Pharmacodynamics of antibiotics …

From what you already knew about "optimizing activity" …
to what you didn't dare to ask about

Emergence of Resistance...

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Catholic University of Louvain, Brussels &
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International Society for Anti-infective Pharmacology (ISAP)
Are antibiotics following a path to madness?

discovery in soil bacteria and fungi
Are antibiotics following a path to madness?

and then we all saw the blooming tree of semi-synthetic and totally synthetic antibiotics
Are antibiotics following a path to madness?

and the General Surgeon told us that the fight was over
Are antibiotics following a path to madness?

But...
Antibiotics and resistance...

Questions...

• Rising resistance and correlation with antibiotic use …
• Did we use antibiotics in a rational way ? …
• What can we do beyond not using antibiotics ?
• Can this also reduce health care costs ? …
Overuse is one of the problems ...

Risk of resistance to β-lactams among invasive isolates of Streptococcus pneumoniae regressed against outpatient sales of beta-lactam antibiotics in 11 European countries
- resistance data are from 1998 to 1999; antibiotic sales data 1997.
- DDD = defined daily doses

How can you be "better"?

• be globally efficacious
  ➔ pharmacodynamics (PK/PD)

• avoid selection of resistance
  ➔ decide on security margins …
  ➔ invest in
    Mutant Prevention Concentration …
  ➔ think about efflux …
A few words about efficacy ...

\[ \Delta \log \text{CFU (24 h - 0 h)} \]

- Oxacillin
- Moxifloxacin
- Gentamicin
- Oritavancin

\[ \text{Cmax} \]

\[ \text{MIC} \]

\[ \text{Emin} \]

\[ \text{Emax} \]
And what if we put pharmacokinetics?
And what if we put pharmacokinetics?

**Cmin-Cmax**

- Low concentration dependency
- High concentration dependency

Conclusions so far ... 

- Contrary to most beliefs, all antibiotics are concentration-dependent (like all other drugs);

- but is all about at which serum concentration $E_{\text{max}}$ will be obtained and how large it is (compared to untreated controls) ....

- If $E_{\text{max}}$ is small and obtained at a low concentration/MIC ratio (relative to what you could reach in serum), all what you are left with is time ... and you get in vivo a time-dependent antibiotic (viz. $\beta$-lactams, vancomycin, ...) 

  ➔ BEWARE ! If the MIC rises, you will need to increase the concentration to reach your (weak) $E_{\text{max}}$ or to use low breakpoints if wishing to avoid clinical failures (viz. cephalosporins ...) ...
Breakpoints for cephalosporins and glycopeptides

### Cephalosporins

<table>
<thead>
<tr>
<th>Cephalosporin</th>
<th>Enterobacteriaceae&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Pseudo-monas&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Non-species related breakpoints&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefazolin</td>
<td>RD</td>
<td>--</td>
<td>1/2</td>
</tr>
<tr>
<td>Cefepime</td>
<td>RD</td>
<td>1/8</td>
<td>8/8</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>RD</td>
<td>1/2</td>
<td>--</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>RD</td>
<td>1/8</td>
<td>8/8</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>RD</td>
<td>1/2</td>
<td>--</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>RD</td>
<td>8/8&lt;sup&gt;5&lt;/sup&gt;</td>
<td>--</td>
</tr>
</tbody>
</table>

2006-03-31 (v 1.0)

### Carbapenem

<table>
<thead>
<tr>
<th>Carbapenem</th>
<th>Enterobacteriaceae</th>
<th>Pseudo-monas</th>
<th>Acinetobacter</th>
<th>Gram-negative anaerobes</th>
<th>Non-species related breakpoints&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ertapenem</td>
<td>0.5/1</td>
<td>--</td>
<td>--</td>
<td>1/1&lt;sup&gt;8&lt;/sup&gt;</td>
<td>0.5/1</td>
</tr>
<tr>
<td>Imipenem</td>
<td>2/8</td>
<td>4/8&lt;sup&gt;6&lt;/sup&gt;</td>
<td>2/8</td>
<td>2/8</td>
<td>2/8</td>
</tr>
<tr>
<td>Meropenem</td>
<td>2/8</td>
<td>2/8</td>
<td>2/8</td>
<td>2/8</td>
<td>2/8</td>
</tr>
</tbody>
</table>

Breakpoints for cephalosporins and glycopeptides

- **European Antimicrobial Breakpoints**
  - Clinical breakpoints:
    - Penicillins
    - Cephalosporins
    - Carbapenems
    - Monobactams
    - Fluoroquinolones
    - Aminoglycosides
    - Glycopeptides
    - Quinolones
    - Macrolides, ketolides & clindamycin
    - Tetracyclines, Tiamulin
    - Chloramphenicol, apramycin, dalloprim, quinupristine, teicoplanin, vancomycin
    - Trimethoprim, sulfamethoxazole, cotrimoxazole, nitrofurantoin, furazolidone

- **EUCAST definitions of resistance & epidemiological cut off values**
- **EUCAST principles for setting breakpoints**
- **Information for companies**

**Brand new!!**

PD of antibiotics: activity and resistance Barcelona - 22-04-06
Conclusions (2d part) ...

- If $E_{\text{max}}$ is large and obtained at serum concentrations higher than the usual $C_{\text{max}}$/MIC ratio, you get in vivo a concentration- and AUC-dependent antibiotic (viz. fluoroquinolones...)

  ➔ BEWARE: the MIC of the offending organism is also critical ...

  ➔ increasing the $C_{\text{max}}$/MIC and the AUC/MIC ratios will increase your effectiveness and may be the only way to act upon offending organisms with elevated MICs ...

  ➔ low Cmax/MIC and AUC/MIC ratios will lead to failures and emergence of resistance ...
After all, that was all known since 1987 ... for the good, old faithful aminoglycosides ...
But it wasn't so for fluoroquinolones...

Comparative activity of the 4-quinolones.

Phillips I, King A

Department of Microbiology, United Medical School, Guy's Hospital, London, United Kingdom.

Minimal inhibitory concentrations (MICs) of the 4-quinolones ciprofloxacin, enoxacin, norfloxacin, ofloxacin, pefloxacin, difloxacin, A-56620, and CI-934 are consistent world-wide, with allowances for differences in acquired resistance. MICs of these drugs for Enterobacteriaceae correlate with those of nalidixic acid, but resistance to the quinolones is rare if a breakpoint of greater than 2 mg/L is accepted. Most intestinal pathogens are sensitive. Acinetobacter, Pseudomonas aeruginosa, and other Pseudomonas species except Pseudomonas maltophilia are usually sensitive. Ciprofloxacin is generally the most active of the 4-quinolones against these organisms. All of the new agents have antistaphylococcal activity, but that of norfloxacin and ofloxacin is borderline. Against streptococci,

with a Cmax at 1.5-2.5 mg/L?
Fluoroquinolones: get a peak and an AUC!

in order to optimize:  
\[ \frac{AUC_{24h}}{MIC} \] should be > 125 * 
\[ \frac{C_{max}}{MIC} \] should be > 10

Get both a peak and a AUC!!
You said AUC/MIC >125 for Gram (+) ?

The saga of *S. pneumoniae* ...

non-neutropenic

neutropenic
You said Cmax/MIC ratio > 10 for Gram (+)?

The saga of *S. pneumoniae* ...


RESULTS (as presented by the authors):

- 134 / 313 had both PK and MIC
- clinical AND bacterial outcomes were related to peak/MIC
  (logistic regression; p < 0.001)
- results were favourable if peak / MIC > 12.2
So, let us be Europeans ...  
i.e. be cautious ... (aka not bold) 

If you believe G. Drusano was telling you the truth when he said "I am a doctor"...  

⇒ peak / MIC > 10  

If you believe your patient is not a healthy mouse … and think that J.J. Schentag is a knowledgeable PK/PD maniac...  

⇒ $\text{AUC}_{24h} / \text{MIC} > 100$
Levofloxacin 500 mg
1X / jr
• AUC [(mg/l)xh] 47
• peak [mg/l] 5
\[\text{MIC}_\text{max} < 0.5\]

Moxifloxacin 400 mg
1X / jr
• AUC [(mg/l)xh] 48
• peak [mg/l] 4.5
\[\text{MIC}_\text{max} < 0.5\]

MIC data: J. Verhaegen et al., 2003

PK/PD in action...
Same exercise for the French pneumococci ...
But we need to invest in something new…
Mutant Prevention Concentration …

MIC<sub>99</sub> = 0.8

"Classic" bactericidal effect

Elimination of resistant organisms

MPC<sub>10</sub> = 9

Dong et al: AAC 1999; 43:1756-1758
Mutant Prevention Concentration ...

Concentration which will inhibit the majority of the organisms

Concentration needed to prevent the selection of resistant organisms

MIC$_{99} = 0.8$

MPC$_{10} = 9$

Dong et al; AAC 43:1756-1758
Mutant Prevention Concentration of ciprofloxacin and levofloxacin in *P. aeruginosa* (clinical isolates) with "normal" susceptibility (MIC = 0.33 and 0.9 mg/L) …
Mutant Prevention Concentration of ciprofloxacin and levofloxacin in a strain of P. aeruginosa with reduced susceptibility (MIC = 2 and 4 mg/L) …

"Window" where selection of mutants/resistants may take place ...

concentration

Time after administration

Mutation selection window

Is this also true for *S. pneumoniae*?

<table>
<thead>
<tr>
<th>Molecule</th>
<th>MIC</th>
<th>MPC</th>
<th>$C_{\text{max}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>levoflox. (500 mg)</td>
<td>1</td>
<td>8</td>
<td>≈ 6</td>
</tr>
<tr>
<td>moxiflox. (400 mg)</td>
<td>0.25</td>
<td>1</td>
<td>≈ 4</td>
</tr>
</tbody>
</table>

Adapted from D. Croisier, 2005, Bondeau et al., 2001, and Hansen et al, 2003
Although fluoroquinolone resistance in *S. pneumoniae* isolates remains low, the opportunity for increased resistance exists as the use of fluoroquinolones for the treatment of respiratory tract infections rises. The potential for resistance formation should thus be considered when specific fluoroquinolones are selected for treatment. Including MPCs as part of a dosing strategy may be one means of limiting the selection of fluoroquinolone-resistant mutants and preserving this class of antibiotic.

### MPCs obtained for *S. pneumoniae* isolates

<table>
<thead>
<tr>
<th>Isolate</th>
<th>Cipro: $\text{MP}_{\text{MIC}}$</th>
<th>Gati: $\text{MP}_{\text{MIC}}$</th>
<th>Gemi: $\text{MP}_{\text{MIC}}$</th>
<th>Levo: $\text{MP}_{\text{MIC}}$</th>
<th>Moxi: $\text{MP}_{\text{MIC}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Wild-type GyrA and ParC, efflux negative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2587</td>
<td>16</td>
<td>2</td>
<td>8</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>2663</td>
<td>8</td>
<td>8</td>
<td>16</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>2670</td>
<td>8</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td><strong>ParC Ser79Phe, wild-type GyrA, efflux negative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4610</td>
<td>16</td>
<td>16</td>
<td>8</td>
<td>16</td>
<td>$&gt;$16</td>
</tr>
<tr>
<td>14744</td>
<td>16</td>
<td>16</td>
<td>16</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td><strong>GyrA Ser81Phe, wild-type ParC, efflux negative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1146</td>
<td>8</td>
<td>1</td>
<td>8</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Efflux positive, wild-type GyrA and ParC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15017</td>
<td>4</td>
<td>8</td>
<td>4</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>16072</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

* $\text{MP}_{\text{MIC}}$ are given in multiples of the MIC of each drug.

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>

MIC and MPC: can the first tell about the second?

TABLE 1. MPC/MIC ratios

<table>
<thead>
<tr>
<th>Isolate*</th>
<th>Levofoxacin</th>
<th>Mositoxin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sp-S</td>
<td>4/1 (4)</td>
<td>20/25 (8)</td>
</tr>
<tr>
<td>Sp-NS</td>
<td>8/1 (8)</td>
<td>20/25 (8)</td>
</tr>
<tr>
<td>Sp-R</td>
<td>4/1 (4)</td>
<td>20/25 (8)</td>
</tr>
<tr>
<td>Hi-N</td>
<td>0.125/0.015 (8)</td>
<td>0.125/0.03 (4)</td>
</tr>
<tr>
<td>Hi-P</td>
<td>0.06/0.015 (4)</td>
<td>0.25/0.03 (8)</td>
</tr>
<tr>
<td>Mc-P</td>
<td>2/0.125 (10)</td>
<td>2/0.125 (16)</td>
</tr>
</tbody>
</table>

*Sp, S. pneumoniae; Hi, H. influenzae; Mc, M. catarrhalis.


See also: Drlica et al., Antimicrob. Agents Chemther. 2006; 50:403-404

Efflux and MIC?

- efflux is a universal mechanism for cell protection against membrane-diffusing agents
- many drugs diffuse through membranes and become opportunistic substrates of efflux pumps
- for AB, efflux decreases the amount of drug in bacteria and impairs activity, increasing the MIC …
- insufficient drug exposure favors the selection of less sensitive organisms
- but
  - recognition by efflux varies widely among closely related drugs
    (e.g. levofloxacin >> moxifloxacin)
  - the increase in MIC is modest and often leaves the strain categorized (falsely …) as "sensitive"…
- true MIC determination may, therefore, become more and more critical …

Why do you need to detect efflux?

Ciprofloxacin / Escherichia coli
Antimicrobial wild type distributions of microorganisms – reference database
EUCAST

how many of your samples would actually fall here ....

But will be brought back to wild type distribution in the presence of efflux inhibitor ...
Efflux is in your backyard..

Typical increase in MIC of *S. pneumoniae* (wild type) towards CIP upon successive 24h incubations in the presence of CIP at concentrations equal to half the MIC observed each day.

Avrain et al., 7th ECC, 2005
And efflux favours resistance ... if you have not a Cmax/MIC ratio $> 8$ ... 

TABLE 2. Frequency of mutation of *S. aureus* ATCC 29213

<table>
<thead>
<tr>
<th>Mutation frequency with ciprofloxacin at:</th>
<th>4× MIC (1 μg/ml)</th>
<th>8× MIC (2 μg/ml)</th>
<th>16× MIC (4 μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;$10^{-6}$</td>
<td>$1.2 \times 10^{-8}$</td>
<td>$&lt;10^{-9}$</td>
<td>$&lt;10^{-9}$</td>
</tr>
<tr>
<td>$1.3 \times 10^{-8}$</td>
<td>$&lt;10^{-9}$</td>
<td>$&lt;10^{-9}$</td>
<td>$&lt;10^{-9}$</td>
</tr>
<tr>
<td>$&lt;10^{-9}$</td>
<td>$&lt;10^{-9}$</td>
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<td>$&lt;10^{-9}$</td>
</tr>
</tbody>
</table>
And efflux favours resistance ... if you have not a Cmax/MIC ratio > 8 ...

This is an efflux pump inhibitor ...

And see how it protects against the risk of mutation...

TABLE 2. Frequency of mutation of S. aureus ATCC 29213

<table>
<thead>
<tr>
<th>Piperine concn (µg/ml)</th>
<th>Mutation frequency with ciprofloxacin at:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4× MIC (1 µg/ml)</td>
</tr>
<tr>
<td>0</td>
<td>&gt;10⁻⁶</td>
</tr>
<tr>
<td>25</td>
<td>1.3 × 10⁻⁸</td>
</tr>
<tr>
<td>50</td>
<td>&lt;10⁻⁹</td>
</tr>
</tbody>
</table>

A clinical algorithm...

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

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 and on the knowledge of the PK/PD properties and of the risk for resistance
And what about health care costs?

Pharmacoeconomics

Economic
- cost minimization
- cost benefit
- cost effectiveness
- cost utility

Humanistic
- quality of life
- patient's preference
- patient's satisfaction

- Pharmacoeconomics of antibiotics is still largely underdeveloped outside the USA (but US-based models cannot easily be applied);
- However, comparisons identifying differences in
  - amount of money needed to reach a given (better?) clinical outcome;
  - expenses related to the same (or better) quality of life and patient's satisfaction;
may already suggest interesting avenues for further fine-tuning therapeutic guidelines

Rational bases for the choice of an antibiotic

- Know your LOCAL epidemiology
  - obtain MIC distributions from your microbiologists…
- know the PK profile of the drugs you consider to purchase
  - aim at obtaining > 90 % efficacy against the organisms of interest (AUC, peak, time above MIC) with a standard dosage, …
- include a safety margin (MPC …)
- Compare products on that basis first …
- Remember that
  - no antibiotic (if possible) is the best…
  - but that treatment failures (when treatment is needed) cost a lot … (so that cheap but 2d class antibiotics may not be a bargain...)
Please, act ...

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