LA SEPSI
DAL CASO CLINICO
ALLE LINEE GUIDA

Sezione SIMI Lazio Molise
GIS Giovani Internisti SIMI

RESPONSABILE SCIENTIFICO
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In Italy, Spain, the UK, France and the USA, a mean of 88% of interviewees had never heard of the term “sepsis” and of people who recognized it, 58% did not recognize that sepsis is a leading cause of death: failure to recognize symptoms of sepsis earlier may lead to a delay access to care.


A preceding survey in those same countries out of a sample of 1058 doctors highlighted their difficulty in defining and diagnosing the syndrome and only 17% agreed upon any definition of sepsis.

Crit Care 2012 8:R409–R413
‘Can I catch it?’

Public understanding of sepsis

@NCEPOD
#sepsis

Just Say Sepsis!
A review of the process of care received by patients with sepsis

A review of the process of care received by patients with sepsis
A report by the NCEPOD (2015)
There was a delay in identifying
in 182/505 (36%) sepsis
in 167/324 (51.5%) severe sepsis
in 63/193 (32.6%) septic shock

A review of the process of care received by patients with sepsis
A report by the NCEPOD (2015)
- only 52.9% patients had GCS/AVPU assessed at the time of diagnosis

- only 61.7% patients had lactate measured

- investigations considered essentials in the diagnosis of sepsis missed in 39.1% patients and delayed in 38.3%

A review of the process of care received by patients with sepsis
A report by the NCEPOD (2015)
NCEPOD (2015) highlighted sepsis as being a leading cause of avoidable death that kills more people than breast, bowel and prostate cancer combined.
Arrivano i Nostri
Fuoco amico

Danni collaterali
Sepsis remains a common, expensive, and deadly problem throughout the world. It is a complicated and dynamic condition that resists one size to all approaches.

Gotts JE, Matthay MS. BMJ 2016;353:i1585
La sepsi non esiste.
Sepsis is a **syndrome**, an **artificial construct** created for operational purposes.

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, Giorgio Costantino, MD, ParCul, LupMan, GranPorc

*JAMA.* 2016;315(8):801-810
illness concept: what sepsis “is.”

not a specific illness but rather a syndrome encompassing a still-uncertain pathobiology.

a constellation of clinical signs and symptoms in a patient with suspected infection.

JAMA. 2016;315(8):801-810
Key Concepts of Sepsis

- **nonhomeostatic** host response to infection,

- **potential lethality** that is considerably in excess of a straightforward infection,

- need for **urgent recognition**

*JAMA. 2016;315(8):801-810*
Key Concepts of Sepsis

• Sepsis is the primary cause of death from infection.

• 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.

*JAMA.* 2016;315(8):801-810
Sepsis should be defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.

*JAMA.* 2016;315(8):801-810
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.
Key Concepts of Sepsis

• May be *occult*; its presence should be considered in any patient presenting with infection.

• Any *unexplained organ dysfunction* should thus raise the possibility of underlying infection.

• Specific infections may result in local organ dysfunction without generating a dysregulated systemic host response.
Limitations of previous definitions included an excessive focus on inflammation, misleading progression from sepsis to severe sepsis - shock, and inadequate specificity and sensitivity of the SIRS criteria.
SIRS (Systemic Inflammatory Response Syndrome)

Two or more of:

- Temperature >38°C or <36°C
- Heart rate >90/min
- Respiratory rate >20/min or PaCO$_2$ <32 mm Hg
- White blood cell count >12 000/mm$^3$ or <4000/mm$^3$ or >10% immature bands

Addio , senza rimpianto
SIRS may simply reflect an appropriate host response that is frequently adaptive.

Sepsis involves organ dysfunction, indicating a pathobiology more complex than infection plus an accompanying inflammatory response alone.

...“severe sepsis” becomes superfluous.
The major emphasis of the new definition is on a simplified system for 
early suspicion of organ dysfunction resulting from suspected infection, rather than a precise pathological definition for sepsis.

Clinical criteria to better identify patients with suspected infection likely to progress to a life-threatening state.

*JAMA.* 2016;315(8):801-810
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%**

*JAMA. 2016;315(8):801-810*
Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score^a

<table>
<thead>
<tr>
<th>System</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \text{Pao}_2/\text{FiO}_2, \text{mm Hg} )</td>
<td>≥400 (53.3)</td>
<td>&lt;400 (53.3)</td>
<td>&lt;300 (40)</td>
<td>&lt;200 (26.7) with respiratory support</td>
<td>&lt;100 (13.3) with respiratory support</td>
</tr>
<tr>
<td><strong>Coagulation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets, ( \times 10^3/\mu L )</td>
<td>≥150</td>
<td>&lt;150</td>
<td>&lt;100</td>
<td>≤50</td>
<td>≤20</td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin, mg/dL (( \mu \text{mol/L} ))</td>
<td>&lt;1.2 (20)</td>
<td>1.2-1.9 (20-32)</td>
<td>2.0-5.9 (33-101)</td>
<td>6.0-11.9 (102-204)</td>
<td>&gt;12.0 (204)</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP ≥70 mm Hg</td>
<td></td>
<td>MAP &lt;70 mm Hg</td>
<td>Dopamine &lt;5 or dobutamine (any dose)</td>
<td>Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1b</td>
<td>Dopamine &gt;15 or epinephrine &gt;0.1 or norepinephrine &gt;0.1b</td>
</tr>
<tr>
<td><strong>Central nervous system</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glasgow Coma Scale score</td>
<td>15</td>
<td>13-14</td>
<td>10-12</td>
<td>6-9</td>
<td>&lt;6</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine, mg/dL (( \mu \text{mol/L} ))</td>
<td>&lt;1.2 (110)</td>
<td>1.2-1.9 (110-170)</td>
<td>2.0-3.4 (171-299)</td>
<td>3.5-4.9 (300-440)</td>
<td>&gt;5.0 (440)</td>
</tr>
<tr>
<td>Urine output, mL/d</td>
<td></td>
<td></td>
<td></td>
<td>≤500</td>
<td>≤200</td>
</tr>
</tbody>
</table>

Abbreviations: \( \text{FiO}_2 \), fraction of inspired oxygen; MAP, mean arterial pressure; \( \text{Pao}_2 \), partial pressure of oxygen.

^a Adapted from Vincent et al.\textsuperscript{27}

b Catecholamine doses are given as \( \mu \text{g/kg/min} \) for at least 1 hour.

c Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.
• **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.

• **Modest dysfunction can deteriorate further**, emphasizing the seriousness of this condition and the need for prompt and appropriate intervention.
It is not necessary to know the full details of the SOFA score; these are useful only for scientific publications.

It is rather the checklist of the six organs that is important for everyday bedside use.

Vincent JL J Thorac Dis 2016;8(9):E996-E998
<table>
<thead>
<tr>
<th>Organ system</th>
<th>Indicative variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Unexplained hypotension</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Unexplained hypoxemia; tachypnea</td>
</tr>
<tr>
<td>Neurological</td>
<td>Altered mental status</td>
</tr>
<tr>
<td>Renal</td>
<td>New onset of oliguria; increase in creatinine</td>
</tr>
<tr>
<td>Hematological</td>
<td>Low platelet count; disseminated intravascular coagulopathy (DIC)</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Unexplained rise in bilirubin concentration</td>
</tr>
</tbody>
</table>
encephalopathy

coagulopathy

AKI

myocardial depression + low SVR

lung injury

immunosuppression

AKI

compromised intestinal barrier

myopathy

bone marrow suppression

BMJ 2016;353:i1585
Patients with a SOFA score of 2 or more had an overall mortality risk of approximately **10%** in a general hospital population with presumed infection.

This is greater than the overall mortality rate of **8.1%** for STEMI.

Seymour CW et al.  JAMA. 2016;315(8):762-774
SOFA score is **not intended to be used as a tool for patient management** but as a means to clinically characterize a septic patient.

Vincent et al. Critical Care (2016) 20:210-12
qSOFA

Hypotension
Systolic BP <100 mmHg

Altered
Mental Status

Tachypnea
RR >22/Min

Score of ≥2 Criteria Suggests a Greater Risk of a Poor Outcome
THAM-THAM

(Tachypnea; Hypotension; Altered Mentation)
quickSOFA (qSOFA)

- respiratory rate of 22/min or greater,
- altered mentation, or
- systolic BP of 100 mm Hg or less.

In out-of-hospital, ED, 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.

*JAMA.* 2016;315(8):801-810
The task force chose to emphasize altered mentation because it represents any GCS less than 15 and will reduce the measurement burden.
Commonly used early warning scores are more accurate than the qSOFA score for predicting death and ICU transfer in non-ICU patients.

qSOFA score should not replace general early warning scores when risk-stratifying patients with suspected infection.

Churpek MM  AJRCCM Published on 20-September-2016 as 10.1164/rccm.201604-0854OC
### 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></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen Saturations</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>Yes</td>
<td>No</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></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>V, P, or U</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.
Fig. 1 Schematic representation illustrating a the almost complete overlap of sepsis and infection when the SIRS criteria of the 1992 criteria [3] are used and b the differences between qSOFA and sepsis. qSOFA quick sequential organ failure assessment, SIRS systemic inflammatory response syndrome.
qSOFA is meant to be used to raise suspicion of sepsis and prompt further action—it is not a replacement for SIRS and is not part of the definition of sepsis.

Vincent et al. Critical Care (2016) 20:210
Because Lactate measurement offered no meaningful change in the predictive validity beyond 2 or more qSOFA criteria in the identification of patients likely to be septic, the task force could not justify the added complexity and cost of lactate measurement alongside these simple bedside criteria.

*JAMA*. 2016;315(8):801-810
Septic shock

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.

JAMA. 2016;315(8):801-810
Septic shock

Patients with septic shock can be clinically identified by

- a *vasopressor* requirement to maintain a MAP of 65 mm Hg or greater and

- *serum lactate level* > 2 mmol/L

- in the *absence of hypovolemia*.

...mortality rates greater than 40%

*JAMA*. 2016;315(8):801-810
We often forget that **bedside evidence of good organ function** (e.g., clear mentation, good urine output) is more valuable than a biomarker measurement alone and should always be used in conjunction with biomarker measurements such as lactate.

Septic shock conceptually comprises an illness with

- **new onset** or **worsening cardiovascular dysfunction,**
- **impaired tissue perfusion** and
- **cellular abnormalities**

caused by *infection*.

Individually, none of these abnormalities truly reflects the complex illness concept but they may do so in **combination**.

Cardiovascular
• Congestive heart failure
• Cardiogenic shock
• Myocardial infarction

Neurological
• Subarachnoid hemorrhage
• Encephalopathy

Pulmonary
• Acute respiratory distress syndrome
• Pulmonary embolism

Tissue Injury
• Pancreatitis
• Trauma
• Transplant rejection

Metabolic
• Thyroid storm
• Acute adrenal collapse
• Tumor lysis syndrome
• Anaphylaxis
• Overdose
• Diabetic ketoacidosis

Iatrogenic
• Blood product reaction
• Anesthesia related
• Neuroleptic malignant syndrome
In many patients who present to the ED the diagnosis of sepsis is obvious...
Not uncommonly patients with sepsis may present with **vague constitutional symptoms**, mild hypotension and tachycardia or with a fever and myalgia that are attributed to ‘a viral syndrome’.

Marik PE  Critical Care 2014, 18:529
The signs and symptoms of sepsis can be very nonspecific and can be missed if clinicians do not think 'could this be sepsis?'

A review of the process of care received by patients with sepsis
A report by the NCEPOD (2015)

Surviving Sepsis Campaign (SSC), Society of Critical Care Medicine (SCCM), and European Society of Intensive Care Medicine (ESICM)

RELEASE DATE January 18, 2017
Fig. 1 The layers of an onion are paralleled to the components of the guidelines document, reflecting the depth of exploration by the user.
EARLY GOAL DIRECTED THERAPY
2001 - 2015

R. I. P.
A volte ritornano
Rivers of ink
Protocols for goal directed therapy for sepsis are pronounced dead

Lilly CM  N Engl J Med. 2014 May 1;370(18):1750-1
Protocolized Care for Early Septic Shock (**ProCESS**)(1,935 subjects)

Australasian Resuscitation in Sepsis Evaluation (**ARISE**) (1,600 subjects),

Protocolised Management of Sepsis (**ProMISe**) (1,260 subjects).

A **ProCESS** *that (do not)* **ARISE** **ProMISe**
The recommendations are intended for a “typical” septic patient. Patients still benefit from the art of medicine, which includes interpretation of data and individualization of treatment.
LMWH

Fluids
Crystalloids ± Albumin
0-1 h: > 1 L
1-6 h: > 2.4 L
6-24 h: 1.6-3.5 L
> 24 h: Fluid balance < 0

PPI

Vasoactive agents
Norepinephrine ± Dobutamine
0-1 h: Too early
1-6 h: Onset+++
6-24 h: Too late

STEROIDS

Source control
Surgery, interventional radiology
< 6 h
after hypotension

Antibiotics
Empirical, broad-spectrum
Administration
< 1 h
after hypotension

Leone M  Crit Care Med 2014  42;10:2494-5