Quinolones in the Hospital
Pros and Cons

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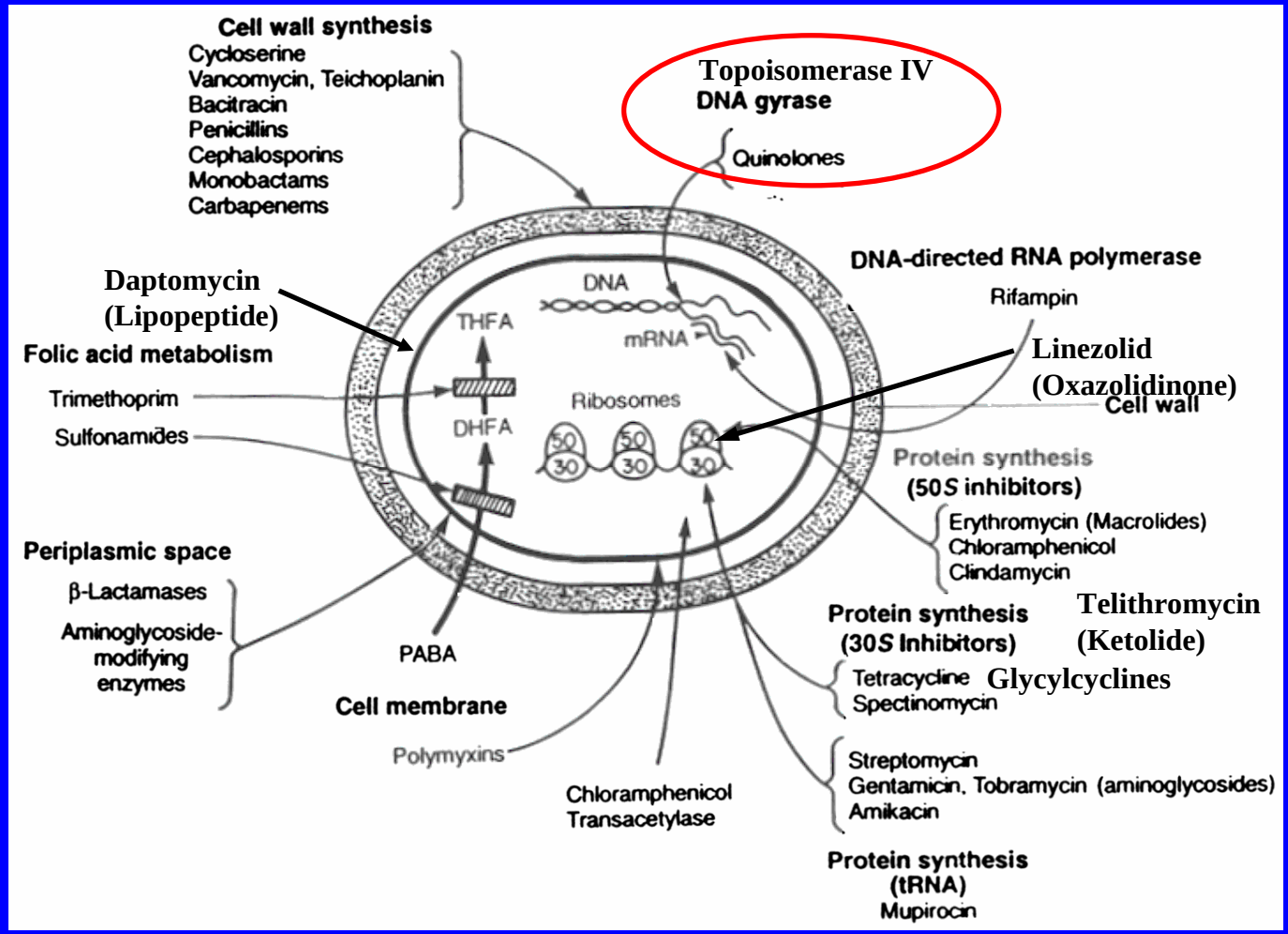
Sites of Action of Antimicrobial Agents in Clinical Use

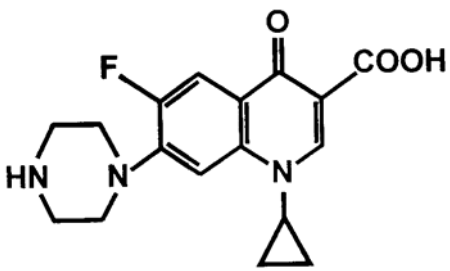


Neu HC. Science 1992; 257:1064-73

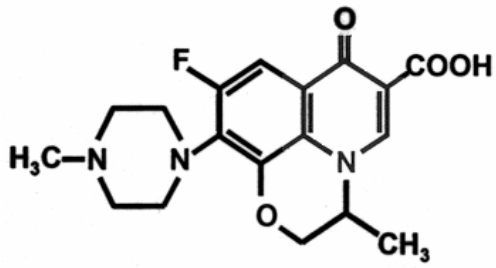
Fluoroquinolones Available in the United States

- 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)

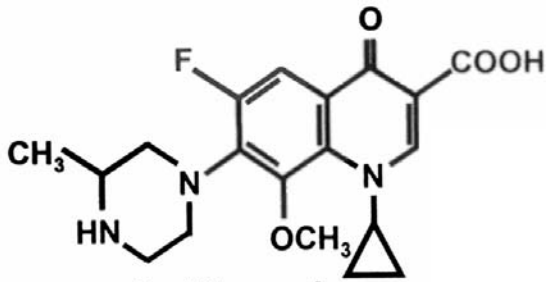
Fluoroquinolone Structures



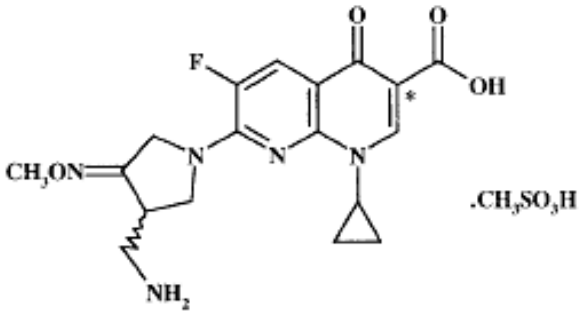
Ciprofloxacin



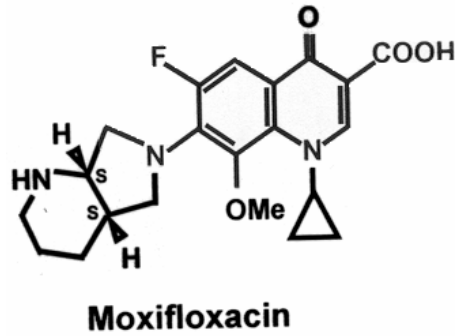
Levofloxacin



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]

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

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)

Risk Factors for Prolonged QT-Associated Arrhthymias

- ↓ K^+, ↓ Mg^{++}
- Cardiomyopathy
- Bradycardia
- Congenital prolonged QT syndromes
- Use of other antiarrhythmics:

Class III
(block K^+ channel)
Amiodarone
Sotalol
Ibutilide
Bretylium

Class Ia
(block Na^+ & K^+ channels)
Quinidine
Disopyramide
Procainamide

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

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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Quinolone Treatment of Hospital-Acquired Pneumonia

Reference	Included patients without NP	No. of patients with NP	Blinded	Agent (dose)	Comparator	Combination therapy permitted	Patients receiving combination therapy, %	Patients with VAP, %	APACHE II score, mean ± SD		Percentage of patients requiring vasopressors at enrollment	
									In quinolone arm	In comparator arm	Among patients receiving quinolones	Among patients receiving comparators
Fink et al. [17]	Yes	312	Yes	Cpfx (400 mg q8h)	Imipenem-cilistatin	Yes	45.1	58.9	17.7± 6.5	17.6 ± 6.4	NR	NR
Saginur et al. [18]	Yes	149	No	Cpfx (300 mg q8h)	Ceftazadime	Yes	52.3	51.7	NR	NR	NR	NR
Krumpe et al. [19]	Yes	138	No	Cpfx (400 mg q8h)	Not standardized; left to primary physician	Yes	22.5	NR	NR	NR	NR	NR
Torres et al. [20]	No	152	No	Cpfx (400 mg q8h)	Imipenem-cilistatin	No	NA	100	13.8 ± 7.5	13.9 ± 8.6	NR	NR
West et al. [21]	No	435	No	Lvfx (750 mg q.d.)	Imipenem-cilistatin	Yes	58.3	50.7	15.0 ± 5.8	14.8 ± 6.0	17.3	11.5

NOTE. Cpfx, ciprofloxacin; Lvfx, levofloxacin; NA, not applicable; NR, not reported in trial; VAP, ventilator-associated pneumonia.

Shorr AF et al. Clin Infect Dis 2005; 40:S115

Quinolone Treatment of Hospital-Acquired Pneumonia

Reference	Microbiologically evaluable population, no. of patients (% of entire cohort)	*Pseudomonas* species isolates, %	*Acinetobacter* species isolates, %	MRSA isolates, %
Fink et al. [17][a]	159 (51.0)	19.5	3.6	0.3
Saginur et al. [18]	119 (79.9)	3.4	0	0
Krumpe et al. [19][a]	109 (79.0)	15.6	1.9	NR
Torres et al. [20]	75 (49.3)	34.7	12.0	1.3
West et al. [21]	187 (43)	18.2	5.9	10.7

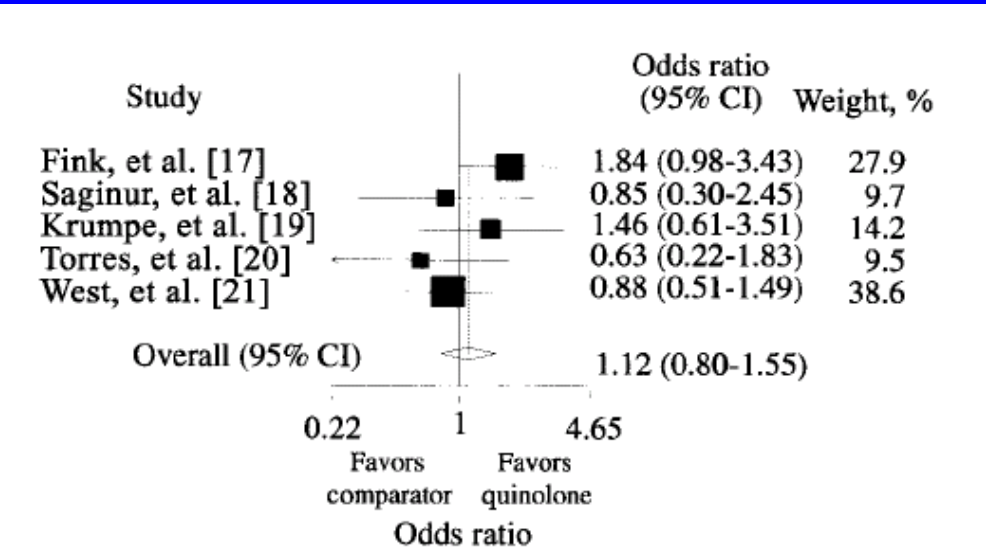
NOTE. MRSA, methicillin-resistant *Staphylococcus aureus;* NR, not reported.

[a] For the trials that included patients with infections other than NP, reported results represent findings based of the data available for the entire study cohort (i.e., patients with both NP and other infections).

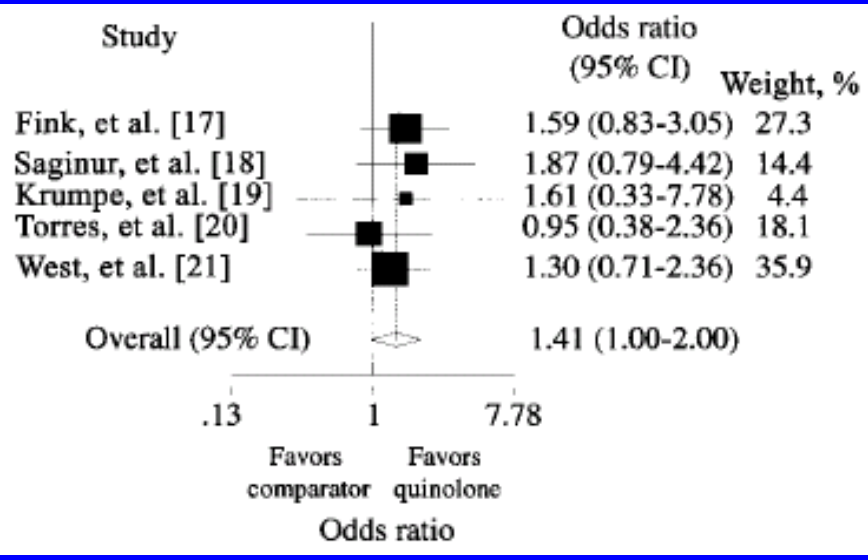
Shorr AF et al. Clin Infect Dis 2005; 40:S115

Outcomes of Quinolone Treatment of Hospital-Acquired Pneumonia

Clinical Outcomes

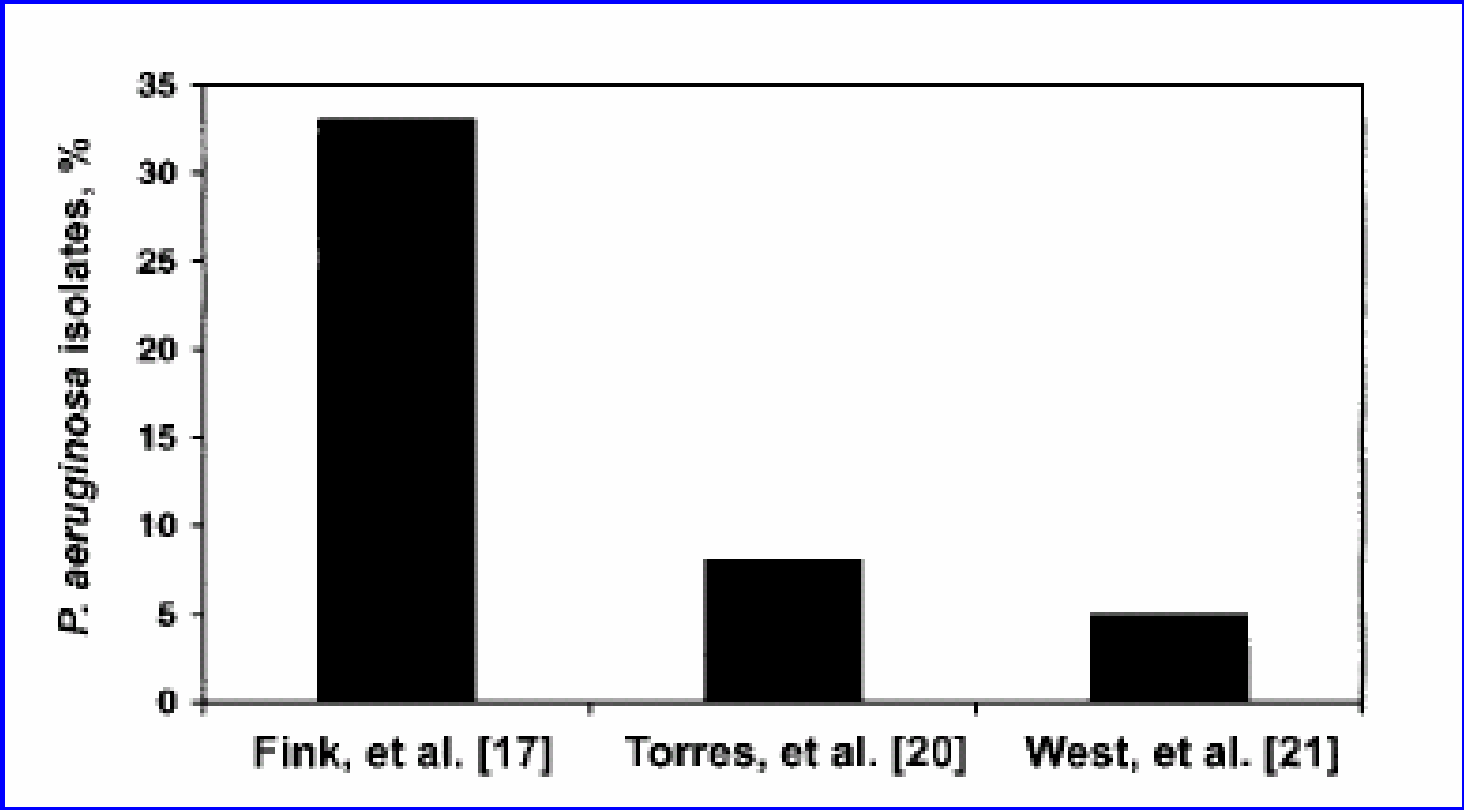


Microbiological Outcomes



Shorr AF et al. Clin Infect Dis 2005; 40:S115

Development of Quinolone Resistance Related to Therapy in Hospital-Acquired Pneumonia



Shorr AF et al. Clin Infect Dis 2005; 40:S115

Moxifloxacin vs. Piperacillin-Tazobactam/Amoxicillin-Clavulanate for Complicated Intra-abdominal Infections

TABLE 4. Clinical Cure Rates by Anatomic Site at Test-of-Cure for the Efficacy-Valid Population

	Clinical Cure Rate [n/N (%)]*	
	Moxifloxacin	**Comparator**
Lower gastrointestinal tract infection (total)	118/150 (79)	121/153 (79)
Complicated appendicitis	84/113 (74)	91/115 (79)
Perforation of small or large bowel	25/27 (93)	19/26 (73)
Ileocolic abscess	9/10 (90)	11/12 (92)
Upper gastrointestinal tract infection (total)	13/16 (81)	15/19 (79)
Perforation of stomach or duodenum	7/8 (87)	8/10 (80)
Other†	6/8 (75)	7/9 (78)
Postoperative upper gastrointestinal tract infection	8/9 (89)	5/7 (71)
Postoperative lower gastrointestinal tract infection	7/8 (87)	12/17 (71)

*n/N = number of patients cured/total number with infection at that site.

†Complicated cholecystitis or cholangitis (3 moxifloxacin, 2 comparator), intra-abdominal abscess (3 moxifloxacin, 3 comparator); miscellaneous upper gastrointestinal tract infections (2 moxifloxacin, 4 comparator).

Malagoni MA et al. Ann Surg 2006; 244:204

Moxifloxacin vs. Piperacillin-Tazobactam/Amoxicillin-Clavulanate for Complicated Intra-abdominal Infections

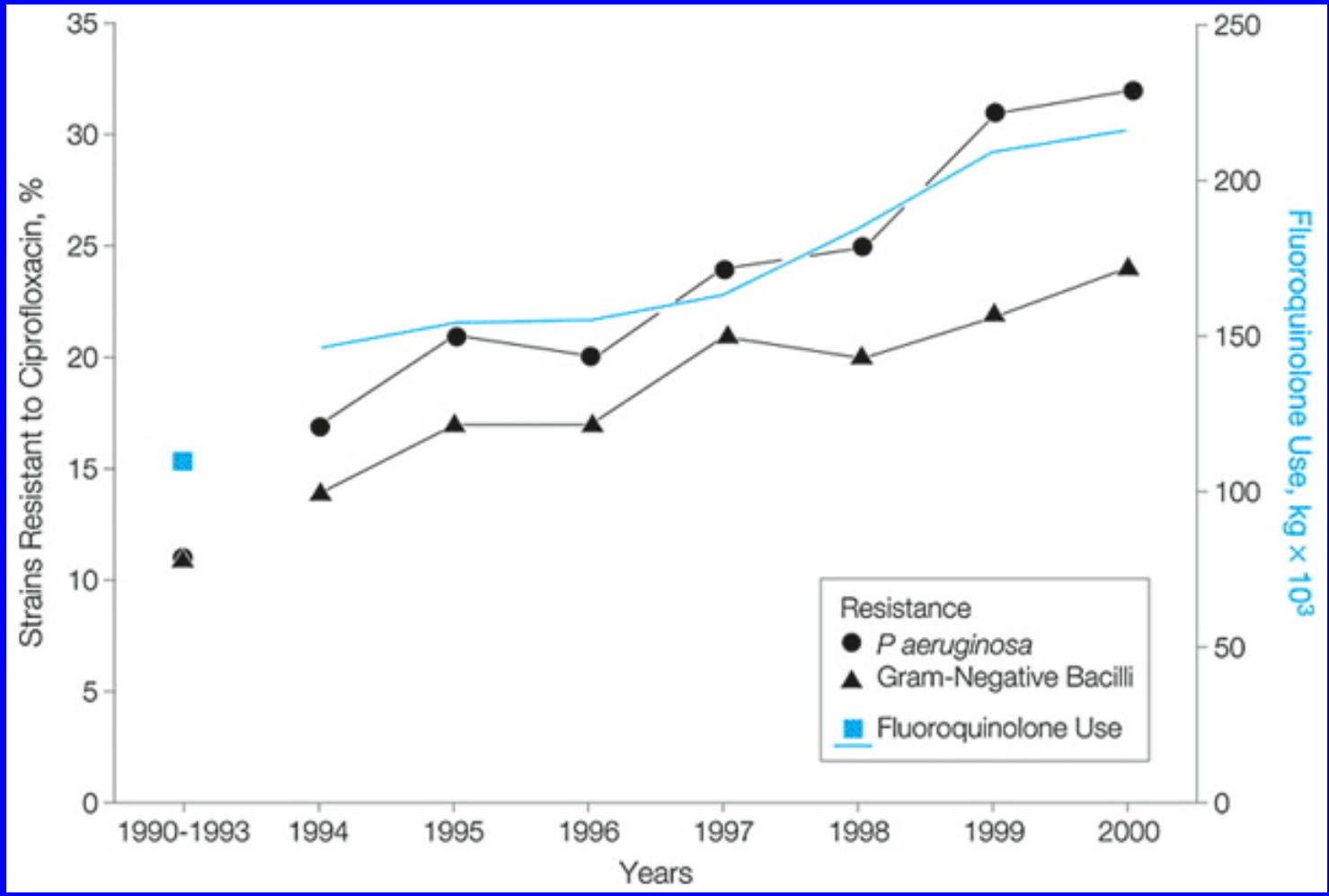
TABLE 5. Bacteriologic Response at the Test-of-Cure Visit for Microbiologically Valid Patients (Organisms With ≥10 Isolates in Each Treatment Arm)

	Bacteriologic Eradication [n/N (%)]*	
Organism	**Moxifloxacin (150 patients)**	**Comparator (163 patients)**
Gram-positive aerobes		
S. anginosus	25/34 (74)	39/48 (81)
S. constellatus	18/30 (60)	10/15 (67)
E. faecalis	8/11 (73)	8/15 (53)
E. avium	13/14 (93)	9/13 (69)
Gram-negative aerobes		
E. coli	67/87 (77)	69/90 (77)
K. pneumoniae	9/15 (60)	14/24 (58)
P. aeruginosa	18/23 (78)	14/22 (64)
Gram-negative anaerobes		
B. fragilis	35/41 (85)	36/50 (72)
B. thetaiotaomicron	29/36 (81)	27/38 (71)
B. uniformis	12/14 (86)	9/12 (75)
Monomicrobial infections	20/24 (83)	30/34 (88)
Polymicrobial infections	97/126 (77)	96/129 (74)

*Includes eradication and presumed eradication; n/N = number eradicated/total number of isolates.

Malagoni MA et al. Ann Surg 2006; 244:204

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

Prevalence of Bacterial Resistance to Fluoroquinolones

Staphylococci (MRSA, MRSE)	60-95%
Pseudomonas aeruginosa	24-44%
Klebsiella pneumoniae	12-20%
Enterobacter spp.	10-12%
Escherichia coli	3-50%
Campylobacter jejuni	3-70%

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

Risk Factors and Clinical Effects of Ciprofloxacin Resistance in an ICU

TABLE 3. Independent Predictors of Ciprofloxacin Resistance in Bacterial Isolates Recovered From Intensive Care Unit (ICU) Patients

Patient variable	Relative risk (95% confidence interval)	*P*
Duration of ciprofloxacin treatment during ICU stay[a]	1.15 per day (1.08-1.23)	<.001
Duration of levofloxacin treatment during ICU stay[a]	1.39 per day (1.01-1.91)	.04
Length of hospital stay prior to ICU admission	1.02 per day (1.01-1.03)	.005

[a] Before isolation of a ciprofloxacin-resistant organism.

TABLE 4. Outcomes of Intensive Care Unit (ICU) Patients With and ICU Patients Without a Ciprofloxacin-Resistant Isolate

Outcome	Patients with a resistant isolate (n = 20)	Patients without a resistant isolate (n = 318)	*P*
Death in ICU	3 (15)	72 (23)	.58
Death in non-ICU hospital setting	6 (30)	106 (33)	.81
Development of ICU-acquired infection	14 (70)	86 (27)	<.001
Length of ICU stay, d	43.9 ± 44.0	10.8 ± 10.7	<.001
Readmission to ICU	5 (25)	17 (5)	.006

NOTE. Data are no. (%) of patients or mean value ± SD.

Levin PD et al. Infect Control Hosp Epidemiol 2007; 28:331

Epidemiology of Ciprofloxacin Resistance in *Klebsiella pneumoniae*

- 455 Bacteremias (440 patients) in 12 hospitals in 7 countries
- 25 (5.5%) with MIC of ciprofloxacin ≥ 4 μg/ml
  - 15/25 (60%) also ESBL-producing
- 83 (18%) ESBL-producing
  - 15/83 (18%) also ciprofloxacin-resistant

Paterson DL *et al*. Clin Infect Dis 30:473-8 (2000)

Epidemiology of Ciprofloxacin Resistance in *Klebsiella pneumoniae*

- Risk factors for resistance (multivariate)
  - Prior receipt of quinolone (p=0.0065)
  - ESBL-producing strain (p=0.012)
  - Hospitalization in Turkish center (p=0.011)
  - Not prior receipt of 3rd-gen cephalosporin (p=0.17)
  - Not indwelling urinary catheter (p=0.24)

Paterson DL *et al*. Clin Infect Dis 30:473-8 (2000)

Epidemiology of Ciprofloxacin Resistance in *Klebsiella pneumoniae*

- Nosocomial acquisition
  - 72% of ciprofloxacin-resistant cases
  - 54% of ciprofloxacin-susceptible cases (p=0.08)
- Clustering based on PFGE genotype
  - 4 clusters of 2-4 cases each in 3 hospitals
  - In 2 clusters exposure to quinolone occurred in 1st case
- Mortality (14 days)
  - 4/25 (16%) Cip-R vs. 120/427 (28%) Cip-S (p=0.19)

Paterson DL *et al*. Clin Infect Dis 30:473-8 (2000)

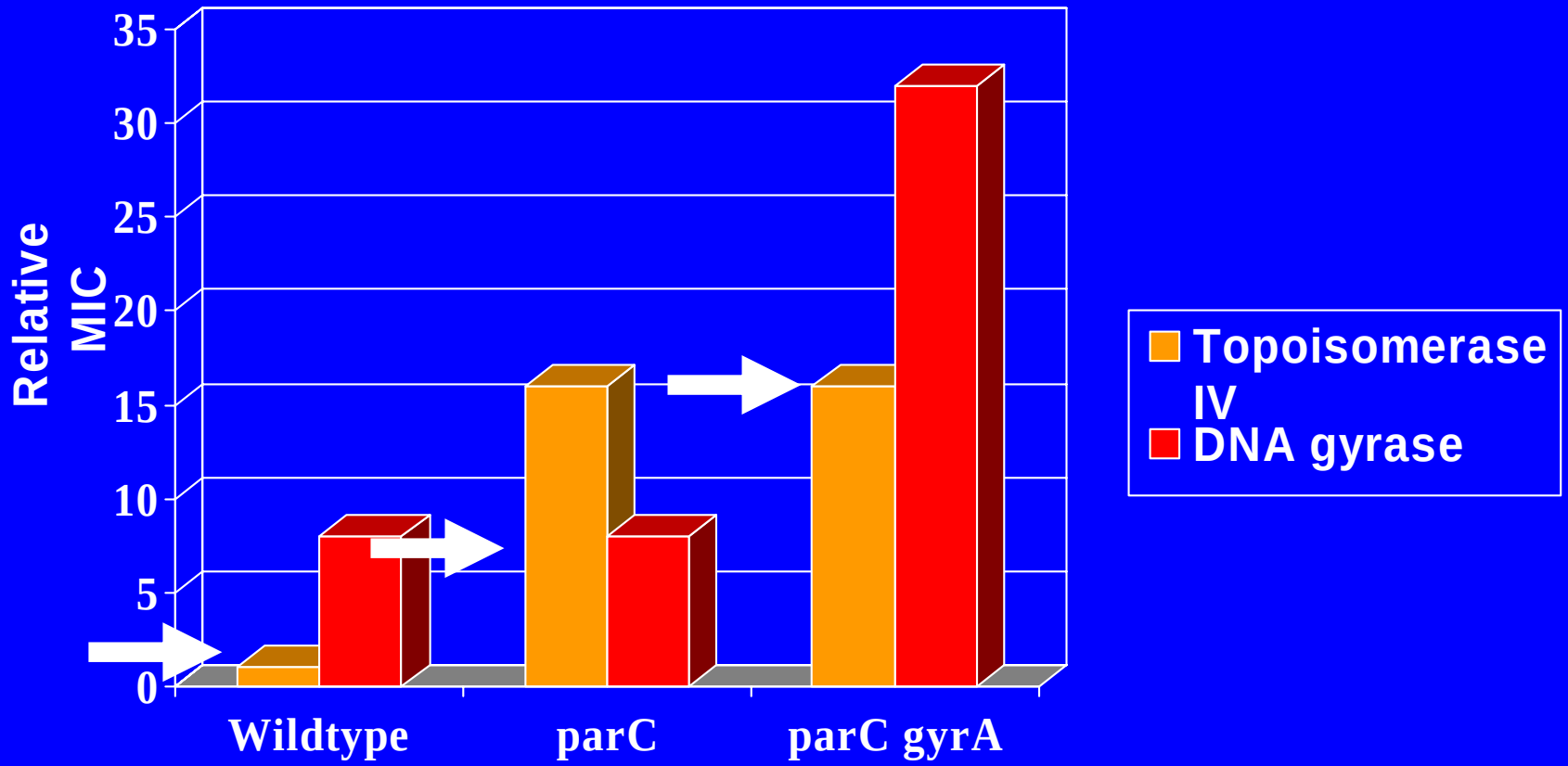
Mechanisms of Resistance to Fluoroquinolones

- 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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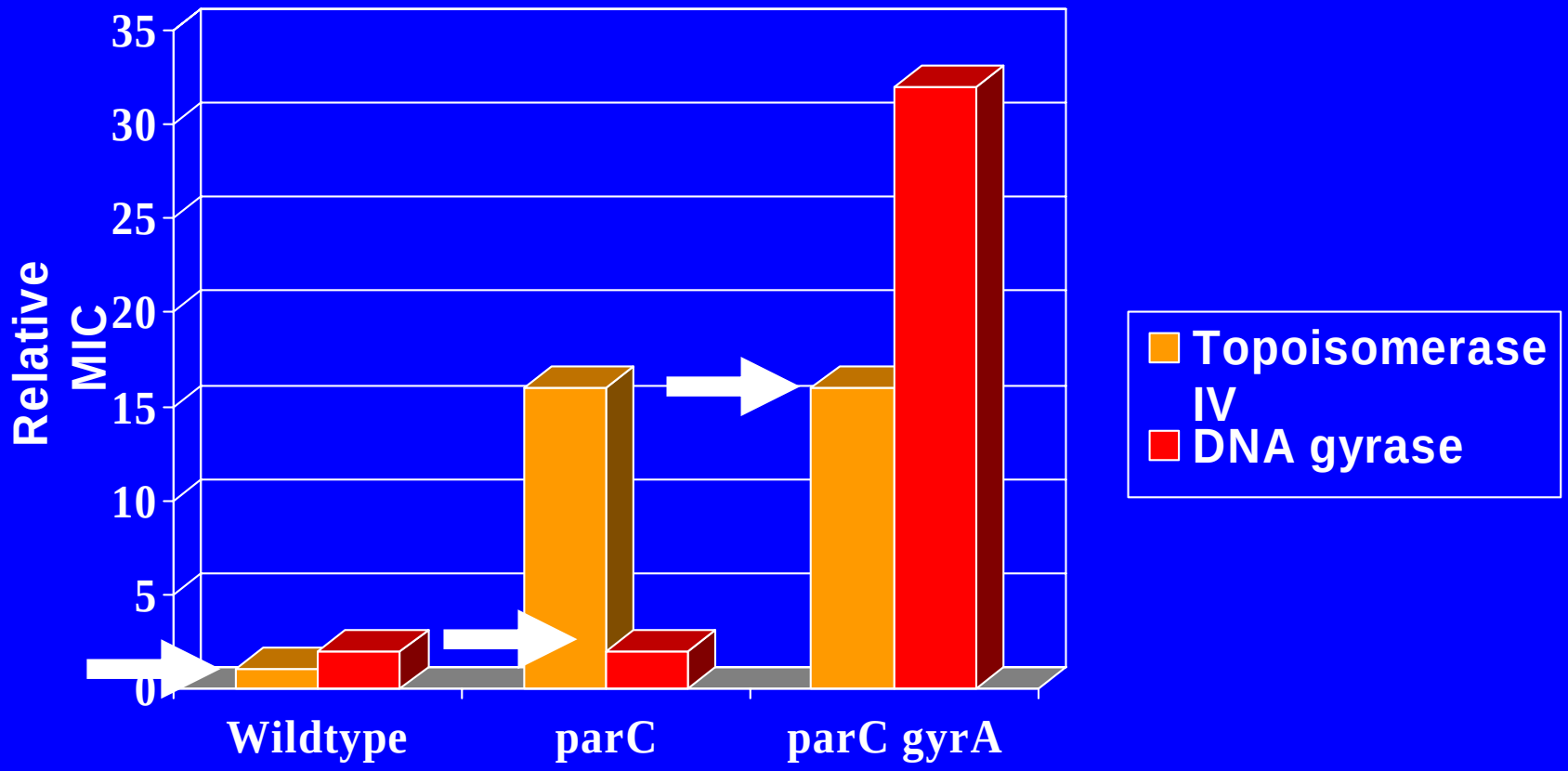

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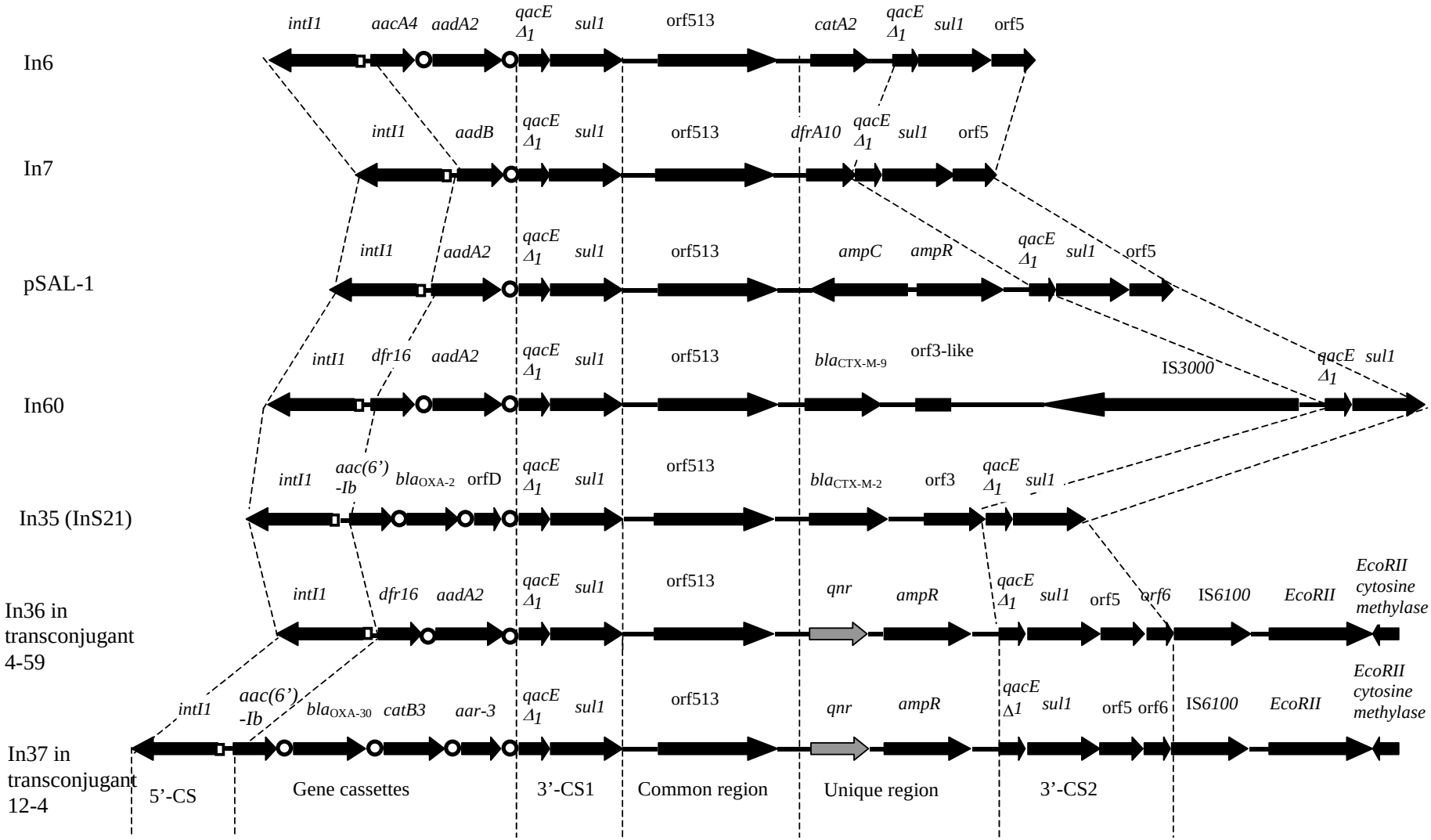


Wang M *et al*. Antimicrob Agents Chemother. 2003; 47:2242-8

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

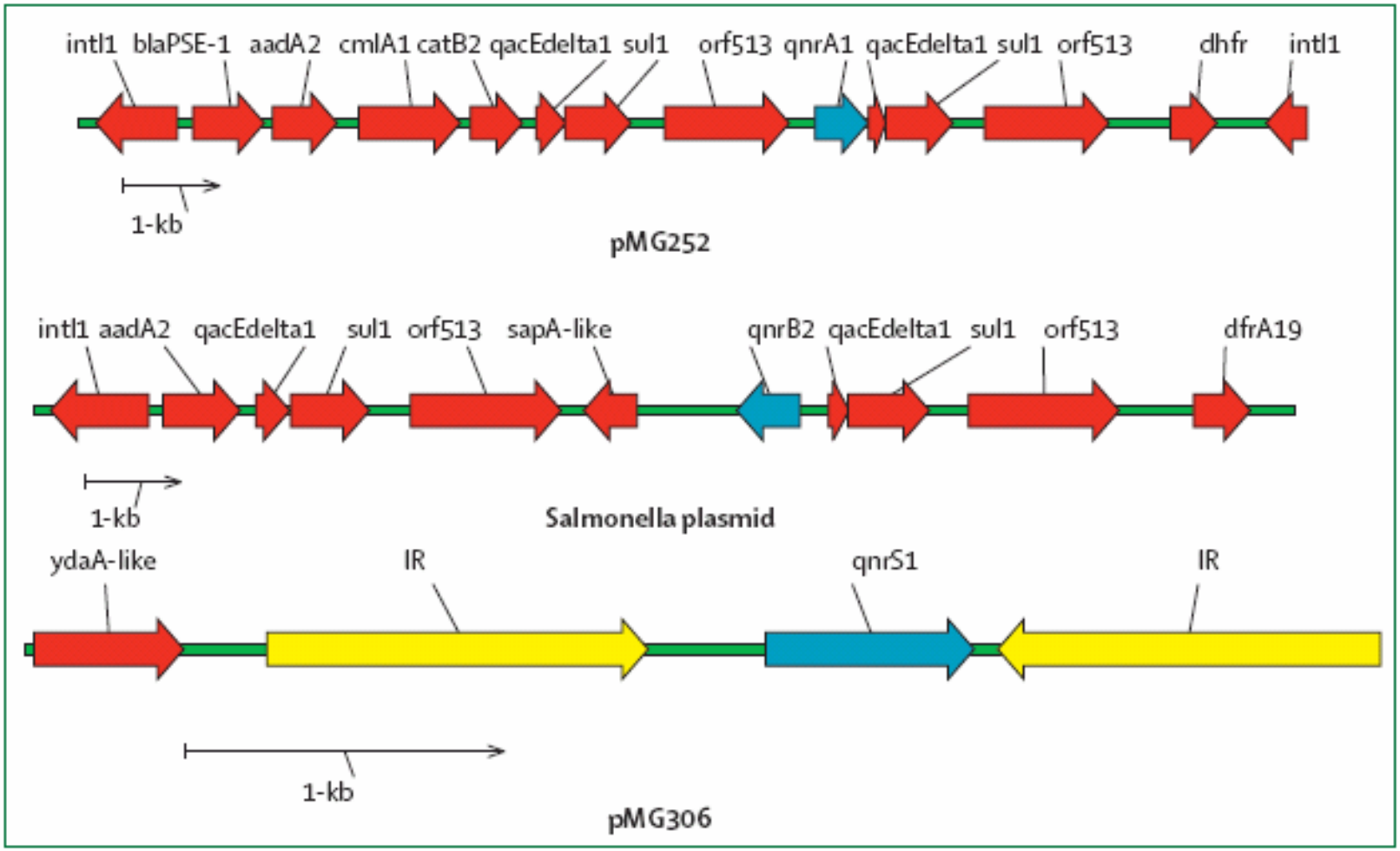
Nijssen S et al. Clin Infect Dis. 2005; 41:1-9.

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*

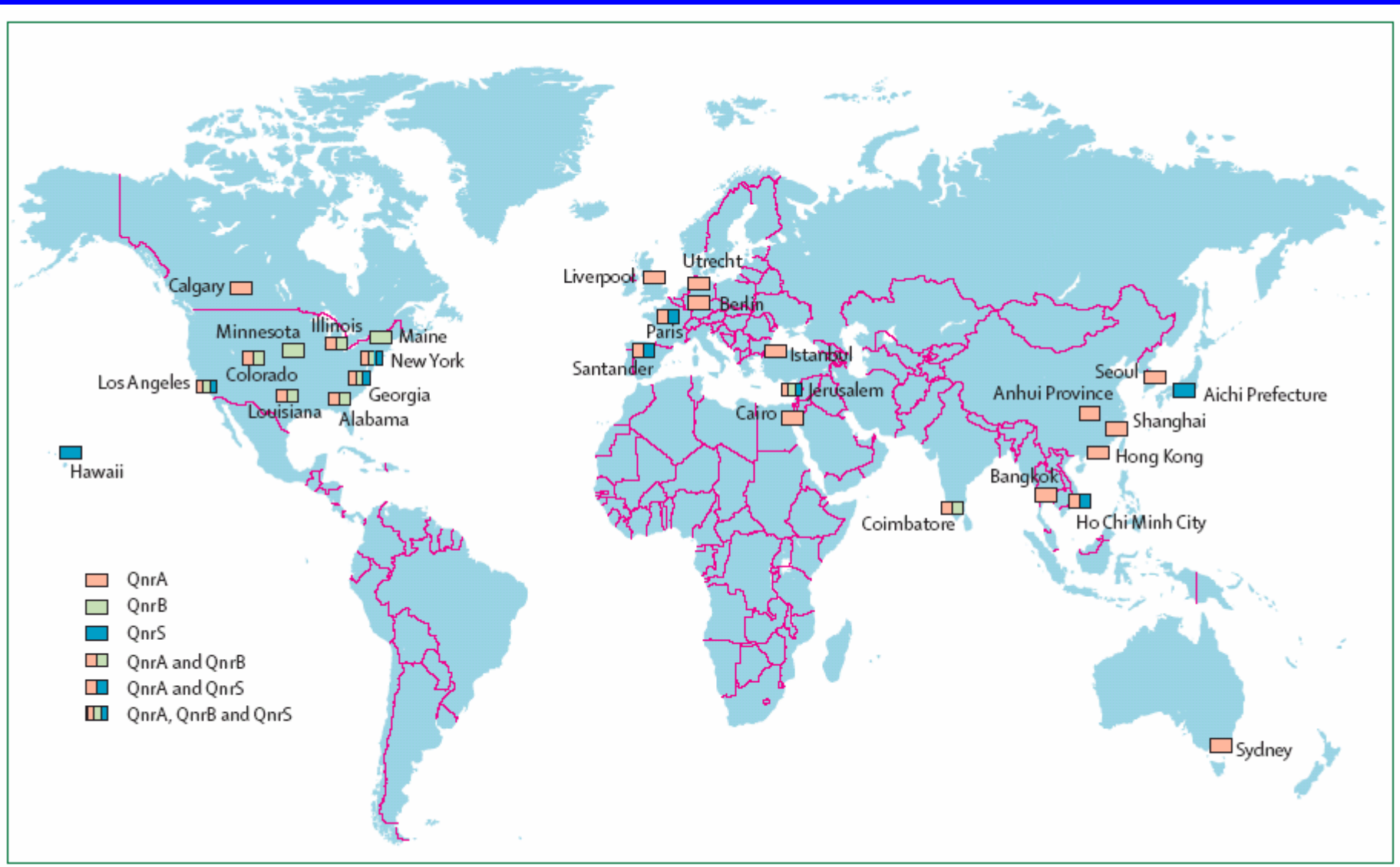
Nijssen S et al. Clin Infect Dis. 2005; 41:1-9.

Plasmid-Encoded Quinolone Resistance: Qnr Genes



Robicsek A et al. Lancet Infect Dis 2006; 6:629-40

Worldwide Distribution of Qnr Quinolone Resistance Genes



Robicsek A et al. Lancet Infect Dis 2006; 6:629-40

Characteristics of *qnr*-positive and *qnr*-negative Isolates

TABLE 3. Characteristics of *qnr*-positive and *qnr*-negative isolates

Characteristic	No. with characteristic/ total no. with *qnr* result (%)		Odds ratio (95% confidence interval)	*P* value[a]
	Positive	Negative		
Patient characteristics				
Age of ≥65 yr	22/70 (31)	77/196 (39)	0.7 (0.4–1.3)	0.25
Male	38/71 (53)	102/194 (53)	1.0 (0.6–1.8)	1
Inpatient	49/68 (72)	111/191 (58)	1.86 (1.0–3.4)	0.04
Strain characteristics[b]				
K. pneumoniae				
CIP resistant	13/21 (62)	62/85 (73)	0.6 (0.2–1.6)	0.42
GEN resistant	12/21 (57)	50/85 (59)	0.9 (0.4–2.5)	1
SXT resistant	17/21 (81)	67/85 (79)	1.1 (0.3–3.8)	1
Enterobacter spp.				
CIP resistant	35/50 (70)	71/110 (65)	1.28 (0.6–2.6)	0.59
GEN resistant	43/50 (86)	38/110 (35)	11.6 (4.8–28.4)	<0.001
SXT resistant	47/50 (94)	46/110 (42)	21.8 (6.4–74.0)	<0.001

[a] *P* values were determined by Fisher's two-tailed exact test.
[b] CIP, ciprofloxacin; GEN, gentamicin; SXT, trimethoprim-sulfamethoxazole.

Robicsek A et al. Antimicrob Agents Chemother 2006; 50:2872

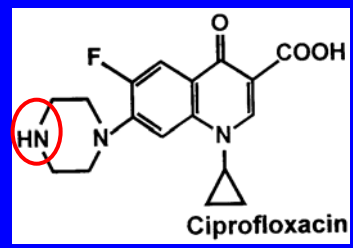
QnrA Promotes Selection of Higher-Level Quinolone Resistance

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

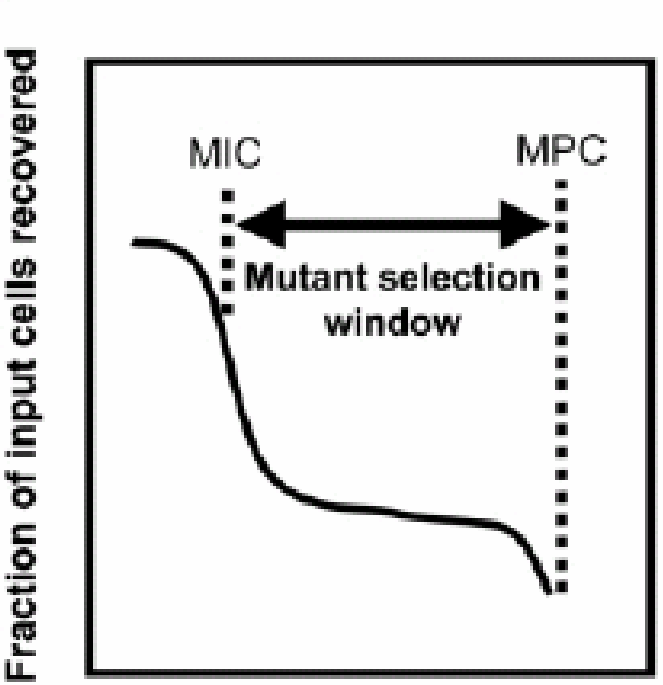
Limiting Bacterial Resistance to Fluoroquinolones

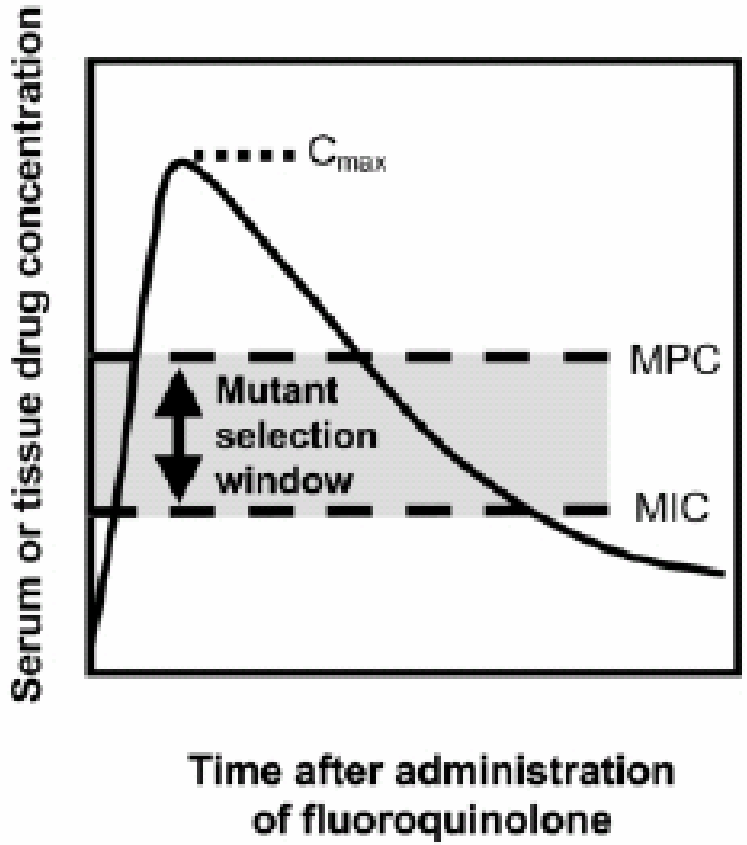
- Monitor Resistance
- Good Infection Control to Limit Spread
- Focused and Balanced Use to Limit Selective Pressures
- Adequate Dosing to Limit Mutant Selection

Pharmacodynamic Factors Affecting Risk of Selection of Quinolone Resistance

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

Pharmacodynamics of Quinolone-Resistant Mutant Selection





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

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