior to the composite outcome
Discussion

• Churpek et al. 2016 is the first study to attempt validation of qSOFA.
• qSOFA and SIRS have similar overall performance in predicting the combined outcome of death or ICU transfer.
  • qSOFA has a higher specificity, but a lower sensitivity.
• qSOFA is <40% sensitive for detecting a patient who will die or need ICU transfer in 12 hours.
• qSOFA is consistently out-performed by the NEWS score.
• NEWS score is endorsed by NICE, Royal college EM, UK sepsis trust.
Summary

- The lack of a reliable definition of sepsis makes assessment of incidence and changes in outcomes difficult to quantify reliably.

- Consider sepsis even when qSOFA score is <2 as it
  - has a poor sensitivity
  - is a late indicator of deterioration
  - is inferior to the NEWS score

- The NEWS score is more complex but is based on easy to obtain bedside observations