Towards clinical Applications of PK-PD

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with many things borrowed from

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http://www.isap.org

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& 46th Infectious Diseases Society of America
Washington, DC
The problem ...

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>Adults</th>
<th>Severe Disease</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First Generation</strong></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>12.5-33 mg/kg q6-8h</td>
</tr>
<tr>
<td>Cephalothin</td>
<td>0.5-1 g q8h</td>
<td>2 g q4-6h</td>
<td>20-25 mg/kg q6h</td>
</tr>
<tr>
<td>Cephapirin</td>
<td>0.5-1 g q8h</td>
<td>2 g q4-6h</td>
<td>10-20 mg/kg q6h</td>
</tr>
</tbody>
</table>
The problem ...

2. Clinicians tend to ask only (and clinical microbiologists to provide only) "S – I – R" answers based on accepted beakpoints …
The problem as seen from a question of the FDA...

And what about those ones?

**Figure 2. TROVAFLOXACIN vs Staphylococcus aureus**
(N = 458)

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?

- $AUC_{24h} / MIC$
- $C_{max} / MIC$
- Time above MIC

Exercice with
- the fluoroquinolones
- the $\beta$-lactams
The saga of the AUC / MIC vs $C_{\text{max}} / \text{MIC}$ 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)
- was derived from studies on Gram-negative infections
Is 125 good for all ??

The saga of *S. pneumoniae* ...

---

**non-neutropenic**

- **Emax at** 30 ...

**neutropenic**

- **Emax at** 125 ...
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
- Aplastic anemia

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

**Glucocorticosteroid treatment**
Renal insufficiency?

**Poorly avid receptors for FCGRII (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 with fluoroquinolones

If you wish to get a faster eradication and reduce mergence of resistant

➡ peak / MIC > 10

If you are interested in global effect …

➡ $\text{AUC}_{24h} / \text{MIC}: 30 \text{ to } 125$
1st Example:
You want to control fluoroquinolone 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 ⇒3000 !
  - 100 mg/day is plenty !

- E-test MIC = 1 mg/L
  - 30/2 ⇒ 30 !
  - 400 mg q8h may fail

Mouton & Vinks, PW 134:816
## Breakpoint issues ...

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage (mg/24h)</th>
<th>AUC/MIC* (24h)</th>
<th>peak / MIC**</th>
<th>former 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$^a$</th>
<th>Typical PK values</th>
<th>Proposed PK/PD upper limit of sensitivity (μg/ml) for Efficacy$^b$</th>
<th>Prevention of resistance$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$C_{\text{max}}$ in mg/L total/free (dose)</td>
<td>$AUC_{24\ h}$ (mg x h/L) total/free</td>
<td></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>

2\textsuperscript{d} example: you want to control fluoroquinolone choice and 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
  - MIC max: 0.5-1.5
- peak [mg/l]: 4.5
  - $\text{MIC}_{\text{max}} \sim 0.5$

Levofloxacin 500 mg 1x/d
- AUC [(mg/l)xh]: 47
  - MIC max: 0.5-1.5
- peak [mg/l]: 5
  - $\text{MIC}_{\text{max}} \sim 0.5$

MIC data: J. Verhaegen et al., ECCMID 2003
Can you do that in another country?

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><strong>Enterobacteriaceae</strong>&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Pseudo-monas</th>
<th>Acinetobacter</th>
<th>Staphylococcus</th>
<th>Enterococcus</th>
<th>Streptococcus</th>
<th>S. pneumoniae&lt;sup&gt;6&lt;/sup&gt;</th>
<th>H. influenzae&lt;sup&gt;7&lt;/sup&gt;</th>
<th>M. catarrhalis</th>
<th>N. gonorrhoeae</th>
<th>N. meningitidis&lt;sup&gt;8&lt;/sup&gt;</th>
<th>Gram-negative</th>
<th>Non-species related breakpoints&lt;sup&gt;1&lt;/sup&gt; S&lt;R&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>RD 0.5/1</td>
<td>0.5/1</td>
<td>1/4</td>
<td>1/5</td>
<td>--</td>
<td>--</td>
<td>0.125/2</td>
<td>0.5/0.5&lt;sup&gt;7&lt;/sup&gt;</td>
<td>0.03/0.06</td>
<td>0.03/0.08</td>
<td>--</td>
<td>0.5/1</td>
<td></td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>RD 1/2</td>
<td>1/2</td>
<td>1/2</td>
<td>1/2</td>
<td>--</td>
<td>1/2</td>
<td>2/2</td>
<td>1/7</td>
<td>IE</td>
<td>IE</td>
<td>IE</td>
<td>IE</td>
<td>1/2</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>RD 0.5/1</td>
<td>--</td>
<td>--</td>
<td>0.5/1</td>
<td>--</td>
<td>0.5/0.5</td>
<td>0.5/0.5</td>
<td>IE</td>
<td>IE</td>
<td>IE</td>
<td>IE</td>
<td>0.5/1</td>
<td></td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>RD 0.5/1</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
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<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>0.5/1</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>RD 0.5/1</td>
<td>--</td>
<td>--</td>
<td>1/1&lt;sup&gt;3&lt;/sup&gt;</td>
<td>--</td>
<td>0.125/4</td>
<td>0.5/0.5&lt;sup&gt;7&lt;/sup&gt;</td>
<td>0.12/0.25</td>
<td>IE</td>
<td>--</td>
<td>--</td>
<td>0.5/1</td>
<td></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 - or 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>0.034 mg/L). The available data relate mainly to S. typhimurium but there are also case reports of poor response with other Salmonella species.

4. The SI breakpoint has been increased from 0.5 to 1.0 mg/L to avoid dividing the wild type MIC distribution. 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 IR breakpoint was increased from 1.0 to 4.0 mg/L and for levofloxacin the 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 malaria) they should be reported resistant.

8. Neisseria meningitidis - breakpoints apply to the use of ciprofloxacin in the prophylaxis of meningococcal disease.

**All EUCAST data are freely available at http://www.eucast.org**
2d example: β-lactams : T > MIC …

You know it is "time above MIC", but…

- How much / How frequent? (Static dose vs maximum effect?)
- 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 time above MIC?

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

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

- Moderately severe infection in a non-immunospressed patient
- Severe infection in an immunosuppressed patient

Graph:
- Y-axis: Log₁₀ cfu per lung at 24 hours
- X-axis: Time above MIC (%)
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 ($\square$). 

Andes & Craig Int.
J. Antimicrob. Agents
2002, 19: 261-268

The same for all $\beta$-lactams?
## 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>Meropenem</td>
<td>22 (18-28)</td>
<td></td>
</tr>
<tr>
<td>Imipenem</td>
<td>24 (17-28)</td>
<td></td>
</tr>
</tbody>
</table>
How do you adjust the dose for a given 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; \( V_d = 0.2 \text{ l/kg} \)
## Reading the labeling (package insert)

<table>
<thead>
<tr>
<th>time (hours)</th>
<th>serum concentration for</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>2</td>
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<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
Simple optimisation of IV β-lactams for "difficult" organisms

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

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

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

PK / PD breakpoint for IV β-lactams: MIC < 8 µg/ml
Cephalosporins

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 -- 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 cefepime 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.

-- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.
IE = There is insufficient evidence that the species in question is a good target for therapy with the drug.
RD = rationale document listing data used by EUCAST for determining breakpoints.
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 target population
- calculate a probability of attaining the desired target
- examine if this is feasible in clinical practice…
Monte Carlo Simulations in PK/PD: application to ceftobiprole

FIG. 4. TARs and 95% CI (thus, attainment rates at 2.5 and 97.5%, respectively) as obtained with simulations using means and SDs with or without the full covariance matrix.

ceftobiprole should be effective (static) up to an MIC of 4 mg/L

Target Concentration for β-lactams: continuous infusion

- Maximum effect time-kill at 4 x MIC
- Maximum effect in vitro model 4 x MIC
- Effect in endocarditis model 4 x MIC (Xiong et al 1994)
- Effect in pneumonia model dependent on severity of infection

**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].
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
Problems with continuous infusion ...

• Clearance estimates

• Variations in clearance (ICU)

• Volume of distribution (ICU, burned patients, ...)

• Non-linear clearance

• drug instability
Ceftazidime concentrations in ICU patients (successive determinations) during continuous infusion (4 g/day)

Laterre et al., ICAAC 2002
Problems with continuous infusion ...

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

You may like to monitor the serum levels if MICs ≥ 4 (also for discontinuous administration)

Temocillin > piperacillin > ceftazidime > cefepime …

Carbapenems are unstable (3-4h max.)
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?

yes

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