Not All Fluoroquinolones Are Equal …

Paul M. Tulkens, MD, PhD

Cellular and Molecular Pharmacology
Louvain Drug Research Institute
Université catholique de Louvain
Brussels, Belgium

Singapore

With approval of the Belgian Common Ethical Health Platform – visa no. 17/V1/7383/093066
Disclosures

Financial support from

• Non-profit Institutions:
  – the Belgian Fonds de la Recherche Scientifique for basic research on pharmacology antibiotics and related topics
  – The European Union for applied research on optimisation of β-lactams treatments through on-line monitoring of free serum levels
  – Université catholique de Louvain for past personal support

• Industry:
  – AstraZeneca, GSK, Sanofi-Aventis, Bayer, Cempra Pharmaceuticals, The Medicines Company, Northern Antibiotics, RibX, Cubist, Galapagos, …

Other past and present relationships in relation to this talk

– Belgian Antibiotic Policy Coordination Committee (BAPCOC)
– European Committee for Antibiotic Susceptibility Testing (EUCAST)
– European Medicines Agency (EMA)
– Drive-AB (a EU programme for a new economical framework for antibiotics)

Slides: http://www.facm.ucl.ac.be → Lectures
The programme…

• A very short view of Belgium and of where I work…

• Differentiating fluoroquinolones in their origin and intrinsic nature

• Differentiating fluoroquinolones in PK/PD and the concept of MPC (prevention of resistance)

• How would moxifloxacin fit into an antibiotic stewardship program

• Questions, objections, suggestions …
The Catholic University of Louvain in brief

- Created in 1425, it was one of the major University of the so-called "Low Countries" in the 1500 – 1800 period, with famous scholars and discoverers (Vesalius for anatomy, Erasmus for philosophy, …). Teaching was in Latin, Greek, and Hebrew (College of the 3 languages…)

The University in the 1500's
Erasmus
Vesalius
The Catholic University of Louvain in brief

- In the 19th century, teaching was in French but in the early 1900's, a Flemish-speaking section was opened. Courses were given in both languages, attracting many students and celebrities…

Prof. G. Lemaitre, professor of Physics and Mathematics at the University who, in the 1930's, made the first suggestion of the continuous expansion of the Universe ("Big Bang")
(here in conversation with A. Einstein)

Professor C. de Duve, professor of Biochemistry at the University, who obtained the Nobel Prize (Physiology and Medicine) in 1974 for his work on intracellular organelles (lysosomes, peroxisomes…)
(here in front of a centrifuge)

- in 1968, the University was divided into
  - a French-speaking Université catholique de Louvain
  - a Flemish-speaking Katholieke Universiteit Leuven…
The Catholic University of Louvain in brief (4 of 4)

- The Flemish-speaking *Katholieke Universiteit Leuven* has remained in Louvain (Leuven) and is named in English "Catholic University Leuven".
- The French-speaking *Université catholique de Louvain* has moved about 25 km South in a place called "Louvain-la-Neuve, with the "Health Sciences Sector" located in Brussels (Woluwe).

Together, the two sister Universities have about **60,000 students**
What do we do?

- Teaching of pharmacology and pharmacotherapy
- Post-graduate training on Drug Development
- Launching of Clinical Pharmacy in Europe
- Web-based courses on anti-infective pharmacology
- 30 graduating students, doctoral fellows and post-graduate fellows working on anti-infective therapy (laboratory and clinical applications)

Activity and toxicity of aminoglycosides and fluoroquinolones
- novel antibiotics
  - beta-lactams (ceftaroline…)
  - fluoroquinolones (delafloxacin *…)
  - Fab inhibitors (Debio1462 * …)
  - oxazolidinones (tedizolid …)
* in development

- re-assessment of older antibiotics

www.facm.ucl.ac.be

- Editorial board of AAC and IJAA
- Member of the General Committee of EUCAST (for ISC) and of its Steering committee (2008-10)
- Member of the Belgian Antibiotic Policy Coordination Committee
- Founder and Past President of the International Society of Antiinfective Pharmacology (ISAP)

www.isap.org

A partial view of our University Clinic (900 beds) and the Education and Research buildings (5,000 students), with the Institute (framed), located in then the outskirts of Brussels, Belgium
Why do I have an interest in fluoroquinolones?

Because, like Obélix, I fell into when I was young ...
Why do I have an interest in fluoroquinolones?

Because, like Obélix, I fell into when I was young …
Why do I have an interest in fluoroquinolones?

Because, like Obélix, I fell into when I was young …

Comment Obélix est tombé dans la marmite du druide quand il était petit

PubMed search results

Tulkens AND (fluoroquinolone OR rifampicin OR clarithromycin OR amoxicillin)

Create RSS Create alert Advanced

Summary 20 per page Sort by Most Recent

Items: 1 to 20 of 57

Cellular uptake, localization and activity of fluoroquinolones in uninfected and infected macrophages

Marie-Béatrice Carlier*, Bernard Scorneaux*, Andrée Zenebergh*, Jean-François Désnottes* and Paul M. Tulkens*

*Laboratoire de Chimie Physiologique, and International Institute of Cellular and Molecular Pathology, Université Catholique de Louvain, Avenue Hippocrate 75, Bte 75.49, B-1200 Bruxelles, Belgium; *Rhône-Poulenc Santé, Centre de Recherches de Vitry/Alfortville, 13, Quai Jules Guesde, B.P. 14, F-94403 Vitry/S/Seine, France

REVIEW ARTICLE

Quinolones in 2005: an update

F. Van Bambekem, J.-M. Michel1, J. Van Elderc and P. M. Tulkens3

1Unit of Cellular and Molecular Pharmacology, Catholic University of Louvain, Brussels and
2Department of Microbiology and Immunology, Rega Institute and Centre for Molecular Diagnostics,
University Hospital, Catholic University of Louvain, Louvain, Belgium

Clin Microbiol Infect 2005; 11: 256-260

ORIGINAL RESEARCH ARTICLE

Moxifloxacin Safety
An Analysis of 14 Years of Clinical Data

Paul M. Tulkens,1 Pierre Arvis2 and Frank Kruesmann3

1 Pharmacologie cellulaire et moléculaire & Centre de Pharmacie clinique, Louvain Drug Research Institute,
Université catholique de Louvain, Brussels, Belgium
2 Bayer Santé SAS, Loos, France
3 Bayer Pharma AG, Wuppertal, Germany
The programme…

• A very short view of Belgium and of where I work…

• **Differentiating fluoroquinolones in their origin and intrinsic nature**

• Differentiating fluoroquinolones in PK/PD and the concept of MPC (prevention of resistance)

• How would moxifloxacin fit into an antibiotic stewardship program

• Questions, objections, suggestions …
Mechanism of action of fluoroquinolones: the basics...
A bit of history: from chloroquine to nalidixic acid...

chloroquine

1939

1958

7-chloroquinoiline (synthesis intermediate found to display antibacterial activity)

1962

nalidixic acid
From nalidixic acid to the 1st fluoroquinolone

3 key modifications *

1. broader Gram(-) activity
2. less protein binding (50%)
3. longer half-life (3-4h)

* Belgian patent 863,429, 1978 to Kyorin

* 6-fluoro-7-pyrimidino-quinoleine
From norfloxacin to ciprofloxacin and ofloxacin

- **norfloxacin**

- **Ciprofloxacin** *

- **Ofloxacin** **

* Ger. pat. 3,142,854 to Bayer AG, 1983

** Eur. pat. Appl. 47,005 to Daiichi, 1982

** Eur. pat. Appl. 47,005 to Daiichi, 1982

** Eur. pat. Appl. 47,005 to Daiichi, 1982
Levofloxacin is the active isomer of ofloxacin

Ofloxacin is a racemic mixture 50/50

Levofloxacin is the pure (-) S isomer of ofloxacin *

The active form of ofloxacin is the (-) S isomer. The (+) R isomer is inactive but toxic

* Eur. pat. 206,283 to Daiichi, 1987
How to improve the chemotherapeutic usefulness of the "first generation" fluoroquinolones

1. Maintain broad Gram(-) activity ?

2. Further Improve Gram(+) activity ?

3. Acquire activity against anaerobes ?
Activity against *S. pneumoniae*

**I**

- Ciprofloxacin
  - MIC = 0.5 - 2

**II**

**III / IV**

- Moxifloxacin
  - MIC = 0.01 - 0.5

**Hint #1:**
Lower MICs = a more potent antibiotic!

**Hint #2:**
Levofloxacin has the same MICs than ciprofloxacin and > than moxifloxacin!
Activity against *B. fragilis* (anaerobe)

ciprofloxacin
MIC = 2-128

moxifloxacin
MIC = 0.125-8
At this point ... 

Not All Fluoroquinolones Are Equal (Singapore)

This is by design!
Killing abilities of fluoroquinolones: Are they all equal against susceptible strains?

*in vitro* kill curves: observations with *S. pneumoniae*

**Fig. 1.** Time kill curves of moxifloxacin versus levofloxacin against *S. pneumoniae* 7362 (average of 2 models).

Schafer *et al.* Diag Microb Infect Dis 2008; 60:155–161
Killing abilities of fluoroquinolones: Are they all equal against less susceptible strains?

Animal survival experiments (*S. pneumonia* i.p. inoculations)

<table>
<thead>
<tr>
<th>strain</th>
<th>MIC (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MXF</td>
</tr>
<tr>
<td>AR33118 (■)</td>
<td>0.12</td>
</tr>
<tr>
<td>FL2812 (●)</td>
<td>0.25</td>
</tr>
<tr>
<td>FL5629 (★)</td>
<td>4</td>
</tr>
</tbody>
</table>

**Hint:** lower dose (more to the left) → more potent antibiotic!

The programme…

• A very short view of Belgium and of where I work…

• Differentiating fluoroquinolones in their origin and intrinsic nature

• Differentiating fluoroquinolones in PK/PD and the concept of MPC (prevention of resistance)

• How would moxifloxacin fit into an antibiotic stewardship program

• Questions, objections, suggestions …
Let us begin with the concept of MPC…

1. Why does an MIC leave resistant subpopulations unaffected?

Figure 2. Schematic representation of resistance selection based on MIC drug concentrations.

Let us begin with the concept of MPC…

2. How do you find these resistant subpopulations?

C$_{\text{max}}$ and "Mutant Prevention Concentration" (MPC) …

$\text{MIC}_{99} = 0.8 \text{ mg/L}$ (in this example)

"Classic" bactericidal effect

poorly sensitive organisms…

Elimination of resistant organisms

$\text{MPC}_{10} = 9$

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

**Concentration that inhibits the majority of the organisms**

**MIC<sub>99</sub> = 0.8**

**MPC<sub>10</sub> = 9**

Concentration needed to prevent the selection of resistant organisms (about 10 x the MIC)

Dong et al; AAC 43:1756-1758
The risk for resistance to fluoroquinolones is to be “within the mutation selection window” …

MPC: moxifloxacin vs levofloxacin

- MPC of moxifloxacin is approximately 10 times the median MIC (0.125 mg/L).
- MPC of levofloxacin is approximately 10 times the median MIC (1 mg/L).

Plasma drug concentration (µg/ml) vs Time post-administration (hr)
So, what should you do with a fluoroquinolone to avoid emergence of resistance

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

⇒ peak / MIC > 10
Let us now move to the AUC / MIC as predictor of activity

AUC / MIC\(^1\) is predictor of activity for Gram (-) ...

\(^1\) The impact of the \(C_{\text{max}}\) could not be tested in this study

Forrest et al., AAC, 1993
Is 125 good for all ??

The saga of *S. pneumoniae* ...

---

**Mortality (%)**

<table>
<thead>
<tr>
<th>1</th>
<th>2.5</th>
<th>5</th>
<th>10</th>
<th>25</th>
<th>50</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**24 Hr AUC/MIC**

**Percent mortality**

<table>
<thead>
<tr>
<th>3</th>
<th>10</th>
<th>30</th>
<th>100</th>
<th>300</th>
<th>1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

*non-neutropenic mice*

*neutropenic mice*
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

So, an AUC/MIC = 125 may be good even for *S. pneumoniae*
Pharmacodynamics of moxifloxacin and levofloxacin against *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Klebsiella pneumoniae* and *Escherichia coli*: simulation of human plasma concentrations after intravenous dosage in an *in vitro* kinetic model

Inga Odenholt and Otto Cars

1. Infectious Diseases Research Unit, Department of Clinical Sciences Malmö, Lunds University, S-20502 Malmö, Sweden; 2. Antibiotic Research Unit, Department of Medical Sciences, Section of Infectious Diseases and Clinical Microbiology, Uppsala University, Uppsala, Sweden

AUC/MIC: modelling the clinical use

Pharmacodynamics of fluoroquinolones in Streptococcus pneumoniae and Escherichia coli: concentrations after intravenous administration.

\[ AUBKC: \text{area under bacterial killing curve} \ (\sim \log \text{CFU}) \]

Figure 5. Relationship between AUBKC and AUC/MIC for S. pneumoniae (open squares) and Gram-negative strains (filled squares).


Odenholt: Infectious Diseases Research Unit, S-20502 Malmö, Sweden. Section of Infectious Diseases, Sahlgrenska University Hospital.

JAC
So, what should you do with a fluoroquinolone to avoid emergence of resistance and be optimal for activity …

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

→ peak / MIC > 10

If you are interested in global effect …

→ $\text{AUC}_{24h} / \text{MIC}: 125$
Pharmacokinetics and “resistance” breakpoint vs. MIC

Levofloxacin 500 mg 1X / day
- AUC [(mg/l)xh] 47
- peak [mg/l] 5
→ MIC$_\text{max}$ ~ 0.5

Moxifloxacin 400 mg 1X / day
- AUC [(mg/l)xh] 48
- peak [mg/l] 4.5
→ MIC$_\text{max}$ ~ 0.5

Maximal MIC to avoid selection of resistance
- AUC/MIC = 100
- peak/MIC = 10

MIC data: EUCAST MIC distributions (wild type)
PK data: US and EU labelling (typical values)
What differentiates fluoroquinolones?

Results with *S. pneumoniae*

Would this cause less emergence of resistance?
Has resistance to moxifloxacin materialized: evidence for *S. pneumoniae* in Belgium from 1999 to 2014 *

*S. pneumoniae* susceptibility to moxifloxacin in Belgium

* Moxifloxacin was introduced in Belgium in 2001 and became the almost only fluoroquinolone used for RTI since 2004

From data of a **national** collection
- Non invasive respiratory tract infections
- similar results in 2008 for a collection of *S. pneumoniae* from clinically-confirmed CAP (n=132)

- Surveys from the Belgian Scientific Institute for Public Health for *S. pneumoniae* from community isolates (n=156 in 1999 and 312 in 2014)

- Data available yearly for 1999 through 2014 at [http://www.iph.fgov.be](http://www.iph.fgov.be)

Vanhoof et al. 19th ECCMID, Helsinki, 2009
Ceyssens et al. 35th RICAI, Paris, 2015
Is there a molecular basis for a lesser emergence of resistance with moxifloxacin?

A C8-methoxy group lowers the MPC for an N-1-cyclopropyl-fluoroquinolone.

**FULL PRESCRIBING INFORMATION**

The bactericidal action of moxifloxacin results from inhibition of the topoisomerase II (DNA gyrase) and topoisomerase IV required for bacterial DNA replication, transcription, repair, and recombination. It appears that the C8-methoxy moiety contributes to enhanced activity and lower selection of resistant mutants of Gram-positive bacteria compared to the C8-H moiety. The presence of the bulky bicycloamine substituent at the C-7 position prevents active efflux, associated with the *NorA* or *pmrA* genes seen in certain Gram-positive bacteria.

Last accessed: 8/2/2015
Head to head comparison…

Clinical Infectious Diseases 2006;42:73-81.

Community-Acquired Pneumonia Recovery in the Elderly (CAPRIE): Efficacy and Safety of Moxifloxacin Therapy versus that of Levofloxacin Therapy

Antonio Anzueto,1,2 Michael S. Niederman,2 James Pearle,1 Marcos I. Restrepo,1,2 Albrecht Heyder,5 and Shurjeel H. Choudhri,6 for the Community-Acquired Pneumonia Recovery in the Elderly Study Group

1Department of Medicine, University of Texas Health Science Center, and 2Veterans Evidence Based Research Dissemination and Implementation Center, Department of Medicine, South Texas Veterans Healthcare System, San Antonio, Texas; 3Department of Medicine, Winthrop-University Hospital, Mineola, New York; 4California Research Medical Group, Fullerton, California; 5Carolina Research Specialists, Elizabeth City, North Carolina; and 6Bayer Pharmaceuticals, West Haven, Connecticut
Head to head comparison…

Clinical Infectious Diseases 2006;42:73-81.

Community-Acquired Pneumonia Recovery in the Elderly (CAPRIE): Efficacy and Safety of Moxifloxacin Therapy versus that of Levofloxacin Therapy.

Visit 1
Day 1

Visit 2
(Day 3–5)

Test of cure + 5–21 days

Randomisation

12-lead ECG

Hospitalised CAP

72-h Holter monitor

12-lead ECG

Moxifloxacin 400mg q.d. IV

Levofloxacin 500mg q.d. PO
and results in a snapshot...

Clinical outcomes

Clinical recovery rate (95% CI: 1.7, 14.1); P=0.01

Clinical cure rate (95% CI: -1.9, 11.9); P=0.2

Clinical cure rate according to severity of CAP

Success rate (% of patients)

Days 3-5  Test of cure

Moxifloxacin  Levofloxacin

97.9  90
92.9  87.9

Clinical cure rate

Mild/Moderate  Severe

92.6  88.6
113/122  101/114

94.7  84.6
18/19  22/26

5% CI: -0.12, 0.32; P=0.5

Moxifloxacin  Levofloxacin
Current official recommendations for pneumonia …

- Levofloxacin: 750 mg q24h \(^1\) or 2 x 500 mg/day \(^2\)
- Moxifloxacin: 400 mg q24h \(^3\) …

\(^1\) US Prescription Information (Levaquin®) updated February 2017

\(^2\) European Levofloxacin Prescription Information (in English: https://www.medicines.org.uk/emc/medicine/24624 [revised: 2 Nov 2012; last accessed: 14 Nov 2017])
See also the recommendations of EUCAST for breakpoint setting (use of “high dose”; http://www.eucast.org/clinical_breakpoints/ [version 2017])

\(^3\) US and European Prescription information for moxifloxacin
The programme…

• A very short view of Belgium and of where I work…

• Differentiating fluoroquinolones in their origin and intrinsic nature

• Differentiating fluoroquinolones in PK/PD and the concept of MPC (prevention of resistance)

• **How would moxifloxacin fit into an antibiotic stewardship program**

• Questions, objections, suggestions …
A reasonable equilibrium for moxifloxacin?

- rapid bactericidal activity
- ad hoc spectrum
  - *S. pneumoniae*
  - *H. influenzae*
  - *M. catarrhalis*
  - intracellular (atypical pneumonia)
- easy iv/po switch
- excellent oral bioavailability
- simple posology (400 mg OD)

- toxicity ?
- cross-resistance ?
- masking TB ?
- keep it as reserve ?
All antimicrobials have associated risks *

<table>
<thead>
<tr>
<th>Class</th>
<th>Drugs</th>
<th>Frequent or serious side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>fluoroquinolones</td>
<td>levofloxacin</td>
<td>• Anaphylactic reactions and allergic skin reactions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Clostridium difficile-associated colitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Hematologic toxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• <strong>Hepatotoxicity (ALT-AST elevation [common])</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Central nervous system effects: headache, insomnia, dizziness, convulsions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• <strong>Musculoskeletal: tendinopathies</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Peripheral neuropathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Prolongation of the QTc interval (cardiac disorders [rare])</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Hypoglycaemia (rare)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Digestive tract: nausea, diarrhoea</td>
</tr>
<tr>
<td>moxifloxacin</td>
<td></td>
<td>• Anaphylactic reactions and allergic skin reactions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Clostridium difficile-associated colitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• <strong>Hepatotoxicity (ALT-AST elevation [common])</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• <strong>Musculoskeletal: Tendinopathies</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Peripheral neuropathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Prolongation of the QTc interval (cardiac disorders [rare])</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Central nervous system effects: headache, insomnia, dizziness, convulsions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Digestive tract: nausea, diarrhoea</td>
</tr>
</tbody>
</table>

* based on an analysis of the current respective labelling (European SmPC)
- common: 1/10 to 1/100
- rare: 1/1000-1/10000

Note: the current EU SmPCs of levofloxacin (TAVANIC®) and of moxifloxacin state:
- For [community-acquired pneumonia], TAVANICc should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections.
- Moxifloxacin should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections.
Side effects of moxifloxacin
(clinical trials database)

Moxifloxacin Safety
An Analysis of 14 Years of Clinical Data

Paul M. Tulkens, Pierre Arvis and Frank Kruesmann

1 Pharmacologie cellulaire et moléculaire & Centre de Pharmacie clinique, Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium
2 Bayer Santé SAS, Loos, France
3 Bayer Pharma AG, Wuppertal, Germany

Based on the analysis of 14,681 patients treated with moxifloxacin vs. 15,023 patients treated with comparators
Side effects of moxifloxacin (clinical trials database)

**Patients at risk?**

<table>
<thead>
<tr>
<th></th>
<th>PO</th>
<th>sequential</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>age (&gt; 65 y)</td>
<td>n = 2551 vs. 2403</td>
<td>n = 1373 vs. 1334</td>
<td>n = 170 vs. 191</td>
</tr>
<tr>
<td>AE</td>
<td>1050 / 1021</td>
<td>929 / 900</td>
<td>83 / 81</td>
</tr>
<tr>
<td>ADR</td>
<td>440 / 448</td>
<td>348 / 307</td>
<td>27 / 31</td>
</tr>
<tr>
<td>SAE</td>
<td>207 / 184</td>
<td>298 / 290</td>
<td>32 / 24</td>
</tr>
<tr>
<td>SADR</td>
<td>16 / 18</td>
<td>49 / 30</td>
<td>4 / 6</td>
</tr>
<tr>
<td>discont. AE</td>
<td>116 / 109</td>
<td>131 / 104</td>
<td>10 / 10</td>
</tr>
<tr>
<td>discont. ADR</td>
<td>78 / 74</td>
<td>62 / 42</td>
<td>4 / 6</td>
</tr>
<tr>
<td>death AE</td>
<td>29 / 32</td>
<td>100 / 98</td>
<td>13 / 10</td>
</tr>
<tr>
<td>death ADR</td>
<td>3 / 1</td>
<td>2 / 3</td>
<td>0 / 1</td>
</tr>
</tbody>
</table>

**Relative risk estimate (moxifloxacin / comparator)**

<table>
<thead>
<tr>
<th></th>
<th>PO</th>
<th>sequential</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>diabetes</td>
<td>n = 777 vs. 717</td>
<td>n = 926 vs. 917</td>
<td>n = 80 vs. 72</td>
</tr>
<tr>
<td>AE</td>
<td>355 - 310</td>
<td>587 / 565</td>
<td>42 - 35</td>
</tr>
<tr>
<td>ADR</td>
<td>158 - 126</td>
<td>196 / 174</td>
<td>13 - 14</td>
</tr>
<tr>
<td>SAE</td>
<td>78 - 56</td>
<td>198 / 182</td>
<td>16 - 11</td>
</tr>
<tr>
<td>SADR</td>
<td>11 - 3</td>
<td>22 / 11</td>
<td>2 - 2</td>
</tr>
<tr>
<td>discont. AE</td>
<td>34 - 26</td>
<td>78 / 64</td>
<td>6 - 6</td>
</tr>
<tr>
<td>discont. ADR</td>
<td>22 - 14</td>
<td>38 / 20</td>
<td>1 - 4</td>
</tr>
<tr>
<td>death AE</td>
<td>10 - 6</td>
<td>46 / 23</td>
<td>9 - 4</td>
</tr>
<tr>
<td>death ADR</td>
<td>0 - 0</td>
<td>2 / 2</td>
<td>0 - 0</td>
</tr>
</tbody>
</table>

Tulkens et al., Drugs R D (2012) 12: 71-100
Side effects of moxifloxacin (clinical trials database)

Patients at risk?

renal impairment

<table>
<thead>
<tr>
<th>PO</th>
<th>n = 1283 vs. 1229</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>1283 - 1229</td>
</tr>
<tr>
<td>ADR</td>
<td>259 - 229</td>
</tr>
<tr>
<td>SAE</td>
<td>94 - 80</td>
</tr>
<tr>
<td>SADR</td>
<td>9 - 9</td>
</tr>
<tr>
<td>discont. AE</td>
<td>49 - 53</td>
</tr>
<tr>
<td>discont. ADR</td>
<td>27 - 33</td>
</tr>
<tr>
<td>death AE</td>
<td>12 - 14</td>
</tr>
<tr>
<td>death ADR.</td>
<td>0 - 3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>sequential</th>
<th>n = 889 vs. 863</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>572 - 549</td>
</tr>
<tr>
<td>ADR</td>
<td>196 - 181</td>
</tr>
<tr>
<td>SAE</td>
<td>202 - 180</td>
</tr>
<tr>
<td>SADR</td>
<td>30 - 23</td>
</tr>
<tr>
<td>discont. AE</td>
<td>75 - 78</td>
</tr>
<tr>
<td>discont. ADR</td>
<td>28 - 25</td>
</tr>
<tr>
<td>death AE</td>
<td>58 - 67</td>
</tr>
<tr>
<td>death ADR.</td>
<td>3 - 3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IV</th>
<th>n = 203 vs. 218</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>102 - 92</td>
</tr>
<tr>
<td>ADR</td>
<td>31 - 32</td>
</tr>
<tr>
<td>SAE</td>
<td>26 - 22</td>
</tr>
<tr>
<td>SADR</td>
<td>2 - 1</td>
</tr>
<tr>
<td>discont. AE</td>
<td>11 - 7</td>
</tr>
<tr>
<td>discont. ADR</td>
<td>2 - 3</td>
</tr>
<tr>
<td>death AE</td>
<td>10 - 7</td>
</tr>
<tr>
<td>death ADR.</td>
<td>0 - 0</td>
</tr>
</tbody>
</table>

relative risk estimate (moxifloxacin / comparator)

hepatic impairment

<table>
<thead>
<tr>
<th>PO</th>
<th>n = 146 vs. 163</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>69 - 70</td>
</tr>
<tr>
<td>ADR</td>
<td>37 - 32</td>
</tr>
<tr>
<td>SAE</td>
<td>5 - 7</td>
</tr>
<tr>
<td>SADR</td>
<td>1 - 1</td>
</tr>
<tr>
<td>discont. AE</td>
<td>6 - 7</td>
</tr>
<tr>
<td>discont. ADR</td>
<td>6 - 3</td>
</tr>
<tr>
<td>death AE</td>
<td>2 - 4</td>
</tr>
<tr>
<td>death ADR.</td>
<td>0 - 1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>sequential</th>
<th>n = 183 vs. 196</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>183 - 196</td>
</tr>
<tr>
<td>ADR</td>
<td>43 - 43</td>
</tr>
<tr>
<td>SAE</td>
<td>60 - 53</td>
</tr>
<tr>
<td>SADR</td>
<td>10 - 7</td>
</tr>
<tr>
<td>discont. AE</td>
<td>24 - 24</td>
</tr>
<tr>
<td>discont. ADR</td>
<td>11 - 7</td>
</tr>
<tr>
<td>death AE</td>
<td>14 - 24</td>
</tr>
<tr>
<td>death ADR.</td>
<td>1 - 2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IV</th>
<th>n = 46 vs. 46</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>23 - 18</td>
</tr>
<tr>
<td>ADR</td>
<td>7 - 6</td>
</tr>
<tr>
<td>SAE</td>
<td>7 - 7</td>
</tr>
<tr>
<td>SADR</td>
<td>1 - 0</td>
</tr>
<tr>
<td>discont. AE</td>
<td>1 - 1</td>
</tr>
<tr>
<td>discont. ADR</td>
<td>1 - 0</td>
</tr>
<tr>
<td>death AE</td>
<td>2 - 0</td>
</tr>
<tr>
<td>death ADR.</td>
<td>0 - 0</td>
</tr>
</tbody>
</table>

relative risk estimate (moxifloxacin / comparator)

Tulkens et al., Drugs R D (2012) 12: 71-100
Side effects of moxifloxacin
(clinical trials database)

Patients at risk?

### Relative Risk Estimate

**Cardiac Disorders**
- n = 1476 vs. 1404
- n = 1136 vs. 1104
- n = 106 vs. 104

<table>
<thead>
<tr>
<th>Event</th>
<th>PO</th>
<th>sequential</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>707 - 655</td>
<td>804 - 804</td>
<td>63 - 57</td>
</tr>
<tr>
<td>ADR</td>
<td>340 - 297</td>
<td>315 - 293</td>
<td>16 - 25</td>
</tr>
<tr>
<td>SAE</td>
<td>132 - 110</td>
<td>251 - 246</td>
<td>23 - 11</td>
</tr>
<tr>
<td>SADR</td>
<td>14 - 8</td>
<td>43 - 35</td>
<td>3 - 2</td>
</tr>
<tr>
<td>discont. AE</td>
<td>70 - 64</td>
<td>119 - 96</td>
<td>7 - 3</td>
</tr>
<tr>
<td>discont. ADR</td>
<td>43 - 45</td>
<td>59 - 43</td>
<td>1 - 1</td>
</tr>
<tr>
<td>death AE</td>
<td>11 - 25</td>
<td>69 - 75</td>
<td>11 - 8</td>
</tr>
<tr>
<td>death ADR.</td>
<td>0 - 2</td>
<td>3 - 4</td>
<td>0 - 1</td>
</tr>
</tbody>
</table>

**BMI < 18**
- n = 318 vs. 365
- n = 116 vs. 115
- n = 45 vs. 53

<table>
<thead>
<tr>
<th>Event</th>
<th>PO</th>
<th>sequential</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>113 - 171</td>
<td>89 - 83</td>
<td>17 - 10</td>
</tr>
<tr>
<td>ADR</td>
<td>70 - 96</td>
<td>26 - 27</td>
<td>5 - 3</td>
</tr>
<tr>
<td>SAE</td>
<td>11 - 28</td>
<td>36 - 30</td>
<td>3 - 3</td>
</tr>
<tr>
<td>SADR</td>
<td>0 - 5</td>
<td>5 - 4</td>
<td>0 - 0</td>
</tr>
<tr>
<td>discont. AE</td>
<td>14 - 27</td>
<td>10 - 11</td>
<td>1 - 0</td>
</tr>
<tr>
<td>discont. ADR</td>
<td>12 - 20</td>
<td>6 - 9</td>
<td>1 - 0</td>
</tr>
<tr>
<td>death AE</td>
<td>3 - 5</td>
<td>15 - 15</td>
<td>1 - 0</td>
</tr>
<tr>
<td>death ADR.</td>
<td>0 - 0</td>
<td>0 - 0</td>
<td>0 - 0</td>
</tr>
</tbody>
</table>

*relative risk estimate (moxifloxacin / comparator)*

**Tulkens et al., Drugs R D (2012) 12: 71-100**
Side effects of moxifloxacin (clinical trials database)

Comparison with other drugs

A. oral therapy

1. moxifloxacin vs β-lactams

<table>
<thead>
<tr>
<th>Risk factor:</th>
<th>Age &gt; 65 y (n=909 vs 788)</th>
<th>Diabetes (n=282 vs 217)</th>
<th>Renal impairment (n=347 vs 380)</th>
<th>Hepatic impairment (n=47 vs 53)</th>
<th>Cardiac disorders (n=526 vs 444)</th>
<th>BMI &lt; 18 (n=70 vs 76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SADR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discont. AE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death AE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death ADR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Relative risk estimate (moxifloxacin / comparator)

2. moxifloxacin vs macrolides

<table>
<thead>
<tr>
<th>Risk factor:</th>
<th>Age &gt; 65 y (n=1252 vs 942)</th>
<th>Diabetes (n=329 vs 255)</th>
<th>Renal impairment (n=484 vs 427)</th>
<th>Hepatic impairment (n=44 vs 64)</th>
<th>Cardiac disorders (n=794 vs 623)</th>
<th>BMI &lt; 18 (n=110 vs 114)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SADR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discont. AE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death AE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death ADR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Relative risk estimate (moxifloxacin / comparator)

Tulkens et al., Drugs R D (2012) 12: 71-100
# Hepatotoxicity in large populations

Crude incidence rates of acute liver injury caused by antibiotics

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>population</th>
<th>Incidence rate (CI)</th>
<th>endpoint</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>fluoroquinolones</td>
<td>Outpatient clinic, Sweden (1995-2005)</td>
<td>0.7 (0.5-1.1)</td>
<td>International consensus</td>
<td>[1]</td>
</tr>
<tr>
<td>(w/o moxifloxacin)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>moxifloxacin</td>
<td>Outpatient clinic, Sweden (1995-2005)</td>
<td>0.08 (0.0-0.5)</td>
<td>International consensus</td>
<td>[1]</td>
</tr>
<tr>
<td>cotrimoxazole</td>
<td>Saskatchewan Health Plan, Canada (1982-1986)</td>
<td>1.0 (0.2-5.7)</td>
<td>International consensus, hospitalisation</td>
<td>[2]</td>
</tr>
<tr>
<td>erythromycin</td>
<td>Saskatchewan Health Plan, Canada (1982-1986)</td>
<td>2.0 (0.7-5.9)</td>
<td>International consensus, hospitalisation</td>
<td>[2]</td>
</tr>
<tr>
<td>amoxicillin-clavulanic acid</td>
<td>General practice research database, United Kingdom (1991-1992)</td>
<td>22.5 (14.7-34.4)</td>
<td>17.4 (11.4-26.5)</td>
<td>International consensus</td>
</tr>
</tbody>
</table>


EMA position

... the risk of arrhythmias appears to increase with the extent of QT/QTc prolongation.

- Drugs [with] QT/QTc interval by around 5 ms or less do not appear to cause TdP.
- ...data on drugs [with] QT/QTc interval by... 5 to < 20 ms are inconclusive, but some of these compounds have been associated with proarrhythmic risk.*

... decisions about [drug] development and approval will depend upon the morbidity and mortality associated with the untreated disease or disorder and the demonstrated clinical benefits of the drug, especially as they compare with available therapeutic modalities.

---

* this includes erythromycin and clarithromycin (Balardinelli et al, TIPS (2003) 24:619-625)
QTc prolongation

Genetics
- LGTS-1-LQTS-7
- Unknown ion channel mutations

Underlying cardiac disease
- Ischemia
- CHF
- Bradycardia
- Atrial fibrillation

Electrolyte derangements
- Hypokalemia
- Hypomagnesemia
- Hypocalcemia

Organ impairment
- Renal insufficiency
- Severe hepatic disease

$\text{i}_\text{Kr}$-blocking comedication
- or CYP3A4 inhibitors

Prescription of QT-prolonging drug (antimicrobials listed)
- Macrolides/lincosamides
- Quinolones
- Azoles
- Penicillins
- TMF-SMZ

Owens & Ambrose CID (2005) 41:S144-157
**Torsade de pointe: comparison of risk**

reporting rate of *Torsades de pointe* induced by antibiotics

<table>
<thead>
<tr>
<th>drug</th>
<th>No. of U.S. Cases Reported to the FDA</th>
<th>No. of Estimated Total U.S. Prescriptions (millions)</th>
<th>No. of Cases /10 Millions Prescriptions (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>moxifloxacin</td>
<td>0</td>
<td>1.4</td>
<td>0 (0-26)</td>
</tr>
<tr>
<td>ciprofloxacin</td>
<td>2</td>
<td>66</td>
<td>0.3 (0.0-1.1)</td>
</tr>
<tr>
<td>ofloxacin</td>
<td>2</td>
<td>9.5</td>
<td>2.1 (0.3-7.6)</td>
</tr>
<tr>
<td>levofloxacin</td>
<td>13</td>
<td>24</td>
<td>5.4 (2.9-9.3)</td>
</tr>
<tr>
<td>gatifloxacin</td>
<td>8</td>
<td>3</td>
<td>27 (12-53)</td>
</tr>
<tr>
<td>erythromycin</td>
<td>11–17</td>
<td>151</td>
<td>0.7 -1.1</td>
</tr>
<tr>
<td>clarithromycin</td>
<td>16–31</td>
<td>90</td>
<td>1.8 -3.4</td>
</tr>
<tr>
<td>azithromycin</td>
<td>7–10</td>
<td>124</td>
<td>0.6–1</td>
</tr>
<tr>
<td>cefuroxime</td>
<td>1–1</td>
<td>42</td>
<td>0.2 –1</td>
</tr>
</tbody>
</table>

*Van Bambeke & Tulkens, Drug Safety (2009) 32:359-78*
Tendinopathies…

• In 2005, all fluoroquinolones marketed in the US have received a black box label about tendinopathies.
Tendinopathies…

- But this is what we found for moxifloxacin in our survey of the whole clinical trial database

<table>
<thead>
<tr>
<th>SMQ/BMQ and preferred term</th>
<th>Treatment route [n (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PO</td>
</tr>
<tr>
<td>Tendinopathies</td>
<td>11 (0.1)</td>
</tr>
</tbody>
</table>

PO = oral
IV = intravenous
MXF: moxifloxacin
COMP = comparator

very rare and no difference
no case

Tulkens et al., Drugs R D (2012) 12: 71-100
Tendinopathies: incidences (revisited)...

QuarterWatch: 2010 Quarter 2
Monitoring MedWatch Reports
January 27, 2011
Signals for Varenicline, Levofloxacin and Fentanyl

Last accessed: 20/02/2015

Levofloxacin (LEVAQUIN) Cases Lead Antibiotics

While antibiotics rank among the safest drugs we monitor, levofloxacin (LEVAQUIN) was suspect in more reports of serious injury than any other antibiotic. Most cases involved tendon rupture and other muscle, tendon and ligament injuries. Case reports of this problem substantially outnumbered those for two chemically similar drugs—ciprofloxacin (CIPRO), with greater volume of prescriptions, and moxifloxacin (AVELOX), with somewhat less frequent medical use.
Tendinopathies: incidences (revisited)...

QuarterWatch: 2010 Quarter 2

<table>
<thead>
<tr>
<th></th>
<th>Levofloxacin</th>
<th>Ciprofloxacin</th>
<th>Moxifloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Rx (millions)*</td>
<td>2.1</td>
<td>5.3</td>
<td>1.5</td>
</tr>
<tr>
<td>Case Reports</td>
<td>246</td>
<td>105</td>
<td>93</td>
</tr>
<tr>
<td>% Direct to FDA</td>
<td>52%</td>
<td>71%</td>
<td>42%</td>
</tr>
<tr>
<td>% Health Professionals</td>
<td>53%</td>
<td>59%</td>
<td>76%</td>
</tr>
<tr>
<td>Tendon Disorders (HLT)</td>
<td>93</td>
<td>29</td>
<td>10</td>
</tr>
<tr>
<td>All Musculoskeletal</td>
<td>156</td>
<td>62</td>
<td>20</td>
</tr>
</tbody>
</table>

*IMS Health National Prescription Audit™ 2010

(AVELOX), with somewhat less frequent medical use.

Last accessed: 20/02/2015
Safety Profile of the Respiratory Fluoroquinolone Moxifloxacin
Comparison with Other Fluoroquinolones and Other Antibacterial Classes

Françoise Van Bambeke and Paul M. Tulkens
Unité de pharmacologie cellulaire et moléculaire & Centre de Pharmacie Clinique, Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium

The data show that using moxifloxacin, in its accepted indications and following the corresponding guidelines, should not be associated with an excessive incidence of drug-related adverse reactions, provided the clinician takes care in identifying patients with known risk factors and pays due attention to the contraindications and warnings mentioned in the labelling.
A reasonable equilibrium for moxifloxacin?

- rapid bactericidal activity
- ad hoc spectrum
  - *S. pneumoniae*
  - *H. influenzae*
  - *M. catarrhalis*
  - intracellular (atypical pneumonia)
- easy iv/po switch
- excellent oral bioavailability
- simple posology (400 mg OD)

- toxicity ?
- cross-resistance ?
- masking TB ?
- keep it as reserve ?

*Not All Fluoroquinolones Are Equal (Singapore)*
Cross-resistance with what?

- **Gram-negative**
  - *K. pneumoniae*
  - *E. coli*
  - *P. aeruginosa*

- **Gram-positive**
  - *C. difficile*
  - *Enterococci*
  - *Staphylococci*

All these show variable levels of resistance to moxifloxacin (i.e. MICs > the EUCAST ECOFF *)

* [https://mic.eucast.org/Eucastr2/](https://mic.eucast.org/Eucastr2/) (EUCAST MIC distributions help to establish the ECOFF but should not be used to determine resistance levels)
Cross-resistance with what?

- **Gram-negative**
  - *K. pneumoniae*
  - *E. coli*
  - *P. aeruginosa*

- **Gram-positive**
  - *C. difficile*
  - *Enterococci*
  - *Staphylococci*

All these show variable levels of resistance to moxifloxacin (i.e. MICs > the EUCAST ECOFF).

*Moxifloxacin / Klebsiella pneumoniae*

**International MIC Distribution - Reference Database 2017-11-21**

- Epidemiological cut-off (ECOFF): 0.25 mg/L
- Wildtype (WT) organisms: ≤ 0.25 mg/L
- 4257 observations (7 data sources)

* [https://mic.eucast.org/Eucast2/](https://mic.eucast.org/Eucast2/) (EUCAST MIC distributions help to establish the ECOFF but should not be used to determine resistance levels)
Cross-resistance with what?

- **Gram-negative**
  - *K. pneumoniae*
  - *E. coli*
  - *P. aeruginosa*

- **Gram-positive**
  - *C. difficile*
  - *Enterococci*
  - *Staphylococci*

*all these show variable levels of resistance to moxifloxacin (i.e. MICs > the EUCAST ECOFF)*

... BUT not more than levofloxacin

* [EUCAST](https://mic.eucast.org/Eucast2/) (EUCAST MIC distributions help to establish the ECOFF but should not be used to determine resistance levels)
Cross-resistance with what?

- **Gram-negative**
  - *K. pneumoniae*
  - *E. coli*
  - *P. aeruginosa*

- **Gram-positive**
  - *C. difficile*
  - *Enterococci*
  - *Staphylococci*

All these show variable levels of resistance to moxifloxacin (i.e. MICs > the EUCAST ECOFF).

**BUT not more than levofloxacin**

* [EUCAST MIC distributions help to establish the ECOFF but should not be used to determine resistance levels](https://mic.eucast.org/Eucast2/).*
A reasonable equilibrium for moxifloxacin?

- rapid bactericidal activity
- ad hoc spectrum
  - *S. pneumoniae*
  - *H. influenzae*
  - *M. catarrhalis*
  - intracellular (atypical pneumonia)
- easy iv/po switch
- excellent oral bioavailability
- simple posology (400 mg OD)

- toxicity ?
- cross-resistance ?
- masking TB ?
- keep it as reserve ?
Does the use of fluoroquinolones for respiratory tract infections mask (an delay the diagnostic of) tuberculosis?

• A number of papers say "Yes"

Fluoroquinolones are associated with delayed treatment and resistance in tuberculosis: a systematic review and meta-analysis

Tun-Chieh Chen\textsuperscript{a,b,c}, Po-Liang Lu\textsuperscript{b,c}, Chun-Yu Lin\textsuperscript{b,c}, Wei-Ru Lin\textsuperscript{b}, Yen-Hsu Chen\textsuperscript{b,c,d,e}\textsuperscript{1}

\textsuperscript{1}Kaohsiung Municipal Ta-Tung Hospital, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung City, Taiwan


MOXIFLOXACIN USE AND ITS ASSOCIATION ON THE DIAGNOSIS OF PULMONARY TUBERCULOSIS IN AN INNER CITY EMERGENCY DEPARTMENT

Barret Rush, MD,\textsuperscript{*} Andrew Wormsbecker, MD,\textsuperscript{*} Rob Stenstrom, MD,\textsuperscript{†} and Barry Kassen, MD\textsuperscript{‡}

\textsuperscript{*}Division of Critical Care Medicine, Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada

\textsuperscript{†}Department of Emergency Medicine, University of British Columbia, St Paul's Hospital, Vancouver, British Columbia, Canada

\textsuperscript{‡}Division of General Internal Medicine, Department of Medicine, University of British Columbia, St Paul's Hospital, Vancouver, British Columbia, Canada

Reprint Address: Barret Rush, MD, Department of Medicine, St. Paul’s Hospital, 5th Floor, Burrard Building, 1081 Burrard Street, Vancouver, BC V6Z 1Y6 Canada

But …

1. Diagnostic tools should aid to identify TB vs non-TB pulmonary infection

A Malaysian study:
- Prospective with 346 hospitalized pts with “CAP”
- *M tuberculosis* in 4.9%
- Clinical features were very helpful in predicting *M tuberculosis* infection


Slide adapted from Prof. R. Grossman's presentation (Singapore, 2016)
But …

2. Non-TB CAP patients improve rapidly (if treated with an active antibiotic)

A very basic study:
- Prospective, observational with 668 pts
- Median time to clinical stability was 3 days (lenient definition) to 7 days (conservative definition)
- Clinical deterioration occurred in < 1% of cases

Halm et al. JAMA 1998;279:1452-7 - PMID 9600479

Slide adapted from Prof. R. Grossman's presentation (Singapore, 2016)
3. Biomarkers should help to separate non-TB and TB-CAP

Prospective study of 87 pts, 57 with bacterial CAP and 30 with TB

- CRP = 14.58 mg/dL in bacterial CAP
  5.27 mg/dL in TB (p<0.001)
- PCT = 0.514 ng/mL in bacterial CAP
  0.029 ng/mL in TB (p<0.001)

- CRP discriminative value: 0.857
  (95% CI, 0.778 to 0.936)
- PCT discriminative value: 0.872
  (95% CI, 0.792 to 0.951)


Figure 1. Receiver-operating characteristics curve for discriminating between pulmonary tuberculosis and bacterial community-acquired pneumonia for C-reactive protein (CRP) and procalcitonin (PCT). No difference was detected in the discriminative value between CRP and PCT.
But here is a practical solution...

Review

Does empirical treatment of community-acquired pneumonia with fluoroquinolones delay tuberculosis treatment and result in fluoroquinolone resistance in *Mycobacterium tuberculosis*? Controversies and solutions

Gwan-Han Shen, Thomas Chang-Yao Tsao, Shang-Jyh Kao, Jen-Jyh Lee, Yen-Hsu Chen, Wei-Chung Hsieh, Gwo-Jong Hsu, Yen-Tao Hsu, Ching-Tai Huang, Yeu-Jun Lau, Shih-Ming Tsao, Po-Ren Hsieh

but here are solutions...

Review

Does empirical treatment of community-acquired pneumonia with fluoroquinolones delay tuberculosis treatment and result in fluoroquinolone resistance in *Mycobacterium tuberculosis*? Controversies and solutions

Gwan-Han Shen\(^a\), Thomas Chang-Yao Tsao\(^b\), Shang-Jyh Kao\(^c\), Jen-Jyh Lee\(^d\), Yen-Hsu Chen\(^e\), Wei-Chung Hsieh\(^f\), Gwo-Jong Hsu\(^g\), Yen-Tao Hsu\(^h\), Ching-Tai Huang\(^i\), Yeu-Jun Lau\(^j\), Shih-Ming Tsao\(^k\), Po-Ren Huo\(^l\)

\(^{a}\) Division of Respiratory and Critical Care Medicine, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan

\(^{b}\) Division of Respiratory and Critical Care Medicine, National Taiwan University Hospital, Taipei, Taiwan

\(^{c}\) Pulmonary Division, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan

\(^{d}\) TB Laboratory Section, Department of Infectious Diseases, National Taiwan University College of Medicine, Taipei, Taiwan

\(^{e}\) Division of Infectious Diseases, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan

\(^{f}\) Division of Respiratory and Critical Care Medicine, National Taiwan University Hospital, Taipei, Taiwan

\(^{g}\) Division of Infectious Diseases, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan

\(^{h}\) Division of Pulmonary Critical Care Medicine, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan

\(^{i}\) Infectious Diseases, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan

\(^{j}\) Infectious Section, Internal Medicine Division, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan

\(^{k}\) Departments of Laboratory Medicine and Microbiology, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan


- Empirical treatment of CAP with a FQ might mask active TB, delay treatment and contribute to the development of FQ resistance.

- BUT … FQ resistance in M. tuberculosis is related to FQ duration (> 10 days) and the timing of exposure (> 60 days before TB diagnosis

- Consequently, a short-course (5-day) regimen of a FQ (levofloxacin, moxifloxacin and gemifloxacin) is still recommended for empirical therapy for CAP patients if the patient is at low risk for TB.

- Furthermore, FQ resistance is less likely to occur amongst M. tuberculosis strains isolated from patients with short-term exposure (<10 days) to FQ.
A reasonable equilibrium for moxifloxacin?

- rapid bactericidal activity
- ad hoc spectrum
  - *S. pneumoniae*
  - *H. influenzae*
  - *M. catarrhalis*
  - intracellular (atypical pneumonia)
- easy iv/po switch
- excellent oral bioavailability
- simple posology (400 mg OD)

- toxicity?
- cross-resistance?
- masking TB?
- keep it as reserve?
Why keeping the best on reserve?

- It's largely a political decision..
  - Reserve for what?
  - Reserve for how long?
  - Reserve for which patients?
  - What do you want to keep it for?
  - Do I need to wait for failures?
  - Who can I treat with old drugs?

- Which are my comparators?
  - A β-lactam (TID) + a macrolide (CYP inhibitor!)?
  - A less potent fluoroquinolone (at larger dose)

- Is my patient eligible?
  - A "real" bacterial infection?
  - Without known risk factors?

Make a rational choice for the goal you aim at...
At the end of the day…
It will be your (informed) choice!

- rapid bactericidal activity
- ad hoc spectrum
  - *S. pneumoniae*
  - *H. influenzae*
  - *M. catarrhalis*
  - intracellular
    (atypical pneumonia)
- easy iv/po switch
- excellent oral bioavailability
- simple posology (400 mg OD)

- toxicity ?
- cross-resistance ?
- masking TB ?
- keep it as reserve ?
Please, ask questions ... 

be critical, ask for facts!

Vesalius - anatomy

All slide are available on http://www.facb.ucl.ac.be → Lectures