

The quinolones: decades of development and use

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The discovery of nalidixic acid in 1962, and its introduction for clinical use in 1967, marks the beginning of five decades of quinolone development and use. It was not until the discovery and licensing of the fluoroquinolones in the 1970s and 1980s that these drugs began to establish their place in the armamentarium of clinically useful antimicrobials. At the beginning of the 21st century, in their fifth decade of discovery and use, our understanding of structure–function relationships has improved, and better compounds, in terms of both spectrum of antimicrobial cover and pharmacokinetics, have been developed. The clinical utility of this expanding class of antimicrobial agents, and the lower propensity for the development of resistance with the ‘newer’ fluoroquinolones will need to be continually monitored in the changing therapeutic environment. Antibiotic drug choice will remain difficult in the presence of increasing resistance, but the introduction of the new fluoroquinolones has created a new and exciting era in antimicrobial treatment. The role of these agents has already been acknowledged in a number of clinical guidelines, and appropriate use of these agents may help to preserve their clinical utility, enabling them to realize their full therapeutic potential.

Keywords: fluoroquinolones, quinolones, drug design

Introduction

The discovery of nalidixic acid in 1962, and its introduction for clinical use in 1967, marks the beginning of five decades of quinolone development and use (Figure 1). However, following the introduction of nalidixic acid for the treatment of uncomplicated urinary tract infections (UTIs) caused by enteric bacteria, the quinolones became a neglected group of antimicrobials until the development of the fluoroquinolones in the 1970s and 1980s. The fluoroquinolones have an extended spectrum of activity and improved pharmacokinetics compared with the earlier compounds. In two decades, the quinolones moved from a relatively small and unimportant group of drugs used predominantly for the treatment of UTIs, to a class that had worldwide sales of US\$3.04 billion in 1997,¹ and this figure is likely to continue to rise. These compounds have now been used in clinical practice for over a decade, and during this time an increased understanding of structure–function relationships of the fluoroquinolones has led to the development of even better compounds in terms of both the spectrum of antimicrobial cover and improved

pharmacokinetics, allowing once-daily dosing and use as a monotherapy.

Although globally many new and improved fluoroquinolones are either on or approaching the market, the development of these new compounds has not been without casualties. A small number of compounds have been withdrawn soon after launch or had their development halted at a late stage due to unforeseen side-effects.

Clinical efficacy studies are still in the early stages for some of these new agents but a few already show evidence of a promising future. Their role in the antibacterial armamentarium still remains to be determined, but with the inevitable emergence of resistant strains, appropriate use of these new fluoroquinolones must be advocated.

The first decades of discovery and use

Based on the 4-quinolone nucleus, the quinolones comprise a relatively large and expanding group of synthetic compounds. The first of these compounds to be discovered was the naphthyridine agent, nalidixic acid,² an antibacterial by-product of

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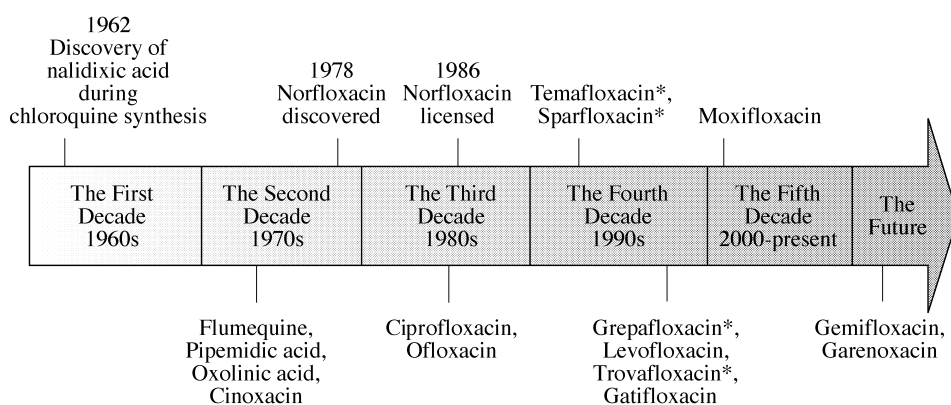


Figure 1. Quinolones: decades of discovery and use. *, withdrawn.

chloroquine synthesis. Two years after its discovery the mechanism of action was defined as the inhibition of bacterial DNA gyrase synthesis, thus inhibiting tertiary negative supercoiling of bacterial DNA,³⁻⁷ and is rapidly bactericidal. In 1990 a homologue of gyrase, topoisomerase IV, that had a potent decatenating activity was discovered, and it is now clear that topoisomerase IV, rather than gyrase, is responsible for decatenation of interlinked chromosomes.⁸ The dual action against DNA gyrase and topoisomerase IV has subsequently proved to be the same mechanism for all the antibacterial quinolones.^{6,8} These remarkable enzymes are involved in maintaining the integrity of the supercoiled DNA helix during replication and transcription. If their action is impeded the bacterial chromosome remains unwound and is too long and large to fit into the two progeny cells.⁸ The comparable mammalian enzyme is not susceptible to the actions of the quinolones at concentrations used in clinical practice.

The first decade of quinolone development and use was the 1960s. In 1967, nalidixic acid was licensed for the treatment of UTIs caused by the majority of Gram-negative bacteria, with the exception of *Pseudomonas aeruginosa*. Gram-positive organisms are usually resistant (Table 1) to the early quinolones. The clinical usefulness of nalidixic acid, other than in the treatment of urinary infection, was limited by its low serum concentrations and high minimum inhibitory concentrations (MIC 4–16 mg/L).⁹ Subsequent derivations, such

as pipemidic acid (the first piperazinyl quinolone), oxolinic acid and cinoxacin were discovered in the 1970s, and represented only marginal improvements over nalidixic acid. These early agents, however, proved invaluable in the treatment of uncomplicated UTIs, such as cystitis. Nalidixic acid has several structural features retained by the newer compounds, and is based on a 4-oxo-1,8-naphthyridin-3-carboxylic acid nucleus.¹⁰

Soon after the introduction of nalidixic acid into widespread clinical use, it was found that resistance developed rapidly in a number of organisms. This feature proved to be a characteristic of the early quinolones. With nalidixic acid, resistance develops readily following serial passages in the laboratory, but primary resistance amongst urinary pathogens is unusual. In 1969, resistance to nalidixic acid in *Escherichia coli* was mapped to chromosomal mutations (*nalA*, *nalB*).¹¹ These resistance loci were further identified in 1977 as encoding mutant subunits of DNA gyrase of *E. coli*.¹² The adverse reactions associated with nalidixic acid are generally those common to all quinolones, i.e. gastrointestinal tract and CNS disturbances and skin rashes, including eruptions related to photosensitivity. Quinolone safety and tolerability is discussed by P. Ball in this supplement.

The fluoroquinolones

Until the development of flumequine, the first monofluoroquinolone in 1976, none of the earlier compounds had offered any significant improvements over nalidixic acid. Flumequine was the first compound to be developed with a fluoro-group at position 6, and gave the first indications that modifications of the basic chemical structure could improve Gram-positive activity.¹ (The structural modifications to the pharmacore common to all quinolones are discussed elsewhere in this supplement by M. Andersson & A. MacGowan.) Its range of activity embraced the Enterobacteriaceae, including some strains that were resistant to nalidixic acid with useful activity against uncomplicated gonorrhoea, albeit with a two- or three-dose regimen.

Table 1. The first decade of discovery and use: ‘early’ quinolones (nalidixic acid, oxolinic acid, cinoxacin)

Almost no activity against:
Gram-positive organisms
anaerobes
<i>P. aeruginosa</i>
Toxicity, especially involving:
central nervous system
gastrointestinal tract
Rapid emergence of resistance

The quinolones: decades of development and use

In 1978 norfloxacin, a 6-fluorinated quinolone with a piperazinyl side-chain at position 7, was developed. In 1986 norfloxacin was licensed in the United States for use in genitourinary infections. Norfloxacin had a longer half-life than the earlier compounds (3–4 h), less protein binding (50%) and improved Gram-negative activity.⁹ With the development of fleroxacin in 1986, the first trifluorinated quinolone, the class entered the third decade of development and use. Fleroxacin was distinguished from its predecessors by its excellent bioavailability, high concentrations in the plasma and other body fluids, good tissue penetration and a long half-life of 10–12 h, allowing for once-a-day administration.¹³ In clinical trials, fleroxacin has been evaluated in the treatment of UTIs, gonorrhoea and chancroid with bacteriological cure rates of $\geq 90\%$.¹⁴ However, the incidence of side-effects reported with fleroxacin, including severe phototoxic reactions, limited the clinical utility of this drug.¹⁴

Having taken two decades to produce significant improvements in bioavailability and spectrum from the early compounds, the next phase of development followed very rapidly. Between 1979 and 1982 a number of fluoroquinolones were patented, including ciprofloxacin in 1981, which is still in widespread clinical use today. These compounds were much more active than earlier derivatives against Enterobacteriaceae, *P. aeruginosa* and many Gram-positive cocci (Table 2). The fluoroquinolones developed since the 1980s are usually administered orally, although some can also be given by injection. The option of switch therapy will be discussed later. Therapeutic doses achieve relatively low concentrations in plasma but the compounds are well distributed in tissues and are concentrated within mammalian cells. Of the improved fluoroquinolones, ciprofloxacin is the most widely used.

Ciprofloxacin

Overall, ciprofloxacin is the most potent of the currently available fluoroquinolones against Gram-negative bacteria, although some of the new fluoroquinolones currently under investigation may challenge this. Ciprofloxacin is also active against *P. aeruginosa* and *Acinetobacter* spp. It is very active against *Haemophilus influenzae*, *Moraxella catarrhalis* and *Neisseria* spp., including β -lactamase-producing strains of *Neisseria gonorrhoeae*. Following oral absorption the drug is widely distributed in body water, with concentrations in most tissues and in phagocytic cells approximating to those in plasma. Most of the absorbed dose can be recovered from faeces and urine. Significant untoward reactions are uncommon; the most frequent being gastrointestinal tract disturbances (approximately 3.4%) and rashes (<1%). CNS disturbances, typical of quinolones, have been reported in 1.1% of patients.¹⁵

Table 2. The fourth decade of discovery and use: 'improved' fluoroquinolones (norfloxacin, pefloxacin, ciprofloxacin, ofloxacin, lomefloxacin, enoxacin)

Improved potency against Enterobacteriaceae including <i>P. aeruginosa</i>
Good activity against some Gram-positive organisms
Limited activity against anaerobes
Less likely to select bacteria with single-step mutations to high-level resistance
More favourable toxicological profiles

Ciprofloxacin has been shown to be of benefit in the treatment of a wide range of infections, including UTIs, osteomyelitis caused by Enterobacteriaceae, ENT infections, gonococcal infections and chronic bacterial prostatitis. It has a place in the treatment of septicaemia and skin and soft tissue infections, and has been shown to be effective in the eradication of nasopharyngeal carriage of *Neisseria meningitidis*.^{15,16} The availability of both intravenous (iv) and oral formulations also allows major benefits to be accrued by early switching from parenteral to oral therapy,¹⁷ and published data now support the use of single dose (500 mg), low dose (100 mg twice a day) and short course therapy (3 days) for UTIs.^{18,19} Resistance to the fluoroquinolones has increased over the years and local antimicrobial resistance patterns need to be monitored. (The mechanisms of quinolone action and microbial response are discussed in this supplement by P. Hawkey, and the pharmacodynamic properties of different quinolones by R. Wise and J. Paladino & W. Callen.)

Despite a period of cautious quinolone use over the past 10 years, ciprofloxacin has become established as the mainstay of quinolone therapy, particularly in the treatment of Gram-negative infections. Many early studies involved the use of a 200 mg iv twice-daily regimen.^{20–23} More recent studies have employed more adventurous dosing and outcomes are much improved using a 400 mg iv dose given three times a day.^{24–29} Caution was also exercised over the use of the quinolones for chest infections where there was a strong likelihood of a heavy or pure growth of *Streptococcus pneumoniae*. The fluoroquinolones developed in the third and fourth decades, such as ciprofloxacin and ofloxacin, are considered as having only moderate activity against pneumococcus, although clinical outcomes have been somewhat better than those predicted by laboratory MICs. A meta-analysis of 37 trials reporting failure of ciprofloxacin therapy confirmed that *S. pneumoniae* bacteriological eradication rates were high, but overall clinical response was higher (Table 3), and that treatment failure was probably due to inadequate or inappropriate therapy.³⁰ However, recent reports of treatment failure in the management of respiratory infections with levofloxacin

Table 3. Ciprofloxacin use in respiratory infections: a decade of 'cautious' use

Early studies employed 200 mg iv twice a day regimen
More recent studies, 400 mg iv three times a day regimen
Concern with pure pneumococcal infections
Confidence with mixed infections
Meta-analysis ³⁰
<i>S. pneumoniae</i> eradication high (86%)
overall clinical response higher (94%)

^{31–33} have highlighted the need for compounds with enhanced pneumococcal activity. Newer fluoroquinolone derivatives, such as moxifloxacin, display good anti-pneumococcal activity.^{34,35}

More controversial is the use of fluoroquinolones (or any antibiotic) in the prophylaxis or treatment of traveller's diarrhoea. Ciprofloxacin has good activity against many gut pathogens including *E. coli*, *Campylobacter* spp., *Salmonella* spp. and *Shigella* spp. Worldwide resistance to tetracyclines and co-trimoxazole in gut pathogens is high, and resistance to ciprofloxacin is rising (Table 4).^{36,37} A strong temporal association between increases in the occurrence of resistance to ciprofloxacin (MICs 0.25–1.0 mg/L) in certain *Salmonella* spp. and the use of enrofloxacin in animal food additives has been demonstrated, whereas for *Salmonella enteritidis*, ciprofloxacin resistance was most common in a phage type associated with foreign travel.³⁶ In practice, ciprofloxacin (500 mg twice daily for 3–5 days) remains a highly effective treatment for the majority of gastrointestinal infections.

The current practice for treating intra-abdominal infections is to use combination regimens to cover both aerobes and anaerobes. These regimens may be cumbersome combinations, such as penicillins together with a nitroimidazole (e.g. metronidazole) and an aminoglycoside (e.g. gentamicin); others include clindamycin, carbapenems and cephalosporins. Treatment regimens now available include pefloxacin or ciprofloxacin with metronidazole or clinafloxacin alone. A recent review³⁸ of three studies^{39–41} of complicated intra-abdominal infections showed the combination of ciprofloxacin and metronidazole to be as effective (73.9–89.4%) as piperacillin/tazobactam (62.9%), imipenem/cilastatin (80.5%) or ceftriaxone/metronidazole (86.6%) in terms of overall clinical success.

Hopes for the fifth decade of discovery and use

Novel fluoroquinolones

Over the past 10 years fluoroquinolone research has been aimed at generally improving activity against Gram-positive

Table 4. Ciprofloxacin-resistant^a *Salmonella* serotypes—England and Wales (1994–1997)

Serotype	Total received	Percentage change in susceptibility
<i>S. enteritidis</i>	17 701–22 723	0.4–1.3
<i>S. typhimurium</i>	5603–4690	1.0–10.0
<i>S. virchow</i>	2797–704	5.0–14.0
<i>S. hadar</i>	753–692	40.0–50.0
Others	4293–3315	1.0–3.0

^aMIC ≥ 0.25 mg/L.

Adapted from Threlfall *et al.* (1997)³⁶

cocci, particularly against pneumococci, and improved activity against anaerobes, whilst retaining the activity against Gram-negative organisms. Further attempts to improve the pharmacological and antimicrobial properties of these compounds have led to the development of a new group of 'novel', 'third generation' or 'respiratory' fluoroquinolones. These compounds are characterized by enhanced activity against Gram-positive cocci as well as many intracellular pathogens. Whilst retaining excellent activity against Gram-negative organisms, they also have some useful activity against anaerobes⁴² (Table 5).

'Newer' fluoroquinolone activity against respiratory pathogens

These new agents, e.g. trovafloxacin, moxifloxacin, gatifloxacin, gemifloxacin and grepafloxacin, are active against all the primary pathogens that cause typical respiratory disease, e.g. *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*.^{43,44} Development and use of some of these newer agents, trovafloxacin, gemifloxacin and grepafloxacin, has been restricted or suspended because of adverse drug reactions (ADRs).^{45–47} Table 6 shows the comparative activity of these 'newer' fluoroquinolones against respiratory pathogens. In addition, they have very good *in vitro* activity against sensitive and resistant strains, i.e. β-lactamase producers,⁴⁸ and have high activity against the so-called atypical pathogens, such as *Chlamydia pneumoniae*, *Mycoplasma pneumoniae* and *Legionella pneumophila*.^{49–51} All penetrate phagocytic cells and a range of tissues very well and have good activity against intracellular pathogens.^{52–54} Although trovafloxacin has been withdrawn because of serious hepatotoxicity,⁴⁶ and grepafloxacin because of an association with sudden cardiac death,⁵⁵ data published to date show that moxifloxacin^{56,57} and gatifloxacin⁵⁸ have a satisfactory ADR profile. The differences between the different compounds are discussed within this supplement in the review by P. Ball. Early clinical trial

The quinolones: decades of development and use

Table 5. *In vitro* activities of gatifloxacin, trovafloxacin and moxifloxacin against anaerobes

Group	MIC ₉₀ (mg/L)		
	trovafloxacin ^a	gatifloxacin	moxifloxacin
<i>B. fragilis</i> group	0.5–1.0	2.0	4.0
<i>Prevotella/Bacteroides/Porphyromonas</i> spp.	1.0	4.0	0.5–2.0
<i>Fusobacterium</i> spp.	1.0–2.0	4.0	0.6–8.0
<i>Peptostreptococcus</i> spp.	0.25–1.0	1.0	0.25
Non-spore forming Gram-positive bacilli	1.0–4.0	1.0	0.25 (few strains)
<i>Clostridium</i> spp.	0.25–1.0	2.0	0.5–1.0

^aWithdrawn.

Adapted from Appelbaum (1999).⁴²

Table 6. *In vitro* activities of selected fluoroquinolones against respiratory tract pathogens (range of published MIC₉₀ values)

Species	Gatifloxacin ^a	Grepafloxacin	Moxifloxacin	Trovafloxacin ^a
<i>S. pneumoniae</i>				
penicillin susceptible	0.06–1	0.03–1	0.03–0.25	0.03–0.25
penicillin resistant	0.1–1	0.06–1	0.03–0.25	0.03–0.25
<i>H. influenzae</i>				
ampicillin susceptible	0.004–0.016	0.008–0.06	0.008–0.13	0.004–0.03
ampicillin resistant	0.004–0.016	0.008–0.06	0.008–0.13	0.004–0.03
<i>M. catarrhalis</i>				
β-lactamase negative	0.004–0.03	0.004–0.03	0.004–0.03	0.002–0.03
β-lactamase positive	0.004–0.03	0.004–0.03	0.004–0.03	0.002–0.03
<i>C. pneumoniae</i>	0.06–0.5	0.12	0.12	0.12
<i>Legionella</i> spp.	0.06	0.25	0.06	0.008
<i>M. pneumoniae</i>	0.12	0.25	0.12	0.25

^aWithdrawn.

Adapted from Dalhoff (1999).⁶⁴

data would seem to support the use of these compounds as monotherapy in the management of respiratory infections.^{59–61}

Activity against *S. pneumoniae*

Until the mid-1970s *S. pneumoniae* infections were successfully treated with β-lactam antibiotics in modest doses. Since then, however, increasing resistance to penicillin has been reported on a worldwide scale,⁶² together with increased resistance to the tetracyclines and the macrolides.⁶³ Thus, a major problem exists with the emergence of multiple antibiotic-resistant strains of *S. pneumoniae*. Strains with intermediate penicillin resistance (MIC 0.12–1 mg/L) can still be treated with high parenteral doses of penicillin, but

strains with MICs > 1 mg/L are refractory to treatment, and third-generation cephalosporins, carbapenems or glycopeptides have to be considered. The ‘ideal’ fluoroquinolone would combine good clinical efficacy with a low MIC₉₀ for *S. pneumoniae*, and several of the ‘newer’ fluoroquinolones do possess such features (Table 7).^{7,64} In *S. pneumoniae*, the primary targets for most fluoroquinolones tested so far are *parC* and *parE*, which encode the two subunits of topoisomerase IV, with GyrA as the secondary target. In general, resistance will appear first in the gene encoding the most sensitive drug target (discussed in detail in this supplement by P. Hawkey). However, as with all groups of antibiotics, the use of fluoroquinolones may increase the emergence of resistance.^{7,65} It is therefore important that they are used appro-

Table 7. Differential activities of representative fluoroquinolones against *S. pneumoniae*

	MIC ₉₀ (mg/L)
Ciprofloxacin	2
Norfloxacin	16
Levofloxacin	1–2
Sparfloxacin ^a	0.5
Grepafloxacin ^a	0.25
Trovafoxacin ^a	0.12
Gatifloxacin	0.5
Moxifloxacin	0.25
Gemifloxacin ^b	0.016

^aWithdrawn.^bNot approved.Adapted from Ball (2000).⁶⁶

priately and ‘targeted’ at the most suitable groups of patients for therapy.

Advantages of the ‘newer’ fluoroquinolones

All of the new fluoroquinolones have high bioavailability, low protein binding and longer serum elimination half-lives compared with the earlier quinolones¹ (discussed in this supplement by R. Wise), thus permitting once-daily dosing and increased patient compliance. Tissue penetration is high and the agents are very widely distributed in body fluids. The routes of elimination are variable, and each drug requires evaluation on an individual basis. An important facet of the activity of the newer fluoroquinolones is the rate of development of resistant mutants. Fluoroquinolone resistance may result from chromosomal mutations coding for modifications in target subunits (primarily *GyrA*, but also *GyrB*) of bacterial topoisomerase II and, in Gram-positive species, by variations in the uptake reflux process and mutations in topoisomerase IV.⁶⁶ There is increasing evidence that the newer fluoroquinolones, because of their dual activity against DNA gyrase and topoisomerase IV, do not select for resistance as rapidly as the earlier compounds.^{1,8} (This topic is discussed in detail in the article by P. Hawkey.)

Future role of the fluoroquinolones

Without doubt, the newer fluoroquinolones have very attractive ‘*in vitro*’ activities against a plethora of community and nosocomial pathogens, and many possess improved pharmacokinetic properties. The availability of oral and intravenous formulations for the majority of these compounds facilitates flexible dosing and iv-to-oral switch therapy. Preliminary data are encouraging,^{59–61} although it would be premature to assess their clinical efficacy until the number of

patients recruited into properly designed clinical trials has increased further. However, their use has already been advocated in published guidelines⁶⁷ as an alternative to β -lactams and macrolides in the treatment of adults with non-severe community acquired pneumonia.

It is inevitable that with the increase in fluoroquinolone use, resistance will also increase, despite the remarkable features of these new agents. It is recognized that new clinical strategies need to be developed to delay or minimize the risk of antibiotic resistance developing, and the fluoroquinolones are no exception to this. Strategies may include the more widespread adoption of clinical guidelines advocating the use of appropriate dose/duration and/or combination with other agents, and the continuous monitoring of local resistance patterns.

Antibiotic drug choice will continue to remain a difficult challenge, but the introduction of the new fluoroquinolones has created a new and exciting era in antimicrobial treatment. The clinical utility of this expanding class of antimicrobial agents and the lower propensity for the development of resistance with the ‘newer’ fluoroquinolones will need to be continually monitored in the changing therapeutic environment if these agents are to realize their full therapeutic potential.

References

1. Appelbaum, P. C. & Hunter, P. A. (2000). The fluoroquinolone antibacterials: past, present and future perspectives. *International Journal of Antimicrobial Agents* **16**, 5–15.
2. Leshner, G. Y., Froelich, E. J., Gruett, M. D., Bailey, J. H. & Brundage, R. P. (1962). 1,8-Naphthyridine derivatives: a new class of chemotherapeutic agents. *Journal of Medicinal and Pharmaceutical Chemistry* **91**, 1063–5.
3. Crumplin, G. C. & Smith, J. T. (1976). Nalidixic acid and bacterial chromosome replication. *Nature* **260**, 643–5.
4. Gellert, M., Mizuuchi, K., O’Dea, M. H. & Nash, H. A. (1976). DNA gyrase: an enzyme that introduces superhelical turns into DNA. *Proceedings of the National Academy of Sciences, USA* **73**, 3872–6.
5. Gellert, M., Mizuuchi, K., O’Dea, M. H., Itoh, T. & Tomizawa, J. I. (1977). Nalidixic acid resistance: a second genetic character involved in DNA gyrase activity. *Proceedings of the National Academy of Sciences, USA* **74**, 4772–6.
6. Wang, J. C. (1985). DNA topoisomerases. *Annual Review of Biochemistry* **54**, 665–97.
7. Gootz, T. D. & Brighty, K. E. (1996). Fluoroquinolone antibacterials: SAR mechanism of action, resistance, and clinical aspects. *Medicinal Research Reviews* **16**, 433–86.
8. Drlica, K. & Zhao, X. (1997). DNA gyrase, topoisomerase IV, and the 4-quinolones. *Microbiology and Molecular Biology Reviews* **61**, 377–92.
9. Wise, R. (1984). Norfloxacin – a review of pharmacology and tissue penetration. *Journal of Antimicrobial Chemotherapy* **13**, Suppl. B, 59–64.

The quinolones: decades of development and use

10. Domagala, J. M. (1994). Structure-activity and structure-side-effect relationships for the quinolone antibacterials. *Journal of Antimicrobial Chemotherapy* **33**, 685–706.
11. Hane, M. W. & Wood, T. H. (1969). *Escherichia coli* K-12 mutants resistant to nalidixic acid: genetic mapping and dominance studies. *Journal of Bacteriology* **99**, 238–41.
12. Gudas, L. J. & Mount, D. W. (1977). Identification of the *recA* (*tif*) gene product of *Escherichia coli*. *Proceedings of the National Academy of Sciences, USA* **74**, 5280–4.
13. Naber, K. G. (1996). Fleroxacin overview. *Chemotherapy* **42**, Suppl. 1, 1–9.
14. Balfour, J. A., Todd, P. A. & Peters, D. H. (1995) Fleroxacin. A review of its pharmacology and therapeutic efficacy in various infections. *Drugs* **49**, 794–850.
15. Schacht, P., Arcieri, G., Branolte, J., Bruck, H., Chysky, V., Griffith, E. *et al.* (1988). Worldwide clinical data on efficacy and safety of ciprofloxacin. *Infection* **16**, Suppl. 1, S29–43.
16. Segev, S., Yaniv, I., Haverstock, D. & Reinhart, H. (1999). Safety of long-term therapy with ciprofloxacin: data analysis of controlled clinical trials and review. *Clinical Infectious Diseases* **28**, 299–308.
17. Nathwani, D., Tillotson, G. & Davey, P. (1997). Sequential antimicrobial therapy—the role of quinolones. *Journal of Antimicrobial Chemotherapy* **39**, 441–6.
18. Auquer, F., Cordon, F., Gorina, E., Caballero, J. C., Adalid, C. & Batlle, J. (2002). Single-dose ciprofloxacin versus 3 days of norfloxacin in uncomplicated urinary tract infections in women. *Clinical Microbiology and Infection* **8**, 50–4.
19. Richard, G. A., Mathew, C. P., Kirstein, J. M., Orchard, D. & Yang, J. Y. (2002). Single-dose fluoroquinolone therapy of acute uncomplicated urinary tract infection in women: results from a randomized, double-blind, multicenter trial comparing single-dose to 3-day fluoroquinolone regimens. *Urology* **59**, 334–9.
20. Rapp, R. P., Billeter, M., Hatton, J., Young, A. B., Tibbs, P. A. & Dempsey, R. J. (1991). Intravenous ciprofloxacin versus ceftazidime for treatment of nosocomial pneumonia and urinary tract infection. *Clinical Pharmacy* **10**, 49–55.
21. Sifuentes-Osornio, J., Macias, A., Amieva, R. I., Ramos, A. & Ruiz-Palacios, G. M. (1989). Intravenous ciprofloxacin and ceftazidime in serious infections. A prospective, controlled clinical trial with third-party blinding. *American Journal of Medicine* **87**, 202S–205S.
22. Scully, B. E. & Neu, H. C. (1987). Treatment of serious infections with intravenous ciprofloxacin. *American Journal of Medicine* **82**, 369–75.
23. Giamarellou, H. & Galanakis, N. (1987). Use of intravenous ciprofloxacin in difficult-to-treat infections. *American Journal of Medicine* **82**, 346–51.
24. Kljucar, S., Rost, K. L. & Landen, H. (2002). Ciprofloxacin in the treatment of hospital-acquired pneumonia: a surveillance study in 676 patients. *Pneumologie* **56**, 599–604.
25. Giamarellou, H., Bassaris, H. P., Petrikos, G., Busch, W., Voulgarelis, M., Antoniadou, A. *et al.* (2000). Monotherapy with intravenous followed by oral high-dose ciprofloxacin versus combination therapy with ceftazidime plus amikacin as initial empiric therapy for granulocytopenic patients with fever. *Antimicrobial Agents and Chemotherapy* **44**, 3264–71.
26. Marra, C. A., Frighetto, L., Quaia, C. B., de Lemos, M. L., Warkentin, D. I., Marra, F. *et al.* (2000). A new ciprofloxacin step-down program in the treatment of high-risk febrile neutropenia: a clinical and economic analysis. *Pharmacotherapy* **20**, 931–40.
27. Antabli, B. A., Bross, P., Siegel, R. S., Small, C. D. & Tabbara, I. A. (1999). Empiric antimicrobial therapy of febrile neutropenic patients undergoing haematopoietic stem cell transplantation. *International Journal of Antimicrobial Agents* **13**, 127–30.
28. Krumpke, P. E., Cohn, S., Garreltes, J., Ramirez, J., Coulter, H., Haverstock, D. *et al.* (1999). Intravenous and oral mono- or combination-therapy in the treatment of severe infections: ciprofloxacin versus standard antibiotic therapy. Ciprofloxacin Study Group. *Journal of Antimicrobial Chemotherapy* **43**, Suppl. A, 117–28.
29. Periti, P., Mazzei, T. & Curti, M. E. (1998). Efficacy and safety of high dose intravenous ciprofloxacin in the treatment of bacterial pneumonia. Italian Ciprofloxacin Study Group. *International Journal of Antimicrobial Agents* **10**, 215–22.
30. Ball, A. P. & Tillotson, G. S. (1995). Lower respiratory tract infection therapy—the role of ciprofloxacin. *Journal of International Medical Research* **23**, 315–27.
31. Davidson, R., Cavalcanti, R., Brunton, J. L., Bast, D. J., de Azavedo, J. C., Kibsey, P. *et al.* (2002). Resistance to levofloxacin and failure of treatment of pneumococcal pneumonia. *New England Journal of Medicine* **346**, 747–50.
32. Urban, C., Rahman, N., Zhao, X., Mariano, N., Segal-Maurer, S., Drlica, K. *et al.* (2001). Fluoroquinolone-resistant *Streptococcus pneumoniae* associated with levofloxacin therapy. *Journal of Infectious Diseases* **184**, 794–8.
33. Weiss, K., Restieri, C., Gauthier, R., Laverdiere, M., McGeer, A., Davidson, R. J. *et al.* (2001). A nosocomial outbreak of fluoroquinolone-resistant *Streptococcus pneumoniae*. *Clinical Infectious Diseases* **33**, 517–22.
34. Ball, P. (2000). Moxifloxacin (Avelox): an 8-methoxyquinolone antibacterial with enhanced potency. *International Journal of Clinical Practice* **54**, 329–32.
35. Goldstein, F., Bryskier, A., Appelbaum, P. C., Bauernfeind, A., Jacobs, M., Schito, G. C. *et al.* (1998). The etiology of respiratory tract infections and the antibacterial activity of fluoroquinolones and other oral antibacterial agents against respiratory pathogens. *Clinical Microbiology and Infection* **4**, Suppl. 2, S8–S18.
36. Threlfall, E. J., Ward, L. R., Skinner, J. A. & Rowe, B. (1997). Increase in multiple antibiotic resistance in nontyphoidal salmonellas from humans in England and Wales: a comparison of data for 1994 and 1996. *Microbial Drug Resistance* **3**, 263–6.
37. Threlfall, E. J., Ward, L. R., Skinner, J. A., Smith, H. R. & Lacey, S. (1999). Ciprofloxacin-resistant *Salmonella typhi* and treatment failure. *Lancet* **353**, 1590–1.
38. Tillotson, G. & Jones, A. M. (2002). Effectiveness of ciprofloxacin in combination with metronidazole in complicated intra-abdominal infections, in comparison with other regimens. *Today's Therapeutic Trends* **20**, 373–392.
39. Cohn, S. M., Lipsett, P. A., Buchman, T. G., Cheadle, W. G., Milsom, J. W., O'Marro, S. *et al.* (2000). Comparison of intravenous/oral ciprofloxacin plus metronidazole versus piperacillin/tazobactam in the treatment of complicated intraabdominal infections. *Annals of Surgery* **232**, 254–62.

40. Solomkin, J. S., Dellinger, E. P., Bohnen, J. M. & Rostein, O. D. (1998). The role of oral antimicrobials for the management of intra-abdominal infections. *New Horizons* **6**, S46–S52.
41. Wacha, H. (2001). Treatment of complicated intraabdominal infections with sequential iv/po ciprofloxacin + metronidazole vs ceftriaxone + metronidazole: a randomized trial of the IAI Study Group. In *Program and Abstracts of the Eleventh European Congress of Clinical Microbiology and Infectious Diseases, Istanbul, Turkey, 2002*. Abstract P1459. European Society of Clinical Microbiology and Infectious Diseases, Basel, Switzerland.
42. Appelbaum, P. C. (1999). Quinolone activity against anaerobes. *Drugs* **58**, Suppl. 2, 60–4.
43. Jones, R. N. & Pfaller, M. A. (2000). *In vitro* activity of newer fluoroquinolones for respiratory tract infections and emerging patterns of antimicrobial resistance: data from the SENTRY antimicrobial surveillance program. *Clinical Infectious Diseases* **31**, Suppl. 2, S16–23.
44. Blondeau, J. M. (1999). A review of the comparative *in-vitro* activities of 12 antimicrobial agents, with a focus on five new 'respiratory quinolones'. *Journal of Antimicrobial Chemotherapy* **43**, Suppl. B, 1–11.
45. Ball, P., Mandell, L., Niki, Y. & Tillotson, G. (1999). Comparative tolerability of the newer fluoroquinolone antibacterials. *Drug Safety* **21**, 407–21.
46. Chen, H. J., Bloch, K. J. & Maclean, J. A. (2000). Acute eosinophilic hepatitis from trovafloxacin. *New England Journal of Medicine* **342**, 359–60.
47. Rubinstein, E. (2001). History of quinolones and their side effects. *Chemotherapy* **47**, Suppl. 3, 44–8.
48. Blondeau, J. M. (1999). Expanded activity and utility of the new fluoroquinolones: a review. *Clinical Therapeutics* **21**, 3–40.
49. Braback, M., Riesbeck, K. & Forsgren, A. (2002). Susceptibilities of *Mycobacterium marinum* to gatifloxacin, gemifloxacin, levofloxacin, linezolid, moxifloxacin, telithromycin, and quinupristin-dalfopristin (Synercid) compared to its susceptibilities to reference macrolides and quinolones. *Antimicrobial Agents and Chemotherapy* **46**, 1114–6.
50. Gillespie, S. H., Morrissey, I. & Everett, D. (2001). A comparison of the bactericidal activity of quinolone antibiotics in a *Mycobacterium fortuitum* model. *Journal of Medical Microbiology* **50**, 565–70.
51. Jonas, D., Engels, I., Friedhoff, C., Spitzmuller, B., Daschner, F. D. & Frank, U. (2001). Efficacy of moxifloxacin, trovafloxacin, clinafloxacin and levofloxacin against intracellular *Legionella pneumophila*. *Journal of Antimicrobial Chemotherapy* **47**, 147–52.
52. Speciale, A., Musumeci, R., Blandino, G., Milazzo, I., Caccamo, F. & Nicoletti, G. (2002). Minimal inhibitory concentrations and time-kill determination of moxifloxacin against aerobic and anaerobic isolates. *International Journal of Antimicrobial Agents* **19**, 111–8.
53. Talan, D. A. (2001). Clinical perspectives on new antimicrobials: focus on fluoroquinolones. *Clinical Infectious Diseases* **32**, Suppl. 1, S64–71.
54. Nightingale, C. H. (2000) Moxifloxacin, a new antibiotic designed to treat community-acquired respiratory tract infections: a review of microbiologic and pharmacokinetic–pharmacodynamic characteristics. *Pharmacotherapy* **20**, 245–56.
55. Ball, P. (2000). Quinolone-induced QT interval prolongation: a not-so-unexpected class effect. *Journal of Antimicrobial Chemotherapy* **45**, 557–9.
56. Church, D., Haverstock, D. & Andriole, V. T. (2000). Moxifloxacin: a review of its safety profile based on worldwide clinical trials. *Today's Therapeutic Trends* **18**, 205–23.
57. Iannini, P. B., Kubin, R. & Reiter, C. (2002). Over 10 million patient uses: An update on the safety profile of oral moxifloxacin. In *Abstracts of the Forty-second Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, CA, 2002*. Abstract L374, p. 346. American Society for Microbiology, Washington, DC, USA.
58. Breen, J., Skuba, K. & Grasela, D. (1999). Safety and tolerability of gatifloxacin, an advanced third-generation, 8-methoxy fluoroquinolone. *Journal of Respiratory Diseases* **20**, Suppl. 11, S70–6.
59. Patel, T., Pearl, J., Williams, J., Haverstock, D. & Church, D. (2000). Efficacy and safety of ten day moxifloxacin 400 mg once daily in the treatment of patients with community-acquired pneumonia. Community Acquired Pneumonia Study Group. *Respiratory Medicine* **94**, 97–105.
60. Wilson, R., Jones, P., Schaberg, T., Davey, P., Allegra, L., Izquierdo, J. L. *et al.* (2002). A clinical and outcomes assessment of the management of acute exacerbations of chronic bronchitis (AECB): the MOSAIC study. *European Respiratory Journal* **20**, Suppl. 38, 544s.
61. Wilson, R., Schentag, J. J., Ball, P. & Mandell, L. (2002). A comparison of gemifloxacin and clarithromycin in acute exacerbations of chronic bronchitis and long-term clinical outcomes. *Clinical Therapeutics* **24**, 639–52.
62. Felmingham, D., Feldman, C., Hryniewicz, W., Klugman, K., Kohno, S., Low, D. E. *et al.* (2002). Surveillance of resistance in bacteria causing community-acquired respiratory tract infections. *Clinical Microbiology and Infection* **8**, Suppl. 2, 12–42.
63. Appelbaum, P. C. (2002). Resistance among *Streptococcus pneumoniae*: implications for drug selection. *Clinical Infectious Diseases* **34**, 1613–20.
64. Dalhoff, A. (1999). *In vitro* activities of quinolones. *Expert Opinion on Investigational Drugs* **8**, 123–37.
65. Kays, M. B., Smith, D. W., Wack, M. F. & Denys, G. A. (2002). Levofloxacin treatment failure in a patient with fluoroquinolone-resistant *Streptococcus pneumoniae* pneumonia. *Pharmacotherapy* **22**, 395–9.
66. Ball, P. (2000). The quinolones: history and overview. In *The Quinolones*, 3rd edn (Andriole, V. T., Ed.), pp. 1–31. Academic Press, London, UK.
67. British Thoracic Society Standards of Care Committee. (2001) BTS guidelines for the management of community acquired pneumonia in adults. *Thorax* **56**, Suppl. 4, 1–64.