CURRENT GUIDELINES FOR SEPSIS MANAGEMENT

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CONFLICT OF INTEREST DISCLOSURE

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PILLARS OF SEPSIS MANAGEMENT

Haemodynamic therapy

Source control

Antimicrobials

ADJUNCTIVE THERAPY

EARLY START OF ANTIMICROBIALS: MAIN GOAL
A life-threatening organ dysfunction caused by a dysregulated host response to infection.
# Sequential Organ Failure Assessment (SOFA)

<table>
<thead>
<tr>
<th>SOFA score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>pO₂/FiO₂</td>
<td>≥400</td>
<td>&lt;400</td>
<td>&lt;300</td>
<td>&lt;200</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Platelets</td>
<td>≥150</td>
<td>&lt;150</td>
<td>&lt;100</td>
<td>&lt;50</td>
<td>&lt;20</td>
</tr>
<tr>
<td>(x10⁢³ mm³)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin (mg/dl)</td>
<td>&lt;1.2</td>
<td>1.2-1.9</td>
<td>2.0-5.9</td>
<td>6.0-11.9</td>
<td>≥12.0</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>MAP ≥70mmHg</td>
<td>MAP &lt;70mmHg</td>
<td>&lt;5*</td>
<td>≤1**</td>
<td>&gt;1**</td>
</tr>
<tr>
<td>Glasgow Coma Scale</td>
<td>15</td>
<td>13-14</td>
<td>10-12</td>
<td>6-9</td>
<td>&lt;6</td>
</tr>
<tr>
<td>Creatinine (mg/dl) (or urine/day)</td>
<td>&lt;1.0</td>
<td>1.2-1.9</td>
<td>2.0-3.4</td>
<td>3.5-4.9 (&lt;500)</td>
<td>≥5.0 (&lt;200)</td>
</tr>
</tbody>
</table>

*μg/kg/min of dopamine

**μg/kg/min of noerpinephrine
INFECTION SUSPICION

qSOFA (quick SOFA) ≥2

EVALUATE ORGAN DYSFUNCTION

SOFA ≥2 admitted in the ER or increase from the baseline

SEPSIS

Despite fluid resuscitation
- Mean arterial pressure <65mmHg
- Lactate ≥2 mmol/l
- NEED for vasopressors

SEPTIC SHOCK

qSOFA
- Altered mental status
- ≥22 breaths/minute
- Systolic blood pressure <100 mmHg

ER: emergency department
THE OTHER READ-OUT

Survival
Cumulative effective antimicrobial therapy

<table>
<thead>
<tr>
<th>Time (hours) from start of hypotension</th>
<th>% patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-0.99</td>
<td>100</td>
</tr>
<tr>
<td>1-1.99</td>
<td>80</td>
</tr>
<tr>
<td>2-2.99</td>
<td>60</td>
</tr>
<tr>
<td>3-3.99</td>
<td>40</td>
</tr>
<tr>
<td>4-4.99</td>
<td>20</td>
</tr>
<tr>
<td>5-5.99</td>
<td>0</td>
</tr>
<tr>
<td>6-6.99</td>
<td></td>
</tr>
</tbody>
</table>
RESISTANCE PATTERNS: ER ADMISSION
(Koupetori M, et al. BMC Infect Dis 2014; 14: 272)

*\(p<0.05\) between the two periods
## Epidemiology as a Guiding Tool

(Koupetori M, et al. *BMC Infect Dis* 2014; 14: 272)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>OR</th>
<th>95%CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>APACHE II &gt; 13</td>
<td>1.57</td>
<td>0.79-3.09</td>
<td>0.192</td>
</tr>
<tr>
<td>History of COPD</td>
<td>2.61</td>
<td>0.78-8.77</td>
<td>0.120</td>
</tr>
<tr>
<td>Pigtail ureter catheterization</td>
<td>4.67</td>
<td>0.94-23.23</td>
<td>0.060</td>
</tr>
<tr>
<td>Chronic hemodialysis</td>
<td>7.16</td>
<td>1.93-26.54</td>
<td>0.004</td>
</tr>
<tr>
<td>Intake of antibiotics ≤ 3 months</td>
<td>2.48</td>
<td>1.34-4.57</td>
<td>0.004</td>
</tr>
<tr>
<td>Residence in long-term care facility</td>
<td>4.62</td>
<td>2.12-10.10</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
A MULTI-CENTER SIMULATION: THE HELLENIC SEPSIS STUDY GROUP
EMPIRICAL ANTIMICROBIALS OUTSIDE THE ICU WITH SOFA ≤7
- 3rd gen. cephalosporin +/- metronidazole
- Piperacillin/tazobactam
- Carbapenem

EMPIRICAL ANTIMICROBIALS OUTSIDE THE ICU WITH SOFA >8
- Piperacillin/tazobactam +/- colistin +/- glycopeptide
- Carbapenem +/- colistin +/- glycopeptide
INCREASE T>MIC FOR B-LACTAMS

INCREASE THE DOSE

1g q8h
2g q8h

↑↑↑ 25%

MIC

PROLONG INFUSION

1g 0.5H
2g 3H

↑↑↑ 25%

MIC

1g q8h (0.5H)
2g q8h (3H)

↑↑↑ 50%

MIC

BOTH!!!
Colistin methasulfonate is an inactive pro-drug
- Hydrolyzed into active colistin A and colistin B
- MIC_{breakpoint} \leq 2 \mu g/ml (\leq 4 \mu g/ml for P.aeruginosa)
- 3MU (240mg) q8h in 18 critically ill patients

![Serum concentrations after 1st dose](image1)

![Serum concentrations after 4th dose (24h)](image2)
NEED FOR INITIAL LOADING DOSE OF 9MU
UPDATED DOSING REGIMENS TO ACHIEVE PLASMA COLISTIN $C_{ss}$ 2 mg/L

9 million units loading dose to all patients

<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>Daily dose (millions divided into two)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3.95</td>
</tr>
<tr>
<td>5 to &lt;10</td>
<td>4.40</td>
</tr>
<tr>
<td>10 to &lt;20</td>
<td>4.85</td>
</tr>
<tr>
<td>20 to &lt;30</td>
<td>5.30</td>
</tr>
<tr>
<td>30 to &lt;40</td>
<td>5.90</td>
</tr>
<tr>
<td>40 to &lt;50</td>
<td>6.65</td>
</tr>
<tr>
<td>50 to &lt;60</td>
<td>7.40</td>
</tr>
<tr>
<td>60 to &lt;70</td>
<td>8.35</td>
</tr>
<tr>
<td>70 to &lt;80</td>
<td>9.00</td>
</tr>
<tr>
<td>80 to &lt;90</td>
<td>10.3</td>
</tr>
<tr>
<td>≥90</td>
<td>10.9</td>
</tr>
</tbody>
</table>
OPTIONS FOR ADJUNCTIVE THERAPIES IN SEVERE INFECTIONS: SSC 2016

**INTERVENTION**

- Low-dose hydrocortisone replacement in septic shock
- Treatment with IV Igs

**COMMENT**

- Only if hemodynamic stability cannot be achieved (weak recommendation)
- AGAINST preparations of only IgGs
- Weak recommendation of IgM-enriched preparations

THE FRENCH STUDY *(JAMA 2002; 288: 862)*
(START hydrocortisone replacement 3-8 h from onset of hypotension)

(START hydrocortisone replacement <72 h from onset of hypotension)
THE APPROACH OF THE HELLENIC SEPSIS STUDY GROUP (1)

Late: >9hrs from vasopressors (n= 124)
Early: <9hrs from vasopressors (n= 46)

log-rank: 5.553
p: 0.018
THE APPROACH OF THE HELLENIC SEPSIS STUDY GROUP (2)

Late: >9hrs from vasopressors (n= 124)
Early: <9hrs from vasopressors (n= 46)

log-rank: 18.248
p: 0.000019
SEVERE SEPSIS TO SEPTIC SHOCK: 28-DAY MORTALITY

AUC_{SURVIVORS}: 350.1 mg.day/dl
AUC_{NON-SURVIVORS}: 200.6 mg.day/dl
p: 0.037

ARE THERE ALARMING Ig LEVELS? IMMUNOSCORING


- IgG1 ≤300 mg/dl
- IgM ≤ 35 mg/dl
- IgA ≤150 mg/dl

- IgG1 >300 mg/dl
- IgM >35 mg/dl
- IgA >150 mg/dl

![Graph showing cumulative survival over time with IgG1 ≤300 mg/dl, IgM ≤35 mg/dl, and IgA ≤150 mg/dl associated with higher survival compared to IgG1 >300 mg/dl, IgM >35 mg/dl, and IgA >150 mg/dl with a significance level of P = 0.001.](image-url)
META-ANALYSIS OF CLINICAL TRIALS

IgM-enriched IV polyvalent (IgGAM) (12% IgM, 12% IgA, 76% IgG)

RR: 0.66 ↓34% risk for death

IgG IV polyvalent

RR: 0.85 ↓15% risk for death

RR: relative risk
TOTAL NUMBER OF PATIENTS WITH CLINICAL DATA IN THE REGISTRY = 5,143

Step 1: ICU-ACQUIRED INFECTIONS = 1,299

COMPARATORS (from the same hospitals) = 1,077
- Excluded from matching (n=2 neutropenia)

EXCLUDED = 132
- Lack of microbiology = 72
- Incomplete data = 33
- Catheter-related infections = 20
- Neutropenia = 4
- Gram-positive infections = 2
- Primary immunodeficiency = 1

ANALYZED = 100

Step 2: Severe sepsis/Shock = 622

Step 3: MDR Gram-negative = 213

Step 4: Case control matching
- 1:1 matching for sepsis severity
- 1:1 matching for appropriateness of empirical antimicrobial treatment
- Fuzzy matching for source of infection
- Fuzzy matching for CCI

ANALYZED = 100

IgGAM = 232 (ALL Severe sepsis/Shock)

EXCLUDED = 132

ANALYZED = 100

MDR: multidrug-resistant

### MATCHED BASELINE DEMOGRAPHICS

<table>
<thead>
<tr>
<th></th>
<th>Comparators (n= 100)</th>
<th>IgGAM (n= 100)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>54.2 ± 18.4</td>
<td>51.9 ± 18.6</td>
<td>0.399</td>
</tr>
<tr>
<td>Severe sepsis/shock</td>
<td>14/86</td>
<td>14/86</td>
<td>1.000</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>20.7 ± 6.6</td>
<td>19.6 ± 6.9</td>
<td>0.229</td>
</tr>
<tr>
<td>SOFA score</td>
<td>8.9 ± 3.3</td>
<td>10.2 ± 3.3</td>
<td>0.013</td>
</tr>
<tr>
<td>Appropriateness of empirically prescribed antimicrobials</td>
<td>51/49</td>
<td>51/49</td>
<td>1.000</td>
</tr>
<tr>
<td>Primary bacteremia</td>
<td>24</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Ventilator-associated pneumonia</td>
<td>56</td>
<td>63</td>
<td>0.730</td>
</tr>
<tr>
<td>Ventilator-associated pneumonia + bacteremia</td>
<td>18</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Intrabdominal + bacteremia</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Charlson’s comorbidity index</td>
<td>2.86 ± 2.68</td>
<td>2.67 ± 2.43</td>
<td>0.601</td>
</tr>
</tbody>
</table>

PRIMARY ENDPOINT: 28-DAY MORTALITY


Mortality = 39%

Mortality = 58%

OR\textsubscript{death} under IgGAM

0.37 (95%Cls: 0.18-0.76)

log-rank: 6.88

p: 0.009
SECONDARY ENDPOINT 2: EFFECT ON TIME TO BREAKTHROUGH BACTEREMIA*


*A new episode of bloodstream infection in a patient having sterile blood cultures for ≥72 hours.

log-rank: 17.48
p< 0.0001
• Addition of a macrolide for patients with septic shock after *Streptococcus pneumoniae* bacteremia

• Weak recommendation, low quality of evidence
META-ANALYSIS OF 16 OBSERVATIONAL STUDIES
PROSPECTIVE, RANDOMIZED APPROACH

- Community-acquired pneumonia
- Cefuroxime or amoxycillin/clavulanate
- Clarithromycin 500mg bid iv or po
- Monotherapy β-lactam / β-lactam + clarithromycin combination
- Primary endpoint: patients not reaching clinical stability on day 7
- Powered for non-inferiority
BENEFITS OF ADDING CLARITHROMYCIN

Monotherapy (n= 291) Combination (n= 289)

<table>
<thead>
<tr>
<th></th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Instability Day 7</td>
<td>41.2%</td>
</tr>
<tr>
<td></td>
<td>33.6%</td>
</tr>
<tr>
<td>30-day readmission</td>
<td>7.9%</td>
</tr>
<tr>
<td></td>
<td>3.1%</td>
</tr>
</tbody>
</table>

p: 0.070

p: 0.010
200 patients with VAP + Sepsis/Severe Sepsis/Septic Shock (ACCP/SCCM 1992)

100 iv PLACEBO + ANTIBIOTICS**

100 iv CLARITHROMYCIN* + ANTIBIOTICS**

*1000mg iv daily within one hour x 3 days

**Standard of Care
VAP: ventilator-associated pneumonia

www.clinicaltrials.gov (NCT 00297674)
EFFECT ON RESOLUTION OF VAP

- Placebo
- Clarithromycin

% resolved cases

0% 20% 40% 60% 80%

Days

0 4 8 12 16 20 24 28

50%: 10 days
50%: 15.5 days

p: 0.011

www.clinicaltrials.gov (NCT 00297674)
FINAL OUTCOME!!!

log-rank: 4.278
p: 0.043

Survival (%)

57%
40%

MORTALITY DAYS 29-90 (%)
p: 0.001

Placebo
Clarithromycin
REVERSAL OF IMMUNOPARALYSIS

- IL-10/TNFα
  - No Presence of MODS and septic shock: Placebo 10, Clarithromycin 10
  - Yes: Placebo 20, Clarithromycin 30
  - p: 0.040

- IL-6 production by LPS-stimulated monocytes
  - No Presence of MODS and septic shock: Placebo 700, Clarithromycin 900
  - Yes: Placebo 1400, Clarithromycin 2100
  - p: 0.015

- %CD86 on monocytes
  - No Presence of MODS and septic shock: Placebo 50, Clarithromycin 70
  - Yes: Placebo 25, Clarithromycin 35
  - p: 0.024
HOW TO DEAL WITH IN 2018?

• Early broad-spectrum antimicrobials
• Decision based on epidemiology and SOFA scoring
• Intense “work-up” for hemodynamic stability (fluids + vasopressors)
• Adjunctive approaches