Why monitoring β-lactams on line?

Paul M. Tulkens, MD, PhD

on behalf the

Louvain Drug Research Institute &
the Louvain Toxicology and Applied Pharmacology

Université catholique de Louvain,
Brussels, Belgium

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The problem ... #1 of many ...

1. Infections are (most often) treated with an antibiotic dosing regimen related to the severity of the disease rather than the susceptibility of the micro-organism ...

<table>
<thead>
<tr>
<th>Cephalosporin</th>
<th>Usual Dose</th>
<th>Adults</th>
<th>Severe Disease</th>
<th>Children</th>
<th>Usual Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefazolin</td>
<td>0.5-1 g q6-12h</td>
<td>2 g q6-8h</td>
<td></td>
<td>12.5-33 mg/kg q6-8h</td>
<td></td>
</tr>
<tr>
<td>Cephalexin</td>
<td>0.5-1 g q6h</td>
<td>2 g q4-6h</td>
<td></td>
<td>20-25 mg/kg q6h</td>
<td></td>
</tr>
<tr>
<td>Cephapirin</td>
<td>0.5-1 g q6h</td>
<td>2 g q4-6h</td>
<td></td>
<td>10-20 mg/kg q6h</td>
<td></td>
</tr>
</tbody>
</table>

What is a "severe disease"?
Problem ... #2 (of many)

2. Clinicians tend to ask (and clinical microbiologists to provide only) "S – I – R" answers based on accepted breakpoints …

But, what is a breakpoint?
EUCAST * breakpoints

Clinically Susceptible (S)
- level of antimicrobial activity associated with a high likelihood of therapeutic success

Clinically Intermediate (I)
- level of antimicrobial activity associated with indeterminate therapeutic effect

Clinically Resistant (R)
- level of antimicrobial activity associated with a high likelihood of therapeutic failure.

A microorganism is categorized as S, I or R by applying the appropriate breakpoint in a defined phenotypic test system.

Clinical breakpoints are presented as $S < x \text{ mg/L} ; \ I > x, \leq y \text{ mg/L} ; \ R > y \text{ mg/L}$

where mg/L is the Minimal Inhibitory Concentration (MIC) in broth (microdilution)

* EUCAST: European Committee for Antimicrobials Susceptibility Testing
## EUCAST breakpoints

### Enterobacteriaceae

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MIC breakpoint (mg/L)</th>
<th>S ≤</th>
<th>R &gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillins¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td></td>
<td>8⁴</td>
<td>16⁴</td>
</tr>
<tr>
<td>Cephalosporins¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefepime</td>
<td></td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td></td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Carbapenems¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imipenem²</td>
<td></td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Meropenem</td>
<td></td>
<td>2</td>
<td>8</td>
</tr>
</tbody>
</table>

what do you do with that?
In the good old time…

Good !!

mean serum concentration

MIC (mg/L)
Still good old time ....

Still Easy...

Good !!

mean serum concentration

Bad !!

MIC (mg/L)

0.125 0.25 0.5 1 2 4 8 16 32 64 128 256
But now, what do you do with this?

No longer so easy...

mean serum concentration

May be?
Which pharmacokinetic parameter drives the activity of β-lactams?

Time during which the free concentration remains > MIC

$ft > CMI$

Free serum concentration (mg/L)

Time after administration (h)
Solution for $\beta$-lactams: $fT > MIC$…

You know it is "free time above MIC", but…

- The same for all beta-lactams? (Free fractions of the drug $[Fu]$)?
- The same for all micro-organisms?
- The same for all infections?
- Can you apply to all patients?
- How much / How frequent? (Static dose vs maximum effect?)
Solution for β-lactams: T > MIC…

You know it is "time above MIC", but…

- The same for all beta-lactams?  
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- The same for all micro-organisms?
- The same for all infections?
- **Can you apply to all patients?**
- How much / How frequent?  
  (Static dose vs maximum effect?)
There are variations of PK in individuals...

Concentration-time profile of a beta-lactam in volunteers

\( V_d = 20 \text{ L}, \ k_a = 1.2 \text{ h}^{-1}, \ k_e = 0.3 \text{ h}^{-1} \)

Unlike the Belgian 400 m run team, we are not all (almost) equal
What is, indeed, a standard patient?
Variation of PK in individuals…

Concentration-time profile of a beta-lactam in patients with a simulation with a coefficient var. of 20 %

Mouton, Int J Antimicrob Agents April 2002
Variation of PK in individuals...

Concentration-time profile of a beta-lactam in patients with a simulation with a coefficient var. of 20%

You must STRATIFY

What is, indeed, a standard patient?

You must stratify according to the patient.
But even then, serum levels remain difficult to predict with accuracy…

Continuous Infusion of Ceftazidime (4 g/day) vs Conventional Schedule and Dosis (3 X 2 g/day) for Treatment of Ventilator-associated Pneumonia in Intensive Care Units.

Cliniques universitaires St-Luc & Université catholique de Louvain, Brussels; Akademische Ziekenhuis, Vrije Universiteit Brussel, Brussels; Clinique St-Pierre, Ottignies; Clinique St Joseph, Arlon; Belgium.

• target level: 24 mg/L (max. MIC: 6 mg/L [EUCAST bkpt = 8 mg/L])
• loading dose: 10.8 mg/kg (assumed Vd: 0.4 L/kg)
• infusion: 4 g/day
• assumed clearance: 102 ml/min (6.12 L/h)
• drug diluted in 48 ml of water
• infusion through motor-operated syringe at a rate of 2 ml/h;
• temperature 25°C or lower

patients with continous administration of ceftazidime

- ICAAC 2002 Poster no. A1 1402
Solution for $\beta$-lactams: $T > \text{MIC}$…

You know it is "time above MIC", but…

- The same for all beta-lactams? (Free fractions of the drug [$Fu$]?)?
- The same for all micro-organisms?
- The same for all infections?
- Can you apply to all patients?
- How much / How frequent? (Static dose vs maximum effect?)
How much time above MIC?

- cefotaxime
- neutropenic mice
- *K. pneumoniae*
- pulmonary infection

100% - Maximal effect?
It all depends on your patient!

- Moderately severe infection in a non-immunosuppressed patient (40%)
- Severe infection in an immunosuppressed patient (100%)

Log$_{10}$ cfu per lung at 24 hours vs. Time above MIC (%)
It all depends on your patient!

40% Moderately severe infection in a non-immunosuppressed patient

Severe infection in an immunosuppressed patient

You must STRATIFY according to the risk

100%?
And do not forget about changes in MIC (low-level resistance) during treatment!

Change in MIC of antibiotics used in empiric antipseudomonal therapy (nosocomial pneumonia; intensive care units) towards the isolate identified before onset of therapy (D0) vs. the last isolate (DL) collected from the same patient and with clonal similarity with the first isolate. Differences were analyzed using both raw and log2 transformed data and found significant by both non-parametric (Wilcoxon matched pair test) and parametric (two-tailed paired t-test) analysis.

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As a result, monitoring the serum level of β-lactams has been proposed ...
But available methods are slow and complex, and do not measure the free concentration ...
A clinical algorithm or a path to success...

Pathology and epidemiology → Knowledge or ou “educated” suspicion of the causative agent → Local MIC data

Is the organism probably highly susceptible?

- yes → Use common dosage but with attention to PK/PD
- no → Obtain an MIC and free serum levels
  - S / I / R is insufficient!!
  - Adjust the dosage on a full PK/PD basis and continue monitoring free blood levels
Back-up
But even then, serum levels remain are difficult to predict with accuracy…

patients with continuous administration of ceftazidime

Mouton, unpublished