Looking into the future: routine TDM for beta-lactams in ICU?

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Do we have a problem?

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 ...
Problem ... #2 (of many)

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

But, what is a breakpoint?
In the good old time...

MIC (mg/L)

0.125 0.25 0.5 1 2 4 8 16 32 64 128 256

mean serum concentration

Good!!
No so old but still good time ....

Still Easy

MIC (mg/L)

Good !!

effective serum concentration

Bad !!
Still good old time ....

This is why microbiologists used the 2-fold dilution progression!

**Effective serum concentration**

MIC (mg/L)

0.125 0.25 0.5 1 2 4 8 16 32 64 128 256

Good !!

Bad !!
But now, what do you do with this?

No longer so easy...

effective serum concentration?

May be?
But now, what do you do with this?

No longer so easy...

effective serum concentration?

or here?

MIC (mg/L)
But now, what do you do with this?

No longer so easy...

effective serum concentration?

This where we have problem #2

or there?
Breakpoints do not make things easy

Enterobacteriaceae

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>MIC Breakpoint (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S ≤</td>
</tr>
<tr>
<td>Penicillins¹</td>
<td></td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>8⁴</td>
</tr>
<tr>
<td>Cephalosporins¹</td>
<td></td>
</tr>
<tr>
<td>Cefepime</td>
<td>1</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>1</td>
</tr>
<tr>
<td>Carbapenems¹</td>
<td></td>
</tr>
<tr>
<td>Imipenem²</td>
<td>2</td>
</tr>
<tr>
<td>Meropenem</td>
<td>2</td>
</tr>
</tbody>
</table>

what do you do with that?
Problem #3: which is the correct parameter to take into account?

- Why are $\beta$-lactams time-dependent?

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Full susceptible MSSA

Pharmacodynamic model of antibiotic response
24 incubation at fixed concentrations
Problem #3: which is the correct parameter to take into account?

- Why are $\beta$-lactams time-dependent?

![Diagram](image)

**full susceptible MSSA**

- **oxacillin**
  - Maximal activity in the $C_{\text{min}}$-$C_{\text{max}}$ range

- **gentamicin**
  - Activity is concentration-dependent in the $C_{\text{min}}$-$C_{\text{max}}$ range

Phamacodynamic model of antibiotic response
24 incubation at fixed concentrations
Problem #3: which is the correct parameter to take into account?

- Why are β-lactams time-dependent?

Clinical *P. aeruginosa*

![Pharmacodynamic model of antibiotic response](image)

- The **C\text{min}/MIC** ratio becomes critical!
Problem #3: which is the correct parameter to take into account?

- Are β-lactams really time-dependent?

Clinical *P. aeruginosa* of increasing MIC

Pharmacodynamic model of antibiotic response

24 incubation at fixed concentrations
Solution for β-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?)
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%

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
Solution for $\beta$-lactams: $T > MIC$...

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How much time above MIC?

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

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

- **40%**
  - Moderately severe infection in a non-immunosuppressed patient

- **100%**
  - Severe infection in an immunosuppressed patient

**Graph:**
- **Log_{10} CFU per lung at 24 hours**
- **Time above MIC (%)**
- **C**

**Legend:**
- 0, 9, 8, 7, 6, 5
- 0, 20, 40, 60, 80, 100

100% ?
It all depends on your patient!

Moderately severe infection in a non-immunosuppressed patient

Severe infection in an immunosuppressed patient

You must STRATIFY according to the risk

100 % ?
But back to MIC …!

**Fig. 10.2** Relationship between concentration of ceftazidime (a) and meropenem (b) and kill rate. The relationship follows a Hill type model with a relatively steep curve; the difference between no effect (growth, here displayed as a negative kill rate) and maximum effect is within 2–3 twofold dilutions. The maximum kill rate is attained at around 4× MIC. Figure modified from Mouton and Vinks (2005b, 2007). Reproduced from Mouton JW, Vinks AA. Pharmacokinetic/pharmacodynamic modelling of antibacterials in vitro and in vivo using bacterial growth and kill kinetics: the minimum inhibitory concentration versus stationary concentration. Clin Pharmacokinet. 2005;44(2):201–10 with permission from Adis (© Springer International Publishing AG [2005]. All rights reserved.
But back to MIC …!

Fig. 10.2 Relationship between concentration of ceftazidime (a) and meropenem (b) and kill rate. The relationship follows a Hill type model with a relatively steep curve; the difference between no effect (growth, here displayed as a negative kill rate) and maximum effect is within 2–3 twofold dilutions. The maximum kill rate is attained at around 4× MIC. Figure modified from Mouton and Vinks (2005b, 2007). Reproduced from Mouton JW, Vinks AA. Pharmacokinetic/pharmacodynamic modelling of antibacterials in vitro and in vivo using bacterial growth and kill kinetics: the minimum inhibitory concentration versus stationary concentration. Clin Pharmacokinet. 2005;44(2):201–10 with permission from Adis (© Springer International Publishing AG [2005]. All rights reserved.
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 log$_2$ 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 levels 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...

Knowledge or ou “educated” suspicion of the causative agent

Is the organism probably highly susceptible?

- **Yes**: Use common dosage but with attention to PK/PD
- **No**: Local MIC data

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
A clinical algorithm or a path to success...

Adjust the dosage on a full PK/PD basis and continue monitoring free blood levels

in ICU, the patient's situation changes rapidly!

But what do we need?

• a fast and reliable assay of the serum free fraction…
  → results available within the period of the medical shift!

• a clear definition of the desired target for efficacy … and prevention of emergence of resistance…
  → C_{\text{min}} (or C_{\text{ss}}) at 4 x the MIC?

• a clear definition of the maximal doses without unacceptable toxicity (convulsions…) …
  → C_{\text{max}} not exceed the value of an approved mode of administration?

• an algorithm that calculates the next dose based on population PK but also on real data from the previous administration…
  → adaptive PK/PD modeling
We can always dream …

difficult machinery

acrobatic algorithms

dead ends…
But at the end …

light at the end of the tunnel…
But at the end …

... light at the end of the tunnel…

... and far above sea level

Last accessed: 13-10-2015
Back-up
But even then, serum levels remain are difficult to predict with accuracy…

patients with continuous administration of ceftazidime

Mouton, unpublished
Which pharmacokinetic parameter drives the activity of β-lactams?

**Free serum concentration (mg/L)**

**Time after administration (h)**

- **MIC**
- **$t_T > CMI$**
- **Time during which the free concentration remains > MIC**
Solution for $\beta$-lactams: $f_T > \text{MIC}…$

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