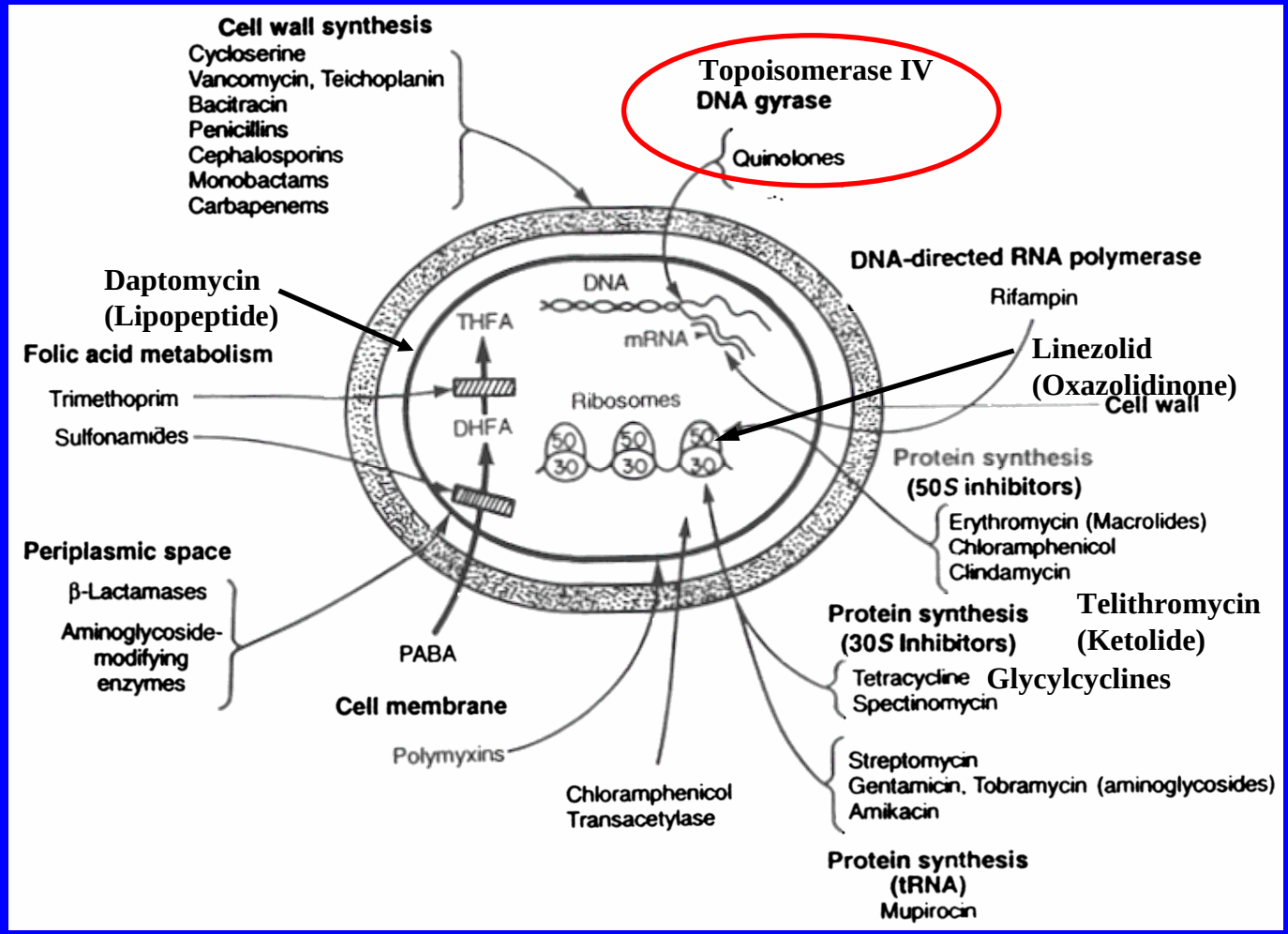
What You Need to Know When You Prescribe Fluoroquinolones to Community Patients

David C. Hooper, M.D.
Division of Infectious Diseases
Infection Control Unit
Massachusetts General Hospital
Harvard Medical School
Boston, Massachusetts

GSK Chair of Infectious Diseases
Lesson to Students – Brussels, March 28th, 2007

Sites of Action of Antimicrobial Agents in Clinical Use

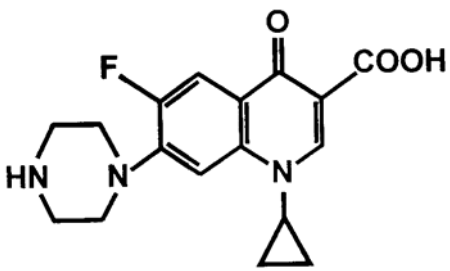


Neu HC. Science 1992; 257:1064-73

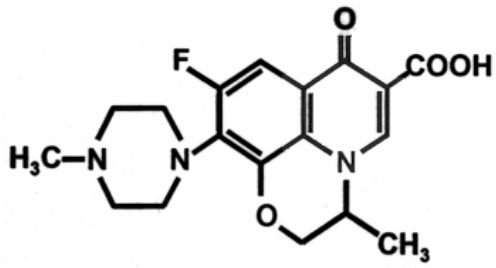
Fluoroquinolones Available in the United States

- 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)

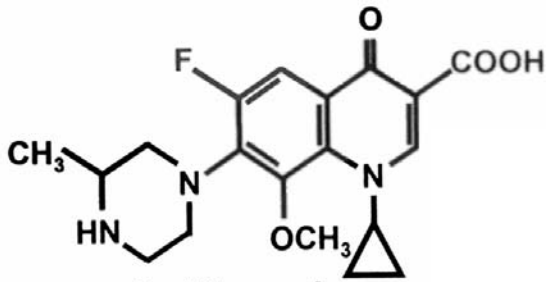
Fluoroquinolone Structures



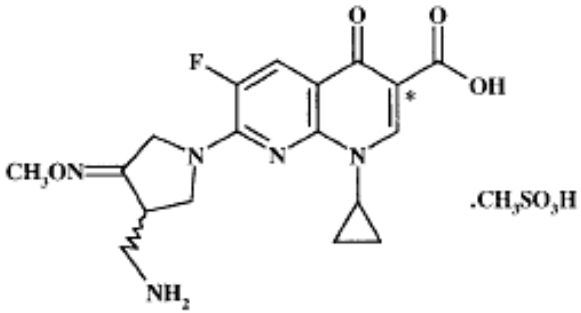
Ciprofloxacin



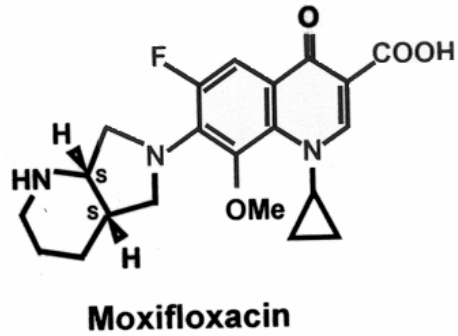
Levofloxacin



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]

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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Community-Acquired Pneumonia

Annually:

- 2-3 Million Cases
- ~10 Million Physician Visits
- 500,000 Hospitalizations
  - 258 per 100,000 population
  - 962 per 100,000 persons ≥ 65 yo
- 45,000 Deaths

Microbial Causes of Community-Acquired Pneumonia

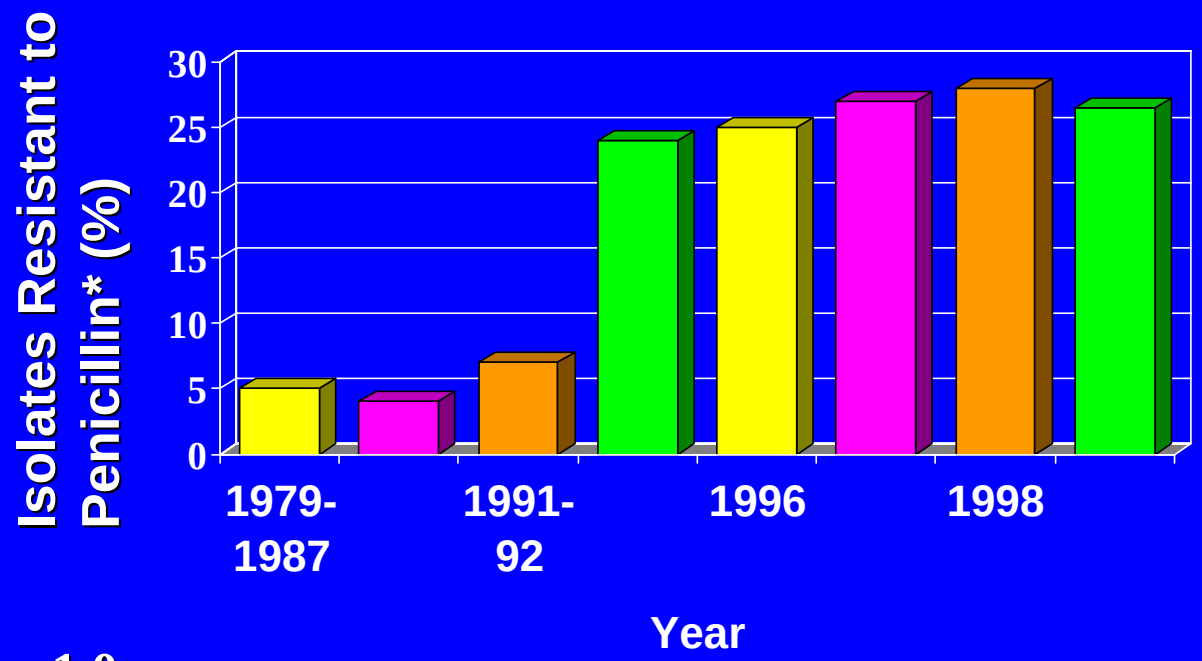
- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- *Moraxella catarrhalis*
- *Staphylococcus aureus*
- *Klebsiella pneumoniae*
- Other Gram-negative bacilli
- Anaerobic bacteria (aspiration)
- *Mycoplasma pneumoniae*
- *Chlamydia pneumoniae*
- *Legionella* spp.
- Influenza virus
- Others: mycobacteria, fungi, *Nocardia* spp., *Pneumocystis carinii*, other viruses
- None found ~ 50%

Streptococcus pneumoniae

Otitis media	**7,000,000 cases**
Pneumonia	**500,000 cases**
Bacteremia	**50,000 cases**
Meningitis	**3,000 cases**
Deaths	**40,000**
Mortality rate for bacteremia	**30 - 40%**

United States data from CDC

Penicillin-Non-Susceptible *Streptococcus pneumoniae* in the United States



*MIC 0.1 - 1.0 µg/ml (intermediate) + ≥ 2.0 µg/ml (high-level) resistance

Applebaum PC et al. Clin Infect Dis. 1992;15:77

Breiman RF et al. JAMA. 1994;271:1831

Doem GV et al. Antimicrob Ag Chemother. 1996;40:1208

Whitney CG et al. N. Engl. J. Med. 2000;343:1917

Cross Resistance Among Penicillin-Resistant Strains of *Streptococcus pneumoniae*

Antimicrobial	% Resistant to Other Antimicrobial		
	Penicillin Susceptible (n=2636)	Penicillin Intermediate (n=356, 10%)	Penicillin Resistant (n=483, 14%)
Amoxicillin	0.0	1.8	82.2
Cefuroxime	0.1	34.8	100
Cefotaxime	0.0	2.8	42.4
Meropenem	0.0	0.8	52.0
Erythromycin	3.2	35.1	61.3
TMP-SMX	6.6	49.4	92.3
Tetracycline	1.3	19.1	25.5

Whitney CG et al. N. Engl. J. Med. 2000;343:1917-24

Cross Resistance Among Penicillin-Resistant Strains of *Streptococcus pneumoniae*

Antimicrobial	% Resistant to Other Antimicrobial		
	Penicillin Susceptible (n=2636)	Penicillin Intermediate (n=356)	Penicillin Resistant (n=483)
Chloramphenicol	0.4	6.7	14.7
Clindamycin	0.5	10.7	12.2
Rifampin	0.2	0.0	0.2
Levofloxacin	0.1	0.3	0.7
Quinupristin-dalfopristin	0.0	0.6	0.2

Whitney CG et al. N. Engl. J. Med. 2000;343:1917-24

Pharmacokinetic Properties of Oral Fluoroquinolones

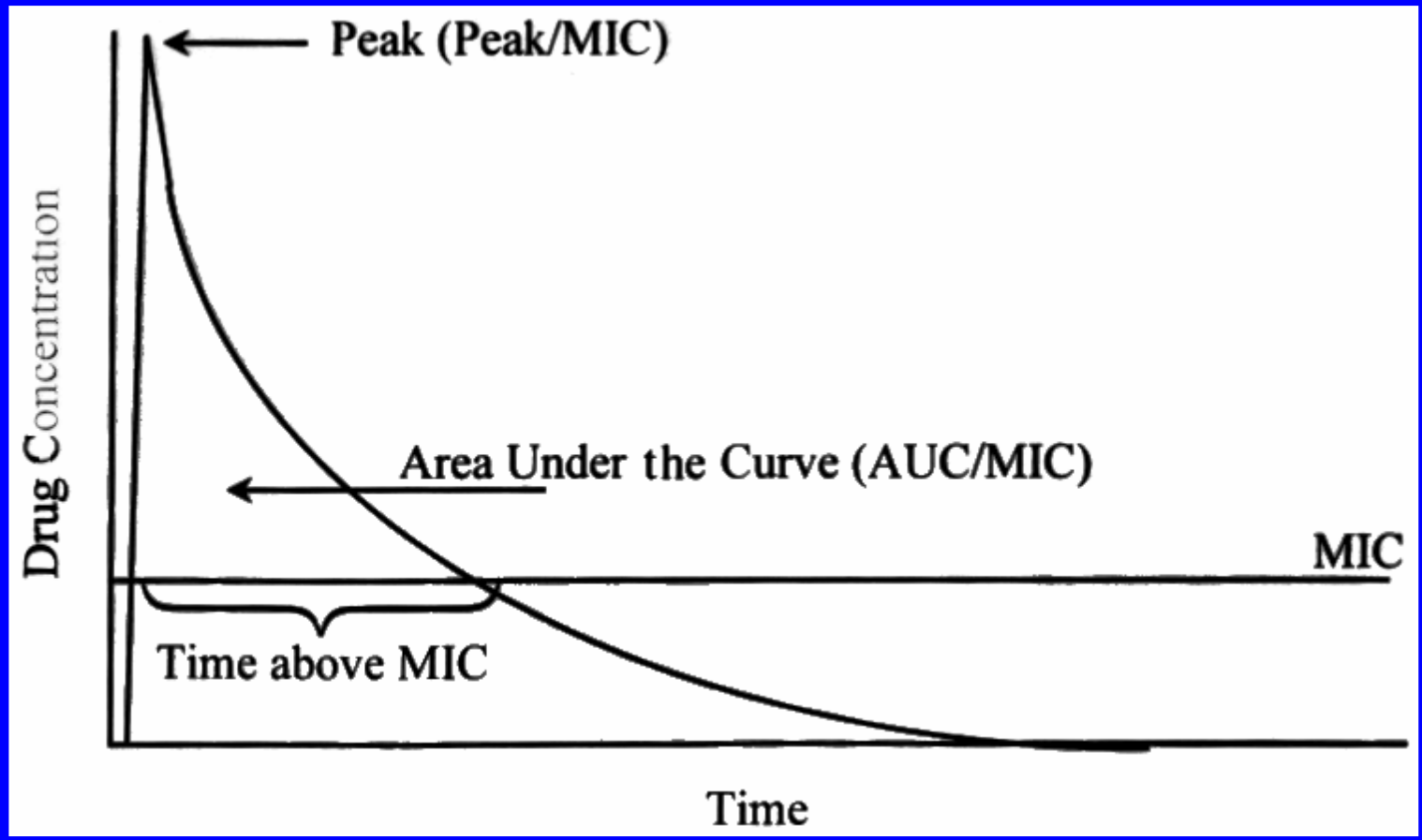
Drug	Dose (mg - frequency)	C_{max} (μg/ml)	$t_{½}$ (h)	Renal Clearance (% of total)
Ciprofloxacin	500 BID	2.2	3.3	50
Levofloxacin	500 QD	5.7	6-8	65
	750 QD	8.6		
Gatifloxacin	400 QD	4.1	7-8	80
Moxifloxacin	400 QD	4.5	13	22
Gemifloxacin	320 QD	1.8	7	30

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			

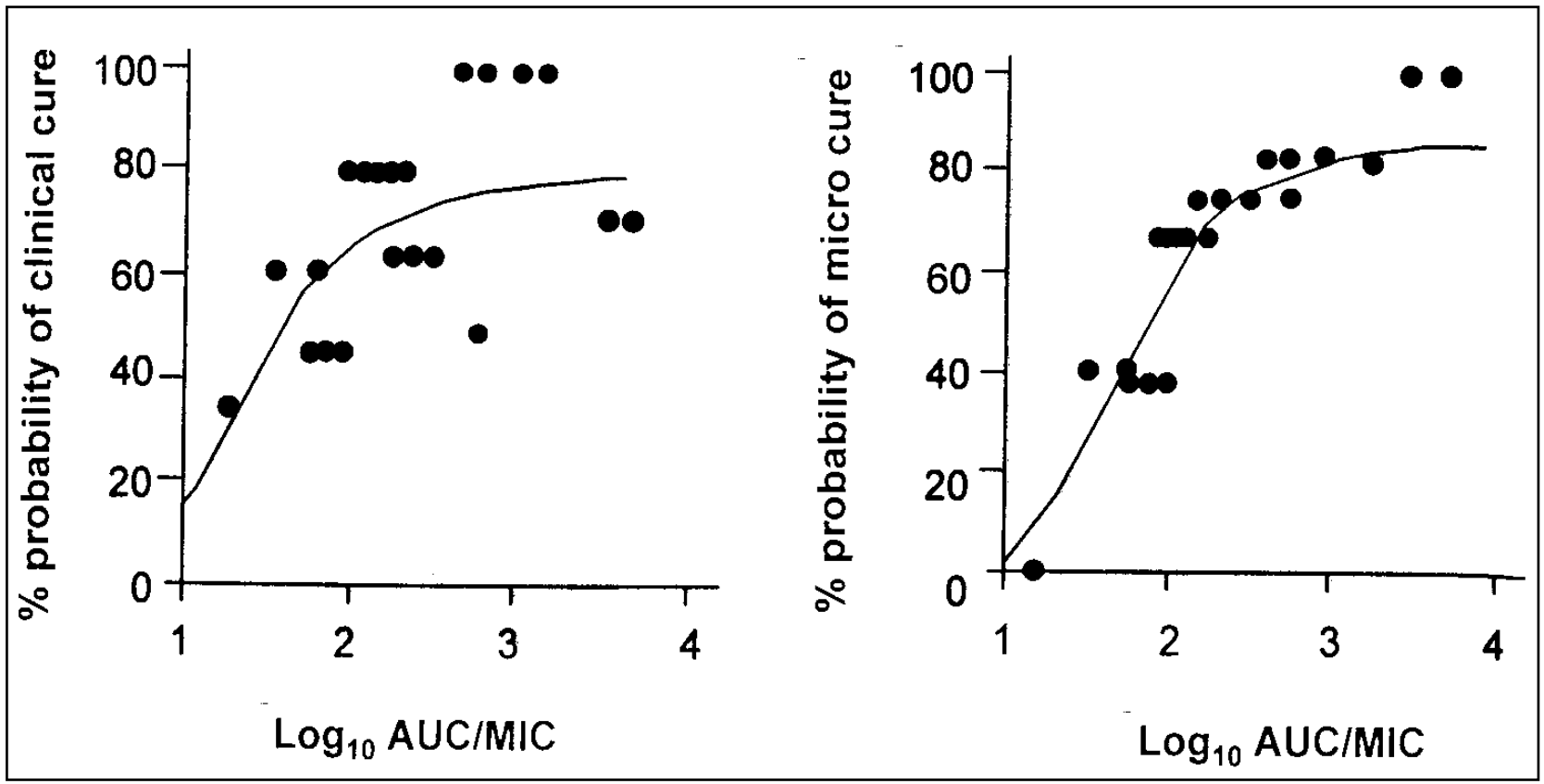
Chen DK et al. 1999. N Engl J Med. 341:233-9

Pharmacodynamic Parameters



Amsden GW *et al*. In: Mandell, Bennett, Dolin. *Principles and Practice of Infectious Diseases*, 5th edition, p. 253, 1999.

Pharmacodynamics of Ciprofloxacin in Patients with Pneumonia



Forrest A *et al*. Antimicrob Agents Chemother. 37:1073 (1993)

Randomized Comparison of Levofloxacin with Ceftriaxone/Cefuroxime for Treatment of Community-Acquired Pneumonia

Pathogen	No. (%) of Patients Responding to:					
	Levofloxacin			Ceftriaxone/Cefuroxime		
	Cured	Improved	Failed	Cured	Improved	Failed
S. pneumoniae	23(77)	7(23)	0	24(73)	7(21)	2(6)
[bacteremic]	7(78)	2(22)	0	4(50)	4(50)	0
H. influenzae	24(80)	6(20)	0	17(71)	2(8)	5(21)
C. pneumoniae	34(72)	12(26)	1(2)	34(63)	16(30)	4(7)
M. pneumoniae	15(79)	4(21)	0	17(77)	5(22)	0
L. pneumophila	4(80)	1(20)	0	2(66)	0	1(33)

File TM *et al.* Antimicrob Agents Chemother. 41:1965 (1997)

Comparison of High-Dose Short-Course with Conventional-Course Levofloxacin for Community-Acquired Pneumonia

Clinical Responses by Severity

Patient category	*n/N* (%)[a] 750-mg group[b] (*n* = 198)	500-mg group[c] (*n* = 192)	95% CI[d]
Evaluable patients	183/198 (92.4)	175/192 (91.1)	−7.0 to 4.4
Stratum I[e]			
Total	69/76 (90.8)	73/86 (84.9)	−16.5 to 4.7
PSI class III[f]	44/49 (89.8)	44/51 (86.3)	−17.2 to 10.2
PSI class IV[g]	25/27 (92.6)	27/32 (84.4)	−26.1 to 9.6
PSI class V[h]	0/0 (0.0)	2/3 (66.7)	Not applicable
Stratum II[i]	114/122 (93.4)	102/106 (96.2)	−3.4 to 9.0

Dunbar LM et al. Clin Infect Dis 2003; 37: 752

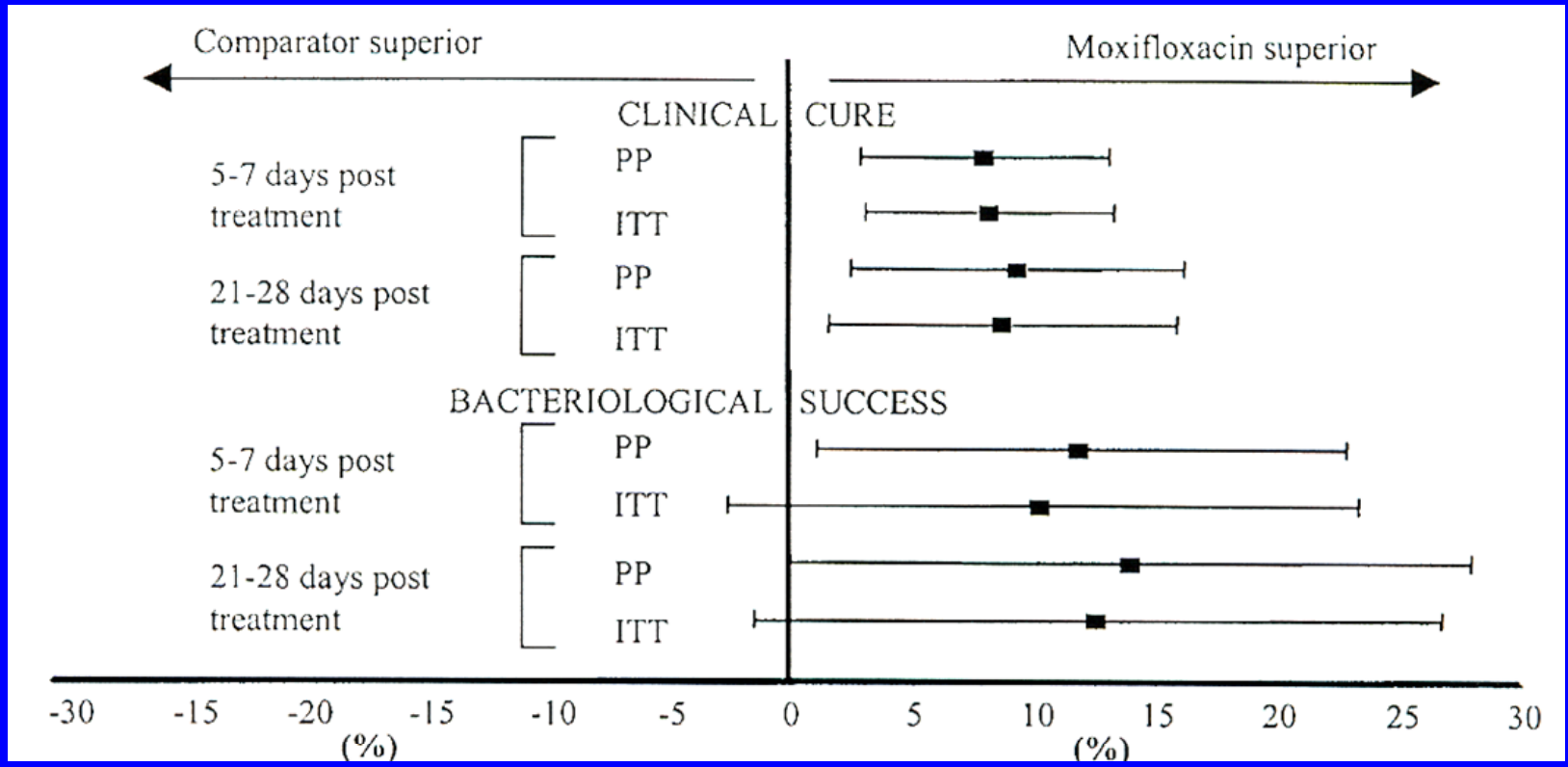
Comparison of High-Dose Short-Course with Conventional-Course Levofloxacin for Community-Acquired Pneumonia

Clinical Responses by Pathogen

Pathogen class, species	*n/N* (%)[a]	
	750-mg group[b]	500-mg group[c]
Typical pathogen[d]		
Haemophilus influenzae	12/13 (92.3)	13/14 (92.9)
Haemophilus parainfluenzae	12/12 (100.0)	9/10 (90.0)
Streptococcus pneumoniae	20/22 (90.9)	18/20 (90.0)
Atypical pathogen[e]		
Chlamydia pneumoniae	20/22 (90.9)	16/16 (100.0)
Legionella pneumophila	11/11 (100.0)	3/3 (100.0)
Mycoplasma pneumoniae	41/43 (95.3)	34/36 (94.4)

Dunbar LM et al. Clin Infect Dis 2003; 37: 752

Moxifloxacin vs Amoxicillin-Clavulanate in Community-Acquired Pneumonia



Moxifloxacin 400 mg QD IV → PO
Amox-clav 1.2g TID IV → 625 mg TID-QID PO (± clarithromycin)

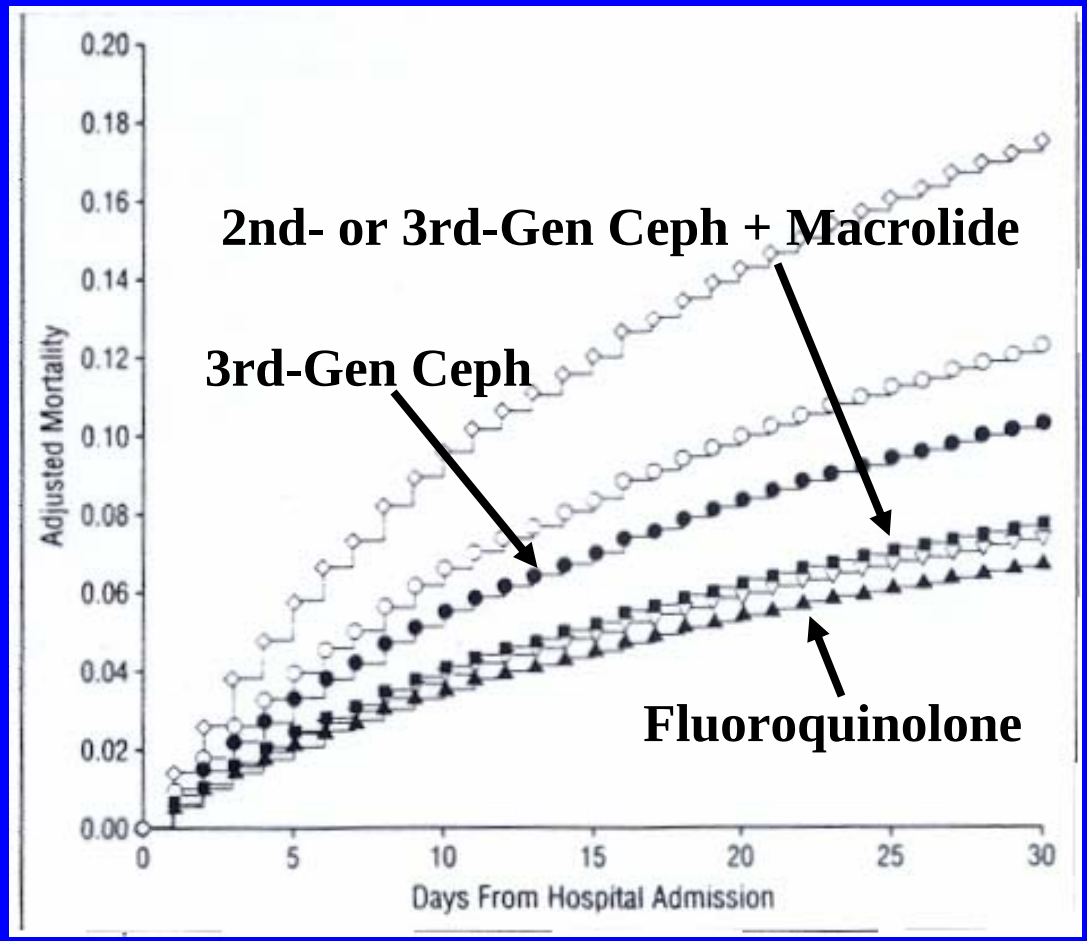
Finch R et al. Antimicrob Agents Chemother. 2002; 46:1746-54

Moxifloxacin vs Amoxicillin-Clavulanate in Community-Acquired Pneumonia

Eradication	Moxifloxacin % (n/N)	Amox-Clav % (n/N)
Total	94 (60/64)	82 (58/71)
S. pneumoniae		
Sputum	100 (18/18)	77 (17/22)
Blood	100 (11/11)	90 (9/10)
H. influenzae	100 (12/12)	90 (9/10)
M. pneumoniae	100 (13/13)	95 (16/17)

Finch R et al. Antimicrob Agents Chemother. 2002; 46:1746-54

Cox Model for Mortality Based on Initial Therapy of Pneumonia



Gleason PP *et al.* Arch Intern Med. 1999; 159:2562-72.

IDSA Guidelines for Initial Empiric Treatment of Patients with Community-Acquired Pneumonia

Outpatients

- Previously healthy without use of antimicrobials within 3 months (except in areas with >25% macrolide resistance)
  - a macrolide or doxycycline
- Patients with co-morbid illness or prior antimicrobials (chronic heart, lung, or liver disease, diabetes, malignancy, immunosuppression or antimicrobials within last 3 mo)
  - Respiratory fluoroquinolone[A] OR
  - β-Lactam plus a macrolide

[A][levofloxacin (750 mg), moxifloxacin (400 mg), or gemifloxacin (320mg)]

Mandell LA *et al*. Clin Infect Dis 2007; 44:S27

IDSA Guidelines for Initial Empiric Treatment of Patients with Community-Acquired Pneumonia

Hospitalized patients (non-ICU)

- Respiratory fluoroquinolone[A] OR
- β-Lactam plus a macrolide

Hospitalized patients (ICU)

- (Cefotaxime, ceftriaxone, or ampicillin-sulbactam) plus (azithromycin or respiratory fluoroquinolone)

[A][levofloxacin (750 mg), moxifloxacin (400 mg), or gemifloxacin (320mg)]

Mandell LA *et al*. Clin Infect Dis 2007; 44:S27

IDSA Guidelines for Initial Empiric Treatment of Patients with Community-Acquired Pneumonia

Special considerations

- If *Pseudomonas aeruginosa*
  - (Piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus (ciprofloxacin or levofloxacin (750 mg) OR
  - (Piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus aminoglycoside plus (azithromycin or respiratory fluoroquinolone[A])
- If community-acquired MRSA
  - Add vancomycin or linezolid

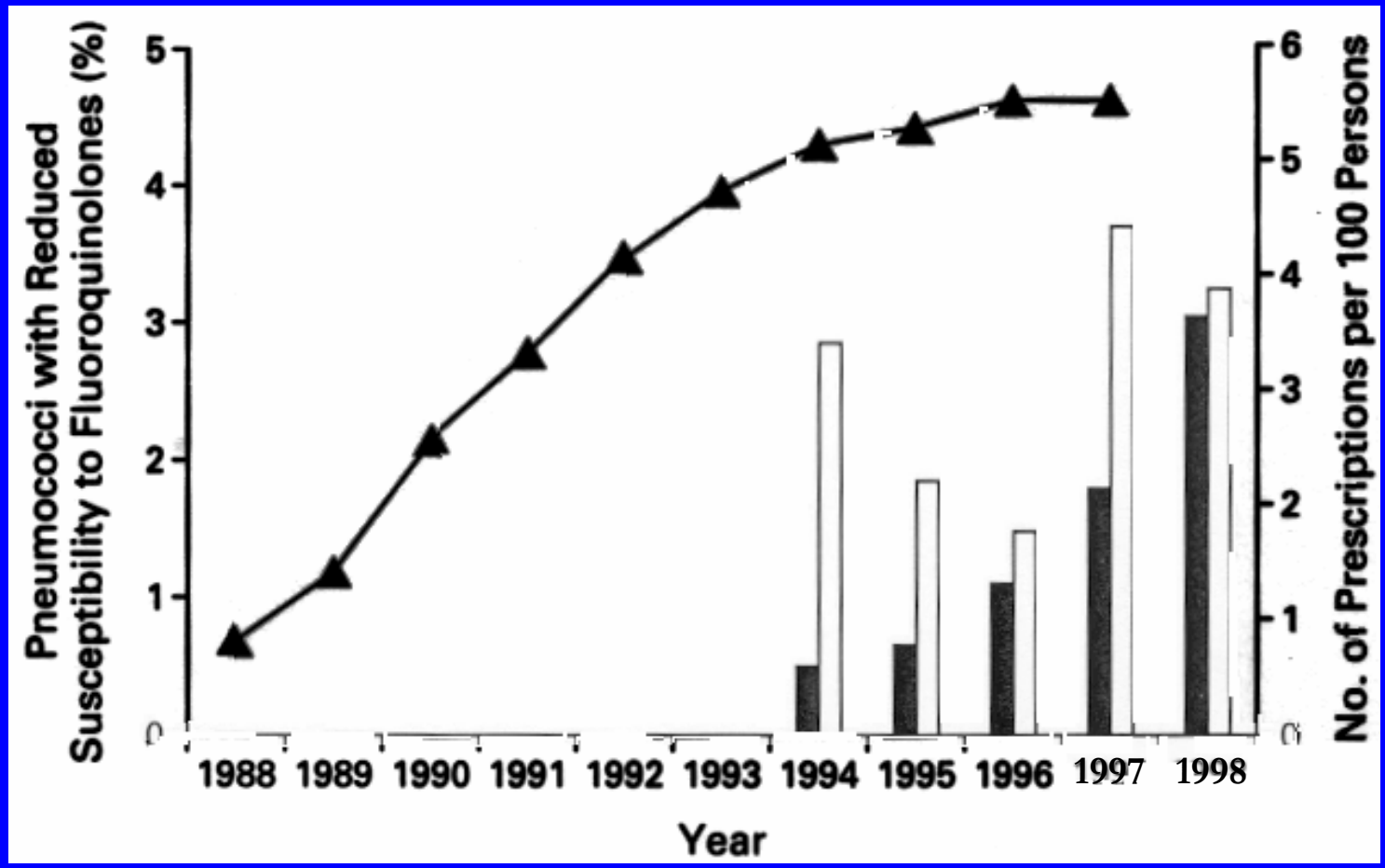
[A][levofloxacin (750 mg), moxifloxacin (400 mg), or gemifloxacin (320mg)]

Mandell LA *et al*. Clin Infect Dis 2007; 44:S27

Fluoroquinolones Adverse Effects

- Nausea, vomiting, diarrhea, taste perversion
- Insomnia, HA, dizziness (trovafloxacin), psychiatric, seizures [inhibit GABA binding to receptors]
- Rash, interstitial nephritis, photosensitivity (lomefloxacin, sparfloxacin)
- Hepatotoxicity (trovafloxacin)
- Dysglycemia (gatifloxacin)
- QT prolongation (sparfloxacin > moxifloxacin)
- Cartilage erosions in juvenile animals
- Tendinitis

Temporal Trends in Quinolone Resistance in *S. pneumoniae*



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

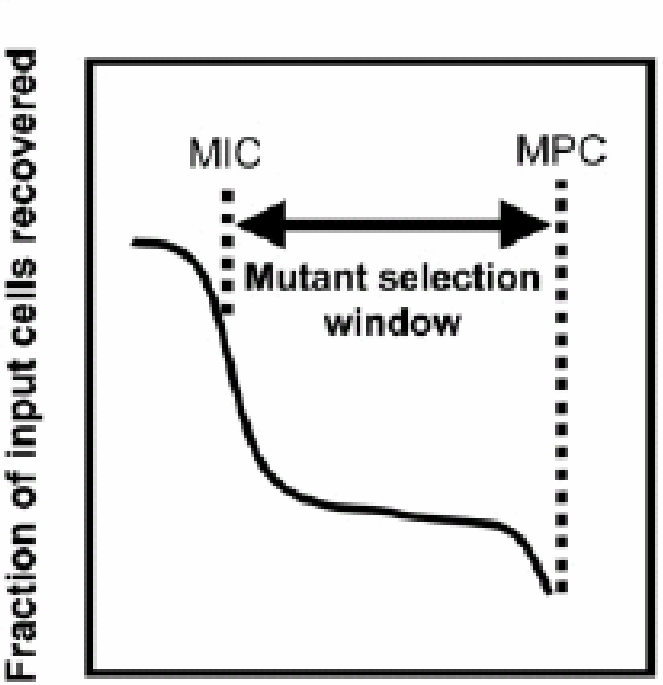
Development of Bacterial Resistance to Fluoroquinolones

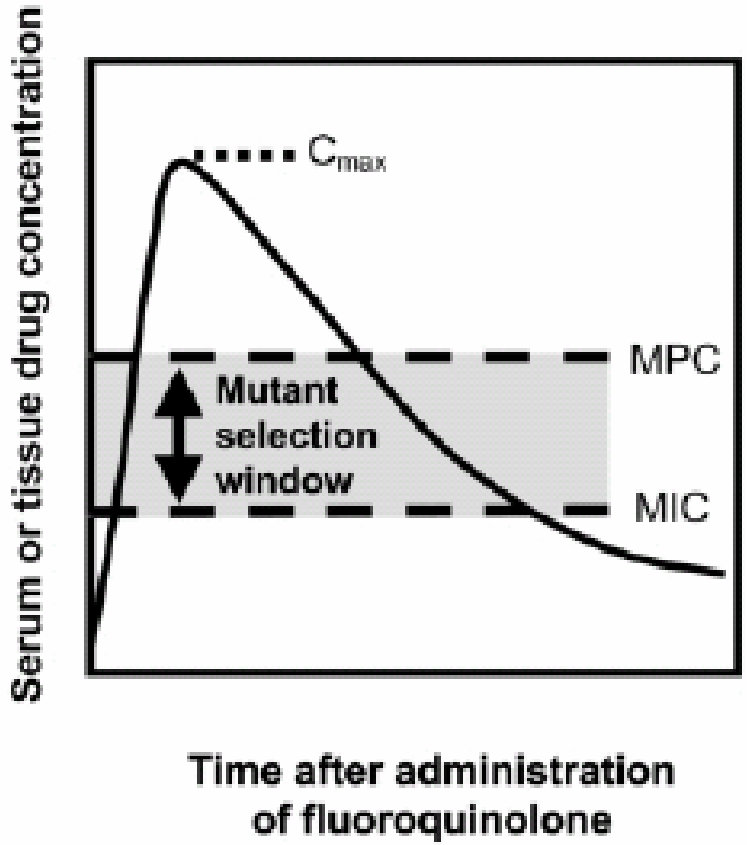
Staphylococci (MRSA, MRSE)	60-95%
Pseudomonas aeruginosa	5-30%
Campylobacter jejuni	3-50%
Escherichia coli	8-26%
Neisseria gonorrheae	6-70%
Streptococcus pneumoniae	1-14%

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 (many enteric bacteria)
  - QnrA, B, S – protection of gyrase and topoisomerase IV
  - Aac(6')-Ib-cr – acetylation of ciprofloxacin and norfloxacin by a variant aminoglycoside acetyltransferase (also causes resistance to tobramycin, amikacin, and kanamycin)
  - Usually on plasmids with multiple resistance determinants

Pharmacodynamics of Quinolone-Resistant Mutant Selection





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

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

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