Antibiotics in 2005: Which one do we need to use and when?

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- rising resistance in key respiratory pathogens!
- use antibiotics sparingly and rationally!
- important differences between antibiotics (PK/PD, rate of kill, Mutant Prevention Concentration) beyond simple MICs vs key pathogens …
- best agent first to minimize resistance and better outcomes
- can we also reduce health care costs?
Resistance in Europe …

Resistance of *S. pneumoniae* (invasive isolates) to erythromycin* in 2003

* = all macrolides (clarithromycin, roxithromycin…), and azalides (azithromycin), but not ketolides (telithromycin)
Which antibiotic? Barcelona, Spain – Nov 24, 2005

Trends of Resistance (Belgian data) ...

- macrolides
- tetracyclines
- penicillin* intermediate
- penicillin* full resistant

* all β-lactams (= penicillins, cephalosporins, …)

Belgian Reference Laboratory for pneumococci, Leuven, 2000
Is there a relationship between (widespread) use and resistance?

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

Use antibiotics with caution … Belgian antibiotic campaigns
Use antibiotics with caution … Belgian antibiotic campaigns

and better …
Success of public campaigns …

- significant reduction of AB prescriptions (sales = prescriptions in Belgium) during the influenza epidemic periods
- no significant-side effect detected
- cost-effective for public health

from Bauraind et al., JAMA 2004; 292:2468-70; more details on http://www.antibiotiques.org/english/
What is "better"?

- to be globally efficacious
  ➔ pharmacodynamics (PK/PD)

- to act fast
  ➔ rate of killing

- to avoid selection of resistance
  ➔ "mutant prevention concentration"
What is Pharmacokinetics / Pharmacodynamics (PK/PD)?

• Pharmacokinetics: what the body does to the drug
  ➔ absorption, distribution, serum and tissue levels elimination, …

• Pharmacodynamics (of AB): what the drug does to the bacteria
  ➔ static vs. bactericidal effect, rate of kill, eradication, prevention of resistance…. 

Dose and schedule

- Cmax
- \( t_{1/2} \)
- clearance

- \( E_{max} \)
- time to \( E_{max} \)
- prevention of relapses
- maintenance of susceptibility
From Pharmacokinetics to Pharmacodynamics of AB …

Which antibiotic?  Barcelona, Spain - Nov 24, 2005
The 3 main groups of antibiotics
after W.A. Craig, 2000; revised 2003)

<table>
<thead>
<tr>
<th>AB</th>
<th>PK/PD parameter</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-lactams</td>
<td>time above MIC</td>
<td>stay above the MIC as needed</td>
</tr>
<tr>
<td>macrolides,</td>
<td>AUC/MIC</td>
<td>give a sufficient daily dose ...</td>
</tr>
<tr>
<td>tetracyclines...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>quinolones</td>
<td>peak/MIC and AUC/MIC</td>
<td>obtain a sufficient peak and give a sufficient total daily dose</td>
</tr>
</tbody>
</table>

To be effective …

You choose a $\beta$-lactam …

• give it several times a day (3 to 4 times), or use an "extended release" form;

• adjust the dose to meet the decrease in susceptibility of S. pneumoniae (from 0.5 to 2 or even 4 g/daily);

• add clavulanic acid (or use a 2d generation cephalosporin like cefuroxime) in case you suspect a $\beta$-lactamase producing organism *;

• do not anticipate activity against organisms causing "atypical pneumonia" and related syndromes **.

* Haemophilus influenzae, Moraxella catarrhalis, …
** Legionella pneumophila, Chlamydia pneumoniae, Mycoplasma spp.
Dosing amoxycillin for respiratory tract infections in Belgium

Sensitivity of *S. pneumoniae* to amoxycillin

Dose and schedule for $T > CMI = 50\%$

Cumulative % of strains

- 1000 mg: 3 x / j
- 500 mg: 3 x / j
- 500 mg: 2 x / j

MIC data: J. Verhaegen et al., 2001
To be effective …

You decide to try a fluoroquinolone …

• no problems with penicillin-insensitive *S. pneumoniae* or with pathogens causing "atypical pneumonia" *,**, BUT you need …

• to get a peak large enough (10 x the MIC);
• to look for an AUC/MIC of at least 100
• to remain above the Mutant Prevention Concentration (MPC)
• try to stay away from efflux pumps…

* Haemophilus influenzae, Moraxella catarrhalis, …
** Legionella pneumophila, Chlamydia pneumoniae, Mycoplasma spp.
What do you mean by "PEAK /MIC > 10" and "AUC / MIC > 100"
What do you mean by PEAK / MIC > 10 and AUC / MIC > 100

AUC\textsubscript{24h} = \frac{\text{dose}}{\text{clearance}}
PK/PD in action …

**Levofloxacin** 500 mg
1X / jr
- AUC [(mg/l)xh] 47
- peak [mg/l] 5
⇒ **MIC**_{max} < 0.5

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

MIC data: J. Verhaegen et al., 2003
The rate of kill may also be important…

A simple experiment …

- put bacteria in broth
- add antibiotic at increasing concentrations
- look at the reduction of the inoculum

Which antibiotic? Barcelona, Spain - Nov 24, 2005
Craig et al., 1998
Mutant Prevention Concentration …

"Classic" bactericidal effect

Elimination of resistant organisms…

\[ \text{MIC}_{99} = 0.8 \]

\[ \text{MPC}_{10} = 9 \]

Dong et al; AAC 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	extsubscript{99} = 0.8**

**MPC	extsubscript{10} = 9**

Dong et al; AAC 43:1756-1758
"Window" where selection of mutants/resistants may take place ...

concentration

Time after administration

Mutation selection window

MPC

MSW

MIC

Which are the MPC values compared to
- MIC for *S. pneumoniae*
- $C_{\text{max}}$ for a standard dose?

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

Adapted from D. Croisier, 2005, Bondeau et al., 2001, and Hansen et al, 2003
Efflux?

• universal mechanism for cell protection against membrane-diffusing agents

• many drugs diffuse though membranes and become opportunistic substrates of efflux pumps

• for AB, efflux decreases the amount of drug in bacteria and impairs activity, favouring selection of less sensitive organisms

• but recognition by efflux varies widely among closely related drugs e.g. levofloxacin >> moxifloxacin

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A rational and (correctly) conservative approach for respiratory tract infections… *

patient with no risk and no comorbidity

amoxyccillin at appropriate doses and frequency

+ clavulanic acid (or cefuroxime) if β-lactamase producing organism

+ macrolide if no success within 3 days (atypicals…)

combined therapy β-lactam (high dose + clavulanic acid) +/- macrolide

fluoroquinolone with optimal PK/PD and MPC/MIC ratio profile

patient with risk or comorbidity

* adapted from Belgian IDAB CAP guidelines – limited to CAP 1, 2, and 3
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 in Europe is still largely underdeveloped (and 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
Quinolones in 2005: an update
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ABSTRACT
Quinolones are one of the largest classes of antimicrobial agents used worldwide. This review considers
the quinolones that are available currently and used widely in Europe (norfloxacin, ciprofloxacin,
ofloxacin, levofloxacin and moxifloxacin) within their historical perspective, while trying to position
them in the context of recent and possible future advances based on an understanding of: (1) their
chemical structures and how these impact on activity and toxicity; (2) resistance mechanisms (mutations
in target genes, efflux pumps); (3) their pharmacodynamic properties (AUC/MIC and C_max/MIC ratios;
mutant prevention concentration and mutant selection window); and (4) epidemiological considerations
(risk of emergence of resistance, clonal spread). Their main indications are examined in relation to their
advantages and drawbacks. Overall, it is concluded that these important agents should be used in an
educated fashion, based on a careful balance between their ease of use and efficacy vs. the risk of
emerging resistance and toxicity. However, there is now substantial evidence to support use of the most
potent drug at the appropriate dose whenever this is required.

Keywords  Ciprofloxacin, pharmacodynamics, quinolones, resistance, review, toxicity

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