Fluoroquinolones: Parenteral use

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Disclosures and slides availability

- Research grants
  - Theravance, Astellas, Targanta, Cerexa/Forest, AstraZeneca, Bayer, GSK, Trius, Rib-X, Eumedica
  - Belgian Science Foundation (F.R.S.-FNRS), Ministry of Health (SPF), and Walloon and Brussels Regions

- Speaking fees
  - Bayer, GSK, Sanofi, Johnson & Johnson, OM-Pharma

- Decision-making and consultation bodies
  - General Assembly and steering committee of EUCAST
  - European Medicines Agency (external expert)
  - US National Institutes of Health (grant reviewing)

Slides: http://www.facom.ucl.ac.be → Lectures
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)

- Toxicity, medicinal chemistry, and improved schedules of aminoglycosides
- novel antibiotics (and last studied)
  - beta-lactams (ceftaroline…)
  - fluoroquinolones (finafloxacine…)
  - kétolides (solithromycin…)
  - oxazolidinones (tedizolid …)

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), in 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 Obélux, I fell into when I was young ...


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

Marie-Béatrice Carlier1, Bernard Scorneaux2, Andrée Zenebergh3, Jean-François Desnottes4 and Paul M. Tulkens5

1Laboratoire 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; 2Rhône-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 Bambeke1, J-M. Michel1, J. Van Eldere1 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 Leuven, Louvain, Belgium

Clin Microbiol Infect 2005; 11: 256–280

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
What shall we discuss?

- The basics: are quinolones different by design?
- When should they be given IV?
- Indications and experience of moxifloxacin IV
- The fights against resistance: the saga of the MPC
- Are they toxicity issues?
- What you can do with an MIC?
Mechanism of action of fluoroquinolones: the basics...
2 key enzymes in DNA replication:

- DNA gyrase
  - Stabilize positive node
  - Break back segment
  - Reseal break on front side

- Topoisomerase IV

Bacterial DNA is supercoiled
Ternary complex
DNA - enzyme - fluoroquinolone

"GyraseCiproTop" by Fdardel - Own work. Licensed under CC BY-SA 3.0 via Wikimedia Commons - http://commons.wikimedia.org/wiki/File:GyraseCiproTop.png#mediaviewer/File:GyraseCiproTop.png
Last accessed: 8/2/2015
Fluoroquinolones are the first entirely man-made antibiotics: do we understand our molecule?

Don’t panic, we will travel together....
From chloroquine to nalidixic acid...

chloroquine

1939

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

1958

nalidixic acid

1962
From nalidixic acid to the 1st fluoroquinolone

naldixic acid

make 3 key modifications *...

1978

norfloxacin *

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

* 6-fluoro-7-pyrimidino-quinoleine

* Belgian patent 863,429, 1978 to Kyorin
From norfloxacin to ofloxacin via pefloxacin

*n Eur. pat. Appl. 47,005 to Daiichi, 1982
From norfloxacin to ciprofloxacin

Norfloxacin

Cyclopropyl to increase potency

Ciprofloxacin *

* Ger. pat. 3,142,854 to Bayer AG, 1983
"1st generation" fluoroquinolones

- Ofloxacin
  - Methyl piperazine
  - Morpholine
- Ciprofloxacin
  - Piperazine
  - Cyclopropyl
From ofloxacin to levofloxacin...

Ofloxacin is a racemic mixture

The active form of ofloxacin is the (-) S isomer

Levofloxacin is the pure (-) S isomer *

* Eur. pat. 206,283 to Daiichi, 1987
Activity against *S. pneumoniae*

- **Ciprofloxacin**: 0.5 - 2
- **Moxifloxacin**: 0.01 - 0.5
- **Levofoxacin**: 0.5 - 2
Activity against \textit{B. fragilis} (anaerobe)

ciprofloxacin
\(2 - 128\)
moxifloxacin
\(0.25 - 8\)
At this point …

Gram (-)

- Ciprofloxacin
- Moxifloxacin
- Levofloxacin

Gram (+)

Anaerobes

This is by design!
A unbiased estimation of antibiotic activity (in the absence of resistance)
Gram negative: *E. coli*

**Ciprofloxacin / Escherichia coli**

*International MIC Distribution - Reference Database 2015-02-08*

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance.

**Levofloxacin / Escherichia coli**

*International MIC Distribution - Reference Database 2015-02-08*

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance.

**http://mic.eucast.org/Eucast2/regShow.jsp?id=1022**

**http://mic.eucast.org/Eucast2/regShow.jsp?id=1072**

Last accessed: 8/2/2015
Gram positive: *S. pneumoniae*

**Moxifloxacin / Streptococcus pneumoniae**
International MIC Distribution - Reference Database 2015-02-08

MIC distributions include isolated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance.

**moxifloxacin**

**Levofloxacin / Streptococcus pneumoniae**
International MIC Distribution - Reference Database 2015-02-08

MIC distributions include isolated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance.

**levofloxacin**


Last accessed: 8/2/2015
Anaerobes: *B. fragilis*

**Moxifloxacin / Bacteroides fragilis**
International MIC Distribution - Reference Database 2015-02-08

MIC distributions include isolated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance.

**Levofloxacin / Bacteroides fragilis**
International MIC Distribution - Reference Database 2015-02-08

MIC distributions include isolated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance.

**B. fragilis**

- **Moxifloxacin**
- **Levofloxacin** (not recommended)

http://mic.eucast.org/Eucast2/regShow.jsp?id=1454
http://mic.eucast.org/Eucast2/regShow.jsp?id=1066
Last accessed: 8/2/2015
What shall we discuss?

• The basics: are quinolones different by design?

• When should they be given IV?

• Indications and experience of moxifloxacin IV

• The fights against resistance: the saga of the MPC

• Are they toxicity issues?

• What you can do with an MIC?
When should a fluoroquinolone be given IV?

- Firsts, they should not in many cases because most have a good oral bioavailability (70 to 90%)

- BUT the patient may require an IV treatment:
  - difficulties to swallow (consciousness, …)
  - vomiting
  - GIT disease
  - hemodynamic instability
  - risk of poor compliance (!)

- and the doctor may be more comfortable:
  - more reliable peak levels and AUC
  - better organ penetration …
What shall we discuss?

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• The fights against resistance: the saga of the MPC

• Are they toxicity issues?

• What you can do with an MIC?
### Moxifloxacin IV indications

<table>
<thead>
<tr>
<th>Type of Infection</th>
<th>Dose Every 24 hours</th>
<th>Duration (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community Acquired Pneumonia (1.1)</td>
<td>400 mg</td>
<td>7–14</td>
</tr>
<tr>
<td>Uncomplicated Skin and Skin Structure Infections (SSSI) (1.2)</td>
<td>400 mg</td>
<td>7</td>
</tr>
<tr>
<td>Complicated SSSI (1.3)</td>
<td>400 mg</td>
<td>7–21</td>
</tr>
<tr>
<td>Complicated Intra-Abdominal Infections (1.4)</td>
<td>400 mg</td>
<td>5–14</td>
</tr>
<tr>
<td>Plague (1.5)</td>
<td>400 mg</td>
<td>10–14</td>
</tr>
<tr>
<td>Acute Bacterial Sinusitis (1.6)</td>
<td>400 mg</td>
<td>10</td>
</tr>
<tr>
<td>Acute Bacterial Exacerbation of Chronic Bronchitis (1.7)</td>
<td>400 mg</td>
<td>5</td>
</tr>
</tbody>
</table>

- No dosage adjustment in patients with renal or hepatic impairment. ([8.6](#), [8.7](#))
- AVELOX Injection: Slow intravenous infusion over 60 minutes. Avoid rapid or bolus intravenous injection. ([2.2](#))
- Do not mix with other medications in intravenous bag or in an intravenous line. ([2.3](#))

### DOSAGE FORMS AND STRENGTHS
- Tablets: Moxifloxacin hydrochloride (equivalent to 400 mg moxifloxacin) ([3.1](#))
- Injection: Moxifloxacin hydrochloride (equivalent to 400 mg moxifloxacin) in 0.8% sodium chloride solution in a 250 mL flexibag ([3.2](#))


Last visited: 11 Nov 2017
A comprehensive meta-analysis of moxifloxacin IV in skin and skin structures infections

A comprehensive meta-analysis of moxifloxacin IV in skin and skin structures infections

Fig. 2 The clinical cure rates comparing moxifloxacin with other antibiotics.

Fig. 3 The bacteriological success rates comparing moxifloxacin with other antibiotics.

Pharmacokinetics and Tissue Penetration of Moxifloxacin in Intervention Therapy for Intra-Abdominal Abscess

Andreas D. Rink,1 Heino Stass,2 Heinz Delesen,2 Dagmar Kubitza2 and Karl-Heinz Vestweber1

1 Department of General Surgery, Leverkusen General Hospital, Leverkusen, Germany
2 Institute of Clinical Pharmacology, Bayer HealthCare AG, Wuppertal, Germany

Tissue penetration: abdominal abscesses

Pharmacokinetics and Tissue Penetration of Moxifloxacin in Intervention Therapy for Intra-Abdominal Abscess

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1 Department of General Surgery, Leverkusen General Hospital, Leverkusen, Germany
2 Institute of Clinical Pharmacology, Bayer HealthCare AG, Wuppertal, Germany


Fig. 1. Concentrations of moxifloxacin in plasma (a) and abscess fluid (b) following a single 400-mg dose administered by 1-hour intravenous infusion. Results are presented as geometric means with SDs (n = 8).
Tissue penetration: abdominal abscesses

Pharmacokinetics and Tissue Penetration of Moxifloxacin in Intervention Therapy of Intra-Abdominal Abscesses

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1 Department of General Surgery, Leverkusen General Hospital, Germany
2 Institute of Clinical Pharmacology, Bayer HealthCare, Leverkusen, Germany


Fig. 2. Abscess fluid/plasma concentration ratio following administration of a single 400-mg dose administered by 1-hour intravenous infusion. Results are presented as geometric means with SDs (n = 8).
Fluid penetration: CSF

Clinical Studies

Pharmacokinetics of intravenous moxifloxacin in the cerebrospinal fluid of a patient with central nervous system shunt infection

Bo Zhang a, Xiaoming Huang b, Hongwei Fan c, Xuejun Zeng b, Dan Mei a, Qiang Fu a,*

a Department of Pharmacy, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China
b Department of Internal Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China
c Department of Infectious Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China
Fluid penetration: CSF

The ratio of the $AUC_{24h}$ in cerebrospinal fluid to the $AUC_{24h}$ in serum was 0.7

Fig. 1. The concentration–time curves of moxifloxacin in serum and CSF after 90-min infusion administration of 400 mg moxifloxacin at steady state in a patient with CNS shunt infection.
Penetration in other tissues and effectiveness

- cancellous and cortical bone: 53.86 and 41.59% of the plasma concentration\(^1\)
  → much above the MIC90s for common susceptible pathogens
  → suitable for treatment of osteomyelitis.

- body and manubrium of the sternal bone after IV administration:
  1.65 g/g and 1.64 g/g at 2 h and 1.4 g/g and 1.45 g/g at 5 h\(^2\)
  → considered for the treatment of osteomyelitis.

- prophylactic treatment of post-endoscopic retrograde cholangiopancreatography cholangitis and cholangitis-associated morbidity\(^3\)
  → moxifloxacin IV not inferior to ceftriaxone.

1 Metallidis et al. J Chemother. 2007;19:682-7 - PMID: 18230551
What shall we discuss?

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• The fights against resistance and the saga of the MPC

• Are they toxicity issues?

• What you can do with an MIC?
Resistance must first be assessed by MIC distributions

- Resistance of Gram-negative (ciprofloxacin/levofloxacin) is widespread and must be assessed locally (often ward by ward)

**EUCAST breakpoints:**
- Cipro: $S \leq 0.5 - R > 0.5$
- Levo: $S \leq 1.0 - R > 1.0$
- Oflo: **-- --**
Resistance must first be assessed by MIC distributions

• Conversely, resistance of Gram-positive is variable
  – High for MRSA (co-resistance frequent)
  – Low for *S. pneumonia* (especially for moxifloxacin; close to breakpoint for levofloxacin)

MIC distributions of *S. pneumonia* in Belgium for CAP (n=249)

Resistance must first be assessed by MIC distributions

• Conversely, resistance of Gram-positive is variable
  – High for MRSA (co-resistance frequent)
  – Low for *S. pneumonia* (especially for moxifloxacin; close to breakpoint for levofloxacin)

MIC distributions of *S. pneumonia* in Belgium for CAP (n=249)

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

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

"Classic" bactericidal effect

Surviving bacteria

Concentration

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$_{99} = 0.8$

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

MPC$_{10} = 9$

Surviving bacteria

Concentration

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

Time after administration

concentration

Mutation selection window

MPC

MSW

MIC

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
MPC: moxifloxacin vs levofloxacin

Moxifloxacin

Levofloxacin

~10 x the median MIC (0.125 mg/L)

~10 x the median MIC (1 mg/L)
The saga of the AUC / MIC vs $C_{\text{max}} / \text{MIC}$ ratio for fluoroquinolones ...

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 ...

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\textsuperscript{1,2,*} and Otto Cars\textsuperscript{2}

\textsuperscript{1}Infectious Diseases Research Unit, Department of Clinical Sciences Malmö, Lunds University, S-20502 Malmö, Sweden; \textsuperscript{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

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

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 emergence 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$_{max}$ ∼ 0.5

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

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
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• What you can do with an MIC?
We all agree about efficacy, but what about side effects…

therapy ?

side effects ?
All antimicrobials have associated risks *

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

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

Note: the current EU SmPCs of levofloxacin (TAVANIC®) and of moxifloxacin state:
- For [community-acquired pneumonia], TAVANIC® 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,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

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)

Distribution of patients valid for the safety analysis, stratified by route of administration (oral only; intravenous followed by oral [sequential]; intravenous only) and by comparator

<table>
<thead>
<tr>
<th>Study design and COMP</th>
<th>Treatment route [n]</th>
<th>IV/PO [n=6846]</th>
<th>IV only [n=1860]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PO [n=21298]</td>
<td>IV/PO [n=6846]</td>
<td></td>
</tr>
<tr>
<td>MXF [n=10613]</td>
<td>COMP [n=10685]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Double-blind studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-lactam</td>
<td>2391</td>
<td>1077</td>
<td>408</td>
</tr>
<tr>
<td>β-lactam + macrolide</td>
<td>274</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fluoroquinolone</td>
<td>2246</td>
<td>444</td>
<td>0</td>
</tr>
<tr>
<td>Macrolide</td>
<td>3659</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>1230</td>
<td>368</td>
<td>180</td>
</tr>
<tr>
<td>Total</td>
<td>8822</td>
<td>1889</td>
<td>588</td>
</tr>
<tr>
<td>Open-label studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-lactam</td>
<td>1318</td>
<td>554</td>
<td>0</td>
</tr>
<tr>
<td>β-lactam + macrolide</td>
<td>186</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>β-lactam ± macrolide</td>
<td>0</td>
<td>532</td>
<td>0</td>
</tr>
<tr>
<td>Fluoroquinolone</td>
<td>263</td>
<td>0</td>
<td>349</td>
</tr>
<tr>
<td>Macrolide</td>
<td>287</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>456</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>1791</td>
<td>1542</td>
<td>349</td>
</tr>
</tbody>
</table>

PO= oral
IV = intravenous
MXF: moxifloxacin
COMP = comparator (see left column)

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

Patients at risk?

**age (> 65 y)**

- PO: n = 2551 vs. 2403
  - AE: 1050 / 1021
  - ADR: 440 / 448
  - SAE: 207 / 184
  - SADR: 16 / 18
  - discont. AE: 116 / 109
  - discont. ADR: 78 / 74
  - death AE: 29 / 32
  - death ADR: 3 / 1

- sequential: n = 1373 vs. 1334
  - AE: 929 / 900
  - ADR: 348 / 307
  - SAE: 298 / 290
  - SADR: 49 / 30
  - discont. AE: 131 / 104
  - discont. ADR: 62 / 42
  - death AE: 100 / 98
  - death ADR: 2 / 3

- IV: n = 170 vs. 191
  - AE: 83 / 81
  - ADR: 27 / 31
  - SAE: 32 / 24
  - SADR: 4 / 6
  - discont. AE: 10 / 10
  - discont. ADR: 4 / 6
  - death AE: 13 / 10
  - death ADR: 0 / 1

**diabetes**

- PO: n = 777 vs. 717
  - AE: 355 - 310
  - ADR: 158 - 126
  - SAE: 78 - 56
  - SADR: 11 - 3
  - discont. AE: 34 - 26
  - discont. ADR: 22 - 14
  - death AE: 10 - 6
  - death ADR: 0 - 0

- sequential: n = 926 vs. 917
  - AE: 587 / 565
  - ADR: 196 / 174
  - SAE: 198 / 182
  - SADR: 22 / 11
  - discont. AE: 78 / 64
  - discont. ADR: 38 / 20
  - death AE: 46 / 23
  - death ADR: 2 / 2

- IV: n = 80 vs. 72
  - AE: 42 - 35
  - ADR: 13 - 14
  - SAE: 16 - 11
  - SADR: 2 - 2
  - discont. AE: 2 - 2
  - discont. ADR: 6 - 6
  - death AE: 1 - 4
  - death ADR: 9 - 4

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

\[\text{Tulkens et al., Drugs R D (2012) 12: 71-100}\]
Side effects of moxifloxacin (clinical trials database)

Patients at risk?

renal impairment

\[
\begin{align*}
\text{AE} & : 1283 - 1229 \\
\text{ADR} & : 259 - 229 \\
\text{SAE} & : 94 - 80 \\
\text{SADR} & : 9 - 9 \\
\text{discont. AE} & : 49 - 53 \\
\text{discont. ADR} & : 27 - 33 \\
\text{death AE} & : 12 - 14 \\
\text{death ADR} & : 0 - 3
\end{align*}
\]

n = 1283 vs. 1229

sequential

\[
\begin{align*}
\text{AE} & : 572 - 549 \\
\text{ADR} & : 196 - 181 \\
\text{SAE} & : 202 - 180 \\
\text{SADR} & : 30 - 23 \\
\text{discont. AE} & : 75 - 78 \\
\text{discont. ADR} & : 28 - 25 \\
\text{death AE} & : 58 - 67 \\
\text{death ADR} & : 3 - 3
\end{align*}
\]

n = 889 vs. 863

IV

\[
\begin{align*}
\text{AE} & : 102 - 92 \\
\text{ADR} & : 31 - 32 \\
\text{SAE} & : 26 - 22 \\
\text{SADR} & : 2 - 1 \\
\text{discont. AE} & : 11 - 7 \\
\text{discont. ADR} & : 2 - 3 \\
\text{death AE} & : 10 - 7 \\
\text{death ADR} & : 0 - 0
\end{align*}
\]

n = 203 vs. 218

relative risk estimate (moxifloxacin / comparator)

hepatic impairment

\[
\begin{align*}
\text{AE} & : 69 - 70 \\
\text{ADR} & : 37 - 32 \\
\text{SAE} & : 5 - 7 \\
\text{SADR} & : 1 - 1 \\
\text{discont. AE} & : 6 - 7 \\
\text{discont. ADR} & : 6 - 3 \\
\text{death AE} & : 2 - 4 \\
\text{death ADR} & : 0 - 1
\end{align*}
\]

n = 146 vs. 163

\[
\begin{align*}
\text{AE} & : 183 - 196 \\
\text{ADR} & : 43 - 43 \\
\text{SAE} & : 60 - 53 \\
\text{SADR} & : 10 - 7 \\
\text{discont. AE} & : 24 - 24 \\
\text{discont. ADR} & : 11 - 7 \\
\text{death AE} & : 14 - 24 \\
\text{death ADR} & : 1 - 2
\end{align*}
\]

n = 183 vs. 196

\[
\begin{align*}
\text{AE} & : 23 - 18 \\
\text{ADR} & : 7 - 6 \\
\text{SAE} & : 7 - 7 \\
\text{SADR} & : 1 - 0 \\
\text{discont. AE} & : 1 - 1 \\
\text{discont. ADR} & : 1 - 0 \\
\text{death AE} & : 2 - 0 \\
\text{death ADR} & : 0 - 0
\end{align*}
\]

n = 46 vs. 46

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 (moxifloxacin / comparator)

BMI < 18

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

### 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><strong>fluoroquinolones</strong> (w/o moxifloxacin)</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>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><strong>cotrimoxazole</strong></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) International consensus</td>
<td>[3]</td>
</tr>
</tbody>
</table>

---


Hepatotoxicity risk of antibiotics
(percentage of prescriptions for antibiotics with main indications for use in the community setting)

<table>
<thead>
<tr>
<th>Ciprofloxacin, levofloxacin and moxifloxacin</th>
<th>Tetracycline</th>
<th>Erythromycin, clarithromycin and penicillins</th>
<th>Co-trimoxazole and amoxicillin/clavulanate</th>
<th>Telithromycin and trovafloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated cases and &lt;=0.00007</td>
<td>&lt;=0.0002</td>
<td>&lt;=0.004</td>
<td>&lt;=0.02</td>
<td>Acute liver failure, high mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Withdrawal or severe restriction does not allow calculating true incidences</td>
</tr>
</tbody>
</table>

*Andrade & Tulkens, JAC (2011) 66: 1431–46*
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)
Update on the Cardiac Safety of Moxifloxacin

Wilhelm Haverkamp*,1, Frank Kruesmann2, Anna Fritsch2, David van Veenhuyzen3 and Pierre Arvis4

1Department of Cardiology, Campus Virchow Clinic, Charité University Medicine Berlin, Berlin, Germany
2Bayer Pharma AG, Wuppertal, Germany
3Bayer Healthcare, Montville, NJ, USA
4Bayer Healthcare, Loos, France

Update on the Cardiotoxic Properties of QTcB Prolongation after IV Use

Wilhelm Haverkamp, 1, Frank K. Schramm, 2 Stefan Zander, 3 and David P. Naughton 4

1 Department of Cardiology, Campus Virchow Klinikum, Charité-Universitätsmedizin Berlin, Germany
2 Bayer Pharma AG, Wuppertal, Germany
3 Bayer Healthcare, Montville, NJ, USA
4 Bayer HealthCare, Loos, France

QTc prolongation

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: main features and incidence

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>OBSERVATIONS/FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Causative quinolones reported</td>
<td>Ciprofloxacin (most commonly reported), norfloxacin, pefloxacin, ofloxacin, levofloxacin</td>
</tr>
<tr>
<td>Associated risk factors</td>
<td>Age &gt;60 years, corticosteroid therapy, renal failure, diabetes mellitus, history of tendon rupture</td>
</tr>
</tbody>
</table>
| Relative risk of tendon disorders | 1.7-fold increase for all tendinopathies  
1.3-fold increase for tendon rupture  
4.1-fold increase of Achilles tendon rupture  
46-fold increase of tendon rupture with concurrent corticosteroid exposure  
1.5-fold increase in tendon disorders if age >60 years  
2.7-fold increase in tendon rupture if age >60 years |
| Affected tendons               | Achilles tendon most commonly affected (89.8% of cases)  
Multiple other tendons reported  
Up to 50% of cases with bilateral involvement  
Symptoms of tendinitis often precede tendon rupture by up to 2 weeks |
| Latency period of tendinopathy | Median onset of 6 days (85% of cases within first month)  
Up to 50% of cases after fluoroquinolone discontinued |

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 VII. Incidence of selected treatment-emergent adverse events presented by Standard MedDRA Queries/ Bayer MedDRA Queries and preferred terms in patients valid for the safety analysis, treated with moxifloxacin or a comparator and stratified by route of administration (oral only; intravenous followed by oral [sequential]; intravenous only).

<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
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)...

Table 2. Tendon disorders for fluoroquinolone antibiotics 2010q2.

<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
What shall we discuss?

• The basics: are quinolones different by design?
• When should they be given IV
• Indications and experience of moxifloxacin IV
• The fights against resistance and the saga of the MPC
• Are they toxicity issues?
• What you can do with an MIC?
## Calculation of the "attainable MIC"

<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>$C_{\text{max}}$ in mg/L total/free (dose)</td>
<td>$\text{AUC}_{24\text{h}}$ (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>

<sup>a</sup> Typical daily dosage as recommended.

<sup>b</sup> Efficacy range for clinical response.

<sup>c</sup> Prevention of resistance range.

---

Check the EUCAST breakpoints…

Enterobacteriaceae

<table>
<thead>
<tr>
<th>Fluoroquinolones</th>
<th>MIC breakpoint (mg/L)</th>
<th>Disk content (µg)</th>
<th>Zone diameter breakpoint (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S ≤</td>
<td>R &gt;</td>
<td>S ≥</td>
</tr>
<tr>
<td>Ciprofloxacin †</td>
<td>0.5</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>1</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>0.5</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>0.5</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>0.5</td>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>

All EUCAST data are freely available at http://www.eucast.org
Check the EUCAST breakpoints…

Enterobacteriaceae

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<td>S ≤</td>
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<td>S ≥</td>
</tr>
<tr>
<td>Ciprofloxacin¹</td>
<td>0.5</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>1</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>0.5</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>0.5</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>0.5</td>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>

Now, if you have an organism with an MIC of

- 0.05 → **easy success for any fluoroquinolone (even oral) !**
- 1 → **borderline for cipro/ moxi / norflo / oflo → ensure correct dosage !**
- 2 → **levo BUT with a high dose !**
- 4 → **likely to fail no matter which fluoroquinolone…**
Check the EUCAST breakpoints…

Enterobacteriaceae

<table>
<thead>
<tr>
<th>Fluoroquinolones</th>
<th>MIC breakpoint (mg/L)</th>
<th>Disk content (µg)</th>
<th>Zone diameter breakpoint (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S ≤</td>
<td>R &gt;</td>
<td>S ≥</td>
</tr>
<tr>
<td>Ciprofloxacin¹</td>
<td>0.5</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>1</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>0.5</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>0.5</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>0.5</td>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>

Maximal Interest for the Clinician

Now, if you have an organism with an MIC of

- **0.05**: easy success for any fluoroquinolone (even oral)!
- **1**: borderline for cipro/ moxi / norflo / oflo → ensure correct dosage!
- **2**: levo BUT with a high dose!
- **4**: likely to fail no matter which fluoroquinolone…
Thank you for your attention!

And ask questions
The "first generation" of fluoroquinolones

1960

• Nalidixic acid
• Oxolinic acid
• Cinoxacin
• Pipemidic acid

1970

• Norfloxacin
• Pefloxacin
• Ofloxacin
• Ciprofloxacin
• Fleroxacin
• Rufloxacin

1980

improved anti Gram (-) activity

$t_{1/2}$

<table>
<thead>
<tr>
<th>activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-4 h</td>
</tr>
<tr>
<td>11 h</td>
</tr>
<tr>
<td>6 h</td>
</tr>
<tr>
<td>3-4 h</td>
</tr>
</tbody>
</table>
An interesting paper...

Impact of poor compliance with levofloxacin and moxifloxacin on respiratory tract infection antimicrobial efficacy: A pharmacokinetic/pharmacodynamic simulation study

N. Carral a, J.C. Lukas a,b, I. Oteo a, E. Suarez a,*
An interesting paper…


Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (S.D.)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{0-24h} (mg h/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LFX 500 mg q24 h</td>
<td>45.78 (3.72)</td>
<td>37.21–57.13</td>
</tr>
<tr>
<td>LFX 750 mg q24 h</td>
<td>68.68 (5.58)</td>
<td>55.82–85.69</td>
</tr>
<tr>
<td>LFX 500 mg q12 h</td>
<td>91.57 (7.34)</td>
<td>77.66–115.48</td>
</tr>
<tr>
<td>MOX 400 mg q24 h</td>
<td>43.63 (8.60)</td>
<td>26.43–72.20</td>
</tr>
</tbody>
</table>

Short Communication

Impact of poor compliance with respiratory tract infection (RTI) treatment:
A pharmacokinetic/pharmacodynamic (PK/PD) analysis

N. Carral a, J.C. Lukas a,b, I. Otte a, I. Otte a
An interesting paper...

Impact of poor community-acquired respiratory tract infection (CA-RTI) on antibiotic resistance: a pharmacokinetic study

N. Carral\textsuperscript{a}, J.C. Lukas\textsuperscript{a,b}

Target attainment rate for S. pneumoniae

- MXF 400 mg q24h (MIC = 0.25 mg/L)
- LVX 500 mg q12h (MIC = 1 mg/L)

Target attainment rate: 90%
A very recent paper…

Impact of poor community respiratory tract infection A pharmacokinetic study
N. Carral, J.C. Lukas

Target attainment rate for S. pneumoniae

- MXF 400 mg q24h (MIC = 0.25 mg/L)
- LVX 500 mg q12h (MIC = 1 mg/L)
- LVX 500 mg q24h (MIC = 1 mg/L)

90%