Appropriate Use of Quinolones in the Hospital: Is Microbiology Telling You All?

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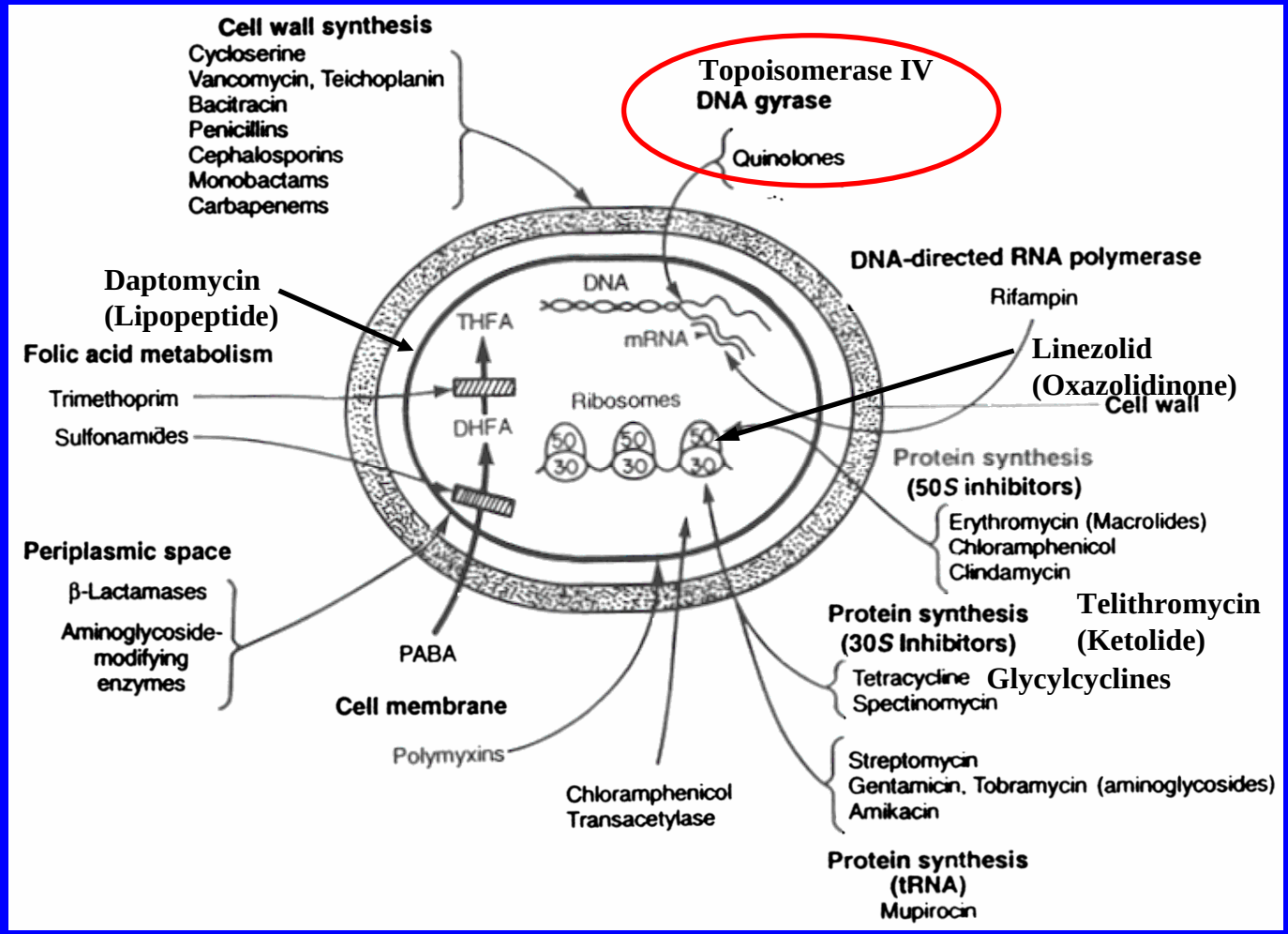
Lesson to Students – Leuven, March 27th, 2007

Sites of Action of Antimicrobial Agents in Clinical Use



Neu HC. Science 1992; 257:1064-73

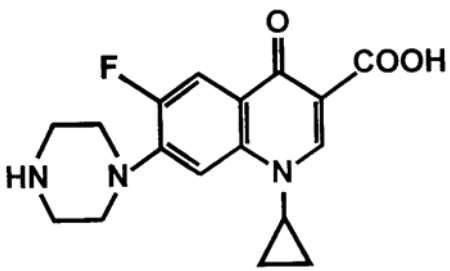
Fluoroquinolones Mechanisms of Action

- Inhibit DNA synthesis
- Stabilize DNA strand breaks created by actions of DNA gyrase and topoisomerase IV by binding enzyme-DNA complexes
- Bactericidal - requires additional events after initial interaction with enzyme-DNA complexes

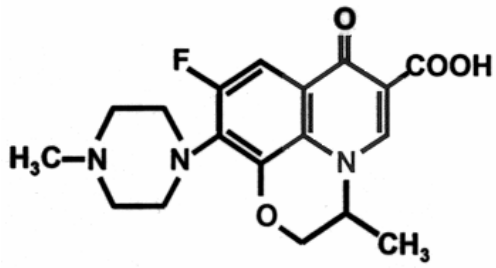
Fluoroquinolones Available in the United States

- Norfloxacin (Noroxin) 1986 (PO)
- Ciprofloxacin (Cipro) 1987 (PO), 1990 (IV)
- Ofloxacin (Floxin) 1990 (PO), 1992 (IV)
- Levofloxacin (Levaquin) 1996 (IV & PO)
- Gatifloxacin (Tequin) 1999 (IV & PO)
- Moxifloxacin (Avelox) 1999 (PO), 2001 (IV)
- Gemifloxacin (Factive) 2003 (PO)

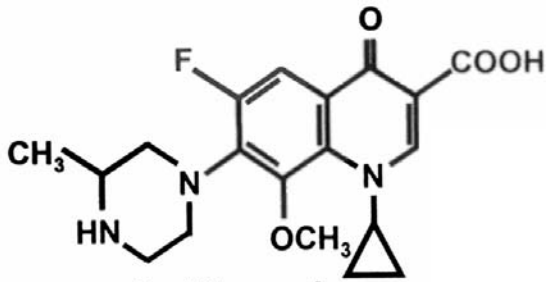
Fluoroquinolone Structures



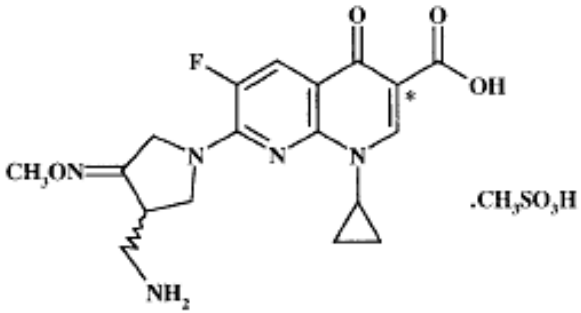
Ciprofloxacin



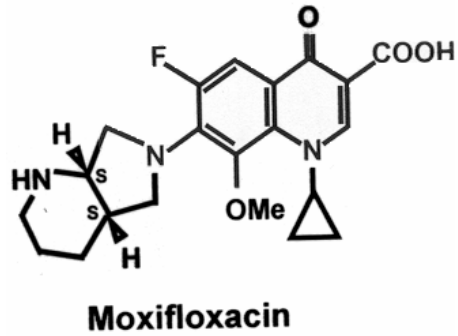
Levofloxacin



Gatifloxacin



Gemifloxacin



Moxifloxacin

Properties of Newer Quinolones

- Broad spectrum activity
  - Gram-negative bacteria
  - Improved against Gram-positive bacteria
  - Improved against Anaerobes
- Once or twice daily dosing
- Some with apparent reduced risk of selection of resistance

Fluoroquinolones Spectrum of Activity

- *Enterobacteriaceae*
- *Haemophilus* spp. *Neisseria* spp.
- *Legionella, Mycoplasma, Chlamydia* [Levofloxacin, Gatifloxacin, Moxifloxacin]
- *Pseudomonas aeruginosa* [Ciprofloxacin, Levofloxacin]

Fluoroquinolones Spectrum of Activity

- Staphylococci (MSSA, MSSE) [Levofloxacin, Gatifloxacin, Moxifloxacin, Gemifloxacin]
- Streptococci (+/- enterococci) [Levofloxacin, Gatifloxacin, Moxifloxacin, Gemifloxacin]
- Anaerobes [Gatifloxacin, Moxifloxacin]
- Mycobacteria (*M. tuberculosis*, *M. kansasii*, *M. fortuitum*) [Ciprofloxacin, Levofloxacin, Gatifloxacin, Moxifloxacin]

Activity of Quinolones Against 75 Ciprofloxacin-Resistant Isolates of *Streptococcus pneumoniae*

Quinolone	Cumulative % Isolates at MIC (μg/ml)					
	≤0.06	0.12-0.25	0.5-1	2-4	8-16	32-64
Levofloxacin			16	67	95	100
Gatifloxacin		4	64	93	100	
Moxifloxacin		56	71	97	100	
Gemifloxacin	61	92	100			

Chen DK et al. 1999. N Engl J Med. 341:233-9

Pharmacokinetic Properties of Oral Fluoroquinolones

Drug	Dose (mg - frequency)	C_{max} (μg/ml)	$t_{½}$ (h)	Renal Clearance (% of total)
Ciprofloxacin	500 BID	2.2	3.3	50
Levofloxacin	500 QD	5.7	6-8	65
	750 QD	8.6		
Gatifloxacin	400 QD	4.1	7-8	80
Moxifloxacin	400 QD	4.5	13	22
Gemifloxacin	320 QD	1.8	7	30

Pharmacokinetic Properties of IV Fluoroquinolones

Drug	Dose (mg - frequency)	C_{max} (μg/ml)	$t_{½}$ (h)	Renal Clearance (% of total)
Ciprofloxacin	400 BID	4.3	3.3	50
Levofloxacin	500 QD	6.4	6-8	65
	750 QD	12.1		
Gatifloxacin	400 QD	4.6	7-8	80
Moxifloxacin	400 QD	4.2	13	22

Specific Uses of Fluoroquinolones

- Typhoid and enteric fever
- Prostatitis (vs trimethoprim-sulfa)
- Complicated urinary tract infections
- Community-acquired pneumonia
  - hospitalized patients (vs ceftriaxone + macrolide)
- Prosthetic joint infection
  - for salvage when prosthesis cannot be removed
  - with rifampin

General Clinical Uses of Fluoroquinolones

- Urinary Tract Infections
- Prostatitis
- Sexually Transmitted Diseases
- Gastroenteritis
- Intraabdominal Infections
- Respiratory Tract Infections
- Bone & Joint Infections
- Skin & Soft Tissue Infections
- Other Broad Uses in Hospitalized Patients

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Fluoroquinolone Drug Interactions

- Antacids, sucralfate, multivalent cations impair oral absorption
- Increase theophylline and caffeine (Enoxacin > Ciprofloxacin)
- NSAIDs possibly potentiate neurotoxicity (Enoxacin)
- Potentiation of warfarin effect is sporadic[A]
- High doses may increase cyclosporin levels (Ciprofloxacin)

[A]Seen in some elderly patients on multiple drugs

Adverse Effects of Fluoroquinolones

- Gastrointestinal
  - Nausea, vomiting, diarrhea
- Hepatic
  - Idiosyncratic hepatitis (trovafloxacin)
- Central Nervous System
  - Dizziness (trovafloxacin), insomnia, seizures
- Cardiovascular
  - QT_C prolongation, arrhythmias (sparfloxacin, grepafloxacin)

Effects of Drugs on Cardiac Conduction

Drug	QT_C Prolongation (msec)	I_{kr}[a] (μM)	hERG IC_{30}[b] (μM)
Sparfloxacin	13-15	0.23	10
Grepafloxacin	10	27.2	39
Moxifloxacin	7	--	92
Gatifloxacin	5-6	26.5	104
Levofloxacin	5		
Erythromycin	8-15		
Clarithromycin	2-6		

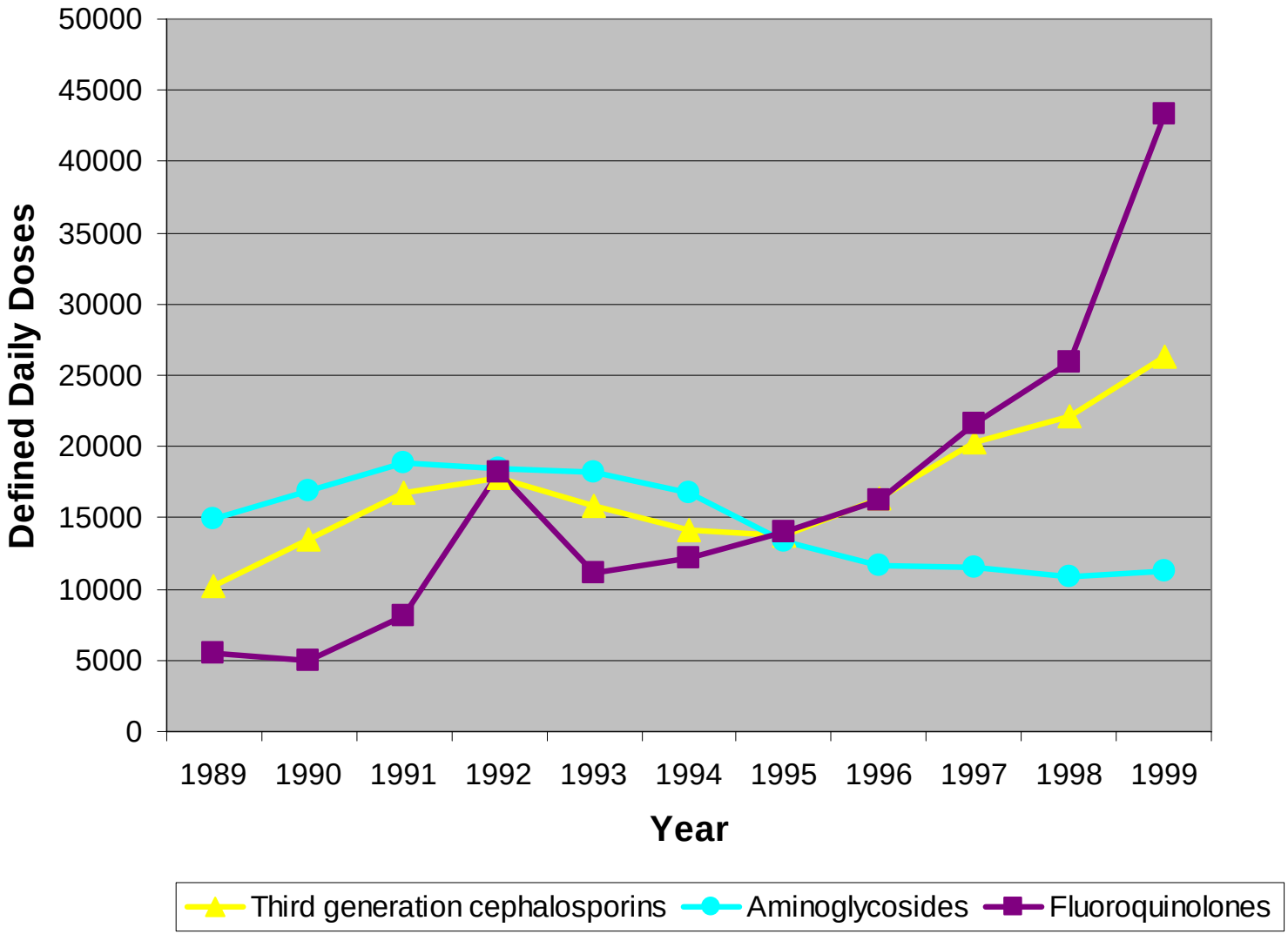
[a]Anderson *et al.* 3rd ECC

[b]Chen *et al.* ICAAC 2000 abstr 765

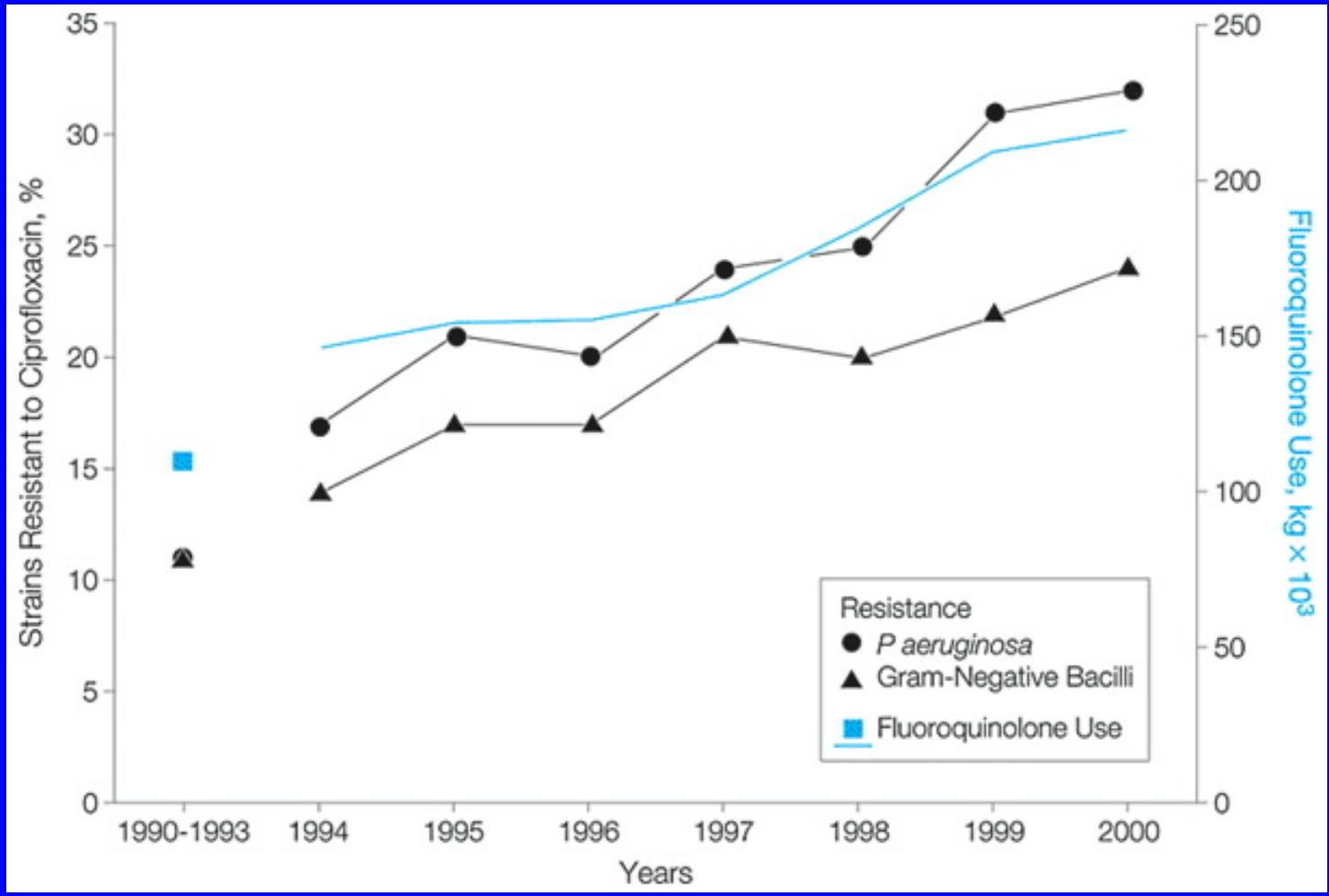
Adverse Effects of Fluoroquinolones

- Metabolic
  - Hypoglycemia and potentiation of hypoglycemic agents (clinafloxacin, gatifloxacin)
- Skin
  - Photosensitivity – UVA (320-420) (sparfloxacin, lomefloxacin)
  - Rash (gemifloxacin – young women, Rx for >10 days)
- Musculoskeletal
  - Cartilage erosion in weightbearing joints (animals, ?children)
  - Tendinopathy, tendon rupture

Trends in Inpatient Antibiotic Use



Increasing Quinolone Resistance Associated with Increasing Use



Neuhauser MM et al. JAMA 2003; 289:885-8

Ciprofloxacin Resistance in Gram-Negative Bacilli in ICUs in the United States - 1994-2000

Species	Resistant (%)	Change[A] (%)	Cross Resistance to: Gent (%, CipR/CipS)	Ceftaz (%, CipR/CipS)	Imip (%, CipR/CipS)
P. aeruginosa	24	+13	66/21	40/14	38/11
Enterobacter sp.	10	+6	49/4	82/32	4/1
K. pneumoniae	12	+7	67/7	65/6	3/0.5
E. coli	3	+2			
All isolates[B]	19	+10			

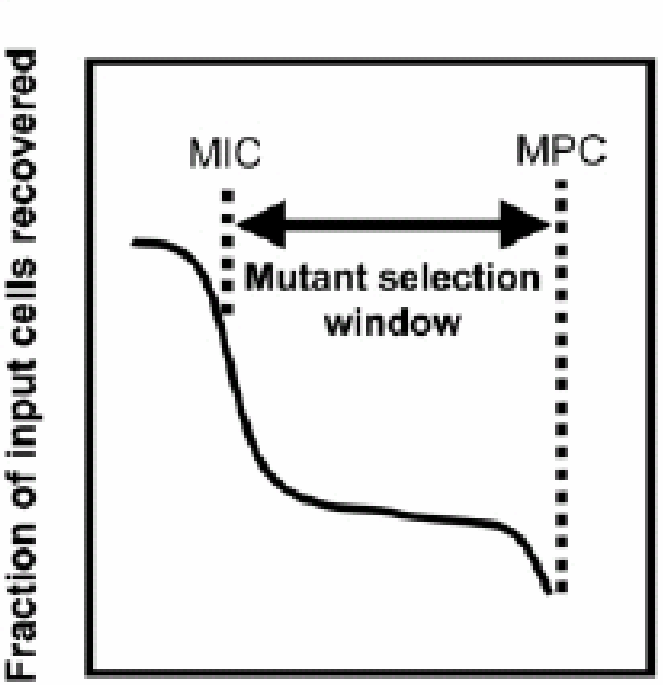
[A]Change relative to 1990-1993 [B]n=35,790

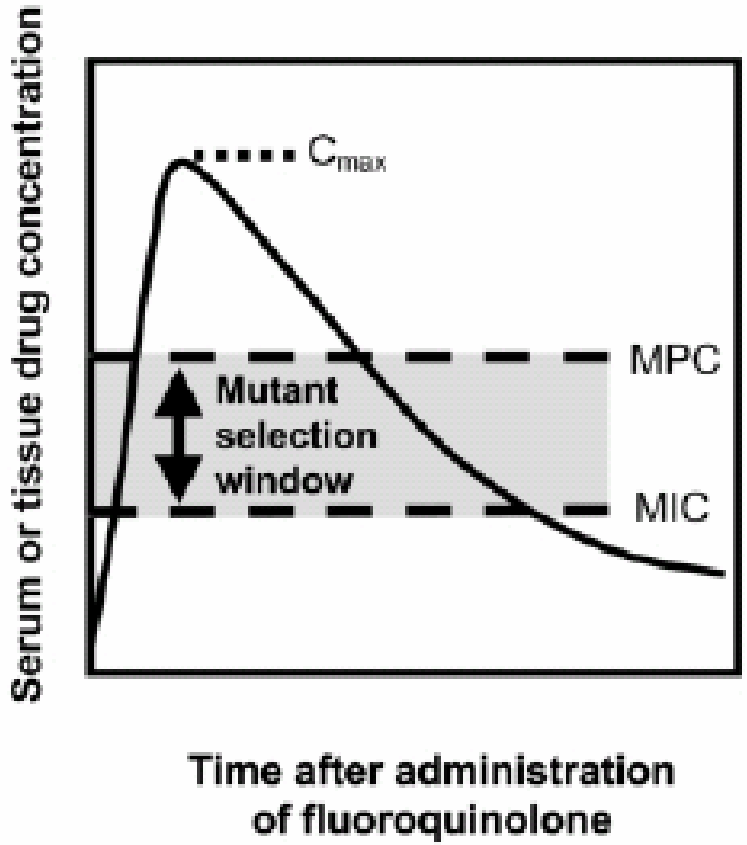
Neuhauser MM *et al*. JAMA 2003; 289:885-888

Factors Associated with Fluoroquinolone Resistance

Resistant Pathogen	Risk Factors
Staphylococci (MRSA, MRCNS)	Quinolone Use, Co-selection, Nosocomial Spread
Pseudomonas aeruginosa	Quinolone Use, Nosocomial Spread
Klebsiella pneumoniae	Quinolone Use, Nosocomial Spread
Campylobacter jejuni	Quinolone Use, Foreign Travel
Escherichia coli	Quinolone Use, ?Animal Use

Pharmacodynamics of Quinolone-Resistant Mutant Selection





Drlica K and Zhao X. Clin Infect Dis. 2007; 44:681

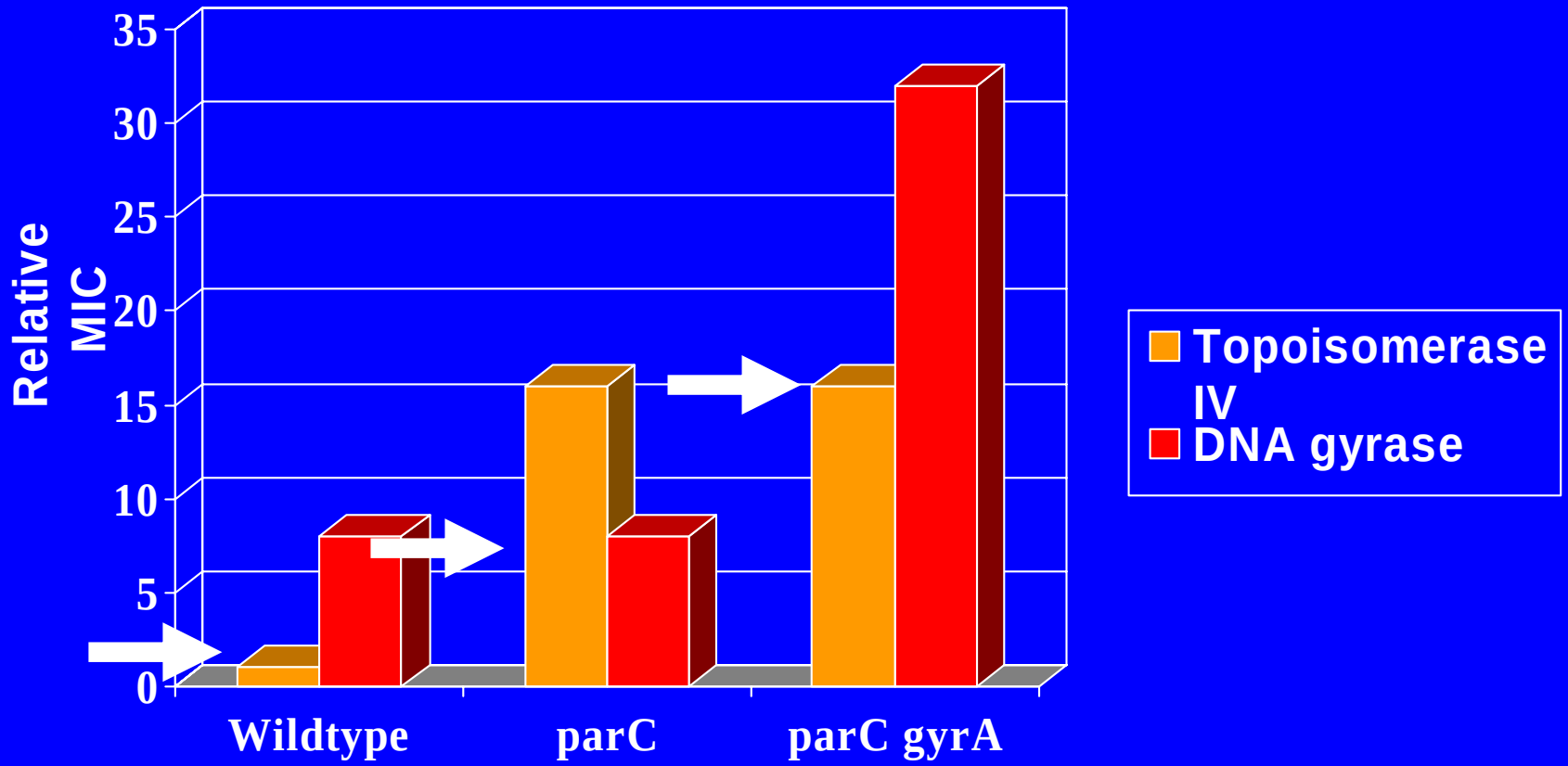
Mechanisms of Resistance to Fluoroquinolones

- Chromosomal mutations
  - Alterations in DNA gyrase and/or topoisomerase IV
  - Active drug efflux (MDR pumps) +/- reduced porin diffusion channels
- Plasmid-mediated resistance
  - Enteric gram-negative bacteria; target protection mechanism by Qnr proteins
  - Drug modification

Bacterial Type II Topoisomerases Quinolone Target Enzymes

Enzyme	Subunits	Activities
DNA Gyrase (Topoisomerase II)	2 GyrA 2 GyrB	DNA Supercoiling (DNA Relaxation) (DNA Decatenation)
Topoisomerase IV	2 ParC (GrlA) 2 ParE (GrlB)	DNA Decatenation (DNA Relaxation)

Stepwise Increases in Quinolone Resistance: Role of Differing Sensitivities of Enzyme Targets



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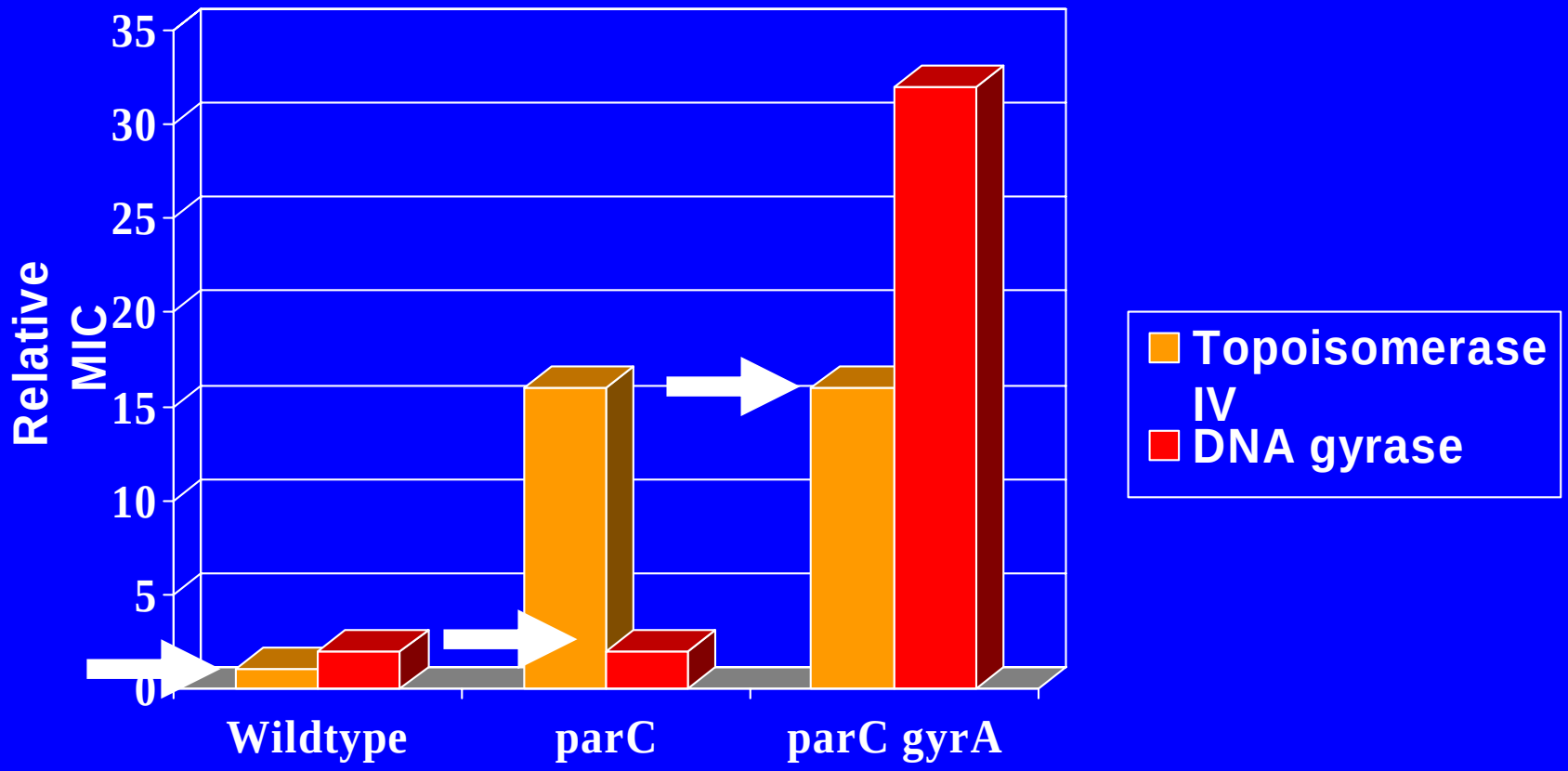

Activity of Gemifloxacin and Ciprofloxacin Against Topoisomerase IV and Gyrase

Enzyme	IC_{50} (μg/ml)			
	Gemifloxacin		Ciprofloxacin	
Topoisomerase IV				
Wildtype	0.25	200x	2.5-5.0	100x
ParC (Ser80Phe)	50		250	
Gyrase		~1x		2-4x
Wildtype	0.31		10	

Ince D *et al*. Antimicrob Agents Chemother. 2003; 47:274-82

Drug Target Differences and Frequency of Mutant Selection

Drug	Selecting drug concn[a]	Frequency of selection of mutants
Gemifloxacin	1 (0.016)	1.5×10^{-5}–2.4×10^{-5}
	2 (0.032)	7.4×10^{-11}–1.1×10^{-10}
	4 (0.064)	$<7.4 \times 10^{-12}$
Ciprofloxacin	2 (0.5)	2.8×10^{-6}–1.5×10^{-5}
	4 (1.0)	3.0×10^{-8}–6.1×10^{-8}

[a] Drug concentrations are given as factors of the MICs, and the numbers in parentheses are the MICs in micrograms per milliliter.

Ince D *et al*. Antimicrob Agents Chemother. 2003; 47:274-82

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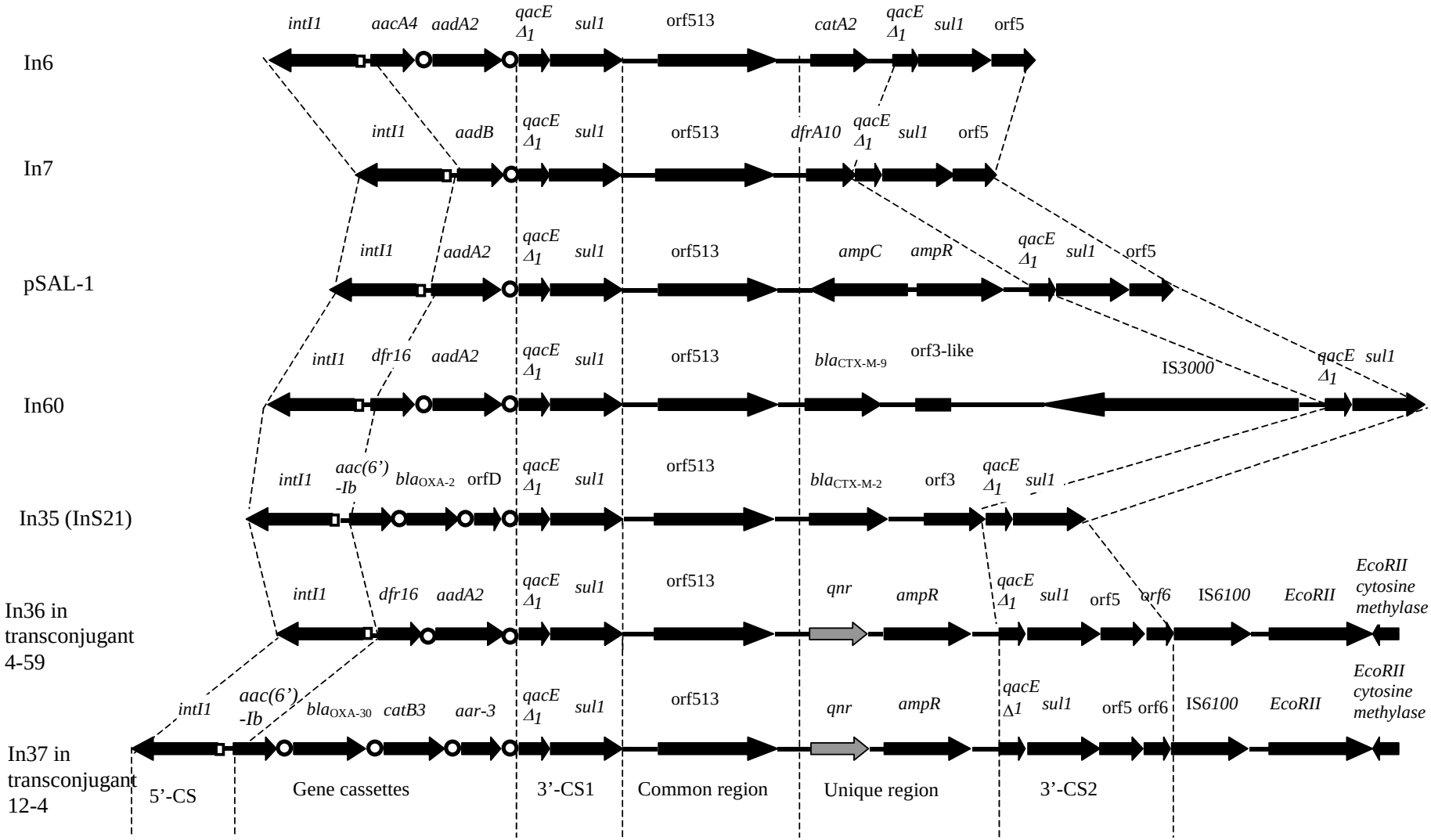


Wang M *et al*. Antimicrob Agents Chemother. 2003; 47:2242-8

Occurrence of Integron-Carrying Enteric Bacteria in ICUs

Variable	No. (%) of ICU Patients	
	Medical (n = 277)	Neurosurgical (n = 180)
Total colonized	19 (7)	12 (7)
Acquired colonization	14 (5)	9 (5)
Time to acquisition (d)	10 ± 10	12 ± 10
Acquisition rate (per 1000 patient-days)	10	8

Nijssen S et al. Clin Infect Dis. 2005; 41:1-9.

Resistance Profiles of Integron-Carrying Enteric Bacteria

Antimicrobial	Percent Resistant	
	Integron (-) (n = 120)	Integron (+) (n = 54)
Piperacillin	24	94*
Ceftazidime	26	33
Cefotaxime	29	44*
Meropenem	0	0
Gentamicin	2	94*
Ciprofloxacin	3	33*

Nijssen S et al. Clin Infect Dis. 2005; 41:1-9.

Effect of *qnrA* on Quinolones

TABLE 1. In vitro activity of newer quinolones against transconjugants containing *qnr* and donor strains[a]

Agent	*E. coli* J53	MIC (μg/ml)					
		Transconjugants (n = 17)			Donors (n = 15)		
		MIC_{50}	MIC_{90}	MIC_R	MIC_{50}	MIC_{90}	MIC_R
AM-1121	0.008	0.5	0.5	0.125–1	16	≥64	2–≥64
BAYy3118	0.004	0.125	0.125	0.06–0.25	4	16	0.5–32
Ciprofloxacin	0.008	0.25	1	0.125–2	16	128	2–≥256
Garenoxacin	0.008	1	2	0.5–2	32	≥64	8–≥64
Gatifloxacin	0.008	0.25	0.5	0.25–1	16	≥32	2–≥32
Gemifloxacin	0.004	0.5	1	0.25–1	16	≥32	2–≥32
Levofloxacin	0.015	0.5	0.5	0.25–1	32	≥32	2–≥32
Moxifloxacin	0.03	0.5	1	0.5–1	32	≥64	2–≥64
Nalidixic acid	4	16	32	8–32	≥256	≥256	32–≥256
Premafloxacin	0.03	0.25	0.25	0.25–0.5	16	≥64	2–≥64
Sitafloxacin	0.008	0.125	0.125	0.06–0.25	4	8	0.5–16
Sparfloxacin	0.008	1	1	0.25–1	32	≥64	2–≥64

[a] MIC_{50}, MIC for 50% of strains; MIC_{90}, MIC for 90% of strains; MIC_R, range of MICs.

Wang M *et al*. Antimicrob Agents Chemother. 2004; 48:1400-1

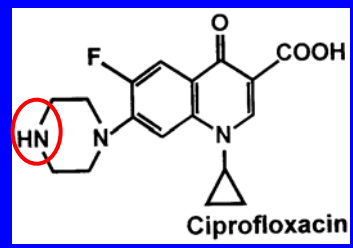
QnrA Promotes Selection of Higher-Level Quinolone Resistance

Selection	*E coli* strain	
	J53	J53 pMG252
Ciprofloxacin 0·25 μg/mL	$<1{\cdot}6\times10^{-8}$	$3{\cdot}5\times10^{-6}$
Nalidixic acid 50 μg/mL	$<1{\cdot}6\times10^{-8}$	$3{\cdot}8\times10^{-6}$
Streptomycin 50 μg/mL	$<1{\cdot}6\times10^{-8}$	$1{\cdot}2\times10^{-4}$
Rifampicin 100 μg/mL	$1{\cdot}3\times10^{-8}$	$2{\cdot}4\times10^{-8}$
Valine 40 μg/mL	$4{\cdot}9\times10^{-8}$	$<2{\cdot}0\times10^{-8}$
Methionine positive	$1{\cdot}6\times10^{-8}$	$<2{\cdot}0\times10^{-8}$
Proline positive	$3{\cdot}3\times10^{-8}$	$5{\cdot}9\times10^{-8}$

Martínez-Martínez L et al. Lancet 1998; 351:797-9

The Newest Mechanism of Plasmid-Mediated Quinolone Resistance

- Specific modification of some quinolones (ciprofloxacin, norfloxacin)
- Mutant of a common aminoglycoside acetyltransferase enzyme, Aac(6')Ib, which causes resistance to kanamycin, tobramycin, and amikacin
  - Mutations Trp102Arg and Asp179Tyr = Aac(6')Ib-cr
  - Acetylates ciprofloxacin at piperazinyl *N*
  - Slight decrease in kanamycin acetylation



- Low-level resistance (4-fold)
- Promotes selection of high-level resistance with quinolone exposure
- *aac(6')-Ib*-cr located on plasmids with and without *qnr* genes

Robicsek A et al. Nature Medicine 2006; 12;83-88

Limiting Bacterial Resistance to Fluoroquinolones

- Monitor Resistance
- Good Infection Control to Limit Spread
- Focused and Balanced Use to Limit Selective Pressures
- Adequate Dosing to Limit Mutant Selection

Pharmacodynamic Factors Affecting Risk of Selection of Quinolone Resistance

- Selecting Drug Concentration in Vitro
- C_{max}/MIC - Animal Models
- AUC/MIC - Human Use

Limiting Bacterial Resistance to Fluoroquinolones

- Possible Use of Combination Regimens:
  - With Other Antibiotics
  - Specific Inhibitors of Resistance Mechanisms
- Development of New Quinolones
  - Similar Activity Against Both Enzyme Targets
  - Improved Therapeutic Index