The good and the bad uses of fluoroquinolones in Urology

Paul M. Tulkens

Unité de pharmacologie cellulaire et moléculaire & Centre de Pharmacie clinique
Université catholique de Louvain

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...

• Is there a problem?
  ➔ Rising resistance and correlation with antibiotic use …

• Resistance in urinary nosocomial isolates …
  ➔ what about quinolones uses in the community and the hospital?

• What are quinolones (adavantages – downsides) ?
  ➔ what are appropriate uses … and misuses ?

• Can this also reduce health care costs …
Overuse is one of the problems ... the classical situation in the community ...

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

Organisms and resistance in nosocomial urological specimens ...

Distribution of microbial species in 486 patients with nosocomially acquired urinary tract infection

- E. coli
- Pseudomonas
- Enterococcus
- Klebsiella
- Enterobacter
- Proteus
- CN S.
- Candida
- Others

A study from the European Society of Infections in Urology (ESIU)
Organisms and resistance in nosocomial urological specimens ...

Resistance of *E. coli*

- **Amoxiclav**
- **2d/3d gen. cephalosp.**
- **Ciprofloxacin**

A study from the European Society of Infections in Urology (ESIU)
Resistance of *P. aeruginosa* (all origins *)

* no recent and global specific data on NAUTI…

Mesaros et al. CMI, in press; http://www.facm.ucl.ac.be
Do we use too much Gram (-) fluoroquinolones in Belgium?

A: in the community per month

![Graph showing the usage of different antibiotic classes over time, with fluoroquinolones highlighted.](image-url)
Do we use too much Gram (-) fluoroquinolones in Belgium?

A: in the community: trends over years

<table>
<thead>
<tr>
<th>Year</th>
<th>total par classe et par an</th>
</tr>
</thead>
<tbody>
<tr>
<td>mai97-98</td>
<td>total</td>
</tr>
<tr>
<td>mai98-99</td>
<td>beta-lactames</td>
</tr>
<tr>
<td>mai99-00</td>
<td>tetracyclines</td>
</tr>
<tr>
<td>mai00-01</td>
<td>macrolides</td>
</tr>
<tr>
<td>mai01-02</td>
<td>quinolones anti Gram-</td>
</tr>
<tr>
<td>mai02-03</td>
<td>quinolones anti Gram+</td>
</tr>
<tr>
<td>mai03-04</td>
<td>sulfa-trimet</td>
</tr>
<tr>
<td>mai04-05</td>
<td>total</td>
</tr>
</tbody>
</table>

DDD/Year (whole country):

- total ≈ 25
- all FQ ≈ 3

DDD per 1,000 inh. per day:

- total ≈ 25
Use of quinolones in the Community in Europe …

Outpatient use of quinolones in 25 European countries in 2003*

Blue error bar represents the difference in national quinolone use in 2003 expressed in DID between ATC/DDD versions 2004 and 2003 due to the change of DDD for levofloxacine from 250 to 500 mg.

* For Iceland total data are use; for Poland 2002 data are used.
Use of quinolones in Hospitals in Europe …

Total antibiotic use per country in hospital care in 2002

DDD per 1000 inh. per day

Other s
Sulfonamides J01E
Quinolone s J01M
Macrolides J01F
Tetracyclines J01A
Cephalosporins J01D
Penicillins J01C

Use and misuses of fluoroquinolones  
GLEM - 9-1-2007
Antibiotics given in nosocomial urinary tract infections (hospitalized patients)

A study from the European Society of Infections in Urology (ESIU)

Use and misuses of fluoroquinolones  
GLEM - 9-1-2007
Thus, we are facing a problem… and looking for a solution …

- Resistance rates are strong arguments for a critical antimicrobial policy.
- Empiric therapy has to be initiated rapidly but culture must be taken before.
- Adjustment is important …
- Prophylaxis and treatment must be based on a continuous surveillance in Urology departments.
- Collaboration between urologists and microbiologists is decisive for good infection control.
- Facilities for preliminary culture of pathogens inside the urological ward may be useful.

A study from the European Society of Infections in Urology (ESIU)
Where do we go from now?

- Understand what quinolones are?
- Are they causing more resistance?
- What could be their limits?
- What do guidelines say?
- Do we use too much?
Which (fluoro)quinolones?

- norfloxacin --
- ciprofloxacin ++
- pefloxacin -
- ofloxacin +
- nalidixic acid
- levofloxacin + (S-isomer of ofloxacin)
- trovafloxacin
- moxifloxacin ++
- gatifloxacin

Gram -
Gram +

1965
2000
Main useful pharmacological properties and drawbacks?

On the positive side

• bactericidal
• concentration ($C_{\text{max}}$) and dose (24h-AUC)-dependent, allowing for rational fine tuning of the therapy including against resistant strains, based on simple rules for posology…
  ➔ $C_{\text{max}}$/MIC $> 10$; 24h-AUC/MIC $> 125$
• good tolerance in general
• excellent bioavailability (rapid oral switch possible…)

On the negative side

• a few side effects that require attention (tendinitis, CNS, ...) and incompatibility with divalent traivalent cations ($Ca^{++}, Al^{+++}$)
• emergence of resistance
  – target mutation (relatively easy ...)
  – unanticipated cross-resistances due to efflux…
  – breakpoints (limits of susceptibility) have been set historically to high (NCCLS), are better with EUCAST, but still need attention
## Quinolones side effects...

### Table 3. Main side-effects of quinolones that contribute to the limitation of their use, the frequency observed, and the populations at risk

<table>
<thead>
<tr>
<th>Side-effect</th>
<th>Quinolone</th>
<th>Frequency</th>
<th>Population at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotoxicity</td>
<td>Fleroxacin, sparfloxacin, grepafloxacin*</td>
<td>&gt; 10%</td>
<td>Pregnant women</td>
</tr>
<tr>
<td>Gastrointestinal effects</td>
<td>Others</td>
<td>2-8% [243]</td>
<td>Cystic fibrosis [245]</td>
</tr>
<tr>
<td>(nausea, vomiting &gt; diarrhea)</td>
<td></td>
<td></td>
<td>Young women</td>
</tr>
<tr>
<td>Skin reaction: phototoxicity</td>
<td>Sparfloxacin* , fleroxacin*, lomefloxacin*, Bay 3118*</td>
<td>&gt; 10% [244]</td>
<td>Children, pregnant women</td>
</tr>
<tr>
<td>Skin reactions: rash</td>
<td>Clinafloxacin*</td>
<td>4% [243]</td>
<td>Elderly, especially if on corticosteroid therapy [250]</td>
</tr>
<tr>
<td>Chondrotoxicity</td>
<td>Genteroxacin</td>
<td>2.8% [266]</td>
<td>Athletes in training [251]</td>
</tr>
<tr>
<td>Tendinitis</td>
<td>Fleroxacin*</td>
<td>14% [247]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; Levofloxacin/oxifloxacin ≥ ciprofloxacin &gt; Others</td>
<td>0.4%</td>
<td></td>
</tr>
<tr>
<td>Minor CNS effects</td>
<td>Trovafloxacin</td>
<td>2-11% dizziness [243]</td>
<td>Elderly [254]</td>
</tr>
<tr>
<td>Major CNS effects</td>
<td>Levofoxacin</td>
<td>0.026% confusion, alteration in mentation and affect [243]</td>
<td>Co-administration of NSAID or of inhibitors of CYP 450 [255]</td>
</tr>
<tr>
<td>Cardiovascular effects</td>
<td>Fleroxacin* [256]</td>
<td>8% insomnia [257]</td>
<td>Female gender [254]</td>
</tr>
<tr>
<td></td>
<td>Sparfloxacin* (0-28 ms)</td>
<td>2.9%</td>
<td>Co-administration of other drugs (prolonging QTc interval or inhibiting CYP 450 metabolism)</td>
</tr>
<tr>
<td></td>
<td>Genteroxacin [10 ms]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moxifloxacin [6 ms]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Levofloxacin [3 ms]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gatifloxacin [2.9 ms]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor hepatic effects (transaminase elevation)</td>
<td>Genteroxacin [2.6 ms] [246,258-260]</td>
<td>12-16% transaminase elevation [243]</td>
<td>Heart disease [254]</td>
</tr>
<tr>
<td>Major hepatic effects</td>
<td>Trovafoxacin*</td>
<td>&lt; 3% [261]</td>
<td>Treatment duration &gt; 14 days [262]</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>Clinafloxacin*</td>
<td>0.002% [243]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Genteroxacin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haematological toxicity</td>
<td>Levofloxacin (one fatal case) [263]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP 450 inhibition</td>
<td>Temofloxacin*</td>
<td>0.02% haemolysis, thrombocytopenia, renal failure [256]</td>
<td>Co-administration of oral hypoglycemic agents [264]</td>
</tr>
</tbody>
</table>

*Further studies have been requested from the manufacturer, an recent pharmacovigilance reports document a significant increase of the QTc interval, mainly in patients with concurrent medical conditions or other medications [243,265]; see also [246] for a recent study in the province of Varese, Italy, using prescription data on all incident users of several antibacterial and anti-arrhythmic drugs during the period July 1997 to December 1999.

NSAID, non-steroidal anti-inflammatory drug; CNS, central nervous system.
Quinolones side effects…: which are the populations (really) at risk?

- pregnant women and children
- elderly, especially with corticoid therapy
- athletes in training (beware of the runners...)
- co-administration of NSAIDs or drugs known for potential of Cytochrome P450 interactions
- heart disease
- patients receiving neutralization anti-acids (Ca++, Mg++, Al+++) or Fe++
• long thought to be restricted to chromosomal mutations of the targets (DNA gyrase / topoisomerase)
  – high frequency of spontaneous mutations ($10^{-7}$)
  – but limited horizontal and interbacterial spread …

• but, later on, observed in relation to decreased accumulation
  – loss of porins in Gram (-) bacteria
  – (over)expression of efflux

• now, seen through plasmidic-associated mechanisms (QnR)
  – risk of rapid horizontal spread …

• and very recently though fluoroquinolone-modifying enzymes !!
  (clinical significance still uncertain…)
Resistance by target mutation: parallel and dissociated resistance and strong-versus weak fluoroquinolones

- **Parallel (A - B)**: The resistance increases step by step in both Q_A and Q_B, indicating parallel resistance.
- **Dissociated (A - C)**: The resistance increases in Q_A but not in Q_C, indicating dissociated resistance.

**Susceptibility limit (arbitrary)**: The horizontal dotted line represents the susceptibility limit for the wild strain. MIC (multiple of wild strain for Q_A) values are shown on the vertical axis.
Application: look at MIC distributions where YOU are … to find "weak" quinolones

MIC distributions in Leuven…

- oflox
- levo
- cipro
Mutant Prevention Concentration ...

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

"Classic" bactericidal effect

Elimination of resistant organisms

Surviving bacteria

poorly sensitive organisms...

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

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

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

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

Mutant Prevention Concentration of ciprofloxacin and levofloxacin in *P. aeruginosa* (clinical isolates) with "normal" susceptibility (MIC = 0.33 and 0.9 mg/L) …

Efflux and MIC?

• efflux is a 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, increasing the MIC …
• insufficient drug exposure favors the selection of less sensitive organisms

→ 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 …

How does efflux work (Gram - bacteria)?

susceptible bacteria

porin

periplasm

cytosol

MexB

MexA

OprM
How does efflux work (Gram - bacteria)?

![Diagram of efflux in Gram-negative bacteria.](image)

- **Susceptible bacteria**
  - **Periplasm**
  - **Cytosol**
  - **Pore**
  - **Porin**

- **Resistant bacteria**
  - **Periplasm**
  - **Cytosol**
  - **Pore**
  - **Porin**

**Lipoprotein**
- **MexA**
- **MexB**

**Pump**
- **MexA**
- **MexB**

Expressed in wild-type strains!
Why do you need to detect efflux?

**Ciprofloxacin / Escherichia coli**

**Antimicrobial wild type distributions of microorganisms – reference database EUCAST**

<table>
<thead>
<tr>
<th>MIC</th>
<th>6423 observations (9 data sources)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical breakpoints: S ≤ 0.5 mg/L, R &gt; 1 mg/L</td>
<td></td>
</tr>
</tbody>
</table>

**Epidemiological cut-off: WT ≤ 0.064 mg/L**

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

But will be brought back to wild type distribution in the presence of efflux inhibitor ...
Application: look at MIC distributions where YOU are …

MIC distributions in Leuven…

- oflox
- levo
- cipro
Application: look at MIC distributions where YOU are …

MIC distributions in Leuven…

EUCAST limit of "wild" population

efflux…

oflox  levo  cipro
Why does efflux cause cross-resistance?  
(example with *P. aeruginosa*)

<table>
<thead>
<tr>
<th>Efflux System</th>
<th>β-lac</th>
<th>ML</th>
<th>TET</th>
<th>AG</th>
<th>FQ</th>
<th>Chl</th>
</tr>
</thead>
<tbody>
<tr>
<td>MexAB-OprM</td>
<td><img src="#" alt="Green" /></td>
<td><img src="#" alt="Green" /></td>
<td><img src="#" alt="Green" /></td>
<td><img src="#" alt="Green" /></td>
<td><img src="#" alt="Green" /></td>
<td><img src="#" alt="Green" /></td>
</tr>
<tr>
<td>MexCD-OprJ</td>
<td><img src="#" alt="Orange" /></td>
<td><img src="#" alt="Orange" /></td>
<td><img src="#" alt="Orange" /></td>
<td><img src="#" alt="Orange" /></td>
<td><img src="#" alt="Orange" /></td>
<td><img src="#" alt="Orange" /></td>
</tr>
<tr>
<td>MexEF-OprN</td>
<td><img src="#" alt="Orange" /></td>
<td><img src="#" alt="Orange" /></td>
<td><img src="#" alt="Orange" /></td>
<td><img src="#" alt="Orange" /></td>
<td><img src="#" alt="Orange" /></td>
<td><img src="#" alt="Orange" /></td>
</tr>
<tr>
<td>MexHI-OprD</td>
<td><img src="#" alt="Orange" /></td>
<td><img src="#" alt="Orange" /></td>
<td><img src="#" alt="Orange" /></td>
<td><img src="#" alt="Orange" /></td>
<td><img src="#" alt="Orange" /></td>
<td><img src="#" alt="Orange" /></td>
</tr>
<tr>
<td>MexJK-OprM</td>
<td><img src="#" alt="Yellow" /></td>
<td><img src="#" alt="Yellow" /></td>
<td><img src="#" alt="Yellow" /></td>
<td><img src="#" alt="Yellow" /></td>
<td><img src="#" alt="Yellow" /></td>
<td><img src="#" alt="Orange" /></td>
</tr>
<tr>
<td>MexXY-OprM</td>
<td><img src="#" alt="Orange" /></td>
<td><img src="#" alt="Orange" /></td>
<td><img src="#" alt="Orange" /></td>
<td><img src="#" alt="Orange" /></td>
<td><img src="#" alt="Orange" /></td>
<td><img src="#" alt="Orange" /></td>
</tr>
</tbody>
</table>

**constitutive expression**  
**inducible expression**

 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!!

- $C_{max} = \frac{\text{Dose}}{V_d}$
- $AUC = \frac{\text{Dose}}{\text{Clearance}}$

Graph showing concentration over time with MIC level as a threshold.
Application: choose a strong quinolone and use low enough break-points … or better … ask for an MIC and use PK/PD …

<table>
<thead>
<tr>
<th>Drug</th>
<th>Typical daily dosage</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_{max} in mg/L</td>
<td>AUC\textsubscript{24 h} (mg x h/L) total/free</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>800 mg</td>
<td>1.4/1.1</td>
<td>14/11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(400 mg PO)</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1000 mg</td>
<td>2.5/1.75</td>
<td>24/18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(500 mg PO)</td>
<td></td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>400 mg</td>
<td>4/3</td>
<td>40/30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(400 mg PO)</td>
<td></td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>500 mg</td>
<td>4/2.8</td>
<td>40/28</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(500 mg PO)</td>
<td></td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>400 mg</td>
<td>3.1/1.8</td>
<td>35/21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(400 mg PO)</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a}Typical daily dosage as recommended by the manufacturer. 
\textsuperscript{b}Efficacy: minimum effective concentration (MEC) or minimum inhibitory concentration (MIC) at which 50% of tested strains are inhibited (50\% Efficacy = MEC \textsubscript{50} = MIC \textsubscript{50}). 
\textsuperscript{c}Prevention of resistance: minimum effective concentration at which 10\% of tested strains are inhibited (10\% Prevention of Resistance = MEC \textsubscript{10}).

Fluoroquinolones downsides in a (scientific) nutshell and how to cope with them

• true risk of emergence of resistance
  ➔ have local epidemiological surveys
  ➔ have cultures and susceptibility data (MIC) for all isolates in difficult situations
  ➔ dose appropriately ...
  ➔ use potent (not weak) quinolones...
  ➔ do not use if not needed...

• a few side effects
  ➔ avoid populations at risk
How do we go from here to clinical practice?

**EAU Guidelines for the Management of Urinary and Male Genital Tract Infections**

*Urinary Tract Infection (UTI) Working Group of the Health Care Office (HCO) of the European Association of Urology (EAU)*

Members of the UTI Working Group: Kurt G. Naber (Chairman), Bo Bergman, Michael C. Bishop, Truls E. Bjerklund-Johansen, Henry Botto, Bernard Lobel, F. Jimenez Cruz, Francesco P. Selvaggi
How do we go from here to clinical practice?

Table 2. Recommendations for antimicrobial therapy in urology [modified according to Naber et al., Chemother J 2000;9:165–170]

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Most frequent pathogen</th>
<th>Initial, empiric antimicrobial therapy</th>
<th>Therapy duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystitis, acute, uncomplicated</td>
<td><em>E. coli</em></td>
<td>Trimethoprim/sulfamethoxazole</td>
<td>3 days</td>
</tr>
<tr>
<td></td>
<td><em>Klebsiella</em></td>
<td>Fluoroquinolone&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3 days</td>
</tr>
<tr>
<td></td>
<td><em>Proteus</em></td>
<td>Alternatives:</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Staphylococcus</em></td>
<td>Fosfomycin trometamol</td>
<td>1 day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pivmecillinam</td>
<td>7 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nitrofurantoin</td>
<td>7 days</td>
</tr>
<tr>
<td>Pyelonephritis, acute,</td>
<td><em>E. coli</em></td>
<td>Fluoroquinolone&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7–10 days</td>
</tr>
<tr>
<td>uncomplicated</td>
<td><em>Proteus</em></td>
<td>Cephalosporin Gr. 2/3a</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Klebsiella</em></td>
<td>Alternatives:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other Enterobacteria</td>
<td>Aminopenicillin/BLI</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Staphylococcus</em></td>
<td>Aminoglycoside</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Fluoroquinolone with mainly renal excretion; BLI = β-lactamase inhibitor.
How do we go from here to clinical practice?

Table 2. Recommendations for antimicrobial therapy in urology [modified according to Naber et al., Chemother J 2000;9:165–170]

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Most frequent pathogen</th>
<th>Initial, empiric antimicrobial therapy</th>
<th>Therapy duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>UTI with complicating factors</td>
<td><em>E. coli</em></td>
<td>Fluoroquinolone*</td>
<td>3–5 days after defervescence or control/elimination of complicating factor</td>
</tr>
<tr>
<td></td>
<td><em>Enterococcus</em></td>
<td>Aminopenicillin/BLI</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Staphylococcus</em></td>
<td>Cephalosporin Gr. 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Klebsiella</em></td>
<td>Cephalosporin Gr. 3a</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Proteus</em></td>
<td>Aminoglycoside</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Enterobacter</em></td>
<td>In case of failure of initial therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other Enterobacteria</td>
<td>within 1–3 days or in clinically severe cases:</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Pseudomonas</em> (Candida)</td>
<td>Anti-<em>Pseudomonas</em> active:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Fluoroquinolone</em>, if not used initially</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Acylaminopenicillin</em>/BLI</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>*Cephalosporin Gr. 3b</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Carbapenem</em></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>± Aminoglycoside</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>In cases of <em>Candida</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Fluconazole</em></td>
<td></td>
</tr>
</tbody>
</table>

* Fluoroquinolone with mainly renal excretion; BLI = β-lactamase inhibitor.
# How do we go from here to clinical practice?

**Table 2.** Recommendations for antimicrobial therapy in urology [modified according to Naber et al., Chemother J 2000;9:165–170]

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Most frequent pathogen</th>
<th>Initial, empiric antimicrobial therapy</th>
<th>Therapy duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostatitis, acute, chronic</td>
<td><em>E. coli</em></td>
<td>Fluoroquinolone*</td>
<td>Acute: 2 weeks</td>
</tr>
<tr>
<td></td>
<td>Other <em>Enterobacteria</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Pseudomonas</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Enterococcus</em></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td><em>Staphylococcus</em></td>
<td></td>
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<tr>
<td></td>
<td><em>Chlamydia</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Ureaplasma</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epididymitis, acute</td>
<td><strong>Fluoroquinolone</strong></td>
<td>Alternative in acute bacterial prostatitis:</td>
<td>Chronic: 4–6 weeks or longer</td>
</tr>
<tr>
<td></td>
<td><strong>Cephalosporin</strong></td>
<td>Cephalosporin Gr. 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Gr. 3a/b</strong></td>
<td>Cephalosporin Gr. 3a/b</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>In case of Chlamydia or Ureaplasma:</strong></td>
<td>Doxycycline</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Macrolide</strong></td>
<td></td>
</tr>
<tr>
<td>Urosepsis</td>
<td><em>E. coli</em></td>
<td>Cephalosporin Gr. 3a/b</td>
<td>3–5 days after defervescence or control/elimination of complicating factor</td>
</tr>
<tr>
<td></td>
<td>Other <em>Enterobacteria</em></td>
<td>Fluoroquinolone*</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>After urological interventions—multi-resistant pathogens:</em></td>
<td>Anti-<strong>Pseudomonas</strong> active</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Proteus</em></td>
<td>Acetylamino penicillin/BLI</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Serratia</em></td>
<td>Carbenem</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Enterobacter</em></td>
<td>± Aminoglycoside</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Pseudomonas</em></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Fluoroquinolone* with mainly renal excretion; *BLI* = β-lactamase inhibitor.
What about Belgium?

Learning appropriate use of antibiotics (PK/PD and guidelines): a CD-rom course for healthcare professionals and students

E. Ampe, Y. Glupczynski, P.M. Tulkens, and F. Van Bambeke

Unité de Pharmacologie cellulaire et moléculaire, Université catholique de Louvain - Brussels - Belgium
Laboratoire de microbiologie, cliniques universitaires UCL, Mont-Godinne

INTRODUCTION

Optimizing the use of current antibiotics based on pharmacokinetics and pharmacodynamics and related application of guidelines can contribute to the limitation of resistance development.

In this respect, education of students and healthcare professionals appears as a priority and can be facilitated by making available to them easy-to-consult informative support.

OBJECTIVES

- To develop an educational programme in which pharmacists and infectious disease specialists train healthcare professionals and students in PK/PD and in a correct implementation of guidelines.
- To distribute to people training the course a CD-rom as a support that can be consulted at any time.

ACKNOWLEDGMENTS

We thank W. Reckwitz (KUL, UZ Sint-Jozef) for useful comments and Bayer Belgium for financial support.

Ampe et al., 15th ECCMID, 2005
Empiric therapy
Large spectrum antibiotic
  • First choice: fluoroquinolone
    – Large spectrum
    – High concentration in urine and urinary tract

Directed therapy
  • According to the results of the antibiogram
  • Choose antibiotic with the smallest spectrum

Duration of treatment:
  7 to 14 days
Mild pyelonephritis

• **Empiric therapy**

  **First choice:**
  
  • *Oral fluoroquinolone in monotherapy*
  
  • *Ambulant therapy if possible:*
    
    – Patient can take oral medication
    – No severe sepsis
    – No renal insufficiency
  
  • No association of aminoglycoside except in severe sepsis
  
  • No first generation fluoroquinolone because of low serum concentrations
  
  • No ampicillin or first generation cephalosporins (or co-trimoxazole) because of resistance pattern in Belgium

  – **If contra-indication to fluoroquinolones:**
    
    • amoxicillin-clavulanic acid
    
    • Second generation cephalosporins
    
    • temocillin
Severe pyelonephritis (hospital)

- **Empiric therapy**
  - *first choice:*
    - Fluoroquinolone
    - Initially parenteral therapy
    - Switch IV-oral and ambulant therapy when possible
  - **Alternatives:**
    - Temocillin
    - Second generation cephalosporin
    - Amoxicilline-clavulanic acid
    - if septic shock: Association of aminoglycoside to cephalo-2 or amoxiclav

- **Directed therapy**
  - Based on urine culture with antibiogram
  - *first choice:*
    - Fluoroquinolone
    - Cotrimoxazol
    - Only if enterococ: amoxicillin
    - ampicillin
    - If necessary combination with aminoglycoside
  - *Ambulant therapy: see next slide*
Switch IV-per os and ambulant treatment

• **Based on:**
  – Clinical recovery (symptoms and fever disappeared)
  – Antibiogram of the urine culture
  – If possible after 24-48 h
  – Ambulant therapy if possible:
    – Patient can take oral medication
    – No severe sepsis
    – No renal insufficiency
  – Patients who fail to improve after 48-72 h of ambulant therapy based on urine culture and the initial antibiotic:
    • parenteral fluoroquinolone or
    • alternative
## Regimens

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>duration</th>
<th>dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>7 – 14 days*</td>
<td>250-500 mg X 2, po</td>
</tr>
<tr>
<td></td>
<td></td>
<td>200-400 mg X 2, IV</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td></td>
<td>250-500 mg X1, po or IV</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td></td>
<td>200-400 mg X1, po or IV</td>
</tr>
<tr>
<td>Amoxi-clav</td>
<td>14 days</td>
<td>500 mg X 3, po</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 g X 4, IV</td>
</tr>
<tr>
<td>Cefuroxim</td>
<td></td>
<td>500 mg X 2, po</td>
</tr>
<tr>
<td></td>
<td></td>
<td>750 mg – 1.5 g X 3, IV</td>
</tr>
<tr>
<td>Temocillin</td>
<td></td>
<td>1 g X 2, IV</td>
</tr>
<tr>
<td>Cotrimoxazol</td>
<td></td>
<td>160/800 mg X2, po of IV</td>
</tr>
<tr>
<td>Ampicillin</td>
<td></td>
<td>1 g X 4, IV</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td></td>
<td>400 mg X 3 of X 4, po</td>
</tr>
</tbody>
</table>

* 7 days: mild infection; 14 days: severe infection

BAPCOC guidelines, 2002
Severe pyelonephritis in the pregnant woman

- **allowed**
  - Nitrofurantoin
  - Cephalosporins
  - Amoxicillin
  - Cotrimoxazol (folic acid antagonism minimal if short treatment using recommended dose)

- **Not allowed**
  - Fluoroquinolones
  - Cotrimoxazol during last weeks of pregnancy (risk of hyperbilirubinemia and icterus in the neonate)
  - Fosfomycin (avoid during first 3 months)
Acute prostatitis: treatment

First choice:
- Fluoroquinolones
  - Ciprofloxacin if suspicion of *P. aeruginosa*, 500 mg X 2 po

Second choice:
- Cotrimoxazol, 800/160 mg X 2 po

Alternatives:
- Cephalosporins (cefuroxim)
- Amoxicillin + clavulanic acid

Minimal duration: 2 weeks, often 4 weeks
  (prevention of chronic infection)
Chronic prostatitis: treatment

Problems:

- Little antibiotics penetrate well in the non-inflamed prostate
- Infection focus can consist of little calculi or abscesses that are difficult to treat.
- High probability of relapsing infections

→ DIFFICULT TO TREAT
Chronic prostatitis: antibiotic treatment

Primary antibiotics

- Only lipophilic and basic molecule penetrate the acidic environment of the prostate:

  - **Good for:**
    - ciprofloxacin: (500 mg 2X/day): 30 days
    - Trimethoprim (800/160 mg 2x/day): 3 months
    - Macrolides (not for empiric therapy because of spectrum)

  - **Bad for:**
    - penicillins
    - cephalosporins
    - Tetracyclins
    - Nitrofurantoin
    - vancomycin
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
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

Prices in Belgium…

![Graph showing total and per class costs over years]
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 rationally...

F. Van Bambeke, Pharm.
Y. Glupczynski, MD
A. Spinewine, Pharm.
S. Carryn, Pharm.
E. Ampe, Pharm.

W.A. Craig, MD
M.N. Dudley, Pharm.
G.L. Drusano, MD
J.J. Schentag, Pharm.
A. McGowan, MD
X. Zao, PhD
V. Firsov, MD
S. Zinner, MD
A. Dalhoff, PhD

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