IDENTIFICARE PREOCCEMENTE IL PAZIENTE CON SEPSI GRAVE
Daniele Coen

Convegno SIMI-SIMEU  Pavia, 8 febbraio 2013
Chè perdere tempo a chi sa più spiace

*Dante Alighieri*
Tempestività di intervento

Stroke
67,000 decessi/anno
FAST Campaign
National Stroke Association
Target: Valutazione specialistica in 60 min
Riduzione mortalità del 40%

IMA
89,000 decessi/anno
National Infarct Angioplasty Project
Target: Chiamata-sala angiografica 60 min
PS-sala angiografica 20 min

Sepsi
42,000 deaths per year
Target: BUNDLE 6 hr (SSC)
Riduzione mortalità del 25%
Crucial issue is not a given value of $\text{DO}_2$ but instead an oxygen supply sufficient to match the energy needs.

“...It is likely that early interventions may reverse the energy failure more than interventions performed later, when mitochondria are structurally impaired. **Time is crucial**.”
“most of the patients (76%) met the criteria for severe sepsis on the same day that they met the criteria for sepsis or met the criteria for septic shock (49%) on the same day as for severe sepsis.

In the rest of the patients, the progression from sepsis to severe sepsis to septic shock occurred over an average of 1 day for each step”.


The Importance of Early Goal-Directed therapy

Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock

Anand Kumar, MD; Daniel Roberts, MD; Kenneth E. Wood, DO; Bruce Light, MD; Joseph E. Parrillo, MD; Satendra Sharma, MD; Robert Suppes, BSc; Daniel Feinstein, MD; Sergio Zanotti, MD; Leo Taiberg, MD; David Gurka, MD; Aseem Kumar, PhD; Mary Cheang, MSc

Objective: To determine the prevalence and impact on mortality of delays in initiation of effective antimicrobial therapy from initial onset of recurrent/persistent hypotension of septic shock.

Design: A retrospective cohort study performed between July 1989 and June 2004.

Setting: Fourteen intensive care units (four medical, four surgical, six mixed medical/surgical) and ten hospitals (four academic, six community) in Canada and the United States.

Patients: Medical records of 2,731 adult patients with septic shock.

Interventions: None.

Measurements and Main Results: The main outcome measure was survival to hospital discharge. Among the 2,154 septic shock patients (78.9% total) who received effective antimicrobial therapy only after the onset of recurrent or persistent hypotension, a strong relationship between the delay in effective antimicrobial initiation and in-hospital mortality was noted (adjusted odds ratio 1.119 [per hour delay], 95% confidence interval 1.103–1.136, \( p < .0001 \)). Administration of an antimicrobial effective for isolated or suspected pathogens within the first hour of documented hypotension was associated with a survival rate of 79.9%. Each hour of delay in antimicrobial administration over the ensuing 6 hrs was associated with an average decrease in survival of 7.6%. By the second hour after onset of persistent/recurrent hypotension, in-hospital mortality rate was significantly increased relative to receiving therapy within the first hour (odds ratio 1.67; 95% confidence interval, 1.12–2.48). In multivariate analysis (including Acute Physiology and Chronic Health Evaluation II score and therapeutic variables), time to initiation of effective antimicrobial therapy was the single strongest predictor of outcome. Median time to effective antimicrobial therapy was 6 hrs (25–75th percentile, 2.0–15.0 hrs).

Conclusions: Effective antimicrobial administration within the first hour of documented hypotension was associated with increased survival to hospital discharge in adult patients with septic shock. Despite a progressive increase in mortality rate with increasing delays, only 50% of septic shock patients received effective antimicrobial therapy within 6 hrs of documented hypotension. (Crit Care Med 2006; 34:1589–1596)

Key Words: sepsis; antimicrobial; timing; delay; outcome
Il Timing della Terapia Antibiotica

- Se il paziente è critico si, **SUBITO**
- Ogni ora di ritardo dopo la prima ora aumenta la mortalità del 7,6%

![Graph showing survival fraction and cumulative effective antimicrobial initiation over time from hypotension onset in hours.](Kumar, Crit Care Med 2006)
Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department*

David F. Gaieski, MD; Mark E. Mikkelsen, MD, MSCE; Roger A. Band, MD; Jesse M. Pines, MD, MBA, MSCE; Richard Massone, MD; Frances F. Furia, MD; Frances S. Shofer, PhD; Munish Goyal, MD

Objective: To study the association between time to antibiotic administration and survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department.


Setting: The emergency department of an academic tertiary care center from 2005 through 2006.

Patients: Two hundred sixty-one patients undergoing early goal-directed therapy.

Interventions: None.

Measurements and Main Results: Effects of different time cutoffs from triage to antibiotic administration, qualification for early goal-directed therapy to antibiotic administration, triage to appropriate antibiotic administration, and qualification for early goal-directed therapy to appropriate antibiotic administration on in-hospital mortality were examined. The mean age of the 261 patients was 59 ± 16 yrs; 41% were female. In-hospital mortality was 31%. Median time from triage to antibiotics was 119 mins (interquartile range, 76–192 mins) and from qualification to antibiotics was 42 mins (interquartile range, 0–93 mins). There was no significant association between time from triage or time from qualification for early goal-directed therapy to antibiotics and mortality when assessed at different hourly cutoffs. When analyzed for time from triage to appropriate antibiotics, there was a significant association at the <1 hr (mortality 19.5 vs. 33.2%; odds ratio, 0.30 [95% confidence interval, 0.11–0.83]; p = .02) time cutoff; similarly, for time from qualification for early goal-directed therapy to appropriate antibiotics, a significant association was seen at the ≤1 hr (mortality 25.0 vs. 38.5%; odds ratio, 0.50 [95% confidence interval, 0.27–0.92]; p = .03) time cutoff.

Conclusions: Elapsed times from triage and qualification for early goal-directed therapy to administration of appropriate antimicrobials are primary determinants of mortality in patients with severe sepsis and septic shock treated with early goal-directed therapy. (Crit Care Med 2010; 38:1045–1053)

Key Words: sepsis; early goal-directed therapy; antimicrobial timing; appropriateness; outcomes; resuscitation
Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department


### Table 7. In-hospital mortality: Time from qualification for early goal-directed therapy to appropriate antibiotics

<table>
<thead>
<tr>
<th>Cutoffs</th>
<th>Number</th>
<th>Mortality, %</th>
<th>Difference, %</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
<th>Probability of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1 hr</td>
<td>144</td>
<td>25.0</td>
<td>13.5</td>
<td>0.50</td>
<td>0.27–0.92</td>
<td>0.03</td>
<td>.20 vs .35</td>
</tr>
<tr>
<td>&gt;1 hr</td>
<td>117</td>
<td>38.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2 hrs</td>
<td>201</td>
<td>28.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;2 hrs</td>
<td>60</td>
<td>40.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤3 hrs</td>
<td>226</td>
<td>28.6</td>
<td>15.3</td>
<td>0.47</td>
<td>0.22–1.01</td>
<td>0.05</td>
<td>.24 vs .43</td>
</tr>
<tr>
<td>&gt;3 hrs</td>
<td>41</td>
<td>43.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤4 hrs</td>
<td>232</td>
<td>29.3</td>
<td>15.5</td>
<td>0.49</td>
<td>0.20–1.18</td>
<td>0.11</td>
<td>.25 vs .42</td>
</tr>
<tr>
<td>&gt;4 hrs</td>
<td>29</td>
<td>44.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5 hrs</td>
<td>238</td>
<td>29.8</td>
<td>13.7</td>
<td>0.48</td>
<td>0.18–1.25</td>
<td>0.13</td>
<td>.25 vs .43</td>
</tr>
<tr>
<td>&gt;5 hrs</td>
<td>23</td>
<td>43.5</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

21 deaths
KEEP CALM AND DO THE SEPSIS 6

Box 2 The sepsis six

The sepsis six to be delivered within 1 h
1. Deliver high-flow oxygen.
2. Take blood cultures.
3. Administer empiric intravenous antibiotics.
4. Measure serum lactate and send full blood count.
5. Start intravenous fluid resuscitation.
6. Commence accurate urine output measurement.
## Compliance in Pre - Formazione

<table>
<thead>
<tr>
<th>Sepsis Six</th>
<th>Intervento DT</th>
<th>Complianti</th>
<th>Missing</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SS1</strong></td>
<td><strong>Hai valutato necessità di O2-NIV-VAM ?</strong></td>
<td>442/464</td>
<td>10</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td><em>L'hai valutata nel tempo corretto</em> ?*</td>
<td>268/442</td>
<td></td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>Non hai indicato il tempo</td>
<td>143/442</td>
<td></td>
<td>32</td>
</tr>
<tr>
<td><strong>SS2</strong></td>
<td><strong>Hai prelevato per emocolture ?</strong></td>
<td>388/464</td>
<td>3</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td><em>L'hai fatto nel modo corretto^ ?</em></td>
<td>255/388</td>
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<td>65</td>
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<tr>
<td></td>
<td><em>L'hai fatto nel tempo corretto</em> ?*</td>
<td>104/388</td>
<td></td>
<td>26</td>
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<tr>
<td></td>
<td><em>L'hai fatto nel tempo e modo corretto ?</em></td>
<td>76/388</td>
<td></td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Non hai indicato tempo o modo</td>
<td>114/388</td>
<td></td>
<td>29</td>
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<tr>
<td><strong>SS3</strong></td>
<td><strong>Hai somministrato antibiotici ?</strong></td>
<td>407/464</td>
<td>8</td>
<td>87</td>
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<tr>
<td></td>
<td><em>Li hai somministrati in tempo corretto</em> ?*</td>
<td>186/407</td>
<td></td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>Non hai indicato il tempo</td>
<td>69/407</td>
<td></td>
<td>16</td>
</tr>
<tr>
<td><strong>SS4</strong></td>
<td><strong>Hai dosato i lattati ?</strong></td>
<td>309/464</td>
<td>3</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td><em>Li hai dosati nel tempo corretto</em> ?*</td>
<td>218/309</td>
<td></td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>Non hai indicato il tempo</td>
<td>35/309</td>
<td></td>
<td>11</td>
</tr>
<tr>
<td><strong>SS5</strong></td>
<td><strong>Hai infuso liquidi nella prima ora ?</strong></td>
<td>404/464</td>
<td>9</td>
<td>87</td>
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<tr>
<td></td>
<td><em>Li hai infusi in modo corretto^^ ?</em></td>
<td>103/404</td>
<td></td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Non hai indicato il modo</td>
<td>55/404</td>
<td></td>
<td>13</td>
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<tr>
<td><strong>SS6</strong></td>
<td><strong>Hai monitorato la diuresi ?</strong></td>
<td>374/464</td>
<td>5</td>
<td>80</td>
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<tr>
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<td><em>L'hai monitorata nel tempo corretto</em> ?*</td>
<td>242/374</td>
<td></td>
<td>64</td>
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<tr>
<td></td>
<td>Non hai indicato il tempo</td>
<td>138/374</td>
<td></td>
<td>36</td>
</tr>
</tbody>
</table>
Ossigeno terapia (+-IOT)
Sedazione-analgesia-controllo TA

CVC e monitoraggio invasivo PVC

PVC

8-12 mm Hg

<8mm Hg

Cristalloidi

<65 mm Hg

Colloidi

<70%

MAP

≥ 65 mm Hg

≥ 70%

Agenti vasoattivi

≥ 70%

SvO₂

≥ 70%

Trasfusione con GRC se Hct<30%

<70%

CaO₂

CO-inotropi

Goal raggiunti

NO
SURVIVING SEPSIS CAMPAIGN BUNDLES

TO BE COMPLETED WITHIN 3 HOURS:
1) Measure lactate level
2) Obtain blood cultures prior to administration of antibiotics
3) Administer broad spectrum antibiotics
4) Administer 30 mL/kg crystalloid for hypotension or lactate ≥4 mmol/L

TO BE COMPLETED WITHIN 6 HOURS:
5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥ 65 mm Hg
6) In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L (36 mg/dL):
   - Measure central venous pressure (CVP)*
   - Measure central venous oxygen saturation (Scvo₂)*
7) Remeasure lactate if initial lactate was elevated*

*Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg, Scvo₂ of ≥70%, and normalization of lactate.
Le difficoltà
Gli ostacoli all’applicazione della EGDT

<table>
<thead>
<tr>
<th>Barrier</th>
<th>MD Director, % (n = 19)</th>
<th>RN Manager, % (n = 29)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nursing staff required to perform EGDT</td>
<td>58</td>
<td>48</td>
<td>.51</td>
</tr>
<tr>
<td>Identifying septic patients</td>
<td>42</td>
<td>38</td>
<td>.77</td>
</tr>
<tr>
<td>Central catheter insertion</td>
<td>5</td>
<td>38</td>
<td>.01</td>
</tr>
<tr>
<td>Monitoring central venous pressure in the ED</td>
<td>47</td>
<td>38</td>
<td>.52</td>
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<tr>
<td>Physical space in the ED</td>
<td>32</td>
<td>38</td>
<td>.65</td>
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<tr>
<td>Monitoring ScVo₂ in the ED</td>
<td>11</td>
<td>28</td>
<td>.16</td>
</tr>
<tr>
<td>Measuring lactate</td>
<td>16</td>
<td>17</td>
<td>.9</td>
</tr>
<tr>
<td>Handoff between ED and ICU teams (transfer of care)</td>
<td>21</td>
<td>17</td>
<td>.74</td>
</tr>
<tr>
<td>Other barrier</td>
<td>16</td>
<td>17</td>
<td>.9</td>
</tr>
<tr>
<td>Central catheter insertion subclavian or internal jugular vein</td>
<td>5</td>
<td>3</td>
<td>.76</td>
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<tr>
<td>Lack of agreement with the Rivers EGDT resuscitation protocol</td>
<td>16</td>
<td>0</td>
<td>.03</td>
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<tr>
<td>Access to protocol medications (pressors and dobutamine)</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Access to an EGDT protocol</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

MD, medical doctor; RN, registered nurse; EGDT, early goal-directed therapy; ED, emergency department; ICU, intensive care unit.
<table>
<thead>
<tr>
<th>Sintomo di presentazione PS 2009</th>
<th>SEPSI</th>
<th>SHOCK</th>
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<tbody>
<tr>
<td>Febbre</td>
<td>60</td>
<td>3</td>
</tr>
<tr>
<td>Dispnea</td>
<td>28</td>
<td>15</td>
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<tr>
<td>PV alterati</td>
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<tr>
<td>Dolore addominale</td>
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<tr>
<td>Convulsioni o deficit neuro focali</td>
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<td>Alteraz. coscienza</td>
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<td>2</td>
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<tr>
<td>Altro</td>
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<td>TOTALE</td>
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<td>SEPSI</td>
<td>SHOCK</td>
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<tr>
<td>VERDE</td>
<td>81</td>
<td>5</td>
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<tr>
<td>GIALLO</td>
<td>47</td>
<td>21</td>
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<tr>
<td>ROSSO</td>
<td>22</td>
<td>17</td>
</tr>
</tbody>
</table>
Infezione

SIRS

Pancreatite

Trauma

Ustioni

Batteriemia

Fungemia

Viremia

Altro*

*IMA-EP-dissecazione, ESA, tireotossicosi,.

Bone R et al., Chest 1992
Strumento di screening per il paziente settico

Presenza di almeno due dei seguenti criteri di SIRS?

- FC > 90/min
- FR > 20/min o PCO2 < 32 mmHg
- TA < 36 o > 38.3 °C
- GB < 4.000 o > 12000 o > 10% di forme immature

Alterazione dello stato di coscienza;
Glicemia > 120 mg/dl (in assenza di DM)

Se Sì
il paziente ha una SIRS
C’è il sospetto di un’ infezione?

Tosse produttiva, dolore toracico, dispnea;
Dolore addominale, diarrea vomito, distensione;
Disuria, urine torbide, dolore al fianco;

Cefalea con rigor nucale, alterazione sensorio, otodinia, faringite;
Dolore localizzato ± flogosi cute o articolazioni;

Se Sì
il paziente ha una SEPSI
C’è un danno d’organo?

- **Pressione**  PAS < 90 o PAM < 65
- **Lattati**  > 2mmol/l  BE <-5
- **Diuresi**  < 0.5 ml/kg/hr for 2 hrs  Creatinina  > 2mg/dl
- **INR**  > 1.5  **PTT**  > 60 s  **PLT**  < 100 x 10⁹/l
- **Bilirubina**  > 2  **ALT/AST**  > 2 volte limite sup

**O₂ necessario per mantenere SpO₂ > 90%**

Se Sì
il paziente ha una SEPSI SEVERA
E' presente ipotensione o ipoperfusione nonostante resuscitazione volemica?

PAS<90mmHg o PAM<65mmHg o riduzione della PAS basale di >40mmHg o Lattati>4mmol/l (Shock criptico) dopo adeguato riempimento volemico;

Se Sì
il paziente ha uno SHOCK SETTICO
Donna 70 aa in PS per lombalgia, APR ipertesa (non assunta tp da 24 ore), obesa, non DM

FC>105 bpm FR 28/min SaO2 96% AA PA 100/75 TA36°C
soporosa EGA: Lattati 2.5 Glicemia 160 mg/dl

C’è il sospetto di infezione?
PIURI A dal catetere vescicale

la paziente ha una SIRS

E’ presente danno d’organo?

PAs calo >40mmHg lattati>2 alterazione del sensorio
LAB: creatinina 2.5 GB16.000 coagulazione e PP nella norma

la paziente ha una SEPSI

la paziente ha una SEPSI SEVERA con ipotensione

Inizia riempimento volemico con Ringer 1500 in bolo
PA 95/60, FC 100, al termine del riempimento volemico adeguato

SEVERE SEPSIS
SCREENING TOOL
Limiti

• L’approccio lineare alla sepsi fin qui presentato (SIRS → sepsi → sepsi severa → shock settico) presenta questa sindrome come se le sue caratteristiche e la sua severità procedessero lungo una dimensione lineare di cui la SIRS è l’ineludibile punto di partenza.

• La sepsi invece, come il cancro, è un insieme di molte malattie, con presentazioni sindromiche di grande diversità.
Il riscontro di una disfunzione d’organo può essere il primo sintomo di sepsi che giunge all’attenzione del clinico che sta valutando un paziente.

E’ per questa ragione che sono stati inseriti parametri quali l’instabilità emodinamica, l’ipossiemia, l’oliguria, la coagulopatia e l’alterazione dei test di funzione epatica tra i criteri che possono essere utilizzati per la diagnosi di sepsi.

*2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference*
Diagnostic criteria for sepsis 2001 SCCM/ESICM/ACCP/ATS/SIS

Infection documented or suspected and some of the following:

**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 >120 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 (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%b Cardiac index >3.5 l min–1 m–2c,d

**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
<table>
<thead>
<tr>
<th>TABLE 1. Diagnostic Criteria for Sepsis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infection, documented or suspected, and some of the following:</strong></td>
</tr>
<tr>
<td><strong>General variables</strong></td>
</tr>
<tr>
<td>Fever (&gt; 38.3°C)</td>
</tr>
<tr>
<td>Hypothermia (core temperature &lt; 36°C)</td>
</tr>
<tr>
<td>Heart rate &gt; 90/min⁻¹ or more than two SD above the normal value for age</td>
</tr>
<tr>
<td>Tachypnea</td>
</tr>
<tr>
<td>Altered mental status</td>
</tr>
<tr>
<td>Significant edema or positive fluid balance (&gt; 20mL/kg over 24hr)</td>
</tr>
<tr>
<td>Hyperglycemia (plasma glucose &gt; 140mg/dL or 7.7 mmol/L) in the absence of diabetes</td>
</tr>
<tr>
<td><strong>Inflammatory variables</strong></td>
</tr>
<tr>
<td>Leukocytosis (WBC count &gt; 12,000 µL⁻¹)</td>
</tr>
<tr>
<td>Leukopenia (WBC count &lt; 4000 µL⁻¹)</td>
</tr>
<tr>
<td>Normal WBC count with greater than 10% immature forms</td>
</tr>
<tr>
<td>Plasma C-reactive protein more than two SD above the normal value</td>
</tr>
<tr>
<td>Plasma procalcitonin more than two SD above the normal value</td>
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<tr>
<td><strong>Hemodynamic variables</strong></td>
</tr>
<tr>
<td>Arterial hypotension (SBP &lt; 90mm Hg, MAP &lt; 70mm Hg, or an SBP decrease &gt; 40mm Hg in adults or less than two SD below normal for age)</td>
</tr>
<tr>
<td><strong>Organ dysfunction variables</strong></td>
</tr>
<tr>
<td>Arterial hypoxemia (Pao₂/Fio₂ &lt; 300)</td>
</tr>
<tr>
<td>Acute oliguria (urine output &lt; 0.5mL/kg/hr for at least 2 hrs despite adequate fluid resuscitation)</td>
</tr>
<tr>
<td>Creatinine increase &gt; 0.5 mg/dL or 44.2 µmol/L</td>
</tr>
<tr>
<td>Coagulation abnormalities (INR &gt; 1.5 or aPTT &gt; 60 s)</td>
</tr>
<tr>
<td>Ileus (absent bowel sounds)</td>
</tr>
<tr>
<td>Thrombocytopenia (platelet count &lt; 100,000 µL⁻¹)</td>
</tr>
<tr>
<td>Hyperbilirubinemia (plasma total bilirubin &gt; 4 mg/dL or 70 µmol/L)</td>
</tr>
<tr>
<td><strong>Tissue perfusion variables</strong></td>
</tr>
<tr>
<td>Hyperlactatemia (&gt; 1 mmol/L)</td>
</tr>
<tr>
<td>Decreased capillary refill or mottling</td>
</tr>
</tbody>
</table>

WBC = white blood cell; SBP = systolic blood pressure; MAP = mean arterial pressure; INR = international normalized ratio; aPTT = activated partial thromboplastin time.

Diagnostic criteria for sepsis in the pediatric population are signs and symptoms of inflammation plus infection with hyper- or hypothermia (rectal temperature > 38.5° or < 36°), tachycardia (may be absent in hypothermic patients), and at least one of the following indicators of altered organ function: altered mental status, hypoxemia, increased serum lactate level, or bounding pulses.

SIRS $\rightarrow$ SEPSI $\rightarrow$ SEPSI SEVERA $\rightarrow$ SHOCK SETTICO

REAZIONE INFIAMMATORIA (SIRS) $\leftrightarrow$ INFEZIONE

DISFUNZIONE D’ ORGANO (SEPSI SEVERA – SHOCK SETTICO)
**SEGNI-SINTOMI D’ALLARME**

**IPOPERFUSIONE**
- tachipnea, tachicardia
- ipotensione
- oliguria
- vasocostrizione periferica,
- polso capillare > 2 sec,
- marezzatura
- agitazione, alterazione sensorio

**INFEZIONE**
- tosse produttiva, dispnea
- dolore addominale, diarrea, vomito
- disuria, urine torbide, dolore lombare
- cefalea, rigor, alterazione sensorio
- otodinia, faringodinia
- flogosi di cute o articolazioni
- nuovo soffio cardiaco

**DANNO D’ORGANO**
- ipossiemia
- oliguria
- ileo
- alterazioni laboratorio
- …
Gli strumenti per la diagnosi precoce

- Identificare i pazienti a rischio elevato
- Monitorizzare i pazienti «acuti»
Alto indice di sospetto clinico

Da che cosa parto?

- Predisposizione (anamnesi)
- Sospetto clinico di infezione (anamnesi + esame clinico)
- Danno d’organo - in particolare ipoperfusione (esame clinico+ esami di laboratorio)
- Parametri vitali ;
Predisposizione

Chi sono i pazienti a rischio di sepsi?

- Pazienti con importanti copatologie (insufficienza cardiaca terminale, insufficienza renale terminale)
- Paziente neoplastico;
- Paziente anziano, degente in RSA;
- Paziente immunodepresso (per trapianto, CT, splenectomia, deficit genetico, HIV)
- Paziente con sorgente d’infezione (ustionato, CV a permanenza, catetere venoso centrale, drenaggio chirurgico)
Identificazione a triage e post triage

- Codice giallo a trapiantati, neoplasie in CT, insufficienti terminali di cuore, fegato, rene ?
- Lattati urgenti point of care a pazienti con sospetta infezione e MEWS > 4 ?
- Quick-look medico a pazienti con condizioni di rischio
<table>
<thead>
<tr>
<th>Score</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>Systolic BP</td>
<td>&lt;70</td>
<td>71-80</td>
<td>81-100</td>
<td>101-199</td>
<td>—</td>
<td>&gt;200</td>
<td>—</td>
</tr>
<tr>
<td>Heart rate (BPM)</td>
<td>—</td>
<td>&lt;40</td>
<td>41-50</td>
<td>51-100</td>
<td>101-110</td>
<td>111-129</td>
<td>&gt;130</td>
</tr>
<tr>
<td>Respiratory rate (RPM)</td>
<td>—</td>
<td>&lt;9</td>
<td>—</td>
<td>9-14</td>
<td>15-20</td>
<td>21-29</td>
<td>&gt;30</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>—</td>
<td>&lt;35</td>
<td>—</td>
<td>35.0-38.4</td>
<td>—</td>
<td>&gt;38.5</td>
<td>—</td>
</tr>
<tr>
<td>AVPU</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>A</td>
<td>V</td>
<td>P</td>
<td>U</td>
</tr>
</tbody>
</table>
Identificazione precoce in reparto

- Definire frequenza dei controlli e utilizzare MEWS e meccanismi di track and trigger
- Pensare alla sepsi di fronte a un deterioramento cognitivo o d’organo
- Utilizzare lattati con maggiore frequenza
Track-and-trigger scoring systems
Systems such as the Early Warning Score (EWS) or modified versions (Modified Early Warning Score (MEWS)), Patient at Risk Scores (PARS) and Medical Emergency Team (MET) calling criteria are based on the identification of physiological derangement from the normal range. Systems vary, but commonly aggregate
In a confidential inquiry into quality of care before admission to the Intensive Care Unit (ICU), two external reviewers assessed the quality of care in 100 consecutive admissions to ICU 1. 20 patients were deemed to have been well managed and 54 to have received suboptimal management, with disagreement about the remainder. Case mix and severity were similar between the groups, but ICU mortality was worse in those who both reviewers agreed received suboptimal care (48% compared with 25% in the well managed group). Admission to the ICU was considered late in 37 patients in the suboptimal group. Overall, a minimum of 4.5% and a maximum of 41% of admissions were considered potentially avoidable. Suboptimal care contributed to morbidity or mortality in most instances. The main causes of suboptimal care were failure of organisation, lack of knowledge, failure to appreciate clinical urgency, lack of supervision and failure to seek advice.

NCEPOD 2006
During the same period, 86 hospital inpatients were admitted on 98 occasions to the ICU, 31 of whom received suboptimal care before the ICU admission either because of non-recognition of the severity of the problem or inappropriate treatment. Mortality rates were significantly higher in these patients than in well managed patients in both the ICU (52% v 35%) and hospital (65% v 42%), p<0.0001. The authors concluded that patients with obvious clinical indicators of acute deterioration are not infrequently overlooked or poorly managed on the ward.

Even more disturbingly, studies of events leading to ‘unexpected’ in-hospital cardiac arrest indicate that many patients have clearly recorded evidence of marked physiological deterioration prior to the event, without appropriate action being taken in many cases 4,5.
Acutely ill patients in hospital
Recognition of and response to acute illness in adults in hospital

NICE clinical guideline 50
Developed by the Centre for Clinical Practice at NICE
1.2.3 Care pathway

Assessment and monitoring

Patient in acute hospital setting:
- at the time of admission to the ward
- in the emergency department after a decision to admit has been made
- transferred to a general ward from a critical care area.

Initial assessment
- Record at least:
  - heart rate
  - respiratory rate
  - systolic blood pressure
  - level of consciousness
  - oxygen saturation
  - temperature.
- Write a clear monitoring plan specifying the physiological observations to be recorded and how often. Take into account:
  - diagnosis
  - the agreed treatment plan.
  - comorbidities

Routine monitoring
Use physiological track and trigger systems to monitor patients.
- Monitor physiological observations at least every 12 hours, unless decided at a senior level to increase or decrease the frequency for an individual patient.
- Use multiple-parameter or aggregate weighted scoring systems, which allow a graded response. The systems should:
  - define the parameters to be measured and the frequency of observations
  - state the parameters, cut-off points or scores that should trigger a response
  - monitor:
    - heart rate
    - respiratory rate
    - systolic blood pressure
    - level of consciousness
    - oxygen saturation
    - temperature.
- Set thresholds locally, and review regularly to optimise sensitivity and specificity.

Consider monitoring:
- biochemistry (for example, lactate, blood glucose, base deficit, arterial pH)
- hourly urine output
- pain.

Response

Patients at risk of deterioration
Follow locally agreed graded response strategy if:
- alerted by track and trigger score
- there is clinical concern.

Low score
Increase frequency of observations and alert the nurse in charge.

Medium score
Urgent call to:
- patient’s primary medical team
- locally agreed personnel with core competencies for acute illness.
- Examples include a critical care outreach team, a hospital-at-night team or a specialist trainee in an acute medical or surgical specialty.

High score
Emergency call to team with critical care competencies and diagnostic skills. The team should:
- include a medical practitioner skilled in assessing critically ill patients and with advanced airway management and resuscitation skills
- provide an immediate response.

Clinical emergency (excluding cardiac arrests).
Take home messages - 1

1. La diagnosi precoce è importante, ma non sempre semplice e si basa in prima istanza su un attento monitoraggio del paziente

2. Da un punto di vista metodologico è importante ricercare una sepsi in tutti i pazienti con segni di ipoperfusione e danno d’organo e ricercare segni di ipoperfusione e di danno d’organo in tutti i pazienti con una infezione
Take home messages - 2

In Pronto Soccorso
• Triage attento a predisposizione
• Frequente controllo PV nei pazienti con infezione → MEWS
• Lattati anche venosi precoci

Nei reparti
• Monitoraggio dei pazienti con infezione di recente ricovero con MEWS e meccanismi t&t
• Pensare alla sepsi se deterioramento cognitivo o d’organo
GRAZIE
We recommend that imaging studies be performed promptly.

SSC 2008
### S-Procalcitonina

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>ng/mL</th>
<th>Aumento:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.6</td>
<td></td>
<td>&lt; 0.5</td>
</tr>
</tbody>
</table>

- 0.5-2.0 leggero
- 2.0-5.0 moderato
- 5.0-10.0 deciso
- >10.0 sepsi, shock settico, MODS
Cut-off Procalcitonina e utilità nella sepsi

Se PCT $\leq 0,5$ ng/ml $\rightarrow$ Improbabile sepsi severa o shock settico

Se PCT $\geq 5$ ng/ml $\rightarrow$ Elevata probabilità di sepsi grave e shock settico da infezione batterica
Comparison of procalcitonin and C-reactive protein as markers of sepsis
Luzzani A. et al *Crit Care Med* 2003 vol 31, n° 6; 1737-1741

<table>
<thead>
<tr>
<th>Classes</th>
<th>PCT Median (Interquartile Range)</th>
<th>CRP Median (Interquartile Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>0.1 (0.09–0.3)</td>
<td>50.4 (25.3–87.6)</td>
</tr>
<tr>
<td>SIRS</td>
<td>0.4 (0.2–0.7)</td>
<td>79.9 (52.9–103.4)</td>
</tr>
<tr>
<td>Localized infection</td>
<td>1.3 (0.6–2.0)</td>
<td>85.5 (58.5–132.4)</td>
</tr>
<tr>
<td>Sepsis group</td>
<td>3.6 (1.7–6.6)</td>
<td>115.9 (69.7–171.2)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>3.1 (1.4–5.2)</td>
<td>125.6 (79.4–174.6)</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>3.2 (1.7–7.4)</td>
<td>73.6 (60.9–148.9)</td>
</tr>
<tr>
<td>Septic shock</td>
<td>10.7 (2.9–33.2)</td>
<td>108.0 (62.9–167.5)</td>
</tr>
</tbody>
</table>

PCT, procalcitonin; CRP, C-reactive protein; SIRS, systemic inflammatory response syndrome.
Comparison of procalcitonin and C-reactive protein as markers of sepsis
Luzzani A. et al *Crit Care Med* 2003 vol 31, n° 6; 1737-1741

<table>
<thead>
<tr>
<th>SOFA Score</th>
<th>Median (Interquartile Range)</th>
<th>PCT</th>
<th>Median (Interquartile Range)</th>
<th>CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>3.1 (1.2–4.9)</td>
<td></td>
<td>135.9 (85.8–178.9)</td>
</tr>
<tr>
<td>1–6</td>
<td></td>
<td>3.9 (1.8–7.3)</td>
<td></td>
<td>82.9 (59.4–149.2)</td>
</tr>
<tr>
<td>7–12</td>
<td></td>
<td>31.0 (4.8–62.1)</td>
<td></td>
<td>113.5 (107.9–222.9)</td>
</tr>
<tr>
<td>13–18</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PCT, procalcitonin; CRP, C-reactive protein; SOFA, sepsis-related organ failure assessment.

*p < .001.
Andamento valori PCR versus PCT in paziente con politrauma senza segni di infezione

- I valori di PCT nello stesso intervallo di tempo sono leggermente aumentati e alla dimissione sono in range di normalità.

- I valori di PCR sono sopra il range di normalità fin dall’ingresso e ancora elevati fino alla dimissione.
IL SISTEMA PIRO
Una migliore caratterizzazione della sepsi:

**Predisposizione:** Malattie croniche preesistenti. Farmaci. Alcol. Stato nutrizionale e immunitario. Età, sesso. Genetica (TLR2)

**Infezione:** Specie e virulenza dell’agente infettante. Sito di infezione. Timing di insorgenza.

**Risposta:** Iper o ipo-risposta. Polimorfismo genetico.

**Organo:** (disfunzione) Intensità, numero e successione degli organi coinvolti, “la presenza di disfunzione d’organo equivale alla presenza di tumore metastatizzato”
IL SISTEMA PIRO

Una migliore caratterizzazione della sepsi:

- PIRO e codice triage
- PIRO e terapia
- PIRO e monitoraggio
- PIRO e ricovero

SEPSI

- meningite giovane sano
- polmonite nosocomiale in trapiantato
- urosepsi anziano, DM, IRC
**Markers di laboratorio**

**Procalcitonina (PCT)**

- **Precursore della calcitonina prodotta dalle Cellule C Tiroide**
- **In corso di infezione batterica viene prodotta da altri organi: cell neuroendocrine, monociti e macrofagi**
- **Aumenta nelle infezioni batteriche**
- **Correla con il quadro clinico**
- **Elevato VPN**
- **Valori di PCT > 5 ng/ml sono indicativi di sepsi**

- **Aumenta dopo già dopo 2 ore**
- **Picco dopo 6-8 h**
- **Plateau dopo 12h**
- **Emivita tra 25 e 30 h**
- **Dopo cessazione stimolo si normalizza nell’arco di 48-72 ore**
- **eliminazione renale:IR non ne modifica la clearance**
- **non influenzata da tp steroidea**
I valori di PCT dimostrano differenze significative tra sepsi / sepsi severa e tra sepsi severa / shock settico

**VALORE PROGNOSTICO**

Procalcitonin for early diagnosis and differentiation of SIRS, sepsis, severe sepsis, and septic shock

• Utile come elemento di INTEGRAZIONE nel differenziare una SIRS-SEPSI (pancreatite, trauma, post-chirurgico, rigetto di trapianto, VAP)
• Valore prognostico
• Diagnosi precoce? → Non sempre disponibile in urgenza
• Sicuramente utile nell’interrompere il trattamento antibiotico