La sepsi
Il ruolo dell’antibiotico terapia

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Infectious Disease Unit - Sant’Orsola Hospital, Bologna, Italy

Disclosures: none
Epidemiology of sepsis


Surviving Sepsis Campaign

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 $\geq$ 4 mmol/L
Antibiotic therapy for the management of sepsis

• Timing of antibiotic treatment
• Adequacy of antibiotic treatment
  – Epidemiology of bacterial infections
  – Choice of right drug
  – Choice of right doses/route/schedule
• Strategies to improve efficacy of antibiotic treatments
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Effect of timing on survival

Adapted with permission from:
Crit Care Med 2006;34:1589-96

Fraction of total patients

Time from hypotension onset (hours)
**Effect of inappropriate antibiotics on survival**

<table>
<thead>
<tr>
<th></th>
<th>Appropriate (n=4579)</th>
<th>Inappropriate (n=1136)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survived</td>
<td>52</td>
<td>10.3</td>
<td>9.45 (7.74 – 11.54)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>P value</strong></td>
</tr>
<tr>
<td>Immuno-suppressed*</td>
<td>15</td>
<td>19.8</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>COPD</td>
<td>13.6</td>
<td>14.1</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Dialysis</td>
<td>7.3</td>
<td>10.7</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

All numbers expressed as % unless otherwise specified

* Immunosuppression = chemotherapy or chronic steroids (>10mg prednisone daily)
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*Escherichia coli*: Percentage of resistance to third generation cephalosporins (ECDC 2014)

*Klebsiella pneumoniae*: Percentage of resistance to carbapenems (ECDC 2014)
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WHAT DOES IT MEAN “CORRECT ANTIBIOTIC THERAPY”?

The microorganism point of view
- A GOOD MICROBIOLOGICAL / EPIDEMIOLOGICAL CHOICE

The drug point of view
- A CORRECT PHARMACOKINETICAL CHOICE and ADMINISTRATION
  - lipophilic vs hydrophilic drugs
  - time dependent vs concentration dependent drugs

The patient point of view
- A TARGETED PHYSIOPHATOLOGICAL DAILY SCHEDULE
  - illness severity grading
  - physio-pathological conditions affecting distribution

Viale P & Pea F  Crit Care Med 2006
Do clinical trials reflect reality?

**“Clinical trial patient”**
- Less-sick
- Less organ dysfunction
- Diagnosis more certain
- Drug levels predictable

**“Your patient?”**
- Critical illness, comorbidities
- Organ dysfunction
- Diagnostic uncertainty
- Drug levels unpredictable

**Host**

**Pathogen**
- Antibiotic susceptible
- Uncomplicated source

**Drug**
- Efficacious dose with emphasis on safety and convenience
- Antibiotic resistance
- Possibly complicated source

- Effective dose???
Pharmacokinetics

• Absorption
  – Decreased gastric or subcutaneous absorption due to shock and vasopressors
  – Intravenous route preferred in severe sepsis / septic shock

• Volume of distribution (Vd)
  – Hydrophilic medications generally stay in the plasma volume (Vd < 0.7 L/kg)
    • Influenced by fluid administration and capillary leak
  – Lipophilic medications distribute into intracellular and adipose tissue (Vd > 1 L/kg)
    • Not generally affected by fluid administration and third spacing

Crit Care Clin 2011;27:1-18
Crit Care Clin 2011;27:19-34
Chest 2012;141;1327-36
Antibiotic Volume of Distribution Often Changes in Critically-Ill Patients

Release of inflammatory mediators causes damage to the vascular endothelium, resulting in expansion of extravascular space (increased volume of distribution)

Use of hydrophilic medication at standard doses may result in subtherapeutical drug levels

Figure: R. Lewis
Pharmacokinetics

• **Metabolism**
  – Hepatic metabolism consists of two phases
    • Phase 1: oxidation, reduction and hydrolysis
      – Cytochrome P450
    • Phase 2: glucuronidation, sulfation and acetylation
  – Drugs can be classified by extraction ratio
    • High (> 0.7): depends on hepatic drug flow
    • Intermediate (0.3-0.7)
    • Low (< 0.3): depends on hepatic (intrinsic) function

• **Excretion**
  – Renal excretion is the primary excretory pathway for most parent drugs or their metabolites
  – Sepsis/shock patients frequently present with acute kidney injury
  – May also present with increased renal excretion
    • Augmented renal clearance

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Crit Care Clin 2011;27:19-34
Chest 2012;141;1327-36
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Surviving Sepsis Campaign

CARE BUNDLES

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The epidemiology of adults with severe sepsis and septic shock in Scottish emergency departments.


308910 ED attendances in 20 hospitals over a 3-month period
1.7% fulfilled criteria for sepsis, with 626 cases of severe sepsis/septic shock (0.2% of ED attendances)

Compliance with SSC bundle

- LACTATE MEASUREMENT: 55%
- FLUID RESUSCITATION: 48%
- BLOOD CULTURES: 29%
- ANTIBIOTICS <3h: 66%
Infectious diseases team for the early management of severe sepsis and septic shock in emergency department

Sara Tedeschi et al

Infectious Disease Unit - Sant’Orsola Hospital, Bologna, Italy
Objective

To assess the impact of the systematic timely involvement of an Infectious Diseases specialist in the management of critically ill patients with infections in the ED on:

1. 30-day mortality (primary objective)

2. Compliance with SSC recommendations

3. Appropriateness of microbiological work-up and antibiotic therapy
Methods

- **Study design:** quasi-experimental pre-post study
- **Setting:** Emergency Department of our 1420-bed teaching hospital in Northern Italy
- **Population:** adult patients accessing the ED with severe sepsis/septic shock
- **Study period:** July 2013 – October 2015
Patients accessing the ED with a suspected or proven infection

**PRE PHASE**
Standard of care

**ED EVALUATION**

↓

Severe sepsis/septic shock diagnosis

↓

RESUSCITATORY BUNDLE
MICROBIOLOGICAL WORK-UP

ANTIBIOTIC THERAPY

**POST PHASE**
Sepsis team intervention

**ED EVALUATION**

↓

Severe sepsis/septic shock diagnosis

↓

RESUSCITATORY BUNDLE
SEPSIS TEAM ACTIVATION

MICROBIOLOGICAL WORK-UP

ED physician

Sepsis Team

ANTIBIOTIC THERAPY
Endpoints

- 30-day mortality

- Proportion of patients undergoing (<3 h from ED admission):
  - Lactate measurement
  - Fluid resuscitation
  - Blood cultures
  - Administration of antibiotics

- Proportion of patients with an etiological diagnosis

- Proportion of patients receiving an appropriate first line antibiotic therapy.

* Appropriateness was assessed by an independent expert, blinded to the study, according to microbiological data, site of infection and epidemiology (CA or HCA infection)
Demographics

382 patients: 195 in the *pre*, 187 in the *post* phase

Median age 82 years (IQR 70-88)

Median Chairson index 6 (IQR 5-8)
Clinical severity

- Severe Sepsis
- Septic Shock

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3).
Singer M et al, JAMA 2016
Sites of infection

- Lung: 43%
- Urinary Tract: 17%
- Intra-abdominal: 8%
- Skin and soft tissues: 5%
- Other sites: 5%
- Unknown: 22%
### Pre vs post phase: study population

<table>
<thead>
<tr>
<th></th>
<th>Pre phase</th>
<th>Post phase</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years) – median (IQR)</strong></td>
<td>84 (73-89)</td>
<td>80 (67-87)</td>
<td>0.009</td>
</tr>
<tr>
<td><strong>Charlson – median (IQR)</strong></td>
<td>7 (6-8)</td>
<td>5 (4-7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Altered mental status – n°(%)</strong></td>
<td>76 (39)</td>
<td>65 (35)</td>
<td>0.393</td>
</tr>
<tr>
<td><strong>Serum lactate &gt; 2 mmol/L – n°(%)</strong></td>
<td>106 (54)</td>
<td>131 (70)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Septic shock – n° (%)</strong></td>
<td>14 (7)</td>
<td>33 (17.6)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Infection site – n° (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>75 (38.5)</td>
<td>89 (48)</td>
<td></td>
</tr>
<tr>
<td>Urinary tract</td>
<td>41 (21)</td>
<td>26 (14)</td>
<td></td>
</tr>
<tr>
<td>Intra-abdominal</td>
<td>14 (7)</td>
<td>16 (9)</td>
<td>0.317</td>
</tr>
<tr>
<td>Skin and soft tissue</td>
<td>11 (5.5)</td>
<td>9 (5)</td>
<td></td>
</tr>
<tr>
<td>Other sites</td>
<td>7 (4)</td>
<td>11 (4.8)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>47 (24)</td>
<td>36 (19.2)</td>
<td></td>
</tr>
</tbody>
</table>
SSC bundle compliance

<table>
<thead>
<tr>
<th>Category</th>
<th>Pre Phase</th>
<th>Post Phase</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate Measurement</td>
<td>76%</td>
<td>90%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fluid Resuscitation</td>
<td>56%</td>
<td>70%</td>
<td>0.004</td>
</tr>
<tr>
<td>Blood Cultures</td>
<td>20%</td>
<td>84%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antibiotics &lt; 3h</td>
<td>42%</td>
<td>58%</td>
<td>0.002</td>
</tr>
<tr>
<td>Etiological Diagnosis</td>
<td>9%</td>
<td>42%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Appropriate 1st Line Antibiotic Therapy</td>
<td>31%</td>
<td>78%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Overall 30-day mortality 41%

**Pre phase**
45%

**Post phase**
37%

$p=0.04$
## Risk factors for mortality

Multivariate Cox regression model adjusted for age, sex and application of SSC bundle

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>HR</th>
<th>95% IC</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown source of infection</td>
<td>1.98</td>
<td>1.39 – 2.83</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Attended during the post phase</td>
<td>0.69</td>
<td>0.50 – 0.97</td>
<td>0.035</td>
</tr>
<tr>
<td>Body temperature &gt; 38.3 o &lt; 36°C</td>
<td>0.6</td>
<td>0.42 – 0.88</td>
<td>0.008</td>
</tr>
<tr>
<td>Serum lactate &gt; 2 mmol/L</td>
<td>1.64</td>
<td>1.14 – 2.35</td>
<td>0.007</td>
</tr>
<tr>
<td>Age</td>
<td>1.01</td>
<td>1.004 – 1.03</td>
<td>0.012</td>
</tr>
<tr>
<td>Septic shock</td>
<td>1.54</td>
<td>1.01 – 2.37</td>
<td>0.045</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>1.71</td>
<td>1.24 – 2.35</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Conclusions

Very old study population, with high overall mortality

The systematic collaboration with ID specialists increased awareness of ED physicians about sepsis identification and proper management and improved patient outcome, also in this difficult population
Aknowledgements

SEPSIS TEAM
- Luciano Attard
- Lorenzo Badia
- Michele Bartoletti
- Alessandra Cascavilla
- Francesco Cristini
- Nicola Dentale
- Giovanni Fasulo
- Maddalena Giannella
- Giorgio Legnani
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