Looking into the future: How to adapt antibiotic use based on pharmacokinetics and pharmacodynamics

Paul M. Tulkens, MD, PhD

Cellular and Molecular Pharmacology & Center for Clinical Pharmacy
Louvain Drug Research Institute
Health Science Sector
Université catholique de Louvain
Brussels, Belgium

CHU "Marie Curie", Lodelinsart
19 December 2017
Disclosures

Financial support from

• Non-profit Institutions:
  – the Belgian *Fonds de la Recherche Scientifique* for basic research on pharmacology antibiotics and related topics
  – The *European Union* for applied research on optimization of β-lactams treatments through on-line monitoring of free serum levels
  – The *Université catholique de Louvain* for past personal support

• Industry:
  – AstraZeneca, GSK, Sanofi-Aventis, Bayer, Cempra Pharmaceuticals, The Medicines Company, Northern Antibiotics, RibX, Cubist, Galapagos, …

Other past and present relationships in relation to this talk
  – Belgian Antibiotic Policy Coordination Committee (BAPCOC)
  – European Committee for Antibiotic Susceptibility Testing (EUCAST)
  – European Medicines Agency (EMA)
  – Drive-AB (a EU program for a new economical framework for antibiotics)

Slides: http://www.facm.ucl.ac.be → Lectures
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 ...

**Table 20.7. Dosing Regimens of Cephalosporins in Adults and Children**

<table>
<thead>
<tr>
<th>Cephalosporin</th>
<th>First Generation</th>
<th>Usual Dose</th>
<th>Adults</th>
<th>Severe Disease</th>
<th>Children</th>
<th>Usual Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefazolin</td>
<td>0.5-1 g q8-12h</td>
<td>2 g q6-8h</td>
<td></td>
<td></td>
<td>12.5-33 mg/kg q6-8h</td>
<td></td>
</tr>
<tr>
<td>Cephalothin</td>
<td>0.5-1 g q6h</td>
<td>2 g q4-6h</td>
<td></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></td>
<td>10-20 mg/kg q6h</td>
<td></td>
</tr>
</tbody>
</table>

What is a "severe disease"?
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…
No so old but still good time ....

Still Easy...

Good !!

effective serum concentration

Bad !!

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

Still Easy...

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

Good !!

Effective 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...

May be?

effective serum concentration?
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...

MIC (mg/L)

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

effective serum concentration?

This where we have problem #2

or there?
Can breakpoints come to help?

EUCAST breakpoints are the only legal in Europe and are implemented for most new antibiotics since 2005.
Can breakpoints come to help?

EUCAST definitions of clinical breakpoints

Clinically Susceptible (S)
- a micro-organism is defined as susceptible by a level of antimicrobial activity associated with a high likelihood of therapeutic success
- a micro-organism is categorized as susceptible (S) by applying the appropriate breakpoint in a defined phenotypic test system
- this breakpoint may be altered with legitimate changes in circumstances

Clinically Resistant (R)
- a micro-organism is defined as resistant by a level of antimicrobial activity associated with a high likelihood of therapeutic failure.
- a micro-organism is categorized as resistant (R) by applying the appropriate breakpoint in a defined phenotypic test system
- this breakpoint may be altered with legitimate changes in circumstances

MIC: Minimal Inhibitory Concentration
(the lowest antibiotic concentration at which bacteria stop growing in a defined in vitro system)

Last updated: 1 Sep 2015; last accessed: 18 Dec 2017
But breakpoints must be interpreted…

<table>
<thead>
<tr>
<th>Enterobacteriaceae</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Penicillins</strong>¹</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
</tr>
</tbody>
</table>

| **Cephalosporins**¹ | **MIC breakpoint (mg/L)** |
| | **S ≤** | **R >** |
| Cefepime | 1 | 4 |
| Ceftazidime | 1 | 4 |

| **Carbapenems**¹ | **MIC breakpoint (mg/L)** |
| | **S ≤** | **R >** |
| Imipenem² | 2 | 8 |
| Meropenem | 2 | 8 |

http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_7.1_Breakpoint_Tables.pdf

Last updated: 10 Mar 2017; last accessed: 18 Dec 2017
Simple use of breakpoints in the hospital...

### Enterobacteriaceae

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MIC breakpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillins¹</td>
<td></td>
</tr>
<tr>
<td>Piperacillin</td>
<td></td>
</tr>
<tr>
<td>Cephalosporins</td>
<td></td>
</tr>
<tr>
<td>Cefepime</td>
<td></td>
</tr>
<tr>
<td>Ceftazidime</td>
<td></td>
</tr>
<tr>
<td>Carbapenems</td>
<td></td>
</tr>
<tr>
<td>Imipenem</td>
<td>2</td>
</tr>
<tr>
<td>Meropenem</td>
<td>2</td>
</tr>
</tbody>
</table>

¹For some organisms

[http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_7.1_Breakpoint_Tables.pdf](http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_7.1_Breakpoint_Tables.pdf)

Last updated: 10 Mar 2017; last accessed: 18 Dec 2017

---

check your epidemiology and/or your isolate…

---
Simple use of breakpoints in the hospital…

<table>
<thead>
<tr>
<th>Enterobacteriaceae</th>
<th>MIC breakpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillins¹</td>
<td></td>
</tr>
<tr>
<td>Piperacillin</td>
<td></td>
</tr>
<tr>
<td>Cephalosporins</td>
<td></td>
</tr>
<tr>
<td>Cefepime</td>
<td></td>
</tr>
<tr>
<td>Ceftazidime</td>
<td></td>
</tr>
<tr>
<td>Carbapenems</td>
<td></td>
</tr>
<tr>
<td>Imipenem</td>
<td>2 8</td>
</tr>
<tr>
<td>Meropenem</td>
<td>2 8</td>
</tr>
</tbody>
</table>

check your epidemiology and/or your isolate…

and see where YOU are!

http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_7.1_Breakpoint_Tables.pdf
Last updated: 10 Mar 2017; last accessed: 18 Dec 2017
Breakpoints are partly based on pharmacokinetics ...

Fig. 3.4  Summary of the process of setting PK/PD breakpoints by EUCAST (Mouton et al. 2012)
Problem #3: 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 %

You must STRATIFY

What is, indeed, a standard patient?

You must STRATIFY according to the patient size.
But what is the relation between pharmacokinetics and efficacy?

- **Pharmacokinetics**
  - Conc vs time

- **Pharmacodynamics**
  - Conc vs effect

- **PK/PD**
  - Effect vs time
From pharmacokinetics to pharmacodynamics.

\[ C_{\text{max}} \]

\[ C_{\text{min}} \]

\[ \text{MIC} \]
From pharmacokinetics to pharmacodynamics.

\[ \frac{C_{\text{max}}}{\text{MIC}} \]

\[ \frac{C_{\text{max}}}{CMI} \]

\[ C_{\text{min}} \]

\[ \text{Time (h)} \]

\[ \text{Concentration} \]
From pharmacokinetics to pharmacodynamics.

- $C_{\text{max}} / \text{MIC}$
- Time $> \text{MIC}$
- Time during which the free concentration remains $> \text{MIC}$
- $fT > \text{CMI}$
- $C_{\text{max}}$
- $C_{\text{min}}$
Which pharmacokinetic parameter drives the activity of β-lactams?
Which pharmacokinetic parameter drives the activity of β-lactams?

- $\frac{C_{\text{max}}}{\text{MIC}}$
- $\frac{\text{AUC}}{\text{MIC}}$
- $t_{\text{T } > \text{ MIC}}$
- $\frac{C_{\text{max}}}{\text{MIC}} \text{ Time (h)}$

Free serum concentration (mg/L)

Time (h)
A few simple rules …

<table>
<thead>
<tr>
<th>Pharmacological class</th>
<th>Parameter</th>
<th>Clinical consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-lactams</td>
<td>time &gt; MIC</td>
<td>• favor frequent administration …</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• continuous infusion</td>
</tr>
<tr>
<td>aminoglycosides</td>
<td>$C_{\text{max}}$/MIC</td>
<td>• favor high peaks (aminoglycosides)</td>
</tr>
<tr>
<td>fluoroquinolones</td>
<td>(AUC/MIC)</td>
<td>• favor peak and total daily dose (fluoroquinolones)</td>
</tr>
<tr>
<td>most other antibiotics</td>
<td>AUC/MIC</td>
<td>• favor total daily dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• some may be eligible for continuous infusion</td>
</tr>
</tbody>
</table>

$C_{\text{max}}$: maximal serum concentration (typically after intermittent administration – $C_{\text{max}} = \text{dose/volume of distribution}$)  
AUC: area under the curve (most often over 24h) – $\text{AUC}_{24\text{h}} = \text{total daily dose/clearance}$
Why are β-lactams time-dependent and aminoglycosides concentration-dependent?

- Simple experiments…

Pharmacodynamic model of antibiotic response
24 incubation at fixed concentrations
Why are β-lactams time-dependent and aminoglycosides concentration-dependent?

- Simple experiments…

Pharmacodynamic model of antibiotic response

24 incubation at fixed concentrations

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

Activity is concentration-dependent in the $C_{\text{min}}-C_{\text{max}}$ range
Aminoglycosides...
In vitro time-kill curves

Time and conc. – dependent killing

Concentration is important in patients also …

C\text{max}/MIC > 8 ! in a TID treatment

In vitro post-antibiotic effect

delay before regrowth

Aminoglycosides: get a peak!

1. Appropriate mode of administration
   - IV route

2. Calculation of the necessary peak value
   - minimal peak: $= 8 \times \text{MIC}$

3. Calculation of the adequate dose
   - $\text{peak} = \frac{\text{dose}}{V_d}$
   - $\text{dose} = \text{peak} \times V_d$
   - $\text{dose} = \text{MIC} \times 8 \times V_d$
## Aminoglycosides: which doses for which MIC?

<table>
<thead>
<tr>
<th>dose (mg/kg)</th>
<th>peak (mg/L) for $V_d = 0.25$ L/kg</th>
<th>peak/MIC for MIC = 4</th>
<th>peak/MIC for MIC = 2</th>
<th>peak/MIC for MIC = 1</th>
<th>peak/MIC for MIC = 0.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>2</td>
<td>4</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>3</td>
<td>6</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>16</td>
<td>4</td>
<td>8</td>
<td>16</td>
<td>32</td>
</tr>
<tr>
<td>6</td>
<td>24</td>
<td>6</td>
<td>12</td>
<td>24</td>
<td>48</td>
</tr>
<tr>
<td>8</td>
<td>32</td>
<td>8</td>
<td>16</td>
<td>32</td>
<td>64</td>
</tr>
</tbody>
</table>
Optimization of aminoglycoside usage: standard patients (Vd ~ 0.25 L/kg)

Do not try to treat with aminoglycosides bacteria with MIC

- > 2 µg/ml for molecules with maximal daily doses of 6 mg/kg
- > 4 µg/ml for molecules with maximal daily doses of 15 mg/kg

PK / PD breakpoints for AG
- Genta, Netil, Tobra (4 mg): 2 mg / L
- Amika / Isépa (15 mg): 8 mg / L

Current EUCAST "S" breakpoints
- ≤ 2 mg/L
- ≤ 8 mg/L
Optimization of aminoglycoside usage: what if the VD is

Assessment of the National French recommendations regarding the dosing regimen of 8 mg/kg of gentamicin in patients hospitalised in intensive care units

Nicolas Allou, Jérôme Allyn, Yaël Levy, Astrid Bouteau, Marie Caujolle, Benjamin Delmas, Dorothée Valance, Caroline Brulliard, Olivier Martinet, David Vandroux, Philippe Montravers, Pascal Augustin

Réanimation polyvalente, CHU Felix-Guyon, allée des Topazes, 97405 Saint-Denis, France
Département d'Anesthésie-Réanimation, AP-HP, CHU Bichat-Claude-Bernard, 46, rue Henri-Huchard, 75018 Paris, France
Optimization of aminoglycoside usage: what if the VD is

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Sites of infection and isolated microorganisms.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sites of infection</td>
</tr>
<tr>
<td></td>
<td>Pulmonary</td>
</tr>
<tr>
<td></td>
<td>Catheter</td>
</tr>
<tr>
<td></td>
<td>Skin and soft tissue</td>
</tr>
<tr>
<td></td>
<td>Urinary tract</td>
</tr>
<tr>
<td></td>
<td>Other</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>Bacteraemia</td>
</tr>
<tr>
<td></td>
<td>Isolated microorganisms</td>
</tr>
<tr>
<td></td>
<td>Cocci</td>
</tr>
<tr>
<td></td>
<td>Staphylococcus aureus</td>
</tr>
<tr>
<td></td>
<td>Other Staphylococci</td>
</tr>
<tr>
<td></td>
<td>Enterococcus faecalis</td>
</tr>
<tr>
<td></td>
<td>Streptococcus spp</td>
</tr>
<tr>
<td></td>
<td>Bacilli</td>
</tr>
<tr>
<td></td>
<td>Enterobacteriaceae</td>
</tr>
<tr>
<td></td>
<td>Escherichia coli</td>
</tr>
<tr>
<td></td>
<td>Enterobacter spp</td>
</tr>
<tr>
<td></td>
<td>Serratia marcescens</td>
</tr>
<tr>
<td></td>
<td>Klebsiella spp</td>
</tr>
<tr>
<td></td>
<td>Pseudomonas aeruginosa</td>
</tr>
<tr>
<td></td>
<td>None</td>
</tr>
</tbody>
</table>
Optimization of aminoglycoside usage: what if the VD is $\uparrow$

$V_d = \text{dose/peak} \rightarrow 0.45 \text{ in this population (8/17.5)}$

Table 3

<table>
<thead>
<tr>
<th>Variable</th>
<th>n = 34</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg)</td>
<td>560 [510–610]</td>
</tr>
<tr>
<td>Dose (mg/kg of total body weight of the day)</td>
<td>8 [7.9–8.1]</td>
</tr>
<tr>
<td>Peak concentration (mg/L)</td>
<td>17.5 [15.4–20.7]</td>
</tr>
<tr>
<td>Patients with peak concentration &gt; 30 mg/L</td>
<td>0</td>
</tr>
<tr>
<td>Patients with peak concentration &gt; 16 mg/L</td>
<td>24 (71)</td>
</tr>
<tr>
<td>Patients with peak concentration &gt; 8 mg/L</td>
<td>33 (97)</td>
</tr>
<tr>
<td>Trough concentration</td>
<td>1.6 [0.7–3.3]</td>
</tr>
</tbody>
</table>

Results are expressed as medians [25th–75th percentiles] or n (%).

it should be 32 mg/L!
Amikacin dosing in ICU: recent data from Leuven

Accepted Manuscript

Title: Higher versus standard amikacin single dose in emergency department patients with severe sepsis and shock: a randomized controlled trial

Author: Sabrina De Winter, Joost Wauters, Wouter Meersseman, Jan Verhaegen, Eric Van Wijngaerden, Willy Peetermans, Pieter Annaert, Sandra Verelst, Isabel Spriet

PII: S0924-8579(17)30426-0
DOI: https://doi.org/10.1016/j.ijantimicag.2017.11.009
Reference: ANTAGE 5301

To appear in: International Journal of Antimicrobial Agents

Received date: 28-2-2017
Accepted date: 18-11-2017
Recent studies suggest that ICU patients treated with amikacin frequently do not attain the PK/PD target, i.e. a peak above minimal inhibitory concentration (MIC) ratio of at least 8, when a single dose of 15 mg/kg is used.

104 ED patients admitted with severe sepsis or septic shock were included and randomly treated with 25 vs. 15 mg/kg. Amikacin peak concentrations were collected.

Primary outcome was target attainment defined as peak/MIC ≥ 8, using both EUCAST susceptibility breakpoints (8 mg/L) and actually documented MIC values as denominator.

The EUCAST based target (64 mg/L) was attained in 76% vs. 40% of patients assigned to the 25 vs. 15 mg/kg dose group (p<0.0001).

Target attainment using actual MIC values (median of 2 mg/L, documented in 48 isolated gram-negative pathogens; target = 16 mg/L) was achieved in 95% vs. 94% of patients in the 25 vs.15 mg/kg group (p=0.969).
Amikacin dosing in ICU: recent data from Leuven

PK/PD target attainment of critically ill ED patients in function of different MIC values
The vancomycin story: discontinuous or continuous infusion?

1. DÉNOMINATION DU MÉDICAMENT

Vamycin 1000 mg, poudre pour solution à diluer pour solution pour perfusion.

4.2 Posologie et mode d'administration

Voie intraveineuse (perfusion) chez les patients présentant une fonction rénale normale:

Adultes et adolescents âgés de plus de 12 ans:
La posologie intraveineuse quotidienne recommandée est de 2 000 mg, répartis en doses de 500 mg toutes les 6 heures ou de 1 000 mg toutes les 12 heures, ou 30 à 40 mg/kg/jour en 2 à 4 administrations quotidiennes.

http://bijsluiters.fagg-afmps.be/registrationSearchServlet?key=BE405291&leafletType=rcp
Last accessed: 18 Dec 2017

Last accessed: 18 Dec 2017
Vancomycin: how to optimize it?

\[ \frac{\text{AUC}_{24\text{h}}}{\text{MIC}} = 400 \]
Vancomycin TDM at CHU Mont-Godinne at the start of the project

- **peak level:** 30-40 mg/L 2 h after the end of infusion
- **trough level:** 5-10 mg/L just before the next dose
Observational study – results

*within 30 min. of recommended sample timing: peak 2h after the end of infusion, trough: just before the next dose

40% incorrect sample timing
Observational study – results

Observed deviations (in min) from recommended sampling times at baseline.

vancomycin peak (n=49)

vancomycin trough (n=83)

*within 30 min. of recommended sample timing: peak 2h after the end of infusion, trough: just before the next dose
But, how could we improve?

“Continuous infusion is easier because it allows to control the duration of administration and samples can be taken at any time.”
TDM of vancomycin by continuous infusion

AUC24h / MIC is independent of the mode of administration of the same daily dose.
Vancomycin CI: which serum concentration should we target for continuous infusion?

Data from a recent study point at a vancomycin AUC_{24h}/MIC of at least 400 to obtain optimal clinical outcome in patients with *S. aureus* lower respiratory tract infections (Moise-Broder et al., Clin Pharmacokinet. 2004;43(13):925-42)

<table>
<thead>
<tr>
<th>MIC (mg/L)</th>
<th>minimal AUC (mg*L^{-1}*h)</th>
<th>target Css (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>400</td>
<td>16.6</td>
</tr>
<tr>
<td>2</td>
<td>800</td>
<td>33.3</td>
</tr>
<tr>
<td>4</td>
<td>1600</td>
<td>66.6</td>
</tr>
</tbody>
</table>
Vancomycin CI: Target for efficacy

![Graph showing VAN serum concentration](image)

- **Target concentration:** 25-30 mg/L
- **MIC:** 1.5 mg/L

Vancomycin CI: efficacy vs toxicity …

**efficacy**

- VAN serum conc. (mg/L)
  - 25-30 mg/L
  - MIC = 1.5 mg/L
  - 400

**toxicity**

- $C_{ss}$ vancomycin $> 28$ mg/L en increased nephrotoxicity risk
  - [OR 21.236; $P = 0.004$]


How to reach the serum target concentration target with CI?

1. loading dose: the correct scheme *

\[ C_t = \frac{D_l}{V_d} \]

* Target serum concentration

* volume of distribution

loading dose

\[ \text{loading dose (in mg/kg)} = C_t \text{ (mg/L)} \times V_d \text{ (L/kg)} \]

\[ \text{loading dose (in mg/kg)} = 20 \text{ mg/kg} = 25 \text{ (mg/L)} \times 0.8 \text{ (L/kg)} \]

* assuming linear pharmacokinetics
How to reach the serum target concentration target with CI?

2: infusion *

\[ C_{ss} = \frac{K_0}{Cl} \]

Target serum concentration

Clearance *

infusion rate

**daily dose** (in mg) = 24 x **VAN clearance** (L/h) x \( C_{ss} \)

**daily dose** (in mg) = 24 x 0.65 **creatinine clearance** (L/h) x \( C_{ss} \)

typically 2.5 g/day

* of vancomycin [assuming linear pharmacokinetics] = 0.65 creatinine clearance
How to reach the serum target concentration target with CI?

2: infusion *

* during the infusion, the necessary dose (in 24h or per min) is only dependent upon the drug clearance and NOT of the weight...

once a bath is at the desired level (i.e. after the loading dose), maintaining this level does not depend upon its volume but of the ratio of tap and drain flows (which must be equal: in = out...)

\[\text{In} = \text{infusion}\]

\[\text{Out} = \text{clearance}\]
7. Total vancomycin serum concentrations

- Target concentration reached at time 0 h

Total vancomycin concentrations over time in all patients with > 3 measures at any time (n=91)
7. Total vancomycin serum concentrations

total vancomycin concentrations over time in all patients with > 3 measures at any time (n=91)

- Decline to 20 mg/L within 6h (initial infusion rate to low)
7. Total vancomycin serum concentrations

**Diagram:**
- **Title:** total vancomycin concentrations over time in all patients with > 3 measures at any time (n=91)
- **Y-axis:** mg/L
- **X-axis:** hours
- **Graph:** After increasing the rate of infusion (in 57% of patients), targeted value reached and maintained from 96h
7. Total vancomycin serum concentrations

- deviations of >10 mg/L according to the recommended range
  - if increased CCrCl (threshold at >104 mL/min)
  - if concomitant use of diuretics
9. AUC$_{24h}$/MIC predictive of clinical success/failure (n=20)

- Recursive partitioning analysis
- best AUC/MIC split value separating failure from success:
  - 667 (total serum concentration)
  - 452 (free serum concentration)
$\beta$-lactams: \( T > \text{MIC} \) ...
In vitro time-kill curves

β-lactams: T > 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?

Static dose?

$R^2 = 94\%$

40%
It all depends on your patient!

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

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

\[ \log_{10} \text{cfu per lung at 24 hours} \]

\[ \text{Time above MIC (%)} \]
It all depends on your patient!

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

You must STRATIFY according to the risk.
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 log₂ transformed data and found significant by both non-parametric (Wilcoxon matched pair test) and parametric (two-tailed paired t-test) analysis.

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.

But how to prevent the emergence of resistance?

Determining β-lactam exposure threshold to suppress resistance development in Gram-negative bacteria

Vincent H. Tam¹, Kai-Tai Chang¹, Jian Zhou², Kimberly R. Ledesma³, Kady Phe¹, Song Gao³, Françoise Van Bambeke², Ana María Sánchez-Díaz³, Laura Zamorano⁴, Antonio Oliver⁵ and Rafael Cantón³

¹University of Houston, Houston, TX, USA; ²Pharmacologie Cellulaire et Moléculaire & Louvain Drug Research Institute, Université Catholique de Louvain, Brussels, Belgium; ³Servicio de Microbiología, Hospital Universitario Ramón y Cajal and Instituto Ramón y Cajal de Investigación Sanitaria (IRYCS), Madrid, Spain; ⁴University Hospital Son Espases, Instituto de Investigación Sanitaria de Palma, Palma de Mallorca, Spain


Simulation of doses and drug exposure in an in vitro dynamic model of infection (hollow fiber)
Prevention of resistance...

Figure 2. Typical bacterial profiles for WT P. aeruginosa. Placebo control (a), Ceftazidime at 500 mg every 8 h (C<sub>min</sub>/MIC = 2.9) (b). Ceftazidime at 3000 mg every 8 h (C<sub>min</sub>/MIC = 7.7) (c). Data are shown as mean ± SD.

Figure 3. Drug exposures (C<sub>min</sub>/MIC) stratified by outcomes. Each data point represents a hollow-fibre infection model experiment. The most significant threshold (C<sub>min</sub>/MIC ≥3.8) is depicted by the horizontal broken line.

To prevent the emergence of resistance in a closed system, the C<sub>min</sub> of β-lactams should be ≥ 3.8 x MIC...
But serum levels of β-lactams 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 continuous administration of ceftazidime

![Graph showing serum levels and target levels](image-url)
As a result, monitoring the serum levels of β-lactams has been proposed ...
And monitoring β-lactams in ICU may be rewarding...

Accepted Manuscript

Title: Association between augmented renal clearance, antibiotic exposure and clinical outcome in critically ill septic patients receiving high doses of β-lactams administered by continuous infusion. a prospective observational study

Author: Cedric Carrie, Laurent Petit, Nicolas D'Houdain, Noemie Sauvage, Vincent Cottenceau, Melanie Lafitte, Cecile Foumenteze, Quentin Hisz, Deborah Menu, Rachel Legeron, Dominique Breilh, Francois Sztark

PII: S0924-8579(17)30430-2
DOI: https://doi.org/10.1016/j.jantimicag.2017.11.013
Reference: ANTAGE 5305

To appear in: International Journal of Antimicrobial Agents

Received date: 21-9-2017
Accepted date: 18-11-2017
And monitoring may be rewarding…

Accepted Manuscript

Highlights

- In patients with augmented creatinine clearance (CrCL), desirable PK/PD targets may not be achieved by the use of high doses of β-lactam administered by continuous infusion.

- Mean values ≥ 170/min remain associated with higher rates of sub-exposure for β-lactams defined by at least one sample under 4 times the MIC of the known pathogen.

- Sub-exposure \(< \text{MIC} \times 4\) is associated with higher rates of therapeutic failure in critically ill patients treated for a first microbiologically documented infection.
Methods are being developed but are slow and complex, and do not measure the free concentration ...

Simultaneous determination of eight β-lactam antibiotics in human serum by liquid chromatography–tandem mass spectrometry

Tomofumi Ohmori a,⁎, Akio Suzuki a, Takashi Niwa a, Hiroaki Ushikoshi b, Kunihiro Shirai b, Shozo Yoshida b, Shinji Ogura b, Yoshinori Itoh a

⁎ Department of Pharmacy, Gifu University Hospital, 1-1 Yanaagido, Gifu 501-1194, Japan
b Department of Emergency and Disaster Medicine, Gifu University Graduate School of Medicine, 1-1 Yanaagido, Gifu 501-1194, Japan

Development and validation of a high performance liquid chromatography assay for the determination of temocillin in serum of haemodialysis patients

Ana C. Miranda Bastos a,b,c, Stefaan J. Vandecasteele d, Paul M. Tulkens a,b,c, Anne Spinewine b,c, Françoise Van Bambeke a,b,c,⁎

⁎ Pharmacologie cellulaire et moléculaire, Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium
d Clinical Pharmacy Research Group, Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium
c Center for Clinical Pharmacy, Université catholique de Louvain, Brussels, Belgium
d Center for Nephrology and Infectious Diseases, AZ Sint-Jan Brugge-Oostende AV, Bruges, Belgium
A clinical algorithm for β-lactams and 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 $4 \times$ 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

A clinical algorithm or a path to success...

Knowledge or "educated" suspicion of the causative agent

Pathology and epidemiology

Local MIC data

Is the organism probably highly susceptible?

Yes:
- Use common dosage but with attention to PK/PD

No:
- Obtain an MIC and serum levels
- \( S/I/R \) is insufficient!!

Adjust the dosage on a full PK/PD basis and continue monitoring free blood levels
The future: which other anti-infectives *?

- **oxazolidinones** (linezolid, tedizolid, …)
  → $C_{\text{min}}$ for prevention of toxicity

- **fluoroquinolones** (ciprofloxacin, levofloxacin, …)
  → $C_{\text{max}}$ for prevention of resistance
  → $AUC_{24h}$ for global antibacterial effect

- **azole antifungals** (fluconazole, voriconazole, …)
  → control of drug-drug interactions and inhibition of metabolism
  → $AUC_{24h}$ for efficacy

- **anti-HIV drugs** (many …)
  → correction/prevention of HIGH variability in blood levels

*many references... See, e.g.:
We can always dream …

difficult machinery

acroatic algorithms

dead ends…
But at the end …

towards successes!
Back-up
But even then, serum levels remain difficult to predict with accuracy…

patients with continuous administration of ceftazidime

concentration (mg/L)

time (h)

Mouton, unpublished