Community Acquired Pneumonia

Maximizing the efficacy of antibiotic therapy

João Gonçalves Pereira, MD, PhD
ICU Director
Hospital Vila Franca Xira
Antibiotics and Pneumonia

Survival in Bacteremic Pneumococcal Bacteremia Treated with Penicillin or Serum

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 Tilton and Finegold (1).

Austrian Ann Intern Med 1964;60:759
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

Septic Shock Pathogenesis

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

Shock Threshold

Kumar, A Virulence 2014; 5:1
Antibiotics and Pneumonia

Pneumonia Bundle

Antibiotics and Pneumonia

►

Figure 6

Antibiotics and Pneumonia

Antibiotics and Pneumonia

Antibiotics and Pneumonia

Antibiotics and Pneumonia

Antibiotics and Pneumonia

Antibiotics and Pneumonia

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Antibiotics and Pneumonia
Early antibiotics and outcome

No difference in a metanalysis (11 studies included). OR 1.16

Table 5

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Setting</th>
<th>Odds Ratio (death)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gaiske (Crit Care Med 2010; 38:1036)</td>
<td>1.30</td>
<td>Surgical ICU</td>
<td>1.30 (0.70, 2.38)</td>
</tr>
<tr>
<td>Puskarich (Crit Care Med 2010; 38:1036)</td>
<td>0.51</td>
<td>Multi-centre</td>
<td>0.51 (0.22, 1.10)</td>
</tr>
<tr>
<td>Vilella (Am J Emerg Med 2014; 32:7)</td>
<td>0.79</td>
<td>Whole hospital</td>
<td>0.79 (0.35, 1.73)</td>
</tr>
<tr>
<td>Joo (2015)</td>
<td>1.54</td>
<td>Surgical ICU</td>
<td>1.54 (0.99, 2.39)</td>
</tr>
<tr>
<td>Bruce (2015)</td>
<td>1.24</td>
<td>Multicentre</td>
<td>1.24 (0.49, 2.96)</td>
</tr>
<tr>
<td>Pooled OR</td>
<td>1.16</td>
<td>Whole hospital</td>
<td>1.16 (0.92, 1.46)</td>
</tr>
</tbody>
</table>

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Sterling Crit Care Med. 2015;43:1907
João G. Pereira

Infection (probable/definite) was associated with a lower mortality (SHR 0.81; 95% CI 0.67–0.97). This means that patients with a confirmed infection diagnosis actually have a lower mortality rate than patients with an unconfirmed infection or an alternative diagnosis. Cause-specific analysis revealed that this reduction was caused by a direct effect on death (CSHR 0.73; 95% CI 0.61–0.89), and not by the indirect effect on a longer ICU length of stay (CSHR 0.93; 95% CI 0.85–1.02). In subgroup analyses, the mortality hazard for each hospital was similar (hospital A: SHR 0.80, 95% CI 0.62–1.03; hospital B: SHR 0.85, 95% CI 0.63–1.13). These estimates were similar when restricting our analysis to cases with none or definite infections only (SHR 0.75, 95% CI 0.55–1.01). Furthermore, the prevalence of the adult respiratory distress syndrome, the prevalence of acute kidney injury, and the length of stay significantly increased with greater infection likelihoods (p < 0.001), whereas the occurrence of ICU-acquired infections did not (p = 0.36) (Fig. 3).

Discussion

We determined the accuracy of the infection diagnosis made by clinicians in the context of presumed sepsis upon admission to the ICU and found that up to 43% of patients treated for sepsis were unlikely to have had an infection on post-hoc assessment. Although the accuracy of the infection diagnosis increased with increasing severity of disease, a considerable proportion of patients with severe sepsis and septic shock still had at most a possible infection. These results show that making an accurate infection diagnosis upon ICU admission in patients with suspected sepsis is difficult in many cases.

Our study is the first prospective comparison of sepsis diagnoses made by ICU physicians and post-hoc analyses of infection likelihoods based on strict diagnostic criteria, revealing that the true incidence of sepsis upon ICU admission is probably overestimated. Only few previous studies have specifically investigated the accuracy of infection diagnoses in patients with suspected sepsis in the ICU. A French study found that 49% of patients were potentially unnecessarily treated for a new infection on the ICU [16]. This finding was based on the level of microbiological evidence and not on well-defined diagnostic criteria, however, making it difficult to appreciate the true percentage of patients without infection in post-hoc analysis. Another study explored the correlation of clinical certainty at the start of antimicrobial therapy with the post-hoc presence of infection [17]. The primary aim of this latter investigation focused on antimicrobial use, namely how often administration of antimicrobials for suspected infection could be justified by the presence of infection; a large proportion of patients treated with empirical antibiotics (58 of the 125; 46%) actually had no infection according to the infectious diseases specialist in the post-hoc assessment [17].

In crude analysis, the likelihood of infection in patients treated for suspected sepsis was not associated with mortality. Since several factors that impact on ICU mortality were unequally distributed between groups, we performed multivariable survival analysis and found that a lower likelihood of infection was associated with increased mortality. In other words, patients who were initially treated for sepsis but had, in retrospect, a...

Fig. 1 Plausibility of infection stratified by clinical severity upon presentation in patients with presumed “sepsis” upon presentation to the ICU.

Fig. 2 Plausibility of infection in patients with presumed sepsis upon presentation for the most frequent sites of infection. Distribution of plausibility of infection for lung infections (community-acquired pneumonia and hospital-acquired pneumonia), abdominal infections (primary and secondary peritonitis), bloodstream infections (primary bloodstream infections, catheter-related bloodstream infections, and endocarditis), urinary tract infections, and skin/soft tissue infections.

Klein Klouwenberg Crit Care 2015;19:319

- 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

1. Arrival to ED
2. Microbiological work-up
3. Time to clinical stability

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

Antimicrobial Therapy: Therapy or Targeted Therapy

- Optimal empirical therapy in regard to antibiotic selection
- Global Changes in the Epidemiology of Community-Acquired Pneumonia
- Several of the CAPO quality indicator data suggest the need to
  - Minimize antibiotic exposure
  - Prolonged antibiotic timing is associated with worse outcomes, initial antibiotics should be administered
  - Immune modulation in hospital-patients with CAP continues to be the optimal use of
  - As an example, the production of exotoxins from CA-MRSA is considered a primary virulence mechanism of this organism
  - Based on this knowledge of pathogen virulence may allow us to implement
  - Several of the CAPO quality indicator data suggest the need to
  - The primary approach to improve outcomes in hospital-patients with pneumonia.

Clinical Outcomes Weeks after Hospitalization

- Empirical therapy in concordance with guidelines
- Optimal empirical therapy in regard to antibiotic selection
- Immune modulation in hospital-patients with CAP continues to be the optimal use of
- Immune modulation in hospital-patients with CAP continues to be the optimal use of
- Immune modulation in hospital-patients with CAP continues to be the optimal use of
- Immune modulation in hospital-patients with CAP continues to be the optimal use of
Antimicrobial dose
Pharmacokinetics

Absorption
Distribution
Elimination

Antibiotics

PK

Concentration at Infection Site

PD

Effect of the antibiotic at the site of infection

Bacterial Killing
Toxicity

Pathogen MIC/MBC

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

$T > \text{MIC}$

Beta-lactams

Carbapenems

$T > \text{MIC}$

Beta-lactams

Carbapenems

$T > \text{MIC}$

Beta-lactams

Carbapenems

$T > \text{MIC}$

Beta-lactams

Carbapenems

$T > \text{MIC}$

Beta-lactams

Carbapenems

$T > \text{MIC}$

Beta-lactams

Carbapenems
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

<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 (0.85–1.26)</td>
<td>0.971</td>
</tr>
<tr>
<td>Middle Income (Reference)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>High Income</td>
<td>0.78 (0.56–1.07)</td>
<td>0.139</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 (0.89–1.24)</td>
<td>0.373</td>
</tr>
<tr>
<td>Obese</td>
<td>1.26 (1.03–1.54)</td>
<td>0.024</td>
</tr>
<tr>
<td>5. Alcohol Consumption</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-drinker</td>
<td>1.20 (1.01–1.43)</td>
<td>0.036</td>
</tr>
<tr>
<td>Moderate (Reference)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Heavy</td>
<td>0.98 (0.72–1.34)</td>
<td>0.883</td>
</tr>
<tr>
<td>6. MRSA</td>
<td>2.33 (1.78–3.02)</td>
<td>0.000</td>
</tr>
<tr>
<td>7. History of Antibiotic Use</td>
<td>1.27 (1.08–1.49)</td>
<td>0.002</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.

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</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><strong>0.75 [0.58, 0.96]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: 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

No Shock

Survival HR 1.69 (95%CI 1.09-2.6)

Rodriguez Crit Care Med 2007;35:1493

Macrolides

Death HR 0.48 (95%CI 0.23-0.97)

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

Clinical Success by PSI Class

![Graph showing clinical success by PSI class with data points and patient counts.]

- **Class I/II**: 93.4% (n=122) (750 mg) vs 96.2% (n=106) (500 mg)
- **Class III**: 89.8% (n=49) (750 mg) vs 86.3% (n=51) (500 mg)
- **Class IV**: 92.6% (n=27) (750 mg) vs 84.4% (n=32) (500 mg)

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

Dunbar Clin Infect Dis. 2003;37:752
A clinical pathway for community-acquired pneumonia: an observational cohort study

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)

Frei, BMC Infect Dis 2011,11: 188
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
- T>MIC of 100%
  Cure 82% vs. 33%; P = 0.002

AUIC/4H: ACHILLES
HR 0.91 (0.63-1.31)

Patients with severe sepsis, there was no difference in 3-lactam antibiotic administration between continuous and intermittent infusion.
Optimization of minimum concentration/MIC ratio

Placebo

$T > \text{MIC} = 100\%$ & $C_{\text{min}}/\text{MIC} = 10$

$T > \text{MIC} = 84\%$

$T > \text{MIC} = 100\%$ & $C_{\text{min}}/\text{MIC} = 1.7+$ tobramycin

Log 10 cfu/mL

Time (days)

Wild type

Amp C mutant

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
  - No
  - Yes

- Vasopressors
- ↑ Cardiac output
- ↑ Diuresis

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

Abstract

Several authors also pointed out that not only should antibiotic therapy be appropriate and early but also antibiotic concentration may be insufficient early in infection and, in our opinion, did not translate into the clinical arena. However, the concept of dose maximization is ill-defined and, in our opinion, did not translate into the clinical arena.

Considerable evidence has shown that adequate antibiotic therapy is of utmost importance in antibiotic de-escalation, meaning that a large-spectrum antibiotic regimen should immediately be started front-line to assure coverage of the pathogen and clinical success. Therefore, dose modulation means concentrating the largest weight of antibiotics according to patient and microorganism characteristics, followed by its reduction after clinical response and patient recovery. Therefore, dose modulation means concentrating the largest weight of antibiotics according to patient and microorganism characteristics, followed by its reduction after clinical response and patient recovery.

• Vasopressors
• ↑ Cardiac output
• ↑ Diuresis

Keywords:
- Antibiotics
- Pharmacokinetics
- Intensive care unit
- Cardiac

Corresponding author. Unidade de Cuidados Intensivos Polivalente, São Francisco Xavier Hospital, CHLO, Estrada do Forte do Alto do Duque, 005 Lisboa, Portugal. Tel.: +351 21 043 1104/5; fax: +351 21 043 1301.

E-mail addresses:
- E-mail addresses:
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.

### Table 1. RCTs on Antimicrobial Duration in Typical Infectious Diseases in Adults, Divided by Year of Publication and Type of Infection

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Type of Infection</th>
<th>Treatment Regimen of comparator</th>
<th>N</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siegel et al (1999, [10])</td>
<td>AP</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>
</tr>
<tr>
<td>Leophonte et al (2002, [11])</td>
<td>AP</td>
<td>Ceftriaxone 1g IV qd, 5d</td>
<td>244</td>
<td>No difference in clinical cure</td>
</tr>
<tr>
<td>Dunbar et al (2003, [12])</td>
<td>AP</td>
<td>Levofloxacin 750mg IV/PO qd, 5d</td>
<td>528</td>
<td>No difference in clinical cure and bacteriological outcome</td>
</tr>
<tr>
<td>Dunbar et al (2004, [13])</td>
<td>AP</td>
<td>Levofloxacin 750mg IV/PO qd, 5d</td>
<td>149</td>
<td>Noninferiority in clinical cure and bacteriological outcome</td>
</tr>
<tr>
<td>Leophonte et al (2004, [14])</td>
<td>AP</td>
<td>Levofloxacin 750mg IV/PO qd, 5d</td>
<td>378</td>
<td>No difference in clinical cure and bacteriological outcome</td>
</tr>
<tr>
<td>Tellier et al (2004, [15])</td>
<td>AP</td>
<td>Telithromycin 800mg PO qd, 5d</td>
<td>559</td>
<td>No difference in clinical cure and bacteriological outcome</td>
</tr>
<tr>
<td>El Moussaoui et al (2006, [16])</td>
<td>AP</td>
<td>Amoxicillin 1g IV q6h, 3d, then amoxicillin 750mg PO q8h, 5d, 8d in total</td>
<td>119</td>
<td>Noninferiority in clinical and radiological success</td>
</tr>
<tr>
<td>File et al (2007, [17])</td>
<td>AP</td>
<td>Gemifloxacin 320mg PO qd, 5d</td>
<td>510</td>
<td>Non-inferiority in clinical, bacteriological, and radiological efficacy</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