Fluoroquinolones: Parenteral use

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Middle East Anti-Infectives Forum
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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.facm.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

A partial view of our University Clinic (900 beds) and the Education and Research buildings (5,000 students), in the outskirts of Brussels, Belgium

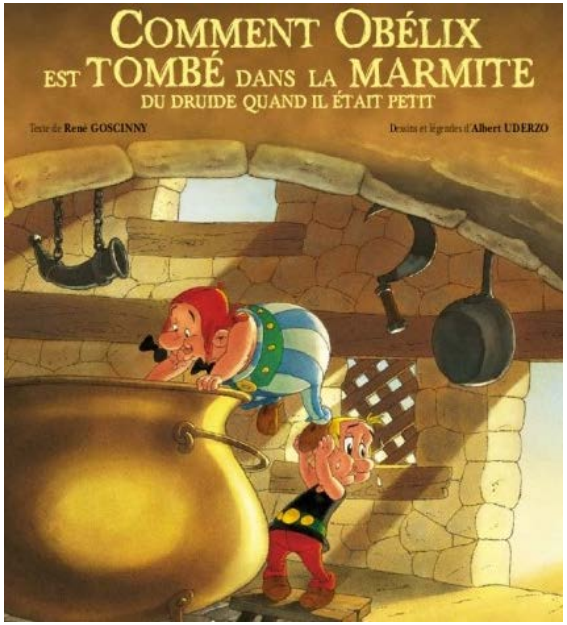
- Editorial board of AAC and IJAA
- Member of the General Committee of EUCAST (for ISC) and of its Steering committee (2008-10)
- Member of the Belgian Antibiotic Policy Coordination Committee
- Founder and Past President of the International Society of Antiinfective Pharmacology (ISAP)

ISAP

www.isap.org

Why do I have an interest in fluoroquinolones ?

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



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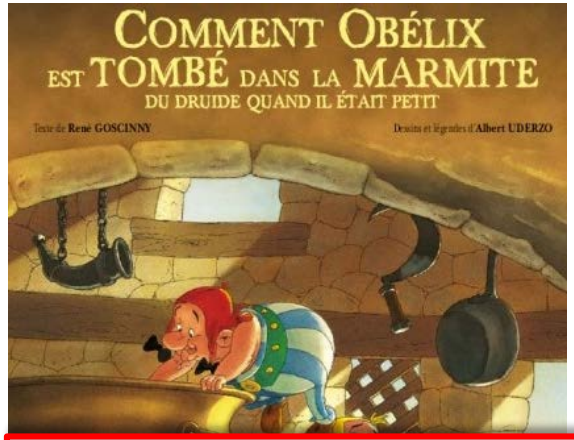

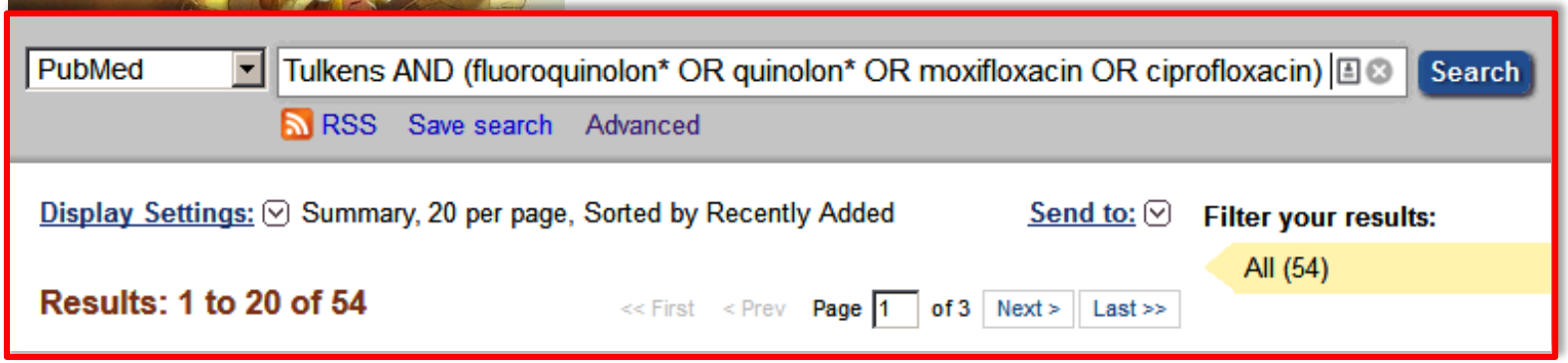

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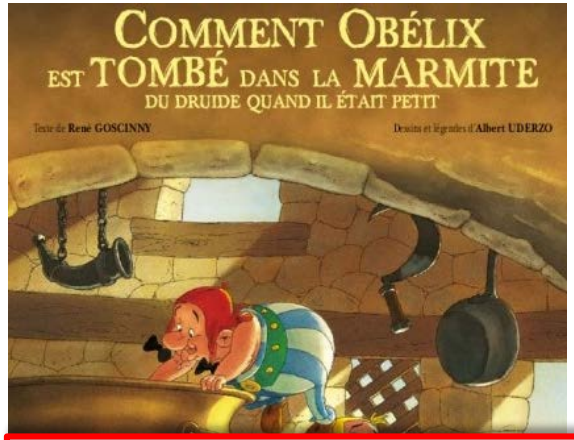
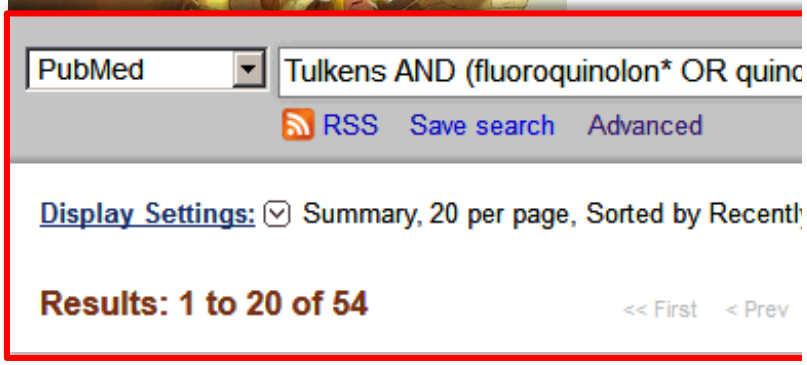




1990

Journal of Antimicrobial Chemotherapy (1990) **26,** *Suppl. B,* 27–39

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

Marie-Béatrice Carlier[a], Bernard Scorneaux[a], Andrée Zenebergh[a,*], Jean-François Desnottes[b] and Paul M. Tulkens[a]

[a]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; [b]Rhône-Poulenc Santé, Centre de Recherches de Vitry/Alfortville, 13, Quai Jules Guesde, B.P. 14, F–94403 Vitry s/Seine, France

2005

REVIEW ARTICLE

10.1111/j.1469-0691.2005.01131.x

Quinolones in 2005: an update

F. Van Bambeke[1], J.-M. Michot[1], J. Van Eldere[2] and P. M. Tulkens[1]

[1]Unit of Cellular and Molecular Pharmacology, Catholic University of Louvain, Brussels and [2]Department 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

2012

ORIGINAL RESEARCH ARTICLE

Drugs R D 2012; 12 (2): 71-100
1179-6901/12/0002-0071

Moxifloxacin Safety

An Analysis of 14 Years of Clinical Data

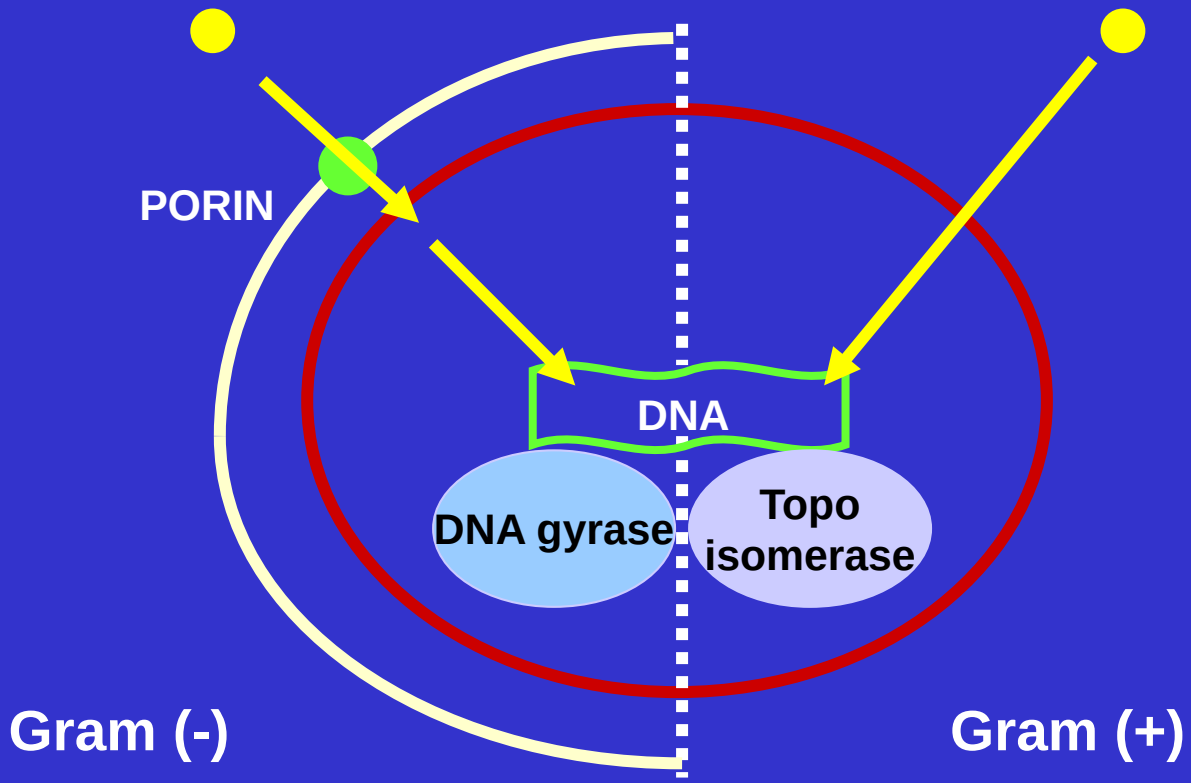
Paul M. Tulkens,[1] Pierre Arvis[2] and Frank Kruesmann[3]

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

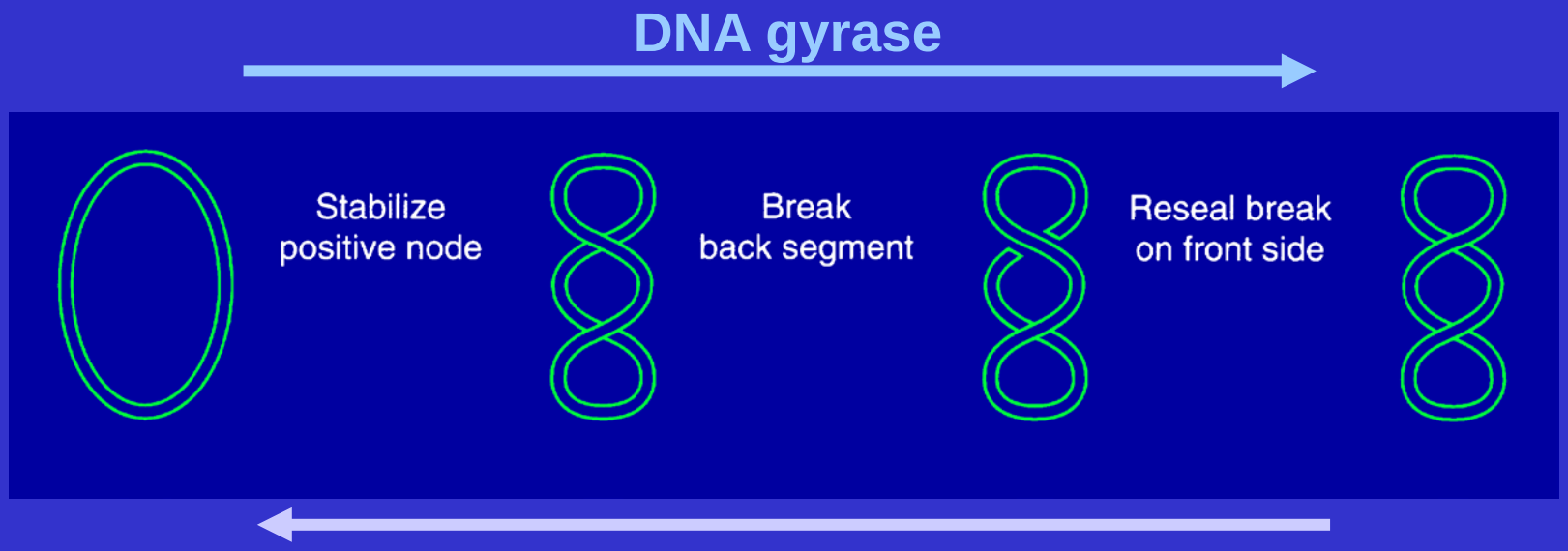
What shall we discuss ?

- **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...

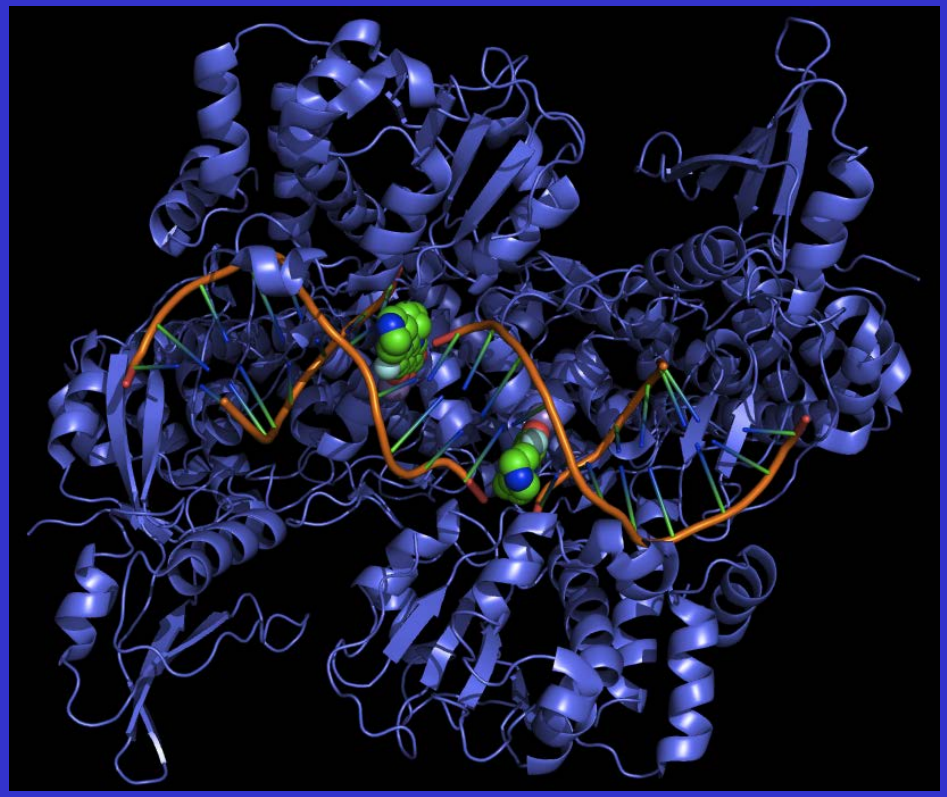


2 key enzymes in DNA replication:



bacterial DNA is supercoiled

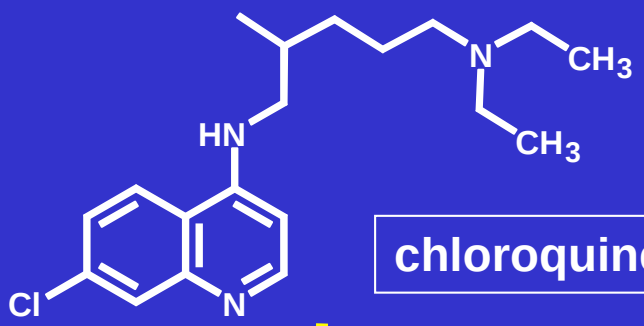
Ternary complex
DNA - enzyme - fluoroquinolone



Fluoroquinolones are the first entirely man-made antibiotics: do we understand our molecule ?

Don’t panic, we will travel together….

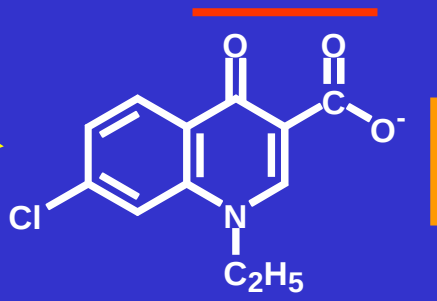
From chloroquine to nalidixic acid...



chloroquine

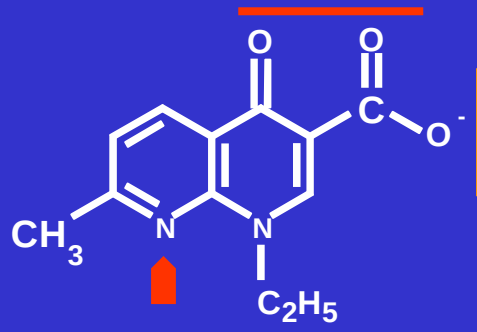
1939

1958



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

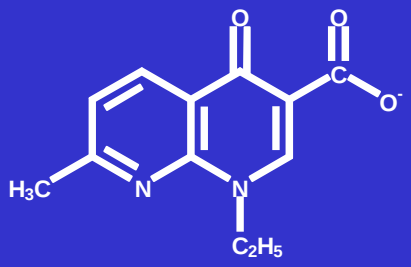
nalidixic acid



1962

From nalidixic acid to the 1st fluoroquinolone

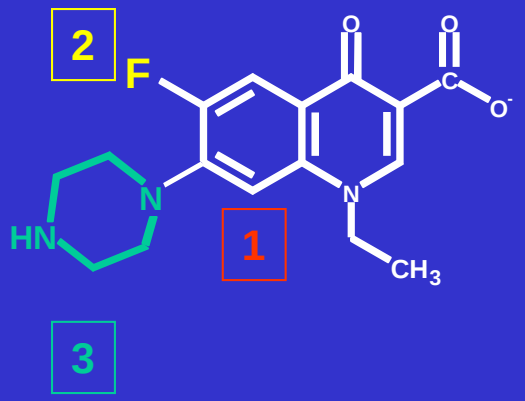
nalidixic acid



make 3 key modifications *...

1978

norfloxacin *



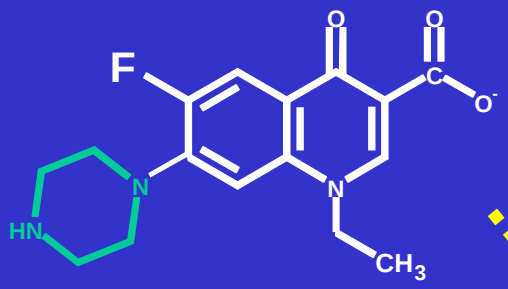
broader Gram(-) activity
less protein binding (50%)
longer half-life (3-4h)

* Belgian patent 863,429, 1978 to Kyorin

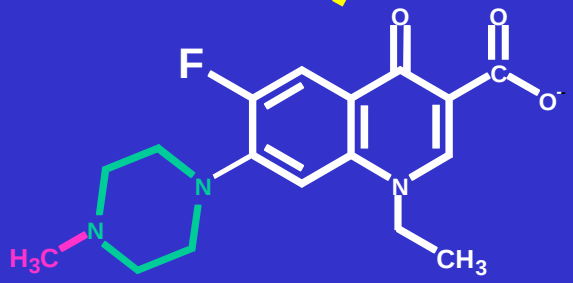
* 6-fluoro-7-pyrimidino-quinoleine

From norfloxacin to ofloxacin via pefloxacin

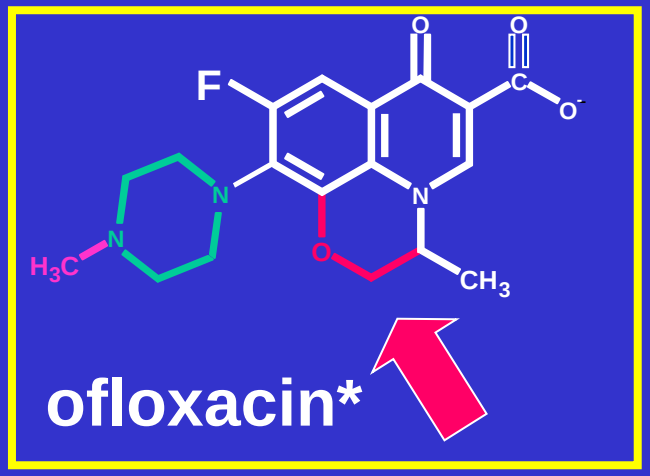
norfloxacin



tricyclic compound
(as in flumequine but morpholine ring)



pefloxacin

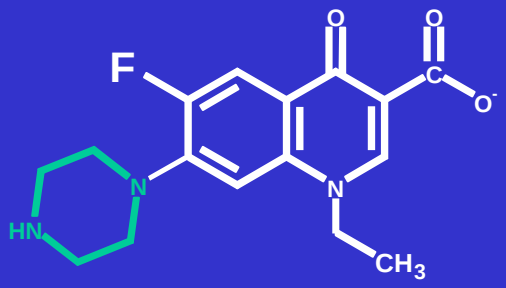


ofloxacin*

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

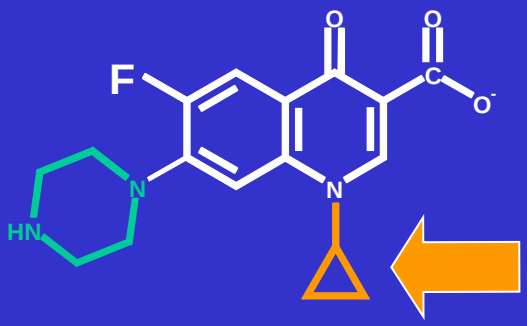
From norfloxacin to ciprofloxacin

norfloxacin



cyclopropyl to increase potency

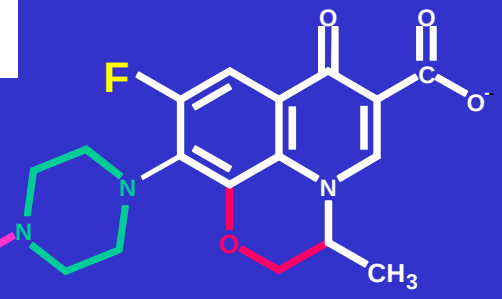
ciprofloxacin *



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

"1st generation" fluoroquinolones

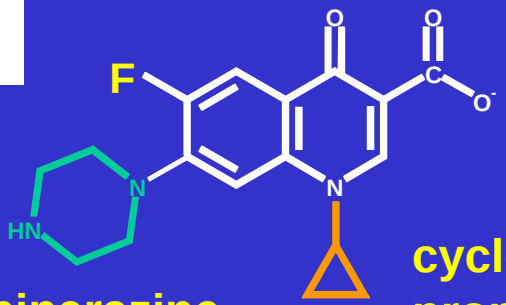
ofloxacin



methyl piperazine

morpholine

ciprofloxacin

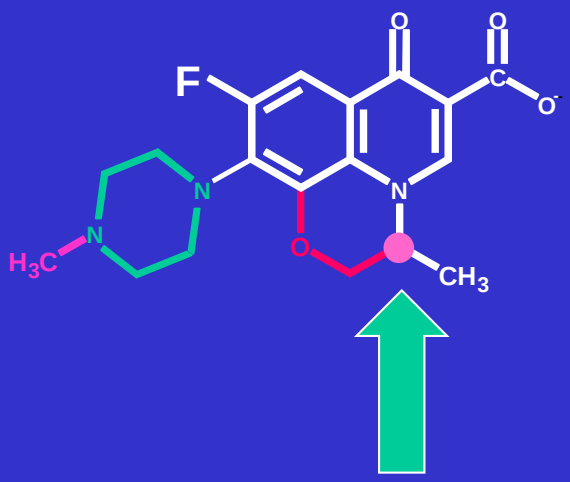


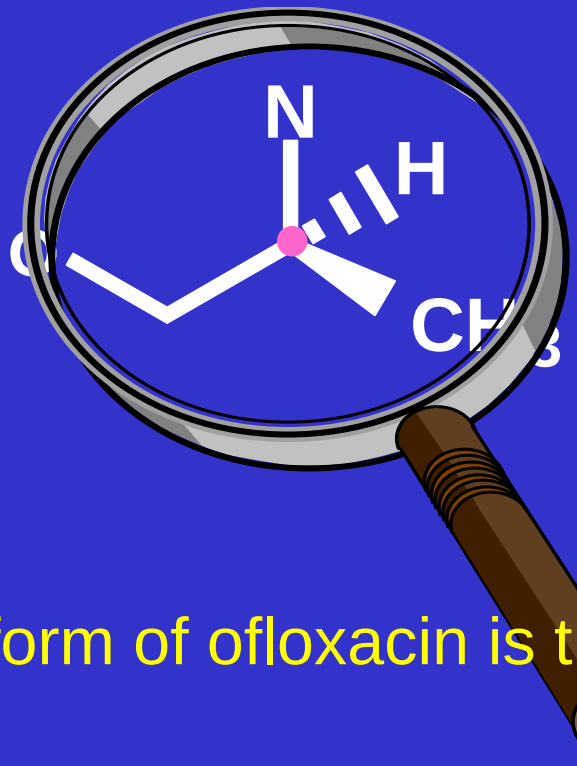
piperazine

cyclo propyl

From ofloxacin to levofloxacin...

Ofloxacin is a racemic mixture





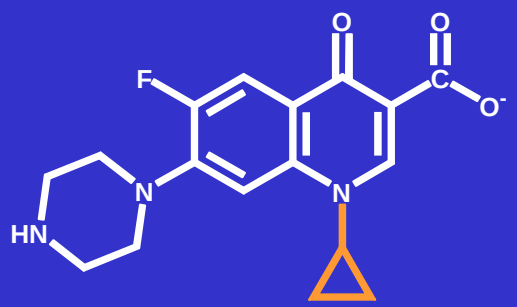
Levofloxacin is the pure (-) S isomer *

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

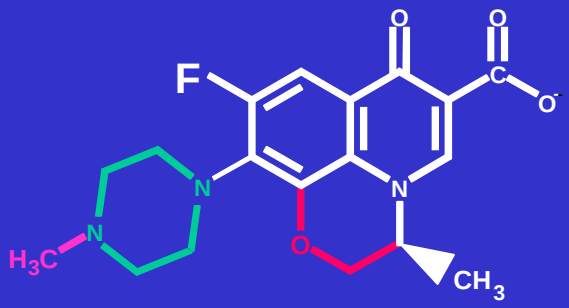
* Eur. pat. 206,283 to Daiichi, 1987

Activity against *S. pneumoniae*

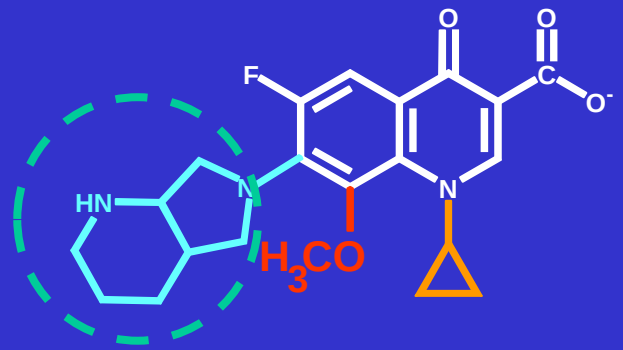
I	II	III / IV



ciprofloxacin
0.5 - 2



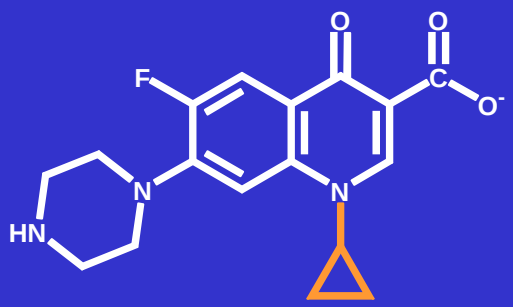
levofloxacin
0.5 -2



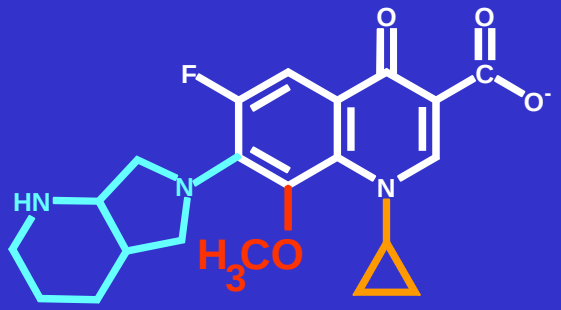
moxifloxacin
0.01 - 0.5

Activity against *B. fragilis (anaerobe)*

I	II	III / IV



ciprofloxacin
2 - 128

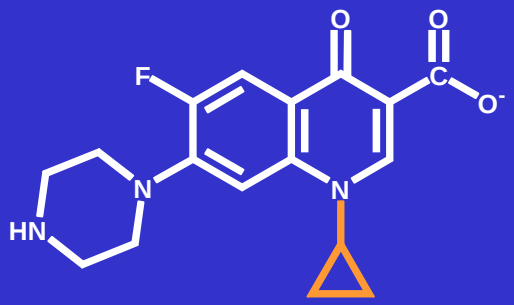


moxifloxacin
0.25 - 8

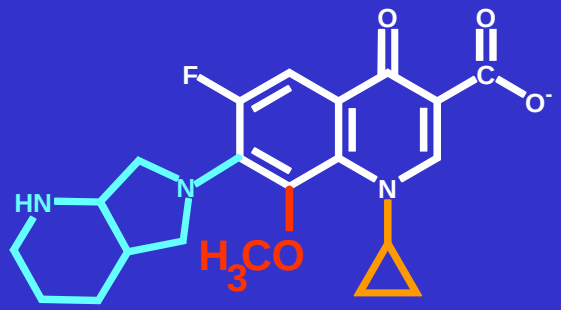
At this point …

Gram (-) **Gram (+)**

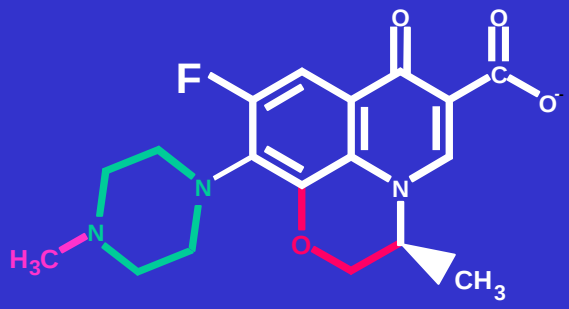
anaerobes



ciprofloxacin



moxifloxacin



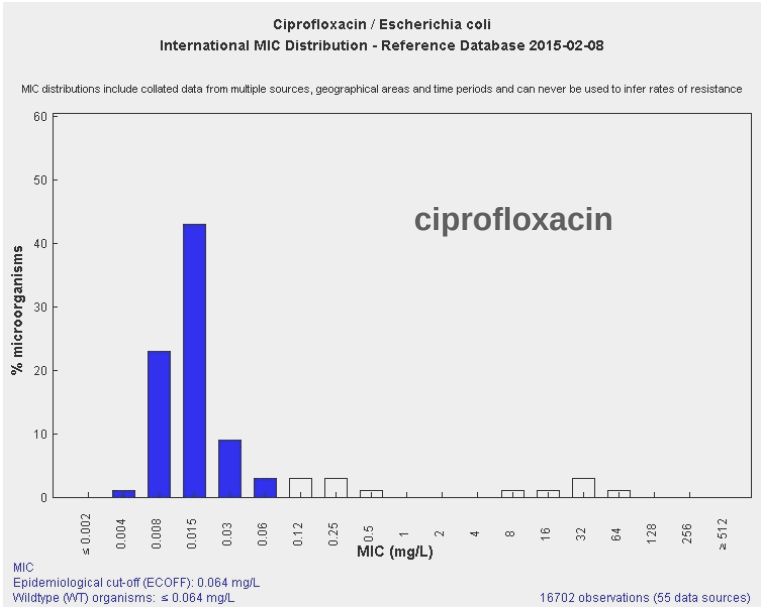
levofloxacin

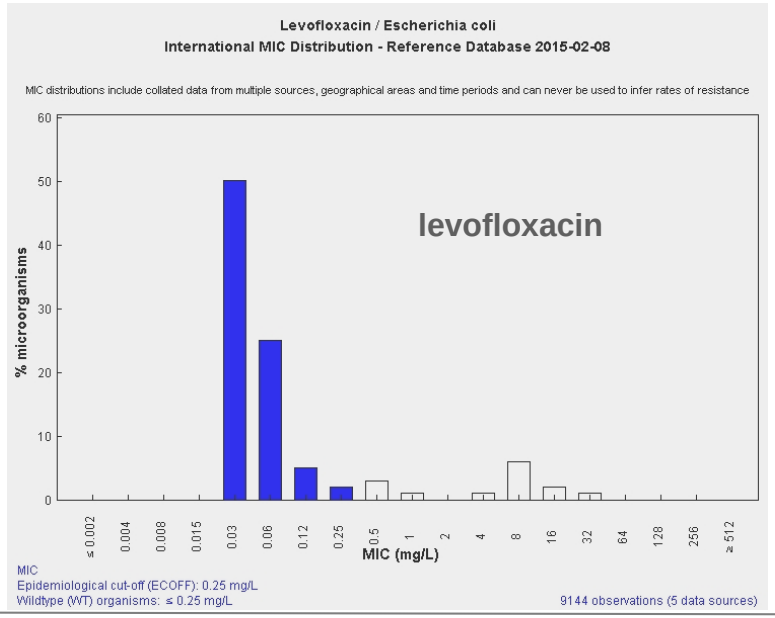
This is by design !

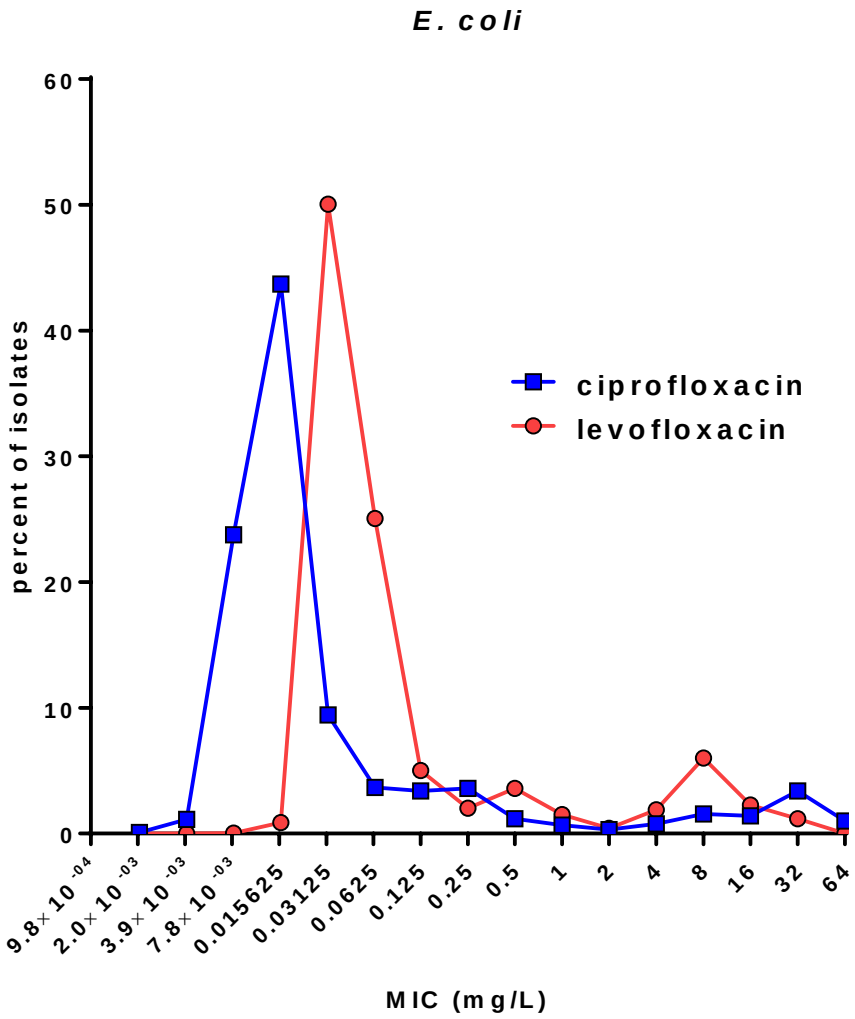
A unbiased estimation of antibiotic activity (in the absence of resistance)

MIC distributions and epidemiological cut-off

Gram negative: *E. coli*

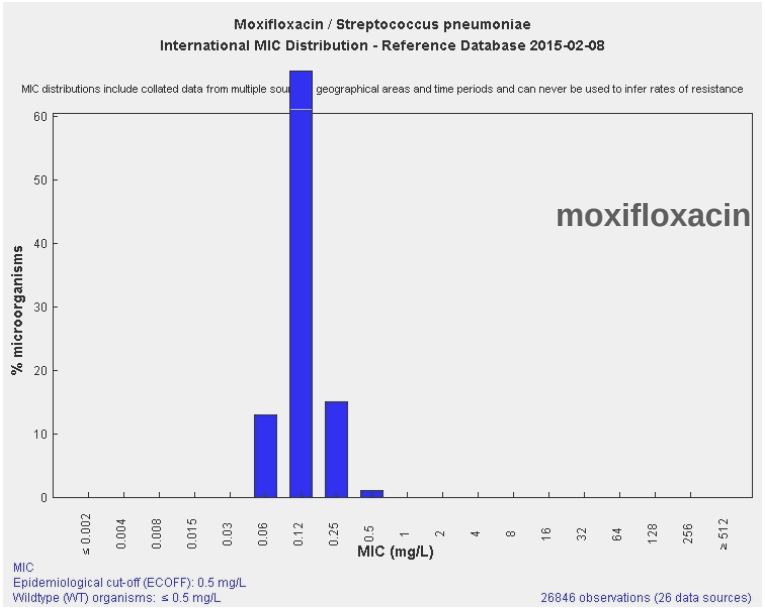


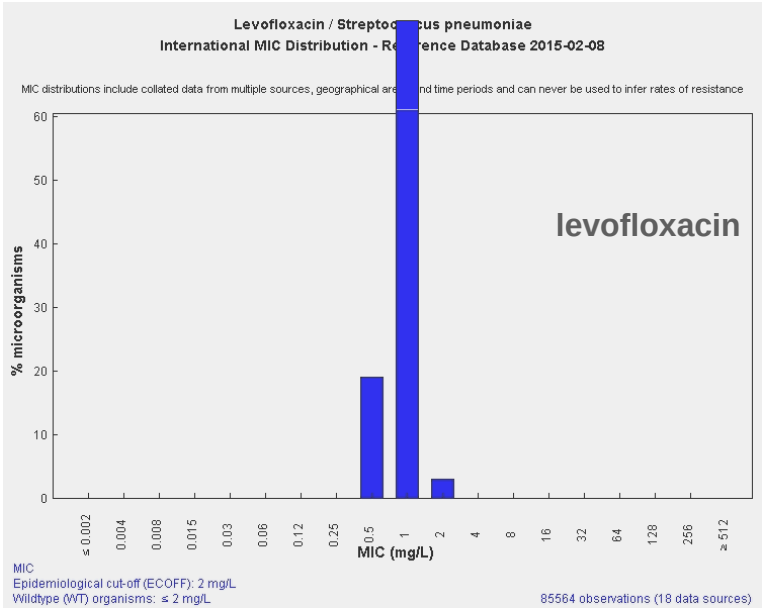


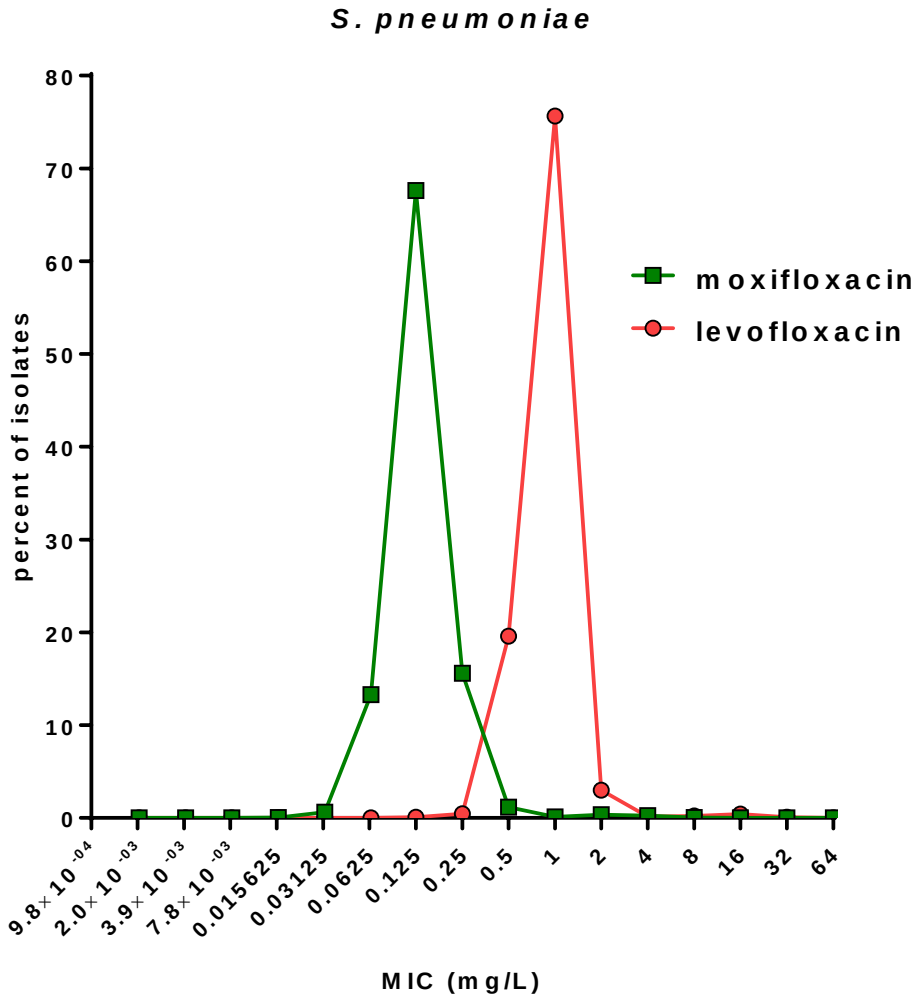


http://mic.eucast.org/Eucast2/regShow.jsp?Id=1022
http://mic.eucast.org/Eucast2/regShow.jsp?Id=1072
Last accessed: 8/2/2015

Gram positive: *S. pneumoniae*

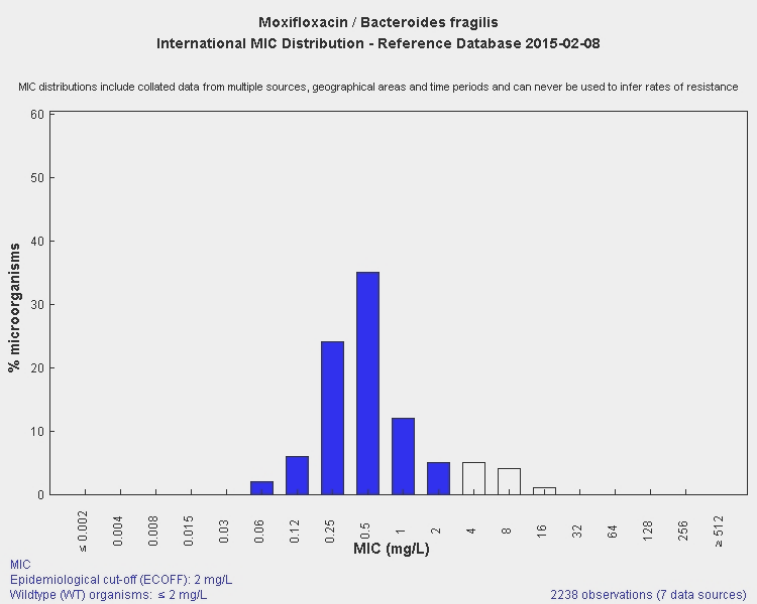


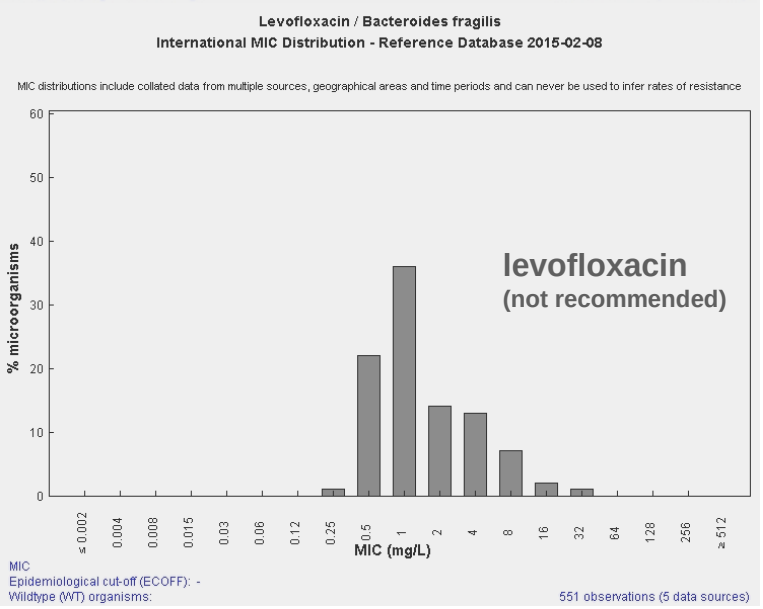


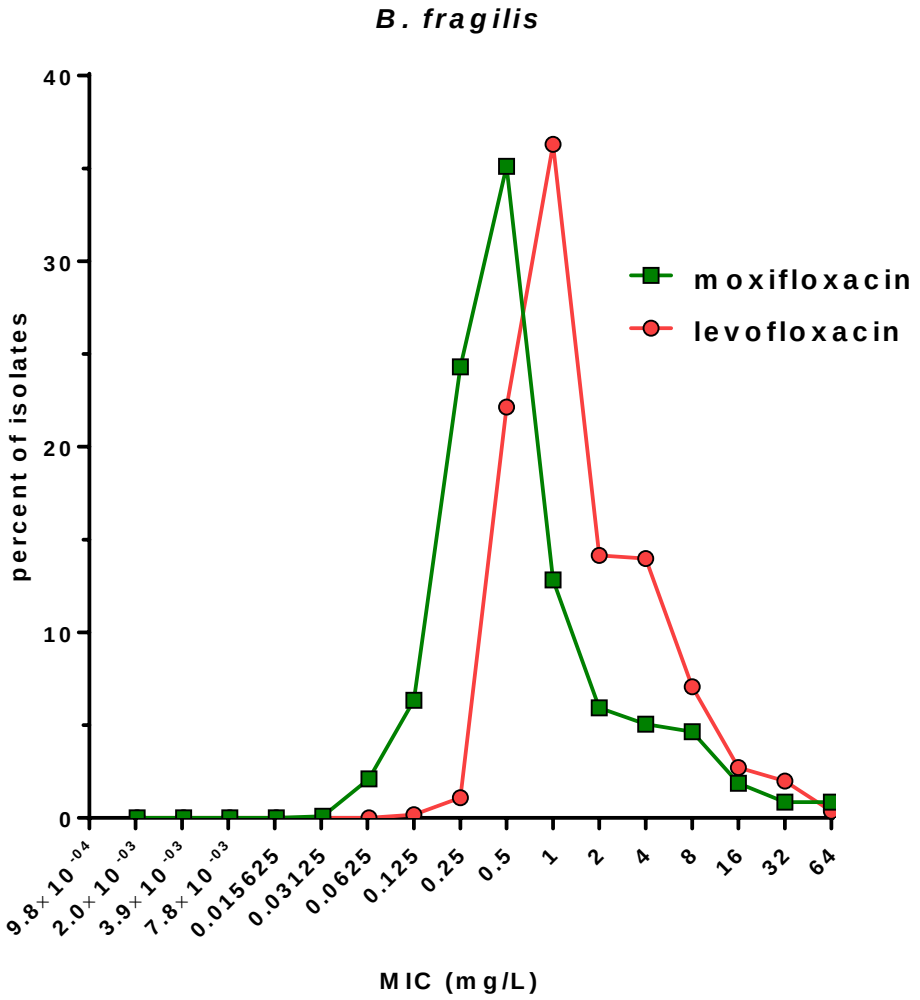


http://mic.eucast.org/Eucast2/regShow.jsp?Id=1099
http://mic.eucast.org/Eucast2/regShow.jsp?Id=1310
Last accessed: 8/2/2015

Anaerobes: *B. fragilis*







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 mots 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 …

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- The basics: are quinolones different by design ?
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Moxifloxacin IV indications

----------DOSAGE AND ADMINISTRATION----------

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

- 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)

https://www.merck.com/product/usa/pi_circulars/a/avelox/avelox_pi.pdf
Last visited: 11 Nov 2017

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

Original Article

A Meta-analysis of Sequential Intravenous/Oral Moxifloxacin Monotherapy for Treatment of Skin and Skin Structure Infections

Authors: Y. Chu[1,2], J. Qu[3], L.-Y. Qu[1,2], Y.-F. Luo[1,2], M.-Y. Jiang[1,2]

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[1] Department of Pharmacy, The First Affiliated Hospital of China Medical University, Shenyang, China
[2] College of Pharmaceutical Science, China Medical University, Shenyang, China
[3] Department of Pharmacy, Dalian Medical University, Dalian, China

Chu et al. Drug Res (Stuttg). 2015;65:650-7 - PMID: 26070015.

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

A Met
Moxif
Skin S

Authors

Affiliations

Study or Subgroup	moxifloxacin Events	Total	other antibiotics Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Benjamin A. Lipsky2007	25	37	25	41	8.2%	1.33 [0.53, 3.38]
Cao Yu-chun 2002	37	40	30	42	2.3%	4.93 [1.27, 19.10]
Inge C. Gyssens 2011	320	361	275	307	35.9%	0.91 [0.56, 1.48]
Parish LC 2000	163	180	155	171	15.9%	0.99 [0.48, 2.03]
Philip Giordano 2005	143	180	153	187	32.8%	0.86 [0.51, 1.44]
Wang Ai-ping2003	33	39	34	49	4.9%	2.43 [0.84, 7.01]
Total (95% CI)		837		797	100.0%	1.11 [0.84, 1.46]
Total events	721		672			

Heterogeneity: $Chi^2 = 8.58$, $df = 5$ ($P = 0.13$); $I^2 = 42\%$

Test for overall effect: $Z = 0.72$ ($P = 0.47$)

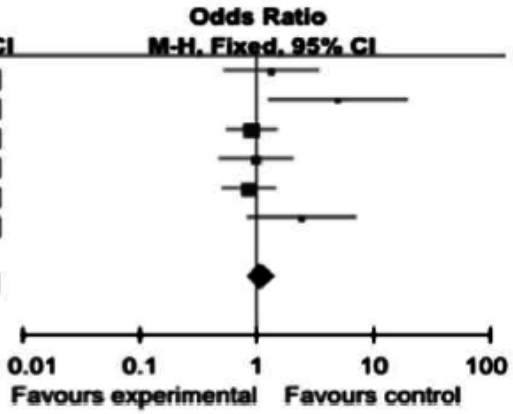

Fig. 2 The clinical cure rates comparing moxifloxacin with other antibiotics.

Study or Subgroup	moxifloxacin Events	Total	other antibiotics Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Benjamin A. Lipsky2007	20	29	21	32	8.2%	1.16 [0.40, 3.40]
Cao Yu-chun 2002	40	40	39	42	0.6%	7.18 [0.36, 143.50]
Inge C. Gyssens 2011	432	497	370	429	68.8%	1.06 [0.73, 1.55]
Parish LC 2000	57	62	50	54	5.7%	0.91 [0.23, 3.58]
Philip Giordano 2005	50	64	47	59	14.2%	0.91 [0.38, 2.17]
Wang Ai-ping2003	37	39	38	40	2.5%	0.97 [0.13, 7.28]
Total (95% CI)		731		656	100.0%	1.07 [0.79, 1.47]
Total events	636		565			

Heterogeneity: $Chi^2 = 1.77$, $df = 5$ ($P = 0.88$); $I^2 = 0\%$

Test for overall effect: $Z = 0.45$ ($P = 0.65$)

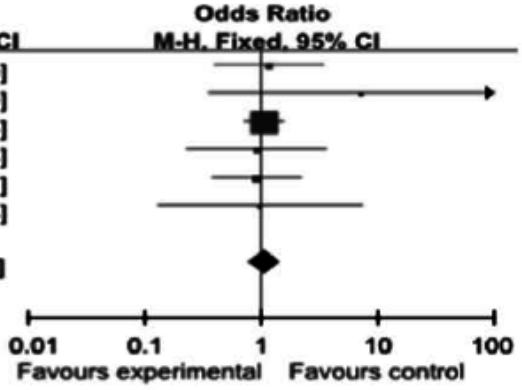

Fig. 3 The bacteriological success rates comparing moxifloxacin with other antibiotics.

Chu et al. Drug Res (Stuttg). 2015;65:650-7 - PMID: 26070015.

Tissue penetration: abdominal abscesses

ORIGINAL RESEARCH ARTICLE

Clin Drug Invest 2008; 28 (2): 71-79
1173-2563/08/0002-0071/$48.00/0

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

Andreas D. Rink,[1] *Heino Stass,*[2] *Heinz Delesen,*[2] *Dagmar Kubitza*[2] and *Karl-Heinz Vestweber*[1]

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

Rink et al. Clin Drug Investig. 2008;28:71-9. PMID: 18211115

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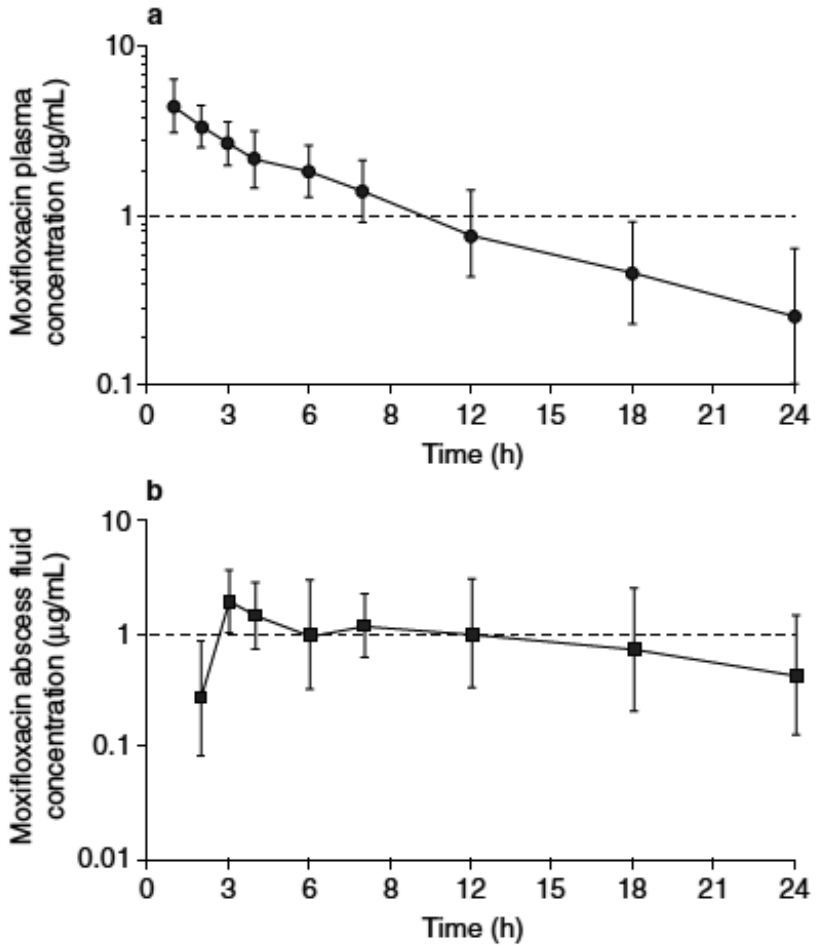

FIg. 1. Concentrations of moxifloxacin in plasma (**a**) and abscess fluid (**b**) following a single 400-mg dose administered by 1-hour intravenous infusion. Results are presented as geometric means with SDs (n = 8).

Tissue penetration: abdominal abscesses

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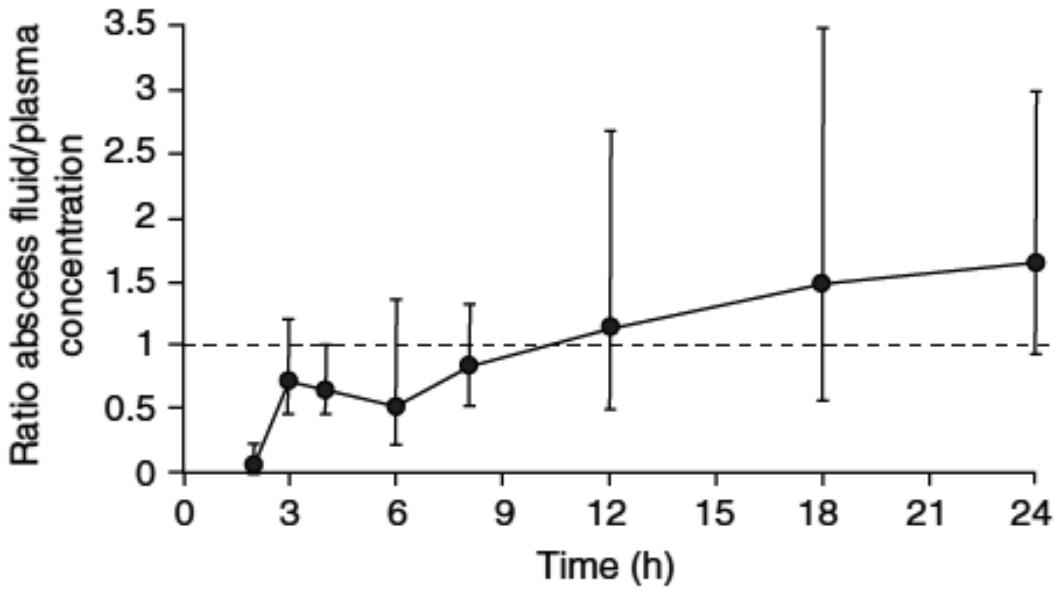

Fig. 2. Abscess fluid/plasma concentration ratio following administration of a single 400-mg dose administered by 1-hour intravenous infusion. Results are presented as geometric means with SDs (n = 8).

Fluid penetration: CSF

Contents lists available at ScienceDirect

Diagnostic Microbiology and Infectious Disease

Diagnostic Microbiology and Infectious Disease 84 (2016) 249–251

journal homepage: www.elsevier.com/locate/diagmicrobio

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

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Pharmacokinetics of intrave
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[a] Department of Pharmacy, Peking Union Medical College Hos
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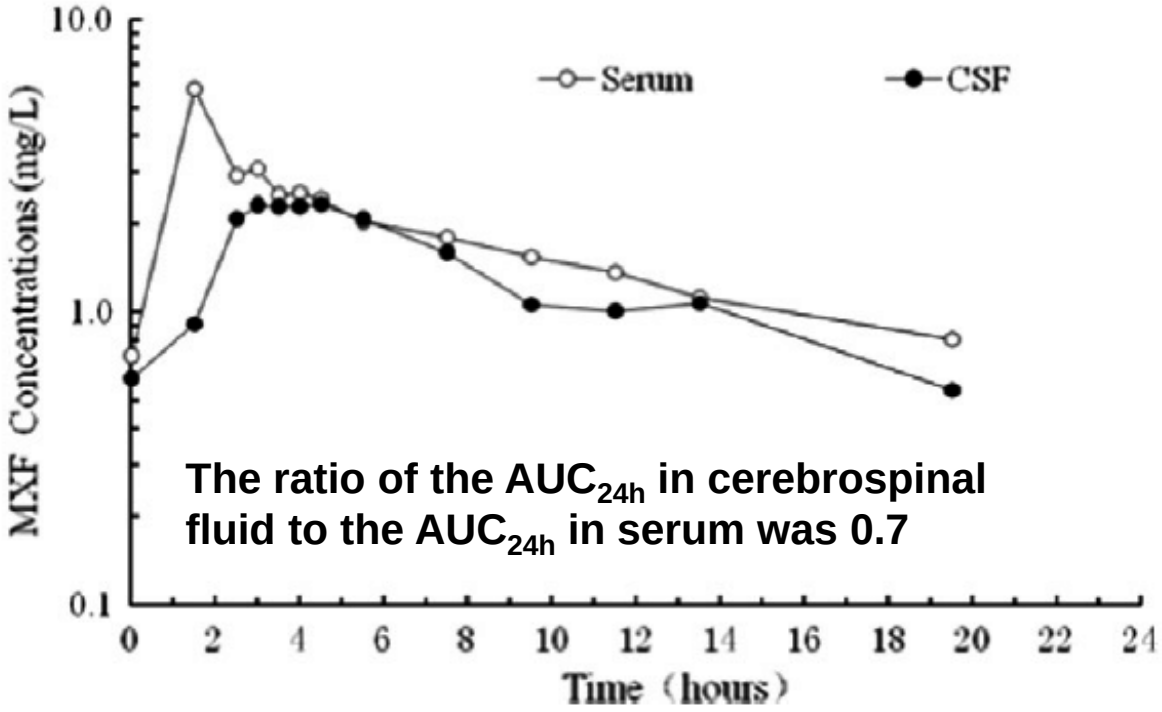


The ratio of the AUC_{24h} in cerebrospinal fluid to the AUC_{24h} in serum was 0.7

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*.

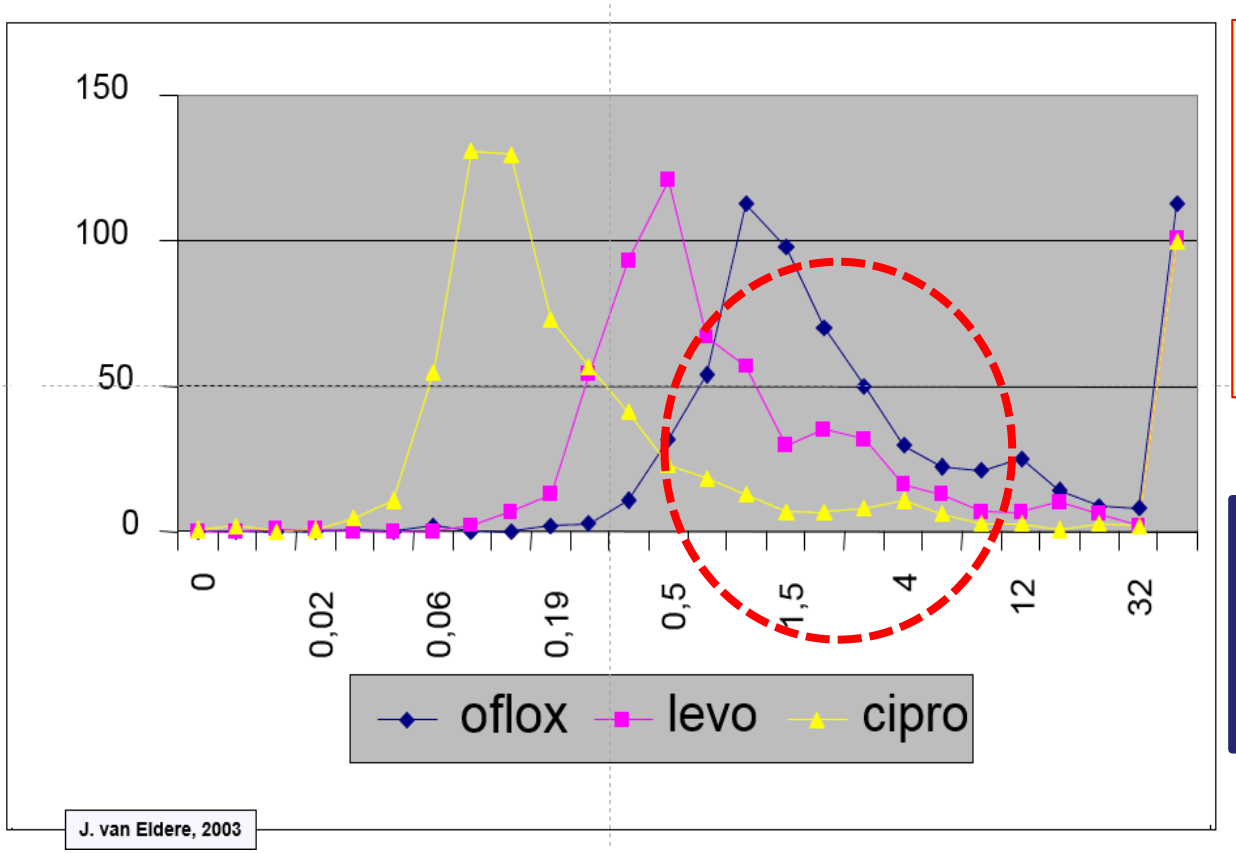
1 Metallidis et al. J Chemother. 2007;19:682-7 - PMID: 18230551
2 Metallidis et al. Int J Antimicrob Agents. 2006;28:428-32 - PMID: 17034992.
3 Kim e al. Hepatobiliary Pancreat Dis Int. 2017;16:512-518 - PMID: 28992884.

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 ?

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)



MIC distributions of fluoroquinolones against *P. aeruginosa* in the Academic Hospital of the University of Leuven, Belgium

EUCAST breakpoints:

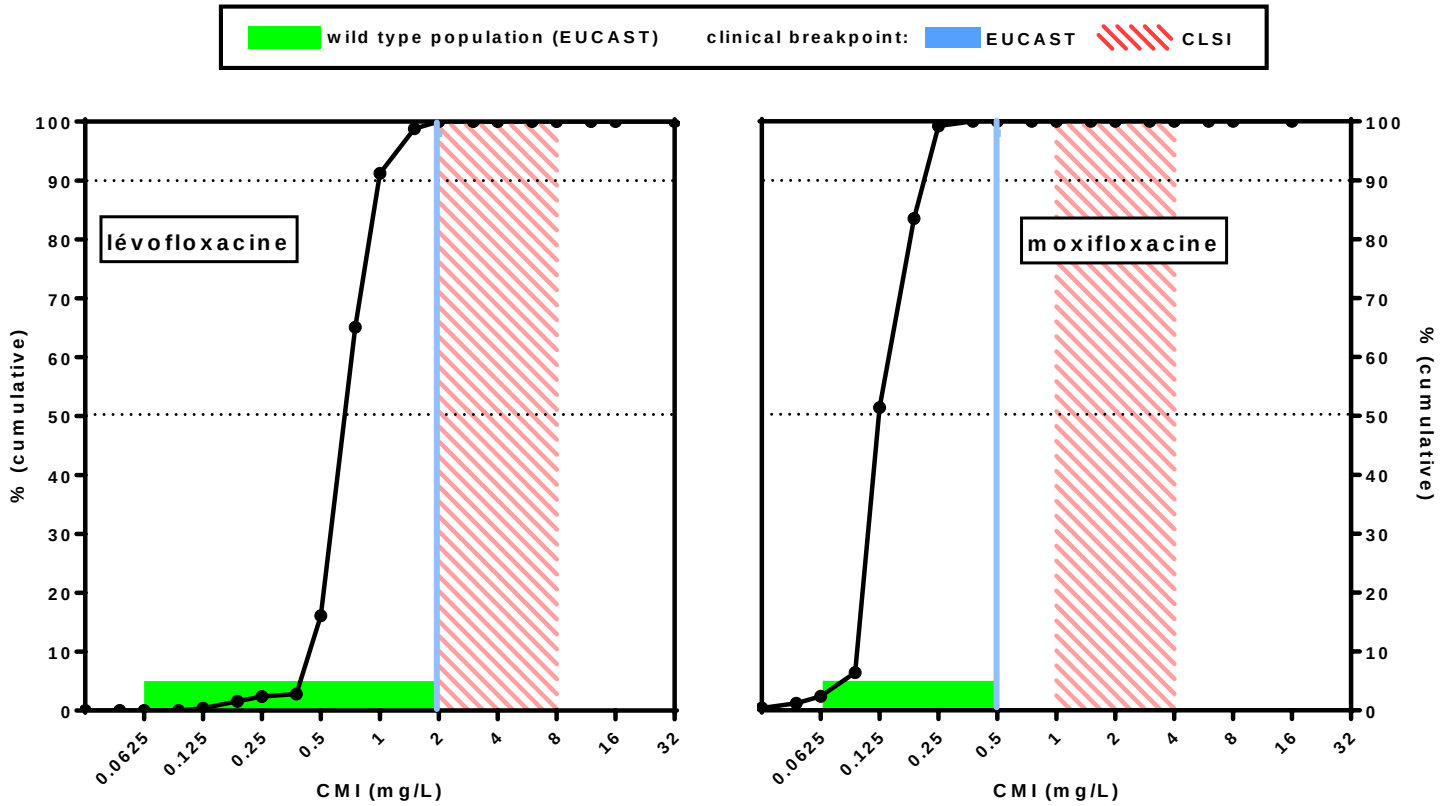
Cipro: S ≤ 0.5 – R > 0.5

Levo: S ≤ 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)

Lismond *et al*. Int J Antimicrob Agents. 2012 Mar;39(3):208-16.

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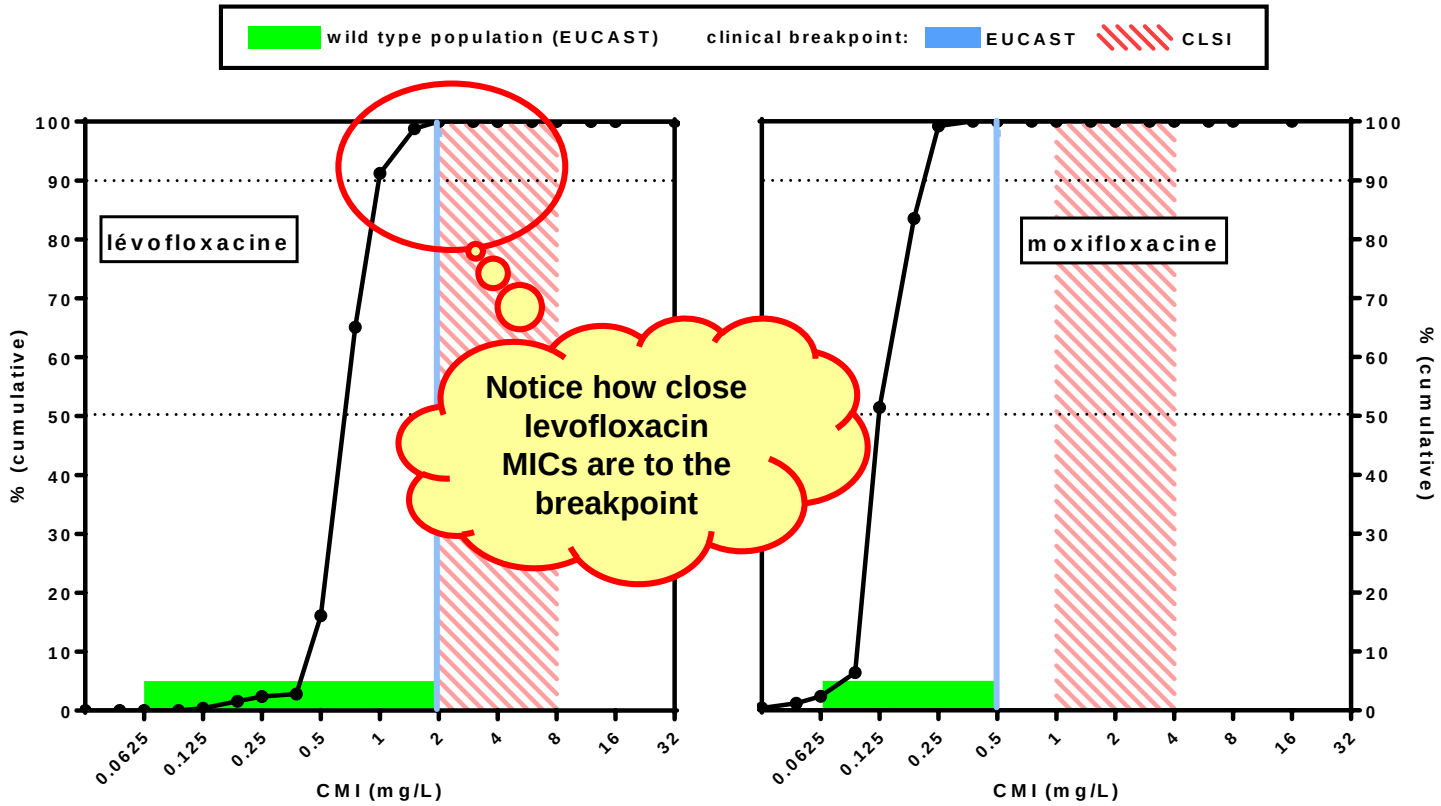
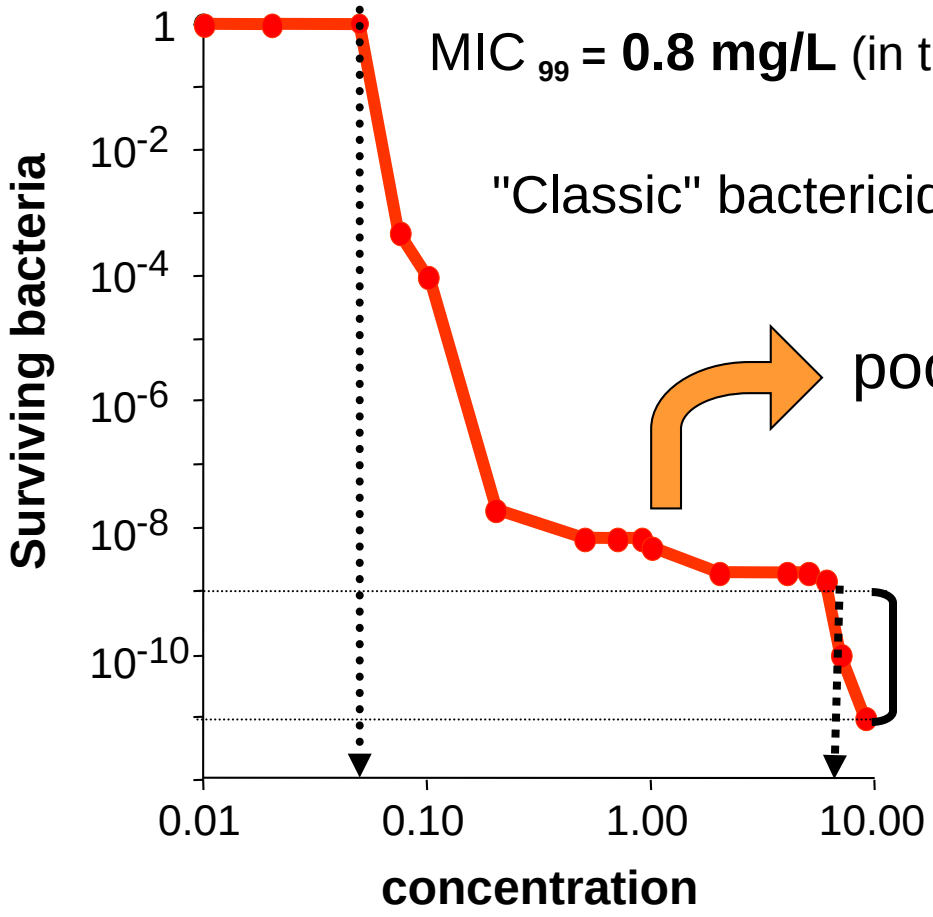


MIC distributions of *S. pneumonia* in Belgium for CAP (n=249)

Lismond *et al*. Int J Antimicrob Agents. 2012 Mar;39(3):208-16.

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



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

"Classic" bactericidal effect

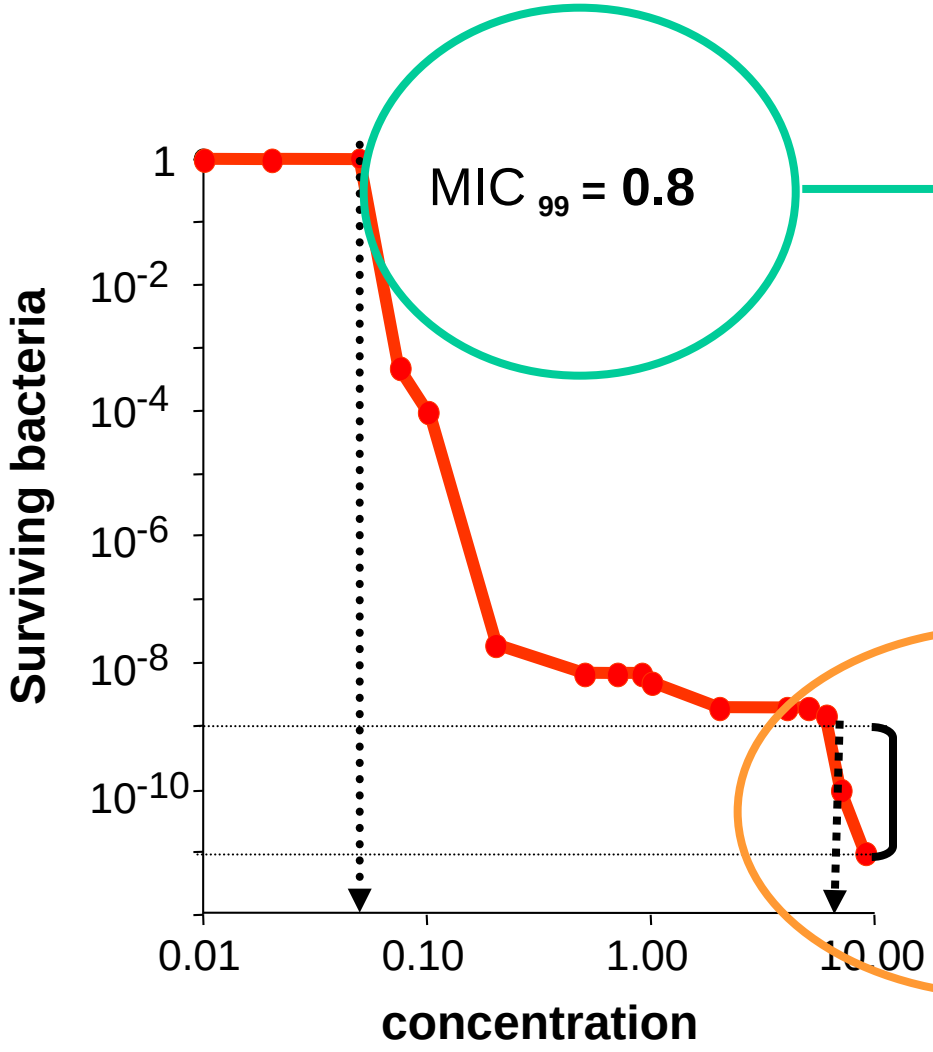
poorly sensitive organisms…

Elimination of resistant organisms

MPC_{10} = 9

Dong et al: AAC 1999; 43:1756-1758

"Mutant Prevention Concentration …"



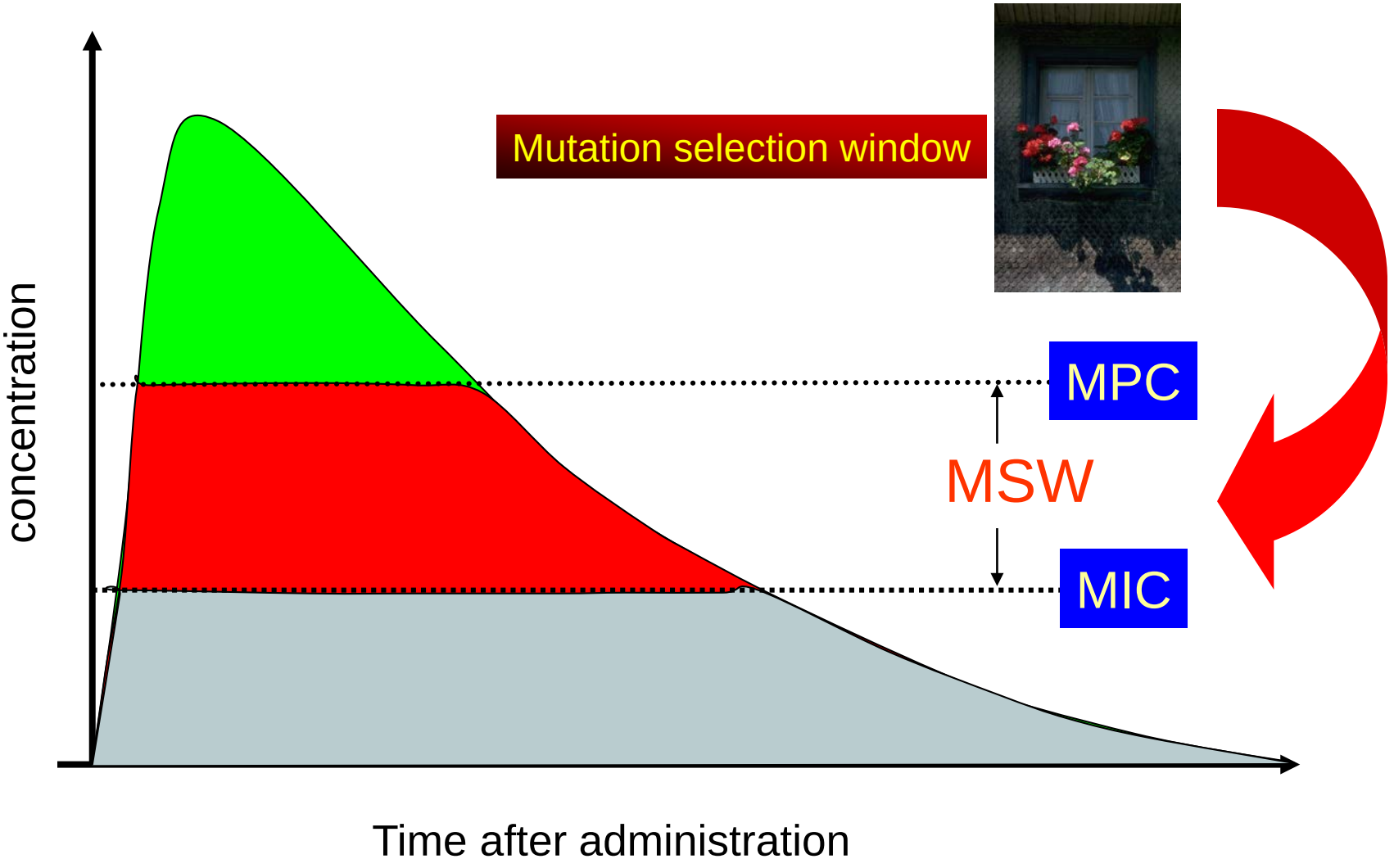
Concentration that inhibits the majority of the organisms

MPC 10 = 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" …



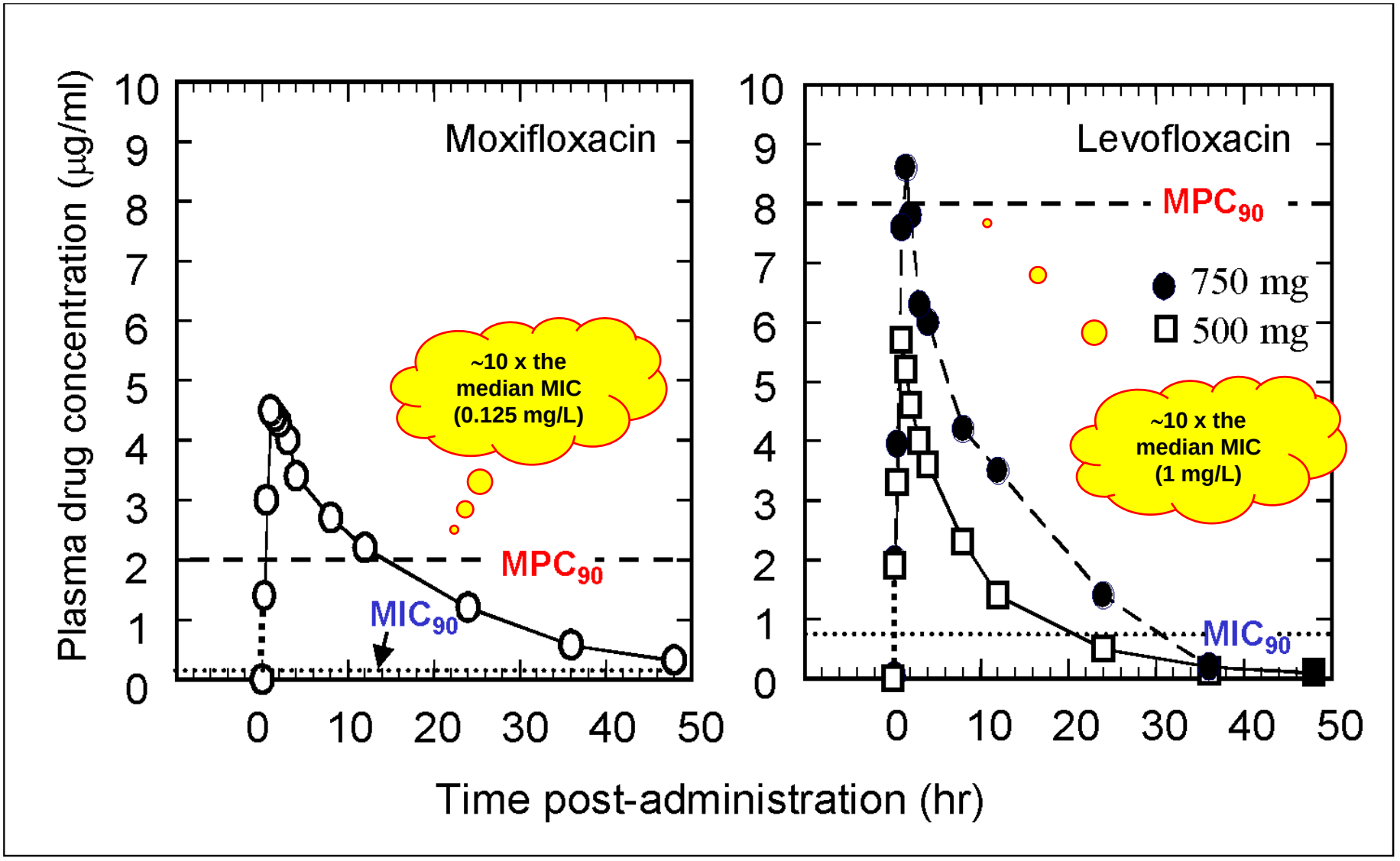
concept from Drlica & Zhao, Rev. Med. Microbiol. 2004, 15:73-80

So, what should you do with a fluoroquinolone to avoid emergence of resistance

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

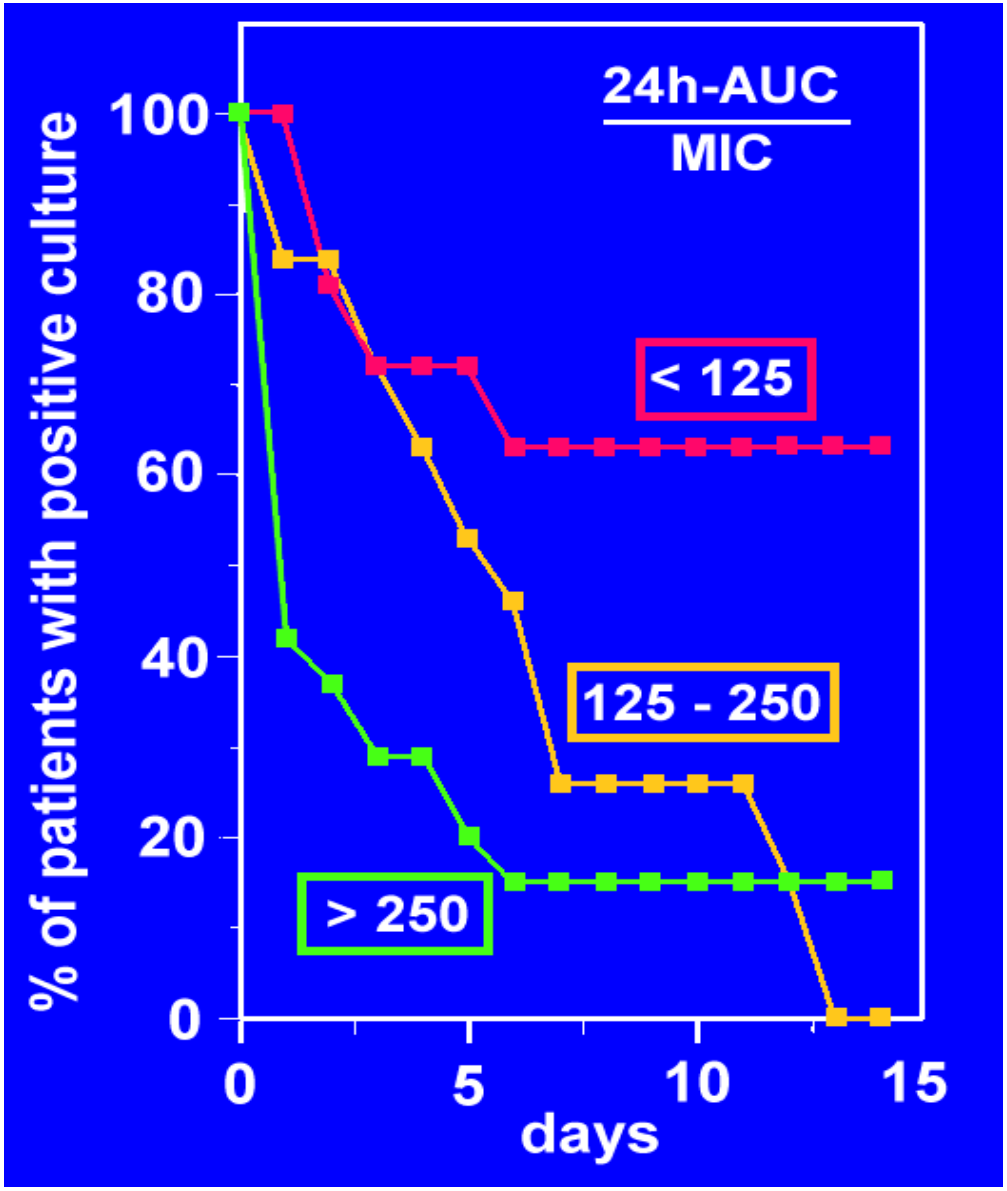
➔ peak / MIC > 10

MPC: moxifloxacin *vs* levofloxacin



The saga of the AUC / MIC vs C_{max} / MIC ratio for fluoroquinolones ...

AUC / MIC [1]
is
predictor of
activity
for Gram (-) ...

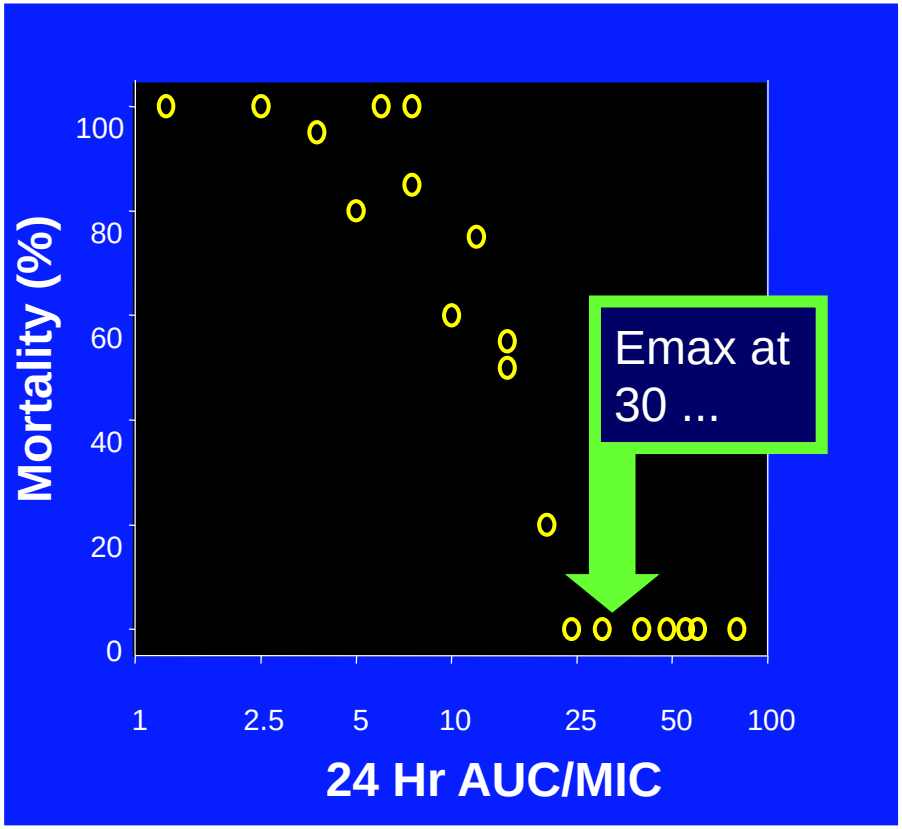


1 The impact of the C_{max} could not b tested in this study

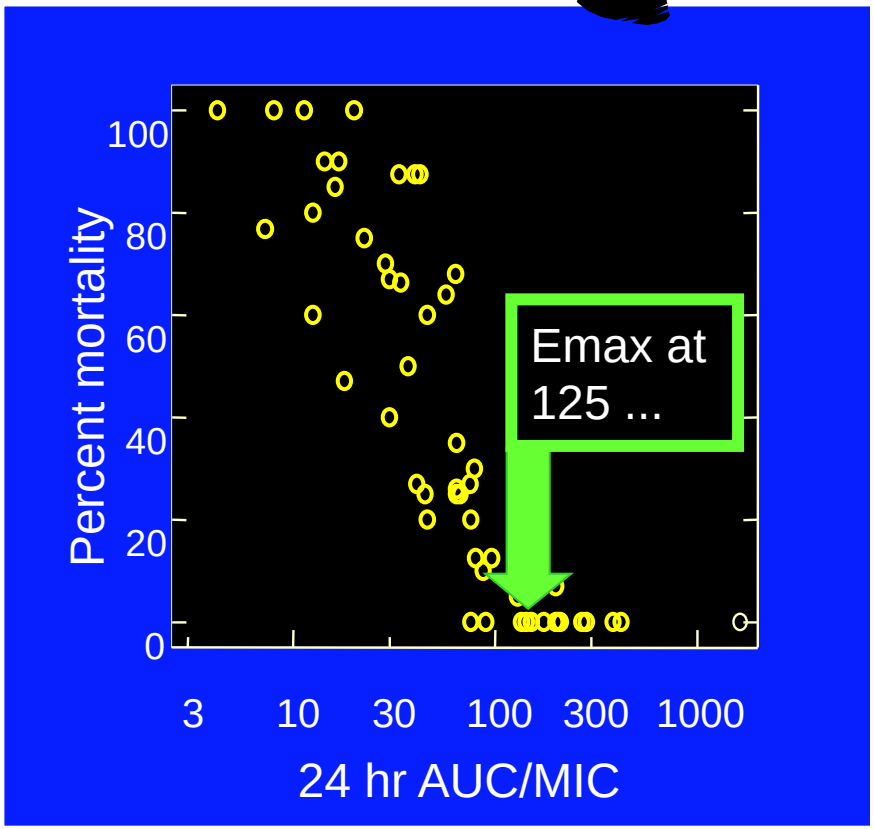
Forrest et al., AAC, 1993

Is 125 good for all ??

The saga of *S. pneumoniae* ...



non-neutropenic mice



neutropenic mice

Conditions That Predispose to Pneumococcal Infection

Defective antibody formation

PrimaryCongenital agammaglobulinemia

Common variable (acquired) hypogammaglobulinemia

Selective IgG subclass deficiency

SecondaryMultiple myeloma

Chronic lymphocytic leukemiaLymphoma

HIV infection

Defective complement (primary or secondary)

Decreased or absent C1, C2, C3, C4

Insufficient numbers of PMNs

PrimaryCyclic neutropenia

SecondaryDrug-induced neutropenia

Aplastic anemia

Poorly functioning PMNs

Alcoholism

Cirrhosis of the liver

So, an AUC/MIC = 125 may be good even for *S. pneumoniae*

Browse Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases

AUC/MIC: modelling the clinical use

Journal of Antimicrobial Chemotherapy (2006) **58**, 960–965
doi:10.1093/jac/dkl356
Advance Access publication 26 August 2006

JAC

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[1,2]* and Otto Cars[2]

[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*

Odenholt & Cars J Antimicrob Chemother. 2006;58:960-5 - PMID: 16936293.

AUC/MIC: modelling the clinical use

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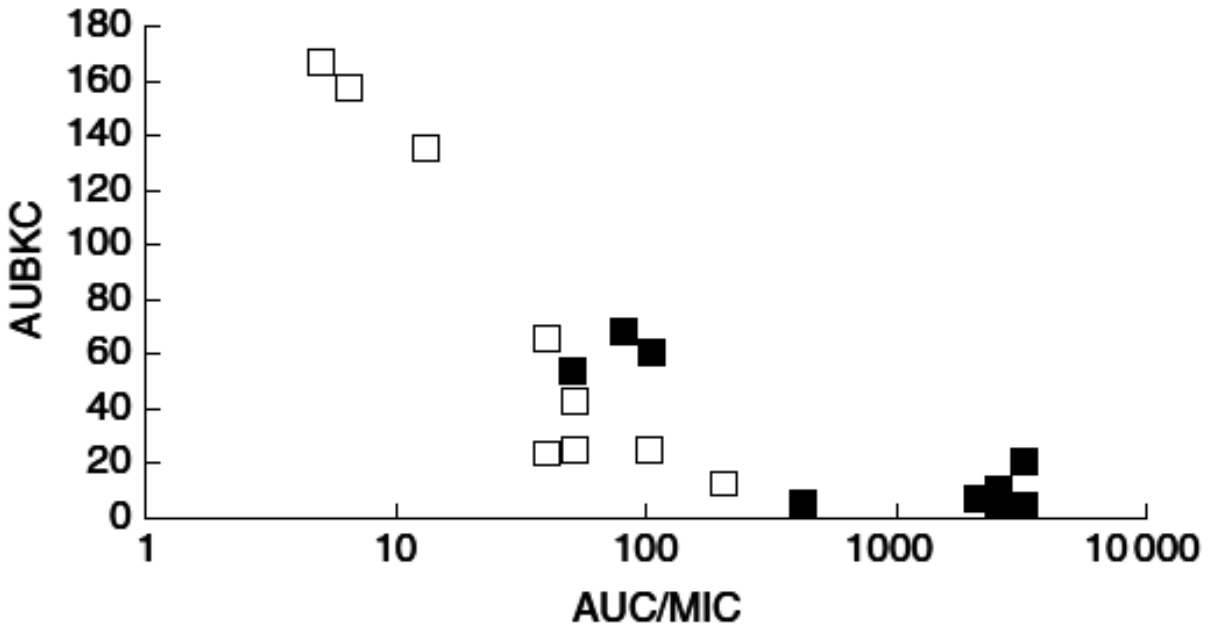


Figure 5.
relationship between AUBKC and AUC/MIC for *S. pneumoniae* (open squares) and Gram-negative strains (filled squares).

AUBKC: area under bacterial killing curve (~ log CFU)

Odenholt & Cars J Antimicrob Chemother. 2006;58:960-5 - PMID: 16936293.

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

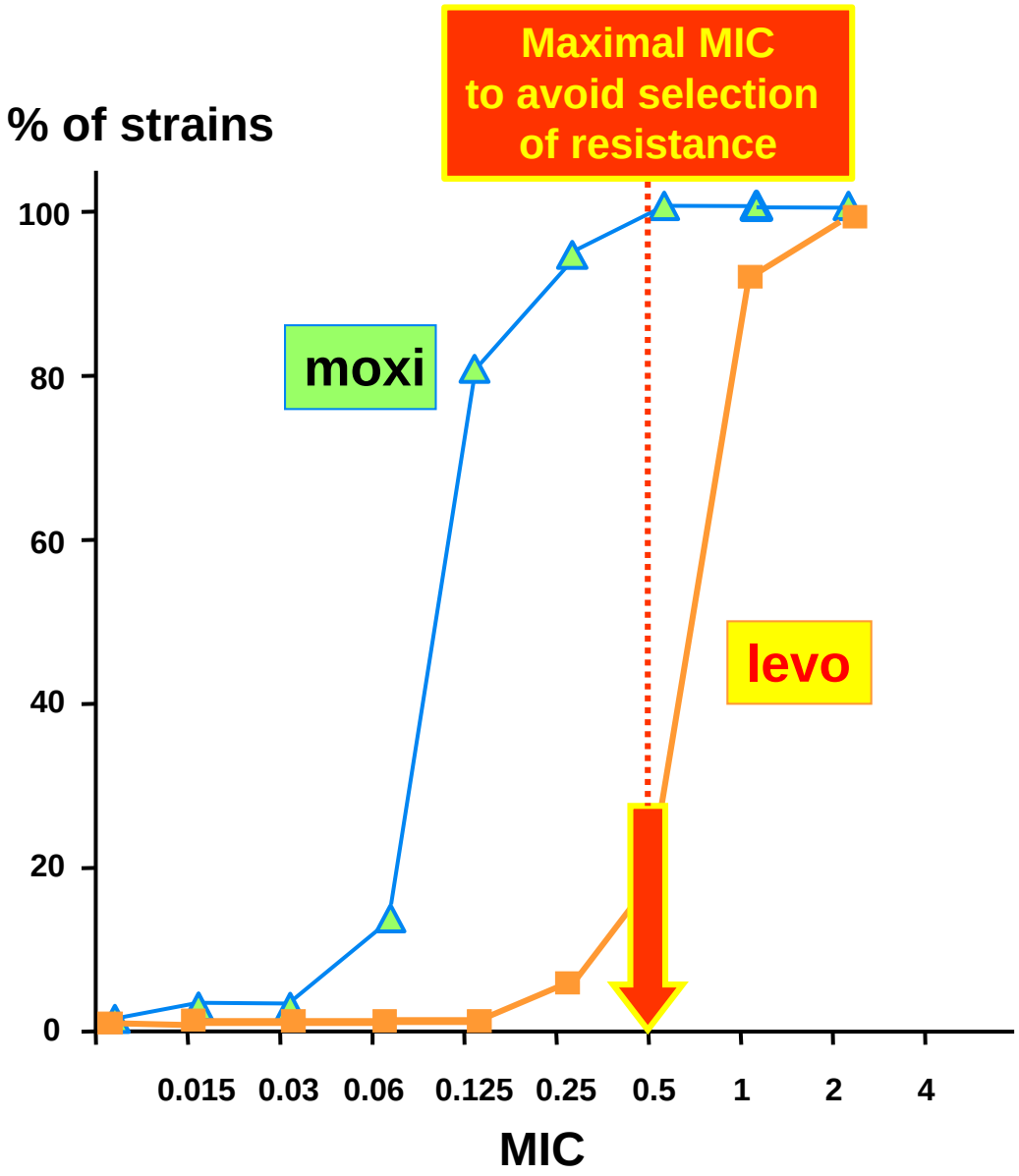
If you wish to get a faster eradication and reduce mergence of resistant

➔ peak / MIC > 10

If you are interested in global effect …

➔ AUC_{24h} / MIC: 125

Pharmacokinetics and "resistance" breakpoint *vs.* MIC



resistance breakpoint
- AUC/MIC = 100
- peak/MIC = 10

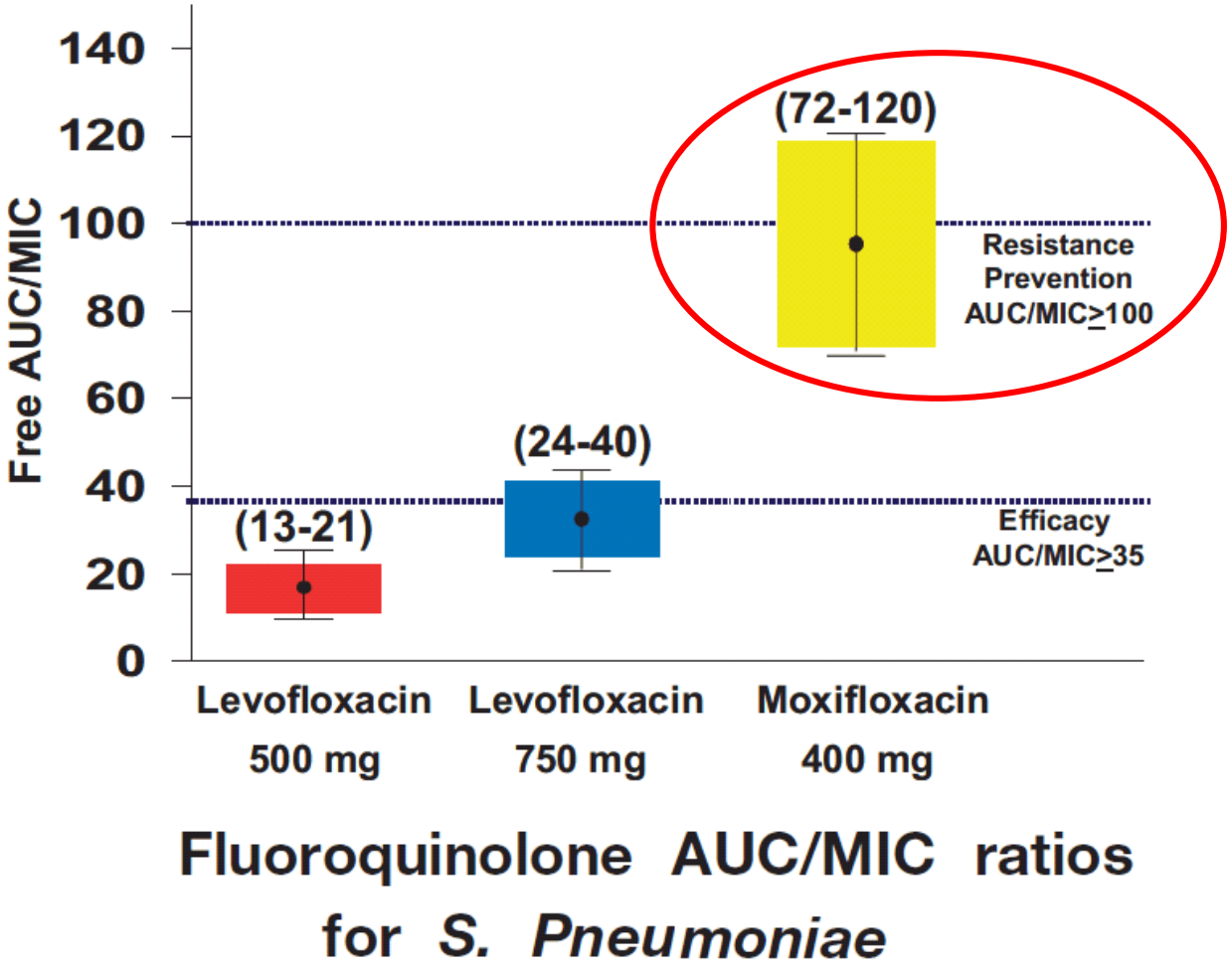
Levofloxacin 500 mg 1X / day
- AUC [(mg/l)xh] 47
- peak [mg/l] 5
- ➔ MIC_{max} ~ 0.5

Moxifloxacin 400 mg 1X / day
- AUC [(mg/l)xh] 48
- peak [mg/l] 4.5
- ➔ MIC_{max} ~ 0.5

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

What differentiates fluoroquinolones ?

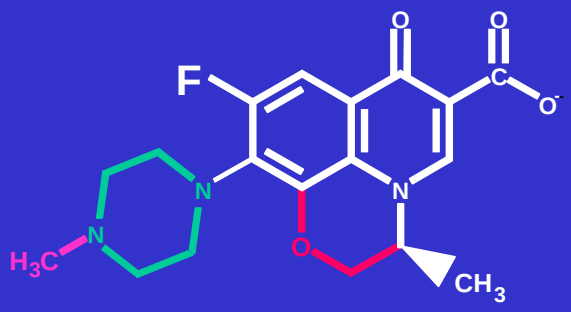
Results with *S. pneumoniae*



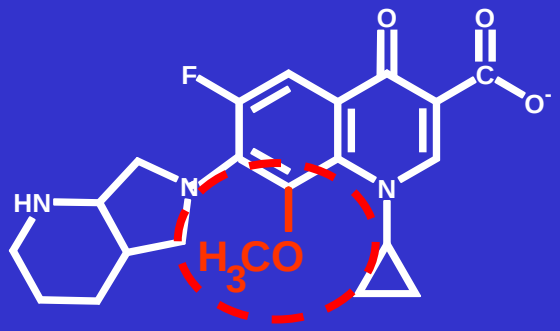
Would this cause less emergence of resistance ?

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-f luoroquinolone"



levofloxacin



moxifloxacin

FULL PRESCRIBING INFORMATION

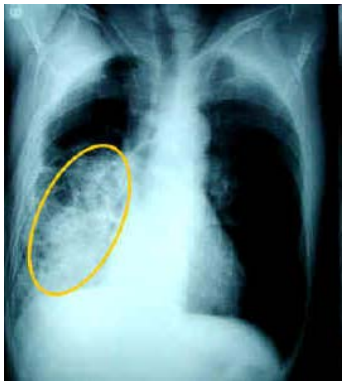
The bactericidal action of moxifloxacin results from inhibition of the topoisomerase II (DNA gyrase) and topoisomerase IV required for bacterial DNA replication, transcription, repair, and recombination. It appears that the C8-methoxy moiety contributes to enhanced activity and lower selection of resistant 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.

https://www.merck.com/product/usa/pi_circulars/a/avelox/avelox_pi.pdf
Last accessed: 8/2/2015

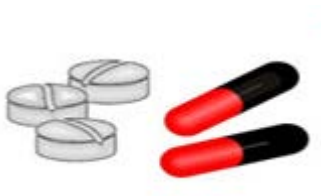
What shall we discuss ?

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

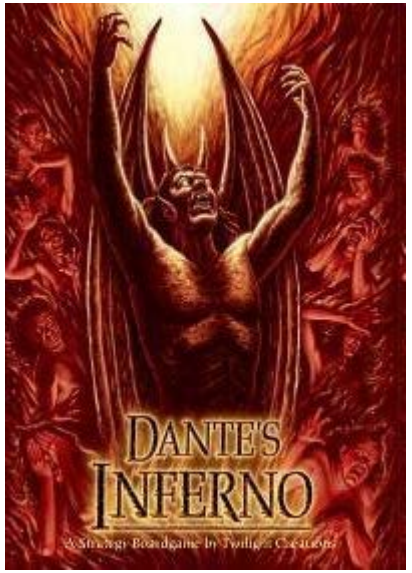
We all agree about efficacy, but what about side effects…



therapy ?



side effects ?



All antimicrobials have associated risks *

Class	Drugs	Frequent or serious side effects
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: 1/1000-1/10000

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.*

Carbonelle *et al.* , in preparation

Side effects of moxifloxacin (clinical trials database)

ORIGINAL RESEARCH ARTICLE

Drugs R D 2012; 12 (2): 71-100
1179-6901/12/0002-0071

Moxifloxacin Safety

An Analysis of 14 Years of Clinical Data

Paul M. Tulkens,[1] *Pierre Arvis*[2] and *Frank Kruesmann*[3]

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

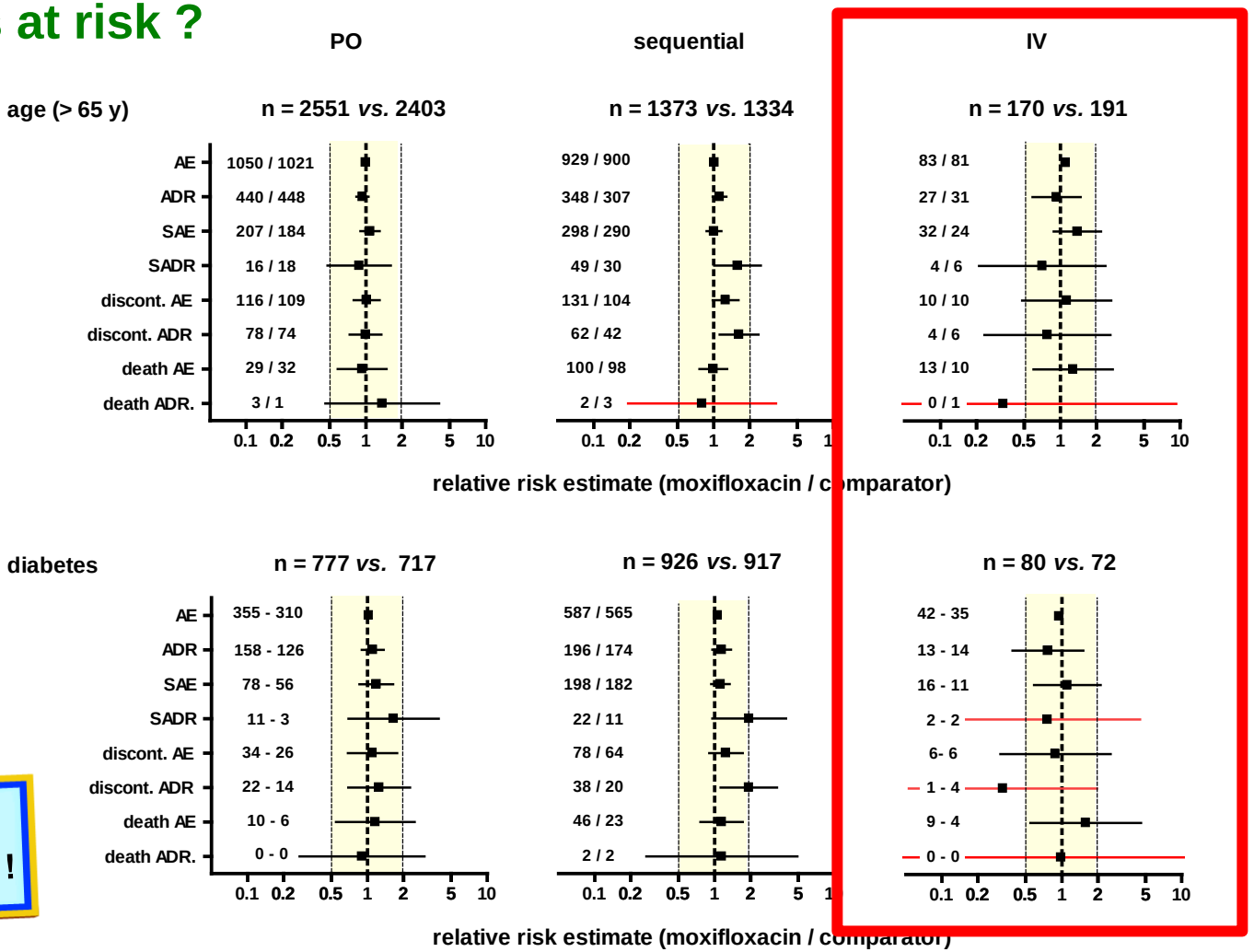
Study design and COMP	Treatment route [n]					
	PO [n = 21 298]		IV/PO [n = 6846]		IV only [n = 1860]	
	MXF [n = 10613]	COMP [n = 10685]	MXF [n = 3431]	COMP [n = 3415]	MXF [n = 937]	COMP [n = 923]
Double-blind studies						
β-lactam	2391	2104	1077	1034	408	390
β-lactam + macrolide	274	155	0	0	0	0
Fluoroquinolone	2246	2287[a]	444	457[b]	0	0
Macrolide	3659	2929	0	0	0	0
Other	1230	1168[c]	368	365[d]	180	181[e]
Total	*8822*[f]	*8643*	*1889*	*1856*	*588*	*571*
Open-label studies						
β-lactam	1318	1301	554	547	0	0
β-lactam + macrolide	186	190	0	0	0	0
β-lactam ± macrolide	0	0	532	549	0	0
Fluoroquinolone	263	270[g]	0	0	349	352[g]
Macrolide	287	281	0	0	0	0
Other	0	0	456	463[h]	0	0
Total	*1791*[f]	*2042*	*1542*	*1559*	*349*	*352*

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 ?



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

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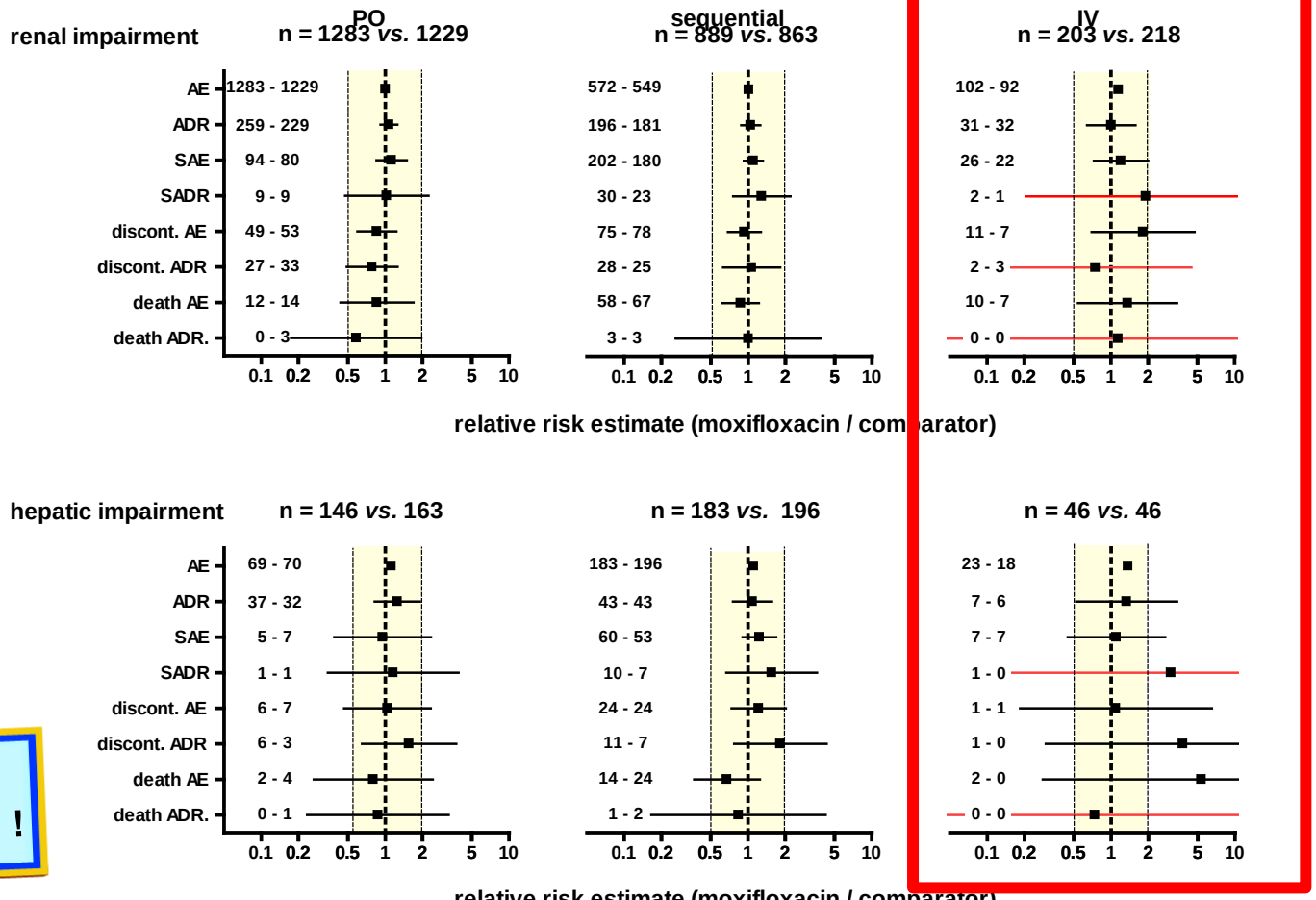
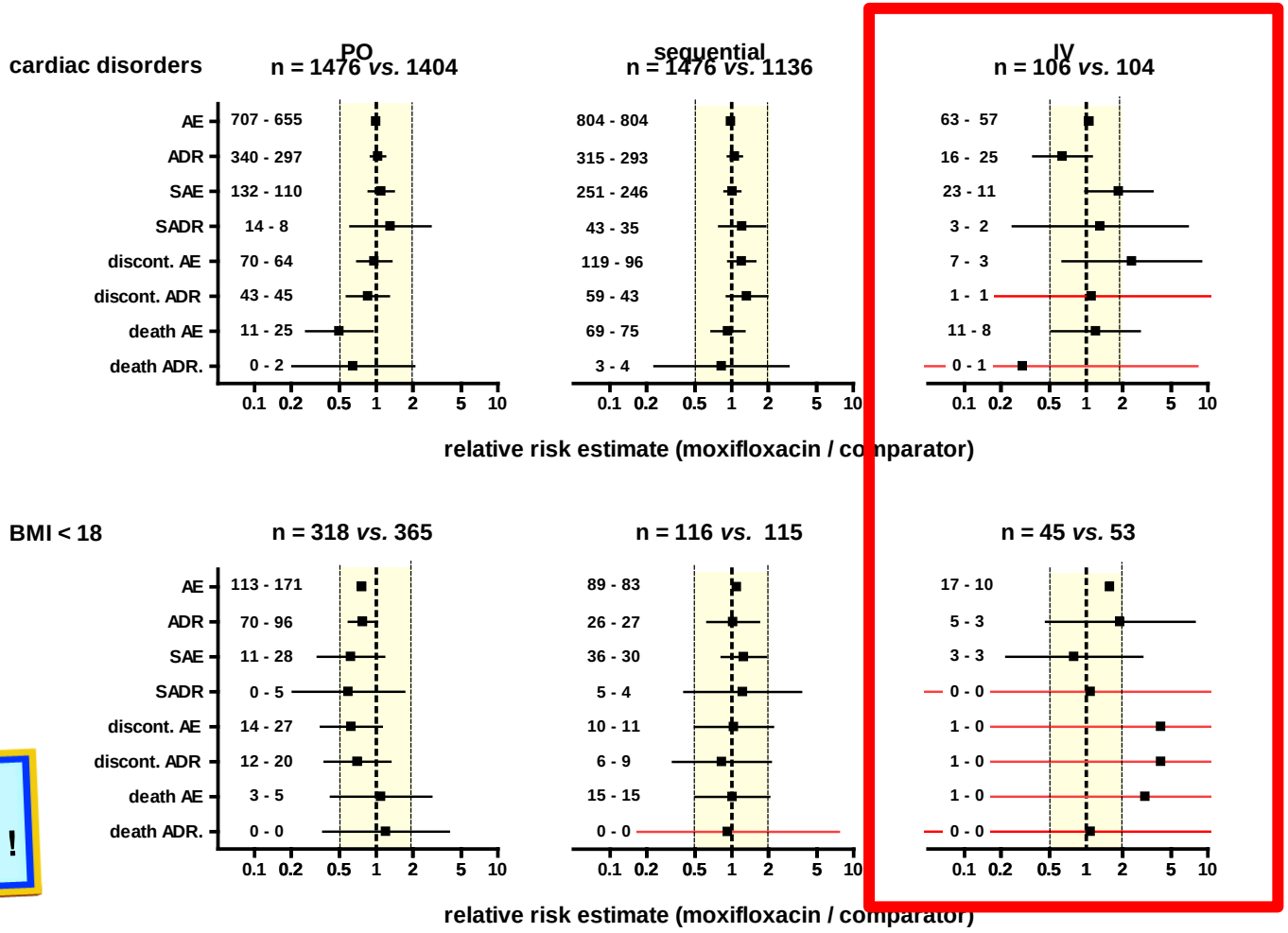


Tulkens et al., Drugs R D (2012) 12: 71-100

Side effects of moxifloxacin (clinical trials database)

Patients at risk ?



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

Hepatotoxicity

Crude incidence rates of acute liver injury caused by antibiotics

Antibiotic	population	Incidence rate (CI)		endpoint	Ref.
		per 100,000 users	per 100,000 prescriptions		
fluoroquinolones (w/o moxifloxacin)	Outpatient clinic, Sweden (1995-2005)	0.7 (0.5-1.1)		International consensus	[1]
moxifloxacin	Outpatient clinic, Sweden (1995-2005)	0.08 (0.0-0.5)		International consensus	[1]
cotrimoxazole	Saskatchewan Health Plan, Canada (1982-1986)	1.0 (0.2-5.7)	4.9 (0.9-27.6)	International consensus, hospitalisation	[2]
erythromycin	Saskatchewan Health Plan, Canada (1982-1986)	2.0 (0.7-5.9)	14.0 (4.8-41.2)	International consensus, hospitalisation	[2]
amoxicillin-clavulanic acid	General practice research database, United Kingdom (1991-1992)	22.5 (14.7-34.4)	17.4 (11.4-26.5)	International consensus	[3]

1. De Valle et al. Aliment Pharmacol Ther 2006 Oct 15; 24(8): 1187-95
2. Perez et al. Epidemiology 1993 Nov; 4(6): 496-501
3. Garcia-Rodriguez et al. Arch Intern Med 1996 Jun 24; 156(12): 1327-32

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

Hepatotoxicity

Hepatotoxicity risk of antibiotics

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

Ciprofloxacin, levofloxacin and moxifloxacin	Tetracycline	Erythromycin, clarithromycin and penicillins	Co-trimoxazole and amoxicillin/ clavulanate	Telithromycin and trovafloxacin
				Acute liver failure, high mortality
Isolated cases and ≤0.00007	≤0.0002	≤0.004	≤0.02	?
				Withdrawal or severe restriction does not allow calculating true incidences

Andrade & Tulkens, JAC (2011) 66: 1431–46

EMA position

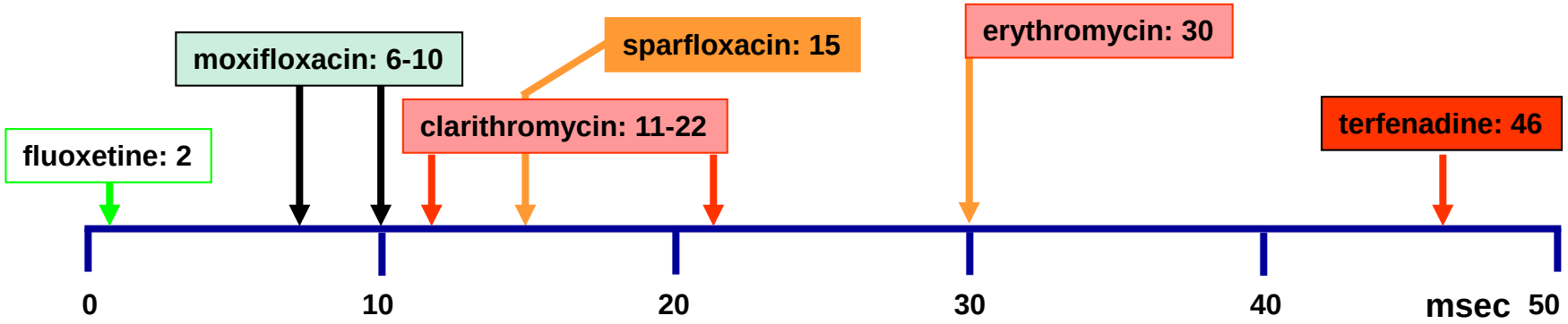
European Medicines Agency

November 2005
CHMP/ICH/2/04

NOTE FOR GUIDANCE ON THE CLINICAL EVALUATION OF QT/QTc INTERVAL PROLONGATION AND PROARRHYTHMIC POTENTIAL FOR NON-ANTIARRHYTHMIC DRUGS
(CHMP/ICH/2/04)

… 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)

QTcB prolongation after IV use

Current Drug Safety, 2012, *7*, 149-163

Update on the Cardiac Safety of Moxifloxacin

Wilhelm Haverkamp[*,1], Frank Kruesmann[2], Anna Fritsch[2], David van Veenhuyzen[3] and Pierre Arvis[4]

[1]*Department of Cardiology, Campus Virchow Clinic, Charité University Medicine Berlin, Berlin, Germany*

[2]*Bayer Pharma AG, Wuppertal, Germany*

[3]*Bayer HealthCare, Montville, NJ, USA*

[4]*Bayer HealthCare, Loos, France*

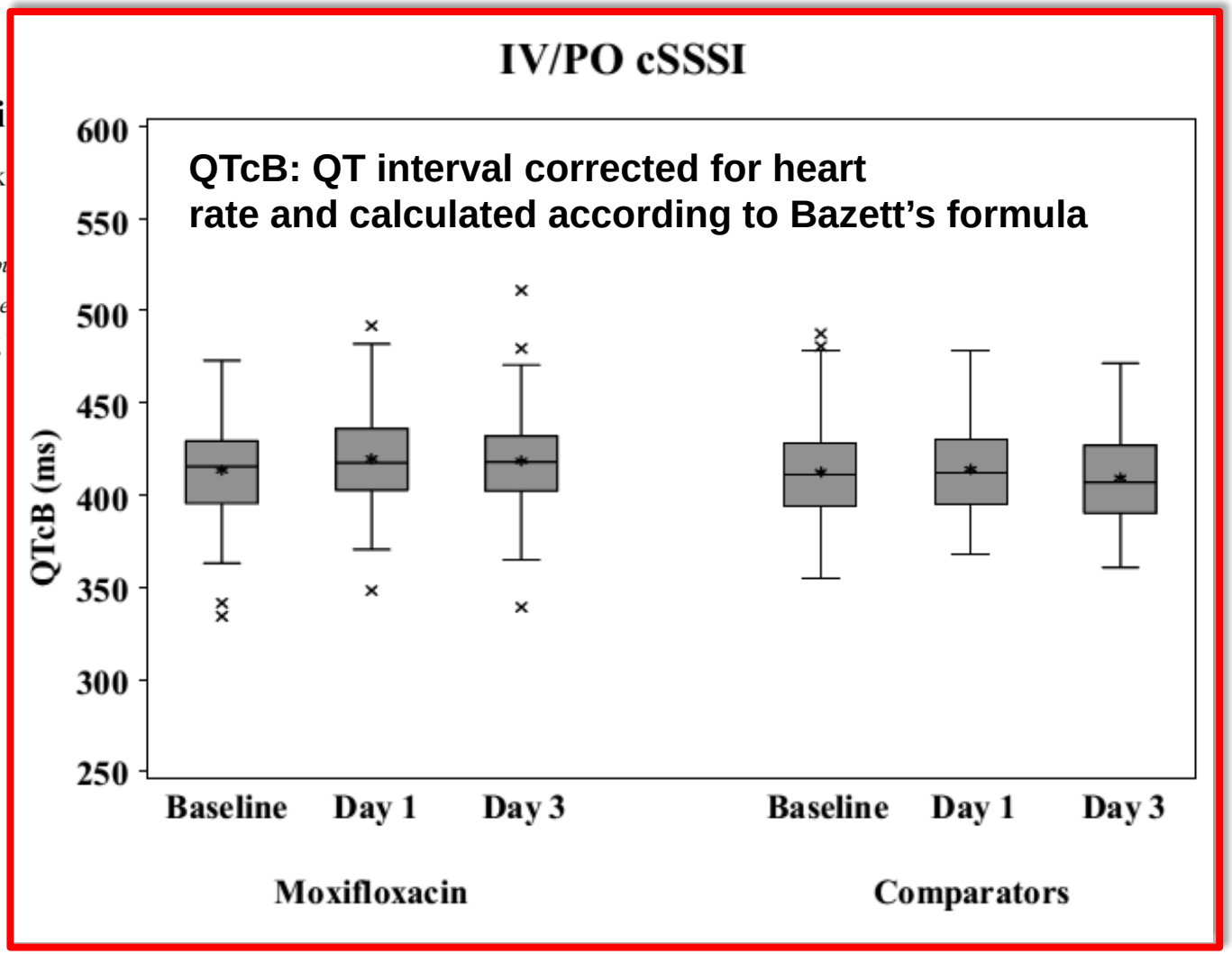
Haverkamp et al. Curr Drug Saf. 2012;7:149-63. PMID 22873499

QTcB prolongation after IV use

Update on the Cardi

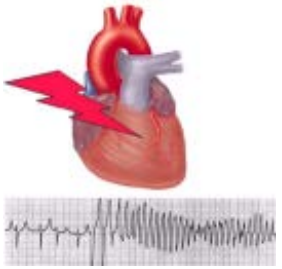
Wilhelm Haverkamp[*,1], Frank

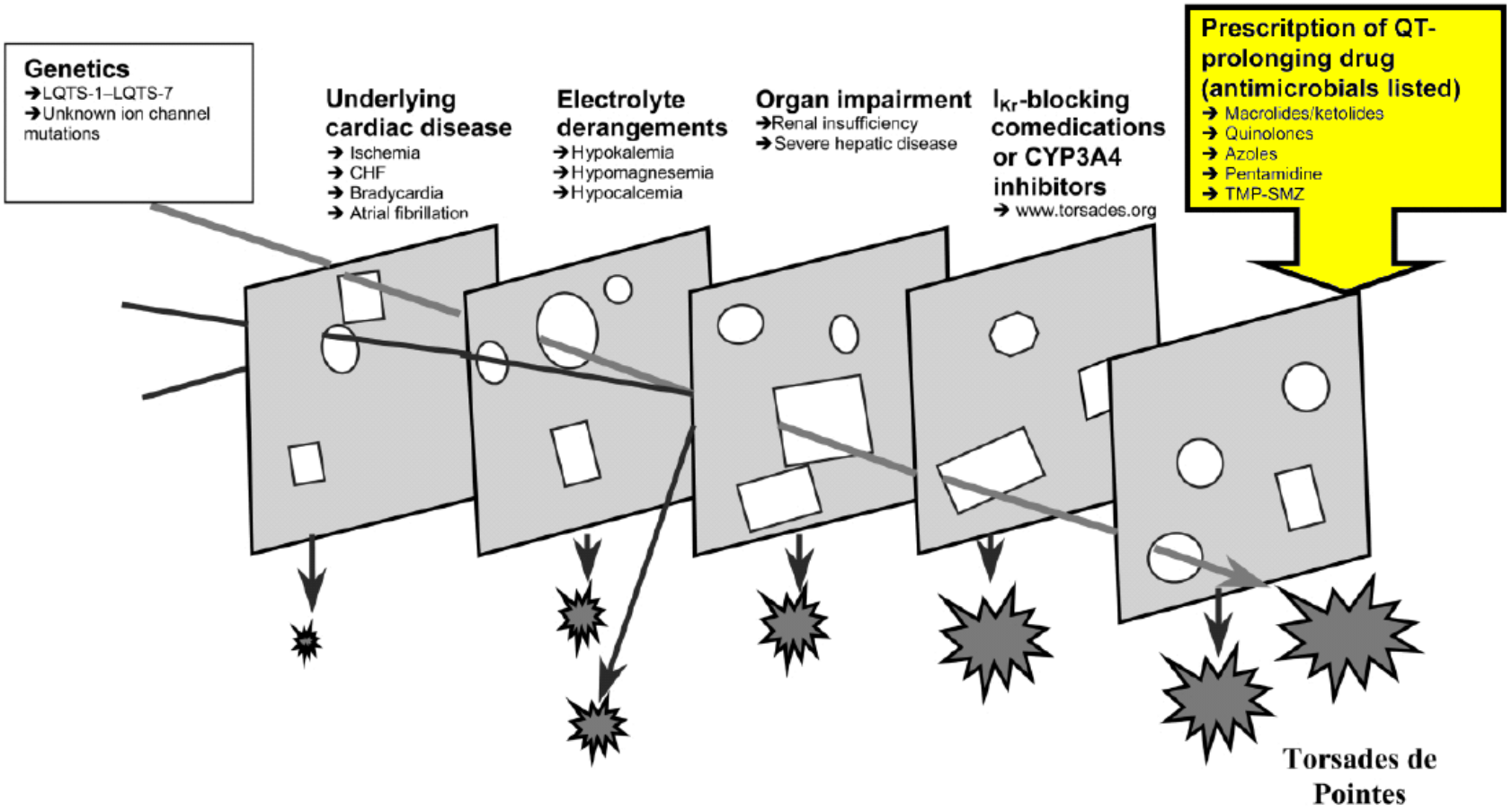
[1]*Department of Cardiology, Campt*
[2]*Bayer Pharma AG, Wuppertal, Ge*
[3]*Bayer HealthCare, Montville, NJ,*
[4]*Bayer HealthCare, Loos, France*



Haverkamp et al. Curr Drug Saf. 2012;7:149-63. PMID 22873499

QTc prolongation





Owens & Ambrose CID (2005) 41:S144-157

Torsade de pointe: comparison of risk

reporting rate of *Torsades de pointe* induced by antibiotics

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

used as negative control in RCT

FDA warning March 12,2013

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

Tendinopathies: main features and incidence…

TABLE 1. Characteristic features of fluoroquinolone-induced tendinopathy/tendon rupture

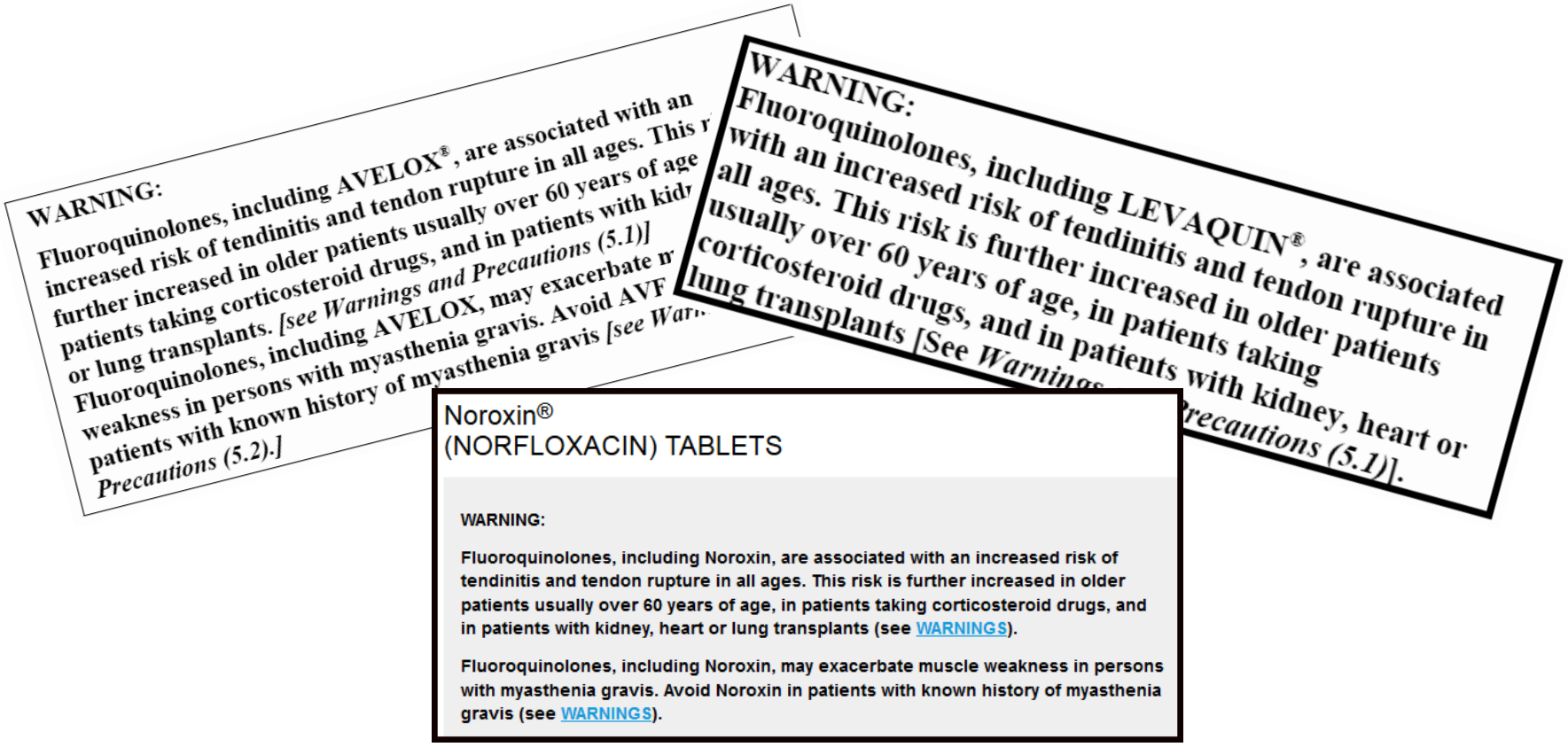
in 2010

FEATURE	OBSERVATIONS/FINDINGS
Causative quinolones reported[6,9,10]	Ciprofloxacin (most commonly reported), norfloxacin, pefloxacin, ofloxacin, levofloxacin
Associated risk factors[11,31,33–37]	Age >60 years, corticosteroid therapy, renal failure, diabetes mellitus, history of tendon rupture
Relative risk of tendon disorders[3,16,31]	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[11,33,44]	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[3,4,6,15]	Median onset of 6 days (85% of cases within first month) Up to 50% of cases after fluoroquinolone discontinued

Kim & Del Rosso, J Clin Aesthet Dermatol. 2010; 3:49–54.

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).

SMQ/BMQ and preferred term	Treatment route [n (%)]					
	PO		IV/PO		IV	
	MXF [n = 10 613]	COMP [n = 10 685]	MXF [n = 3431]	COMP [n = 3415]	MXF [n = 937]	COMP [n = 923]
Tendinopathies	11 (0.1)	10 (<0.1)	3 (<0.1)	2 (<0.1)	0 (0.0)	0 (0.0)

very rare and no difference

no case

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

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

http://www.ismp.org/quarterwatch/2010Q2.pdf
Last accessed: 20/02/2015

in 2011

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)…

Institute for Safe Medication Practices
A Nonprofit Organization Educating the Healthcare Community and Consumers About Safe Medication Practices
A federally certified Patient Safety Organization

in 2011

QuarterWatch: 2010 Quarter 2

Table 2. Tendon disorders for fluoroquinolone antibiotics 2010q2.

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

*IMS Health National Prescription Audit ™ 2010

(AVELOX), with somewhat less frequent medical use.

http://www.ismp.org/quarterwatch/2010Q2.pdf
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"

Drug	Typical daily dosage[a]	Typical PK values		Proposed PK/PD upper limit of sensitivity (μg/ml) for	
		C_{max} in mg/L total/free (dose)	$AUC_{24\ h}$ (mg × h/L) total/free	Efficacy[b]	Prevention of resistance[c]
Norfloxacin	800 mg	1.4/1.1 (400 mg PO)	14/11	0.1–0.4	0.1
Ciprofloxacin	1000 mg	2.5/1.75 (500 mg PO)	24/18	0.2–0.8	0.2
Ofloxacin	400 mg	4/3 (400 mg PO)	40/30	0.3–0.9	0.4
Levofloxacin	500 mg	4/2.8 (500 mg PO)	40/28	0.3–0.9	0.3
Moxifloxacin	400 mg	3.1/1.8 (400 mg PO)	35/21	0.2–0.7	0.2

Van Bambeke F, Michot JM, Van Eldere J, Tulkens PM.
Quinolones in 2005: an update. Clin Microbiol Infect. 2005 Apr;11(4):256-80. PMID: 15760423

Check the EUCAST breakpoints…

Enterobacteriaceae

Fluoroquinolones	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Ciprofloxacin[1]	0.5	1	5	22	19
Levofloxacin	1	2	5	22	19
Moxifloxacin	0.5	1	5	20	17
Norfloxacin	0.5	1	10	22	19
Ofloxacin	0.5	1	5	22	19

All EUCAST data are freely available at http://www.eucast.org

Check the EUCAST breakpoints…

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Ofloxacin	0.5	1	5	22	19

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 fluoroqunolone…**

Check the EUCAST breakpoints…

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Maximal Interest for the Clinician

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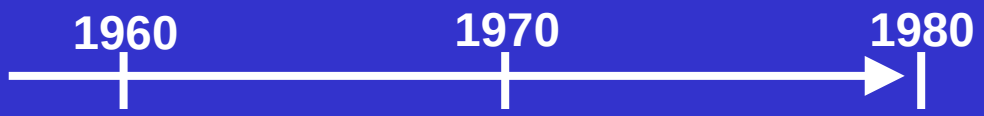
Thank you for your attention!

And ask questions

The "first generation" of fluoroquinolones



- Nalidixic acid
- Oxolinic acid
- Cinoxacin
- Pipemidic acid

- Norfloxacin
- Pefloxacin
- Ofloxacin
- Ciprofloxacin
- Fleroxacin
- Rufloxacin

improved anti Gram (-) activity

$t_{1/2}$	activity
3-4 h	++
11 h	+
6 h	++
3-4 h	+++

An interesting paper…

International Journal of Antimicrobial Agents 45 (2015) 79–83

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

Short Communication

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…

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N. Carral[a], J.C. Lukas[a,b], I. Ot

Table 1
Interindividual variability of $fAUC_{0-24h}$ for levofloxacin (LFX) and moxifloxacin (MOX), estimated for various drug dosing regimens in simulated patients.

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

An interesting paper…

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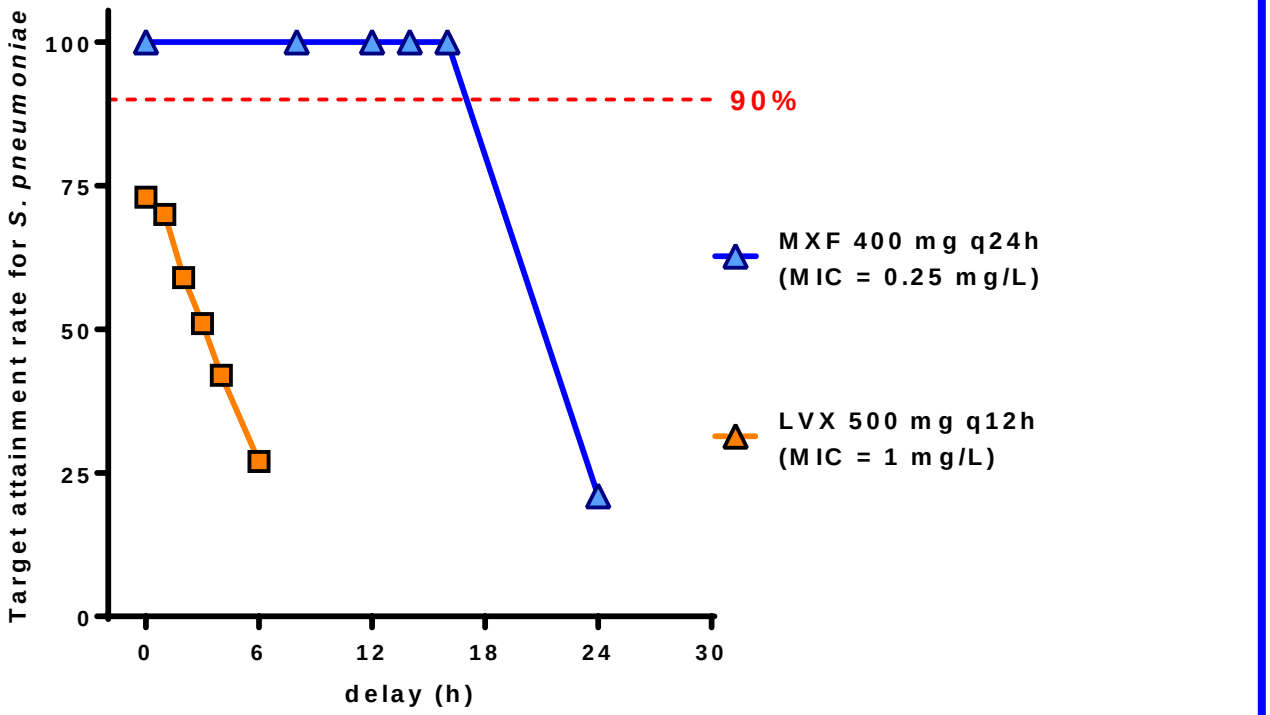

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