Not All Fluoroquinolones Are Equal …

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Disclosures

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- Non-profit Institutions:
  - the Belgian *Fonds de la Recherche Scientifique* for basic research on pharmacology antibiotics and related topics
  - The European Union for applied research on optimisation of β-lactams treatments through on-line monitoring of free serum levels
  - *Université catholique de Louvain* for past personal support
- Industry:
  - AstraZeneca, GSK, Sanofi-Aventis, Bayer, Cempra Pharmaceuticals, The Medicines Company, Northern Antibiotics, RibX, Cubist, Galapagos, …

Other past and present relationships in relation to this talk

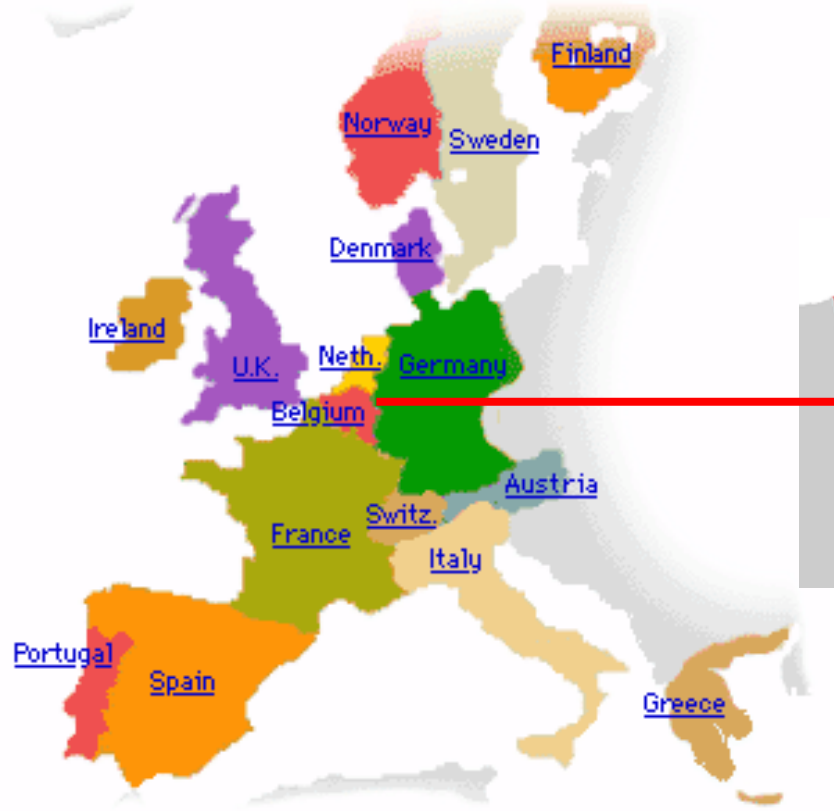
- Belgian Antibiotic Policy Coordination Committee (BAPCOC)
- European Committee for Antibiotic Susceptibility Testing (EUCAST)
- European Medicines Agency (EMA)
- Drive-AB (a EU programme for a new economical framework for antibiotics)

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

The programme…

- **A very short view of Belgium and of where I work…**
- **Differentiating fluoroquinolones in their origin and intrinsic nature**
- **Differentiating fluoroquinolones in PK/PD and the concept of MPC (prevention of resistance)**
- **How would moxifloxacin fit into an antibiotic stewardship program**
- **Questions, objections, suggestions …**

Belgium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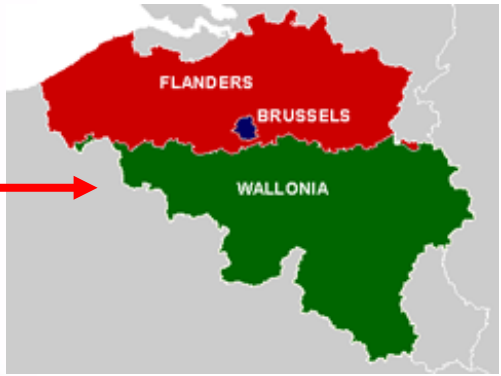
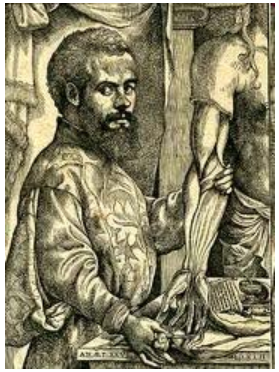

FLANDERS
BRUSSELS
WALLONIA

The *Catholic University of Louvain* in brief

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

The University in the 1500's

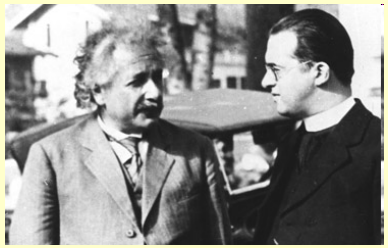
Erasmus



Vesalius

The *Catholic University of Louvain* in brief

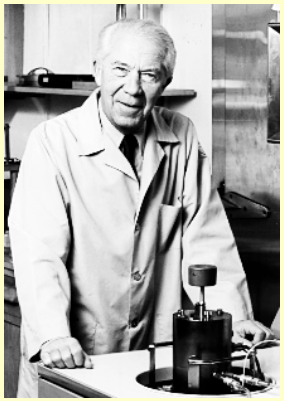
- In the 19th century, teaching was in French but in the early 1900's, a Flemish-speaking section was opened. Courses were given in both languages, attracting many students and celebrities…



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

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

(here in front of a centrifuge)



- in 1968, the University was divided into
  - a French-speaking ***Université catholique de Louvain***
  - a Flemish-speaking ***Katholieke Universiteit Leuven…***

The *Catholic University of Louvain* in brief (4 of 4)

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

Université catholique de Louvain
http://www.uclouvain.be

Katholieke Universiteit Leuven
http://www.kuleuven.be

- Together, the two sister Universities have about **60,000 students**

What do we do ?

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

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

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

  * in development
- re-assessment of older antibiotics

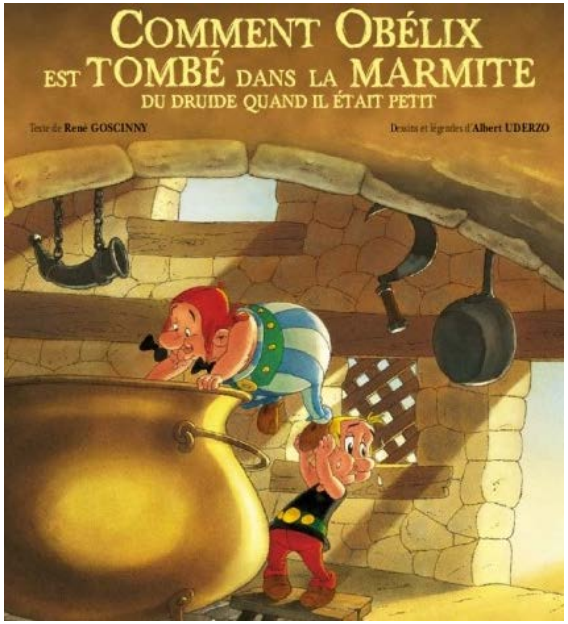
www.facm.ucl.ac.be

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

www.isap.org

Why do I have an interest in fluoroquinolones ?

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



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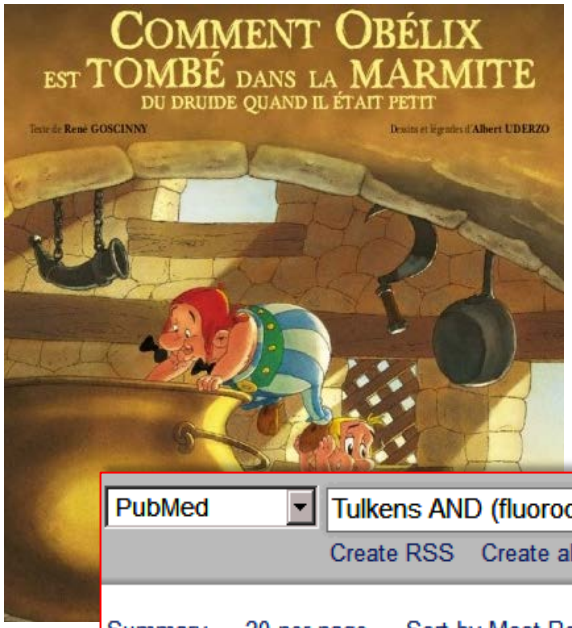

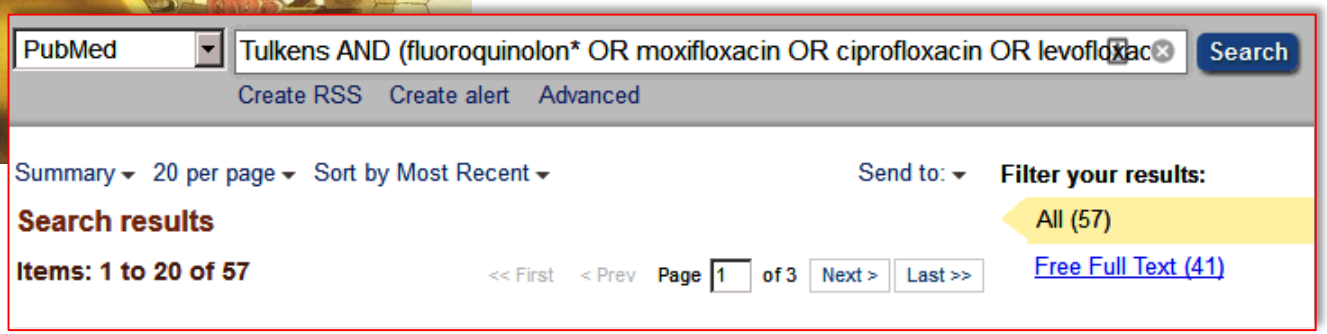

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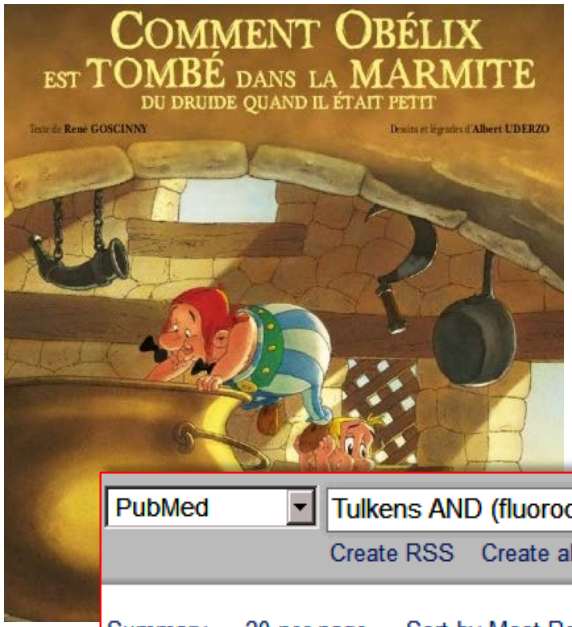


1990

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

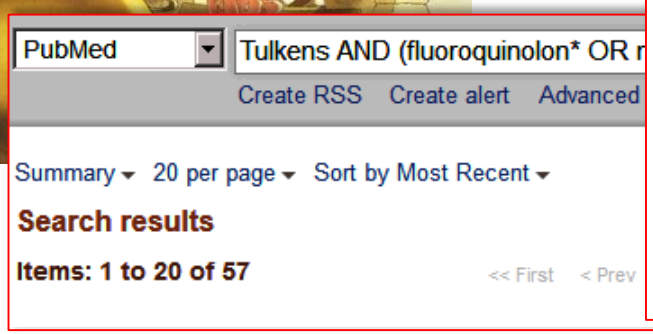
Drugs R D 2012; 12 (2): 71-100
1179-6901/12/0002-0071

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



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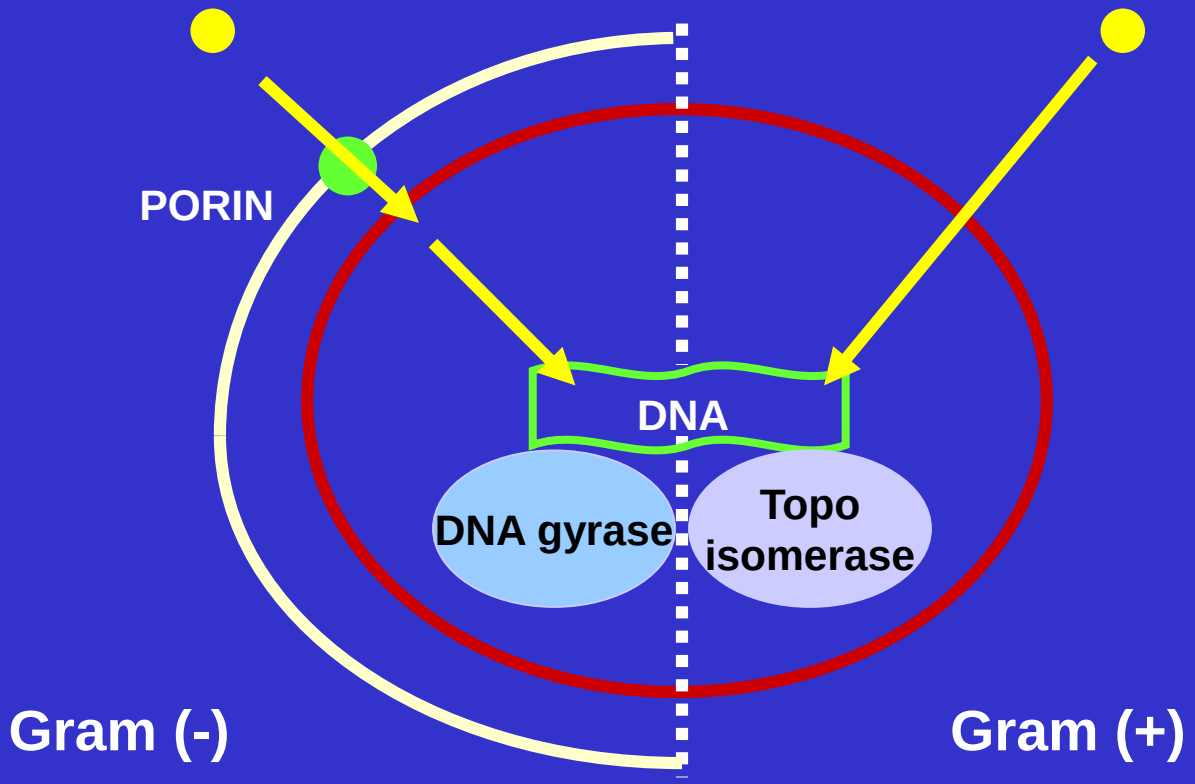
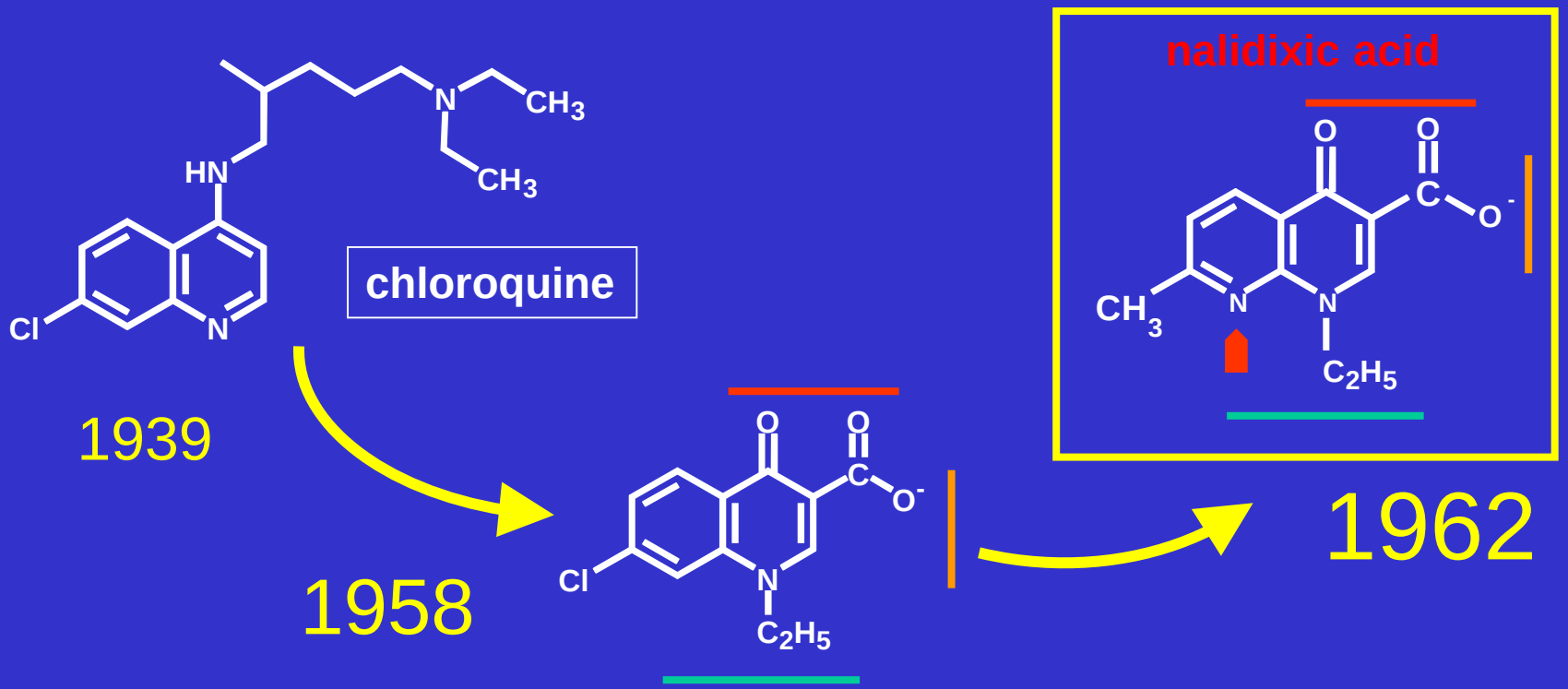
Mechanism of action of fluoroquinolones: the basics...



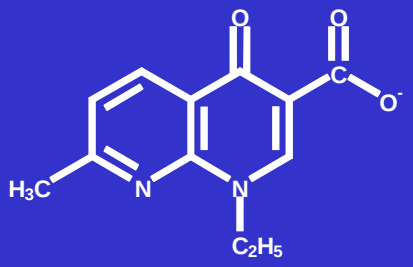
A bit of history: from chloroquine to nalidixic acid...



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

From nalidixic acid to the 1st fluoroquinolone

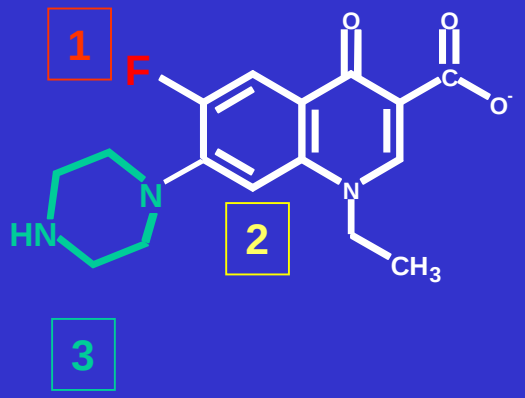
nalidixic acid



3 key modifications *...

1978

norfloxacin *



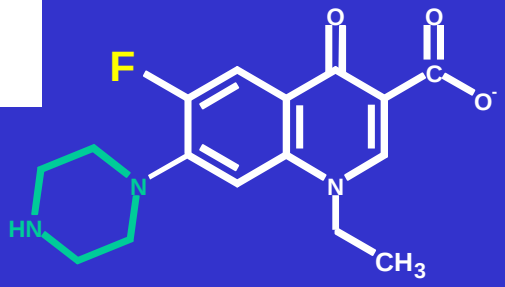
1. broader Gram(-) activity
2. less protein binding (50%)
3. longer half-life (3-4h)

* Belgian patent 863,429, 1978 to Kyorin

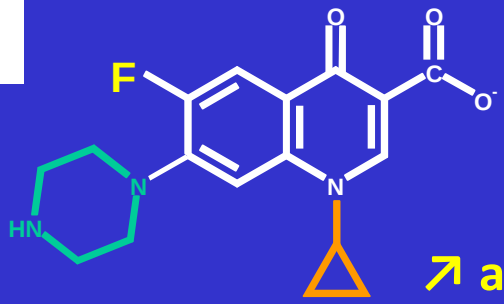
* 6-fluoro-7-pyrimidino-quinoleine

From norfloxacin to ciprofloxacin and ofloxacin

norfloxacin

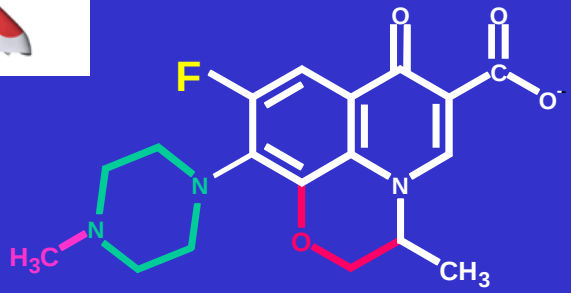


Ciprofloxacin *



↗ activity
(cyclopropyl)

Ofloxacin **



↗ half-life
(methyl)

check this…
(morpholine)

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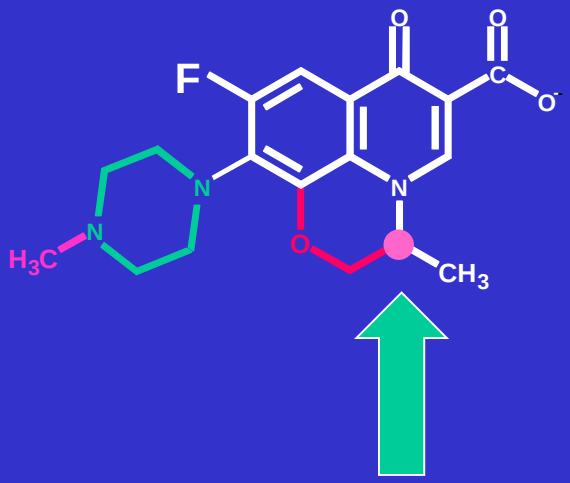
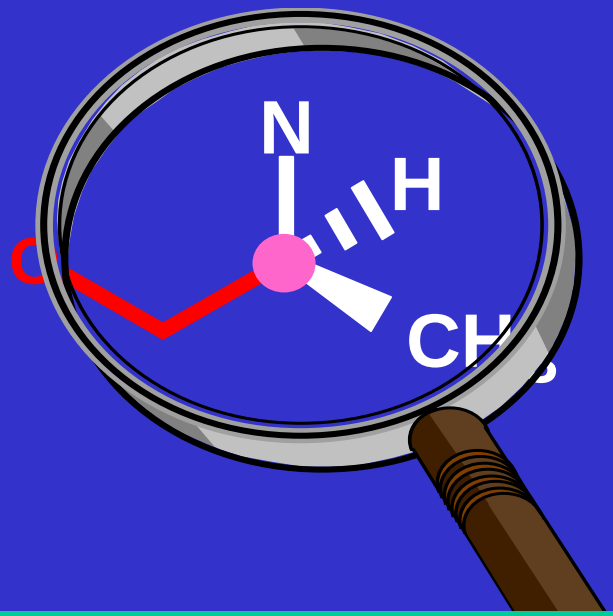
* Ger. pat. 3,142,854 to Bayer AG, 1983

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

Levofloxacin is the active isomer of ofloxacin

Ofloxacin is a racemic mixture 50/50





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

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

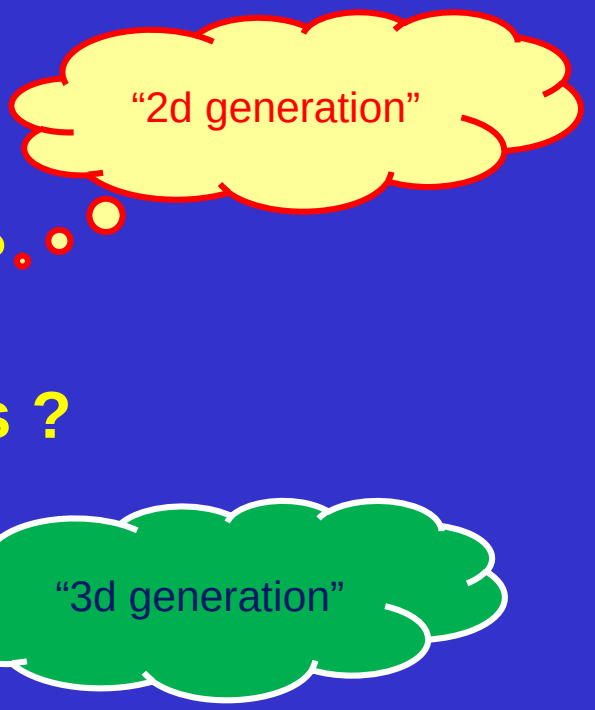
* Eur. pat. 206,283 to Daiichi, 1987

How to improve the chemotherapeutic usefulness of the "first generation" fluoroquinolones

1. Maintain broad Gram(-) activity ?

2. Further Improve Gram(+) activity ?

3. Acquire activity against anaerobes ?

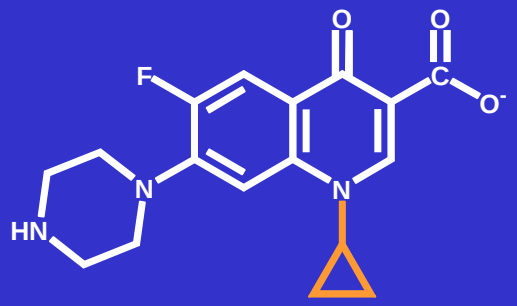


Activity against *S. pneumoniae*

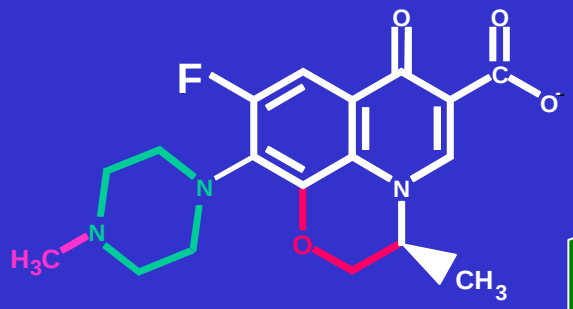
I

II

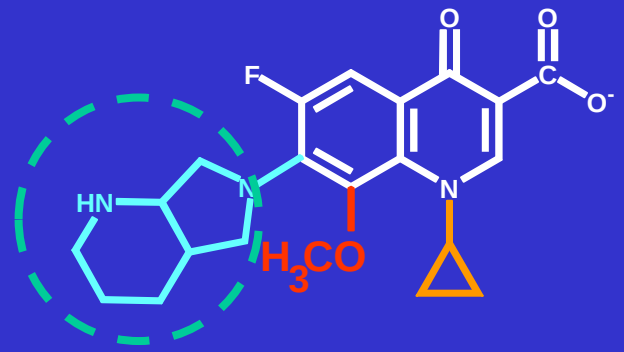
III / IV



ciprofloxacin
MIC = 0.5 - 2



levofloxacin
MIC = 0.5 -2



moxifloxacin
MIC = 0.01 - 0.5

Hint #1 :
lower MICs = a more potent antibiotic !

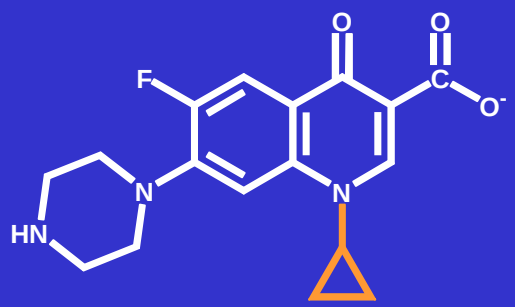
Hint #2 :
Levofloxacin has the same MICs than ciprofloxacin and > than moxifloxacin !

Activity against *B. fragilis (anaerobe)*

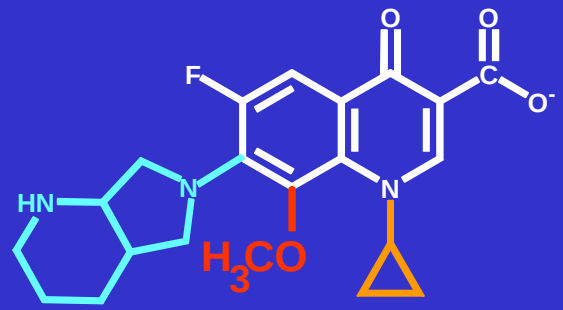
I

II

III / IV



ciprofloxacin
MIC = 2-128

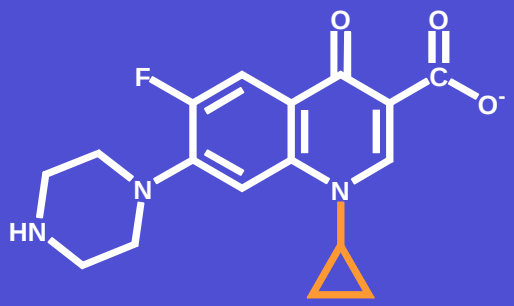


moxifloxacin
MIC= 0.125-8

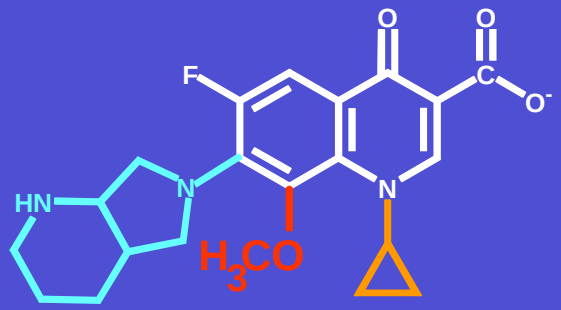
At this point …

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

anaerobes



ciprofloxacin



moxifloxacin

levofloxacin

This is by design !

Killing abilities of fluoroquinolones: Are they all equal against susceptible strains ?

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

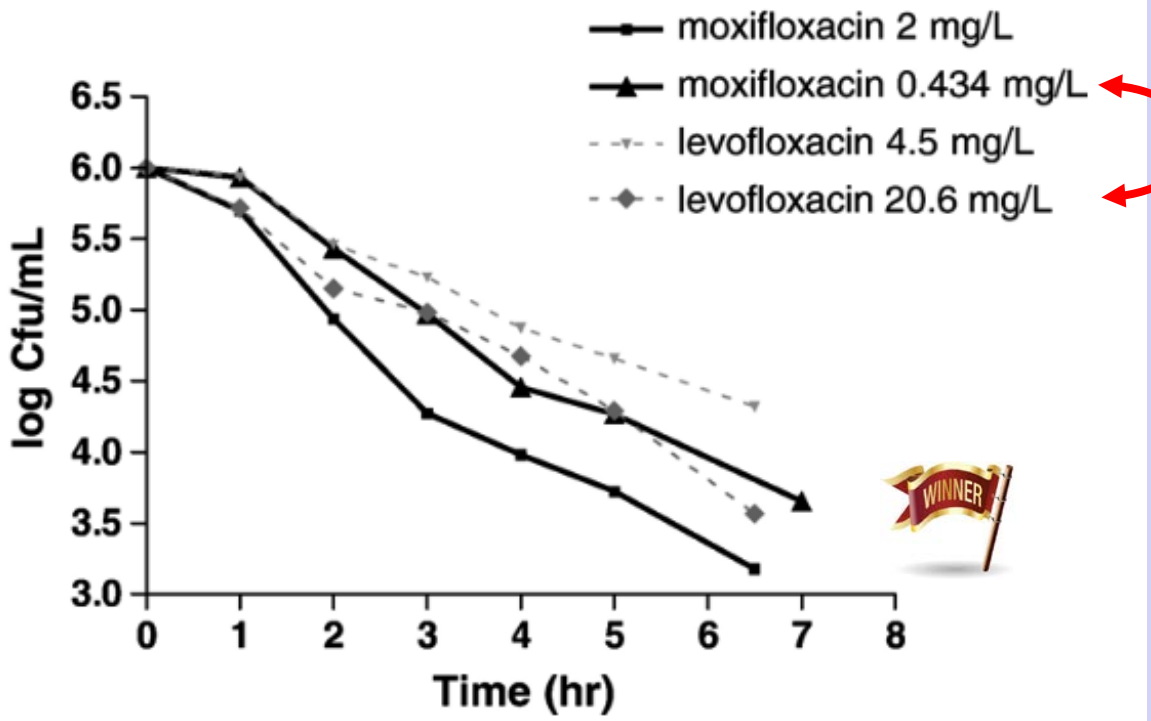


Fig. 1. Time kill curves of moxifloxacin versus levofloxacin against *S. pneumoniae* 7362 (average of 2 models).

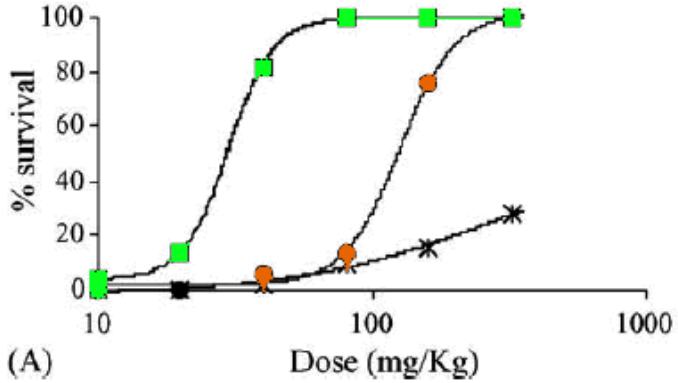
Same effect but at different concentrations…

Schafer *et al*. Diag Microb Infect Dis 2008; 60:155–161

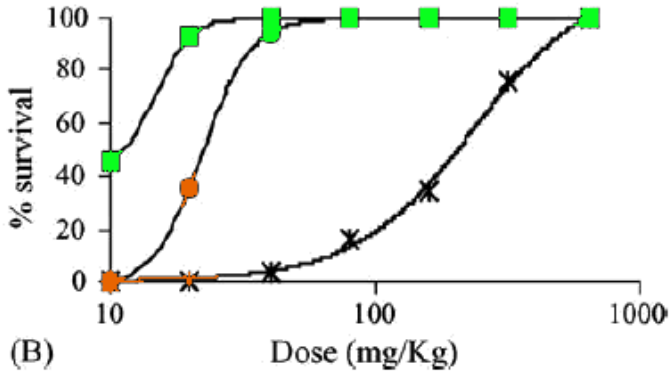
Killing abilities of fluoroquinolones: Are they all equal against less susceptible strains ?

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

Levofloxacin (LVX)



Moxifloxacin (MXF)



strain	MIC (mg/L)	
	MXF	LVX
AR33118 (■)	0.12	1
FL2812 (●)	0.25	2
FL5629 (✶)	4	32

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

Huelves et al. Int J Antimicrob Agents 2006; 27:294–299

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Let us begin with the concept of MPC…

1. Why does an MIC leave resistant subpopulations unaffected ?

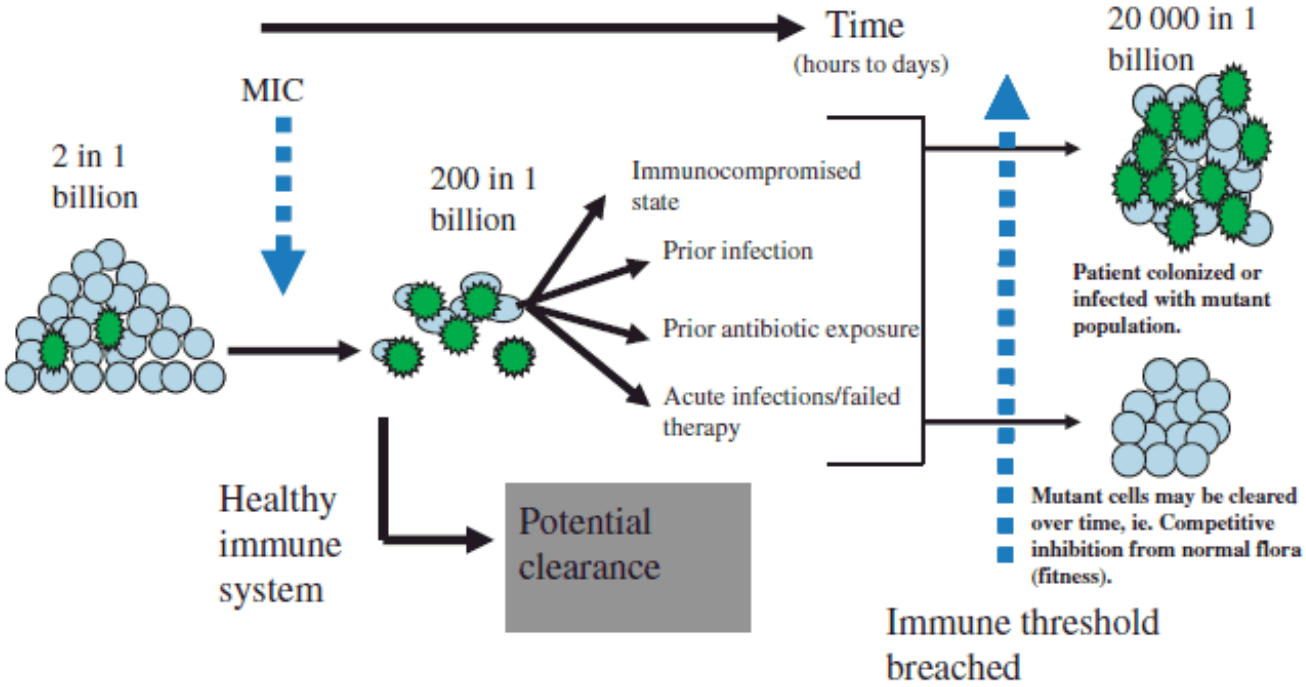


Figure 2. Schematic representation of resistance selection based on MIC drug conentrations.

Blondeau JM. Vet Dermatol 2009;20:383-96 - PMID 20178475

Let us begin with the concept of MPC…

2. How do you find these resistant subpopulations ?

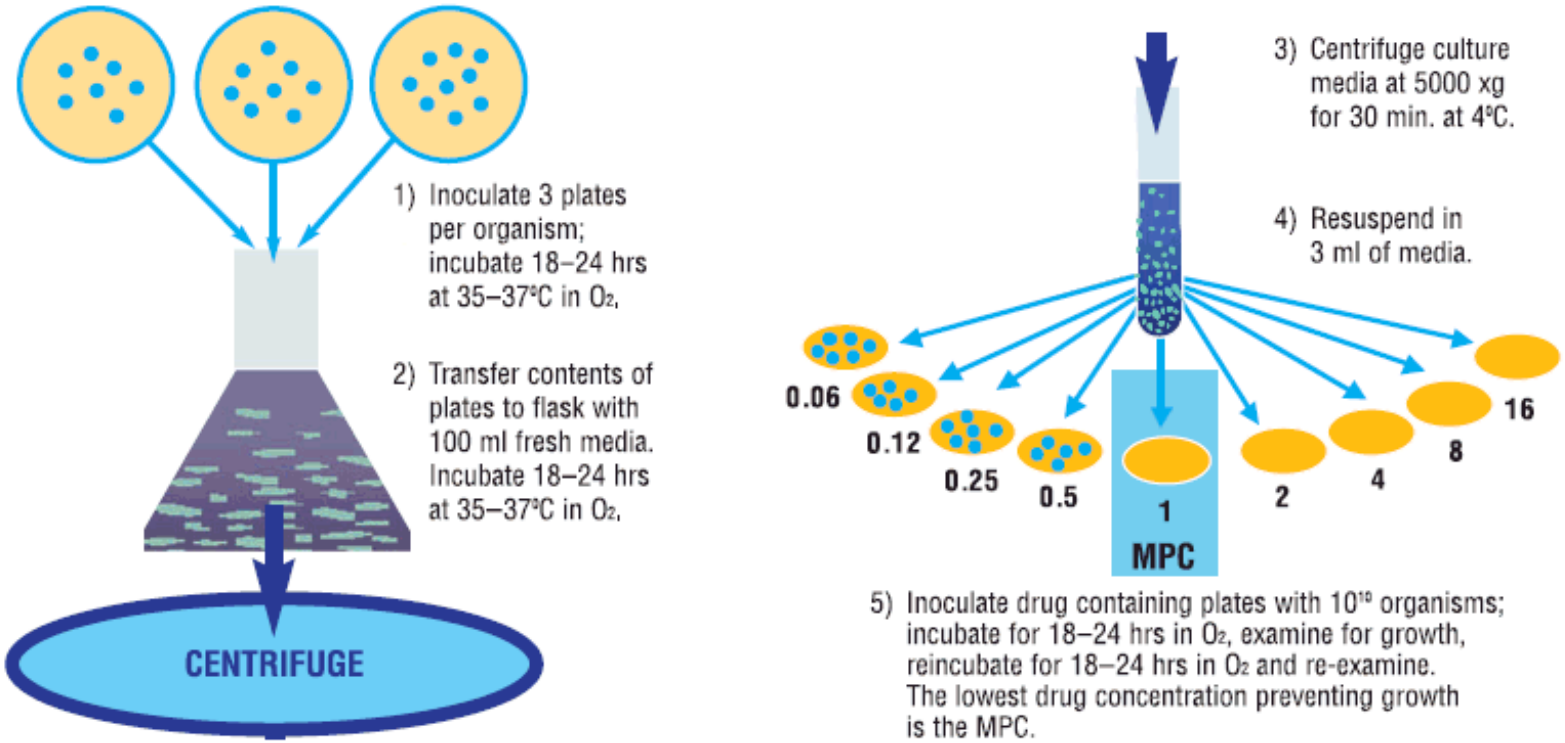
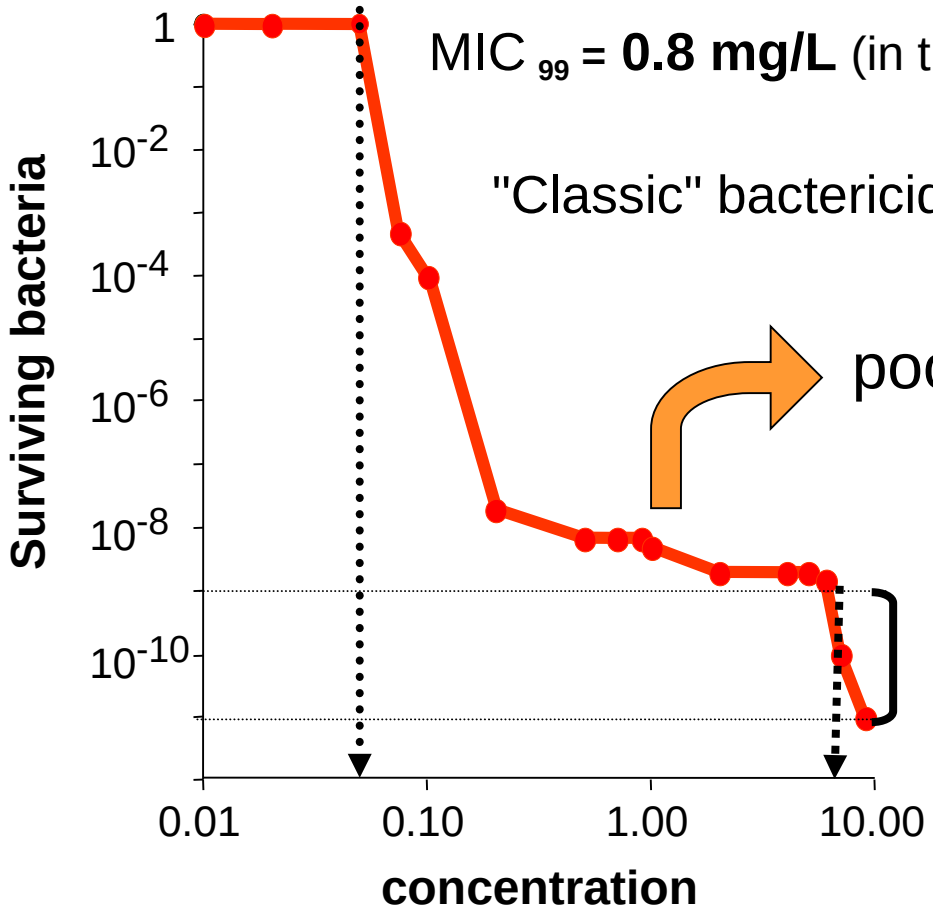


Figure 1. Schematic method of MPC testing.

Blondeau JM. Vet Dermatol 2009;20:383-96 - PMID 20178475

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



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

"Classic" bactericidal effect

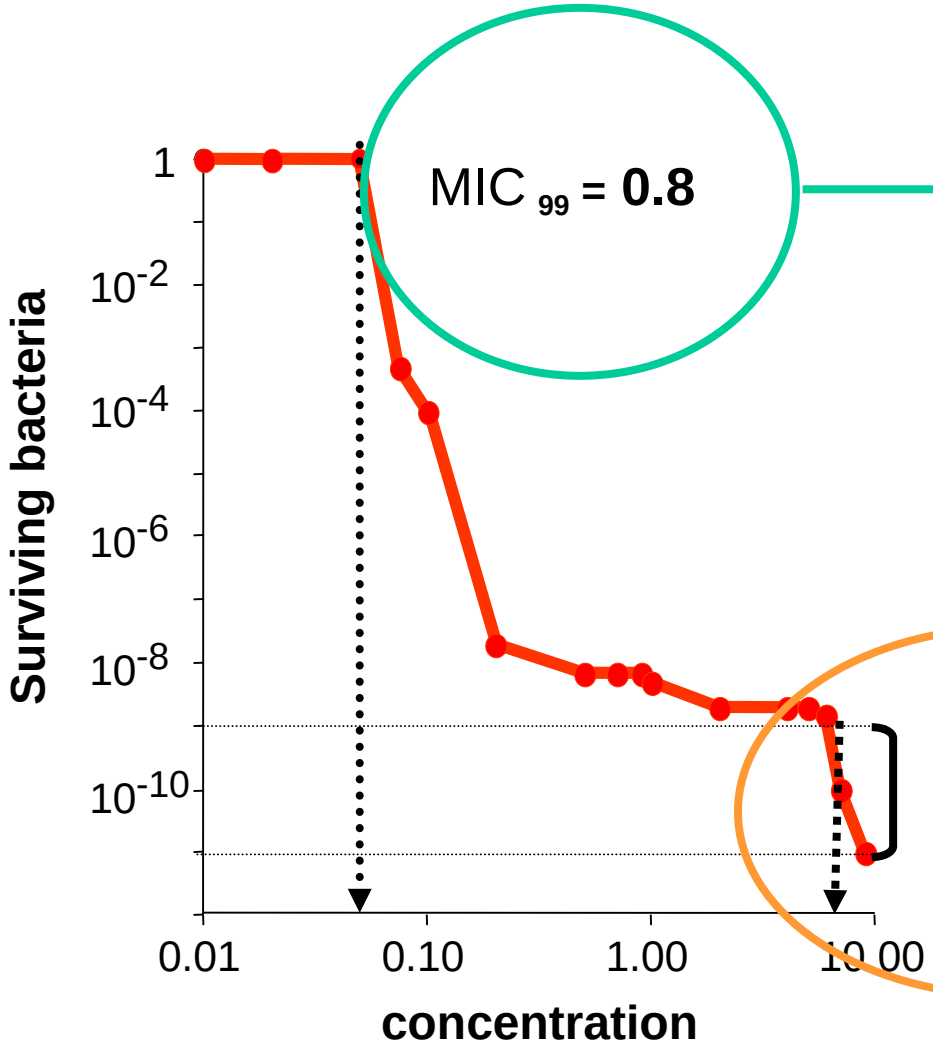
poorly sensitive organisms…

Elimination of resistant organisms

MPC_{10} = **9**

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

"Mutant Prevention Concentration …"



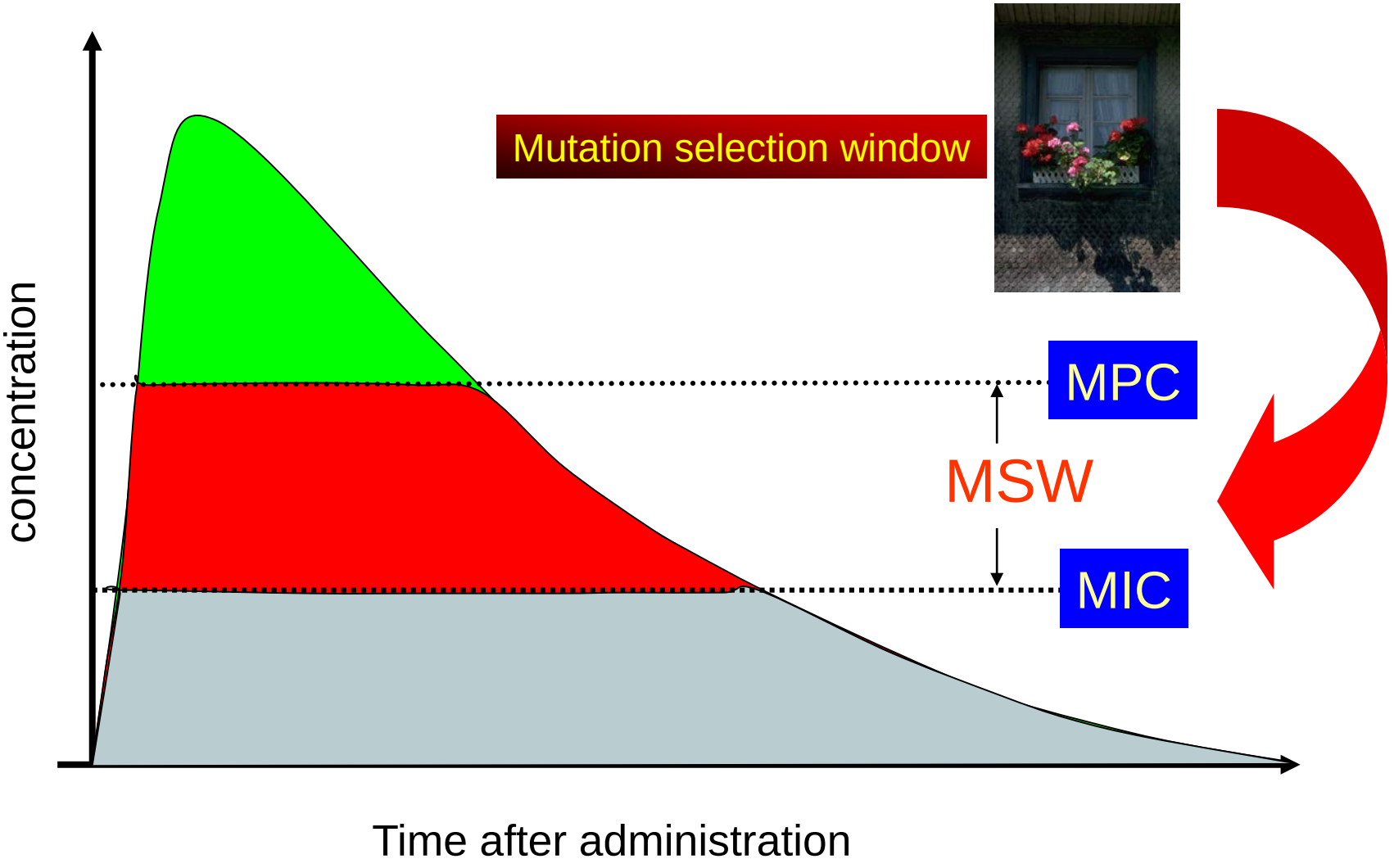
Concentration that inhibits the majority of the organisms

MPC 10 = 9

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

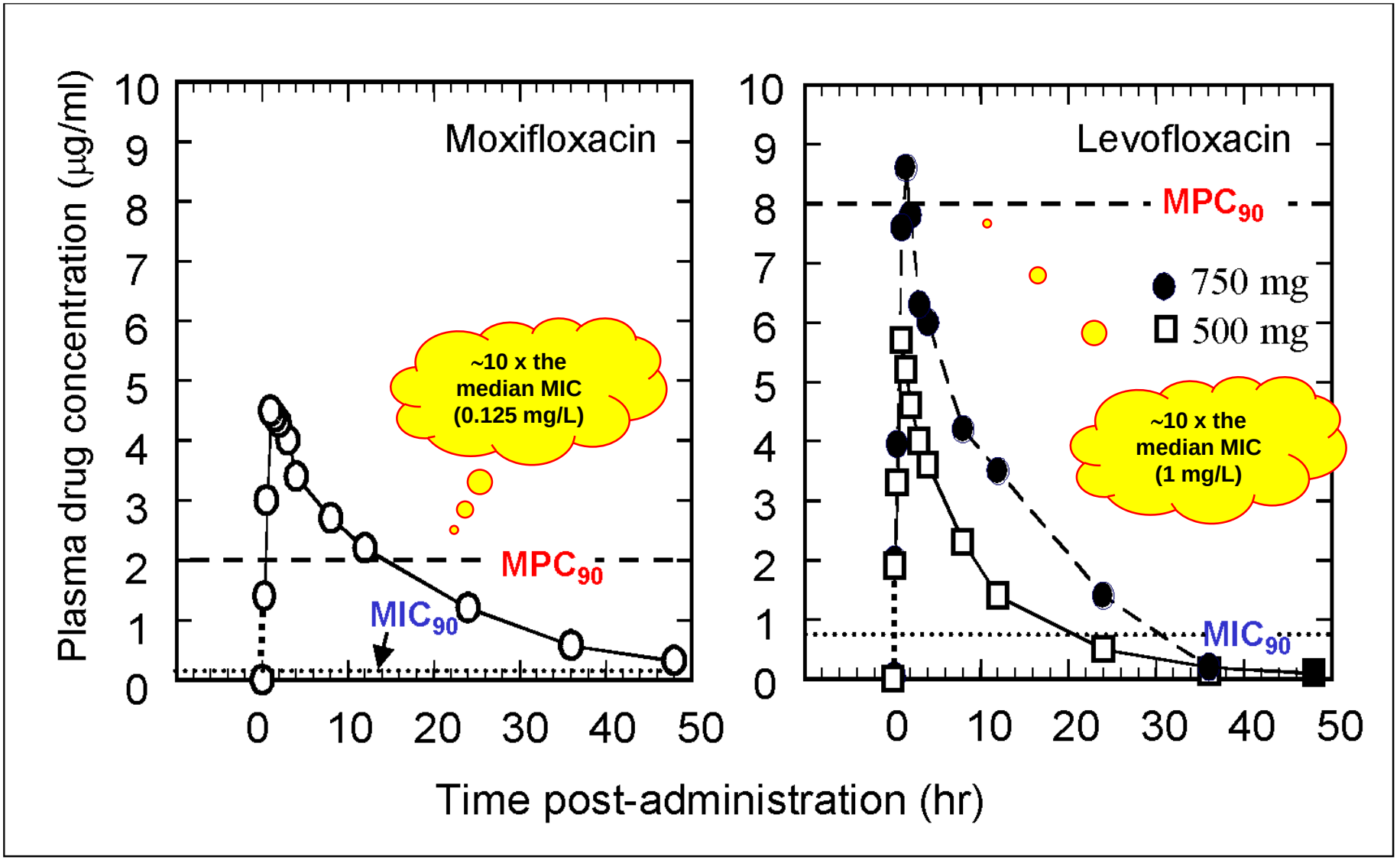
Dong et al; AAC 43:1756-1758

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

MPC: moxifloxacin *vs* levofloxacin



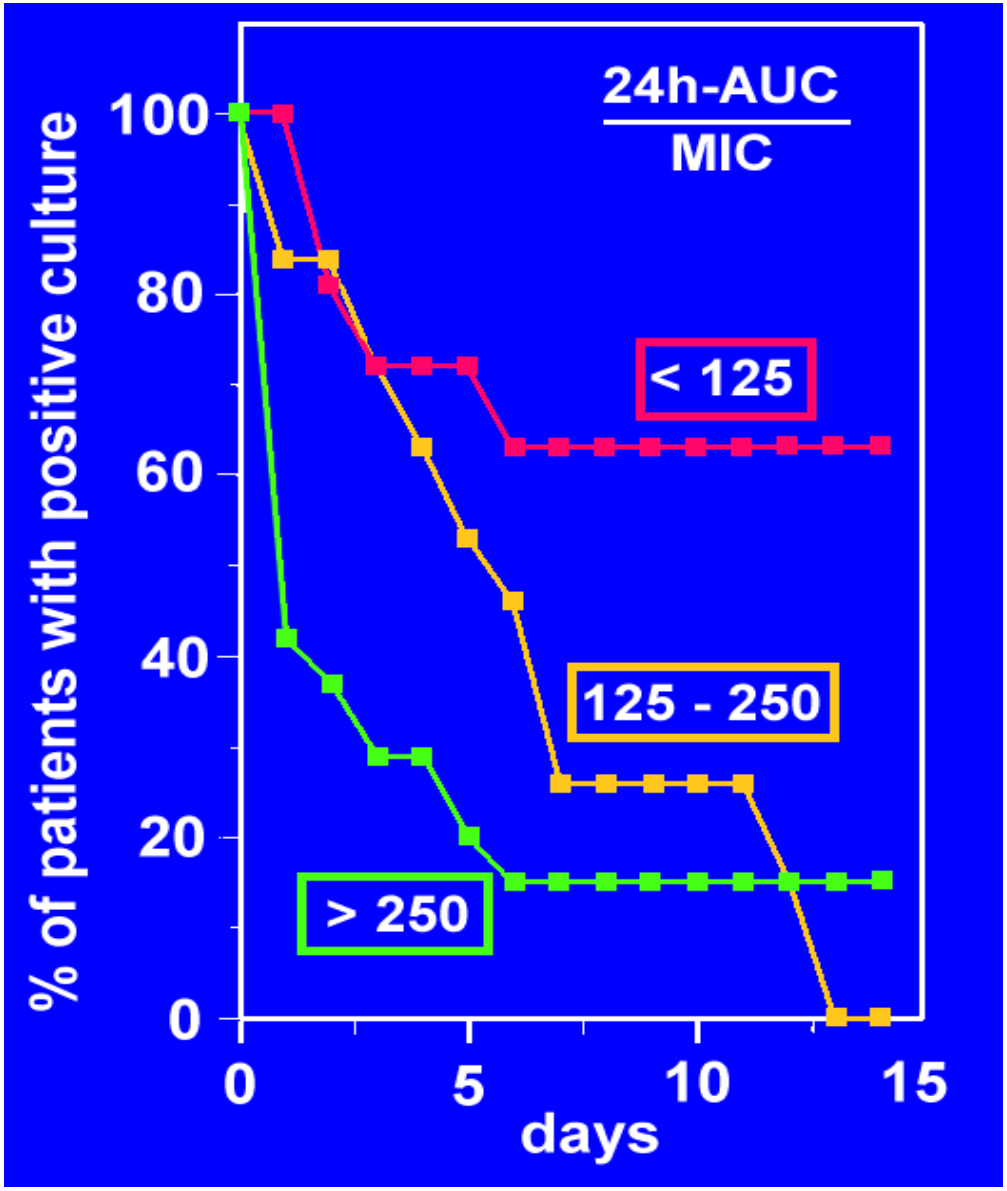
So, what should you do with a fluoroquinolone to avoid emergence of resistance

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

➔ peak / MIC > 10

Let us now move to the AUC / MIC as predictor of activity

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

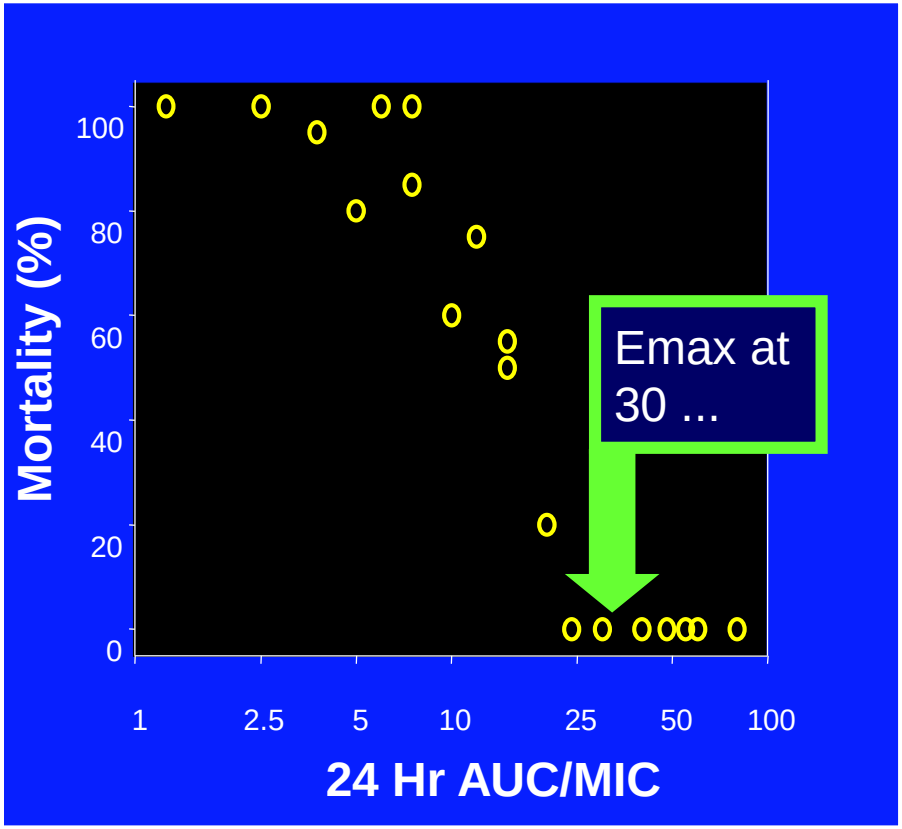


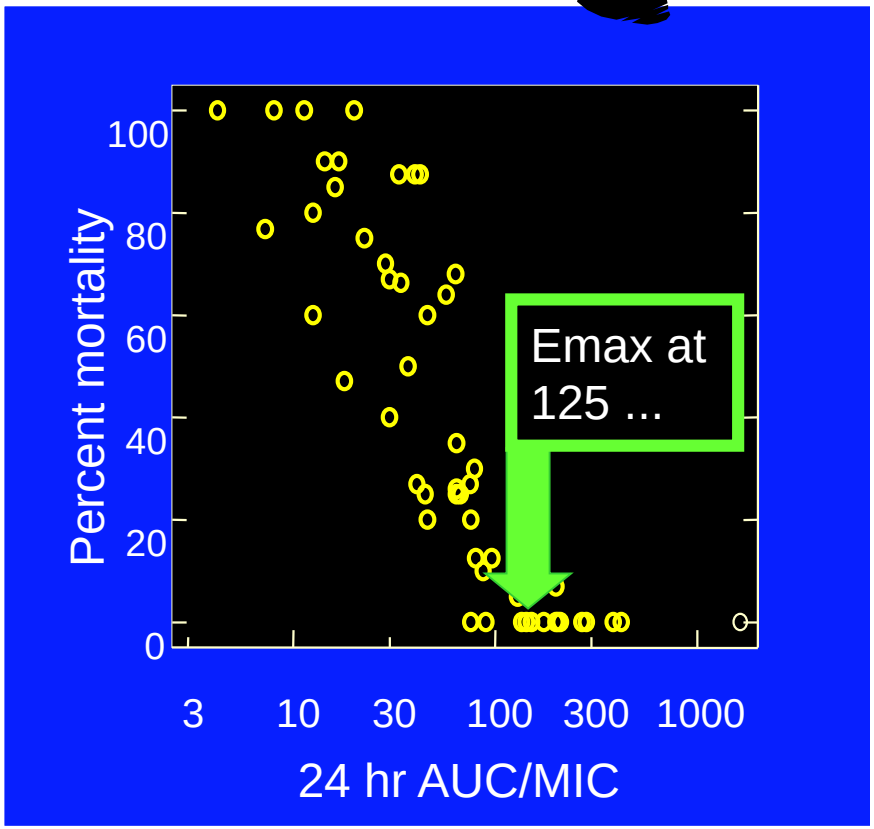
Forrest et al., AAC, 1993

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

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

Journal of Antimicrobial Chemotherapy (2006) **58**, 960–965
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Advance Access publication 26 August 2006

JAC

Pharmacodynami
Streptococcus pne
pneumoniae and *E*
concentrations after

[1]*Infectious Diseases Resea*
S-20502 Malmö, Swed
Section of Infectious Disea

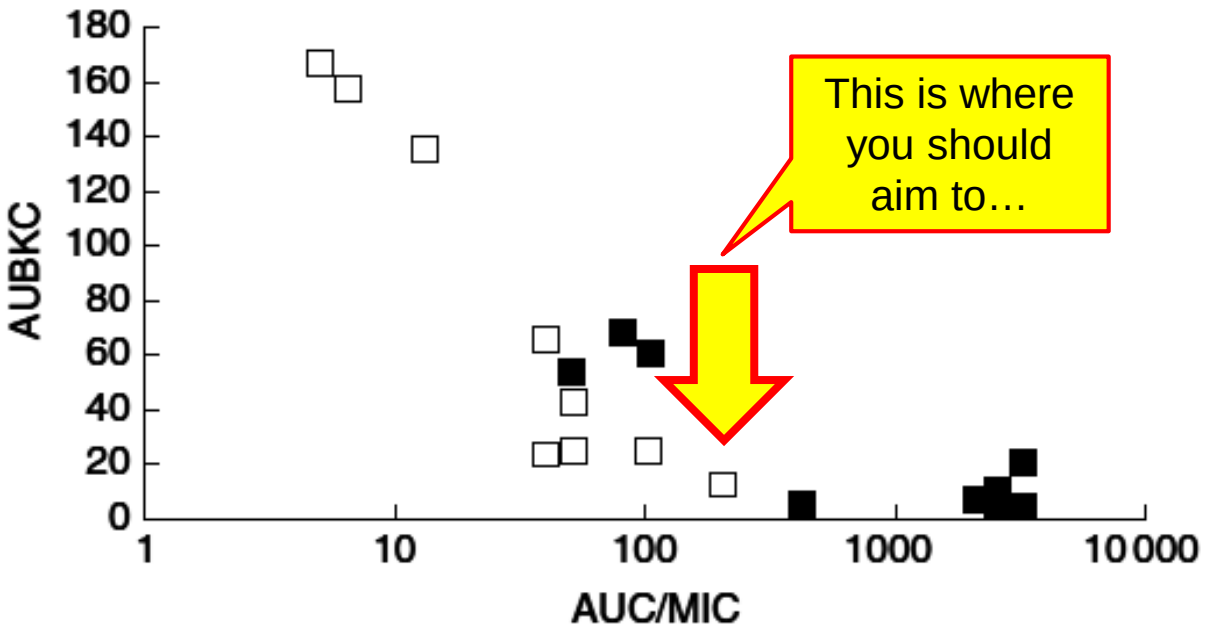


Figure 5.
relationship between AUBKC and AUC/MIC for *S. pneumoniae* (open squares) and Gram-negative strains (filled squares).

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

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

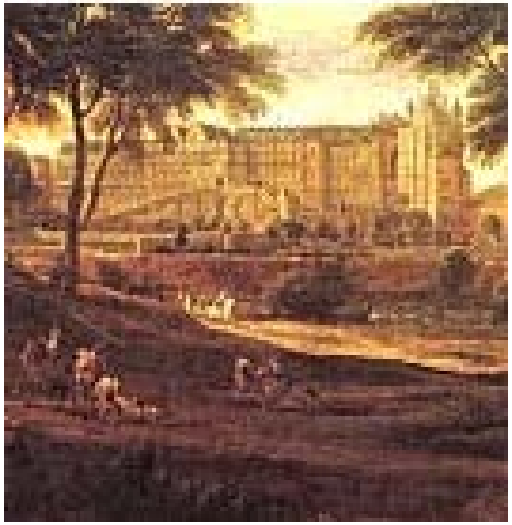
So, what should you do with a fluoroquinolone to avoid emergence of resistance and be optimal for activity …

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

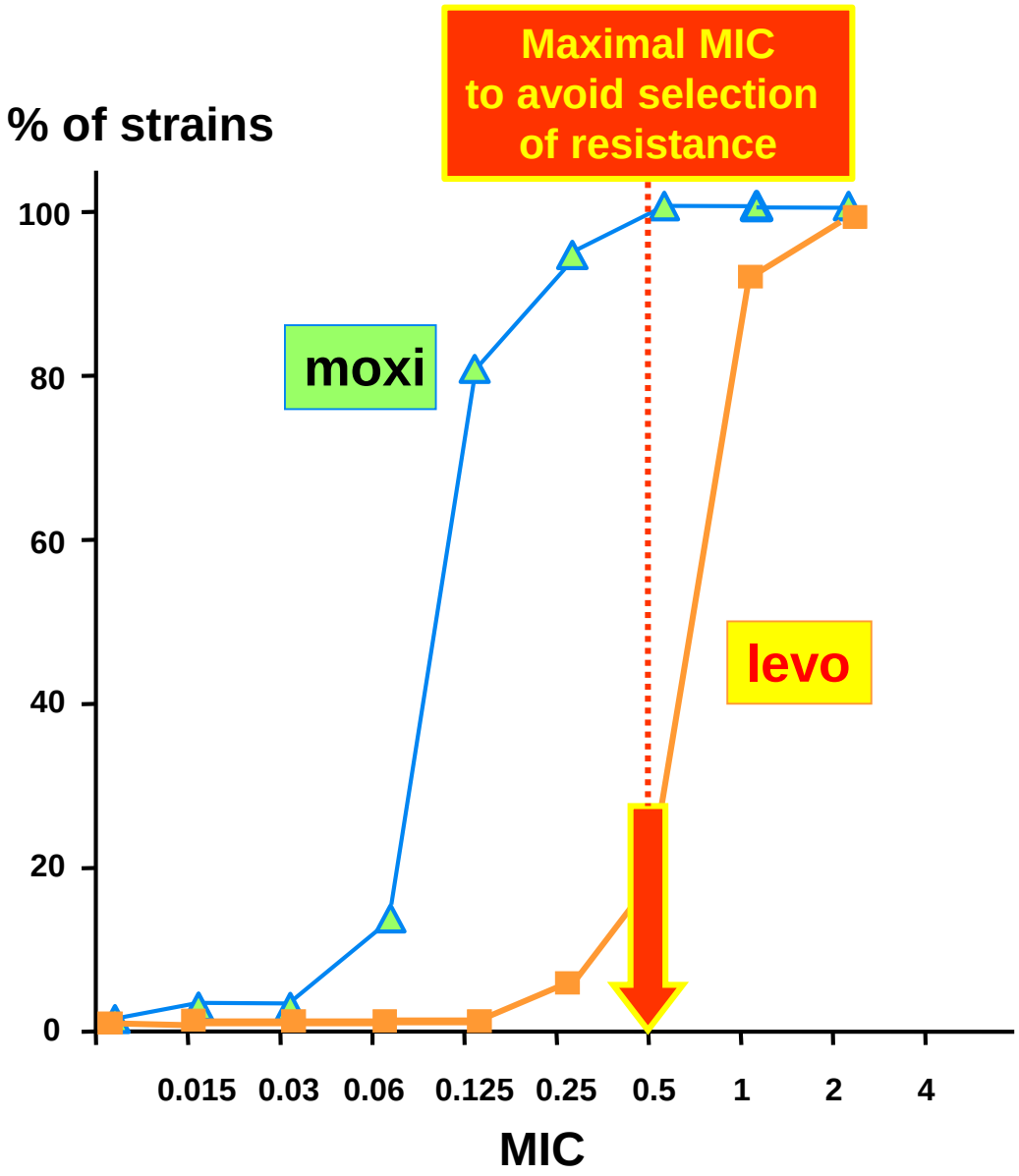
➔ peak / MIC > 10

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

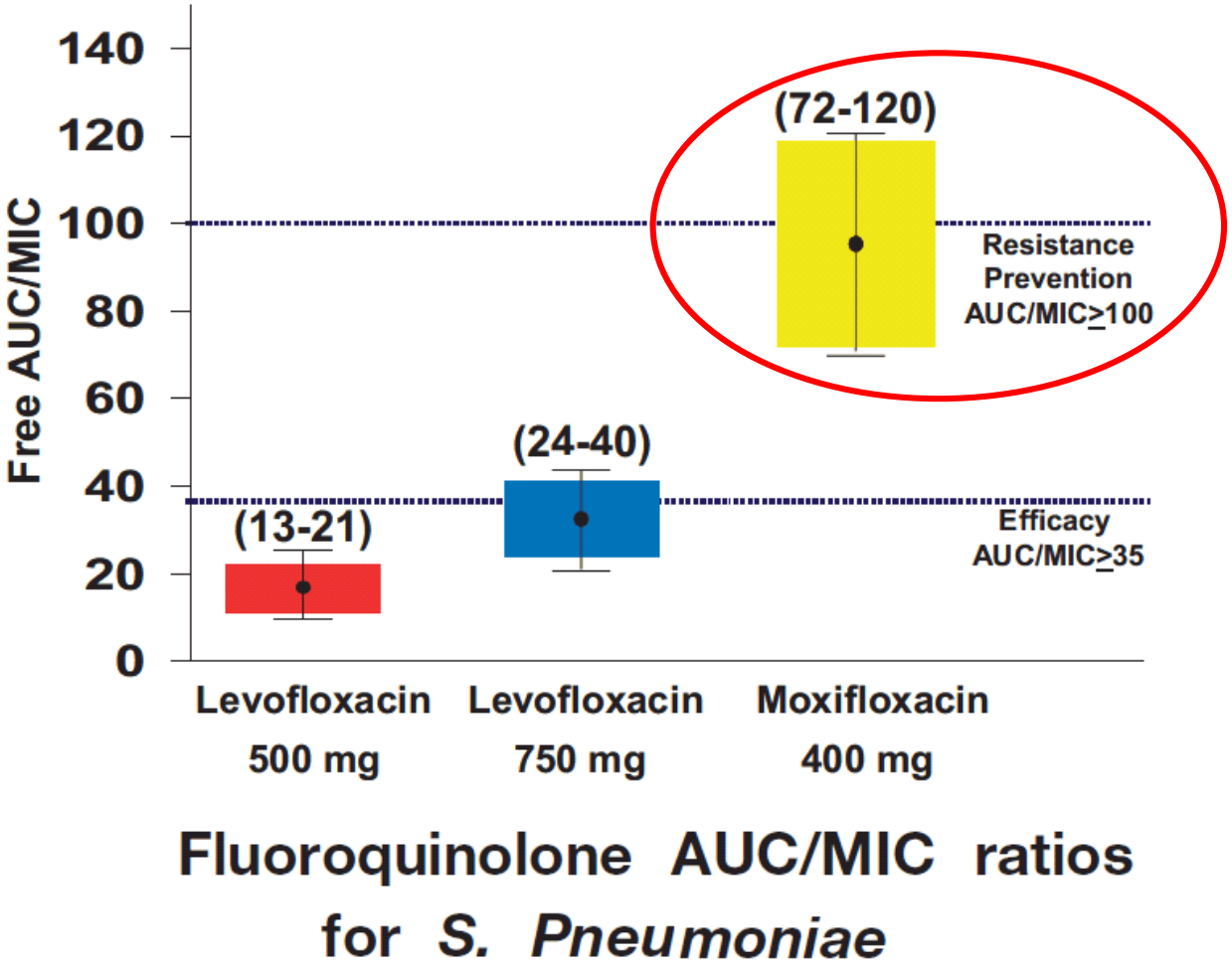
Levofloxacin 500 mg 1X / day
- AUC [(mg/l)xh] 47
- peak [mg/l] 5
- ➔ MIC_{max} ~ 0.5

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)

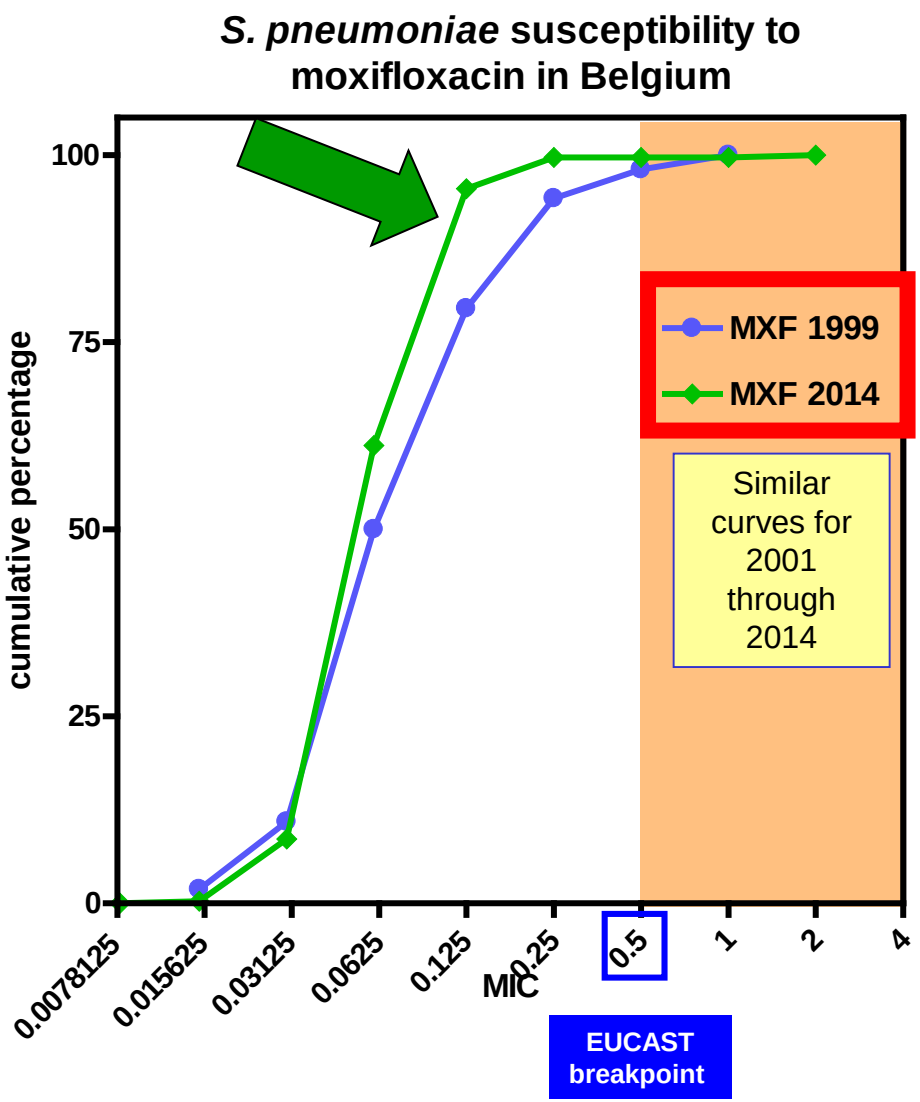
What differentiates fluoroquinolones ?

Results with *S. pneumoniae*



Would this cause less emergence of resistance ?

Has resistance to moxifloxacin materialized: evidence for *S. pneumoniae* in Belgium from 1999 to 2014 *



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

From data of a national collection

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

- Surveys from the Belgian Scientific Institute for Public Health for *S. pneumoniae* from community isolates (n=156 in 1999 and 312 in 2014)
- Data available yearly for 1999 through 2014 at http://www.iph.fgov.be

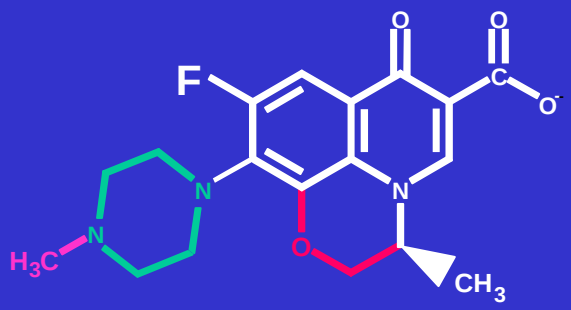
Vanhoof *et al*. 19th ECCMID, Helsinki, 2009

Ceyssens *et al*. 35th RICAI, Paris, 2015

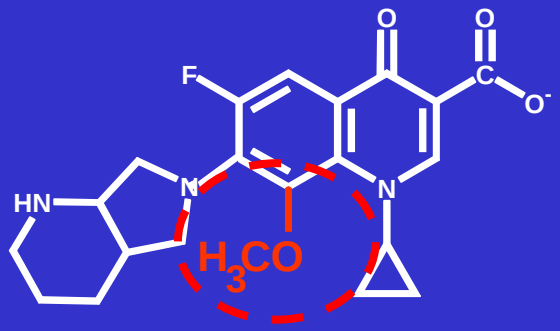
Ceyssens *et al.* PLoS One 2016;11:e0154816 (17 pages) - PMID 27227336

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

Head to head comparison…

Clinical Infectious Diseases 2006;42:73-81.

MAJOR ARTICLE

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

Antonio Anzueto,[1,2] Michael S. Niederman,[3] James Pearle,[4] Marcos I. Restrepo,[1,2] Albrecht Heyder,[5] and Shurjeel H. Choudhri,[6] for the Community-Acquired Pneumonia Recovery in the Elderly Study Group[a]

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

Head to head comparison…

Clinical Infectious Diseases 2006;42:73-81.

MAJOR ARTICLE

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

Antonio Anzueto,[1,2] Mic
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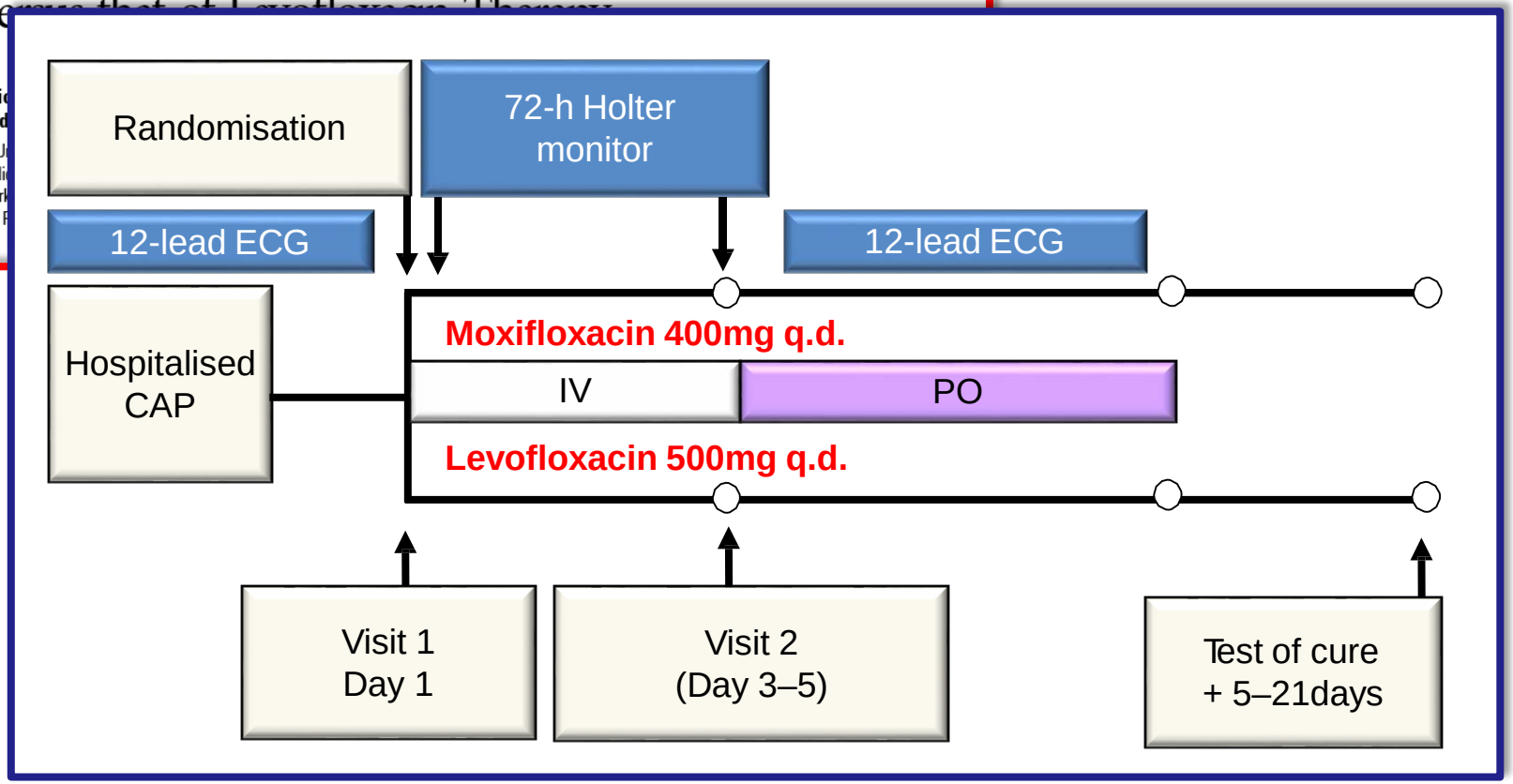
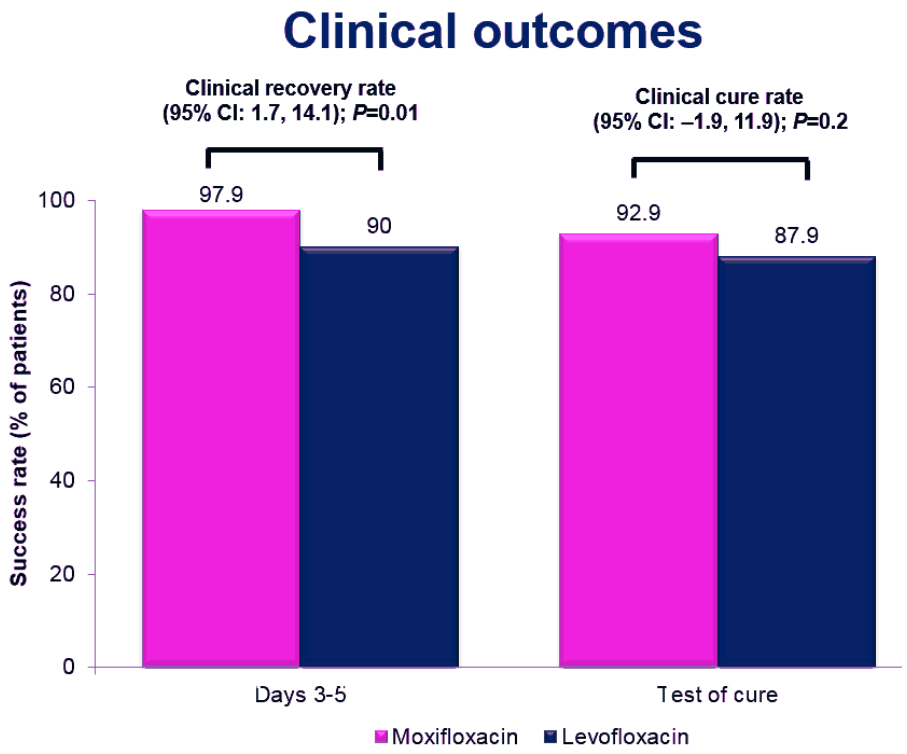
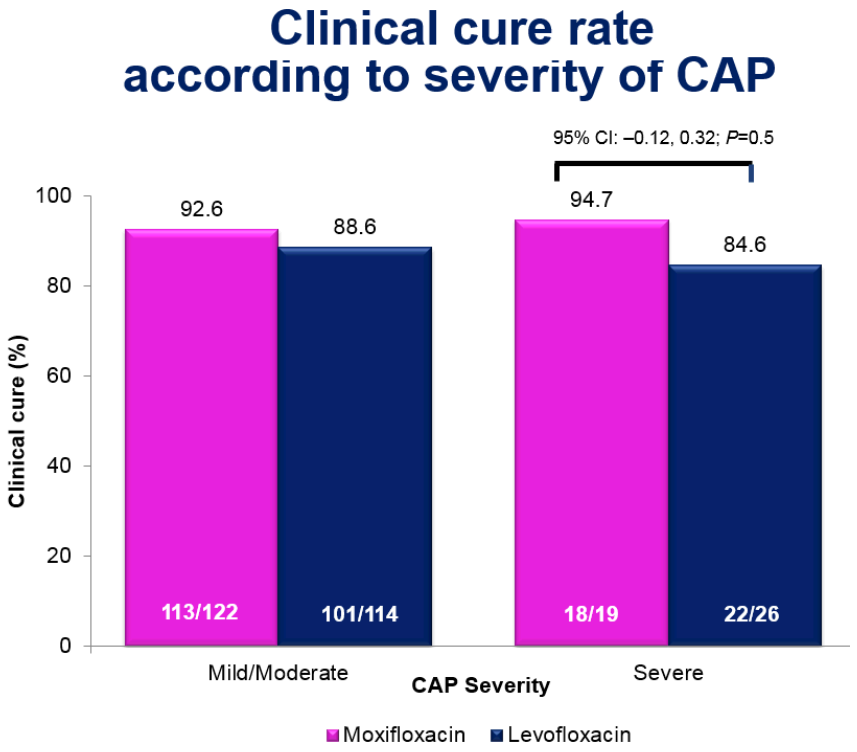
[1]Department of Medicine, U
Center, Department of Medi
Hospital, Mineola, New York
North Carolina; and [6]Bayer P



and results in a snapshot…





Current official recommendations for pneumonia …

- Levofloxacin: 750 mg q24h [1] or 2 x 500 mg/day [2]
- Moxifloxacin: 400 mg q24h [3] …

these differences in dosing are translating the differences in PK.PD properties …

1 US Prescription Information (Levaquin®) updated February 2017
http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/LEVAQUIN-pi.pdf (last accessed: 14 Nov 2017)

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

3 US and European Prescription information for moxifloxacin
US: https://www.merck.com/product/usa/pi_circulars/a/avelox/avelox_pi.pdf (updated: July 2016; last accessed: 14 Nov 2016)
EU (in English): http://www.medicines.org.uk/emc/medicine/11841/SPC/Avelox+400+mg+film-coated+tablets (revised: 31 Aug 2017; last accessed: 14 Nov 2017)

The programme…

- A very short view of Belgium and of where I work…
- Differentiating fluoroquinolones in their origin and intrinsic nature
- Differentiating fluoroquinolones in PK/PD and the concept of MPC (prevention of resistance)
- **How would moxifloxacin fit into an antibiotic stewardship program**
- Questions, objections, suggestions …

A reasonable equilibrium for moxifloxacin ?

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

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

All antimicrobials have associated risks *

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

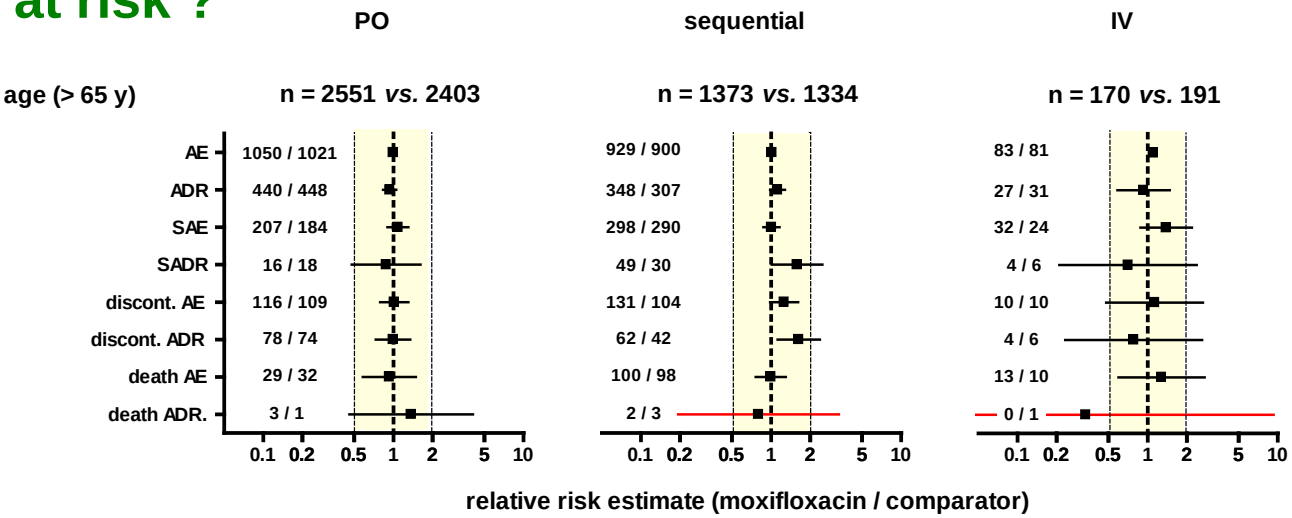
Paul M. Tulkens,[1] *Pierre Arvis*[2] and *Frank Kruesmann*[3]

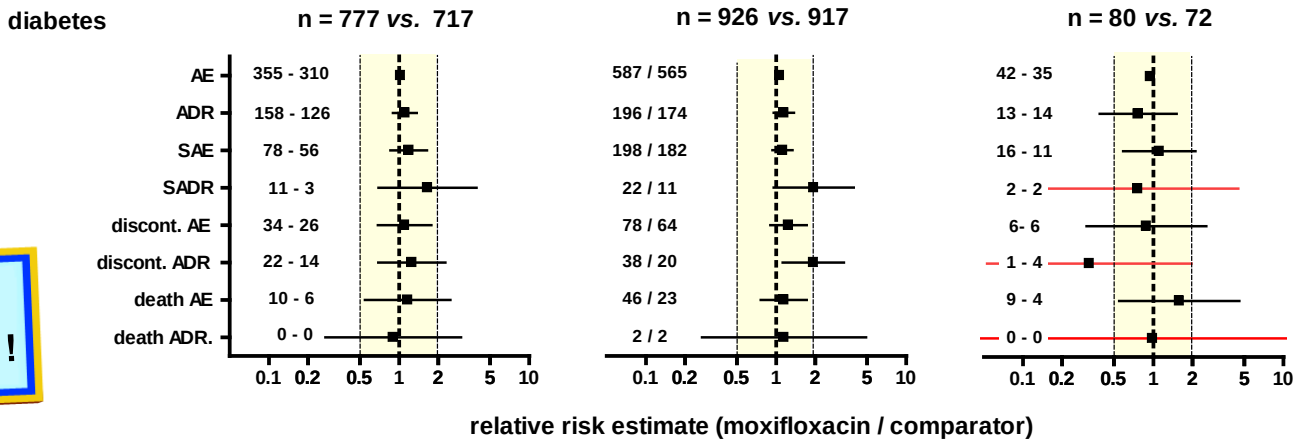
1 Pharmacologie cellulaire et moléculaire & Centre de Pharmacie clinique, Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium
2 Bayer Santé SAS, Loos, France
3 Bayer Pharma AG, Wuppertal, Germany

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)

Patients at risk ?

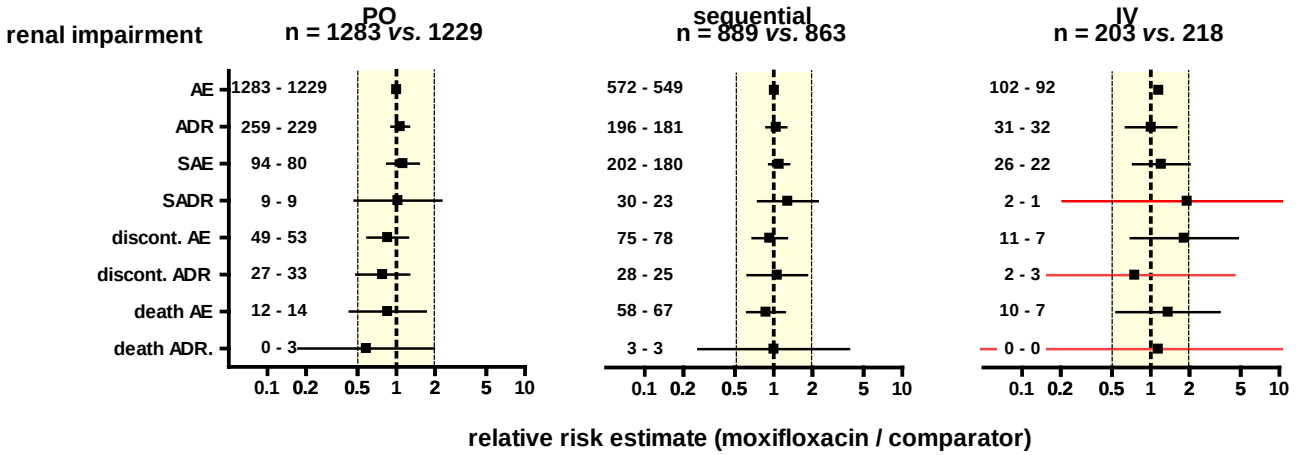


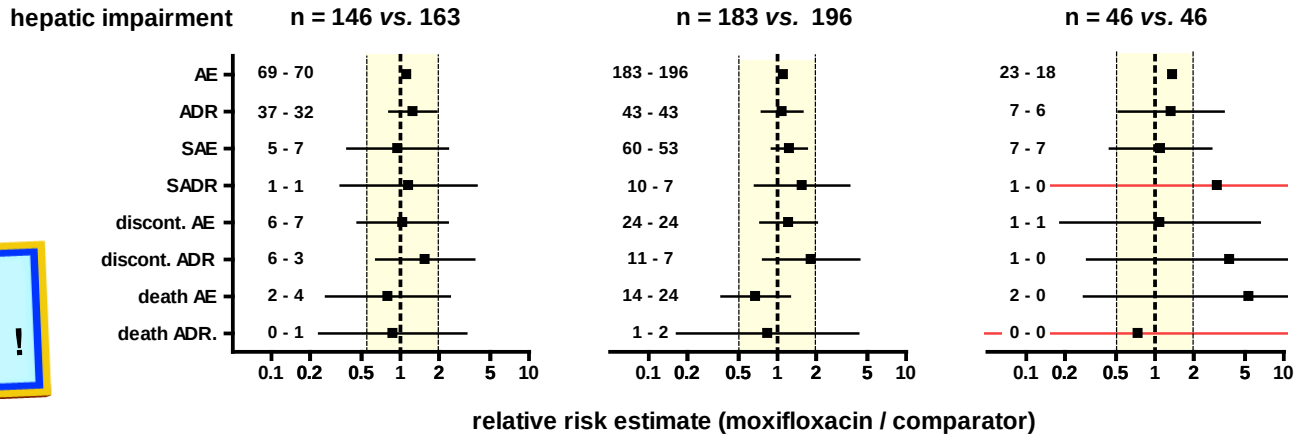


Tulkens et al., Drugs R D (2012) 12: 71-100

Side effects of moxifloxacin (clinical trials database)

Patients at risk ?

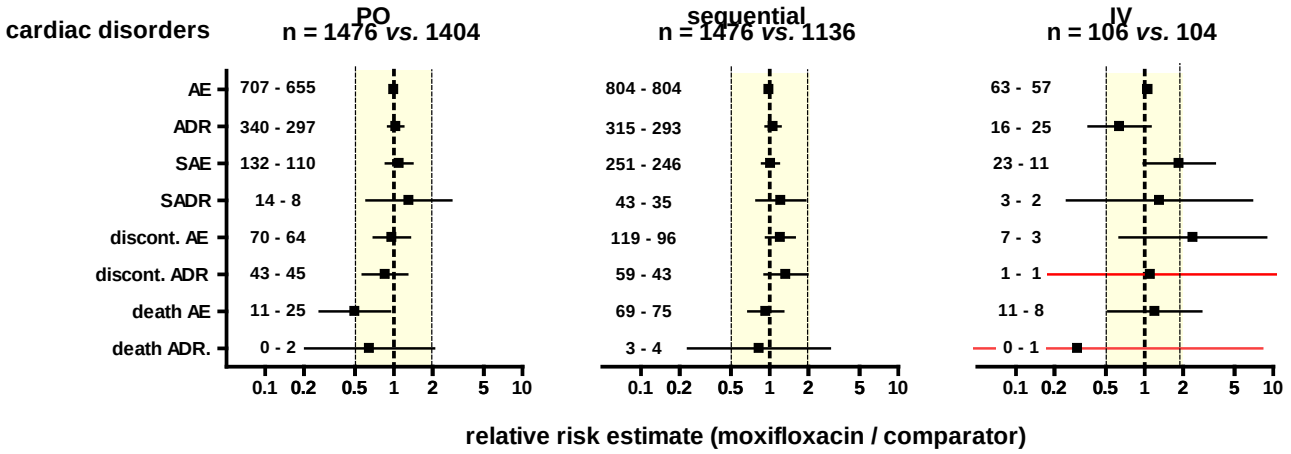


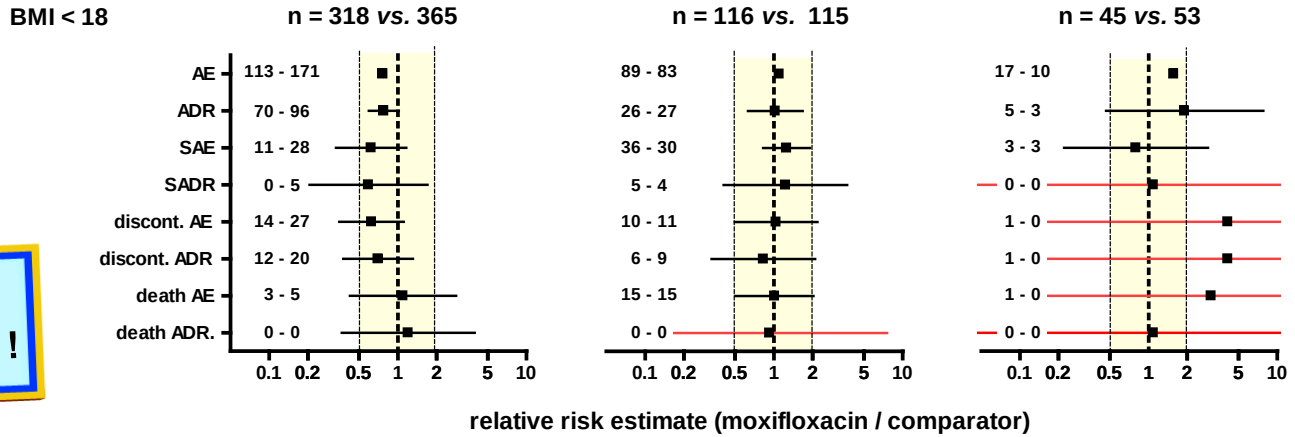


Tulkens et al., Drugs R D (2012) 12: 71-100

Side effects of moxifloxacin (clinical trials database)

Patients at risk ?





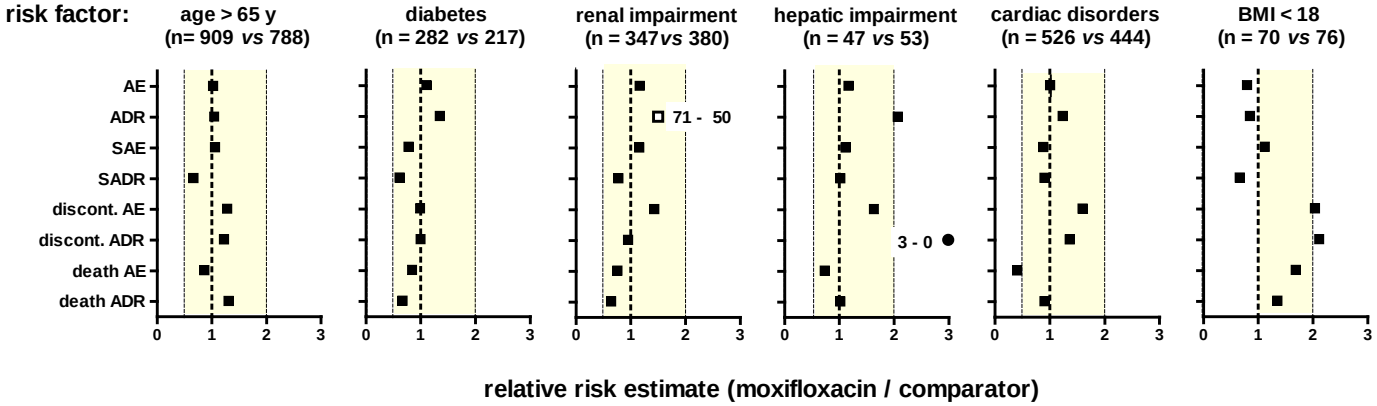
Tulkens et al., Drugs R D (2012) 12: 71-100

Side effects of moxifloxacin (clinical trials database)

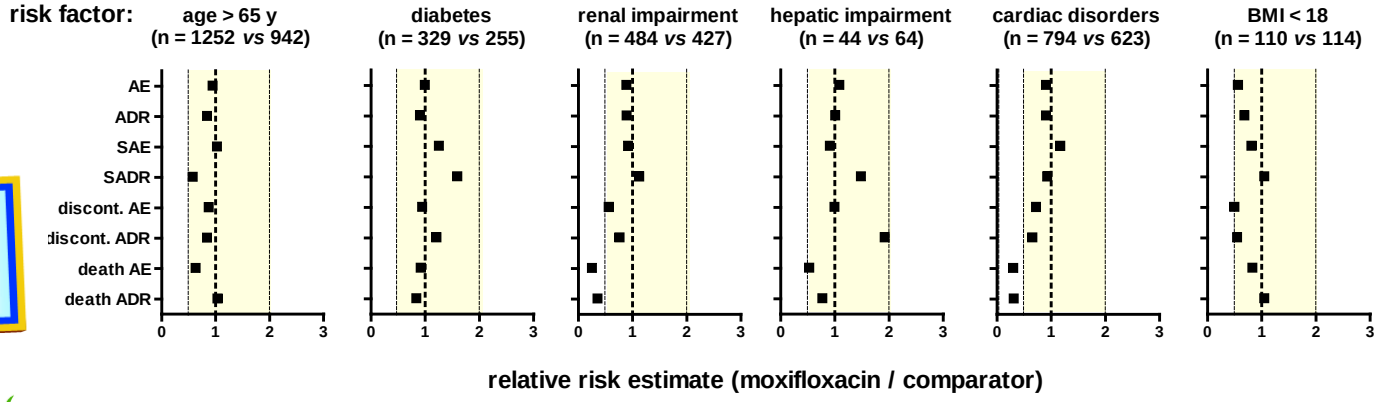
Comparison with other drugs ?

A. oral therapy

1. moxifloxacin *vs* β-lactams



2. moxifloxacin *vs* macrolides



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

Hepatotoxicity in large populations

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

EMA position

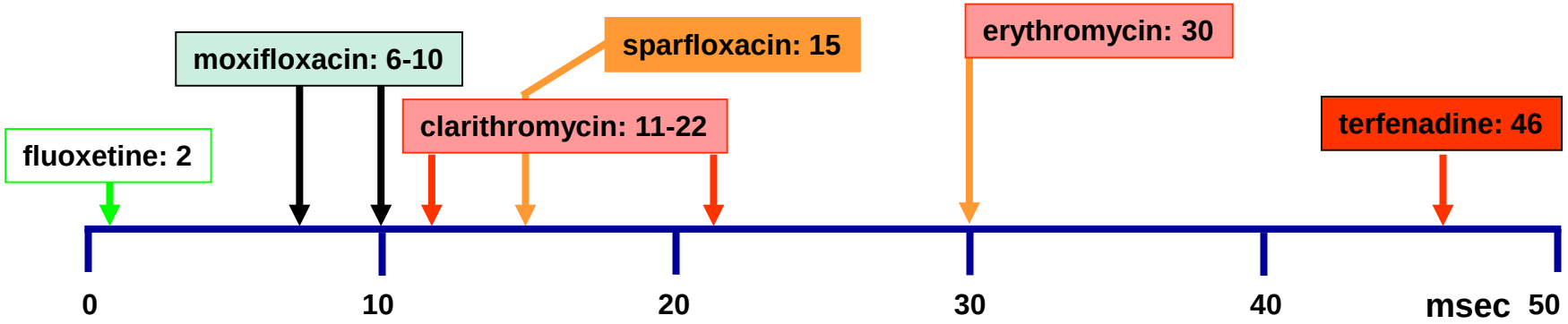
European Medicines Agency

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.

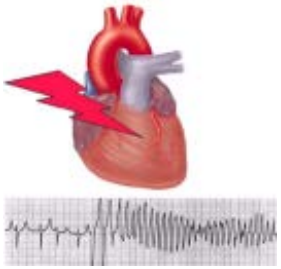
- Drugs [with] QT/QTc interval by around 5 ms or less do not appear to cause TdP.
- …data on drugs [with] QT/QTc interval by… 5 to < 20 ms are inconclusive, but some of these compounds have been associated with proarrhythmic risk.*

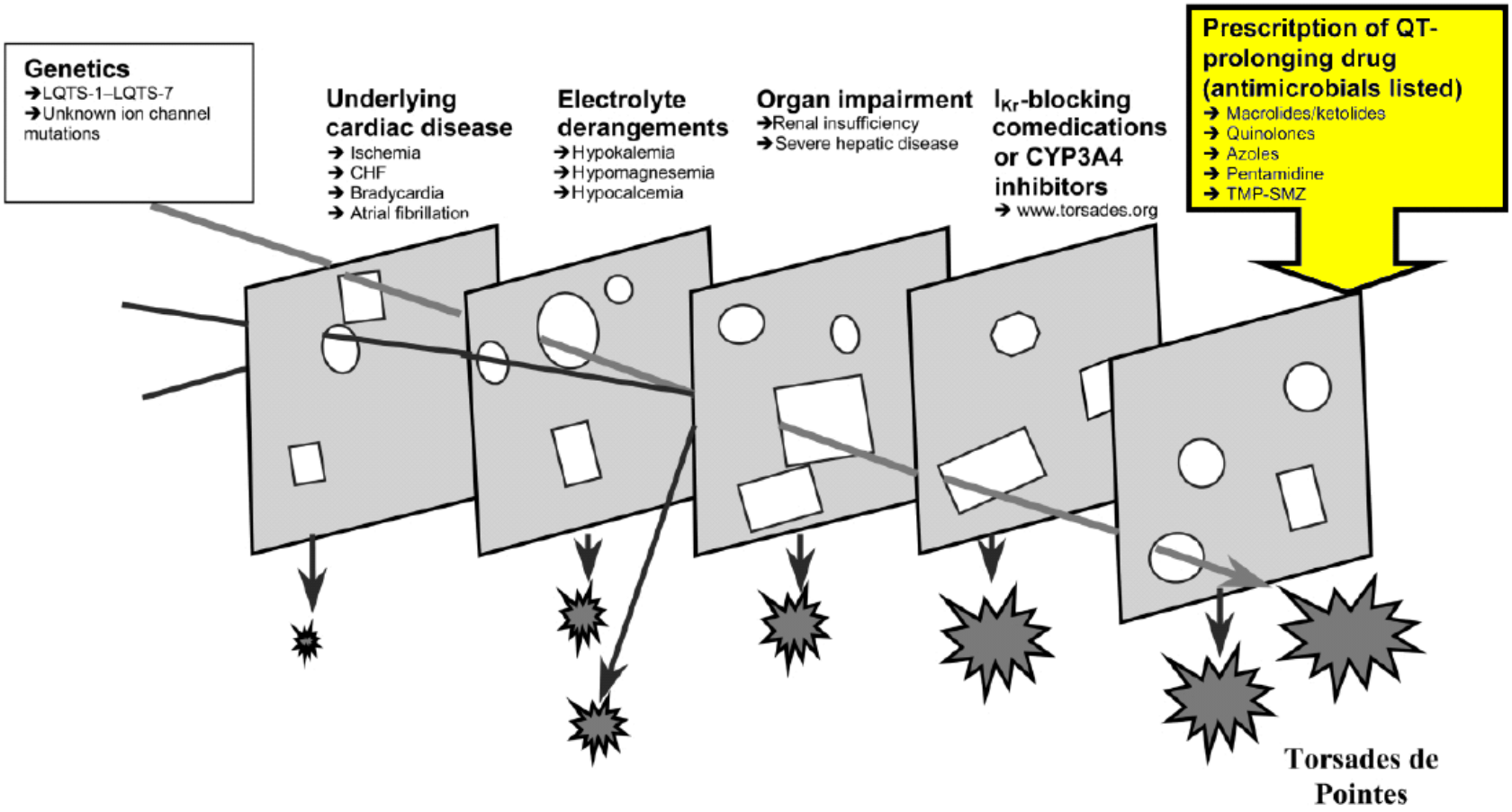


… decisions about [drug] development and approval will depend upon the **morbidity and mortality associated with the untreated disease** or disorder and the **demonstrated clinical benefits of the drug**, especially as they compare with available therapeutic modalities.

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

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

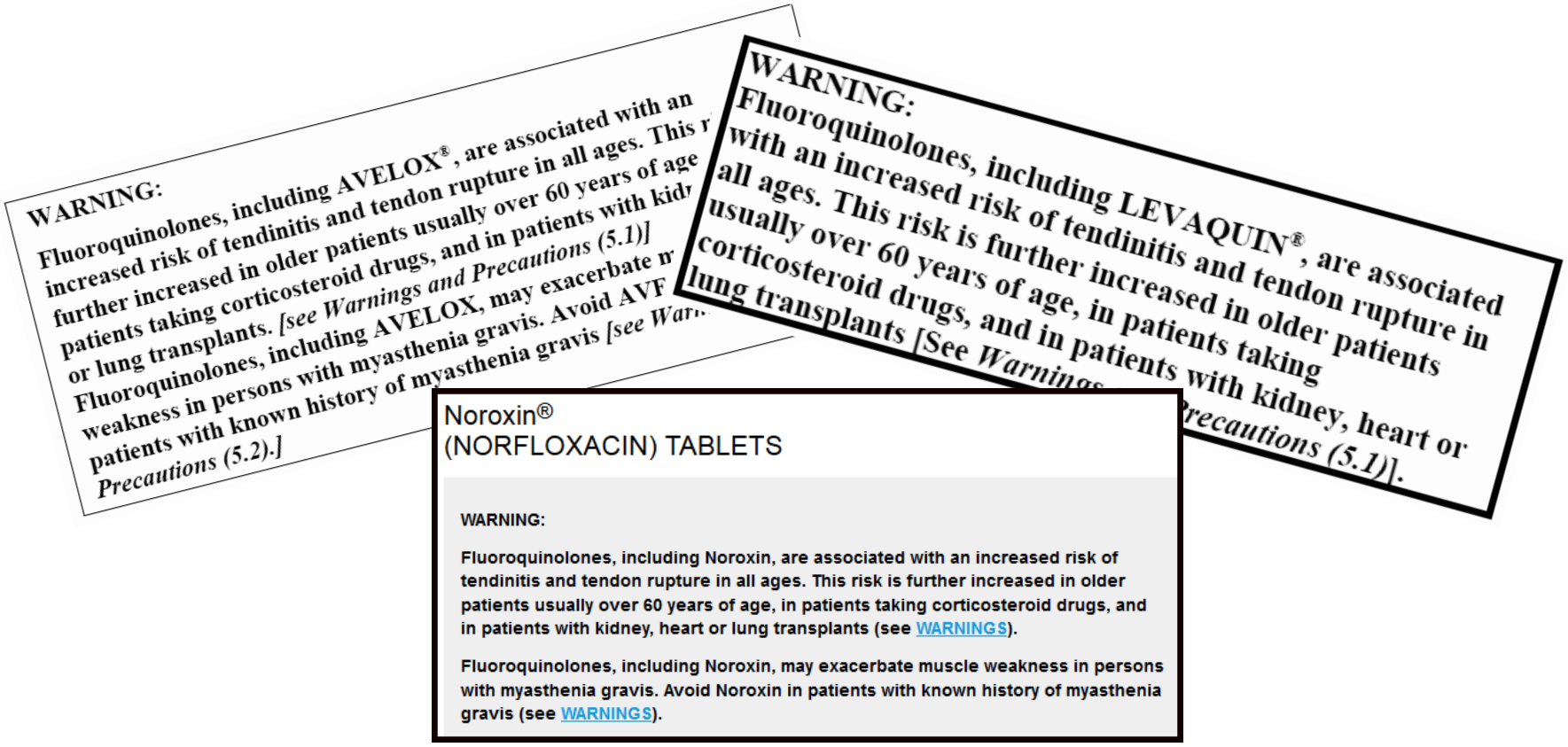
used as positive control in phase I studies

FDA warning March 12,2013

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

Tendinopathies…

- In 2005, all fluoroquinolones marketed in the US have received a black box label about tendinopathies



Tendinopathies…

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

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

Moxifloxacin safety: a conclusion…

LEADING ARTICLE

Drug Safety 2009; 32 (5): 359-378
0114-5916/09/0005-0359/$49.95/0

Safety Profile of the Respiratory Fluoroquinolone Moxifloxacin

Comparison with Other Fluoroquinolones and Other Antibacterial Classes

Françoise Van Bambeke and *Paul M. Tulkens*

Unité de pharmacologie cellulaire et moléculaire & Centre de Pharmacie Clinique, Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium

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

A reasonable equilibrium for moxifloxacin ?

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

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

Cross-resistance with what ?

- Gram-negative
  - *K. pneumoniae*
  - *E. coli*
  - *P. aeruginosa*
- Gram-positive
  - *C. difficile*
  - *Enterococci*
  - *Staphylococci*

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

* https://mic.eucast.org/Eucast2/ (EUCAST MIC distributions help to establish the ECOFF but should not be used to determine resistance levels)

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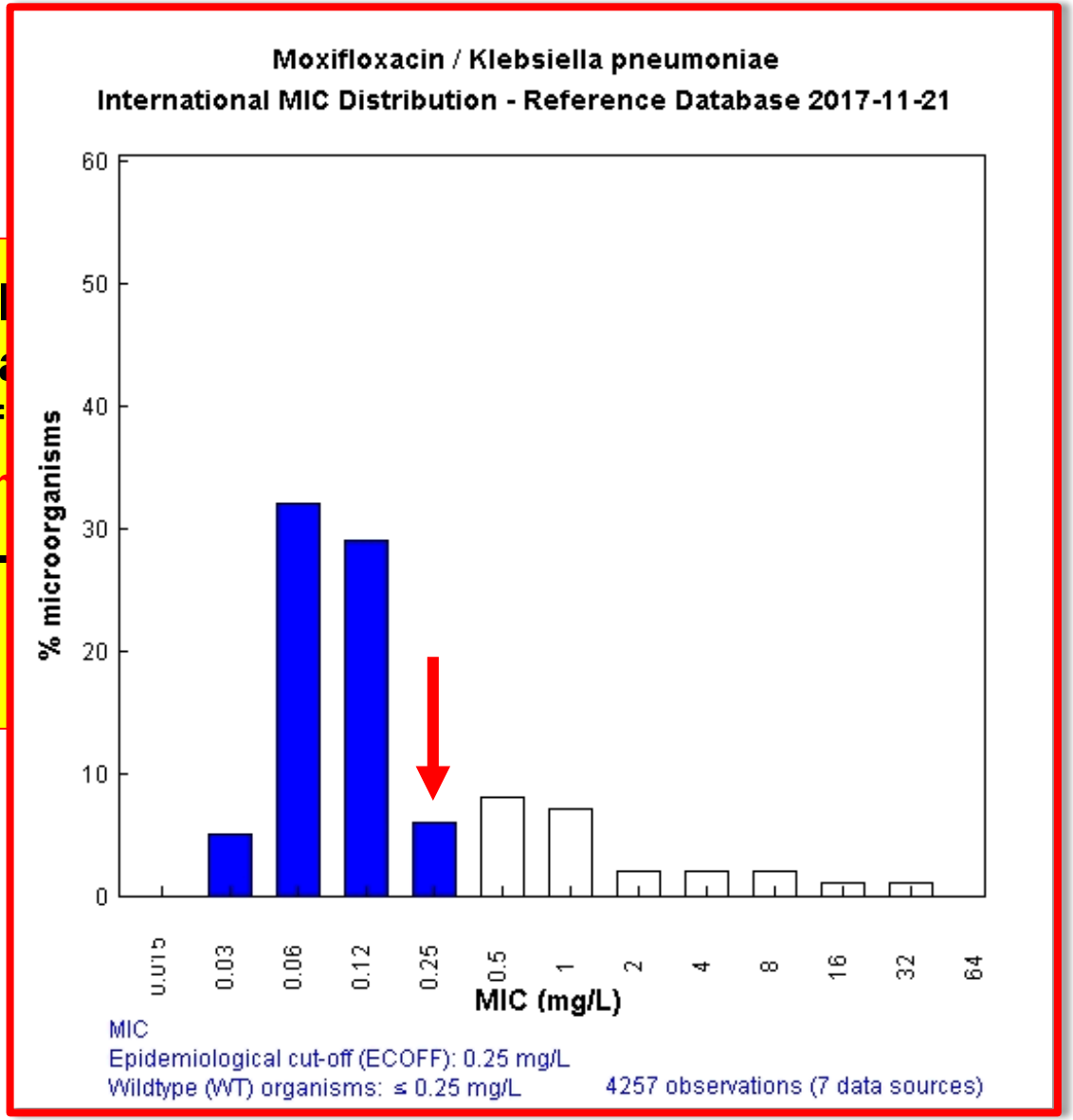

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all these show variable levels of resistance to moxifloxacin (i.e. MICs > the EUCAST ECOFF) ... BUT not more than levofloxacin

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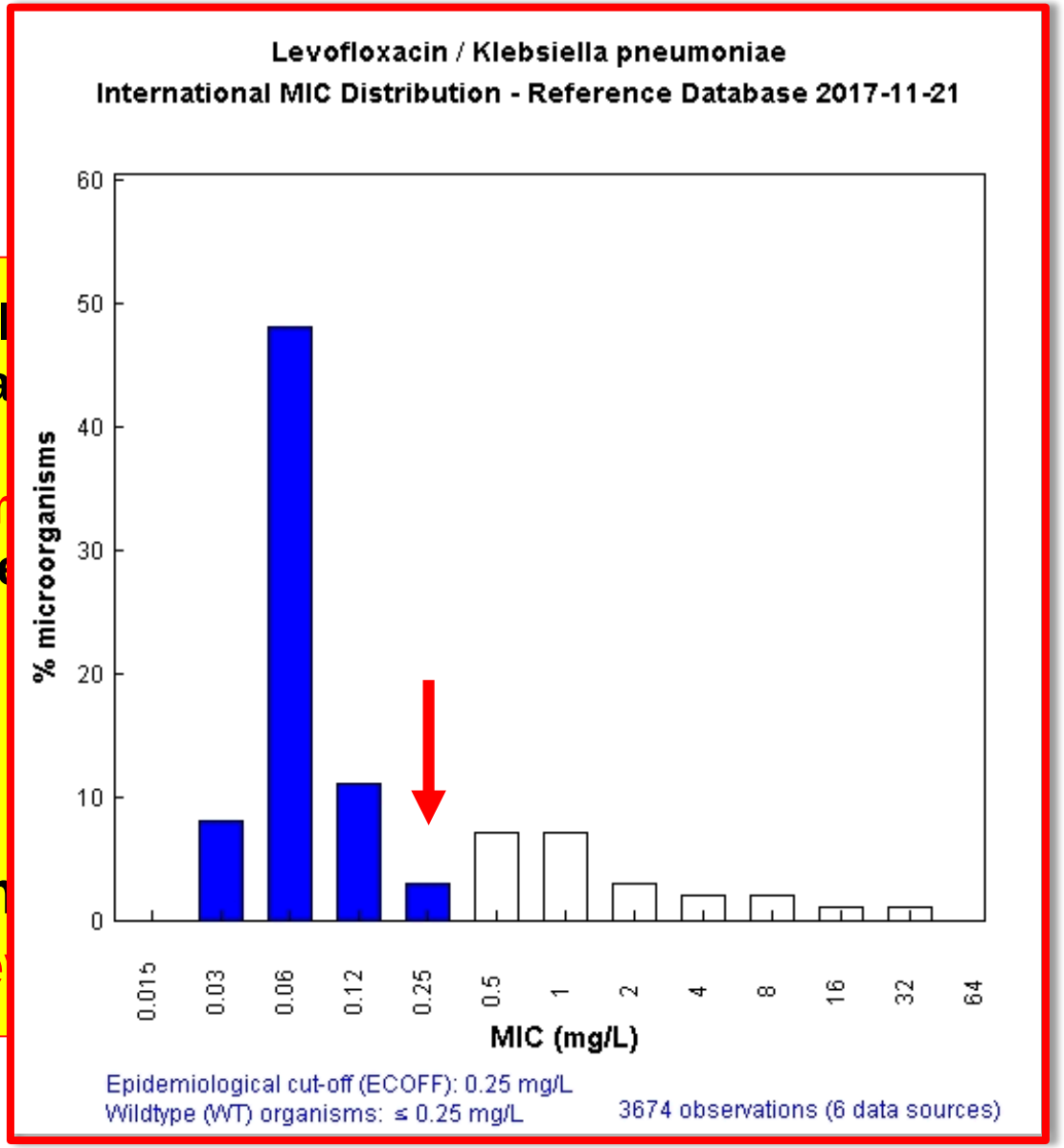

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Does the use of fluoroquinolones for respiratory tract infections mask (an delay the diagnostic of) tuberculosis ?

- A number of papers say "Yes"

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

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

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

Tun-Chieh Chen [a,b,c], Po-Liang Lu [b,c], Chun-Yu Lin [b,c], Wei-Ru Lin [b], Yen-Hsu Chen [b,c,d,*]

[a] Kaohsiung Municipal Ta-Tung Hospital, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung City, Taiwan
[b] Division of Infectious Diseases, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung City, Taiwan
[c] Graduate Institute of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung City, Taiwan
[d] Tropical Medicine Research Center, College of Medicine, Kaohsiung Medical University, Kaohsiung City, Taiwan

Chen et al. Int J Infect Dis 2011;15(3):e211-6 - PMID 21195001

The Journal of Emergency Medicine, Vol. 50, No. 3, pp. 371–375, 2016

0736-4679/$ - see front matter

http://dx.doi.org/10.1016/j.jemermed.2015.07.044

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

Barret Rush, MD,* Andrew Wormsbecker, MD,* Rob Stenstrom, MD,† and Barry Kassen, MD‡

*Division of Critical Care Medicine, Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada, †Department of Emergency Medicine, University of British Columbia, St Paul's Hospital, Vancouver, British Columbia, Canada, and ‡Division of General Internal Medicine, Department of Medicine, University of British Columbia, St Paul's Hospital, Vancouver, British Columbia, Canada
Reprint Address: Barret Rush, MD, Department of Medicine, St. Pauls Hospital, 5th Floor, Burrard Building, 1081 Burrard Street, Vancouver, BC V6Z 1Y6 Canada

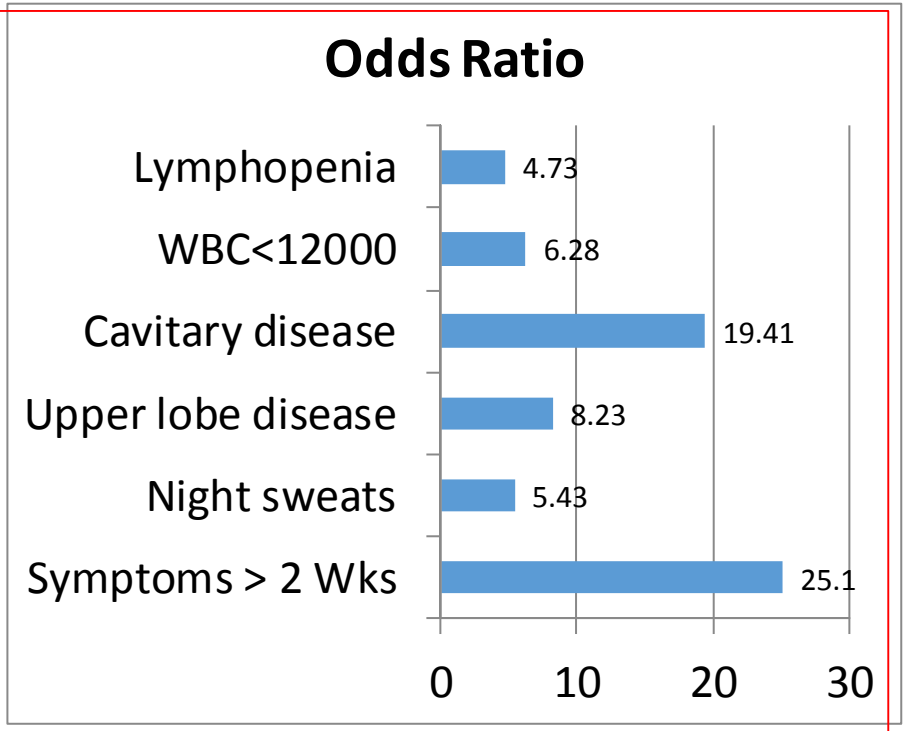
Rush et al. J Emerg Med 2016;50:371-5 - PMID 26416134

But …

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

A Malaysian study:

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



Liam C-K, et al. Respirology 2006; 11:786-92 – PMID 17052309

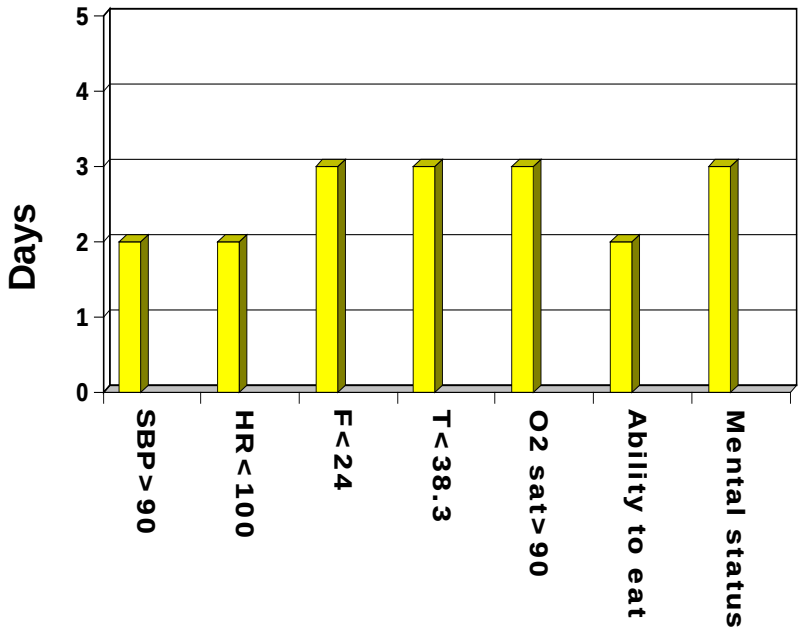
Slide adapted from Prof. R. Grossman's presentation (Singapore, 2016)

But …

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

A very basic study:

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



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

SBP: systolic blood pressure
HR: hear rate
F: respiratory rate
T: temperature

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

But …

3. Biomarkers should help to separate non-TB and TB-CAP

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

- CRP = 14.58 mg/dL in bacterial CAP
  5.27 mg/dL in TB (p<0.001)
- PCT = 0.514 ng/mL in bacterial CAP
  0.029 ng/mL in TB (p<0.001)
- CRP discriminative value: 0.857 (95% CI, 0.778 to 0.936)
- PCT discriminative value: 0.872 (95% CI, 0.792 to 0.951)

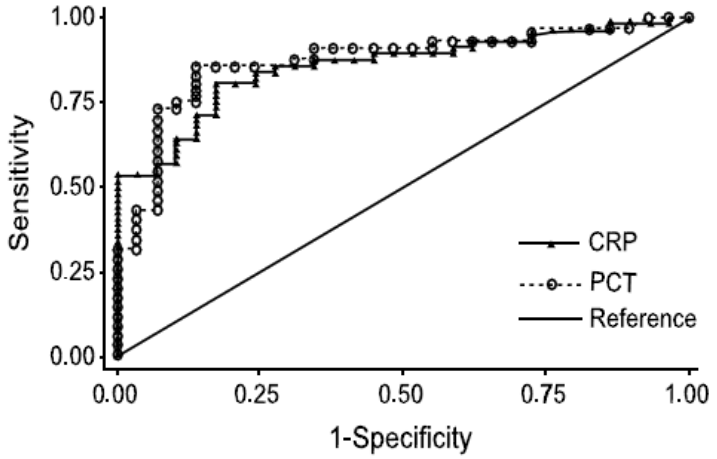


Figure 1. Receiver-operating characteristics curve for discriminating between pulmonary tuberculosis and bacterial community-acquired pneumonia for C-reactive protein (CRP) and procalcitonin (PCT). No difference was detected in the discriminative value between CRP and PCT.

Kang et al. Korean J Intern Med 2009;24:337–42 – PMID: 19949732

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

But here is a practical solution…

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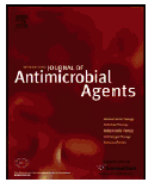
International Journal of Antimicrobial Agents

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



Review

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

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

[a] *Division of Respiratory and Critical Care Medicine, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan*
[b] *Division of Respiratory and Critical Care Medicine, Department of Internal Medicine, School of Medicine, Chung Shan Medical University, and University Hospital, Taichung, Taiwan*
[c] *Pulmonary Division, Department of Internal Medicine, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan*
[d] *TB Laboratory Section, Department of Internal Medicine, Buddhist Tzu Chi General Hospital, Hualien and Tzu Chi University, Hualien, Taiwan*
[e] *Division of Infectious Diseases, Department of Internal Medicine, Kaohsiung Medical University Hospital, Graduate Institute of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan*
[f] *Division of Respiratory and Critical Care Medicine, Department of Internal Medicine, Da Chien General Hospital, Maioli, Taiwan*
[g] *Division of Infectious Diseases, Department of Internal Medicine, Ditmanson Medical Foundation Chia-Yi Christian Hospital, Chia-Yi, Taiwan*
[h] *Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Taipei City Hospital, Heping Fuyou Branch, Taipei, Taiwan*
[i] *Division of Infectious Diseases, Department of Medicine, Chang Gung University and Memorial Hospital, Taiwan*
[j] *Infectious Diseases, Department of Internal Medicine, Show Chwan Memorial Hospital, Taichung, Taiwan*
[k] *Infectious Section, Internal Medicine Department, Institute of Microbiology and Immunology, Chung Shan Medical University, and University Hospital, Taichung, Taiwan*
[l] *Departments of Laboratory Medicine and Internal Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, No. 7 Chung-Shan South Road, Taipei 100, Taiwan*

Shen et al. Int J Antimicrob Agents. 2012;39:201-5 - PMID 22285045

But here are solutions…

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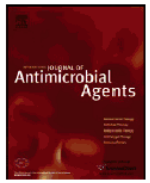

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[l] Departments of Laboratory Medicine a
Taipei 100, Taiwan

Shen et al. Int J Antimicro

- **Empirical treatment of CAP with a FQ might mask active TB, delay treatment and contribute to the development of FQ resistance.**
- **BUT … FQ resistance in M. tuberculosis is related to FQ duration (> 10 dasy) and the timing of exposure (> 60 days before TB diagnosis**
- **Consequently, a short-course (5-day) regimen of a FQ (levofloxacin, moxifloxacin and gemifloxacin) is still recommended for empirical therapy for CAP patients if the patient is at low risk for TB.**
- **Furthermore, FQ resistance is less likely to occur amongst M. tuberculosis strains isolated from patients with short-term exposure (<10 days) to FQ.**

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

Why keeping the best on reserve ?

- Its is largely a political decisions ..
  - reserve for what ? **what do you want to to keep it for ?.**
  - reserve for how long ? **do I need to wait for failures ?**
  - reserve for which patients ? **who can I treat with old drugs ?**

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

make a rational choice for the goal you aim at…

- is my patient eligible ?
  - a "real" bacterial infection ?
  - without known risk factors …

think about YOUR patient …

At the end of the day…
It will be your (informed) choice !

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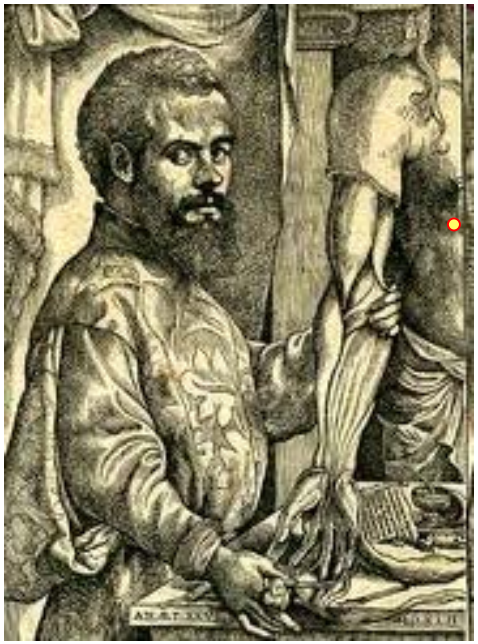
Please, ask questions …



Vesalius - anatomy

be critical,
ask for facts !

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