Sepsis

the clinical syndrome

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Vila Franca Xira Hospital
Systemic Inflammatory Response

≥2

- Temperature ≥38°C or ≤36°C
- HR ≥90/min
- RR ≥20/min
- Leucocytes ≥12,000/mL or ≤4,000/mL or >10% immature
Definitions (ACCP/SCCM)

• **Infection**
  • A microbial phenomenon characterized by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms.

• **Bacteremia**
  • The presence of viable bacteria in the blood.

• **Sepsis**
  • Known or suspected infection, plus ≥2 SIRS Criteria

• **Severe Sepsis**
  • Sepsis plus >1 organ dysfunction.
Severe Sepsis

Incidence and Mortality

Severe Sepsis cases and US Population Over Time

João G. Pereira
Infection

Vasodilation → Inflammatory Mediators → Endothelial Dysfunction

Hypotension → Microvascular Plugging → Vasoconstriction → Edema

Maldistribution of Microvascular Blood Flow

Ischemia → Cell Death

Organ Dysfunction
Clinical Signs of Severe Sepsis

- Myocardial Depression.
- Altered Vasculature.
- Altered Organ Perfusion.
- Imbalance of O2 delivery and Consumption.
- Metabolic (Lactic) Acidosis.

Mythocondrial failure
Organ System Involvement

- **Circulation**
  - Hypotension,
  - increases in microvascular permeability
  - Shock

- **Lung**
  - Pulmonary Edema,
  - hypoxemia,
  - ARDS

- **Hematologic**
  - DIC, coagulopathy
  - (DVT)
Organ System Involvement

- GI tract
  - Stress ulcer
  - Translocation of bacteria,
  - Liver Failure,
  - Gastroparesis and ileus

- Nervous System
  - Encephalopathy

- Skeletal Muscle
  - Rhabdomyolysis

Table 4. Risk of death according to number of evolving organ dysfunctions after bacteremic sepsis

<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>Hazard Ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>1</td>
<td>2.51</td>
<td>0.5–13.7</td>
</tr>
<tr>
<td>2</td>
<td>6.40</td>
<td>1.4–30.1</td>
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<tr>
<td>3</td>
<td>23.49</td>
<td>5.4–101.9</td>
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<tr>
<td>≥4</td>
<td>36.04</td>
<td>8.7–150</td>
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Hugonnet, Crit Care Med, 312003.390-394
Definitions (ACCP/SCCM)

• Septic Shock

• Sepsis induced with hypotension despite adequate resuscitation along with the presence of perfusion abnormalities which may include, but are not limited to lactic acidosis, oliguria, or an acute alteration in mental status.
Sepsis & Mortality

Bone CCM 1992;20:864

Rangel-Frausto JAMA 1995;273:117

Povoa CCM 2009;37:410

Increasing of inflammatory activity and mortality!
Immune response in Sepsis

Activation of the cellular immune response: IL-1, IL-2, γ-IFN, TNF.

Physiologic insult

SIRS

CARS

Downregulation of the cellular immune response: IL-4, IL-10, IL-13.

Protects against insults to the host

Limits host response to infected areas

Bansal: Curr Opin Clin Nutr Metab Care 2003;6:223-228
**Therapeutic Strategies in Sepsis**

- **Early Detection**
  - Obtain serum lactate level.

- **Early Blood Cx/Antibiotics**
  - within 3 hours of presentation.
  - Source control

- **Early EGDT:**
  - Hypotension (SBP < 90, MAP < 65) or lactate > 4 mmol/L:
    - initial fluid bolus 20-40 ml of crystalloid (or colloid equivalent) per kg of body weight.
  - Vasopressors:
    - Hypotension not responding to fluid
    - Titrate to MAP > 65 mmHg.
  - Septic shock or lactate > 4 mmol/L:
    - CVP and ScvO₂ measured.
    - CVP maintained >8 mmHg.
    - MAP maintain > 65 mmHg.
  - ScvO₂<70% CVP > 8 mmHg, MAP > 65 mmHg:
    - PRBCs if hematocrit < 30%.
    - Inotropes.
Severe sepsis at the emergency department

- Usual care
  90 day mortality 18.9%

More than 95% of patients received abs 6h post admission

A Cumulative In-Hospital Mortality to 60 Days

P = 0.52 by log-rank test

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Protocol-based EGDT</th>
<th>Protocol-based standard therapy</th>
<th>Usual care</th>
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<tbody>
<tr>
<td></td>
<td>439</td>
<td>373</td>
<td>356</td>
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<td>446</td>
<td>389</td>
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PROCESS investigators. DOI: 10.1056/NEJMoa1401602
Diagnosis of infection

AB delay ➔ poor outcome ➔ poor outcome

BUT, AB are not benign!

↓AB ➔ ↓ mortality
➔ ↓ MDR
Singh AJRCCM 2000;162:505

↓AB ➔ ↓ mortality
➔ ↓ LOS
Weiss AJRCCM 2011;164:680

Kumar CCM 2006;34:1589

Only 50% receive ab until 6h after admission
Antibiotic detrimental effects?

Neurosurgical patients
Klebsiella aerogens
High LOS
Increase Mortality

Price, Lancet 1970; 1213
“as the physicians say it happens in hectic fever (*sepsis*), that in the beginning of the malady it is easy to cure but difficult to detect, but in the course of time, not having been either detected or treated in the beginning, it becomes easy to detect but difficult to cure”

Niccolò Machiavelli, *The Prince*
### SIRS criteria - criticisms

#### Table 1. SIRS criteria and weighted SIRS scores in predicting microbiologically confirmed infection

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
<th>Positive likelihood ratio</th>
<th>Negative likelihood ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>WCC</td>
<td>52.5%</td>
<td>52.8%</td>
<td>63.3%</td>
<td>41.7%</td>
<td>1.11</td>
<td>0.90</td>
</tr>
<tr>
<td>Temperature</td>
<td>46.6%</td>
<td>59.0%</td>
<td>63.8%</td>
<td>41.6%</td>
<td>1.13</td>
<td>0.90</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>65.2%</td>
<td>41.0%</td>
<td>63.2%</td>
<td>43.2%</td>
<td>1.11</td>
<td>0.85</td>
</tr>
<tr>
<td>Tachypnoea</td>
<td>49.4%</td>
<td>51.9%</td>
<td>61.5%</td>
<td>39.8%</td>
<td>1.03</td>
<td>0.97</td>
</tr>
<tr>
<td>Traditional (≥ 2) SIRS</td>
<td>70.6%</td>
<td>37.5%</td>
<td>63.7%</td>
<td>45.1%</td>
<td>1.13</td>
<td>0.79</td>
</tr>
<tr>
<td>Weighted SIRS ≥ 3</td>
<td>63.5%</td>
<td>45.7%</td>
<td>64.5%</td>
<td>44.6%</td>
<td>1.17</td>
<td>0.80</td>
</tr>
<tr>
<td>Both temp and WCC present</td>
<td>27.3%</td>
<td>77.5%</td>
<td>65.3%</td>
<td>40.7%</td>
<td>1.21</td>
<td>0.94</td>
</tr>
</tbody>
</table>

#### Number of SIRS criteria and the likelihood of documented infection

![Graph showing microbiologically confirmed infection vs SIRS or weighted SIRS score]
Identification of septic focus

- history and physical examination
- imaging
- cultures: Blood, urine, sputum, abscess.

- Lab results are poorly sensitive and have low specificity for the diagnosis of sepsis
- Microbiological cultures usually take 24-48h
### Biomarkers and Diagnosis of Infection

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCT</td>
<td>70-91</td>
<td>68-92</td>
<td>0.64-0.95</td>
</tr>
<tr>
<td>CRP</td>
<td>10-98</td>
<td>44-99</td>
<td>0.68-0.82</td>
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</tbody>
</table>

van der Meer BMJ 2005;331:26  
Uzzan CCM 2006;34:1996  
Tang Lancet Infect Dis 2007;7:210

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#### Why use biomarkers?

For the early diagnosis of infection, before clinical deterioration!

- **Problems:**
  1. Heterogeneity assessment  
  2. ACCP/SCCM Consensus Conference criteria to define the absence of sepsis (assessing degrees of clinical severity)  
  3. Gold standard, that is presence of documented infection and no antibiotic therapy *(Cohen CCM 2001)*

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*Cohen CCM 2001*
PCT and CRP Post operative infections in elective colonic surgery

N=50 pts
Infections 21 (16 surgical site infection)
Time of infection – day 7 (median)

(GLM) \( P=0.001 \)

(GLM) \( P=0.886 \)

*p<0.01 (Bonferroni correction)
§ - p=0.012
† - p=0.02

Rebanda Critical Care 2012;16:S10
Sources of Sepsis
The International Cohort Study

<table>
<thead>
<tr>
<th>Source</th>
<th>Severe Sepsis</th>
<th>Septic Shock</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>66</td>
<td>53</td>
</tr>
<tr>
<td>Abdomen</td>
<td>9</td>
<td>20</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>Urinary</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Multiple</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
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35% mortality
Sources of Sepsis

The INFAUCI study

Hospital mortality 38.2%
Sources of Sepsis

The INFAUCI study

### Hospital mortality
- **38.2%**

### Septic Shock
- **51.8%**

### Positive Microbiology
- **48.3%** (comm 39.9% vs H 57.5%)

### Adequate antibiotics
- **74.4%** (comm 83% vs H 62.8%)

### Mortality after ICU discharge
- **(inf 14.2% vs n inf 9.6%)**

### Late ICU admission (community infections)
- **35.9% vs 35.1%**
PNEUMONIA

Infection on admission to the ICU. Submitted

Gram negative  Gram positive  Fungi  Virus  Others
INTRA-ABDOMINAL

Infection on admission to the ICU. Submitted
Decrease in sepsis mortality in the XXI\textsuperscript{th} century

Antibiotics Pharmacokinetics

Healthy

Organ Failure

Sepsis

Increased Vd
Decreased Cl

Gonçalves-Pereira. Crit Care 2011, 15:R206
Improvements in Sepsis outcome with careful process of care

- Early diagnosis (including adequate microbiological samples)
- Adequate and early referentiation to ICU or ward
- Early and adequate antibiotics
- Avoid nosocomial infections
- Careful post ICU care
SECOND OPINION

STUDY: 70% DROP IN HOSPITAL INFECTIONS WHEN PHYSICIAN'S MOTHER IS PRESENT...

DID YOU WASH YOUR HANDS? NO GOLF FOR A WEEK IF YOU GIVE HIM PNEUMONIA! DID YOU DO YOUR HOMEWORK ON THIS PATIENT? WHEN WAS THE LAST TIME YOU WASHED THAT LAB COAT? STOP SLOUCHING! WOULD IT KILL YOU TO SMILE?