Community Acquired Pneumonia

Maximizing the efficacy of antibiotic therapy

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Hospital Vila Franca Xira
Antibiotics and Pneumonia

Survival in Bacteremic Pneumococcal Bacteremia Treated with Penicillin or Serum

[Graph showing the effect of therapy on the percentage survival in pneumococcal bacteremia.]

Austrian Ann Intern Med 1964;60:759

Figure 6. Numbers in parentheses indicate size of each group of patients. Data for untreated and serum-treated patients (capsular Types I and II only) from Tilghman and Finlaud (1).
## Antibiotics and Pneumonia

### Time until start of antibiotic therapy (CAP)

<table>
<thead>
<tr>
<th>Time to First Dose, h</th>
<th>Patients, No.</th>
<th>In-hospital Mortality, % (95% CI)</th>
<th>30-d Mortality, % (95% CI)</th>
<th>30-d Readmission, % (95% CI)</th>
<th>LOS Above the Median (5 d), % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2</td>
<td>3578</td>
<td>7.4 (6.6-8.3)</td>
<td>12.5 (11.5-13.7)</td>
<td>12.6 (11.5-13.8)</td>
<td>43.6 (41.9-45.2)</td>
</tr>
<tr>
<td>&gt;2-4</td>
<td>4810</td>
<td>6.3 (5.6-7.0)</td>
<td>10.9 (10.0-11.8)</td>
<td>13.5 (12.5-14.5)</td>
<td>41.0 (39.6-42.4)</td>
</tr>
<tr>
<td>&gt;4-6</td>
<td>2331</td>
<td>6.9 (6.0-8.1)</td>
<td>11.7 (10.4-13.0)</td>
<td>13.3 (11.9-14.8)</td>
<td>42.9 (40.9-45.0)</td>
</tr>
<tr>
<td>&gt;6-8</td>
<td>1095</td>
<td>7.2 (5.8-8.9)</td>
<td>13.0 (11.0-15.1)</td>
<td>13.1 (11.1-15.3)</td>
<td>46.1 (43.1-49.1)</td>
</tr>
<tr>
<td>&gt;8</td>
<td>1957</td>
<td>8.0 (6.9-9.3)</td>
<td>13.8 (12.3-15.5)</td>
<td>15.0 (13.4-16.8)</td>
<td>47.2 (45.0-49.5)</td>
</tr>
</tbody>
</table>

### Community acquired Sepsis

Enrollment of N = 897 patients, 63% of which had CAP.

Kumar, A Virulence 2014; 5:1

**Graph**: Septic Shock Progression

- Antimicrobial therapy
- Cellular dysfunction/tissue injury
- Inflammatory response
- Shock Threshold
- Toxic burden
- Microbial load

**Graph**: Time to SOFA (CVS) and % of patients

<table>
<thead>
<tr>
<th>TIME</th>
<th>Kumar, A Virulence 2014; 5:1</th>
<th>% 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>30</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>2</td>
</tr>
</tbody>
</table>
Antibiotics and Pneumonia

Pneumonia Bundle

Wiemken Semin Respir Crit Care Med 2012;33:213
## Early antibiotics and outcome

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Setting</th>
<th>Odds Ratio (death)</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Groot (Critical Care Med 2015; 19:194)</td>
<td>1168</td>
<td>3 ED</td>
<td>No difference independent of PIRO score</td>
</tr>
<tr>
<td>Hranjec (Lancet Infect Dis 2012; 12:774)</td>
<td>201</td>
<td>Surgical ICU: Before - after</td>
<td>Aggressive antibiotic therapy – OR for mortality 2.5</td>
</tr>
<tr>
<td>Puskarich (Crit Care Med 2011; 39:1206)</td>
<td>372</td>
<td>Hospital-acquired surgical infections</td>
<td>No difference in mortality up to 6h after diagnostic delay</td>
</tr>
<tr>
<td>Villela (Am J Emerg Med 2014; 32:7)</td>
<td>184</td>
<td>ED admitted to the ICU</td>
<td>No improvement with decrease in time to antibiotics (5h to 3h)</td>
</tr>
<tr>
<td>Pelletier (Surg Infect [Larchmont] 1999; 134:1300)</td>
<td>372</td>
<td>Surgical patients</td>
<td>No difference 0h, &gt;12h, &gt;24h</td>
</tr>
<tr>
<td>Castellanos-Ortega (Crit Care Med 2010; 38:1036)</td>
<td>480</td>
<td>ED: Before - after</td>
<td>Early antibiotics OR 0.68, p=0.11</td>
</tr>
<tr>
<td>Davies (Shock 2014; 42:185)</td>
<td>7158</td>
<td>Surgical patients</td>
<td>Inappropriate vs. appropriate OR 1.0</td>
</tr>
</tbody>
</table>

No difference in a metanalysis (11 studies included). OR 1.16
Over 50% of patients with suspected pneumonia probably did not have infection

Antibiotics are of no use if patients are not infected (harm?)
Antibiotics and Pneumonia

Pneumonia Bundle

- Better diagnostic tools
- Early directed therapy
- Adequate dose

- Minimize antibiotic exposure
- Reassess diagnostic
- PK and antibiotic dose
- Response to therapy
Pharmacokinetics

- Absorption
- Distribution
- Elimination

PK: Concentration at Infection Site
PD: Effect of the antibiotic at the site of infection

Bacterial Killing
Toxicity

Dose antibiotics to maximize its exposure to bacteria

Craig WA - CID 1998; 26.1
Patterns of Antimicrobial Activity

Concentration

$C_{\text{max}}$  

Aminoglycosides
Metronidazol

Area under the concentration

Azithromycin
Fluoroquinolones
Glycopeptides

Beta-lactams
Carbapenems

$T>MIC$

Log$_{10} \text{CFU/mL}$

MIC

Time (hours)

Concentration

$C_{\text{max}}$

Aminoglycosides
Metronidazol

Area under the concentration

Azithromycin
Fluoroquinolones
Glycopeptides

Beta-lactams
Carbapenems

$T>MIC$

Log$_{10} \text{CFU/mL}$

MIC

Time (hours)
Antibiotics in critically ill patients: a systematic review of the pharmacokinetics of β-lactams

- Two fold variability of PK parameters (Vd and Cl)
- Usually increase
- No clear correlation with clinical parameters

Augmented Volume of Distribution

Augmented renal Clearance

Meropenem

Imipenem

Piperacillin

Cefpirome

Cefepime

Ceftazidime

Udy, Baptista Crit Care Med 2014; 42:520
## Dose of Antibiotics

### Obesity

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted OR (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Sex (Reference: Male)</td>
<td>0.88 (0.76–1.03)</td>
<td>0.106</td>
</tr>
<tr>
<td>2. Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–34 yrs</td>
<td>1.00 (0.78–1.27)</td>
<td>0.974</td>
</tr>
<tr>
<td>35–49 yrs</td>
<td>1.03 (0.84–1.26)</td>
<td>0.812</td>
</tr>
<tr>
<td>50–64 yrs</td>
<td>0.99 (0.82–1.20)</td>
<td>0.954</td>
</tr>
<tr>
<td>65–70 yrs (Reference)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Socioeconomic Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Income</td>
<td>1.00 (0.85–1.17)</td>
<td></td>
</tr>
<tr>
<td>Middle Income (Reference)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Income</td>
<td>0.78 (0.56–1.09)</td>
<td></td>
</tr>
<tr>
<td>4. BMI Category</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (Reference)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>1.06 (0.89–1.26)</td>
<td></td>
</tr>
<tr>
<td>Obese</td>
<td>1.26 (1.03–1.55)</td>
<td></td>
</tr>
<tr>
<td>5. Alcohol Consumption</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-drinker</td>
<td>1.20 (1.01–1.42)</td>
<td></td>
</tr>
<tr>
<td>Moderate (Reference)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy</td>
<td>0.98 (0.72–1.29)</td>
<td></td>
</tr>
<tr>
<td>6. MRSA</td>
<td>2.33 (1.78–3.03)</td>
<td></td>
</tr>
<tr>
<td>7. History of Antibiotic Use</td>
<td>1.27 (1.03–1.57)</td>
<td></td>
</tr>
</tbody>
</table>

**KEY POINTS**

- Of the 828 (13.4%) persons who suffered an antibiotic treatment failure (ATF) event, nearly 64% were either overweight or obese.
- Significant predictors of ATF were obesity, antibiotic resistance, recent history of antibiotic use, and being a non-drinker.
- Alternative antibiotic dosing strategies may be necessary when treating obese patients for acute infections as a means of reducing the risk of ATF.

Patterns of Antimicrobial Activity
MIC and resistance

- Increase in MIC 0.5 → 1mg/L: Bacteria remain sensitive.
- However AUC:MIC and Cmax:MIC decrease to one half; T>MIC also decreases
- Changes in PK may impact clinical efficacy
Bacterial load and mortality

Pneumococcal Pneumonia \( n = 353 \)

Rt-PCR positive – 26.3% (36.5% positive BC)

Septic shock – OR 6.29
Mech. Ventilation – OR 7.96
Mortality – OR 7.08

Patients with positive Rt-PCR
Bacterial Load > \( 10^3 \) cop/mL (29%)
Shock OR 8 Mech. Vent OR 10.5
Mortality OR 5.4

Rello Chest 2009;136:832
Selection of initial antibiotics

Single vs. double

Use of a macrolide in CAP

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Risk Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Risk Ratio IV, Random, 95% CI</th>
<th>Risk Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arnold 2013</td>
<td>-0.713</td>
<td>0.199</td>
<td>15.0%</td>
<td>0.49 [0.33, 0.72]</td>
<td></td>
</tr>
<tr>
<td>Bratzler 2008</td>
<td>0.135</td>
<td>0.663</td>
<td>3.1%</td>
<td>1.00 [0.27, 3.67]</td>
<td></td>
</tr>
<tr>
<td>Bratzler 2008</td>
<td>-0.357</td>
<td>0.212</td>
<td>14.3%</td>
<td>0.70 [0.46, 1.06]</td>
<td></td>
</tr>
<tr>
<td>Karhu 2013</td>
<td>0.307</td>
<td>0.402</td>
<td>6.9%</td>
<td>1.36 [0.62, 2.99]</td>
<td></td>
</tr>
<tr>
<td>Martin–Loeches 2010</td>
<td>-0.73</td>
<td>0.37</td>
<td>7.8%</td>
<td>0.48 [0.23, 1.00]</td>
<td></td>
</tr>
<tr>
<td>Rodrigo 2013</td>
<td>-0.062</td>
<td>0.135</td>
<td>18.8%</td>
<td>0.94 [0.72, 1.22]</td>
<td></td>
</tr>
<tr>
<td>Shorr 2013</td>
<td>-1.298</td>
<td>0.506</td>
<td>4.9%</td>
<td>0.27 [0.10, 0.74]</td>
<td></td>
</tr>
<tr>
<td>Sligl 2013</td>
<td>-0.131</td>
<td>0.337</td>
<td>8.8%</td>
<td>0.88 [0.45, 1.70]</td>
<td></td>
</tr>
<tr>
<td>Wilson 2012</td>
<td>-0.049</td>
<td>0.108</td>
<td>20.4%</td>
<td>0.95 [0.77, 1.18]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td>100.0%</td>
<td>0.75 [0.58, 0.96]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\text{Tau}^2 = 0.07$; $\chi^2 = 18.68$, df = 8 ($P = 0.02$); $I^2 = 57$

Test for overall effect: $Z = 2.31$ ($P = 0.02$)

Sligl Crit Care Med 2014; 42:420
Selection of initial antibiotics

Single vs. double

The CAPUCI study

Shock

Survival HR 1.69 (95%CI 1.09-2.6)

No Shock

p = 0.99

Macrolides

Death HR 0.48 (95%CI 0.23-0.97)

Rodriguez Crit Care Med 2007;35:1493

Martin-Loeches Intensive Care Med 2010; 36:612
Dose of Antibiotics

Clinical Success by PSI Class

 Patients in Each PSI

*Clinically evaluable patients at the 7- to 14-day post therapy visit

Dunbar Clin Infect Dis. 2003;37:752
PK/PD guided dose

- Lower adjusted 90d mortality (p=0.02)
- Lower LOS (3.9 vs. 5d, p<0.001)
- Lower Costs ($2485 vs. $3281, p=0.02)
A Multicenter Randomized Trial of Continuous versus Intermittent β-Lactam Infusion in Severe Sepsis

Joel M. Dulhunty¹,², Jason A. Roberts¹,²,³, Joshua S. Davis⁴,⁵, Steven A. R. Webb⁶,⁷, Rinaldo Bellomo⁸,⁹, Charles Gomersall¹⁰,¹¹, Charudatt Shirwadkar¹², Glenn M. Eastwood⁸, John Myburgh¹³,¹⁴, David L. Paterson¹⁵,¹⁶, Therese Starr¹,², Sanjoy K. Paul¹⁷, and Jeffrey Lipman¹,²; for the BLING II Investigators for the ANZICS Clinical Trials Group

Clinical success

Cefepime or ceftazidime

- AUIC≥250
  Cure 79% vs. 33%; \( P = 0.002 \)

- >MIC of 100%
  Cure 82% vs. 33%; \( P = 0.002 \)

Dulhunty Am J Resp Crit Care Med 2015; 192: 1298


HR 0.91 (0.63-1.31)

Dulhunty Am J Resp Crit Care Med 2015; 192: 1298
Optimization of minimum concentration/MIC ratio

Placebo

T>MIC=100% & Cmin/MIC=10

T>MIC=84%

T>MIC=100% Cmin/MIC=1.7+ tobramycin

Tam Antimicrob Agents Chemother 2005; 49. 4920
Dose modulation: A new concept of antibiotic therapy in the critically ill patient?

Joao Goncalves-Pereira MD, José-Artur Paiva MD, PhD

Critical ill septic patient

- Large Volume of Distribution

Renal or Hepatic failure

- Initial High Dose
  - No
  - Yes

Increased Clearance
(measure Cr Clearance)

Maintain High Dose

Reassess after 48-72h

Any of:
- Bacteria with a low MIC
- Normalization of (measured) Cr Clearance
- Sepsis resolution

Adjust Dose accordingly

- Large volume resuscitation
- Invasive Ventilation
- Surgical procedure

Accumulation and Toxicity

Ceftriaxone 2 g/d – Increase 2-3* from D1 to D7

<table>
<thead>
<tr>
<th>Cr Cl</th>
<th>&gt;50 mL/min</th>
<th>&lt;50 mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>19.5 μg/mL</td>
<td>46.5 μg/mL</td>
</tr>
<tr>
<td>Day 7</td>
<td>38.5 μg/mL</td>
<td>125 μg/mL</td>
</tr>
</tbody>
</table>

Heinemeyer Int Care Med 1990; 16; 448

Betalactamin-induced central nervous side effects include confusion, disturbances of behaviour, hallucinations, asterixis, myoclonic jerks, and generalised convulsive or nonconvulsive seizures. Those are probably underreported but may contribute to morbidity and mortality.

Chatellier Int Care Med 2002; 28. 214

May promote mitochondrial damage and shutdown.

May interfere with mitochondrial biogenesis and delay recovery.

Chatellier Int Care Med 2002; 28. 214

# Duration of Antimicrobial Activity

## Reduction of Exposure

<table>
<thead>
<tr>
<th>Study</th>
<th>Antimicrobial Agent</th>
<th>Duration</th>
<th>Clinical Cure</th>
<th>Bacteriological Outcome</th>
<th>Radiological Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siegel et al (1999, [10])</td>
<td>Cefuroxime 750mg q8h IV, 2d, then cefuroxime axetil 500mg q12 PO, 5d, 7d in total</td>
<td>52</td>
<td>No difference in clinical cure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leophonte et al (2002, [11])</td>
<td>Ceftriaxone 1g IV qd, 5d</td>
<td>244</td>
<td>No difference in clinical cure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dunbar et al (2003, [12])</td>
<td>Levofloxacin 750mg IV/PO qd, 5d</td>
<td>528</td>
<td>No difference in clinical cure and bacteriological outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dunbar et al (2004, [13])</td>
<td>Levofloxacin 750mg IV/PO qd, 5d</td>
<td>149</td>
<td>Noninferiority in clinical cure and bacteriological outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leophonte et al (2004, [14])</td>
<td>Levofloxacin 500mg IV/PO qd, 10d</td>
<td></td>
<td>Difference in clinical, bacteriological, and radiological efficacy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tellier et al (2004, [15])</td>
<td>Telithromycin 800mg PO qd, 5d</td>
<td>378</td>
<td>No difference in clinical cure and bacteriological outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tellier et al (2004, [15])</td>
<td>Telithromycin 800mg PO qd, 5d or 7d</td>
<td>559</td>
<td>No difference in clinical cure and bacteriological outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>El Moussaoui et al (2006, [16])</td>
<td>Amoxicillin 1g IV q6h, 3d</td>
<td>119</td>
<td>Noninferiority in clinical and radiological success</td>
<td></td>
<td></td>
</tr>
<tr>
<td>File et al (2007, [17])</td>
<td>Gemifloxacin 320mg PO qd, 5d</td>
<td>510</td>
<td>Non-inferiority in clinical, bacteriological, and radiological efficacy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**3-7 d vs. 7-10 d**

No difference in outcomes
"I see no hope for the future of our people if they are dependent on the frivolous youth of today, for they are reckless beyond words. When I was young, we were taught to be discreet, respectful of elders, but the present youth are exceedingly disrespectful and impatient."

Hesiod, 700 BC