TDM of antibiotics

(Laboratory testing guideline in the intensive care unit)

Paul M. Tulkens, MD, PhD

Pharmacologie cellulaire et moléculaire
Louvain Drug Research Institute,
Université catholique de Louvain,
Brussels, Belgium
http://www.facm.ucl.ac.be
Disclosures

Industry support for work on investigational compounds from

- Cempra Pharmaceuticals
- GSK
- Melinta Therapeutics
- The Medicine Company
- MerLion Pharmaceuticals
- Trius Therapeutics
- Debiopharm

Non-profit support from

- the Fond de la Recherche Scientifique (F.R.S.-FNRS)
- the Région Wallone
- the European Union (FP7 programme)

Influenced by my participation to the

- Belgian Drug Reimbursement Committee (CRM/CTG; up to 2006)
- EUCAST steering committee (2008-2010) and General Assembly (current)
  (an EU programme aiming at (re)designing the economic framework of the discovery, development and commercialization processes for new antibiotics)

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1 merged in 2017 with and renamed as Melinta Therapeutics
2 formerly RibX Pharmaceuticals; world rights holder for delafloxacin (with license to Menarini for EU and other countries)
3 antibiotic portfolio acquired by Melinta Therapeutics in 2018
4 acquired by Cubist (2014), which was then acquired by Merck (2016)
Our program

• How to define the right antibiotic?

• The basis of the antibiotic
  Pharmacokinetics/Pharmacodynamics (PK/PD)

• TDM of
  – aminoglycosides once daily dosing: ↗ efficacy - ↘ toxicity
  – vancomycin AUC driven TDM – continuous infusion
  – fluoroquinolones rational breakpoints - ↘ emergence of resistance
  – β-lactames coping with patients' variations and susceptibility loss
  – linezolid minimizing toxicity

• a few words about the techniques and the need of bedside approach
Chapter 17: Principles of Anti-infective Therapy
George M. Eliopoulos
Robert C. Moellering Jr.*

"In choosing the appropriate antimicrobial agent for therapy for a given infection, a number of factors must be considered.

- First, the **identity of the infecting organism must be known** or, at the very least, it must be possible to arrive at a statistically **reasonable guess as to its identity** on the basis of clinical information.

- Second, information about the **susceptibility of the infecting organism**, or **likely susceptibility**, must be as accurate as possible.

- Finally, a series of **factors specific to the patient who is being treated** (and his/her disease) must be considered to arrive at the optimal choice of antimicrobial agent."
Here are the questions …

When choosing an antibiotic, do we know

1. for the organism
   – its identity and whether it is causal or not?
   – its susceptibility to and the main key properties of the proposed antibiotic?

2. for the patient
   – the antibiotic effectiveness in the specific disease?
   – how to dose the antibiotic appropriately?
   – how to prevent / avoid patient- and drug-related side effects?

3. for the society
   – how to prevent emergence of resistance?
   – how to get "value for money"?
Here are the questions …

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3. for the society
   – how to prevent emergence of resistance?
   – how to get "value for money"?

But we cannot ignore this!
Possible answers for the organism ...

When choosing an antibiotic, do we know

1. for the organism
   - its susceptibility to the proposed antibiotic

Susceptibility

• are *in vitro* methods predictive (and which ones to use) ?
• which interpretive criteria ?
Possible answers for the patient …

When choosing an antibiotic, do we know

2. for the patient
   - how to dose the antibiotic appropriately?

This is where the PK/PD guys came in (Stockholm, 1989)
Starting PK/PD with a simple *in vitro* microbiological comparison

- bacteria in broth
- increasing concentrations (multiples of MIC)
- measure of the change in CFUs over time

**Fast and concentration-dépendant**

**Slow and time-dépendant**

Moving to patients: PK parameters governing the activity of antibiotics

- $C_{\text{max}}$ / MIC
- $f \ T > \text{MIC}$
- $\text{AUC}_{24\text{h}}$ / MIC

![Graph showing concentration over time with key PK parameters: $C_{\text{max}}$, $f \ T > \text{MIC}$, $\text{AUC}_{24\text{h}}$.](Image)
How to determine which PK parameter is critical?

- If you fractionate the daily dose, you change $C_{\text{max}}$ without changing $AUC_{24h}$.

\[
AUC_{24h} = \frac{\text{Dose}_{24h}}{\text{Clearance}}
\]

$AUC_{24h}$ is independent of the schedule.
How to determine which PK parameter is critical?

- If you increase the dose without change of schedule, you increase BOTH $C_{\text{max}}$ and AUC$_{24h}$.

$$AUC_{24h} = \frac{\text{Dose}_{24h}}{\text{Clearance}}$$

$AUC_{24h}$ is proportional to the dose.
The 3 main patterns of antibiotic PK/PD properties
(W.A. Craig, 2000; revised in 2003)

<table>
<thead>
<tr>
<th>Antibiotic Group</th>
<th>PK/PD Parameter</th>
<th>What to do?</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\beta)-lactams</td>
<td>time &gt; MIC</td>
<td>stay &gt; MIC as needed</td>
</tr>
<tr>
<td>macrolides, oxazolidinones,</td>
<td>AUC(_{24h})/MIC</td>
<td>give a sufficient total daily dose</td>
</tr>
<tr>
<td>vancomycin…</td>
<td></td>
<td></td>
</tr>
<tr>
<td>quinolones</td>
<td>peak / MIC and</td>
<td>obtain a peak and aim for a sufficient total daily dose</td>
</tr>
<tr>
<td>aminoglycosides</td>
<td>AUC(_{24h})/MIC</td>
<td></td>
</tr>
</tbody>
</table>

An important consideration: What should we aim for?

Maximal effect: $E_{\text{max}}$

Minimal effect: $E_{\text{min}}$

Slope: $E_{\text{max}}/4$

Intercept: $\ln EC_{50} - 2$

% of maximum effect vs. concentration ($\ln C$ [ng/ml])
How to be optimal?

If you select a β-lactam ...

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

**Static dose**

100% - Maximal effect

$R^2 = 94%$

Log$_{10}$ cfu per lung at 24 hours

Time above MIC (%)
Fig. 2.6  Change in \( \log_{10} \) CFUs/thigh over 24 h for various Enterobacteriaceae following treatment with multiple fluoroquinolones in neutropenic mice. Redrawn from data in Andes and Craig (2002)
Aminoglycosides are concentration-dependent and need to be given once-daily both for increased efficacy and possible reduction of toxicity.

Aminoglycosides are concentration-dependent and need to be given once-daily both for increased efficacy and possible reduction of toxicity.

1. Clinical efficacy is maximal if $C_{\text{max}} = 8 \times \text{MIC}$

2. Select the appropriate route of administration (IV > IM)

3. Compute the desired based on MIC (if available) or breakpoint (see EUCAST documents)

4. Compute the dose ($C_{\text{max}} \times V_d$)
   - Note: $V_d = 0.2 \text{L/kg}$ in "normal" patients but can be increased to $0.3 \text{L/kg}$ in infected patients

For most patients:
- Gentamicin / Tobramycin / Netilmicin daily dose: $6 \text{mg/kg}$
  - $C_{\text{max}}$: $16 \text{mg/L}$ – will cover up to an MIC of $2 \text{mg/L}$
- Amikacin daily dose: $15 \text{mg/kg}$
  - $C_{\text{max}}$: $32 \text{mg/L}$ – will cover up to an MIC of $4 \text{mg/L}$

After Schorderet, 1998
Aminoglycoside TDM: correct sampling !!

Observations of a clinical pharmacist about the correct peak sampling

eligible patients: 102

inclusion: 94 patients

111 treatments

vancomycin: 46

peak: 44

amikacin: 65

trough: 62

amikacin peak

exclusions: • 2 for inability to perform observation • 6 for limited life expectancy

A large number of samples were not taken at the defined optimal time

Ampe et al., unpublished
Therapeutic Drug Monitoring: aminoglycosides

Aminoglycosides: The "Nicolau's" nomogram with an 8h sampling time

Single concentration measured at 8 h
- if level falls in q24h area, dosing interval is q24h
- same applies for areas q36h q48h (decr. creat. clearance).
- if near line, choose longer interval
- if above the nomogram between the 6- and 14-h time points, stop therapy and monitor for concentr. < 1 mg/L before next dose

FIG. 1. ODA nomogram for gentamicin and tobramycin at 7 mg/kg.

When choosing an antibiotic, do we know

2. for the specific patient
   – how to prevent / avoid patient- and drug-related side effects
Aminoglycosides: can you do better?

A high-dose aminoglycoside regimen combined with renal replacement therapy for the treatment of MDR pathogens: a proof-of-concept study

Alexandre Brasseur1, Maya Hites2, Sandrine Raisin3, Frédéric Cotton4, Jean-Louis Vincent1, Daniel De Backer1, Frédérique Jacobs2 and Fabio Silvio Taccone1*

1Department of Intensive Care, Erasme Hospital, Université Libre de Bruxelles, Route de Lennik, 808-1070 Brussels, Belgium;
2Department of Infectious Diseases, Erasme Hospital, Université Libre de Bruxelles, Route de Lennik, 808-1070 Brussels, Belgium;
3Department of Clinical Microbiology, Erasme Hospital, Université Libre de Bruxelles, Route de Lennik, 808-1070 Brussels, Belgium;
4Department of Clinical Biochemistry, Erasme Hospital, Université Libre de Bruxelles, Route de Lennik, 808-1070 Brussels, Belgium

*Corresponding author. Tel: +322-555-5587; Fax: +322-555-4698; E-mail: ftaccone@ulb.ac.be

Table 3. Characteristics of aminoglycoside dosing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial dose (mg/kg)</th>
<th>Maximal daily dose (mg/kg)</th>
<th>Initial peak (mg/L)</th>
<th>Number of patients with optimal C_{peak}/MIC on day 1</th>
<th>Total dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin (n=11)</td>
<td>29 (25–37)</td>
<td>29 (26–67)</td>
<td>77 (66–89)</td>
<td>8</td>
<td>22500 (14250–37875)</td>
</tr>
<tr>
<td>Gentamicin (n=3)</td>
<td>11 (10–18)</td>
<td>13 (11–18)</td>
<td>27 (21–39)</td>
<td>2</td>
<td>14400 (7900–16800)</td>
</tr>
<tr>
<td>Tobramycin (n=1)</td>
<td>16</td>
<td>20</td>
<td>15</td>
<td>0</td>
<td>12480</td>
</tr>
</tbody>
</table>

Data are expressed as median (range)
A high-dose aminoglycoside regimen: therapy for the treatment of MDR pathogens

Alexandre Brasseur¹, Maya Hites², Sandrine Roisin³, Frédéric Jacobs² and Frédéric Jacobs²

¹Department of Intensive Care, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium
²Department of Infectious Diseases, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium
³Department of Clinical Microbiology, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium
⁴Department of Clinical Biochemistry, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium

*Corresponding author. Tel: +322-555-5587; Fax: +322-555-5588

Figure 1. Daily evolution of $C_{\text{peak}}$/MIC ratio. Broken horizontal lines show $C_{\text{peak}}$/MIC ratios of 8 and 12.
Pharmacodynamics of Intravenous Ciprofloxacin in Seriously Ill Patients

ALAN FORREST, DAVID E. NIX, CHARLES H. BALLOW, THOMAS F. GOSS, MARY C. BIRMINGHAM, AND JEROME J. SCHENTAG*

Center for Clinical Pharmacy Research, School of Pharmacy, State University of New York at Buffalo, Buffalo, New York 14260, and The Clinical Pharmacokinetics Laboratory, Millard Fillmore Hospital, Buffalo, New York 14209-1194

Received 19 February 1992/Accepted 5 February 1993
FIG. 5. Time (days of therapy) to bacterial eradication versus AUIC illustrated by a time-to-event (survival) plot. Shown is the day of therapy versus the percent patients remaining culture positive on that day. The three AUIC groups differed significantly ($P < 0.005$).
PKP/PD of ciprofloxacin: a Japanese testimonial

Investigation of the Clinical Efficacy and Dosage of Intravenous Ciprofloxacin in Patients with Respiratory Infection

Kazuhiro Matsuo¹, Minako Azuma¹, Maki Kasai², Itsuka Hanji¹, Itsuki Kimura¹, Takayoshi Kosugi¹, Noriko Suga¹ and Mitsutoshi Satoh²

¹Department of Pharmacy, Toho University Omori Medical Center, 6-11-1 Omorinishi, Ota-ku, Tokyo 143-8540, JAPAN; ²Department of Toxicology and Pharmacology, Faculty of Pharmaceutical Sciences, Toho University, 2-2-1 Miyama, Funabashi, Chiba 274-8510, JAPAN
Table 2. Efficacy and pharmacokinetic/pharmacodynamic parameters of CPFX for patients who had *P. aeruginosa* infections.

<table>
<thead>
<tr>
<th></th>
<th>Mean ± S.D.</th>
<th>N</th>
<th>Range</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AUC / M IC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cures</td>
<td>87.8 ± 23.1</td>
<td>7</td>
<td>60.9–123.0</td>
<td>66.4–109.2</td>
<td>0.0035</td>
</tr>
<tr>
<td>Failures</td>
<td>37.2 ± 23.1</td>
<td>12</td>
<td>1.1–154.2</td>
<td>10.8–63.7</td>
<td></td>
</tr>
<tr>
<td><strong>AUC (µg · min/mL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cures</td>
<td>48.6 ± 19.4</td>
<td>42</td>
<td>22.5–113.3</td>
<td>42.5–54.6</td>
<td>0.0342</td>
</tr>
<tr>
<td>Failures</td>
<td>42.2 ± 19.0</td>
<td>52</td>
<td>15.8–87.7</td>
<td>36.9–47.5</td>
<td></td>
</tr>
<tr>
<td><strong>Ccr (mL/min)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cures</td>
<td>69.3 ± 36.8</td>
<td>40</td>
<td>12.2–147.6</td>
<td>59.6–79.3</td>
<td>0.0686</td>
</tr>
<tr>
<td>Failures</td>
<td>82.0 ± 43.1</td>
<td>41</td>
<td>11.0–170.3</td>
<td>68.4–95.6</td>
<td></td>
</tr>
<tr>
<td><strong>Body weight (kg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cures</td>
<td>51.5 ± 12.0</td>
<td>40</td>
<td>24.1–75.0</td>
<td>47.7–55.3</td>
<td>0.3379</td>
</tr>
<tr>
<td>Failures</td>
<td>52.9 ± 16.6</td>
<td>41</td>
<td>29.1–98.0</td>
<td>47.6–58.1</td>
<td></td>
</tr>
</tbody>
</table>

Creatinine level; Ccr = {[(140 – age(years)) × weight(kg)] (X0.85 if female)/{72 × [serumCr(mg/dL)]}. Predictive plasma clearance (CL): CL (mL/min) = weight × (0.167 + 0.00145 × Ccr). Predictive AUC for individual patients were obtained from a modified formula reported by Forrest et al. (1993) [1]: AUC = dose (mg/day)/weight(kg) × (0.167 + 0.00145 CL).
PK/PD breakpoints for fluoroquinolones

<table>
<thead>
<tr>
<th>Drug</th>
<th>Typical daily dosage(^a)</th>
<th>Typical PK values</th>
<th>Proposed PK/PD upper limit of sensitivity (µg/ml) for Efficacy(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norfloxacin</td>
<td>800 mg</td>
<td>1.4/1.1 (400 mg PO)</td>
<td>14/11</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1000 mg</td>
<td>2.5/1.75 (500 mg PO)</td>
<td>24/18</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>400 mg</td>
<td>4/3 (400 mg PO)</td>
<td>40/30</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>500 mg</td>
<td>4/2.8 (500 mg PO)</td>
<td>40/28</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>400 mg</td>
<td>3.1/1.8 (400 mg PO)</td>
<td>35/21</td>
</tr>
</tbody>
</table>

\(^{a}\) Typical daily dosage

Suboptimal Ciprofloxacin Dosing as a Potential Cause of Decreased *Pseudomonas aeruginosa* Susceptibility in Children with Cystic Fibrosis

Emmanuelle Guillot, Pharm.D., Isabelle Sermet, Ph.D., Agnèses Ferroni, Ph.D., Stéphanie Chhun, Pharm.D., Gérard Pons, Ph.D., Jean-Ralph Zahar, M.D., and Vincent Jullien, Ph.D.

Suboptimal Ciprofloxacin Dosing as a Potential Cause of Decreased *Pseudomonas aeruginosa* Susceptibility in Children with Cystic Fibrosis

**Figure 1.** Probability of achieving a 24-hour area under the plasma concentration–time curve (AUC):minimum inhibitory concentration (MIC) ratio greater than 125 (A) or less than 110 (B) for ciprofloxacin against *Pseudomonas aeruginosa* for each respective ciprofloxacin MIC value.
Population Pharmacokinetics and Pharmacodynamics of Levofloxacin in Acutely Hospitalized Older Patients with Various Degrees of Renal Function

Pier Giorgio Cojuti,1,2 Virginia Ramos-Martín,3 Isabella Schiavon,3 Paolo Rossi,3 Massimo Baraldo,1,2 William Hope,3 Federico Pea1,2

Institute of Clinical Pharmacology, Santa Maria della Misericordia University Hospital of Udine, Udine, Italy1;
Department of Experimental and Clinical Medical Sciences, University of Udine, Udine, Italy2; Antimicrobial Pharmacodynamics and Therapeutics, Department of Molecular and Clinical Pharmacology, Institute of Translational Medicine, University of Liverpool, Liverpool, United Kingdom3; First Division of Internal Medicine Santa Maria della Misericordia University Hospital of Udine, Udine, Italy4
Population Pharmacokinetics and Pharmacodynamics of Levofloxacin in Acutely Hospitalized Older Patients with Various Degrees of Renal Function

**TABLE 3** Probabilities of achieving underexposure, normal target exposure, and overexposure with different levofloxacin dosing regimens in older patients in relation to different classes of renal function

<table>
<thead>
<tr>
<th>Levofloxacin regimen (mg)</th>
<th>Probabilitya</th>
<th>0–19</th>
<th>20–39</th>
<th>40–59</th>
<th>60–79</th>
<th>&gt;80</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt;50</td>
<td>50–160</td>
<td>&gt;160</td>
<td>&lt;50</td>
<td>50–160</td>
</tr>
<tr>
<td>125 every 48 h</td>
<td></td>
<td>91.8</td>
<td>8.2</td>
<td>0.0</td>
<td>99.8</td>
<td>0.2</td>
</tr>
<tr>
<td>250 every 48 h</td>
<td></td>
<td>48.5</td>
<td>50.5</td>
<td>1.0</td>
<td>91.4</td>
<td>8.6</td>
</tr>
<tr>
<td>500 every 48 h</td>
<td></td>
<td>6.4</td>
<td>77.2</td>
<td>16.4</td>
<td>32.2</td>
<td>67.0</td>
</tr>
<tr>
<td>750 every 48 h</td>
<td></td>
<td>1.4</td>
<td>53.9</td>
<td>44.7</td>
<td>7.2</td>
<td>86.2</td>
</tr>
<tr>
<td>500 every 24 h</td>
<td></td>
<td>2.3</td>
<td>50.3</td>
<td>47.4</td>
<td>5.5</td>
<td>81.3</td>
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<td>17.1</td>
<td>81.8</td>
<td>1.7</td>
<td>51.3</td>
</tr>
<tr>
<td>500 every 12 h</td>
<td></td>
<td>0.1</td>
<td>3.6</td>
<td>96.4</td>
<td>0.2</td>
<td>12.3</td>
</tr>
</tbody>
</table>

aProbability of achieving underexposure (AUC_{24} < 50 mg · h/liter), normal target exposure (AUC_{24} between 50 and 160 mg · h/liter), and overexposure (AUC_{24} > 160 mg · h/liter) with different levofloxacin dosing regimens in older patients in relation to different classes of renal function. The classes of renal function (ml/min/1.73 m²) are shown in the top row, and those of levofloxacin AUC_{24} (mg · h/liter) are shown in the bottom row in the header.
# PK/PD of levofloxacin: limits in MICs

## Population Pharmacokinetics and Pharmacodynamics of Levofloxacin in Acutely Hospitalized Older Patients

Various Degrees of Renal Function

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### TABLE 3 Probabilities of achieving underexposure in older patients in relation to different classes of renal function

<table>
<thead>
<tr>
<th>Levofloxacin regimen (mg)</th>
<th>Probability&lt;sup&gt;a&lt;/sup&gt;</th>
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<th>Probability&lt;sup&gt;a&lt;/sup&gt;</th>
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<td>125 every 48 h</td>
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<td>8.2</td>
<td>0.0</td>
</tr>
<tr>
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<td>96.4</td>
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<sup>a</sup>Probability of achieving underexposure (AUC<sub>24</sub> < 50 mg · h/liter) with different levofloxacin dosing regimens in older patients with different renal function classes is shown. AUC<sub>24</sub> values were calculated in mg · h/liter based on the patient’s weight (kg) and height squared (m<sup>2</sup>).
PK/PD of levofloxacin: limits in MICs

Population Pharmacokinetics and Pharmacodynamics of Levofloxacin in Acutely Hospitalized Older Patients with Various Degrees of Renal Function

<table>
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</tbody>
</table>

- Probability of achieving underexposure (AUC_{24} < 50 mg · h/liter), normal target exposure (AUC_{24} between 50 and 160 mg · h/liter), and overexposure (AUC_{24} > 160 mg · h/liter) with different levofloxacin dosing regimens in older patients in relation to different classes of renal function. The classes of renal function (ml/min/1.73 m²) are shown in the top row, and those of levofloxacin AUC_{24} (mg · h/liter) are shown in the bottom row in the header.
Population Pharmacokinetics and Pharmacodynamics of Levofloxacin in Acutely Hospitalized Older Patients: Various Degrees of Renal Function

<table>
<thead>
<tr>
<th>Levofoxacin regimen (mg)</th>
<th>Probability&lt;sup&gt;a&lt;/sup&gt;</th>
<th>&lt;50</th>
<th>50–160</th>
<th>&gt;160</th>
<th>&lt;50</th>
<th>50–160</th>
<th>&gt;160</th>
</tr>
</thead>
<tbody>
<tr>
<td>125 every 48 h</td>
<td></td>
<td>100.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>250 every 48 h</td>
<td></td>
<td>99.9</td>
<td>0.1</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>500 every 48 h</td>
<td></td>
<td>97.2</td>
<td>2.8</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>750 every 48 h</td>
<td></td>
<td>89.0</td>
<td>11.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>500 every 24 h</td>
<td></td>
<td>78.7</td>
<td>21.0</td>
<td>0.3</td>
<td>0.0</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>750 every 24 h</td>
<td></td>
<td>50.3</td>
<td>47.6</td>
<td>2.1</td>
<td>0.0</td>
<td>2.1</td>
<td>2.1</td>
</tr>
<tr>
<td>500 every 12 h</td>
<td></td>
<td>2.8</td>
<td>82.8</td>
<td>14.4</td>
<td>0.0</td>
<td>14.4</td>
<td>14.4</td>
</tr>
</tbody>
</table>

<sup>a</sup>Probability of achieving underexposure (AUC<sub>24</sub> < 50 mg · h/liter, mg · h/liter) with different levofloxacin dosing regimens in older patients ( renal function class) are shown in the top row, and those of levofloxacin AUC<sub>24</sub> (> 160 mg · h/liter) are shown in the bottom row.
The opportunity to define permissible doses of levofloxacin in older patients was further strengthened by the findings of two recent reviews showing that levofloxacin is the fluoroquinolone associated with the highest risk of causing tendon damage.

This may further strengthen the valuable role that a real-time therapeutic drug monitoring (TDM)-guided approach to levofloxacin dosage adjustments may have in preventing drug-related toxicity in older patients.
Vancomycin

- Vancomycin is an AUC\textsubscript{24h}/MIC-driven antibiotic.
- Vancomycin effective AUC\textsubscript{24h}/MIC should be around 400 (more than for fluoroquinolones) because of its poor tissue penetration.
- Yet, most (US) guidelines suggest to only measure trough (C\textsubscript{min}) levels.

**IDSA GUIDELINES**

Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant *Staphylococcus aureus* Infections in Adults and Children

Catherine Liu,\textsuperscript{1} Arnold Bayer,\textsuperscript{3,5} Sara E. Cosgrove,\textsuperscript{6} Robert S. Daum,\textsuperscript{7} Scott K. Fridkin,\textsuperscript{8} Rachel J. Gorwitz,\textsuperscript{9} Sheldon L. Kaplan,\textsuperscript{10} Adolf W. Karchmer,\textsuperscript{11} Donald P. Levine,\textsuperscript{12} Barbara E. Murray,\textsuperscript{14} Michael J. Rybak,\textsuperscript{12,13} David A. Talan,\textsuperscript{45} and Henry F. Chambers\textsuperscript{1,2}

Vancomycin

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- Vancomycin effective AUC$_{24h}$/MIC should be around 400 (more than for fluoroquinolones) because of its poor tissue penetration
- Yet, most (US) guidelines suggest to only measure trough ($C_{min}$) levels!

**Trough vancomycin concentrations are the most accurate and practical method to guide vancomycin dosing (B-II).**

- For serious infections, such as bacteremia, infective endocarditis, osteomyelitis, meningitis, pneumonia, and severe SSTI (eg, necrotizing fasciitis) due to MRSA, vancomycin trough concentrations of 15–20 µg/mL are recommended (B-II).
Vancomycin: things are moving …

A Quasi-Experiment To Study the Impact of Vancomycin Area under the Concentration-Time Curve-Guided Dosing on Vancomycin-Associated Nephrotoxicity

Natalie A. Finch,* Evan J. Zasowski,† Kyle P. Murray,* Ryan P. Mynatt,* Jing J. Zhao,* Raymond Yost,* Jason M. Pogue,* Michael J. Rybak†*‡,§

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FIG 1 Time to nephrotoxicity by Cox proportional hazards regression. AUC-TD, AUC- and trough concentration-guided dosing.
But there could be a better approach: continuous infusion

- 54 patients (40 documented infections)
- target concentration: 25-30 mg/L
- loading dose: 20 mg/kg;
- infusion rate: 2.5 g/day
  (adapted to renal function and corrected by therapeutic drug monitoring)

Ampe et al., International Journal of Antimicrobial Agents (2013) 41:439-446
Results are quite clear for efficacy….

relation between $\text{AUC}_{24\text{h}} / \text{MIC}$ (E-Test) and clinical efficacy ($n=19$)

Ampe et al., International Journal of Antimicrobial Agents (2013) 41:439-446
But there still are huge variations in blood levels

\[ \text{subsequent vancomycin serum levels values in individual patients} \]
\[ \text{with } > 3 \text{ determinations after the first } 96\text{h of treatment} \] (n = 52)

Ampe et al., International Journal of Antimicrobial Agents (2013) 41:439-446
But there still are huge variations in blood levels of vancomycin serum levels in individual patients with >3 determinations after the first 96h of treatment (n = 52).

Monitoring remains essential.

Ampe et al., International Journal of Antimicrobial Agents (2013) 41:439-446
• β-lactams have been long considered as drugs with a very large therapeutic ratio… So, why bother about monitoring them… ?

• but two things have now appeared as critical
  – the rise in MICs, creating a risk of under-treatment with the current dosages
  – the huge variability of PK parameters ($V_d$ and clearance) between patients and over time (ICU)
    → under-treatment
    → toxicity
What is the correct target for a β-lactam?

Optimizing β-lactams treatment in critically-ill patients using pharmacokinetics/pharmacodynamics targets: are first conventional doses effective?


What is the correct target for a β-lactam?

Optimizing β-lactams treatment in critically-ill patients using pharmacokinetics/pharmacodynamics targets: are first conventional doses effective?

Table 1. Percentage of the dosing interval over which the unbound (free) drug concentration remains above the minimum inhibitory concentration (MIC) of the infecting pathogen (ft>MIC) for various β-lactams after bolus dosing in animal infection models [13,16].

<table>
<thead>
<tr>
<th>β-lactams</th>
<th>Bacteriostatic effect</th>
<th>Maximal bactericidal effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillins</td>
<td>30%</td>
<td>50%</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>35–40%(^a)</td>
<td>60–70%(^a)</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>20%</td>
<td>40%</td>
</tr>
</tbody>
</table>
Illustration from animal data…

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

\[ R^2 = 94\% \]

100% - Maximal effect?
What is the correct dose for your patient?

Mild infections in a non-immunocompromised patient:
- 40% efficiency

Severe infection in an immunocompromised patient:
- 100% efficiency

Log_{10} CFU per lung at 24 hours vs. Time above MIC (%) graph.
but maybe even more?

Figure 2 Relationship between concentration of ceftazidime 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 two to threefold dilutions. The maximum kill rate is attained at around four times the minimum inhibitory concentration (MIC). Modified with permission from [16].

But which MICs?

But are all patients equal?

Concentration profile of a β-lactam in volunteers

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

But are all patients really alike?
What is a "standard" patient?
Here is the daily reality …

Concentration profiles in real patients

Today, monitoring β-lactams becomes a reality
β-lactam monitoring: a typical and early example
**β-lactam monitoring: a typical and early example**

Fig. 1. Change in percentage of time during which the concentration remained above 4x the minimum inhibitory concentration (%T > 4× MIC) for patients who received dosage adjustment due to below-target serum concentrations. Horizontal bars represent the mean %T > 4× MIC.
Monitoring of β-lactams in special populations (1)

Wong et al. BMC Infectious Diseases 2014, 14:288
http://www.biomedcentral.com/1471-2334/14/288

REVIEW

How do we use therapeutic drug monitoring to improve outcomes from severe infections in critically ill patients?

Gloria Wong1†, Fekade Bruck Sime2,3†, Jeffrey Lipman1,4 and Jason A Roberts1,2,4*
How do we use therapeutic drug monitoring to improve outcome in critically ill patients?

Gloria Wong*, Fekade Bruck Sime

Table 1 Summary of common factors associated with altered pharmacokinetics of antibiotics in critically ill patients

<table>
<thead>
<tr>
<th>Increased Vd</th>
<th>Decreased Cl</th>
<th>Increased Cl</th>
<th>Variable changes in Vd and/or Cl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoalbuminaemia, leading to increased unbound drug</td>
<td>Renal hypoperfusion</td>
<td>Augmented renal clearance</td>
<td>Extracorporeal interventions (eg RRT, ECMO)</td>
</tr>
<tr>
<td>Capillary leakage</td>
<td>Acute kidney injury</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluid resuscitation</td>
<td>Renal/hepatic dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Third space loss</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
In the context of critical illness, there is strong data demonstrating that standard dosing regimens for many antibiotics frequently fail to provide optimal PK/PD exposure in critically ill patients.

- Given that pharmacokinetic exposures can be very difficult-to-predict in some patients, TDM is valuable to identify these patients and guide dose optimization.

- TDM can ensure attainment of PK/PD surrogate indicators of antibiotic efficacy, and therefore potentially improve patient outcome.
Monitoring of β-lactams in special populations (2)

β-Lactam Dosage Regimens in Septic Patients with Augmented Renal Clearance

Alexandra Jacobs,a,b Fabio Silvio Taccone,a Jason A. Roberts,c,d,e,f Frédérique Jacobs,b Frederic Cotton,g Fleur Wolff,g Jacques Creteur,g Jean-Louis Vincent,a Maya Hitesb

Currently, we recommend, when possible, TDM-guided therapy to optimize PK/PD target attainment in critically ill patients and particularly in those at risk of ARC.
Monitoring of β-lactams in special populations (3)

Repeated Piperacillin-Tazobactam Plasma Concentration Measurements in Severely Obese Versus Nonobese Critically Ill Septic Patients and the Risk of Under– and Overdosing*

Boris Jung, MD, PhD1,2; Martin Mahul, MD, MSc1,2; Dominique Breilh, PharmD, PhD2;
Rachel Legeron, PharmD3; Jeremy Signe, MD1,2; Helene Jean-Pierre, MD4;
Anne-Catrin Uhlemann, MD, PhD5; Nicolas Molinari, PhD6; Samir Jaber, MD, PhD1,2

Monitoring of β-lactams in special populations (3)

Reprinted from: Laboratory Medicine at the Clinical Interface, Antalya, Turkey


Piperacillin blood concentrations (median, quartiles, and individual values) over the 7-d study period for non-obese (n = 12) and severely obese (n = 11) patients. The Pseudomonas aeruginosa minimal inhibitory concentration breakpoint (16 mg/L), 4-fold the breakpoint (64 mg/L), and the potential piperacillin toxic concentration threshold (150 mg/L) are represented as dashed lines..

*Between obese and non-obese patients over time, adjusted to SOFA score.
Today, TDM of β-lactams may become a reality

• Therapeutic drug monitoring (TDM) is a strategy that may help to optimize dosing.

• Ideally, methods used for routine TDM should have a short turnaround time (fast run-time and fast sample preparation), a low limit of quantification and a sufficiently high upper limit of quantification.

• There is also a growing number of methods measuring free concentrations.
What about oxazolidinones (linezolid)?
Linezolid: huge variations in $C_{\text{min}}$ ...
Drug monitoring and individual dose optimization of antimicrobial drugs: oxazolidinones

Table 2. Factors affecting pharmacokinetics, efficacy, and/or safety of LZD.

<table>
<thead>
<tr>
<th>Effect on LZD pharmacokinetics</th>
<th>Effect on clinical outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal insufficiency</td>
<td>Patients with renal insufficiency are more likely to experience LZD-related adverse events (mainly hematological, neurological, and metabolic complications) [15,20-23,44]</td>
</tr>
<tr>
<td>Kidney impairment is associated with reduced LZD clearance [15,20,22,23]</td>
<td>Patients undergoing peritoneal dialysis [27] or hemodialysis are more likely to experience LZD-related hematologic and metabolic complications [45]</td>
</tr>
<tr>
<td>Renal replacement therapy</td>
<td>Patients concomitantly treated with LZD and rifampicin experience less hematological toxicity compared with those given only LZD [41]</td>
</tr>
<tr>
<td>LZD is partially cleared by dialysis. However, dose reductions are still required to avoid excessive LZD accumulation [28,29]</td>
<td></td>
</tr>
<tr>
<td>Co-medications</td>
<td>Low body weight (&lt;55 kg) was associated with the development of thrombocytopenia [46]</td>
</tr>
<tr>
<td>Coadministration of clarithromycin, omeprazole, amiodarone, or amlodipine increases LZD concentrations, whereas rifampicin or levothyroxine decreases LZD exposure.[12]</td>
<td>Anecdotal case reports of obese patients failing to reach the PK/PD targets even if treated with higher than conventional doses [36]</td>
</tr>
<tr>
<td>Body weight</td>
<td>Duration of LZD treatment of more than 15 days was significantly associated with the development of thrombocytopenia [23,47]</td>
</tr>
<tr>
<td>A significant inverse correlation was reported between body weight and LZD AUC [21,31]</td>
<td>Patients experiencing hematological toxicity were older compared to patients who tolerated LZD treatment [15]</td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
</tr>
<tr>
<td>Mild reduction in the plasma concentrations of LZD in obese patients treated with the oral 600 mg bid dose [32,33]</td>
<td></td>
</tr>
<tr>
<td>Duration of LZD treatment</td>
<td></td>
</tr>
<tr>
<td>Duration of LZD treatment</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>A significant direct association was reported in adults between age and LZD AUC [31]</td>
<td></td>
</tr>
</tbody>
</table>
Toxicodynamics: what drives linezolid toxicity...

Fig. 16.13 Linezolid $C_{\text{min}}$ and logistic regression model for thrombocytopenia (Pea et al. 2012), reproduced with permission. The symbols refer to the $C_{\text{min}}$ observed over time in each patient with (top) or without (bottom) thrombocytopenia. The continuous line represents the result of the logistic regression model. The vertical broken line identifies the $C_{\text{min}}$ value predicting 50 % probability of thrombocytopenia.

1. know your antibiotic and its PD parameter
   - time-, $AUC_{24h}$-, of $C_{max}$- driven

2. look for the pertinent PK data and the recommended dosages …

3. compute the pertinent "PK/PD parameter – MIC" ratio / target that will ensure efficacy
   - $\beta$-lactams: $f \, T > MIC = 30$ to $100$ % of the dosing interval
   - aminoglycosides: $C_{max} = 8 \times MIC$
   - fluoroquinolones: $AUC_{24h}/MIC = 30$ (min.) -125 (preferred)
   - vancomycin: $AUC_{24h}/MIC = 400$
   - macrolides: $AUC_{24h}/MIC = 30$
   - tetracyclines (includ. tigecycline): $AUC_{24h}/MIC = 7-10$
   - linezolid: avoid $C_{min} > 7$ mg/L (for toxicity)

4. Check your local epidemiology for MICs … →

[Check the drug label and pertinent publications … or rely on a clinical pharmacist!]

[Ask your microbiologist]
When choosing an antibiotic, do we know

3. for the society
   - how to prevent emergence of resistance?

This is probably a **most difficult challenge** because
- resistance genes are already present in nature (**resistome**)
- bacteria quickly adapt to new environments (**mutation/selection**)

Fig. 1 The antibiotic resistome gene flow in environments, human, and animals. We propose that the antibiotic resistome gene flow is “from the natural environments” and “to the natural environments.” The natural environments are the reservoirs for antibiotic resistome. The original ARGs in environmental bacteria can be captured by human or animal pathogens and gradually evolved under the antibiotic selection pressure and become qualified. These ARGs or ARG-bearing bacteria are then disseminated back to the natural environments due to the human activities on producing and using antibiotics. In most cases, the ARGs are more easily transferred within respective ecological niches (the natural environments, and the human- and animal-associated environments). This resistance gene flow scenario is not very applicable to antibiotic resistance caused by chromosomal mutation.

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- resistance genes are already present in nature (re sistome)
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MIC may increase 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.

Optimization may prevent 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 Oliver⁴ 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 serum concentration levels (hollow fibers model)
Optimization may prevent emergence of resistance

To prevent emergence of resistance, $C_{\text{min}}$ of β-lactams must stay > 4 x MIC (mean), which commands higher dosages…

Figure 2. Typical bacterial profiles for WT P. aeruginosa. Placebo control (a), Ceftazidime at 500 mg every 8 h ($C_{\text{min}}$/MIC = 2.9) (b). Ceftazidime at 3000 mg every 8 h ($C_{\text{min}}$/MIC = 7.7) (c). Data are shown as mean ± SD.

Figure 3. Drug exposures ($C_{\text{min}}$/MIC) stratified by outcomes. Each data point represents a hollow-fibre infection model experiment. The most significant threshold ($C_{\text{min}}$/MIC ≥ 3.8) is depicted by the horizontal broken line.

Avoiding the window for selection of resistance

Mutation selection window

Time after administration

concentration

MIC

MPC

MSW

Avoiding the window for selection of resistance

- **MIC**
- **MPC**
- **MSW**

**AUC_{24h} / MIC = 125 en C_{max} / MIC > 10** as parameters for efficacy and prevention of resistance of fluoroquinolones: which MICs can you cover with standard treatments?

<table>
<thead>
<tr>
<th>Drug</th>
<th>Typical daily dosage$^a$</th>
<th>Typical PK values</th>
<th>Proposed PK/PD upper limit of sensitivity (µg/ml) for</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>C_{max} in mg/L total/free (dose)</td>
<td>AUC_{24 h} (mg × h/L) total/free</td>
<td>Efficacy$^b$</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>800 mg</td>
<td>1.4/1.1 (400 mg PO)</td>
<td>14/11</td>
<td>0.1–0.4</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1000 mg</td>
<td>2.5/1.75 (500 mg PO)</td>
<td>24/18</td>
<td>0.2–0.8</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>400 mg</td>
<td>4/3 (400 mg PO)</td>
<td>40/30</td>
<td>0.3–0.9</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>500 mg</td>
<td>4/2.8 (500 mg PO)</td>
<td>40/28</td>
<td>0.3–0.9</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>400 mg</td>
<td>3.1/1.8 (400 mg PO)</td>
<td>35/21</td>
<td>0.2–0.7</td>
</tr>
</tbody>
</table>

TDM of antibiotics …

Dosage → Serum concentrations → Concentration at the site of infection → Therapeutic effects

Concentration in non-target organs → Toxic effects

prevention of resistance

TDM might be the key …