REVISIONE DEI CRITERI DIAGNOSTICI PER LA SEPSI

Fabio Guerini
Dipartimento Medicina e Riabilitazione
Istituto Clinico Sant’Anna - Brescia

Brescia, 24 Novembre 2017
Venerdì 1 Dicembre 2017

17:15 – 18:45  SIMPOSIO
SEPSIS IN OLDER ADULTS
Moderatori: Amato De Paulis (Napoli), Fabio Di Stefano (Verbania)

Fisiopatologia della sepsi e nuove Guidelines SEPSIS 3: criticità, rivisitazione e loro impatto e conseguenze
Luca Laghi (Birmingham)

Presentazione clinica negli anziani ed organi bersaglio
Ciro Paolillo (Udine)

Sepsi e shock settico degli anziani in Pronto Soccorso
Antonio Cherubini (Ancona)

Sepsis non batterica e biomarkers della infezione
Giovanni Ricevuti (Pavia)

Patogeni coinvolti, antibioticoterapia e strategie antimicrobiche
Piero Marone (Pavia)

Discussione e indicazioni linee guida
- Sepsis definition
- Sepsis: epidemiology, pathophysiology, diagnosis
- Sepsis: a new definition
- Treatment guidelines: Early Goal Directed Therapy (EGDT) and the Surviving Sepsis Campaign
The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)
In the early 1990s, a consensus statement was developed by the American College of Chest Physicians and the Society of Critical Care Medicine (SCCM) that defined Systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock in terms of both clinical and laboratory abnormalities, emphasizing a continuum of acute inflammation and organ dysfunction.
Revised modestly in 2001, these definitions have formed the basis of the past quarter century of research into sepsis and catalyzed the evolution of its clinical recognition and management, and the design of clinical trials.

However, the sensitivity and specificity of SIRS criteria have been questioned, as has the contention that SIRS, sepsis, severe sepsis, and septic shock occur along a continuum rather than as discrete clinical entities.
In February 2016, the European Society of Intensive Care Medicine and the SCCM published new consensus definitions of sepsis and related clinical criteria (Sepsis-3).
<table>
<thead>
<tr>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis and vasopressor therapy needed to increase mean arterial pressure to ≥65 mm Hg and lactate to ≥2 mmol/L despite septic shock.</td>
</tr>
</tbody>
</table>

**Revised Definitions**

<table>
<thead>
<tr>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis with evidence of acute organ dysfunction (hypoperfusion, lactate acidosis, reduced urine output, reduced PaO₂/FIO₂).</td>
</tr>
</tbody>
</table>

**Severe Sepsis**

<table>
<thead>
<tr>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIRS with infection (presumed or proven).</td>
</tr>
</tbody>
</table>

**SIRS**

<table>
<thead>
<tr>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell count ≥12×10⁹/L or ≤4×10⁹/L.</td>
</tr>
</tbody>
</table>

**Respiratory**

<table>
<thead>
<tr>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory rate ≥20 breaths/min or arterial carbon dioxide pressure &gt;52 mm Hg.</td>
</tr>
</tbody>
</table>

**Hematologic**

<table>
<thead>
<tr>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate ≥90 beats/min.</td>
</tr>
</tbody>
</table>

**Temperature**

<table>
<thead>
<tr>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature ≥38°C or ≤36°C.</td>
</tr>
</tbody>
</table>

**Two of the following:**

<table>
<thead>
<tr>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septic syndrome.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic inflammatory response syndrome (SIRS).</td>
</tr>
</tbody>
</table>
Sepsis: pathophysiology and clinical management

Jeffrey E Gotts, Michael A Matthay
Over the past 40 years the incidence of severe sepsis has substantially increased, partly because of the increasing age of the population. The latest estimates in the United States, Europe, and the United Kingdom range between 0.4/1000 and 1/1000 of the population. Remarkably, in-hospital mortality for patients with sepsis during this period has decreased from 28 to 18%.
Using objective definitions of acute organ dysfunction, severe sepsis in patients admitted to the ICU was estimated to increase from 7.2% to 11.1% during the study period.

At the same time, hospital mortality in severe sepsis declined from 35% to 18%.
<table>
<thead>
<tr>
<th>Parasites</th>
<th>Aspergillus spp</th>
<th>Candida spp</th>
<th>Anaerobes</th>
<th>ESBL producing GNR</th>
<th>Acinetobacter spp</th>
<th>Pseudomonas spp</th>
<th>Klebsiella spp</th>
<th>Enterobacter spp</th>
<th>Escherichia coli</th>
<th>VRE</th>
<th>VSE</th>
<th>Streptococcus pneumoniae</th>
<th>Staphylococcus aureus/MRSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western Europe</td>
<td>20/9</td>
<td>11</td>
<td>11</td>
<td>5</td>
<td>11/0</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>11/0</td>
<td>11/0</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>22/10</td>
<td>12</td>
<td>12</td>
<td>12/0</td>
<td>12/10</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12/10</td>
<td>12/10</td>
<td>12/10</td>
<td>12/10</td>
<td>12/10</td>
</tr>
<tr>
<td>Central/South America</td>
<td>19/11</td>
<td>12</td>
<td>12</td>
<td>12/10</td>
<td>12/10</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12/10</td>
<td>12/10</td>
<td>12/10</td>
<td>12/10</td>
<td>12/10</td>
</tr>
<tr>
<td>North America</td>
<td>27/18</td>
<td>12</td>
<td>12</td>
<td>12/10</td>
<td>12/10</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12/10</td>
<td>12/10</td>
<td>12/10</td>
<td>12/10</td>
<td>12/10</td>
</tr>
<tr>
<td>Oceania</td>
<td>28/9</td>
<td>12</td>
<td>12</td>
<td>12/10</td>
<td>12/10</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12/10</td>
<td>12/10</td>
<td>12/10</td>
<td>12/10</td>
<td>12/10</td>
</tr>
<tr>
<td>Africa</td>
<td>30/20</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Asia</td>
<td>16/10</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
</tr>
</tbody>
</table>
• the cardiovascular system undergoes major perturbations.

• Use of pulmonary arterial catheters in the 1980s, it became clear that after intravascular volume is restored, most patients with sepsis have a normal or raised cardiac output with low systemic vascular resistance.

• The preservation or enhancement in cardiac output occurs despite acute biventricular dysfunction that can last longer than a week.

: BMJ 2016;353:i1585
• Increased **lactate** in these patients predicts mortality.

• This has traditionally been thought to reflect tissue hypoxia as a result of hypoperfusion.

• In sepsis, profound alterations to the **endothelium** occur, including increased leukocyte adhesion, a shift to a procoagulant state, vasodilation, and loss of barrier function, which all lead to widespread tissue edema.
• Increased **lactate** in these patients predicts mortality.
• This has traditionally been thought to reflect tissue hypoxia as a result of hypoperfusion.

• In sepsis, profound alterations to the **endothelium** occur, including increased leukocyte adhesion, a shift to a procoagulant state, vasodilation, and loss of barrier function, which all lead to widespread tissue edema.
• Widespread tissue factor expression, fibrin deposition, and impaired anticoagulant mechanisms (including activated protein C) can produce **disseminated intravascular coagulation (DIC)**

• The endothelial changes in severe sepsis are associated with altered barrier function in other organs.

: *BMJ* 2016;353:i1585
• More permeable lung capillaries result in the accumulation of protein-rich edema fluid in the interstitial spaces of the lung, and in the presence of sepsis induced alveolar epithelial barrier dysfunction, the interstitial edema fluid floods into the alveoli.

• These changes result in perfusion-ventilation mismatch, arterial hypoxemia, and reduced lung compliance: ARDS.
• Gut epithelium becomes more permeable in the setting of hypercytokinemia.  
• This increased permeability sets in motion a vicious cycle of bacterial translocation, gut injury by luminal contents including activated pancreatic enzymes (autodigestion)
• **Acute kidney injury (AKI)** is common in severe sepsis and substantially increases the risk of death.

• The **nervous system** is not simply an injured bystander in severe sepsis but an active participant in its early development, playing mostly an anti-inflammatory role.
• **Encephalopathy** is an early and common clinical finding in severe sepsis that can range from mildly impaired concentration to deep coma.

• **Delirium**, as assessed by the confusion assessment method (CAM)-ICU method, is very common in ventilated patients, and it is independently associated with mortality and long lasting neurocognitive deficits.

*BMJ* 2016;353:i1585
• Coincident **hepatic and renal dysfunction** exacerbate toxin influx into the CNS.
• In addition, coagulopathy and impaired autoregulation of cerebral blood flow can together produce areas of ischemia and hemorrhage.

*BMJ* 2016;353:i1585
Inflammatory system
• Septic organ dysfunction often perpetuates critical illness in a self reinforcing manner through several pathways:
  • ARDS often requires mechanical ventilation, which itself can further injure the lungs and enhance systemic inflammation
  • Sedatives needed for ventilation can worsen septic associated encephalopathy and delirium, leading to reduced mobility, worsened catabolism, severe neuromuscular weakness
  • Intestinal barrier dysfunction causes ongoing systemic translocation of pathogenic organisms and impaired nutritional status

: BMJ 2016;353:i1585
for Sepsis and Sepsic Shock (Sepsis-3)

The Third International Consensus Definitions

Special Communication | Caring for the Critically Ill Patient
<table>
<thead>
<tr>
<th>Definition</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis and vasopressor therapy needed to increase mean arterial pressure to ≥55 mm Hg and lactate to ≥2 mmol/L despite abrogated fluid resuscitation</td>
<td>Sepsis shock</td>
</tr>
<tr>
<td>Organ dysfunction caused by a dysregulated host response to infection</td>
<td>Sepsis</td>
</tr>
</tbody>
</table>

**Revised Definitions**

- Sepsis with persistent hypotension after fluid resuscitation
- Sepsis with evidence of acute organ dysfunction (hypotension, lactate acidosis, reduced urine output, reduced PaO2/FiO2)
- Severe sepsis
- SIRS with infection (proven or presumed)

**SIRS**
- White blood cell count >12×10⁹/L or <4×10⁹/L
- Respiratory rate >20 breaths/min or arterial carbon dioxide pressure >42 mm Hg
- Heart rate >90 beats/min
- Temperature >38°C or <36°C

**Sepsis Syndrome**
- Two or more of the following

**Sepsis (Systemic Inflammatory Response Syndrome)**
SIRS
SINDROME di RISPOSTA INFIAMMATORIA SISTEMICA

Risposta infiammatoria sistemica
a VARIE TIPOLOGIE di grave insulto clinico

Due o più dei seguenti segni e sintomi

- Temperatura >38°C o <36°C
- Frequenza cardiaca >90 bpm
- Frequenza respiratoria >20 atti/min o PaCO$_2$<32 mm Hg
- Leucociti >12.000/mm$^3$ o <4.000/mm$^3$ oppure >10% forme immature

ACCP/SCCM CONSENSUS CONFERENCE. Chest, 1992;101(6):1644-55
SEPSI

SIRS + infezione accertata (documentata microbiologicamente) o sospettata clinicamente
Sepsi: continuum fisiopatologico

Sepsis: The Continuum

Localized Infection

Systemic Response

Fever, Increased Heart Rate
Increased Respiratory Rate

Organ Failure(s) Distant from Site of Infection

Sepsis

Hypotension & Shock

Septic Shock

Clinical Diagnosis

Death

-Acidosi metabolica (aumento dei lattati)

SEPTIC SHOCK

“...a state of acute circulatory failure characterized by persistent arterial hypotension unexplained by other causes. Hypotension is defined by a systolic arterial pressure below 90 mmHg, a mean arterial pressure < 60, or a reduction in systolic blood pressure of > 40 mmHg from baseline, despite adequate volume resuscitation...”

2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference
Relationship Of Infection, SIRS, Sepsis, Severe Sepsis and Septic Shock

Bone et al. Chest 1992;101:1644
La terza definizione della sepsi: Luci ed Ombre

LIMITI DELLA PRECEDENTE DEFINIZIONE:
Ad amplificare la risposta all’infezione nella sepsi concorrono:
- fattori endogeni (età, sesso, razza, comorbilità, determinanti genetici)
- Fattori esogeni (caratteristiche del patogeno)

Segue attivazione pro- ed antinfiammatoria, modificazioni cardiovascolari, neuronali, ormonali, metabolici ed altre modificazioni non immunologiche.

1) I criteri SIRS:
   - focalizzano solo sull’infiammazione sistemica
   - 1/8 con sepsi non mostrano SIRS
   - aspecifici riscontrabili anche in altri tipi di insulto

2) I pazienti affetti mostrano eterogeneità clinica e biologica non ben definita dalla definizione sepsi I-II
Study Design, Setting, and Population
A retrospective cohort study was performed among adult encounters (age ≥18 years) with suspected infection. The primary cohort was all hospital encounters from 2010 to 2012 at 12 community and academic hospitals in the UPMC health care
# Summary of Data Sets

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>UPMC(^a)</th>
<th>KPNC</th>
<th>VA</th>
<th>ALERTS</th>
<th>KCEMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of hospitals</td>
<td>12</td>
<td>20</td>
<td>130</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>Total No. of encounters</td>
<td>1,309,025</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 design</td>
<td>Retrospective study</td>
<td>Retrospective study</td>
<td>Retrospective study</td>
<td>Prospective cohort study</td>
<td>Retrospective study of administrative records</td>
</tr>
<tr>
<td>Setting</td>
<td>Integrated health</td>
<td>Integrated health</td>
<td>All hospitals in the US</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>system in southwestern Pennsylvania</td>
<td>system in northern California</td>
<td>VA system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definition of suspected infection</td>
<td>Combination of body fluid culture and nonprophylactic antibiotic administration in the EHR(^a)</td>
<td>Combination of body fluid culture and nonprophylactic antibiotic administration in the EHR(^a)</td>
<td>Combination of body fluid culture and nonprophylactic antibiotic administration in the EHR(^a)</td>
<td>CDC criteria for hospital-acquired infections(^c)</td>
<td>ICD-9-CM codes for infection, with present-on-admission indicators(^d)</td>
</tr>
<tr>
<td>No. with suspected infection (% of total)</td>
<td>148,907 (11)</td>
<td>321,380 (17)</td>
<td>377,325 (23)</td>
<td>1,186 (3)</td>
<td>6,508 (13)</td>
</tr>
<tr>
<td>Location at onset of infection, No. (% infected)</td>
<td>15,768 (11)</td>
<td>7,031 (2)</td>
<td>73,264 (19)</td>
<td>300 (25)</td>
<td>0</td>
</tr>
<tr>
<td>Intensive care unit</td>
<td>133,139 (89)</td>
<td>314,349 (98)</td>
<td>304,061 (81)</td>
<td>886 (75)</td>
<td>6,508 (100)</td>
</tr>
<tr>
<td>Outside of intensive care unit</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-hospital mortality, No. (% infected)</td>
<td>6,347 (4)</td>
<td>16,092 (5)</td>
<td>22,593 (6)</td>
<td>210 (18)</td>
<td>700 (11)</td>
</tr>
</tbody>
</table>

\(^a\) EHR: Electronic Health Record
\(^c\) CDC: Centers for Disease Control and Prevention
\(^d\) ICD-9-CM: International Classification of Diseases, 9th Revision, Clinical Modification
Accrual of Encounters for Primary Cohort

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
74454 Included in validation cohort

7836 in ICU
66617 Outside of ICU
7932 In ICU
66522 Outside of ICU
### 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) (^a) (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, (\degree 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></td>
<td></td>
<td>Urine output, L/d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Serum urea, mmol/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prothrombin time, % of standard</td>
</tr>
</tbody>
</table>
Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score

<table>
<thead>
<tr>
<th>System</th>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></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>Respiration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pao₂/Fio₂, mm Hg (kPa)</td>
<td></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>Coagulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets, x10⁹/μL</td>
<td>≥150</td>
<td>&lt;150</td>
<td>&lt;100</td>
<td>&lt;50</td>
<td>&lt;20</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin, mg/dL (μmol/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>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP ≥70 mm Hg</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 ≤0.1</td>
<td>Dopamine &gt;15 or epinephrine &gt;0.1 or norepinephrine &gt;0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central nervous system</td>
<td></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>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine, mg/dL (μmol/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>
<td></td>
</tr>
<tr>
<td>Urine output, mL/d</td>
<td></td>
<td>&lt;500</td>
<td>&lt;200</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: Fio₂, fraction of inspired oxygen; MAP, mean arterial pressure; Pao₂, partial pressure of oxygen. Adapted from Vincent et al.²⁷

b Catecholamine doses are given as μg/kg/min for at least 1 hour.
c Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.
La terza definizione della sepsi: Luci ed Ombre

DEFINIZIONE SEPSIS-III: La sepsi è una disfunzione d’organo potenzialmente fatale causata da una sregolata risposta dell’ospite ad un infezione

Criteri Diagnostici SEPSIS III:
- Infezione sospetta + SOFA ≥2
- SOFA: score disfunzione organo:
  - Respirazione: P/F
  - Coagulazione: PLT
  - Fegato: Bilirubina
  - Cardiovascolare: MAP e vasopressori
  - SNC: GCS
  - Rene: Creatinina e Diuresi

Abolito il concetto di SIRS e sepsi severa
la sepsi è una condizione severa per definizione

La disfunzione d’organo può essere definita come cambiamento acuto ≥ 2 punti rispetto al basale del SOFA score (Sequential Organ Failure Assessment Score)
(sofa >2 = mortalità 10%)

Enfatizza il concetto di risposta non omeostatica

Infezione ≠ Sepsi

12% sepsi occulte (1/8 pz)

 criteri SIRS non adeguati
Nuova Definizione di Shock Settico

Shock Settico III: Sottotipo di sepsi in cui le alterazioni del metabolismo cellulare e circolatorie sono tali da aumentarne la mortalità

La task force 2016 vuole:
ampliare la visione rispetto al passato concetto di “Circulatory failure” del 2001 per differenziarlo dagli altri tipi di shock

<table>
<thead>
<tr>
<th>Condizione</th>
<th>Mortalità</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipotensione + lact &gt;2+ vasopressore</td>
<td>42-50%</td>
</tr>
<tr>
<td>Solo Ipotensione</td>
<td>18-25%</td>
</tr>
<tr>
<td>Solo Lact &gt;2 (cryptic shock)</td>
<td>6.8-18%</td>
</tr>
<tr>
<td>Solo Sepsi con disfunzione d’organo</td>
<td>20%</td>
</tr>
</tbody>
</table>

Criteri Diagnostici Shock Settico
Necessità di terapia vasopressoria per mantenere una pressione arteriosa media ≥ 65mmHg

SEPSI +
PAM < 65 mmHg
Lact > 2 mmol/L
Bisogno di Vasopressore

Modificato da Shankar-Hari et al. JAMA 02-2016
Which score to use !!

- "The SOFA score found patients more likely to be septic both in and out of the ICU. But it involves the use of many lab tests and is a bit complex.

- For patients not in the ICU, the performance of Quick SOFA score was similar to that of the sequential organ failure assessment score.
Area Under the Receiver Operating Characteristic Curve and 95% Confidence Intervals for In-Hospital Mortality of Candidate Criteria (SIRS, SOFA, LODS, and qSOFA) Among Suspected Infection Encounters in the UPMC Validation Cohort (N = 74,454)
Box 4. qSOFA (Quick SOFA) Criteria

- Respiratory rate $\geq 22$/min
- Altered mentation
- Systolic blood pressure $\leq 100$ mm Hg
qSOFA SOFA ed Algoritmo Diagnostico

- qSOFA: 1) FR > 22 atti/min 2) PA < 100 mmHg 3) GCS ≤ 13

Ci permette di identificare in modo veloce i pazienti con più alto rischio di mortalità ospedaliera e persistenza in UTI.
1) Il sospetto d’infezione resta soggettivo

2) SEPSI-III è meno specifica per infezione rispetto a SEPSI II (“mancano” criteri SIRS)

3) I criteri SIRS criticati per ipo-sensibilità hanno performance simili a qSOFA

4) SOFA e qSOFA sono test di severità e predittori di Mortalità non Test per Sepsi

5) qSOFA non è screen test → pericolo di sottodiagnosi

6) Sospetto + Tardivo?

7) La sequenza qSOFA → SOFA non è ottima consecutio test sensibile → test Specifico

8) La nuova definizione renderà inutilizzabili i dati degli ultimi 20 anni?

9) La sensibilità per sepsi III al di fuori da UTI potrebbe essere <50%
The Sepsis Trilogy

**ProCESS**
Protocolized Care for Early Septic Shock (ProCESS) – 31 ED’s in US

**ARISE**
Australasian Resuscitation in Sepsis Evaluation (ARISE) – 51 ED’s in Australia, New Zealand, Finland, Hong Kong, Ireland

**ProMISe**
The Protocolised Management in Sepsis (ProMISe) Trial – 56 ED’s in the UK


© 2017 SCCM and ESICM
We recommend the protocolized, quantitative resuscitation of patients with sepsis-induced tissue hypoperfusion. During the first 6 hours of resuscitation, the goals of initial resuscitation should include all of the following as a part of a treatment protocol:

a) CVP 8–12 mm Hg  
b) MAP ≥ 65 mm Hg  
c) Urine output ≥ 0.5 mL/kg/hr  
d) Scvo2 ≥ 70%.
Supplemental oxygen ± endotracheal intubation and mechanical ventilation

Central venous and arterial catheterization

Sedation, paralysis (if intubated), or both

CVP
- <8 mm Hg: Crystalloid
- 8–12 mm Hg: Colloid

MAP
- <65 mm Hg: Vasoactive agents
- ≥65 and <90 mm Hg: Inotropic agents

ScvO₂
- <70%: Transfusion of red cells until hematocrit ≥30%
- ≥70%: Inotropic agents

Goals achieved
- No
- Yes: Hospital admission

Early insertion of ScvO₂ catheter

Therapy titrated to CVP, MAP and ScvO₂

Potential for RBC and Inotropes
A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISE Investigators

**A Primary mortality outcome of each study**

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
<th>Events, EGDT</th>
<th>Events, control</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivers et al. (2001)</td>
<td>0.52 (0.31, 0.86)</td>
<td>38/130</td>
<td>59/133</td>
<td>10.40</td>
</tr>
<tr>
<td>Jones et al. (2010)</td>
<td>1.47 (0.82, 2.60)</td>
<td>34/150</td>
<td>25/150</td>
<td>4.87</td>
</tr>
<tr>
<td>ProCESS Investigators (2014)</td>
<td>1.17 (0.88, 1.55)</td>
<td>92/439</td>
<td>167/902</td>
<td>21.78</td>
</tr>
<tr>
<td>ARISE Investigators (2014)</td>
<td>0.98 (0.76, 1.26)</td>
<td>147/792</td>
<td>150/796</td>
<td>30.71</td>
</tr>
<tr>
<td>ProMISE Investigators (2015)</td>
<td>1.02 (0.80, 1.30)</td>
<td>184/623</td>
<td>181/620</td>
<td>32.23</td>
</tr>
<tr>
<td>Overall (I² = 56.7%, p = 0.055)</td>
<td>1.01 (0.88, 1.16)</td>
<td>495/2134</td>
<td>582/2601</td>
<td>100.00</td>
</tr>
</tbody>
</table>

DOI 10.1007/s00134-015-3822-1
A Randomized Trial of Protocol-Based Care for Early Septic Shock

The ProCESS Investigators*

Intravenous Fluids

<table>
<thead>
<tr>
<th>EGDT</th>
<th>Usual Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.8 L</td>
<td>2.3 L</td>
</tr>
</tbody>
</table>

Intravenous Antibiotics

<table>
<thead>
<tr>
<th>EGDT</th>
<th>Usual Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>97.5%</td>
<td>96.9%</td>
</tr>
</tbody>
</table>

*The ProCESS Investigators: [Names of investigators]

DOI: 10.1056/NEJMoa1401602
Copyright © 2014 Massachusetts Medical Society.
Caveats / Limitations of ProCESS, ARISE & Promise

• The overall management of sepsis has changed…
  – In all three studies patients had early antibiotics, > 30ml/kg of intravenous fluid prior to randomization.

• We need therefore to be very careful about over interpreting the results in areas where this paradigm is not valid.
The River’s work was useful….

• As it provided us a construct on how to understand resuscitation:
  – Start early- (give antibiotics)
  – Correct hypovolaemia
  – Restore perfusion pressure
  – And in some cases a little more may be required..!

• These concepts are as important today as they ever were.
Sepsis and septic shock are medical emergencies and we recommend that treatment and resuscitation begin immediately.

Best Practice Statement
Source Control

• We recommend that a specific anatomic diagnosis of infection requiring emergent source control be identified or excluded as rapidly as possible in patients with sepsis or septic shock, and that any required source control intervention be implemented as soon as medically and logistically practical after the diagnosis is made.

(Best Practice Statement).
Antibiotics

• We recommend that administration of IV antimicrobials be initiated as soon as possible after recognition and within 1 h for both sepsis and septic shock. (strong recommendation, moderate quality of evidence).

• We recommend empiric broad-spectrum therapy with one or more antimicrobials to cover all likely pathogens. (strong recommendation, moderate quality of evidence).
Initial Resuscitation

• We recommend that in the resuscitation from sepsis-induced hypoperfusion, at least 30ml/kg of intravenous crystalloid fluid be given within the first 3 hours. (Strong recommendation; low quality of evidence)

• We recommend that following initial fluid resuscitation, additional fluids be guided by frequent reassessment of hemodynamic status. (Best Practice Statement)


**Fluid Therapy**

- We recommend crystalloids as the fluid of choice for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock  
  (Strong recommendation, moderate quality of evidence).

- We suggest using albumin in addition to crystalloids when patients require substantial amounts of crystalloids  
  (weak recommendation, low quality of evidence).
We recommend an initial target mean arterial pressure of 65 mmHg in patients with septic shock requiring vasopressors.

High versus Low Blood-Pressure Target in Patients with Septic Shock

**Figure 2.** Mean Arterial Pressure during the 5-Day Study Period.

**Figure 3.** Kaplan–Meier Curves for Cumulative Survival.

DOI: 10.1056/NEJMoa1312173

Copyright © 2014 Massachusetts Medical Society.
Vasoactive agents

- We recommend norepinephrine as the first choice vasopressor (strong recommendation, moderate quality of evidence).

- We suggest adding either vasopressin (up to 0.03 U/min) or epinephrine to norepinephrine with the intent of raising MAP to target, or adding vasopressin (up to 0.03 U/min) to decrease norepinephrine dosage. (weak recommendation, low quality of evidence)
If shock is not resolving quickly.....

• We recommend further hemodynamic assessment (such as assessing cardiac function) to determine the type of shock if the clinical examination does not lead to a clear diagnosis.

(Best Practice Statement)

• We suggest that dynamic over static variables be used to predict fluid responsiveness, where available.

(Weak recommendation; low quality of evidence)
Lactate can help guide resuscitation

- We suggest guiding resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion.

(Weak recommendation; low quality of evidence)
Summary

• Start resuscitation early with source control, intravenous fluids and antibiotics.

• Frequent assessment of the patients’ volume status is crucial throughout the resuscitation period.

• We suggest guiding resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion.
SCREENING FOR SEPSIS AN[ PERFORMANCE IMPROVEMENT

1. We recommend that hospitals and hospital systems have a performance improvement program for sepsis including sepsis screening for acutely ill, high-risk patients. (BPS)
Diagnosis

1. We recommend that appropriate routine microbiologic cultures (including blood) be obtained before starting antimicrobial therapy in patients with suspected sepsis and septic shock if doing so results in no substantial delay in the start of antimicrobials. (BPS)

   - Remarks: Appropriate routine microbiologic cultures always include at least two sets of blood cultures (aerobic and anaerobic).
Antibiotics

• We suggest empiric combination therapy (using at least two antibiotics of different antimicrobial classes) aimed at the most likely bacterial pathogen(s) for the initial management of septic shock.
  – (Weak recommendation; low quality of evidence)
Antibiotics

• We suggest that combination therapy not be routinely used for on-going treatment of most other serious infections, including bacteremia and sepsis without shock.
  – (Weak recommendation; low quality of evidence).

• We recommend against combination therapy for the routine treatment of neutropenic sepsis/bacteremia.
  – (Strong recommendation; moderate quality of evidence).
Antimicrobial Therapy
Antibiotic Stewardship

- We recommend that empiric antimicrobial therapy be narrowed once pathogen identification and sensitivities are established and/or adequate clinical improvement is noted.
  - (BPS)
- We suggest that an antimicrobial treatment duration of 7-10 days is adequate for most serious infections associated with sepsis and septic shock.
  - (Weak recommendation; low quality of evidence)
- We recommend daily assessment for de-escalation of antimicrobial therapy in patients with sepsis and septic shock.
  - (BPS)
- We suggest that measurement of procalcitonin levels can be used to support shortening the duration of antimicrobial therapy in sepsis patients.
  - (Weak recommendation; low quality of evidence)
CORTICOSTEROIDS

1. We suggest against using intravenous hydrocortisone to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. If this is not achievable, we suggest intravenous hydrocortisone at a dose of 200 mg per day. (Weak recommendation; low quality of evidence)
Mechanical Ventilation

• We suggest using higher PEEP over lower PEEP in adult patients with sepsis-induced moderate to severe ARDS.
  – Weak recommendation; moderate quality of evidence

• We recommend using prone over supine position in adult patients with sepsis-induced ARDS and a PaO$_2$/FIO$_2$ ratio <150.
  – (Strong recommendation; moderate quality of evidence)
Mechanical Ventilation

• We recommend against the use of HFOV in adult patients with sepsis-induced ARDS.
  – (Strong recommendation; moderate quality of evidence)

• We recommend against the use of beta-2 agonists for the treatment of patients with sepsis-induced ARDS without bronchospasm.
  – (Strong recommendation; moderate quality of evidence)
GLUCOSE CONTROL

1. We recommend a protocolized approach to blood glucose management in ICU patients with sepsis, commencing insulin dosing when 2 consecutive blood glucose levels are >180 mg/dL. This approach should target an upper blood glucose level ≤180 mg/dL rather than an upper target blood glucose ≤110 mg/dL. (Strong recommendation; high quality of evidence)

2. We recommend that blood glucose values be monitored every 1 to 2 hrs until glucose values and insulin infusion rates are stable, then every 4 hrs thereafter in patients receiving insulin infusions. (BPS)
Renal Replacement Therapy

• We suggest against the use of renal replacement therapy in patients with sepsis and acute kidney injury for increase in creatinine or oliguria without other definitive indications for dialysis.
  – (Weak recommendation; low quality of evidence)
Nutrition

- We recommend against the administration of early parenteral nutrition alone or parenteral nutrition in combination with enteral feedings (but rather initiate early enteral nutrition) in critically ill patients with sepsis or septic shock who can be fed enterally. (Strong recommendation; moderate quality of evidence)
• We recommend against the administration of parenteral nutrition alone or in combination with enteral feeds (but rather to initiate IV glucose and advance enteral feeds as tolerated) over the first 7 days in critically ill patients with sepsis or septic shock in whom early enteral feeding is not feasible. (Strong recommendation; moderate quality of evidence).
Nutrition

• We suggest the early initiation of enteral feeding rather than a complete fast or only IV glucose in critically ill patients with sepsis or septic shock who can be fed enterally. (Weak recommendation; low quality of evidence)

• We suggest either early trophic/hypocaloric or early full enteral feeding in critically ill patients with sepsis or septic shock; if trophic/hypocaloric feeding is the initial strategy, then feeds should be advanced according to patient tolerance. (Weak recommendation; moderate quality of evidence)
Nutrition

• We suggest against routinely monitoring gastric residual volumes in critically ill patients with sepsis or septic shock. (Weak recommendation; low quality of evidence). However, we suggest measurement of gastric residuals in patients with feeding intolerance or who are considered to be high risk for aspiration. (Weak recommendation; very low quality of evidence)
• We suggest the use of prokinetic agents in critically ill patients with sepsis or septic shock and feeding intolerance. (Weak recommendation; low quality of evidence)
Biomarkers infiammatori

- VES
- PCR
- Procalcitonina
Biomarkers infiammatori

Biomarkers infiammatori / Procalcitonina

Biomarkers infiammatori

CRP OR: 5.43, 95% CI [3.19; 9.23]
PCT OR: 14.99, 95% CI [7.12; 30.27]

Biomarkers infiammatori

Biomarkers infiammatori

Table 1. Indications for PCT measurement other than bacterial or fungal infection

<table>
<thead>
<tr>
<th>Condition</th>
<th>Comments/Pear</th>
<th>Expected range</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery, trauma, burn, and inhalation trauma. Surgery/trauma, thoracic</td>
<td>Maximum values on day 1, rapidly declining CRP peak day 2 or 3, slow decline (1-2 weeks)</td>
<td>&lt;0.5-1 ng/mL for peripheral, non-abdominal trauma or minor abdominal surgery; &lt;2 ng/mL for abdominal surgery or trauma, cardiac surgery; &gt;2 ng/mL expected in patients with major retroperitoneal or abdominal surgery, liver transplantation</td>
<td>[23, 68, 69]; [70, 71]; [72-75]</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>Initially low, but increasing within 1-3 days, if vasopressor support is required</td>
<td>May be intermediate to high (e.g., &gt;0.5 ng/mL to &gt;10 ng/mL)</td>
<td>[76-78]</td>
</tr>
<tr>
<td>MODS, severe SIRS</td>
<td>Increases with severity. After infection of pseudomembranous or septic remains undefined. The utility of procalcitonin levels or other biomarkers (such as C-reactive protein) to discriminate the acute inflammatory pattern of sepsis from other causes of generalized inflammation (e.g., postoperative, other forms of shock) has not been demonstrated. No recommendation can be given for the use of these markers to distinguish between severe infection and other acute inflammatory states (56–58).</td>
<td>0.5 ng/mL-2 ng/mL, rarely &gt;10 ng/mL</td>
<td>[79, 80]; [79, 81]; [79, 82]</td>
</tr>
<tr>
<td>After prolonged resuscitation, myocardial infarction</td>
<td>Peak Day 1.</td>
<td>Only in case of prolonged CPR, levels are unrelated with prognosis after CPR. Very faint increase after myocardial infarction.</td>
<td>[97, 98]</td>
</tr>
<tr>
<td>Neonates after birth</td>
<td>Peak Day 1-2</td>
<td>Use adapted reference range</td>
<td>[99-102]</td>
</tr>
<tr>
<td>End stage of tumor disease</td>
<td>Slow increase. Para neoplastic induction very rare, always by C-cell carcinoma.</td>
<td>Low (0.5-2 ng/mL)</td>
<td>[103]; [104]</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>Acute</td>
<td>May be very high</td>
<td>Individual reports</td>
</tr>
</tbody>
</table>

Take Home

• La necessità di ridefinire la sepsi dimostra la complessità della problematica;

• La diagnosi di sepsi è prevalentemente clinica e ogni tentativo di definire un chiaro e rigido protocollo diagnostico potrebbe risultare inadeguato per la diagnosi, vista l’eterogeneità dei quadri clinici;

• I markers infiammatori e di sepsi supportano la diagnosi clinica, non «fanno» la diagnosi;

• La gran parte dei dati in letteratura su sepsi e shock settico deriva da casistiche di pazienti di terapia intensiva.
Journal Club del Venerdì

GRAZIE