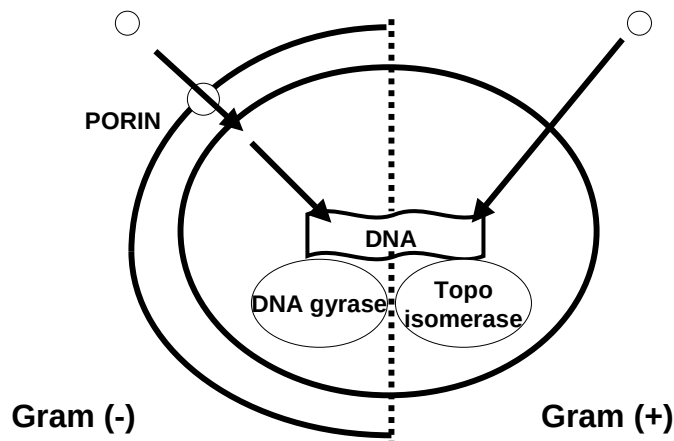


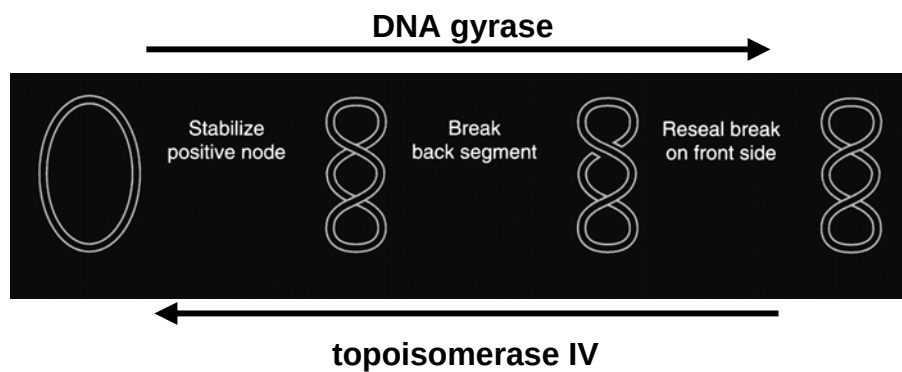
Mechanism of action of fluoroquinolones: the basics...



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1

2 key enzymes in DNA replication:

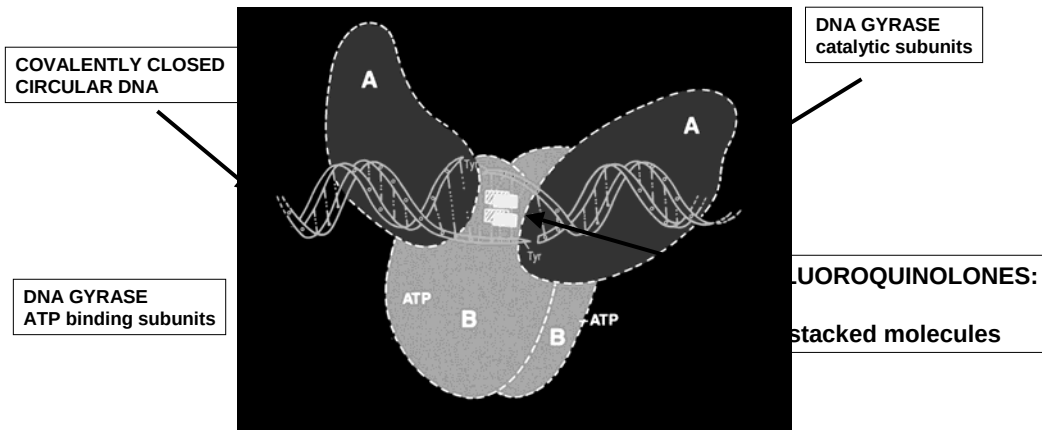


bacterial DNA is supercoiled

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2

Ternary complex DNA - enzyme - fluoroquinolone

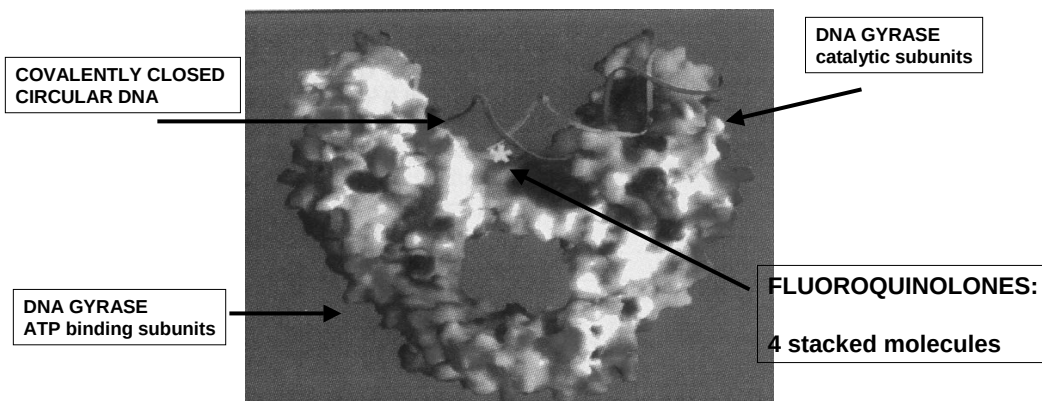


(Shen, *in* Quinolone Antimicrobial Agents, 1993)

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3

Ternary complex DNA - enzyme - fluoroquinolone

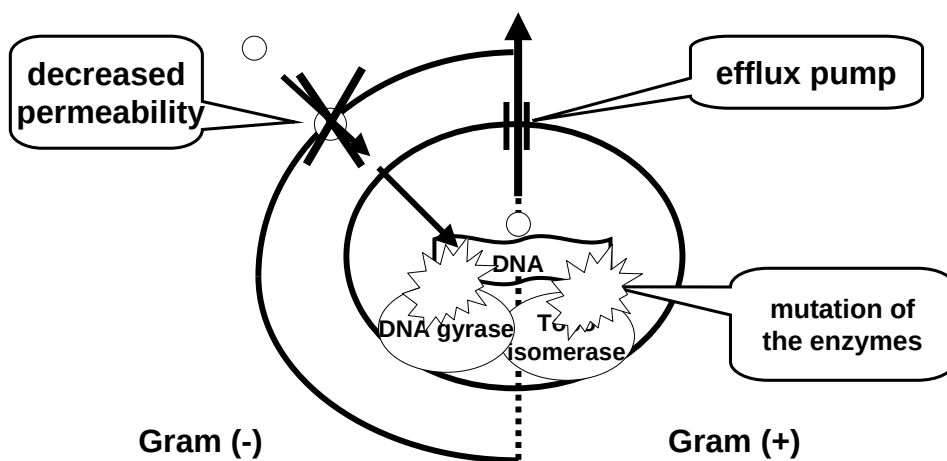


Cabral *et al.*, *Nature*, 1997

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4

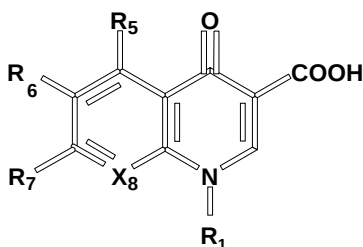
Resistance to fluoroquinolones: the basics



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5

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



Don't panic, we will travel together....

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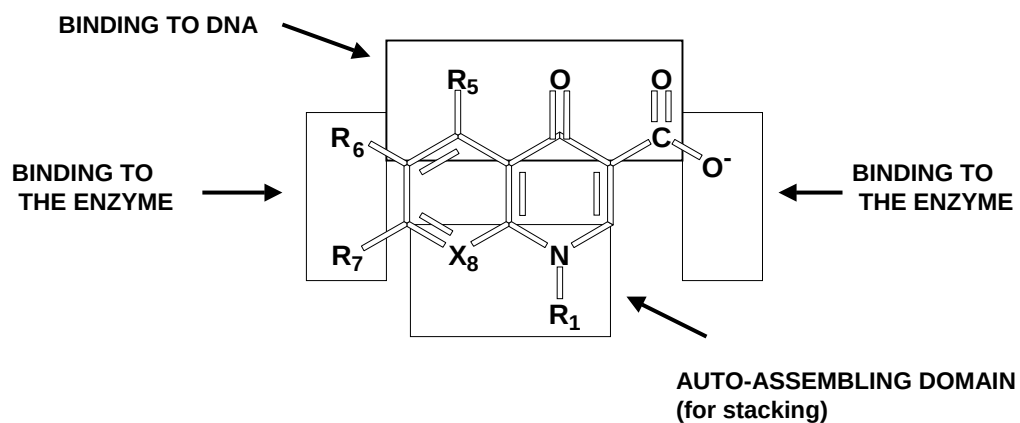
6

Chemistry and Activity

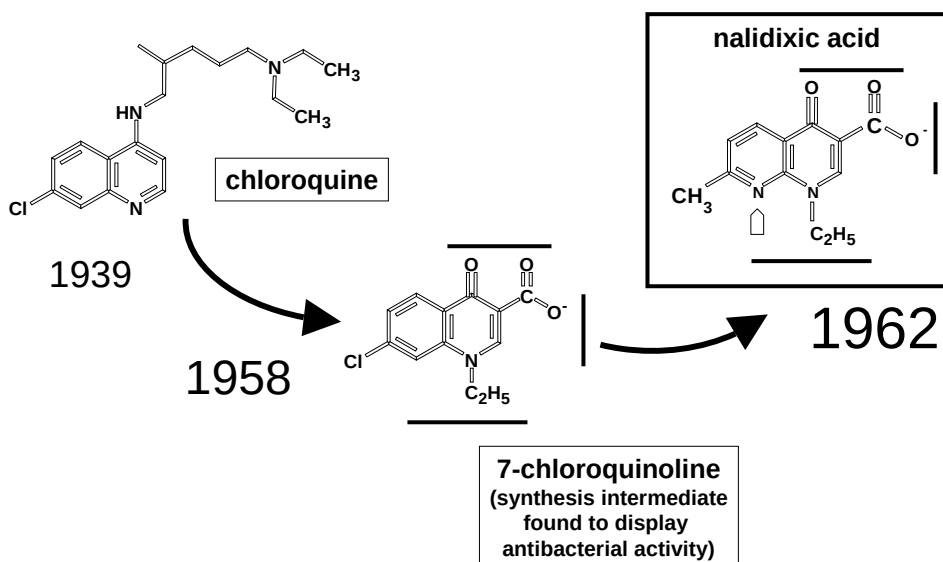


This is where all begins...

The pharmacophore common to all fluoroquinolones



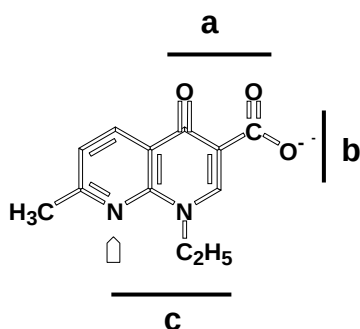
From chloroquine to nalidixic acid...



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Nalidixic acid *



- typical chemical features of fluoroquinolones (a, b, c)
BUT a naphthridone (N at position 8: )
- limited usefulness as drug
 - narrow antibacterial spectrum (*Enterobacteriaceae* only)
 - short half-life (1.5h)
 - high protein binding (90%)

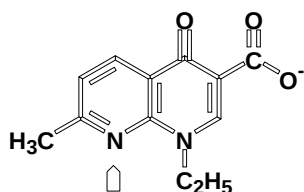
* Belg. pat. 612,258 to Sterling Drugs, 1962

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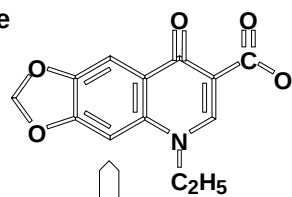
From nalidixic acid to the 1st fluoroquinolone (1 of 4)

nalidixic acid



1. modify naphthyridone
into quinolone

oxolinic acid *



shows reduced protein binding...

* Ger. pat. to Warner Lambert, 1967

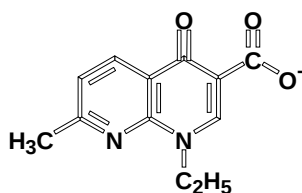
* quinoleine

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11

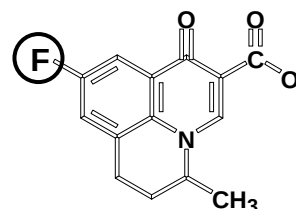
From nalidixic acid to the 1st fluoroquinolone (1 of 4)

nalidixic acid



2. discovery of
flumequine *

flumequine *



shows weak but broad
Gram(-) activity

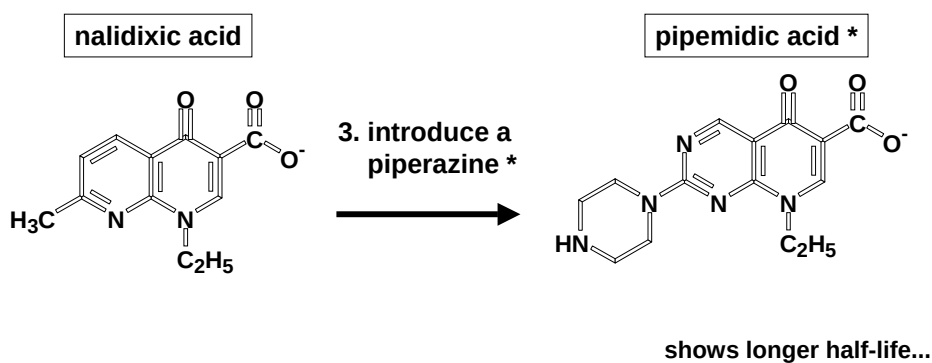
* Ger pat. to Rikker Labs, 1973

* benzo-quinolizine

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From nalidixic acid to the 1st fluoroquinolone (1 of 4)



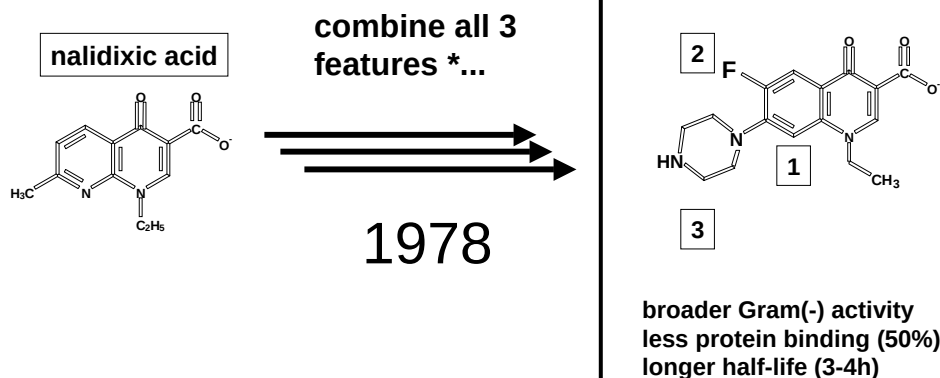
* Ger. Pat. to Roger Bellon, 1974

* pyrido-2-3-pyrimidine

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13

From nalidixic acid to the 1st fluoroquinolone (1 of 4)



* Belgian patent 863,429, 1978 to Kyorin

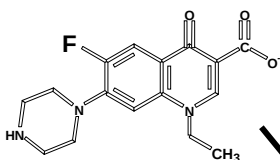
* 6-fluoro-7-pyrimidino-quinoleine

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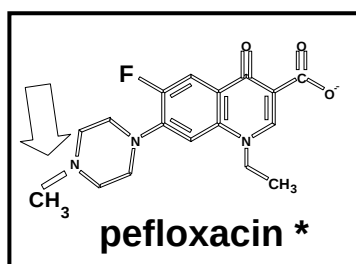
14

From norfloxacin to the other 1st generation fluoroquinolones: pefloxacin

norfloxacin



Add a methyl
to still increase
half-life



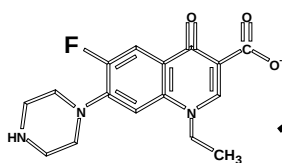
* Ger. pat. 2,840,910 to
Roger Bellon/Dainippon, 1979

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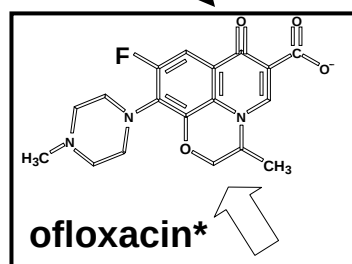
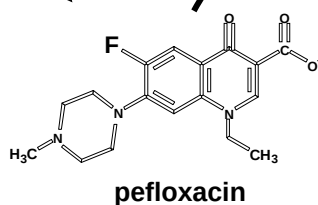
15

From norfloxacin to the other 1st generation fluoroquinolones: ofloxacin

norfloxacin



tricyclic compound
(as in flumequine but
morpholine ring)

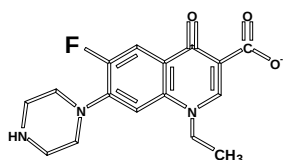


* Eur. pat. Appl. 47,005 to Daiichi, 1982
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From norfloxacin to the other 1st generation fluoroquinolones: ciprofloxacin

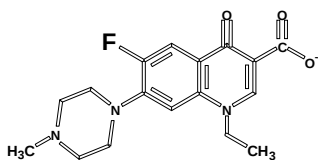
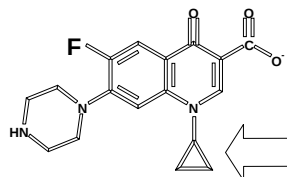
norfloxacin



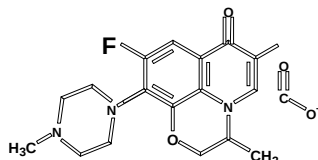
cyclopropyl to
increase potency



ciprofloxacin *



pefloxacin



ofloxacin

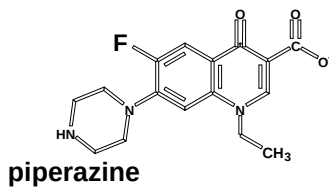
FARM 2146 Fluoroquinolones 2/10/2005

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

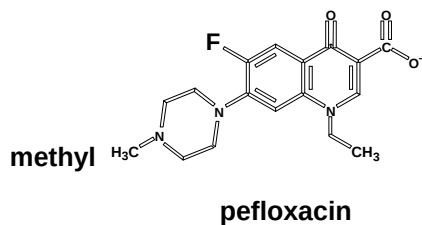
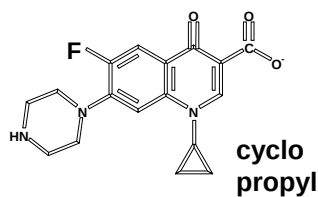
17

"1st generation" fluoroquinolones

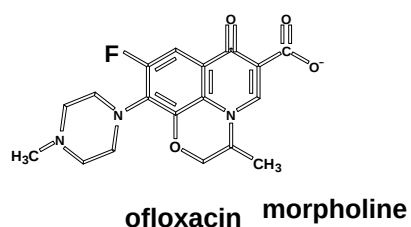
norfloxacin



ciprofloxacin



pefloxacin

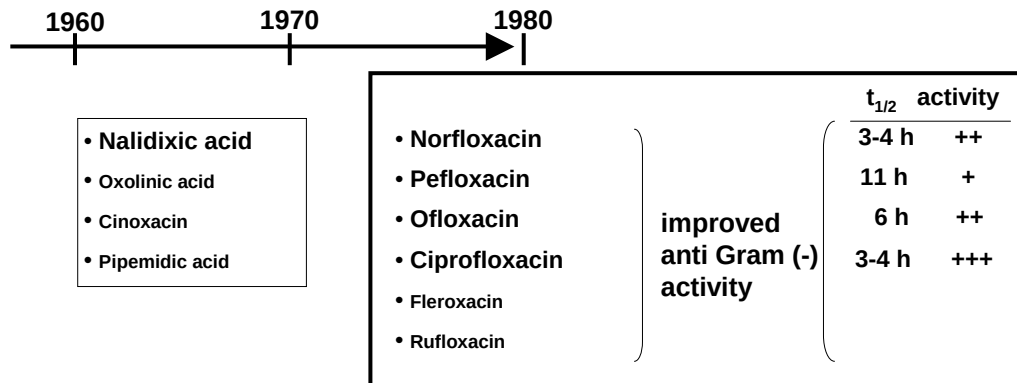


ofloxacin

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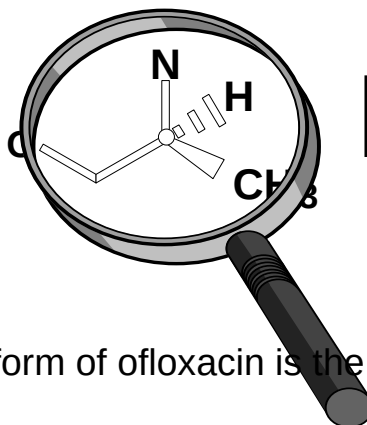
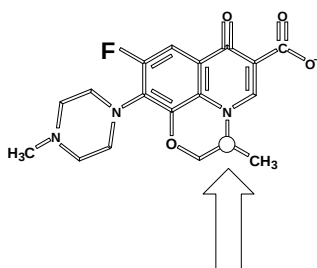
18

The "first generation" of fluoroquinolones



From ofloxacin to levofloxacin...

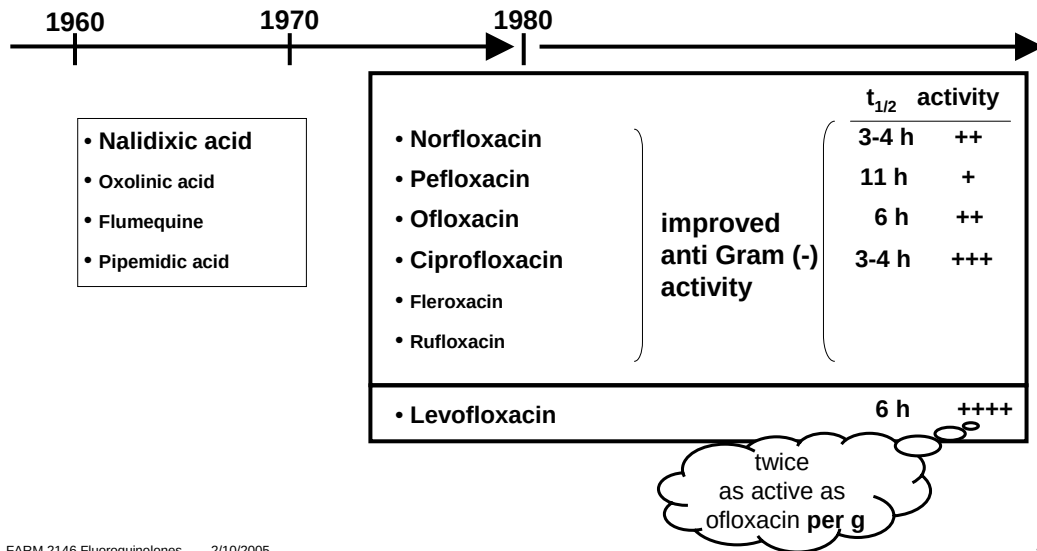
Ofloxacin is a racemic mixture



Levofloxacin is the pure (-) S isomer *

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

The present "first generation" of fluoroquinolones ...



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

1. Maintain broad Gram(-) activity

2. Improve Gram(+) activity

3. Acquire activity against anaerobes

"2d generation"

"3d generation"

22

The “second generation” fluoroquinolones



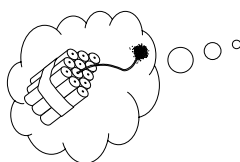
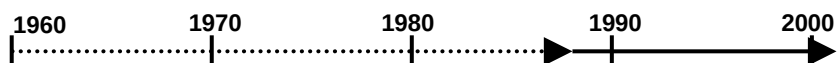
- Temafloxacin ^a
 - Sparfloxacin ^b
 - Grepafloxacin ^c
 - Gatifloxacin ^d
- Gram (-);
- improved Gram (+)
- anti-anaerobe

a: Toyama, 1988 (?); b: Dainippon, 1985-1987; c: Otskuda, 1989; d: Kyorin, 1988

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The “third generation” fluoroquinolones

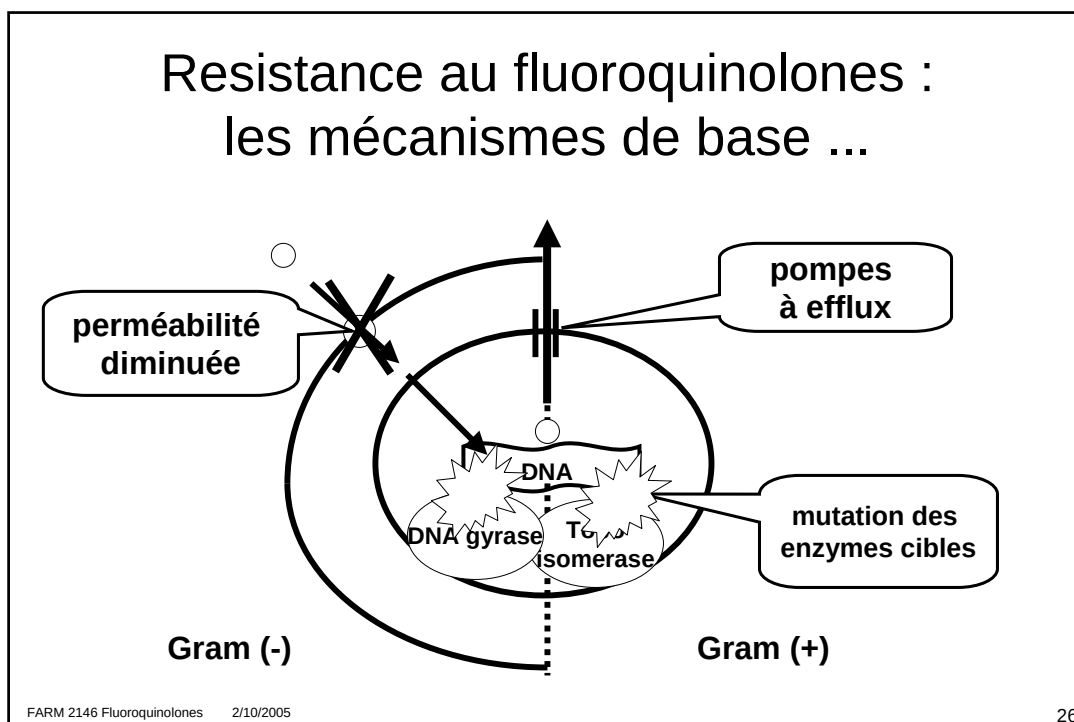
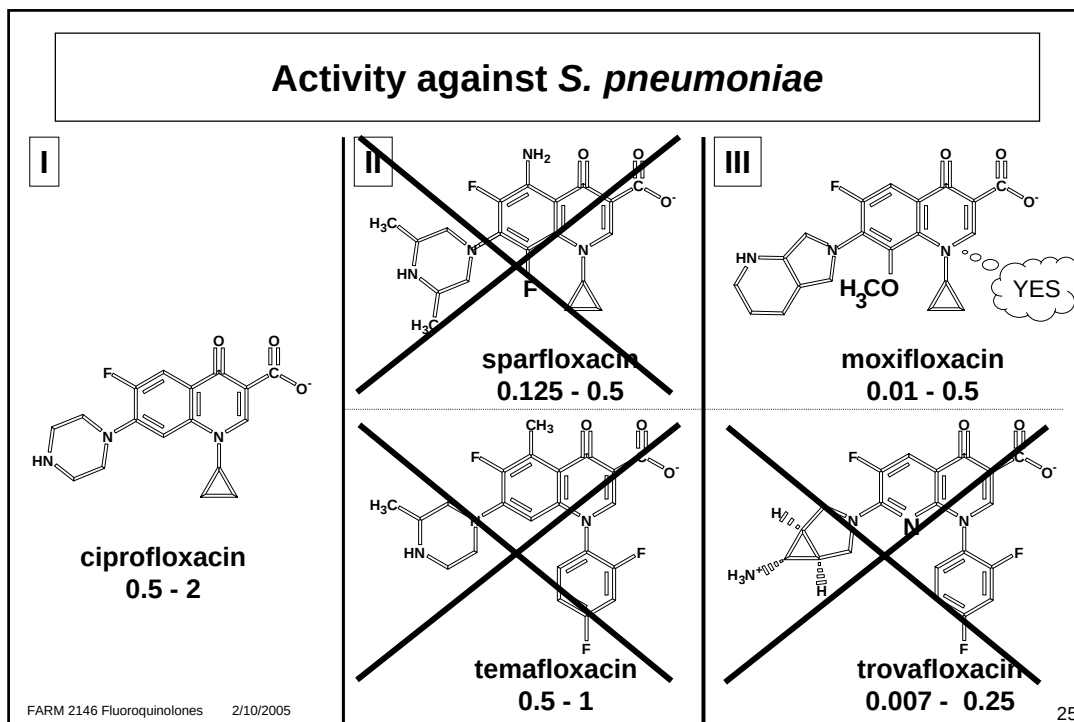


- Clinafloxacin ^a
 - Trovafloxacin ^b
 - Moxifloxacin ^c
 - Gemifloxacin ^d
- anti-Gram (-)
- anti-Gram (+)
- anti-anaerobe

a: Kyorin, 1987; b: Pfizer, 1993; c: Bayer, 1994; d: LG Chemical Ltd., S. Korea, 1994-98

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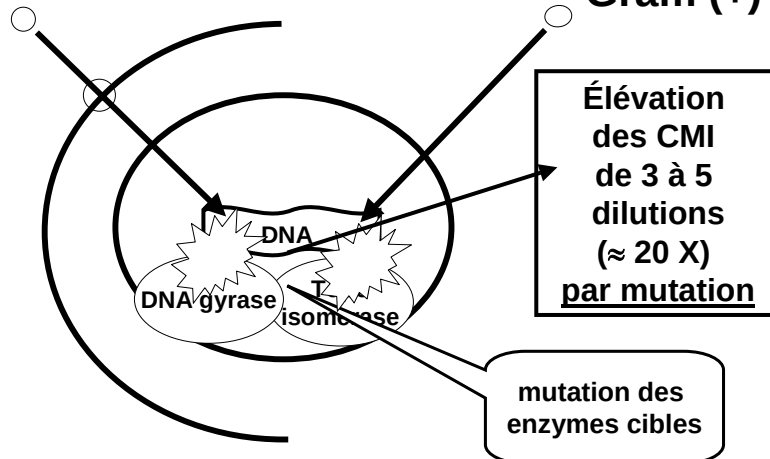
24



Resistance au fluoroquinolones : rôle des mutations au niveau de la cible

Gram (-)

Gram (+)



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Is there a SAR for emergence of resistance ?

The "Mutant Prevention Concentration" *



"When *Mycobacterium bovis* BCG and *Staphylococcus aureus* were plated on agar containing increasing concentrations of fluoroquinolone, colony numbers exhibited a sharp drop, followed by a plateau and a second sharp drop.

The plateau region correlated with the presence of first-step resistant mutants. Mutants were not recovered at concentrations above those required for the second sharp drop, thereby defining a mutant prevention concentration (MPC).

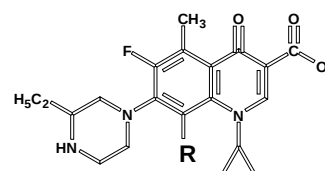
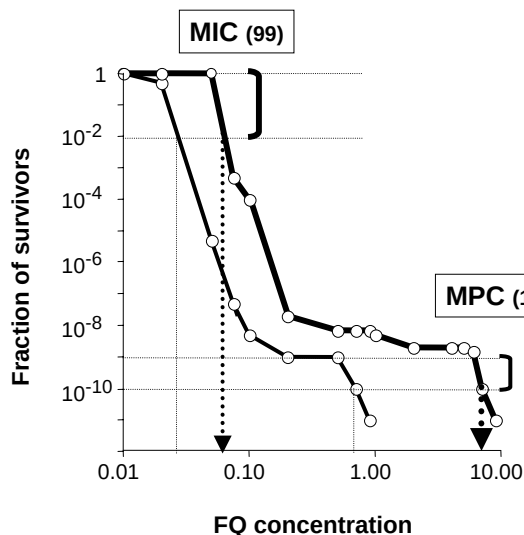
A C8-methoxy group lowered the MPC for an N-1-cyclopropyl fluoroquinolone"

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Is there a SAR for emergence of resistance ?

Bactericidal activity of FQs against *Mycobacterium bovis*



PD160793 PD161148

R = OCH₃ R = H

MIC 99	0.25	0.8
MPC 10	0.9	9
MPC/MIC	3.6	12

Dong et al; AAC 43:1756-1758

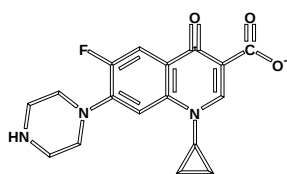
FARM 2146 Fluoroquinolones

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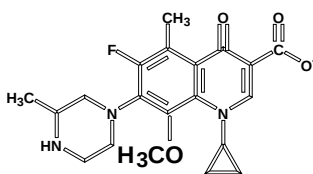
Fluoroquinolones with a C8-methoxy

I



ciprofloxacin

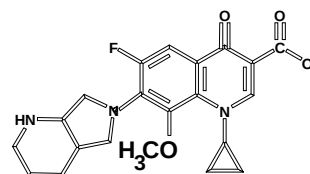
II



gatifloxacin

Not in Belgium

III



moxifloxacin

Yes

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Toxicity



This is where all may fail...

Frequent side effects of fluoroquinolones: is there a SAR ?



COMPLEXATION WITH METALLIC IONS (Fe, Al, Mg, Ca)



PHOTOTOXICITY



DRUG INTERACTIONS: INHIBITION OF cyt P450 (1A2)



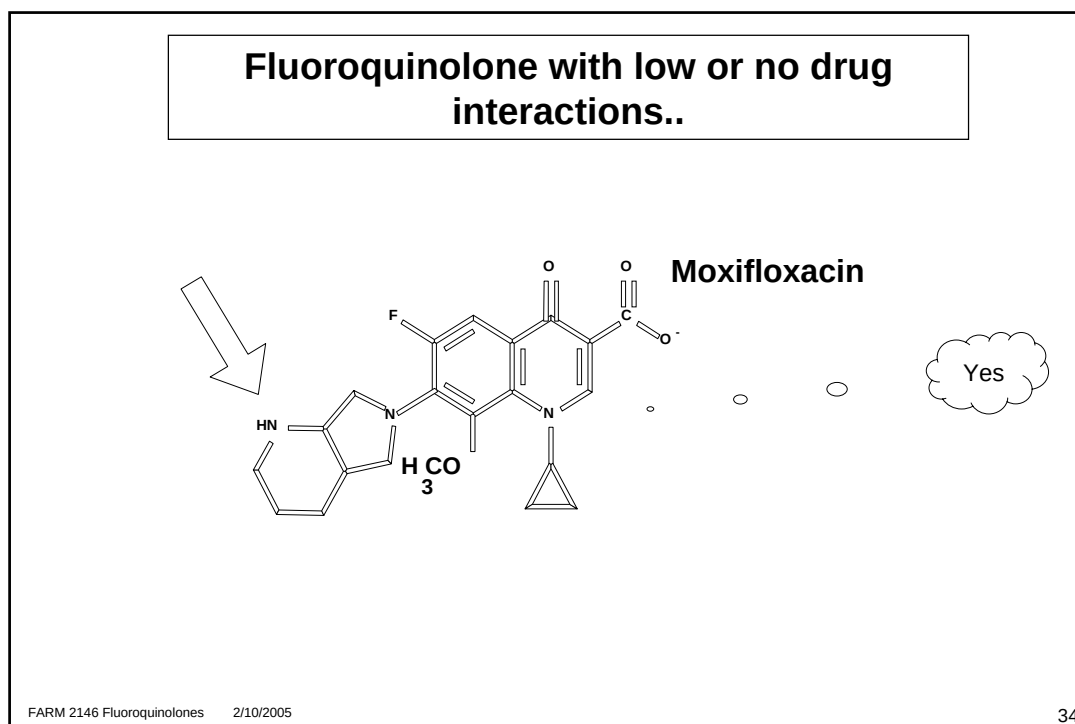
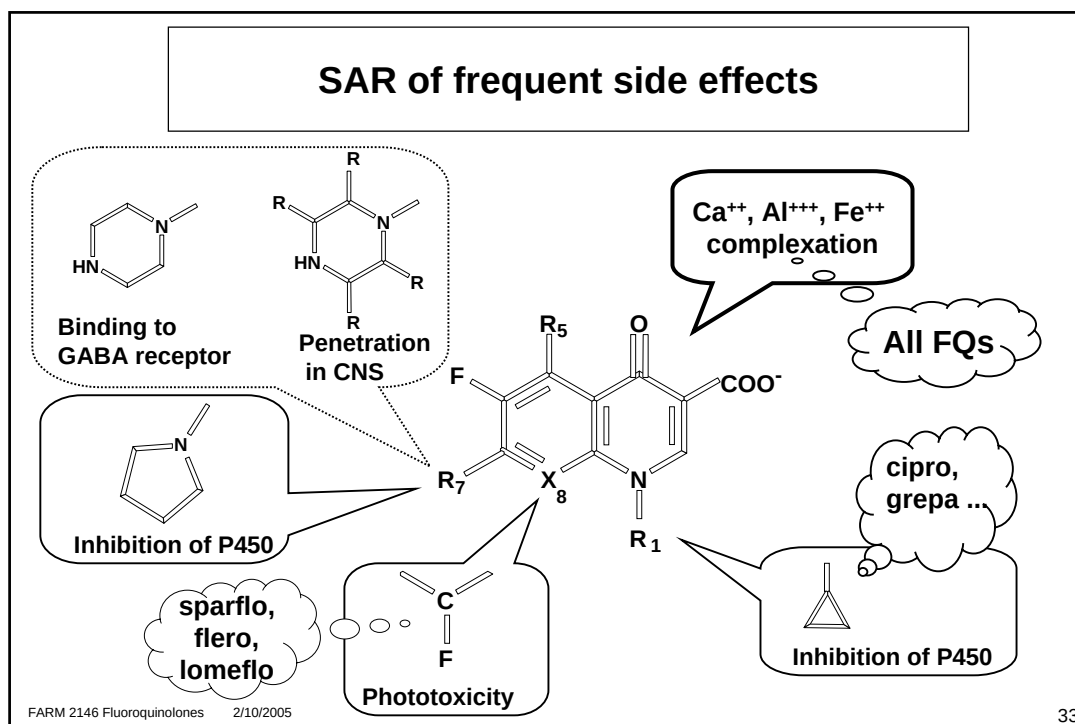
CNS TOXICITY (BINDING TO GABA RECEPTOR)



GASTRO-INTESTINAL DISCOMFORT



CARTILAGE and MUSCULOSQUELETAL TOXICITY



Rare side effects of fluoroquinolones:



RENAL TOXICITY

crystalluria, hematuria, interstitial nephritis, acute renal failure



CARDIAC TOXICITY (QT prolongation, *Torsades de pointe*)



HEPATOTOXICITY

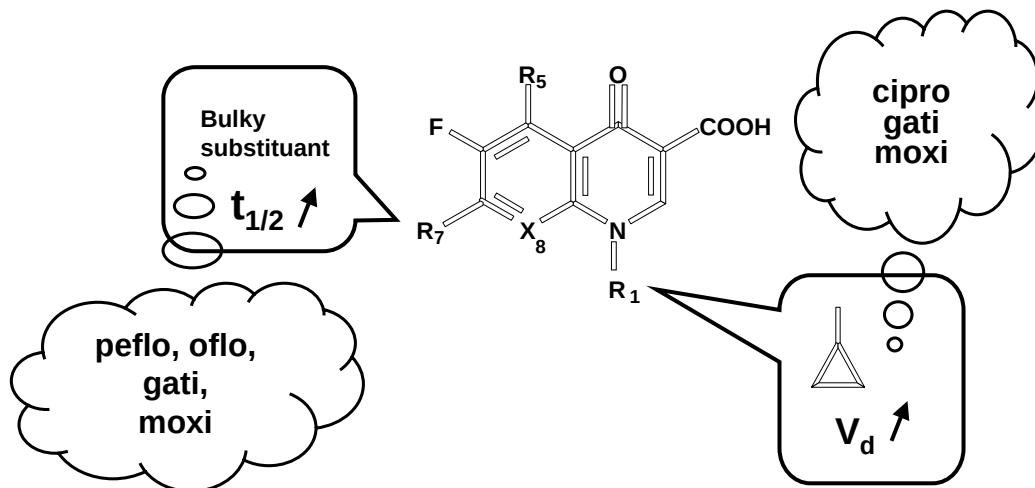
temafloxacin syndrome / trovafloxacin syndrome

Pharmacokinetics



This is where people start sleeping..

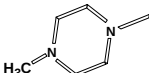
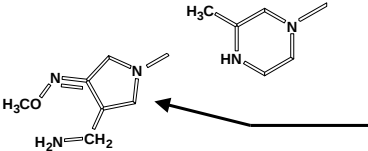
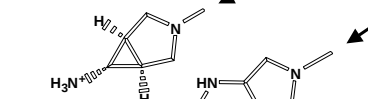
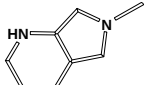
SAR of pharmacokinetic parameters



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SAR of main pharmacokinetic parameters: how to get a long half life

	$t_{1/2}$ (h)	no. of daily administrations
	oflo / lévo 5 - 7	2 x*
	peflo 10	2 x*
	flero 9 - 13	1 x
	grepa 10 - 12	1 x
	gati 13	1 x
	gemi 8	1 x
	trova 10	1 x
	moxi 12	1 x
	other FQ 3 - 6	2 x

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* higher MIC...₃₈

Resistance: do not forget the correct dosing...

“Inadequate dosing of antibiotics is probably an important reason for misuse and subsequent risk of resistance. A recommendation on proper dosing regimens for different infections would be an important part of a comprehensive strategy. The possibility to produce such a dose recommendation based on pharmacokinetic and pharmacodynamic considerations will be further investigated in one of the CPMP working parties...”

European Agency of the Evaluation of Medicinal Products (London)

*EMEA discussion paper
on Antimicrobial resistance
3 January 1999 EMEA/9880/99*



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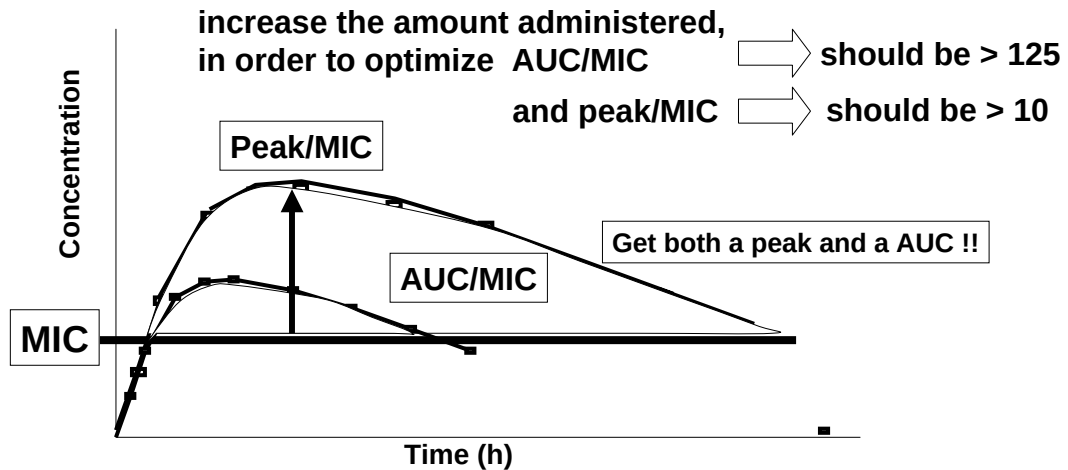
Pharmacokinetic parameters in relation with efficacy

	Dose (mg)	Cmax (mg/l)	MIC for pk/MIC=10	AUC (mg.h/l)	MIC for AUIC=125
norflo	400 (x2)	1.6	0.2	14	0.1
peflo	400 (x2)	4.6	0.4	108	1.0
cipro	500 (x2)	1.5	0.2	17	0.1
oflo	200 (x2)	3.1	0.4	66	0.4
levoflo	500	5.0	0.5	47	0.4
moxi	400	4.5	0.4	48	0.4

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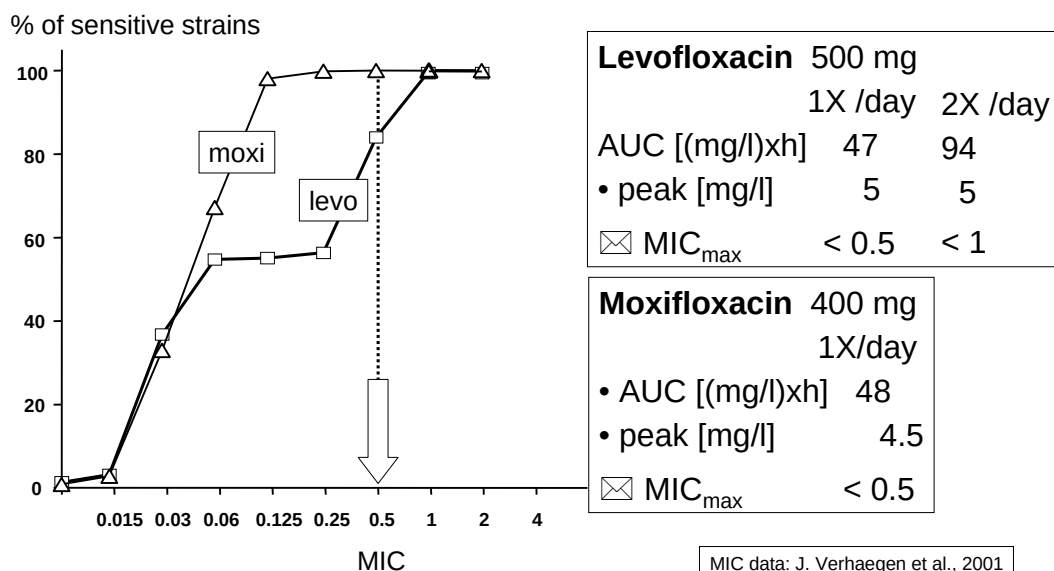
Optimizing dosage for fluoroquinolones



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How to apply this ?



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Take home” message

- Dosage is key to success
- Dosage should match bacterial sensitivity
- peak, AUC/MIC are keys to success
- use a single, appropriate dose for long-life fluoroquinolones (moxifloxacin), or
- repeat the dose for short-lived fluoroquinolones (all others so far...)
- for fluoroquinolones, the limit is an **MIC of 0.5 µg/ml**