Moxifloxacin: PK/PD and safety profile

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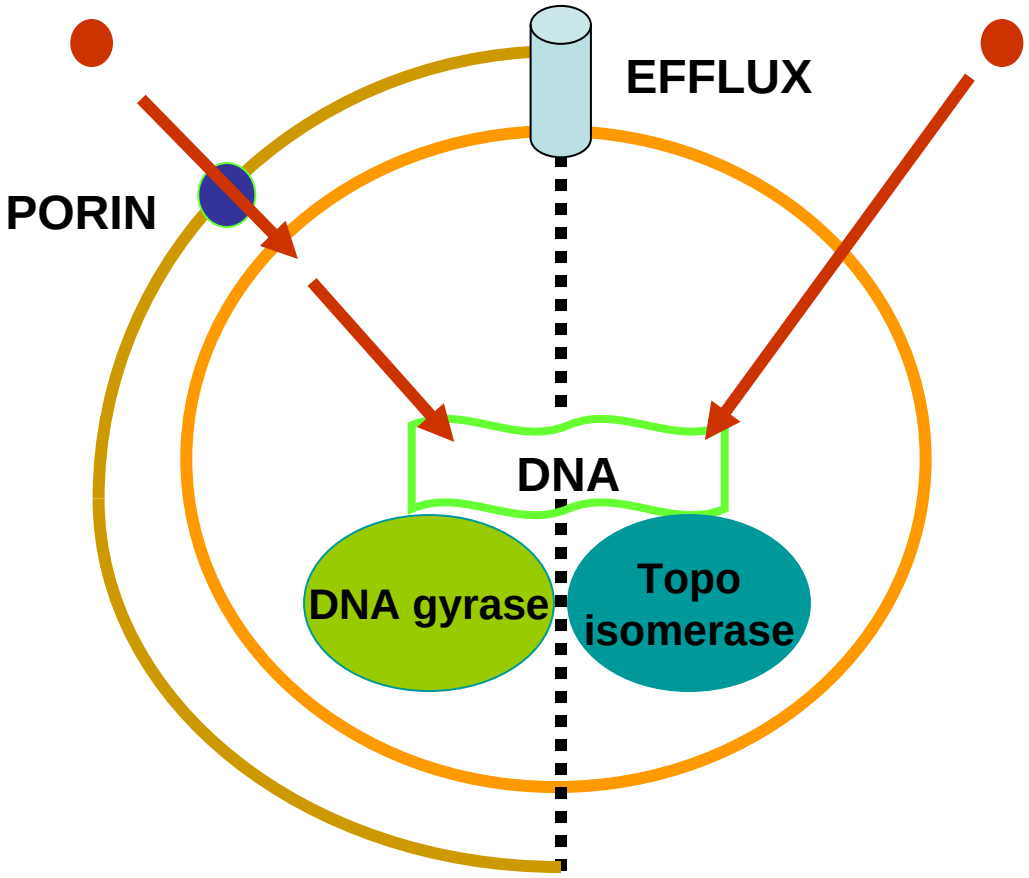
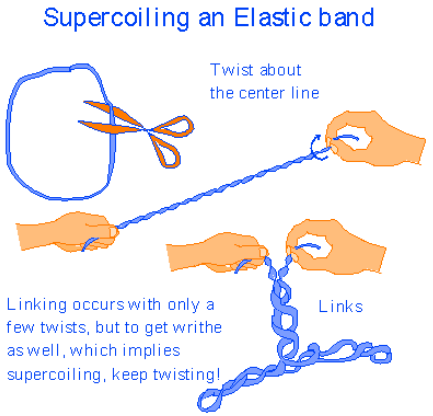
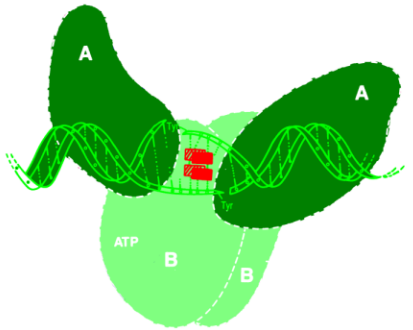
fluoroquinolones:
mode of action and mechanisms of resistance

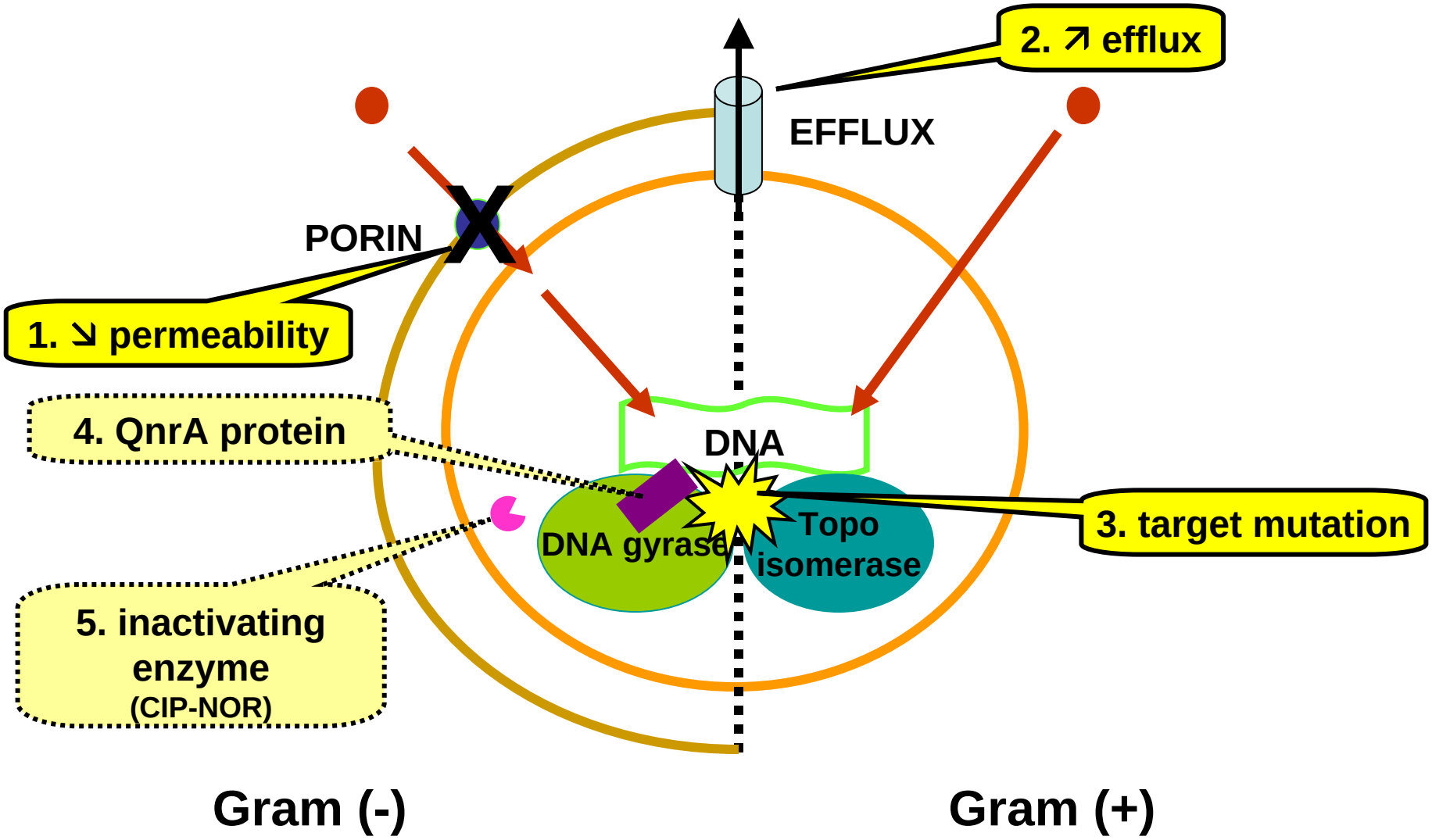






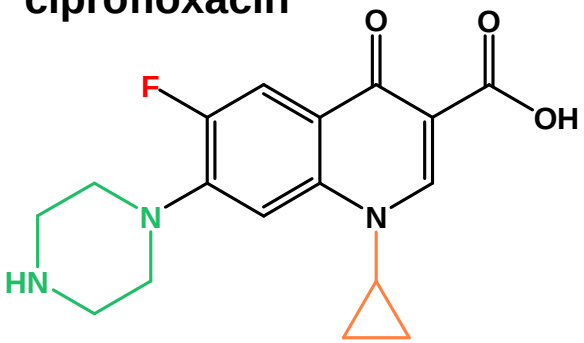
Gram (-) **Gram (+)**

fluoroquinolones: mode of action and mechanisms of resistance



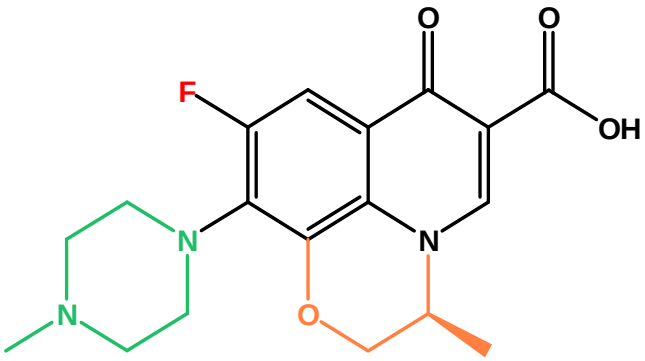
« Respiratory » fluoroquinolones: structure-activity relationship

ciprofloxacin



substituents contributing to increase in potency

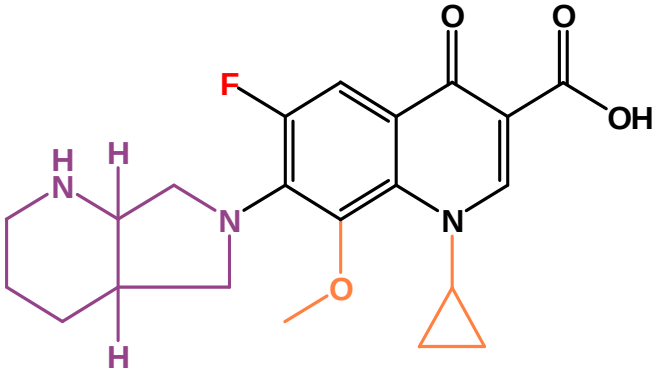
levofloxacin



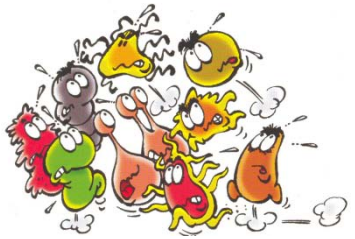
Gram(-)

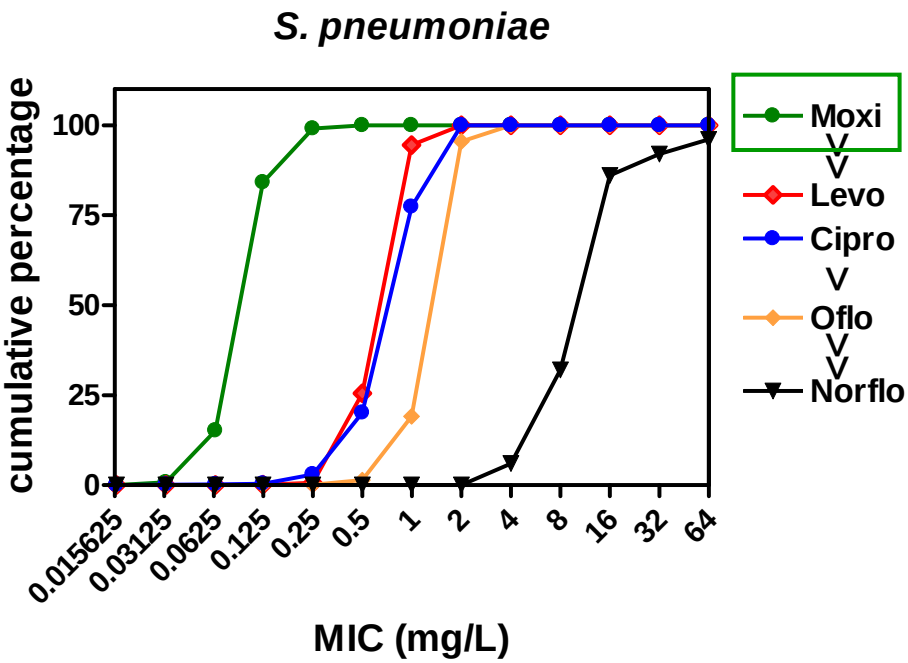
Gram(+)

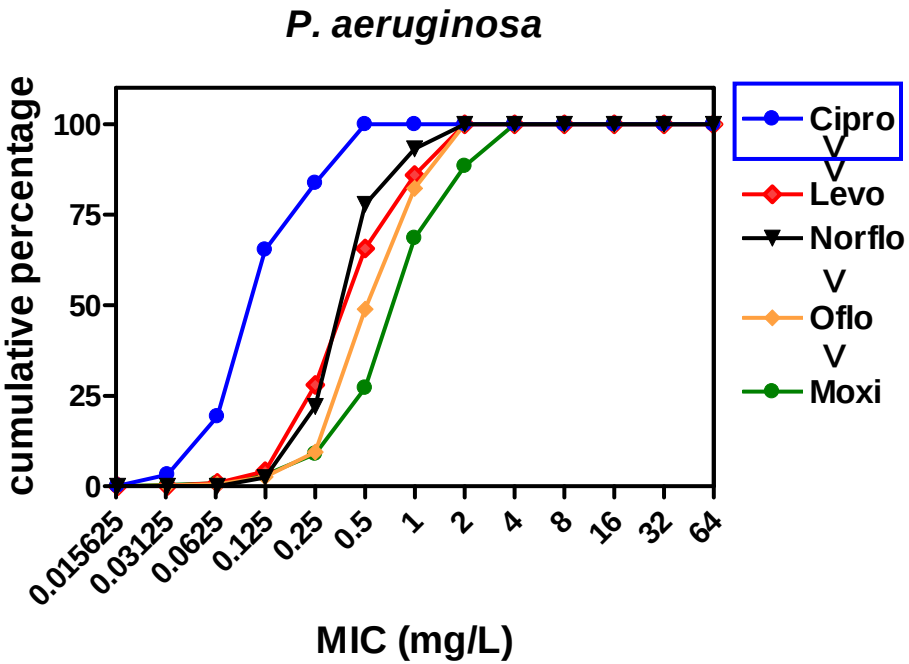
moxifloxacin



Fluoroquinolone activity towards respiratory pathogens







Cumulative MIC distributions for wild-type populations of *S. pneumoniae or P. aeruginosa*
(redrawn from data of EUCAST)
[European Committee on Antimicrobial Susceptibility Testing]

Van Bambeke et al. CMI (2005) 11: 256–80

Comparative antibacterial activity against community respiratory pathogens [$MIC_{90;}$ mg/L]*

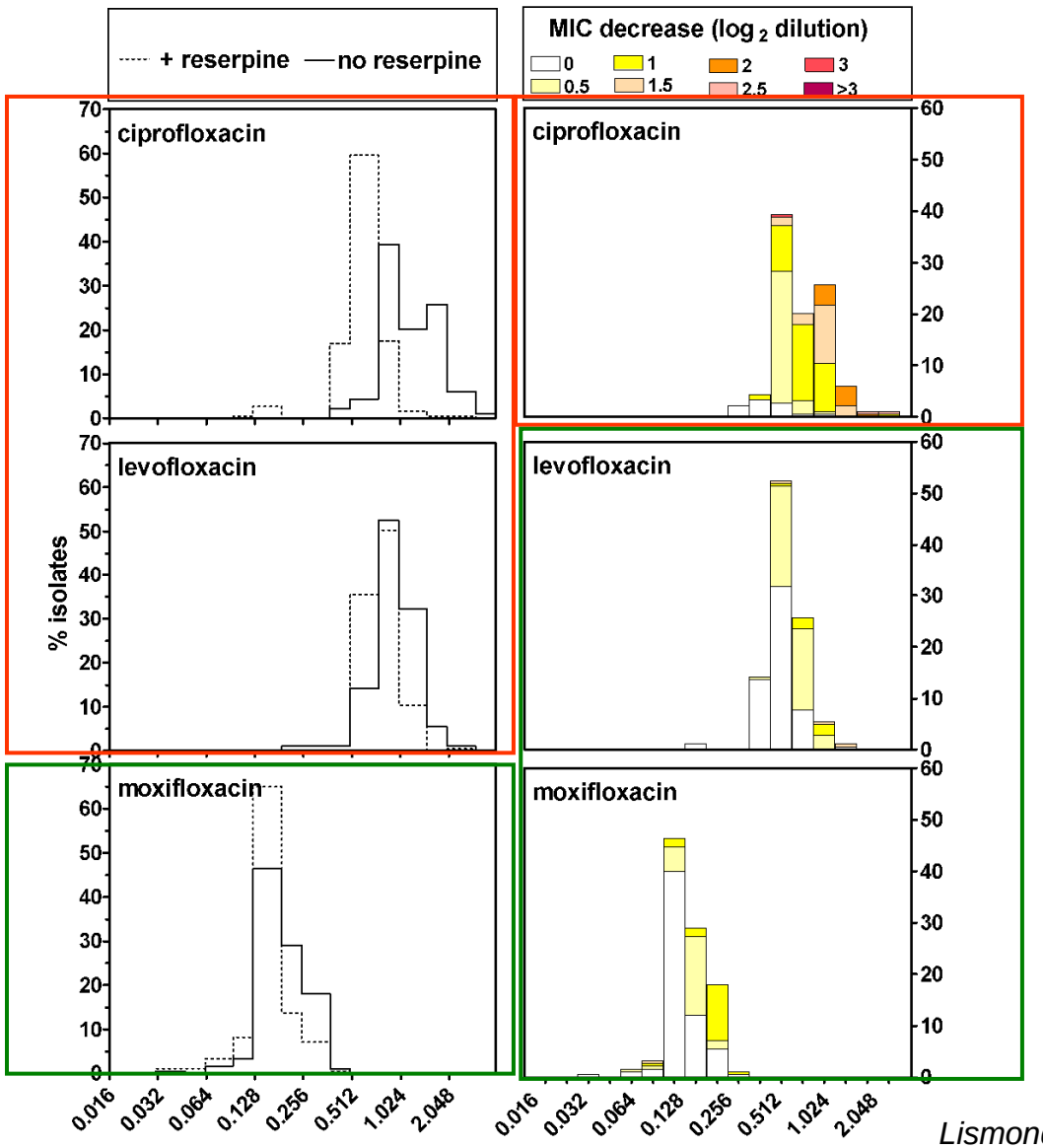
species	Levoflox.	Moxiflox.	Gatiflox. **	Gemiflox. **	Co Amoxi clav	Clarithro
S. pneumoniae	1.0	0.12-0.25	0.5	0.03-0.06	0.047	4.00
H. influenzae	0.015-0.03	0.03-0.06	0.015	0.008-0.015	1.5	32.00
M. catarrhalis	0.06	0.06-0.12	0.03	0.015-0.03	0.25	0.125
M. pneumoniae	0.5-1	0.12	0.12-0.25	0.12	NT	0.008-0.03
C. pneumoniae	0.5-1	0.06-1	0.25	0.25	NT	0.03
L. pneumophila	0.015	0.015	0.015-0.03	0.015-0.03	NT	0.03-0.06

** Adapted from Ferrara Infection (2005) 33:106-114; Jacobs et al. Intl. J. Antimicrob. Ag. (2009) 33: 52-57; Blondeau, J..Antimicrob. Chemother. 1999, 43 Suppl. B, 1-11*

*** Gatifloxacin: withdrawn from market due to effects on gluc. metabol./Gemifloxacin: not approved in Europe due to genotoxic effects*

Fluoroquinolone activity towards respiratory pathogens

S. pneumoniae from CAP collected in Belgium (2007-2009)



very similar MIC distribution

lower MICs

highly susceptible to efflux

lower susceptibility to efflux

Lismond et al. JAC (2011) 66:948-51

How to optimize the dose ?

Cmax / MIC

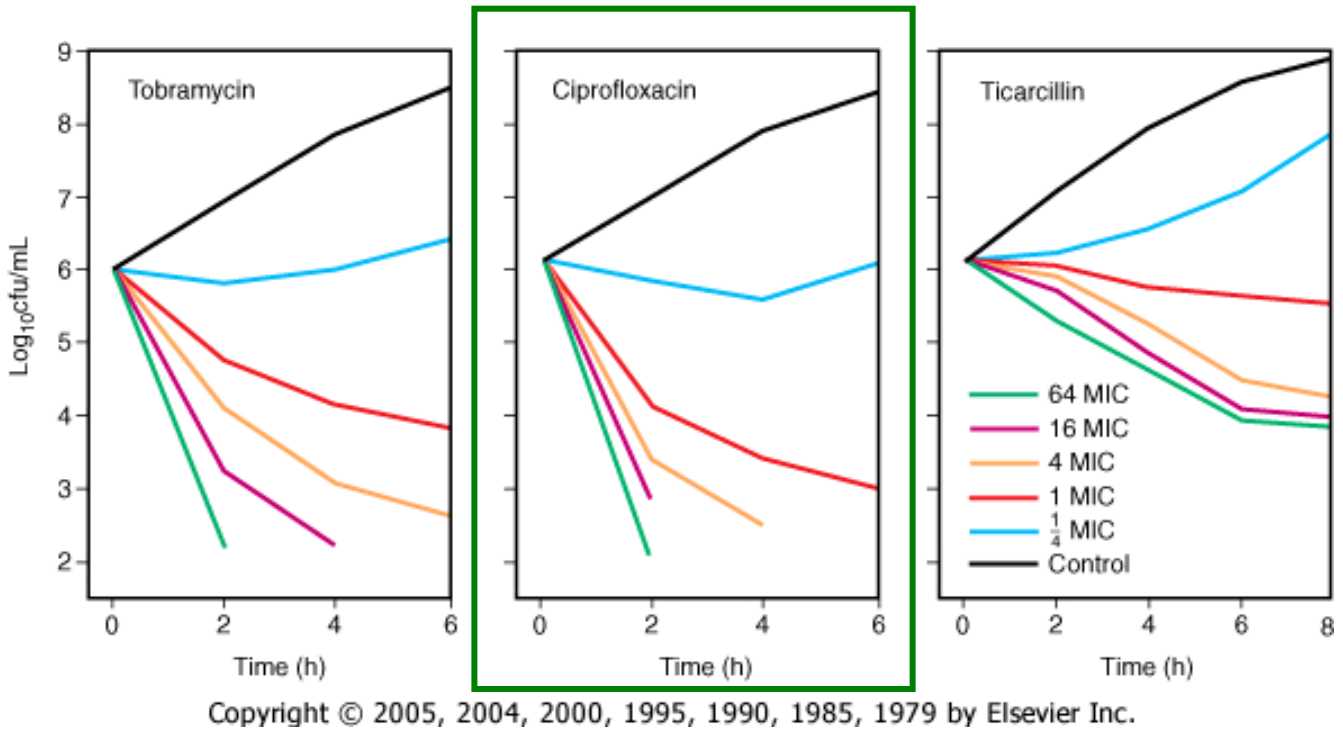
AUC / MIC

Time ~ conc > MIC

Fluoroquinolone PK/PD

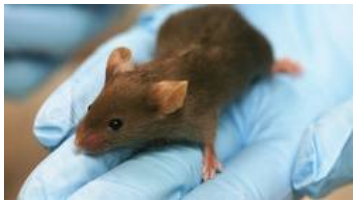
1. *in vitro* kill curves

conc. dependent



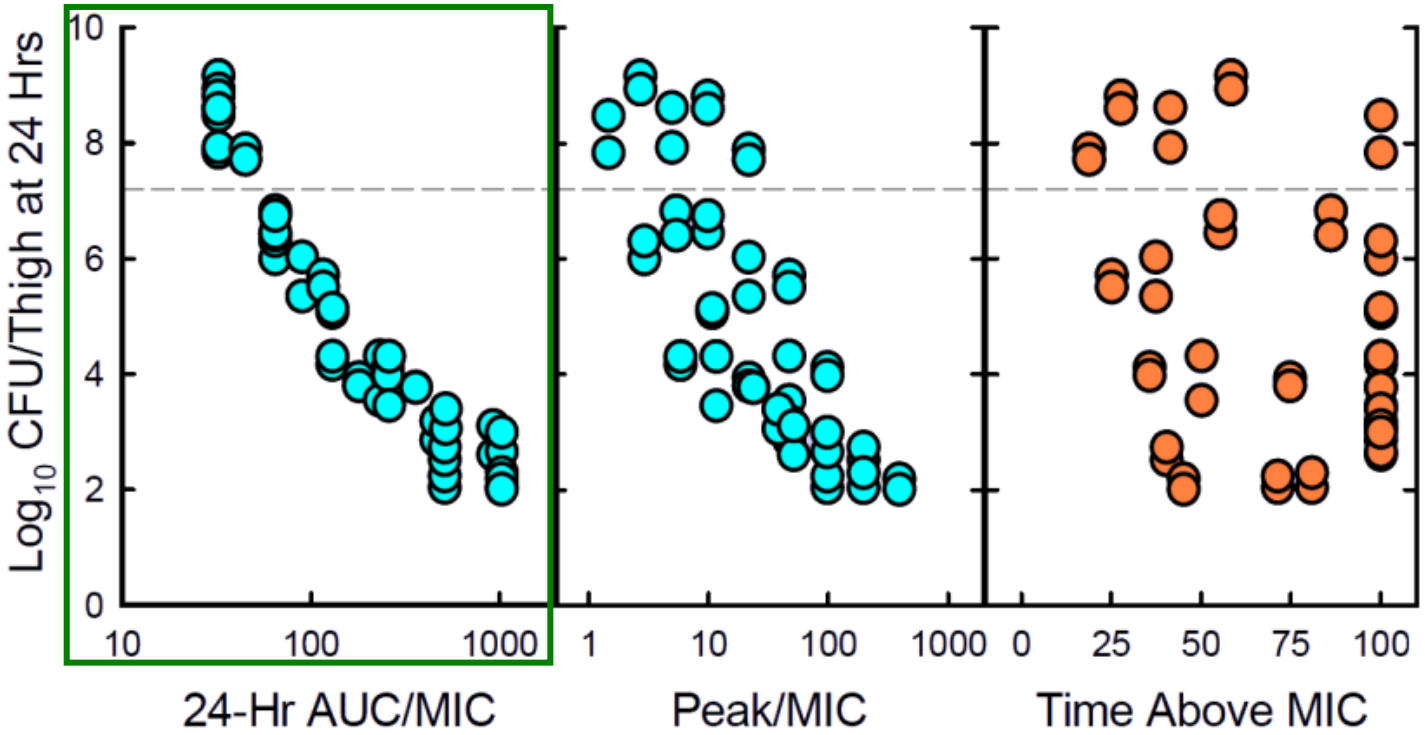
Time kill curves for *Pseudomonas aeruginosa* ATCC 27853 with exposure to tobramycin, ciprofloxacin, and ticarcillin at concentrations from one fourth to 64 times the minimum inhibitory concentration.
(From Craig WA, Ebert SC. Killing and regrowth of bacteria in vitro: A review. Scand J Infect Dis. 1990;74:63–70.)

Fluoroquinolone PK/PD



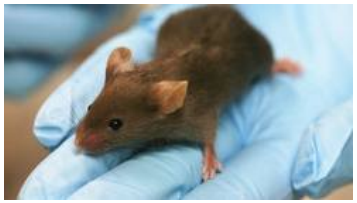
2. Animal studies

AUC/MIC. dependent

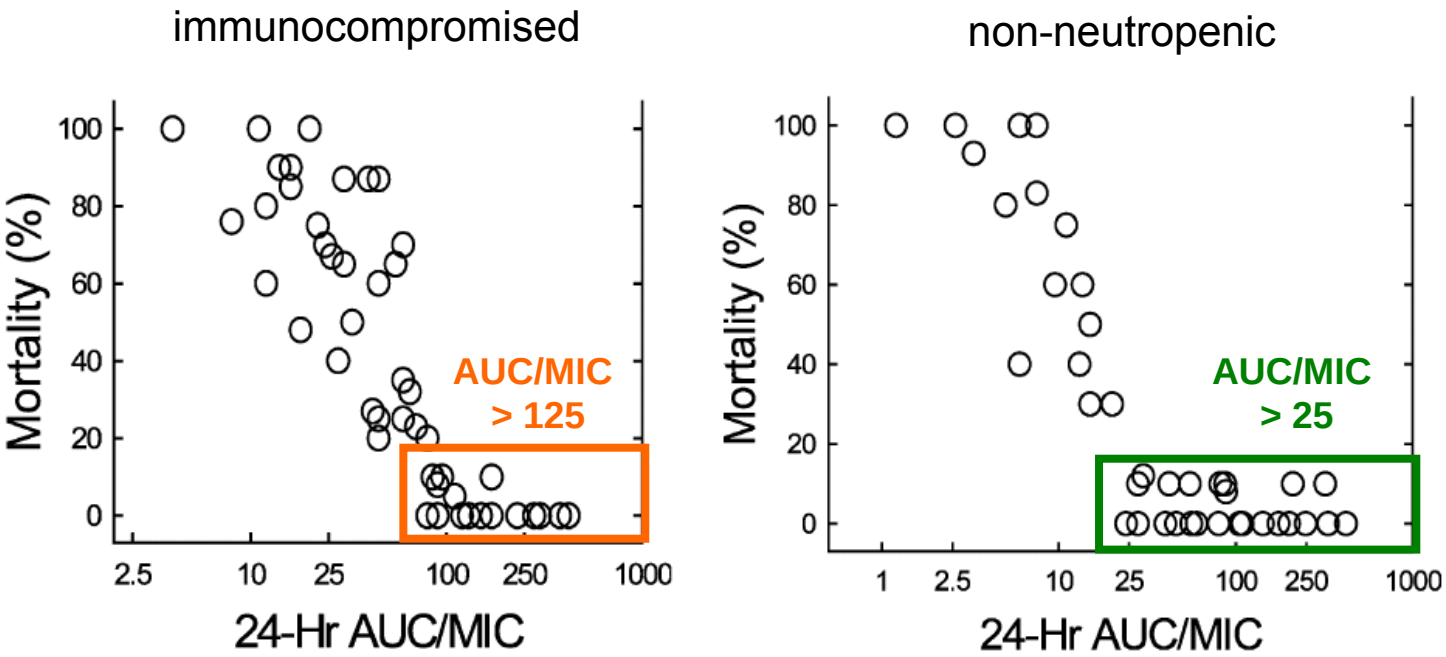


Correlation of PK/PD Indices with Efficacy of Levofloxacin against *Streptococcus pneumoniae* in Thighs of Neutropenic Mice (W.A. Craig – ISAP workshop – ICAAC 2009)

Fluoroquinolone PK/PD



2. Animal studies: influence of immune status on the value of the PK/PD target

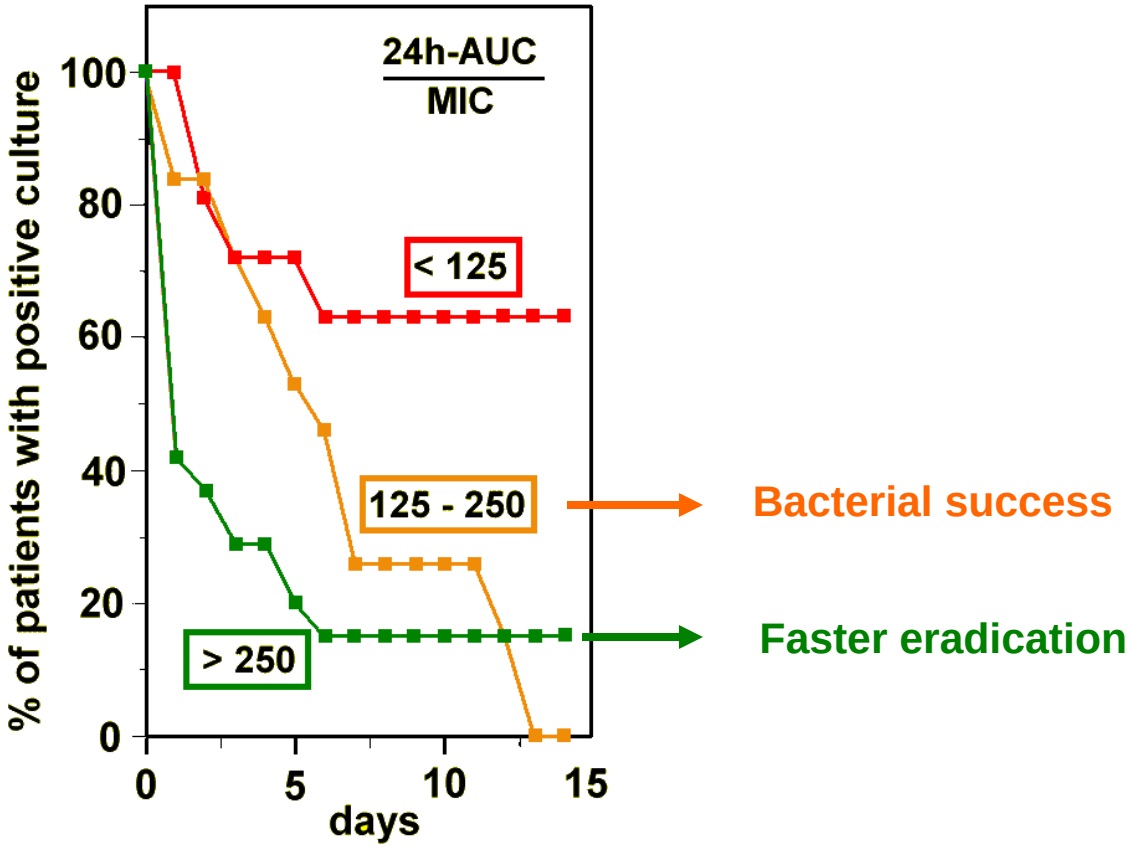


Relationships between mortality at the end of therapy and the 24 h AUC/MIC of fluoroquinolones with multiple pathogens (left panel) in different animal models (mostly immunocompromised) and with *S. pneumoniae* in non-neutropenic models (right panel).

Andes & Craig. Int. J. Antimicrob. Ag. (2002) 19: 261-68

Fluoroquinolone PK/PD

3. Clinical data

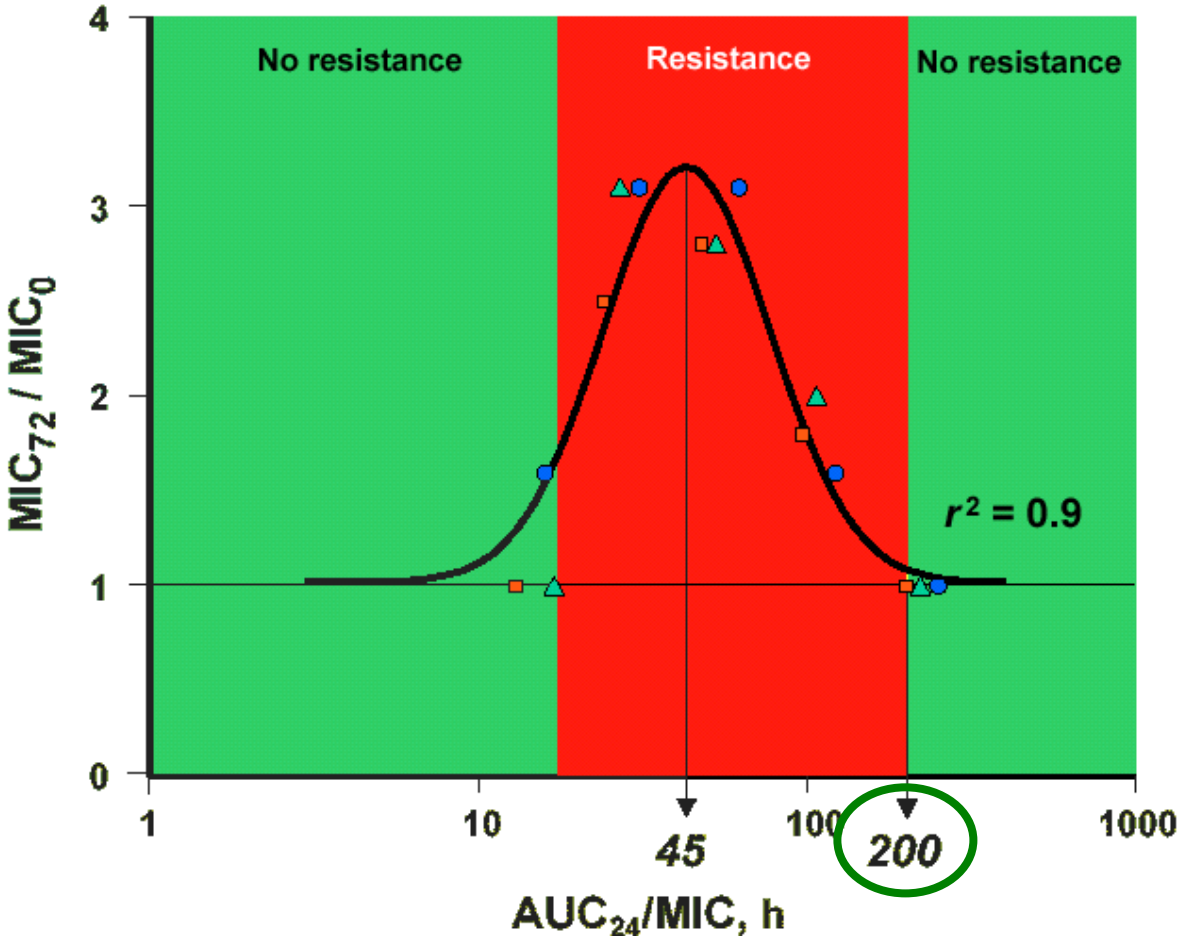


Time (days of therapy) to bacterial eradication versus AUC/MIC in severely ill patients treated with ciprofloxacin
The three groups differed significantly ($P < 0.005$).

Forrest et al., AAC (1993) 37:1073-81

Fluoroquinolone PK/PD

4. Prevention of resistance



Resistance of *S. aureus* related to exposure to 3 fluoroquinolones

AUC/MIC >> 125
&
Peak/MIC > 8
to prevent resistance selection

Firsov, ICAAC 2002

How to optimize AUC ?

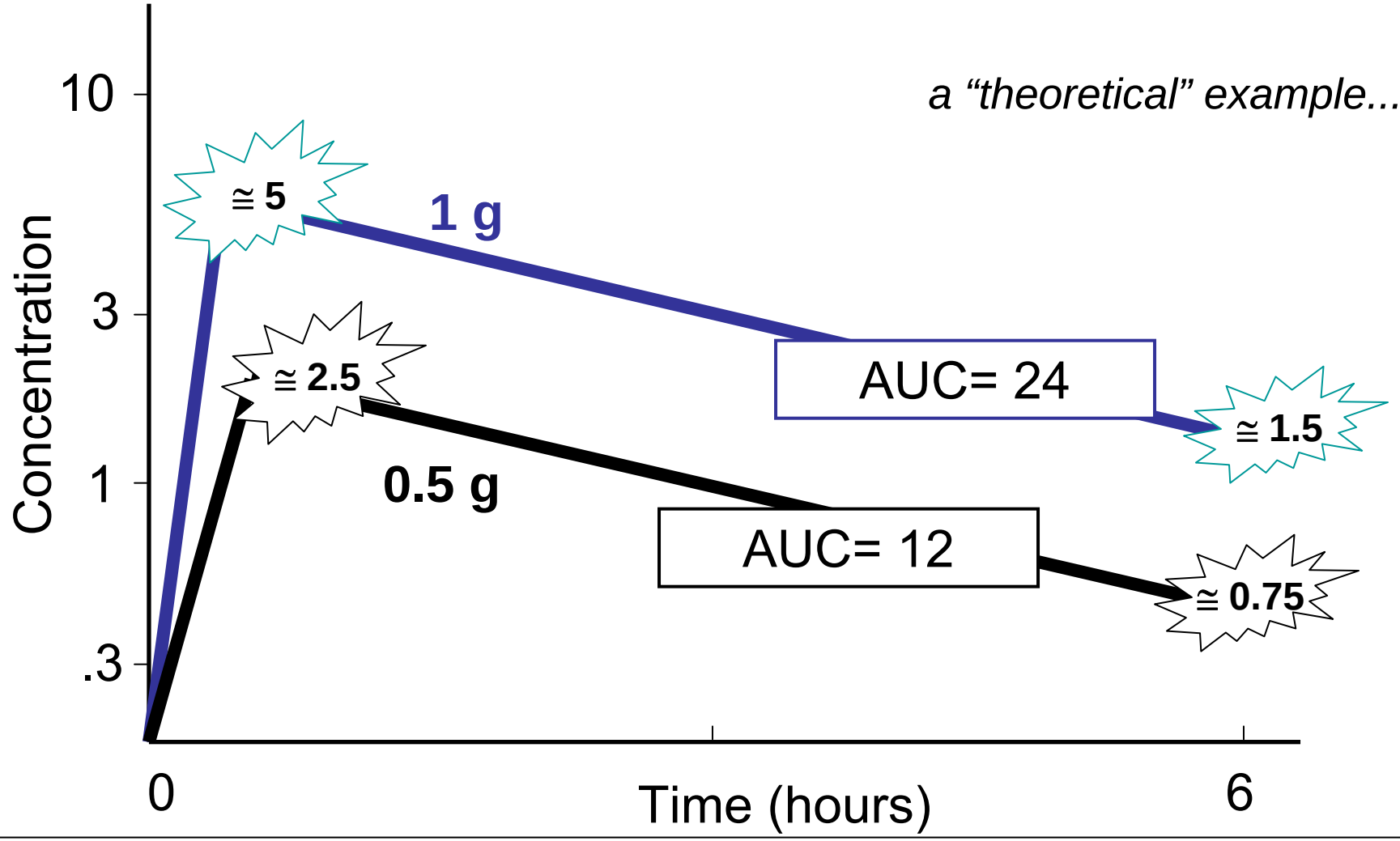
AUC = dosis / Cl

Adjust the daily dosis
~ target AUC

Adapt the number of administrations
~ pharmacokinetics of the drug

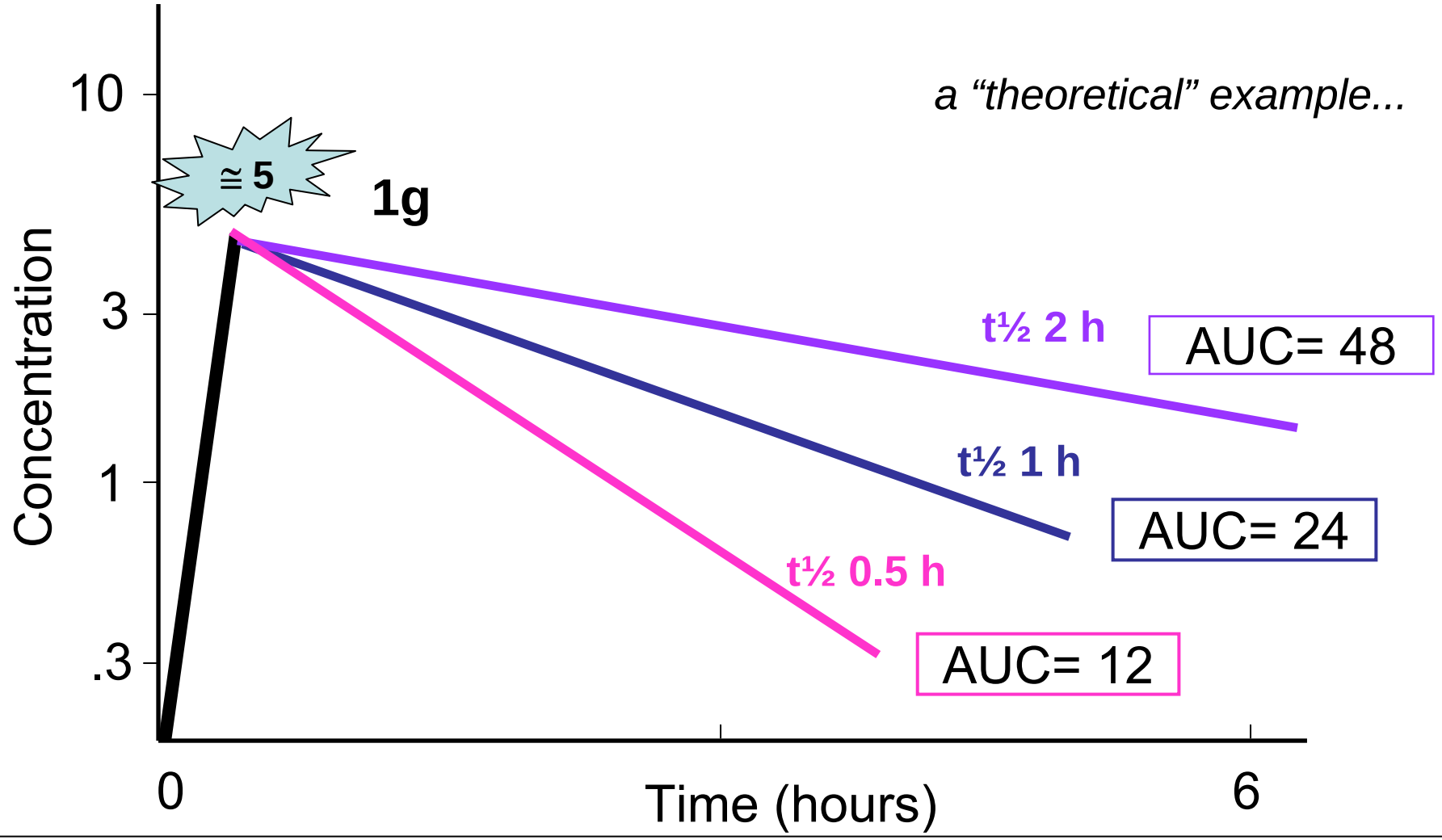
How to optimize AUC ?

AUC and peak after one dose are directly related to this dose



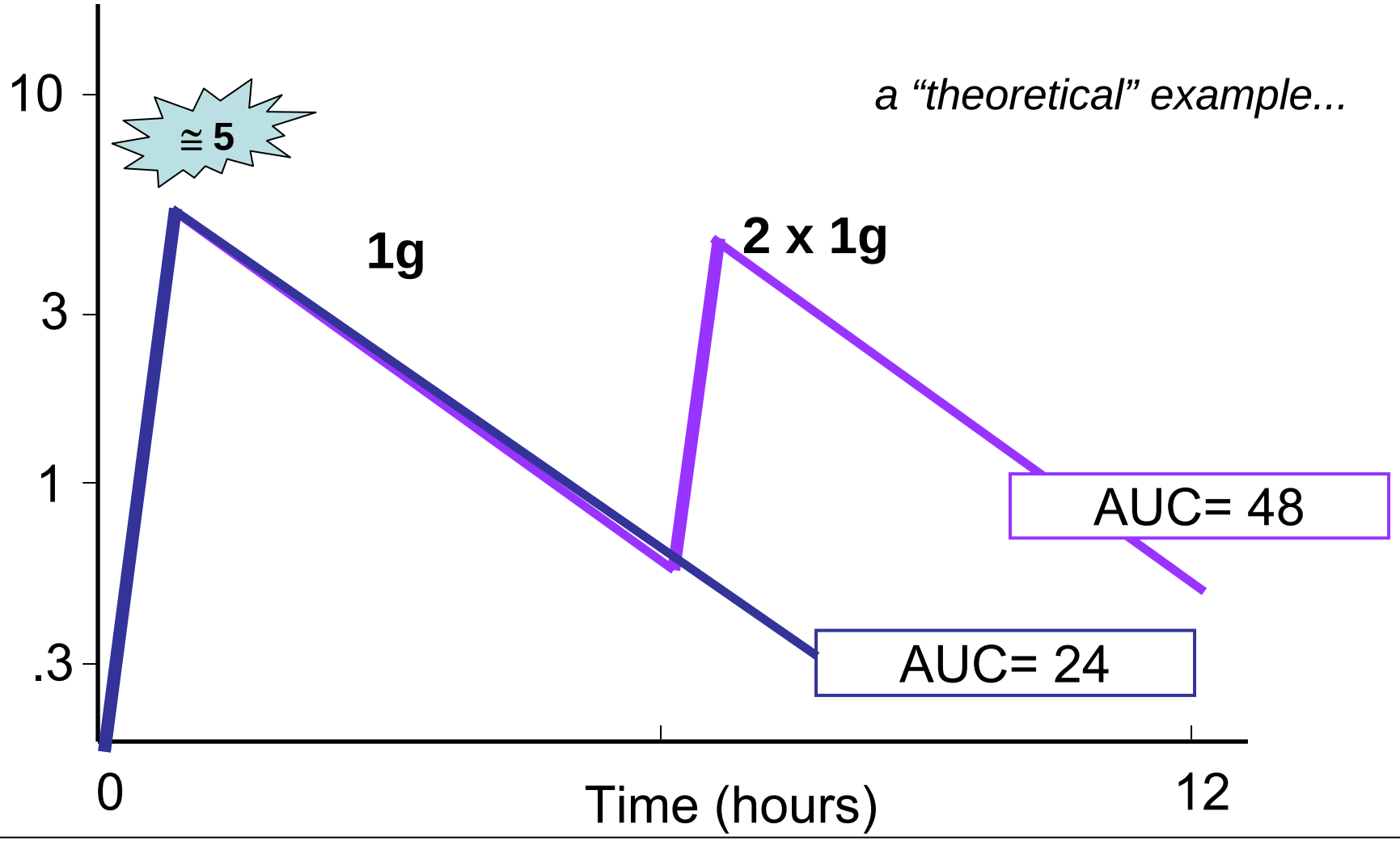
How to optimize AUC ?

24h-AUC is inversely related to the drug clearance
(BUT so is NOT the peak …)



How to optimize AUC ?

24h-AUC is correlated to the number of unit doses
(BUT, again, so is NOT the peak …)



PK/PD of fluoroquinolones in a nutshell

Remember:

- 24h-AUC is proportional to the daily dose
- peak is proportional to the unit dose...

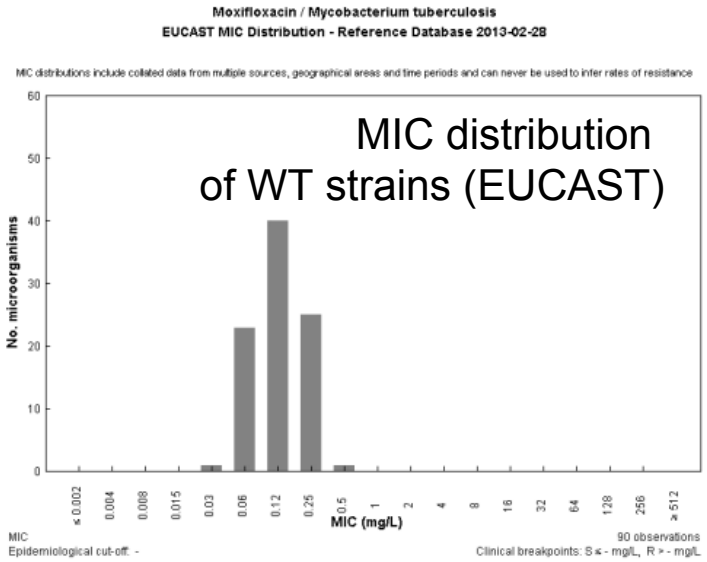
- get a **24h-AUC /MIC >> 125**, **and**
- get a **peak / MIC ratio > 8**

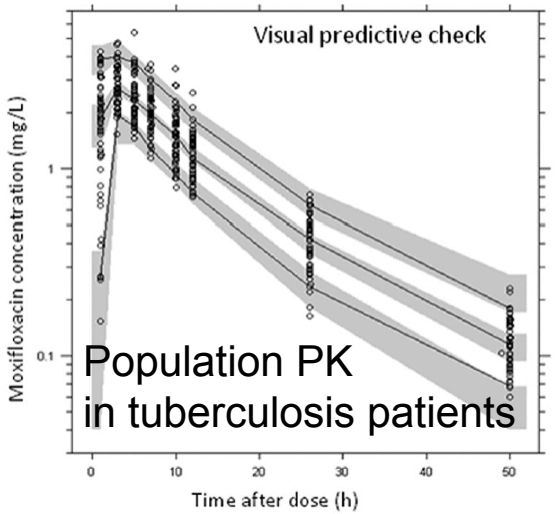
→ efficacy

- get this with the total daily dose and the appropriate unit dose …

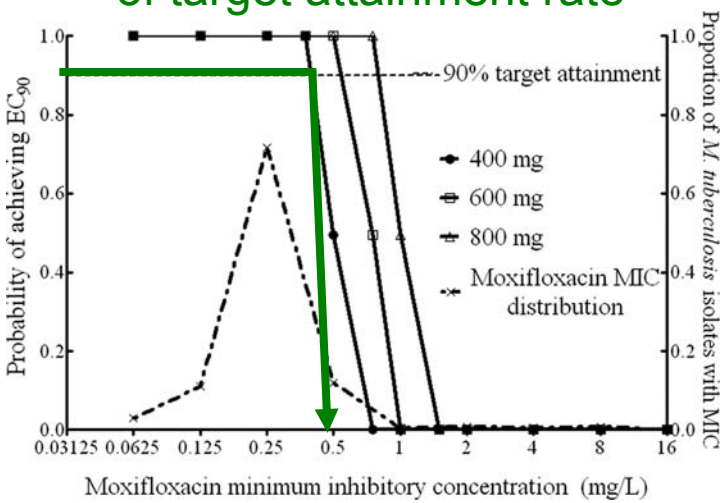
Establishing pharmacodynamic breakpoints

An example with *M. tuberculosis*





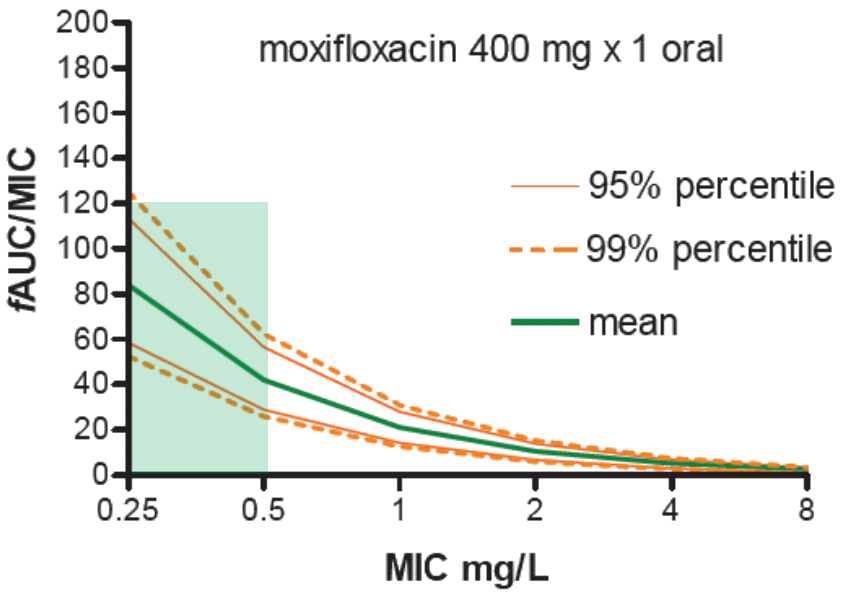
Calculation
of target attainment rate



Gumbo et al., AAC (2010) 54:1484-91
Zvada et al., AAC (2012) 56: 4471–73

Establishing pharmacodynamic breakpoints

An example with *S. pneumoniae*



PK/PD target
reached for MIC ≤ 0.5 mg/L

Probabilities of Target Attainment for moxifloxacin 400 mg x 1 oral.

The following pharmacokinetic parameters were used to obtain the PTA:

Volume of Distribution (Vd) 140L, CV 16%
Clearance (Cl) 11.5 L/h, CV 13%
Fraction unbound (Fu) 60%
Absorption rate coefficient (Ka) $2h^{-1}$
Bioavailability (F) 1.0

Results of simulations for the 400 mg IV dose do not markedly influence conclusions.

EUCAST rational documents: www.eucast.org

Fluoroquinolone pharmacodynamic breakpoint

An example with *S. pneumoniae*

fluoroquinolone		PK parameters		PK/PD Bkpt		Bkpt (S ≤)	
drug	daily dose	Cmax (total/free)	AUC (total/free)	efficacy	prevention resistance	EUCAST	FDA
cipro	1000 mg	2.5/1.75 [500]	24/18	**0.2-0.8**	0.2	**-**	-
levo	500 mg	6/4.2 [500]	47/33	**0.3-1**	0.4	**1**	2
	750 mg	10/7 [750]	70/49	**0.4-2**	0.7		
	1000 mg	6/4.2 [500]	94/66	**0.5-2**	0.4		
moxi	400 mg	3.1/1.8 [400]	35/21	**0.2-0.7**	0.2	**0.5**	1

EUCAST bkpts do integrate PK/PD

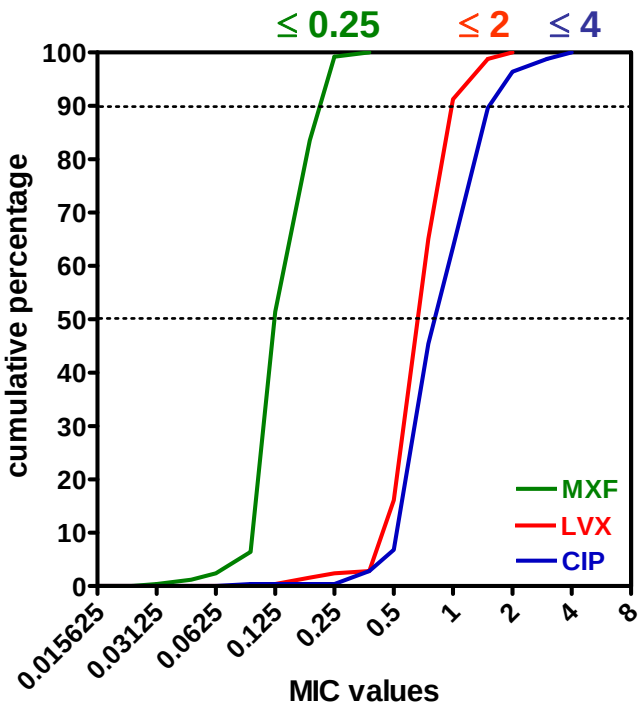
FQ selection based on PK/PD criteria

An example with *S. pneumoniae*

fluoroquinolone		PK/PD Bkpt	Bkpt (S ≤)	MIC of WT strains
drug	daily dose	efficacy	EUCAST	
cipro	1000 mg	**0.2-0.8**	-	0.25-4
levo	500 mg	**0.3-1**	**1**	0.5-2
	750 mg	**0.4-2**		
	1000 mg	**0.5-2**		
moxi	400 mg	**0.2-0.7**	**0.5**	**0.01-0.5**

moxi MIC << bkpt: key to success ?

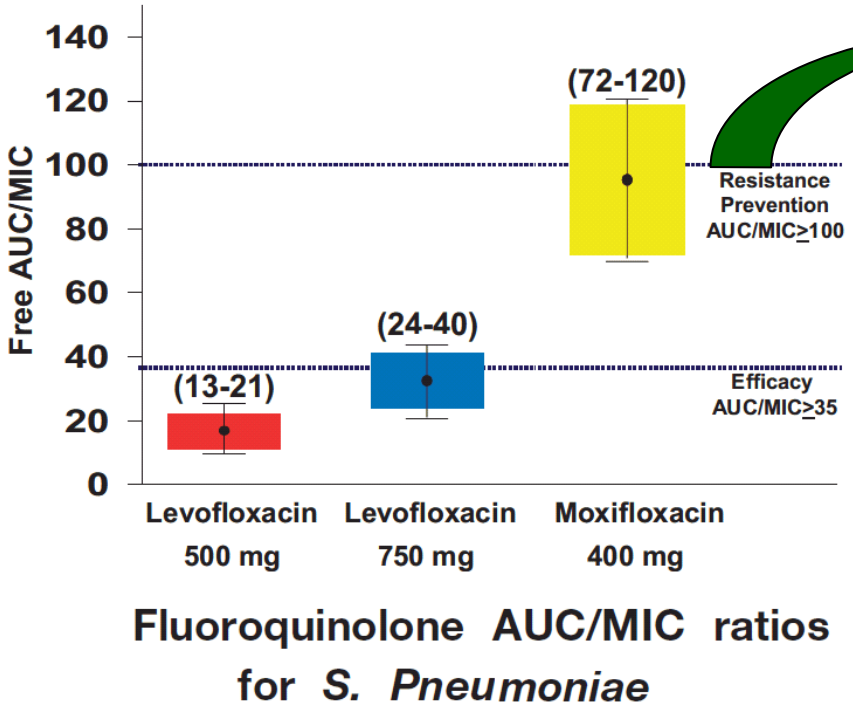
MIC of clinical isolates from CAP



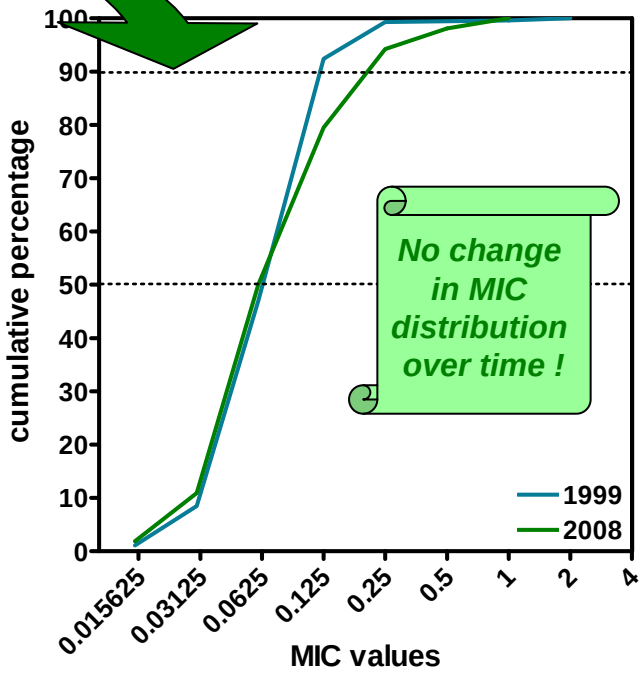
Lismond et al., Int. J. Antimicrob. Ag. (2012) 39:208-16

FQ selection based on PK/PD criteria

An example with *S. pneumoniae*



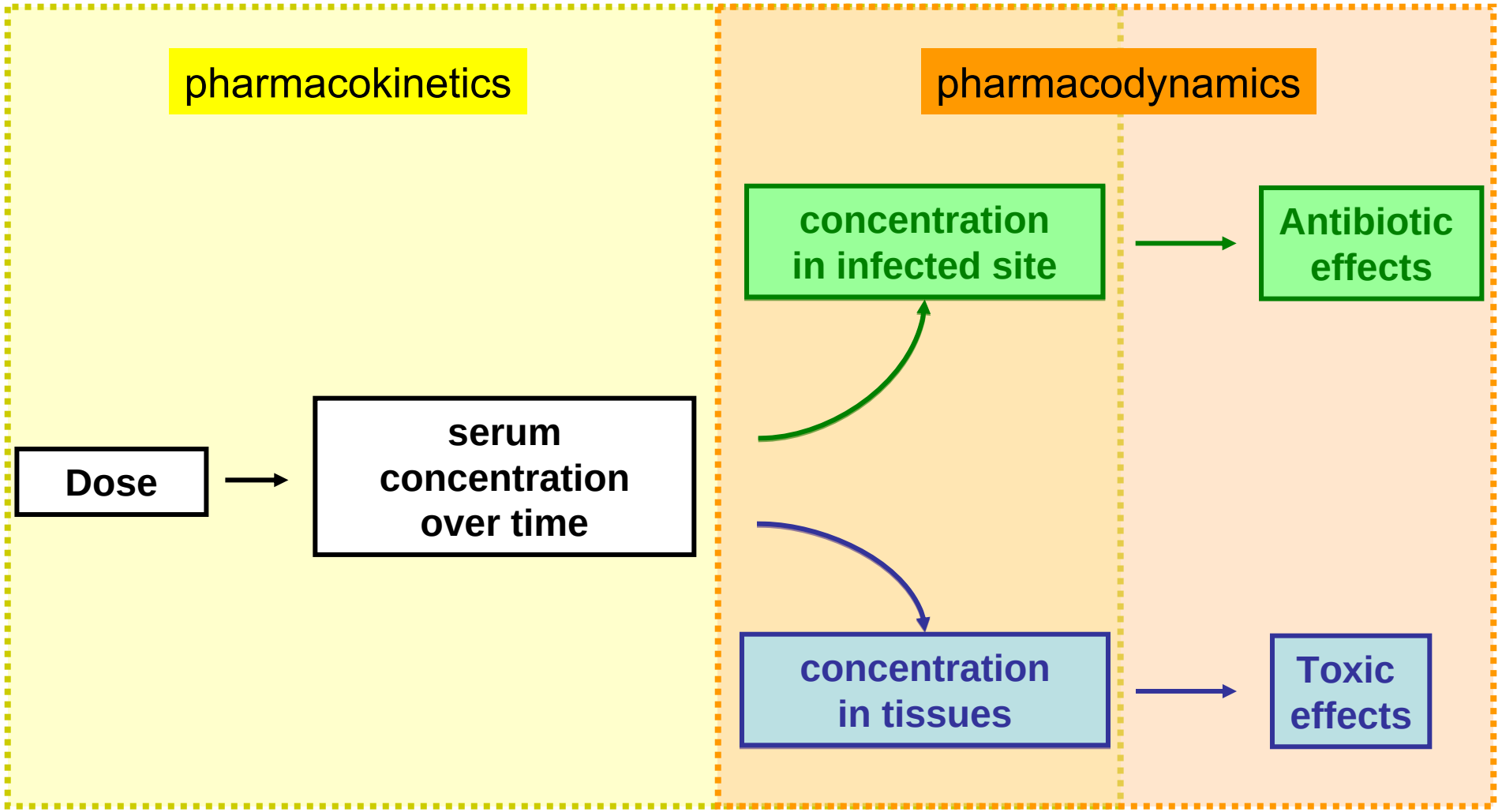
MIC of clinical isolates from CAP



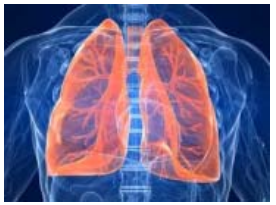
Surveys from the Belgian Scientific Institute for Public Health
for *S. pneumoniae* from community isolates
(n=156 in 1999 and 448 in 2008)
http://www.iph. fgov.be
Presented at ECCMID 2009

Moran, J. Emerg. Med.(2006) 30: 377–87

serum vs tissue concentrations ?



Distribution of moxifloxacin in the respiratory tract



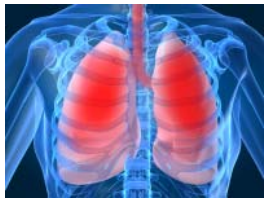
Summary of the geometric mean moxifloxacin concentrations (S.D.) in serum, epithelial lining fluid (ELF), alveolar macrophages (AM) and bronchial biopsies (BM)

Group	Site	Mean concentration (mg/L or mg/kg) (S.D.)	Mean site/serum ratio (mean of individual data) (S.D.)
(mean time after last dose = 24.1 h)			
	Serum	0.51 (1.19)	
	ELF	3.57 (1.58)	6.95 (1.43)
	AM	35.9 (1.71)	70.04 (1.58)
	BM	1.06 (1.19)	2.07 (1.19)

tissular conc. >> serum conc.

Soman et al., JAC (1999) 44:835-48

PK/PD indices in the respiratory tract



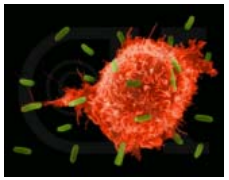
Mean areas under the curves (AUC) and areas under the inhibitory curves (AUIC) relating to serum and pulmonary sites

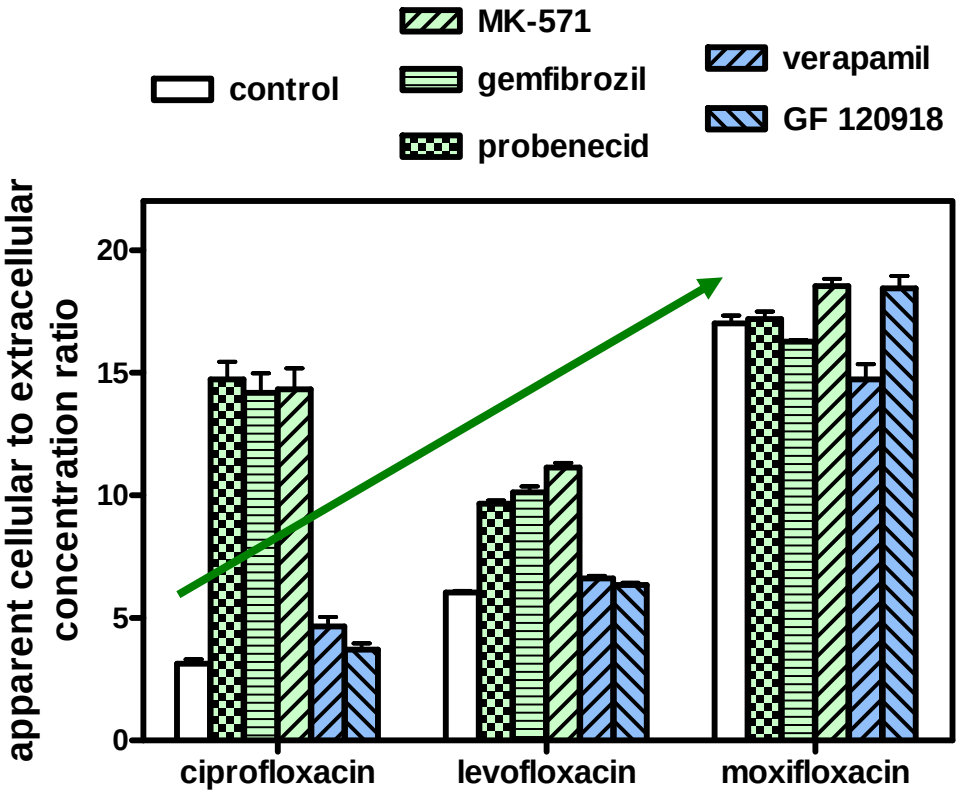
		AUIC		
	AUC (mg/L/h)	*S. pneumoniae* (MIC_{90} = 0.25 mg/L)	*H. influenzae* (MIC_{90} = 0.03 mg/L)	*M. catarrhalis* (MIC_{90} = 0.12 mg/L)
Serum	36.5	145	1210	302
Bronchial mucosa	53.8	215	1793	448
Epithelial lining fluid	189	756	6300	1575
Alveolar macrophages	496	1984	16533	4133

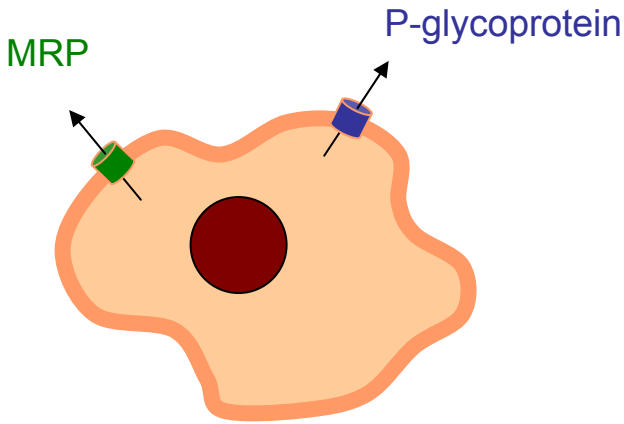
AUC/MIC >>> 125
towards respiratory pathogens

Soman et al., JAC (1999) 44:835-48

Accumulation of FQ in macrophages



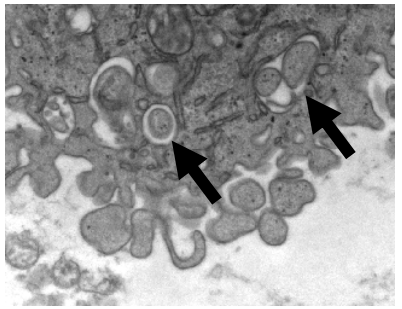


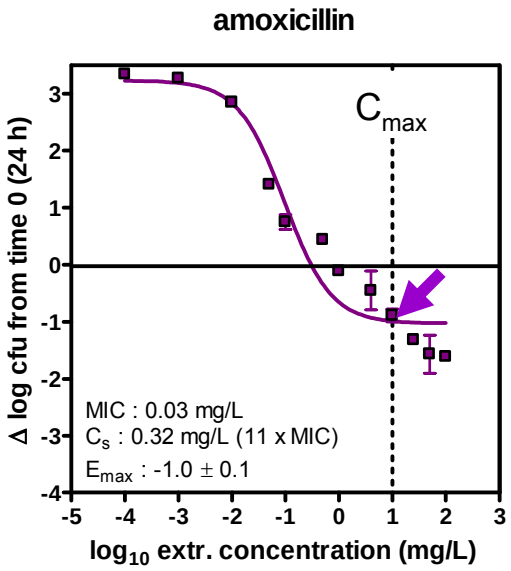


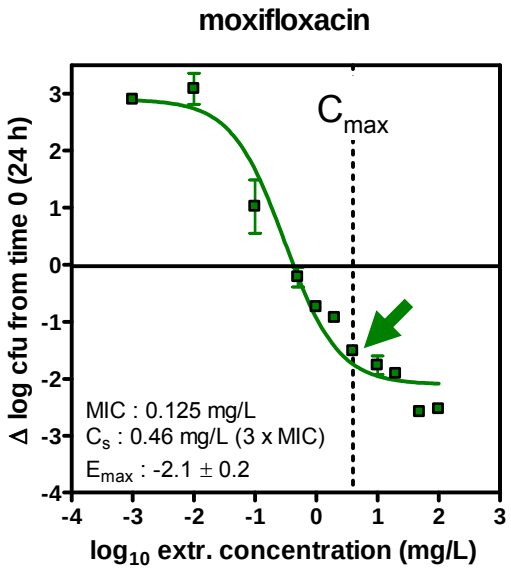
higher accumulation…
because of reduced efflux !

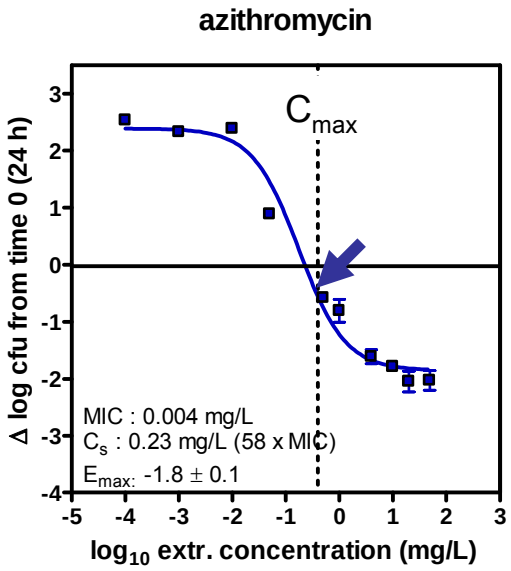
Michot et al., AAC (2005) 49:2429-37

Antibiotic activity against intracellular *S. pneumoniae*





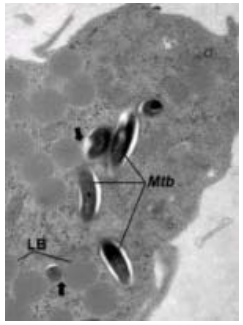


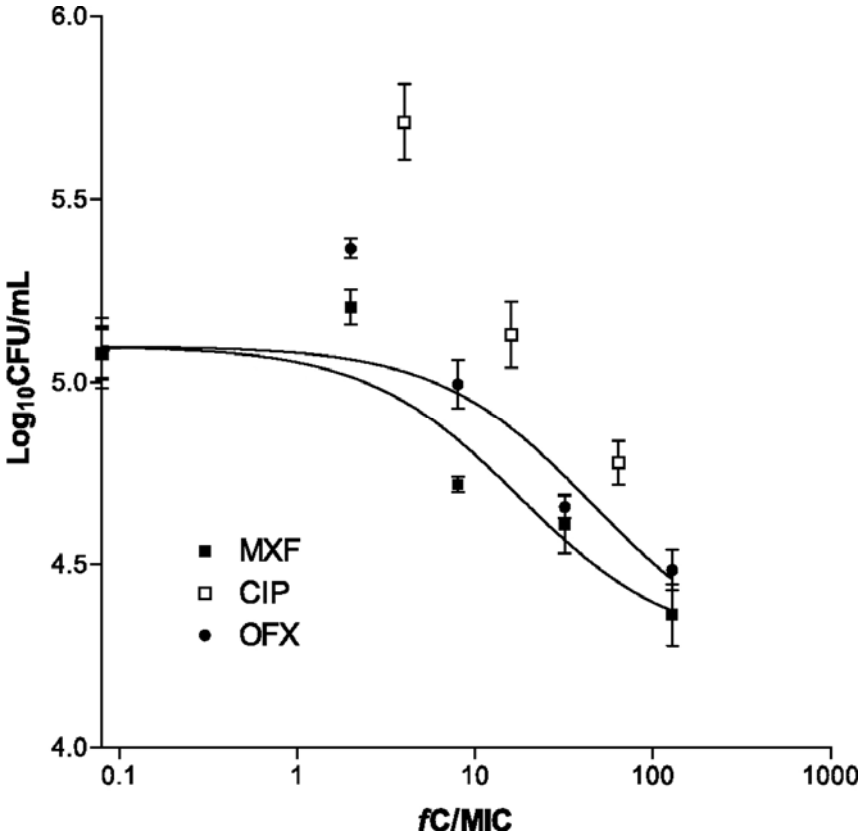


Moxifloxacin is the more efficient,
especially at clinically relevant concentrations.

Lemaire et al., ECCMID 2011

FQ activity against intracellular *M. tuberculosis*





At equivalent C/MIC ratios, moxi and oflo more efficient than cipro

Effects of increasing fC/MIC ratios on the intracellular bactericidal activities of fluoroquinolones against M. tuberculosis in the J774A.1 murine macrophages 3 days of exposure to the drug.

Shandil et al., AAC (2007) 51:576-82

Safety profile

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

- toxicity ?

Side effects of fluoroquinolones (SPC)

What about moxifloxacin ?

system	Frequent < 10 % and ≥ 1 %	Uncommon < 1 % and ≥ 0.1 %	Rare < 0.1 % & ≥ 0.01 %	Uncommon < 1 % & ≥ 0.1 %
Infection	surinfections			
Digestive tract	digestive disconfort, diarrhea		colitis (*C. difficile*)	
Hepatobiliary disorders	transaminase elevation			fulminant hepatitis
Psychiatric disorders	headache, dizziness	anxiety, agitation		
Immune system		allergy	anaphylaxis	
Cardiac disorders		QTc prolongation		torsade de pointe
Musculoskelettal disorders		arthralgy, myalgy	tendonitis	
Metabolism			dysglycemia, hyperuricemia	
Renal disorders			renal impairment	

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]

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2 Bayer Santé SAS, Loos, France
3 Bayer Pharma AG, Wuppertal, Germany

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 = 10 613]	COMP [n = 10 685]	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*

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

Side effects of moxifloxacin (clinical trials database)

Table III. Summary of safety data for 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) and by study design. An asterisk (*) indicates differences observed between treatment groups in disfavor of moxifloxacin that were ≥2.5% for events with an incidence ≥2.5% in both groups or ≥2-fold for events with an incidence <2.5% in one or both groups and for which the number of patients experiencing an event was ≥10 in either group

Study design and event	Treatment route [n (%)]					
Double-blind studies	PO [n = 17 465]		IV/PO [n = 3745]		IV [n = 1159]	
	MXF [n = 8822]	COMP [n = 8643]	MXF [n = 1889]	COMP [n = 1856]	MXF [n = 588]	COMP [n = 571]
Any AE	3782 (42.9)	3711 (42.9)	1202 (63.6)	1138 (61.3)	305 (51.9)*	253 (44.3)
Any ADR	2211 (25.1)	2026 (23.4)	455 (24.1)	439 (23.7)	85 (14.5)	83 (14.5)
SAE	318 (3.6)	316 (3.7)	315 (16.7)	282 (15.2)	74 (12.6)*	54 (9.5)
SADR	47 (0.5)	48 (0.6)	53 (2.8)	46 (2.5)	9 (1.5)	7 (1.2)
Premature discontinuation due to AE	366 (4.1)	337 (3.9)	144 (7.6)	131 (7.1)	16 (2.7)	9 (1.6)
Premature discontinuation due to ADR	261 (3.0)	251 (2.9)	74 (3.9)	63 (3.4)	4 (0.7)	4 (0.7)
AE with fatal outcome	28 (0.3)	36 (0.4)	66 (3.5)	54 (2.9)	21 (3.6)	13 (2.3)
ADR with fatal outcome[a,b,c]	3 (<0.1)	4 (<0.1)	3 (0.2)	3 (0.2)	0 (0.0)	1 (0.2)
Open-label studies	PO [n = 3833]		IV/PO [n = 3101]		IV [n = 701]	
	MXF [n = 1791]	COMP [n = 2042]	MXF [n = 1542]	COMP [n = 1559]	MXF [n = 349]	COMP [n = 352]
Any AE	764 (42.7)*	766 (37.5)	891 (57.8)	899 (57.7)	86 (24.6)	84 (23.9)
Any ADR	330 (18.4)*	325 (15.9)	348 (22.6)	315 (20.2)	49 (14.0)	50 (14.2)
SAE	104 (5.8)	96 (4.7)	280 (18.2)	245 (15.7)	0 (0.0)	1 (0.3)
SADR	12 (0.7)*	5 (0.2)	42 (2.7)*	19 (1.2)	0 (0.0)	0 (0.0)
Premature discontinuation due to AE	70 (3.9)	67 (3.3)	137 (8.9)	109 (7.0)	21 (6.0)*	11 (3.1)
Premature discontinuation due to ADR	51 (2.8)	49 (2.4)	66 (4.3)	54 (3.5)	17 (4.9)	9 (2.6)
AE with fatal outcome	10 (0.6)	15 (0.7)	64 (4.2)	80 (5.1)	0 (0.0)	0 (0.0)
ADR with fatal outcome[d]	0 (0.0)	0 (0.0)	1 (<0.1)	2 (0.1)	0 (0.0)	0 (0.0)

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

Side effects of moxifloxacin (clinical trials database)

- **AE, ADR and SADR were mainly gastrointestinal disorders and "changes observed during investigations" such as asymptomatic QT prolongation.**
- **Incidence rates of hepatic disorders, tendon disorders, surrogates of QT prolongation, serious cutaneous reactions and *Clostridium difficile*-associated diarrhoea were similar with moxifloxacin and comparators.**

Study design and event	Treatment route [n (%)]					
Double-blind studies	PO [n = 17 465]		IV/PO [n = 3745]		IV [n = 1159]	
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Open-label studies	PO [n = 3833]		IV/PO [n = 3101]		IV [n = 701]	
	MXF [n = 1791]	COMP [n = 2042]	MXF [n = 1542]	COMP [n = 1559]	MXF [n = 349]	COMP [n = 352]
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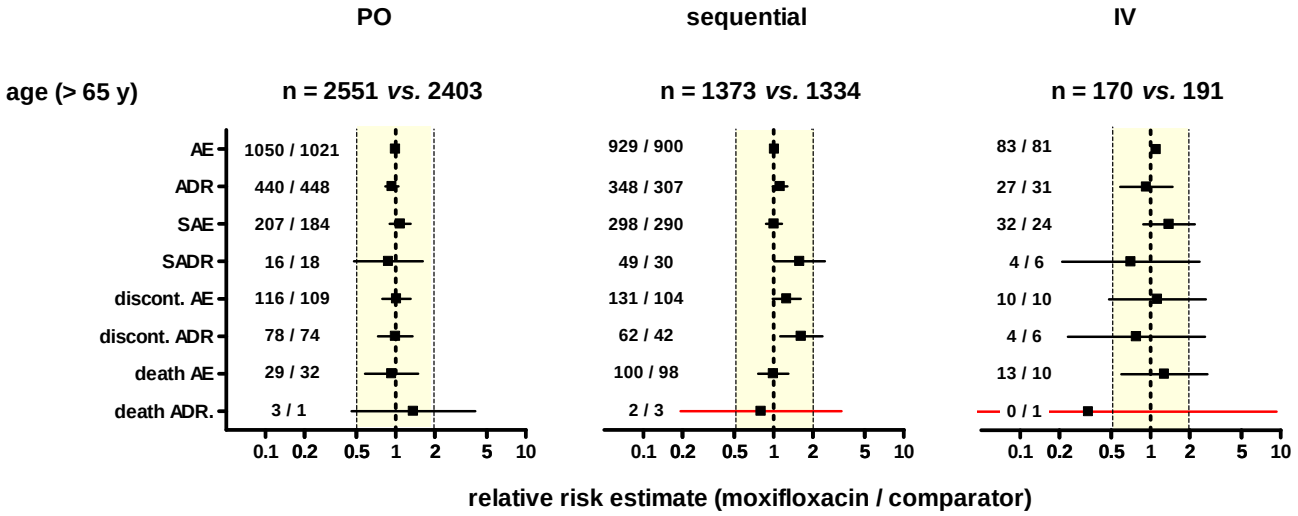
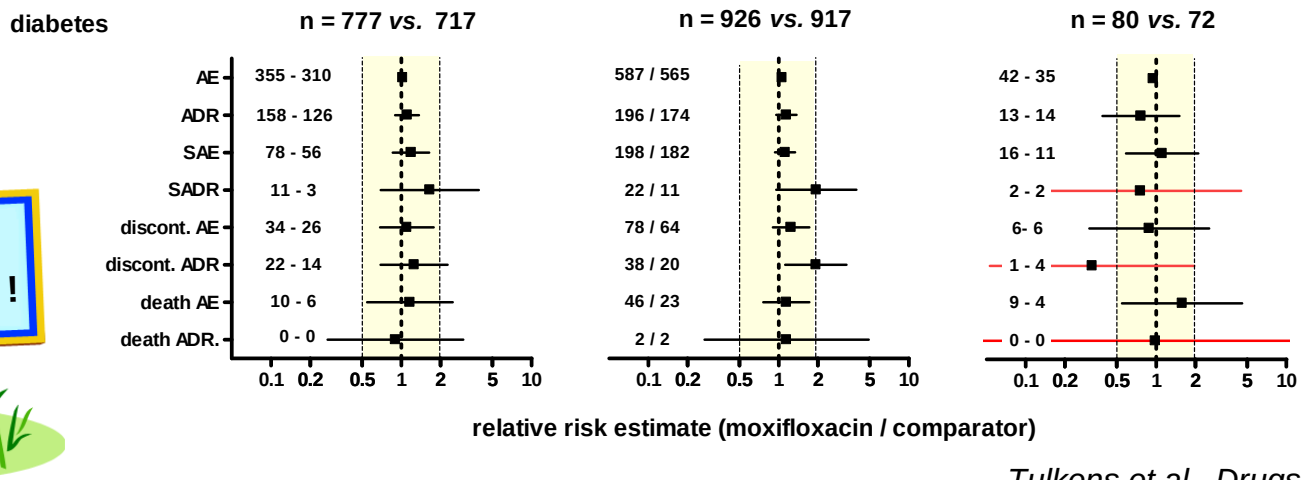
AE with fatal outcome	10 (0.6)	15 (0.7)	64 (4.2)	80 (5.1)	0 (0.0)	0 (0.0)
ADR with fatal outcome[d]	0 (0.0)	0 (0.0)	1 (<0.1)	2 (0.1)	0 (0.0)	0 (0.0)

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

Side effects of moxifloxacin (clinical trials database)

Patients at risk ?

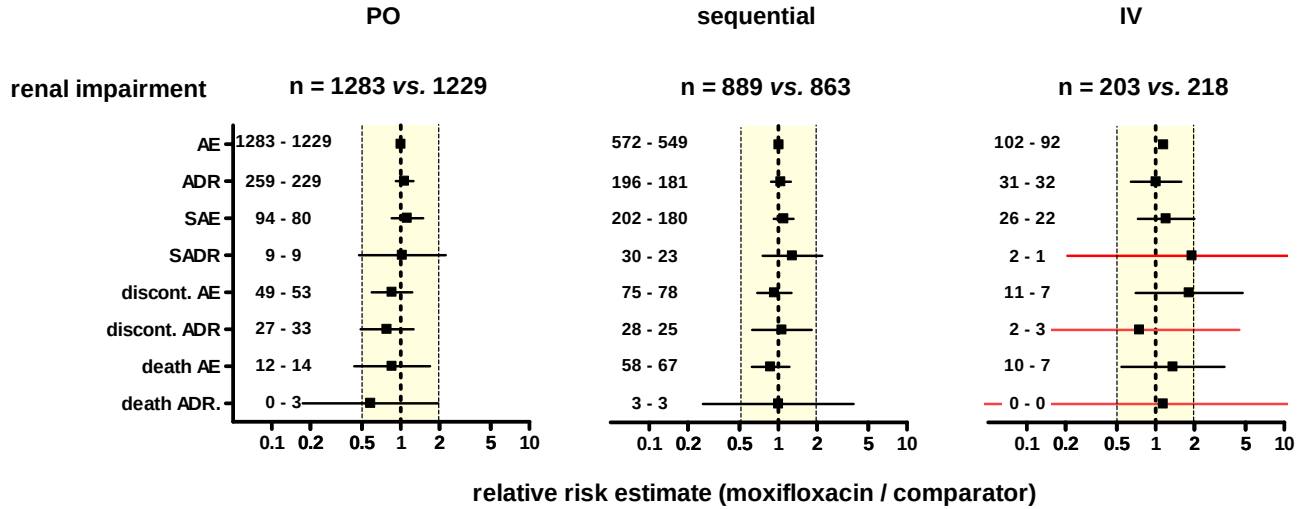


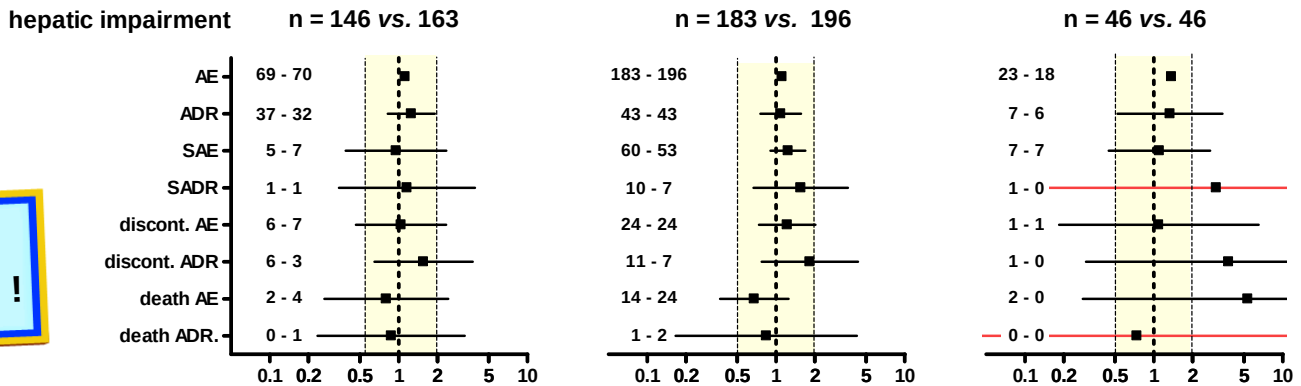


Tulkens et al., Drugs R D (2012) 12: 71-100

Side effects of moxifloxacin (clinical trials database)

Patients at risk ?

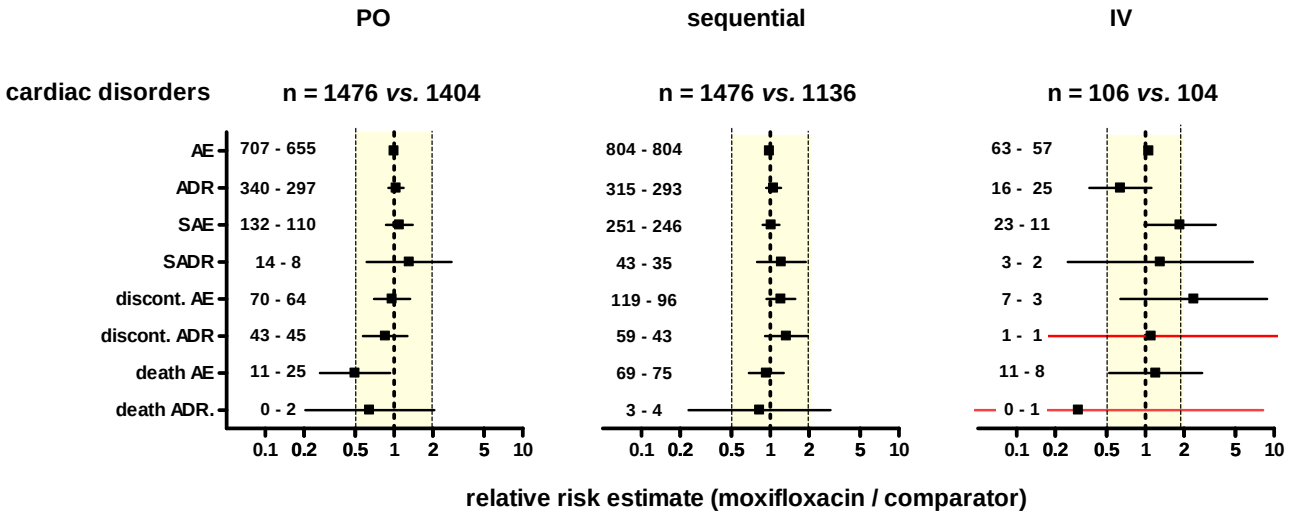


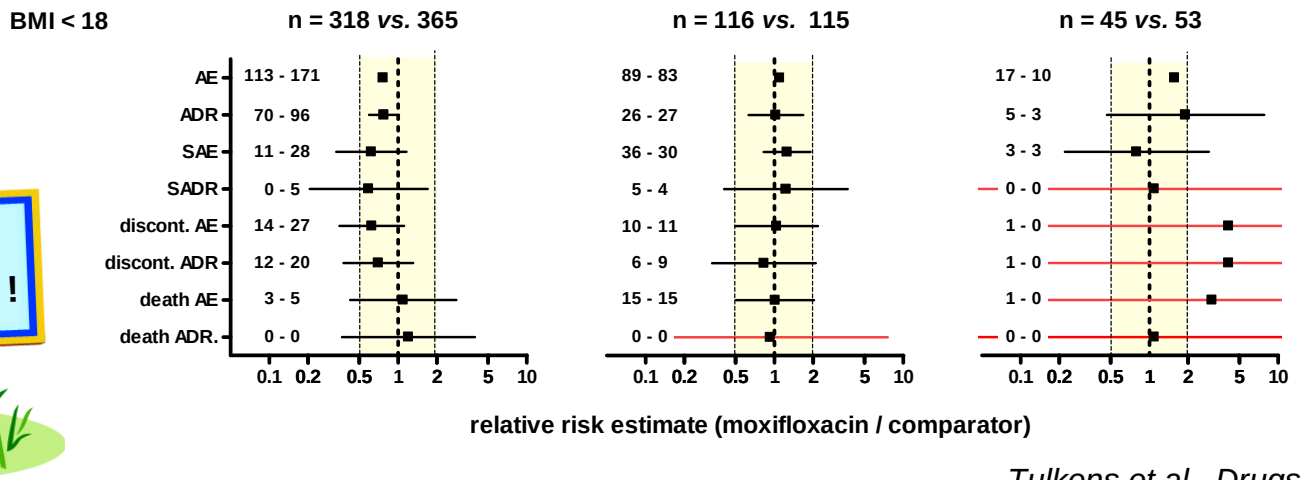


Tulkens et al., Drugs R D (2012) 12: 71-100

Side effects of moxifloxacin (clinical trials database)

Patients at risk ?





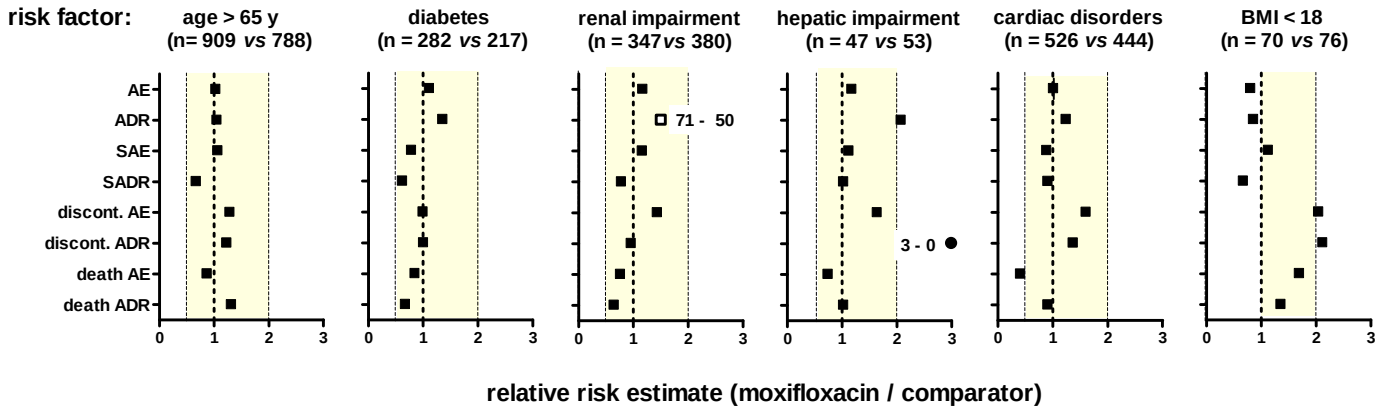
Tulkens et al., Drugs R D (2012) 12: 71-100

Side effects of moxifloxacin (clinical trials database)

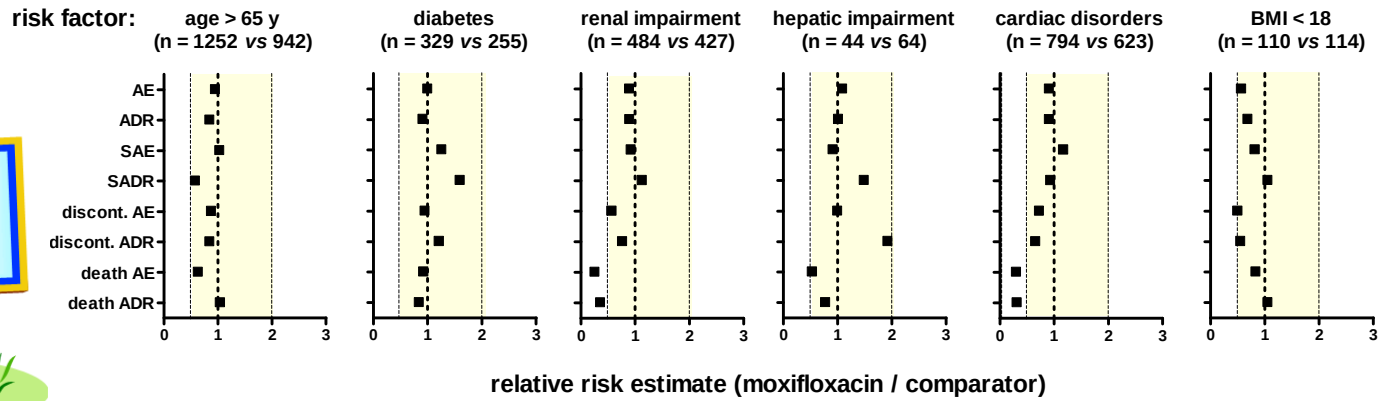
Comparison with other drugs ?

A. oral therapy

1. moxifloxacin *vs* β-lactams



2. moxifloxacin *vs* macrolides



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

Hepatotoxicity

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

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

SMQ-search for "severe events": Hepatic overview by event type/diagnosis

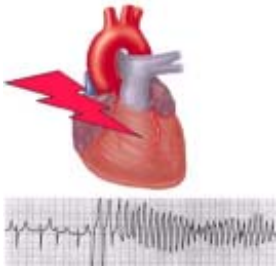
	Moxifloxacin AE [ADR]	Comparator AE [ADR]
Total	**19 [16]**	**17 [7]**
Hepatitis		
CTC grade ≥3 (severe)	3 [2]	1 [0]
CTC grade <3 (non-severe)	4 [4]	5 [3]
Hepatic failure		
CTC grade ≥3 (severe)	1 [0]	0
CTC grade <3 (non-severe)	2 [2]	1 [1]
Liver disorder		
CTC grade ≥3 (severe)	0	3 [1]
CTC grade <3 (non-severe)	9 [8]	5 [2]
Liver neoplasm	0	2 [0]
Outcomes		
Resolved/improved	17	10
Unchanged	1	2
Worsened/death	0	1
Unknown	1	4

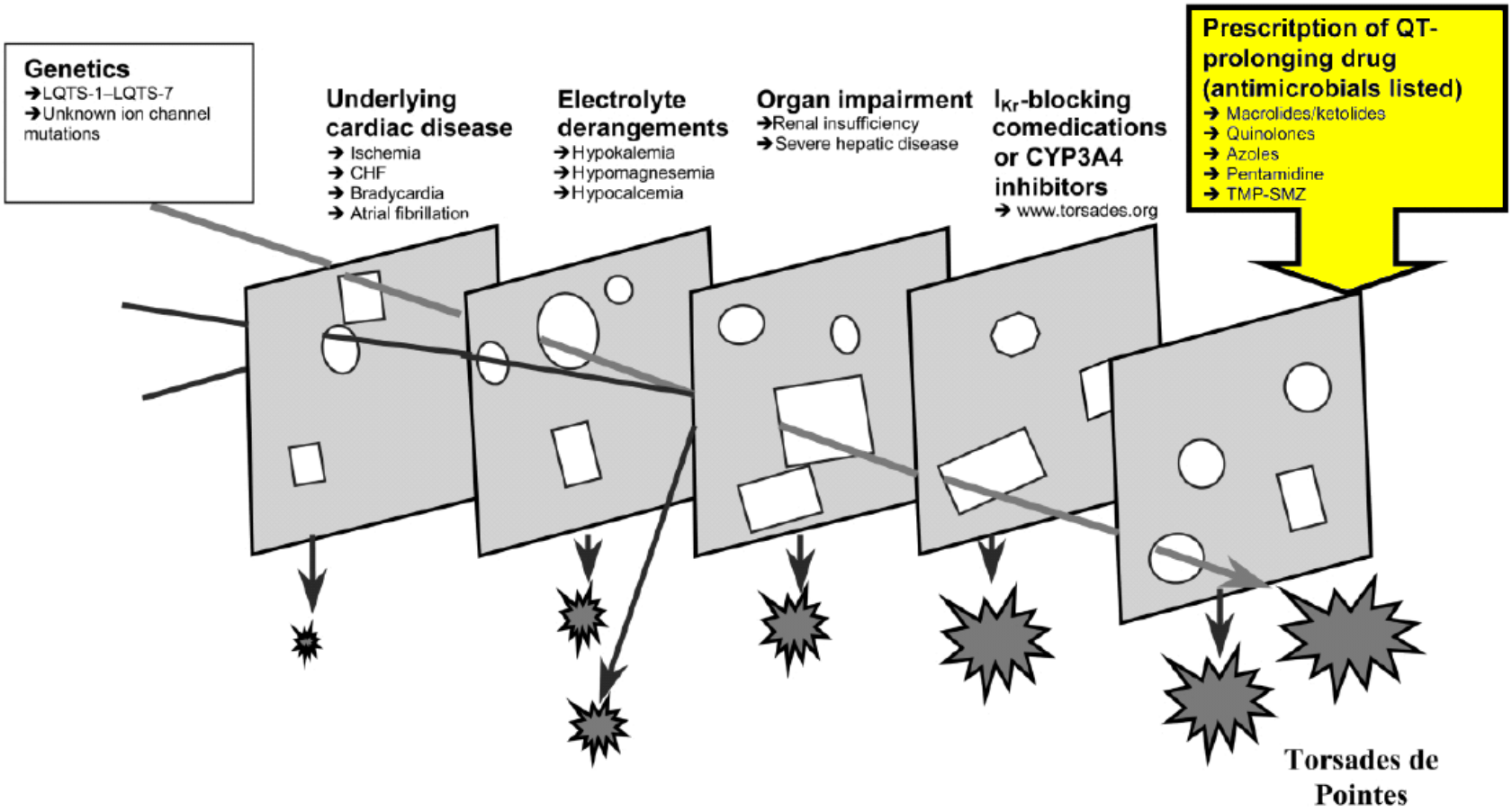
AE: adverse event; ADR: adverse drug reaction

Common Terminology Criteria for Adverse Events v3.0:

- AP, GGT, AST, ALT: Grade 1 (mild), >ULN – 2.5x ULN; Grade 2 (moderate), >2.5 – 5.0x ULN; Grade 3 (severe), >5.0 – 20.0x ULN; Grade 4 (life-threatening), >20.0x ULN
- Total bilirubin: Grade 1 (mild), >ULN – 1.5x ULN; Grade 2 (moderate), >1.5 – 3.0x ULN; Grade 3 (severe), >3.0 – 10.0x ULN; Grade 5 (life-threatening), >10.0x ULN

QTc prolongation





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

EMA position

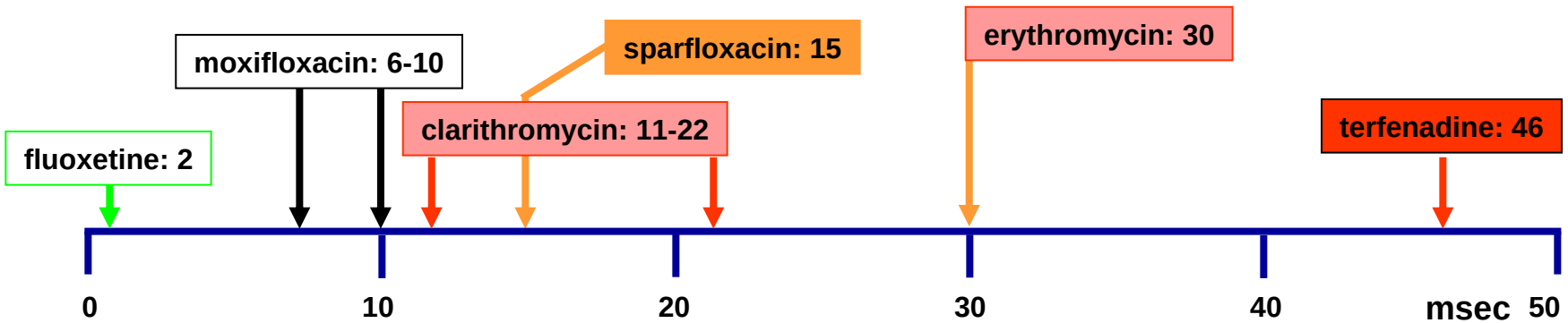
European Medicines Agency

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)

Moxifloxacin cardiac safety: data from phase II-IV trials

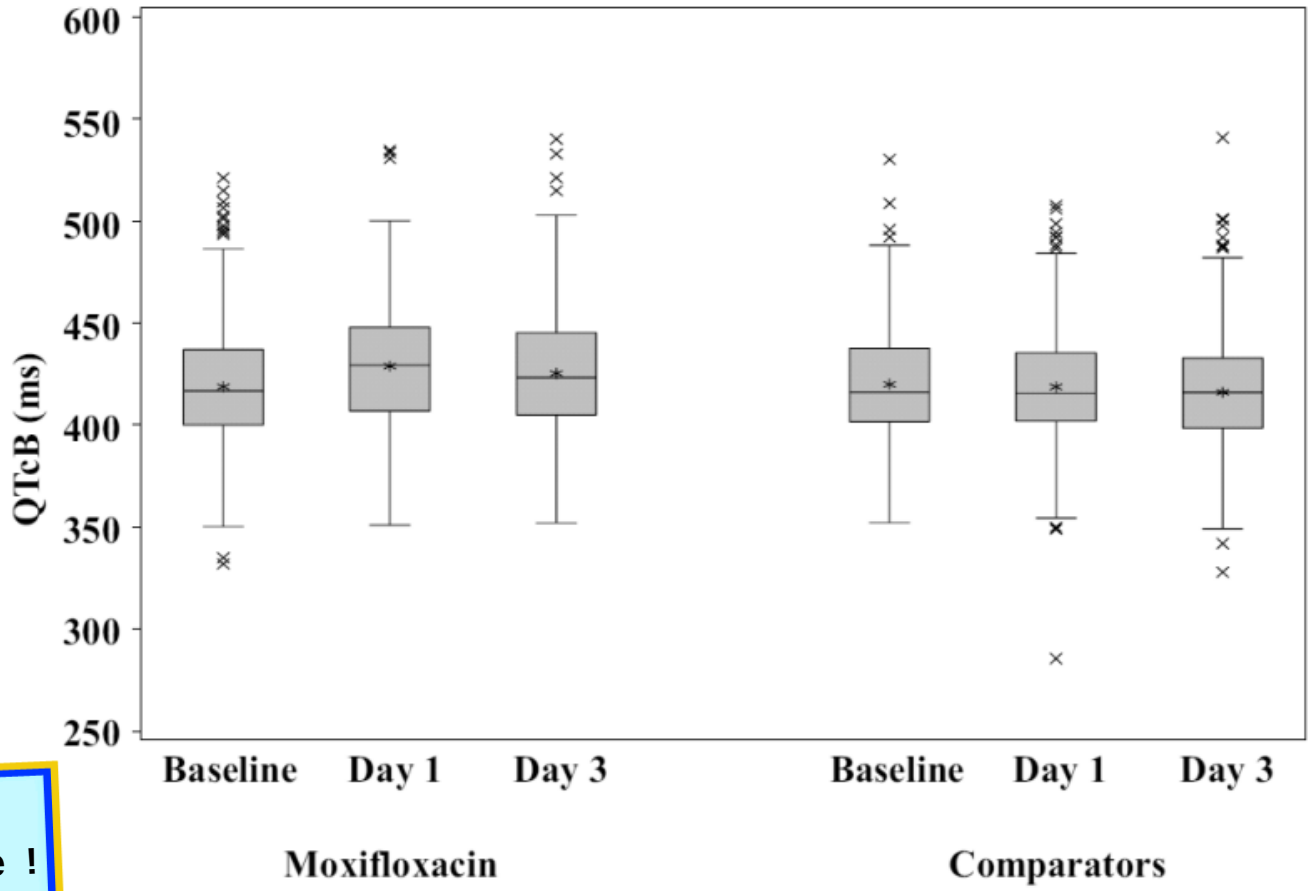
Baseline Patient Characteristics Across All Phase II to IV Randomized Active-Controlled Studies with PO or IV/PO Moxifloxacin

	PO (N = 21,298)		IV/PO (N = 6846)	
	Moxifloxacin (N = 10,613)	Comparators[a] (N = 10,685)	Moxifloxacin (N = 3431)	Comparators[a] (N = 3415)
Age, mean ± SD (years)	48.2 ± 18.0	48.0 ± 17.9	56.8 ± 19.1	56.1 ± 19.2
Age ≥ 65 years, n (%)	2451 (23.1)	2403 (22.5)	1373 (40.0)	1334 (39.1)
Female sex, n (%)	5773 (54.4)	5817 (54.4)	1349 (39.3)	1323 (38.7)
Body mass index, mean ± SD (kg/m^2)	26.0 ± 5.9	25.9 ± 5.8	26.9 ± 6.6	26.7 ± 6.4
Heart rate, mean ± SD (bpm)[b]	82.8 ± 13.6	83.0 ± 13.7	93.7 ± 18.2	93.7 ± 18.1
Cardiac disease, n (%)	1475 (13.9)	1402 (13.1)	1167 (34.0)	1136 (33.3)
Comedication known to cause QT prolongation, n (%)[c]	430 (4.1)	426 (4.0)	343 (10.0)	298 (8.7)
Indication, n (%)				
Acute bacterial sinusitis	2331 (22.0)	2641 (24.7)	n/a	n/a
Acute exacerbation of chronic bronchitis	4029 (38.0)	3820 (35.8)	n/a	n/a
Community-acquired pneumonia	1790 (16.9)	1822 (17.1)	1511 (44.0)	1539 (45.1)
Complicated skin and skin structure infection	n/a	n/a	1130 (32.9)	1077 (31.5)
Complicated intra-abdominal infection	n/a	n/a	618 (18.0)	622 (18.2)
Uncomplicated pelvic inflammatory disease	946 (8.9)	919 (8.6)	n/a	n/a
Other	1517[d] (14.3)	1483[d] (13.9)	172[e] (5.0)	177[e] (5.2)

PO = oral administration; IV/PO = sequential intravenous/oral administration; SD = standard deviation; n/a = not applicable.
[a]For a list of comparators see Table 1.
[b]PO: n = 7499 moxifloxacin, n = 7170 comparators; IV/PO: n = 3401 moxifloxacin, n = 3398 comparators.
[c]Comedications known to cause QTc prolongation were selected according to [30] and [31].
[d]Uncomplicated skin and skin structure infection, complicated urinary tract infection, streptococcal pharyngitis.
[e]Aspiration pneumonia or lung abscess, hospital-acquired pneumonia.

Haverkamp et al.,Curr Drug Saf. (2012) 7: 149–63

Moxifloxacin cardiac safety: data from phase II-IV trials



Haverkamp et al.,Curr Drug Saf. (2012) 7: 149–63

Moxifloxacin cardiac safety: data from phase II-IV trials

Treatment-Emergent Events Considered Potential Surrogates for TdP/QTc Prolongation: Pooled Data from Phase II to IV Randomized Active-Controlled Studies with Moxifloxacin

System Organ Class • MedDRA[a] Preferred Term	PO Studies, n[b] (%)		IV/PO Studies, n (%)	
	Moxifloxacin (N[c] = 10613)	Comparators[d] (N = 10685)	Moxifloxacin (N = 3431)	Comparators[d] (N = 3415)
Any event	25 (0.2)	23 (0.2)	37 (1.1)	36 (1.1)
Cardiac disorders				
• Cardiac arrest	1 (< 0.1)	1 (< 0.1)	9 (0.3)	11 (0.3)
• Cardiac flutter	2 (< 0.1)	1 (< 0.1)	0 (0)	0 (0)
• Cardiorespiratory arrest	2 (< 0.1)	1 (< 0.1)	4 (0.1)	5 (0.1)
• *Torsade de pointes*	0 (0)	0 (0)	0 (0)	1 (< 0.1)
• Ventricular arrhythmia	2 (< 0.1)	0 (0)	0 (0)	3 (< 0.1)
• Ventricular fibrillation	1 (< 0.1)	0 (0)	0 (0)	1 (< 0.1)
• Ventricular tachycardia	0 (0)	2 (< 0.1)	11 (0.3)	8 (0.2)
General disorders and administration				
• Death	2 (< 0.1)	2 (< 0.1)	2 (< 0.1)	0 (–)
• Sudden death	2 (< 0.1)	1 (< 0.1)	2 (< 0.1)	2 (< 0.1)
• Sudden cardiac death	0 (0)	0 (0)	1 (< 0.1)	0 (0.0)
Nervous system disorders				
• Loss of consciousness	4 (< 0.1)	5 (< 0.1)	0 (0.0)	1 (< 0.1)
• yncope	9 (< 0.1)	10 (< 0.1)	6 (0.2)	5 (0.1)
l and medicinal procedures				
esuscitation	0 (0)	0 (0)	2 (< 0.1)	0 (0)

PO = oral administration; IV/PO = sequential intravenous/oral administration.
[a]Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query.
[b] = mber of patients with event.
mber of patients in group.
of comparators see Table 1.

Haverkamp et al.,Curr Drug Saf. (2012) 7: 149–63

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

Moxifloxacin safety: a conclusion…

LEADING ARTICLE

Drug Safety 2009; 32 (5): 359-378
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Safety Profile of the Respiratory Fluoroquinolone Moxifloxacin

Comparison with Other Fluoroquinolones and Other Antibacterial Classes

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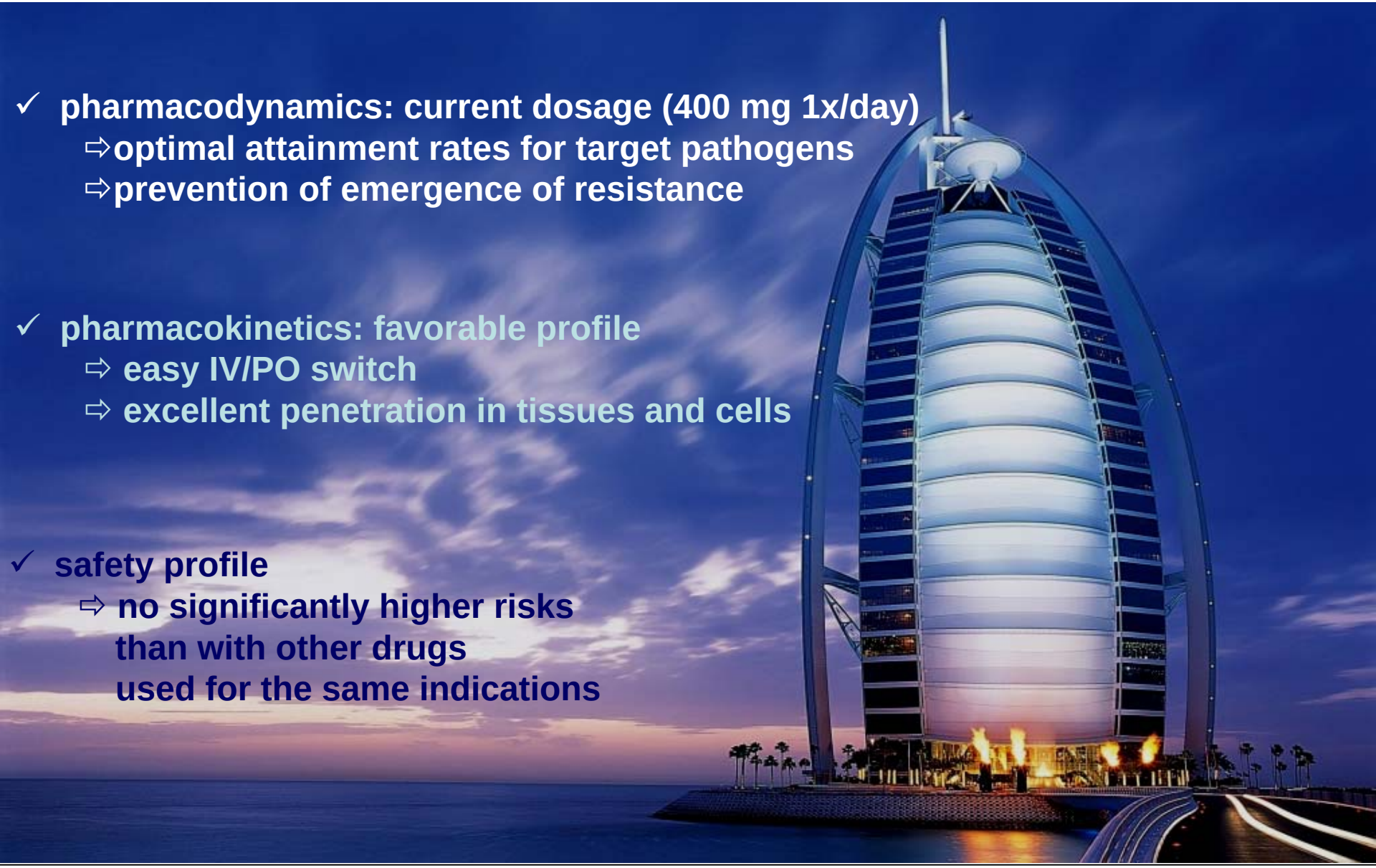
The data show that using moxifloxacin, in its accepted indications and following the corresponding guidelines, should not be associated with an excessive incidence of drug-related adverse reactions, provided the clinician takes care in identifying patients with known risk factors and pays due attention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

Take home message …



- ✓ **pharmacodynamics: current dosage (400 mg 1x/day)**
  - ⇨ **optimal attainment rates for target pathogens**
  - ⇨ **prevention of emergence of resistance**
- ✓ **pharmacokinetics: favorable profile**
  - ⇨ **easy IV/PO switch**
  - ⇨ **excellent penetration in tissues and cells**
- ✓ **safety profile**
  - ⇨ **no significantly higher risks than with other drugs used for the same indications**

Disclosures

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- ✓ Professor at the Université catholique de Louvain

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Back-up slides

In vitro antimicrobial activities against common SSSI pathogens

pathogens	MIC_{90} (mg/L)				
	Moxifloxacin[1]	Levofloxacin[1]	Ertapenem[2]	Amoxicillin/ clavulanate[2]	Piperacillin/ tazobactam[2]
MSSA†	0.125	0.5	0.25	1	2
MRSA††	2	8	>16	>16	>32
S. pyogenes	0.25	0.5	0.03	0.03	0.125
P. aeruginosa	16	8	16	>16	16
E. coli	0.063	0.063	≤0.016	8	16
K. pneumoniae	0.125	0.125	0.016	4	4
***Enterococcus* spp.**	8	≥16	16	4	8

†***Methicillin-sensitive S. aureus***

††***Methicillin-resistant S. aureus.*** ***Moxifloxacin is not indicated for MRSA infections***

[1] *Blondeau et al. Int J Antimicrob Ag. (2003) 22: 147–54*

[2] *Pelak et al. Diagn Microbiol Infect Dis (2002) 43: 129–33*

In vitro antimicrobial activities against most common pathogens found in cIAI

Organism (no. of isolates)	% susceptibility (MIC_{90}; mg/L)			
	Moxifloxacin	Ciprofloxacin	Levofloxacin	Piperacillin-Tazobactam
Gram positives				
E. faecalis (20)	90 (1.0)	70 (>8.0)	65 (>8.0)	90 (16.0)
Streptococcus spp. (30)	100 (0.5)	85.7 (>8.0)	100 (2.0)	100 (8.0)
Gram negatives				
E. coli (100)	100 (0.06)	100 (0.03)	100 (0.03)	90 (4.0)
P. mirabilis (10)	100 (1.0)	100 (0.12)	100 (0.12)	90 (2.0)
Anaerobes				
B. fragilis (130)	96.9 (1.0)	NI*	NI*	93.8 (8.0)
C. perfringens (35)	100 (2.0)	NI*	NI*	100 (0.25)
B. thetaiotamicrons (40)	95 (2.0)	NI*	NI*	85 (32.0)
Peptostreptococcus spp. (65)	100 (0.5-1.0)	NI*	NI*	100 (0.25-0.5)

Edmiston et al. Antimicrob. Ag. Chemother. (2004) 48:1012-1016