Towards clinical Applications of PK-PD

P.M. Tulkens
Cellular and Molecular Pharmacology, Catholic University of Louvain, Brussels, Belgium

with many things borrowed from

J.W. Mouton
Dept Medical Microbiology, Canisius Wilhelmina Hospital, Nijmegen, The Netherlands

http://www.isap.org

47th Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL. – Workshops
September 16th, 2007
The problems ...

1. Infections are (most often) treated with the same dosing regimen irrespective of the absolute susceptibility of the micro-organism ...

<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>Cefazolin</td>
<td>0.5-1 g q6-12h</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 q8h</td>
<td>2 g q4-5h</td>
<td></td>
<td></td>
<td>20-25 mg/kg q6h</td>
<td></td>
</tr>
<tr>
<td>Cephrapirin</td>
<td>0.5-1 g q8h</td>
<td>2 g q4-5h</td>
<td></td>
<td></td>
<td>10-20 mg/kg q6h</td>
<td></td>
</tr>
</tbody>
</table>
The problems ...

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

Les concentrations critiques séparent les souches sensibles des souches de sensibilité intermédiaire et ces dernières, des résistantes :

$S \leq 4 \text{ mg/l }$ et $R > 32 \text{ mg/l}$
The problem as seen from a question of the FDA...

**Figure 2. TROVAFLOXACIN vs Staphylococcus aureus**

(N = 458)

- Same dose ??
- And what about those ones?

Breakpoints tend to set up quantic limits in what is fundamentally a continuous distribution...
So, you need to know the enemy ...

For a fluoroquinolone....

\[
\text{MIC} = 0.016 \text{ mg/L} \quad \text{Susceptible}
\]

\[
\text{MIC} = 2.0 \text{ mg/L} \quad \text{Susceptible ?}
\]
Which parameter are you going to use in your hospital?

- AUC$_{24h}$/MIC
- C$_{\text{max}}$/MIC
- Time above MIC

Exercice with
- the fluoroquinolones
- the $\beta$-lactams
The saga of the AUC / MIC vs C_{max} / MIC ratio for fluoroquinolones ...

AUC / MIC is the parameter ...

Forrest et al., AAC, 1993
AUC/MIC$_{24h}$ = 125: a magical number??

125 was the limit below which failure rates became unacceptable because of either

- a large MIC
- or a too low dosage

(AUC is proportional to the dosage)
1st Example:
You want to control antibiotic dosing at the level of the patient

- Patient 60 yr, pneumonia and suspected bacteraemia/sepsis
- Ixacin 400 mg IV q8h ⇒ AUC = 30
- Gram negative rod, E-test MIC=0.01 mg/L
- $30/0.01 \Rightarrow 3000$
- You can quietly adjust dose to 100 mg/day

Mouton & Vinks, PW 134:816
Is 125 good for all ??

The saga of *S. pneumoniae* ...

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**24 Hr AUC/MIC**

**Mortality (%)**

- **non-neutropenic**

- **neutropenic**
Conditions That Predispose to Pneumococcal Infection

**Defective antibody formation**
- Primary: Congenital agammaglobulinemia
- Common variable (acquired): hypogammaglobulinemia
- Selective IgG subclass deficiency
- Secondary: Multiple myeloma, Chronic lymphocytic leukemia, Lymphoma, HIV infection

**Defective complement (primary or secondary)**
- Decreased or absent C1, C2, C3, C4

**Insufficient numbers of PMNs**
- Primary: Cyclic neutropenia
- Secondary: Drug-induced neutropenia

**Poorly functioning PMNs**
- Aplastic anemia
- Alcoholism
- Cirrhosis of the liver
Conditions That Predispose to Pneumococcal Infection

**Glucocorticosteroid treatment**
Renal insufficiency?

**Poorly avid receptors for FCγII (R131 allele)**

**Defective clearance of pneumococcal bacteremia**

**Primary Congenital asplenia, hyposplenia**

**Secondary Splenectomy**
Sickle cell disease (autosplenectomy)
Multifactorial

**Infancy and aging**
Malnutrition
Diabetes mellitus
Prior respiratory infection
Influenza
Cigarette smoking
Asthma
COPD
Quinolones: to peak or not to peak?

- Three studies have shown AUC/MIC predictive for outcome
- One prospective study showed Peak/MIC to be more predictive

Modelling studies show that:
- Survival linked to Peak/MIC when ratio > 10/1
- Survival linked to AUC/MIC when ratio < 10/1
- the risk of resistance is minimized if the peak/MIC > 10
So, let us accept values with some degree of precaution

If you follow Drusano and wish to prevent resistance

- peak / MIC > 10

If you believe your patient is not a healthy mouse …

- $AUC_{24h} / MIC > 100$
## Breakpoint issues ...

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage (mg/24h)</th>
<th>AUC/MIC* (mg/24h)</th>
<th>peak / MIC** (24h)</th>
<th>NCCLS Bkpts</th>
</tr>
</thead>
<tbody>
<tr>
<td>norfloxacin</td>
<td>800</td>
<td>0.1</td>
<td>0.2</td>
<td>&lt; 4</td>
</tr>
<tr>
<td>ciprofloxacin</td>
<td>500</td>
<td>0.1</td>
<td>0.2</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>ofloxacin</td>
<td>400</td>
<td>0.2-0.4</td>
<td>0.3-0.4</td>
<td>&lt; 2</td>
</tr>
<tr>
<td>levofloxacin</td>
<td>500</td>
<td>0.4</td>
<td>0.4-0.5</td>
<td>&lt; 2</td>
</tr>
<tr>
<td>gatifloxacin</td>
<td>400</td>
<td>0.3</td>
<td>0.4</td>
<td>&lt; 2</td>
</tr>
<tr>
<td>moxifloxacin</td>
<td>400</td>
<td>0.4</td>
<td>0.4</td>
<td>&lt; 2</td>
</tr>
</tbody>
</table>

Based on US prescrib. inf. (adult of 60 kg) of NOROXIN®, CIPRO®, FLOXIN®, LEVAQUIN®, TEQUIN® and AVELOX®

* AUC/MIC = 125
** peak / MIC = 10
A proposal for PK/PD based-breakpoints for fluoroquinolones...

<table>
<thead>
<tr>
<th>Drug</th>
<th>Typical daily dosage&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Typical PK values</th>
<th>Proposed PK/PD upper limit of sensitivity (μg/ml) for</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>C&lt;sub&gt;max&lt;/sub&gt; in mg/L total/free (dose)</td>
<td>AUC&lt;sub&gt;24 h&lt;/sub&gt; (mg × h/L) total/free</td>
</tr>
<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>

Van Bambeke F, Michot JM, Van Eldere J, Tulkens PM.
2d example: you want to control antibiotic dosing at the level of the hospital

- You have two Ixacins: L-xacin and M-xacin
- They have essentially the same pharmacokinetics and tolerance
- Which one will you recommend in YOUR set-up for CAP?
Application to pneumococci in Belgium

Moxifloxacin 400 mg 1x/d
- AUC [(mg/l)xh] 48
- peak [mg/l] 4.5
- $\text{MIC}_{\text{max}} < 0.5$
- EUCAST bkpt: 1

Levofloxacin 500 mg 1x/d
- AUC [(mg/l)xh] 47
- peak [mg/l] 5
- $\text{MIC}_{\text{max}} < 0.5$
- EUCAST bkpt: 1-2 *

the S/I-breakpoint from 1.0 to 2.0 avoids dividing the wild type MIC distribution. The breakpoint of 2 relates to high dose (750-1,000 mg) therapy.

MIC data: J. Verhaegen et al., ECCMID 2003
Is France like Belgium?

PK/PD breakpoint for a dose of 400 / 500 mg/day (0.5 mg/L)

- moxifloxacin
- levofloxacin

Fig. 1. Distribution of fluoroquinolone MICs for *S. pneumoniae* blood isolates.
Is France like Belgium?

PK/PD breakpoint for a dose of 1 g/day (0.5 mg/L)

- Moxifloxacin
- Levofloxacin

Fig. 1. Distribution of fluoroquinolone MICs for S. pneumoniae blood isolates.
EUCAST

• formed in 1997
• convened by the main ad-hoc scientific and breakpoints committees in Europe
• sets common breakpoints for surveillance of antimicrobial resistance and harmonise clinical breakpoints for existing drugs
• sets breakpoints for all newly registered antimicrobials for inclusion in the labeling (SPC) through ongoing agreement with the European Medicines Agency (EMEA)
• all breakpoints are based on a combination of
  • PK/PD data (in vitro, animals, …)
  • PK in humans with Monte-Carlo simulations and target attainment rates with dose simulations
  • Clinical data
### Fluoroquinolones - EUCAST clinical MIC breakpoints 2006-06-20 (v 2.2)

<table>
<thead>
<tr>
<th>Fluoroquinolone</th>
<th>Species-related breakpoints (S&lt;\textit{R}&gt;)</th>
<th>Non-species related breakpoints S&lt;\textit{R}&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Entero-&lt;br&gt;bacteriaceae</td>
<td>Pseudo-monas</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>RD</td>
<td>0.5/1</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>RD</td>
<td>1/2</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>RD</td>
<td>0.5/1</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>RD</td>
<td>0.5/1</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>RD</td>
<td>0.5/1</td>
</tr>
</tbody>
</table>

1. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (marked with \textit{RD} or \textit{IE} in the table).
2. For breakpoints for other fluoroquinolones (eg. pefloxacin and enoxacin) - refer to breakpoints determined by national breakpoint committees.
3. Salmonella spp - there is clinical evidence for ciprofloxacin to indicate a poor response in systemic infections caused by Salmonella spp with low-level fluoroquinolone resistance (MIC>0.064 mg/L). The available data relate mainly to S. typhi but there are also case reports of poor response with other Salmonella species.
4. The SI breakpoint has been increased from 0.5 to 1 mg/L to avoid dividing the wild type MIC distribution. Thus there is no intermediate category for Acinetobacter species.
5. Staphylococcus spp - breakpoints for ciprofloxacin and ofloxacin relate to high dose therapy.
6. Staphylococcus pneumoniae - wild type S. pneumoniae are not considered susceptible to ciprofloxacin or ofloxacin and are therefore categorized as intermediate. For ofloxacin the \textit{IR} breakpoint was increased from 1.0 to 4.0 mg/L and for levofoxacin the \textit{SI} breakpoint from 1.0 to 2.0 to avoid dividing the wild type MIC distribution. The breakpoints for levofloxacin relate to high dose therapy.
7. Strains with MIC values above the SI breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint (in decimals) they should be reported resistant.
8. Neisseria meningitidis - breakpoints apply to the use of ciprofloxacin in the prophylaxis of meningococcal disease.

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All EUCAST data are freely available at http://www.eucast.org
2d example
\( \beta \)-lactams : \( T > MIC \ldots \)

but how much, how long, etc... ??

- Static dose vs maximum effect ?
- Free fractions of the drug (\( Fu \)) ?
- The same for all micro-organisms ?
- The same for all beta-lactams ?
- The same for all infections ?
- Variance of PK in population ?
- Value in combination therapy ?
How much time above MIC?

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

100 % - Maximal effect?
Here is a proposal ...

40% Moderately severe infection in a non-immunospressed patient

100% Severe infection in an immunosuppressed patient

100% ?
The same for all microorganisms?

T > MIC for static effect

<table>
<thead>
<tr>
<th>Drug</th>
<th>Enterobacteriaceae</th>
<th>S. pneumoniae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone (free)</td>
<td>38 (34-42)</td>
<td>39 (37-41)</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>38 (36-40)</td>
<td>38 (36-40)</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>36 (27-42)</td>
<td>39 (35-42)</td>
</tr>
<tr>
<td>Cefpirome</td>
<td>35 (29-40)</td>
<td>37 (33-39)</td>
</tr>
<tr>
<td>MK-0826</td>
<td>32 (20-39)</td>
<td></td>
</tr>
<tr>
<td>Meropenem</td>
<td>22 (18-28)</td>
<td></td>
</tr>
<tr>
<td>Imipenem</td>
<td>24 (17-28)</td>
<td></td>
</tr>
<tr>
<td>Linezolid</td>
<td></td>
<td>40 (33-59)</td>
</tr>
</tbody>
</table>
Fig. 7. Relationship between the change in $\log_{10}$ CFU per thigh or lung for various pathogens following 24 h of therapy with different doses of penicillins ($\triangle$), cephalosporins ($\bigcirc$) and carbapenems ($\square$).


The same for all $\beta$-lactams?
How do you adjust the dose for Time > MIC?

- "out of the package insert" PK data
- Monte-Carlo simulations and target attainment approaches
## Typical pharmacokinetics of an IV β-lactam

<table>
<thead>
<tr>
<th>time (hours)</th>
<th>serum concentration for</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5 g</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>12.5</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>10</td>
<td>1.5</td>
</tr>
<tr>
<td>12</td>
<td>0.75</td>
</tr>
</tbody>
</table>

* Single administration unique; half-life 2h; $V_d = 0.2$ l/kg
Typical pharmacokinetics of an IV β-lactam

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</tr>
<tr>
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<tr>
<td>10</td>
<td>1.5</td>
</tr>
<tr>
<td>12</td>
<td>0.75</td>
</tr>
</tbody>
</table>

* Single administration unique; half-life 2h; $V_d = 0.2\ l/kg$

Where would you like to be?
Simple optimisation of IV $\beta$-lactams for "difficult" organisms

- 2 g every 12 h  
  \[ T > \text{MIC} = 100\% \]
  if $\text{MIC} \leq 3\, \text{mg/L} !$

- 2 g every 8 h  
  \[ T > \text{MIC} = 100\% \]
  if $\text{MIC} \leq 12\, \text{mg/L}$

More frequent administrations is the best way to increase the activity of $\beta$-lactams in difficult-to-treat infections...

PK / PD breakpoint for IV $\beta$-lactams: $\text{MIC} < 8\, \mu\text{g/ml}$
But there are variation of PK in individuals...

Concentration-time profile of a beta-lactam in volunteers
\( V_d = 20 \text{ L}, k_a = 1.2 \text{ h}^{-1}, k_e = 0.3 \text{ h}^{-1} \)
Variation of PK in individuals...

Concentration-time profile of a beta-lactam in patients with a simulation with a coefficient var. of 20%
Monte Carlo Simulations in pk/pd

• Have estimates of PK parameter values and a measure of their dispersion (usually SD)
• Simulate PK curves
• use MIC distribution values in the the target population
• calculate a probability of attaining the desired target
• examine if this is feasible in clinical practice…
Example: target Attainment Rates of a β-lactam

The response to this β-lactam may be largely unpredictable.
### Cephalosporins

<table>
<thead>
<tr>
<th>Cephalosporins</th>
<th>Enterobacteriaceae</th>
<th>Pseudomonas</th>
<th>Acinetobacter</th>
<th>Staphylococcus</th>
<th>Enterococcus</th>
<th>Streptococcus A,B,C,G</th>
<th>S.pneumoniae</th>
<th>S.pneumoniae</th>
<th>H.influenzae M.catarrh</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefazolin</td>
<td>RD</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>note</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Cefepime</td>
<td>RD</td>
<td>1/8</td>
<td>8/8</td>
<td>--</td>
<td>note</td>
<td>--</td>
<td>0.5/0.5</td>
<td>0.1/0.2</td>
<td>0.25/0.2</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>RD</td>
<td>1/2</td>
<td>--</td>
<td>--</td>
<td>note</td>
<td>--</td>
<td>0.5/0.5</td>
<td>0.5/2</td>
<td>0.12/0.1</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>RD</td>
<td>1/8</td>
<td>8/8</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>RD</td>
<td>1/2</td>
<td>--</td>
<td>--</td>
<td>note</td>
<td>--</td>
<td>0.5/0.5</td>
<td>0.5/2</td>
<td>0.12/0.1</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>RD</td>
<td>8/8</td>
<td>--</td>
<td>--</td>
<td>note</td>
<td>--</td>
<td>--</td>
<td></td>
<td>0.5/1</td>
</tr>
</tbody>
</table>

---

1. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only in species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (marked with -- or IE in the table).

2. The cephalosporin breakpoints for Enterobacteriaceae will detect resistance mediated by most ESBLs and other clinically important beta-lactamases in Enterobacteriaceae. However, some ESBL-producing strains may appear susceptible or intermediate with these breakpoints. Laboratories may want to use a test which specifically screens for the presence of ESBL.

3. For ceftazidime and ceftazidime the susceptible breakpoint for *Pseudomonas aeruginosa* has been increased to avoid dividing the MIC wild type distribution. The breakpoint relates to high dosage of both drugs, i.e. 2 g x 3

4. Susceptibility of staphylococci to cephalosporins is inferred from the methicillin susceptibility (except ceftazidime which should not be used for staphylococcal infections).

5. The non-species related S/I breakpoint of 4, mg/L divides the wild type MIC distributions of relevant Enterobacteriaceae. To avoid this, the S/I breakpoint has been increased to 8 mg/L. The breakpoint pertains to a dosage of 1.5 g x 3 and to *E.coli* and *Klebsiella* spp only.

6. Strains with MIC values above the S/I breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint (in italics) they should be reported resistant.

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RD = rationale document listing data used by EUCAST for determining breakpoints.

IE = There is insufficient evidence that the species in question is a good target for therapy with the drug.

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*EUCAST clinical MIC breakpoints - cephalosporins - Mozilla Firefox*
Target Concentration :
continuous infusion

- Maximum effect time-kill at 4 x MIC
- Maximum effect in vitro model 4 x MIC (Mouton et al 1994)
- Effect in endocarditis model 4 x MIC (Xiong et al 1994)
- Effect in pneumonia model dependent on severity of infection (Roosendaal et al 1985, 1986)
Continuous Infusion
Pharmacokinetic Considerations

• Protein binding
• Linear relationship between clearance and dose
• Linear relationship between protein binding and dose
• Third compartment effects (CNS)
Dose Calculations for continuous infusion

- Total Clearance estimate
- Elimination rate constant

$$C_{ss} = \frac{K_o}{Cl}$$

- Volume of distribution for the initial loading dose (loading dose = $$C_{target} / Vd$$)
An example of application with temocilin (a stable, narrow spectrum β-lactam with high protein binding): comparison with BID

- **dose:**
  - 2 g/12h vs.
  - 2 g loading dose followed by 4g over 24h

- **assay:** free and total drug

De Jongh et al., submitted
Target Controlled Dosing for β-lactam by continuous infusion

- obtain an MIC (or guess it…)
- aim at (free) serum concentration of > 4 MIC (to be discussed)
- adjust
  - the loading dose ($C_{\text{max}} = \text{dose} / \text{volume of distribution}$)
  - the infusion rate ($C_{\text{ss}} = \text{infusion rate} / \text{clearance}$)

<table>
<thead>
<tr>
<th>Concentrations reached (in mg/l) :</th>
<th>(\text{mg/kg})</th>
<th>(\text{Vd (L/kg)})</th>
<th>(\text{Cl (ml/min)})</th>
<th>(\text{g/24h})</th>
</tr>
</thead>
<tbody>
<tr>
<td>after loading dose</td>
<td>15 (^a)</td>
<td>75</td>
<td>32.5</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>30 (^a)</td>
<td>150</td>
<td>75</td>
<td>6</td>
</tr>
<tr>
<td>during infusion</td>
<td>0.2</td>
<td>0.4</td>
<td>120</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>0.4</td>
<td></td>
<td>40</td>
<td>103</td>
</tr>
</tbody>
</table>

\(^a\) approx. 1 g for a 70 kg patient
Problems with continuous infusion ...

- Clearance estimates
- Variations in clearance (ICU)
- Volume of distribution (ICU, burned patients, ...)
- Non-linear clearance
- drug instability
Ceftazidime concentrations (ICU patients)

Variation in $V_d$?
Ceftazidime concentrations in ICU patients (successive determinations) during continuous infusion (4 g/day)

Laterre et al., ICAAC 2002
Conclusions … or what do you need with any antibiotic for "difficult to treat patients" or environments where susceptibility is no longer to its best… ?

- Obtain MIC distributions in YOUR clinical environment

- On this basis, construct nomograms to examine which doses (AUC*, peak*) and/or frequency of administration (time*) are necessary for the MIC you are interested in …

- Examine whether this is feasible for YOUR patients… with the drug you want to use

* get these informations from your pharmacist and/or the Industry …
A clinical algorithm or a path to success...

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

- **Yes**
  - Is the organism probably highly susceptible?
  - Use common dosage but with attention to PK/PD

- **No**
  - Obtain an MIC
  - S/I/R is insufficient!!
  - Adjust the dosage on a full PK/PD basis
A clinical algorithm (follow.) ...

Success?

- no
  - re-evaluate
    - the dosage
    - the therapeutic scheme
    - the antibiotic class based on PK/PD properties

- yes
  - Consider step-down therapy if acceptable on a microbiological point of view

Use these pieces of information to establish recommendations based on local epidemiology, knowledge of PK/PD properties and awareness of the risk for resistance, and SHARE YOUR EXPERIENCE.