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A review of the comparative in-vitro activities of 12 antimicrobial agents, with a focus on five new 'respiratory quinolones'

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The efficacies of many antimicrobial agents are being threatened by a global increase in the numbers of resistant bacterial pathogens—microorganisms that were once susceptible to some of these agents. In particular, antimicrobial resistance amongst strains of *Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae* has limited the usefulness of first-line agents in some clinical settings. Quinolones were introduced in the 1980s and represented a significant therapeutic advancement in the treatment of patients with infectious diseases. While these compounds possessed potent in-vitro activities against a wide range of Gram-negative pathogens, their activities against some Gram-positive and 'atypical' pathogens remained borderline. Further advancement in the development of quinolones has overcome some of these problems. The 'respiratory quinolones' represent a new generation within this class of molecules and comprise compounds possessing broad spectrum activities against Gram-negative, Gram-positive and atypical pathogens. This review will focus on the in-vitro activities of five new respiratory quinolones (gatifloxacin, grepafloxacin, levofloxacin, moxifloxacin and trovafloxacin), ciprofloxacin and six non-quinolone agents (azithromycin, clarithromycin, amoxycillin, co-amoxiclav, cefuroxime and co-trimoxazole) against a range of bacterial and atypical pathogens, including those that are now resistant to several of these compounds.

Introduction

Although compounds with antibacterial activities have been known for centuries, antibiotics, or antibacterials, evolved from the pioneering discoveries of penicillin by Fleming in 1928 and sulphonamides in 1935.[1] For two decades, β-lactams, sulphonamides, with or without trimethoprim, macrolides and tetracyclines were the backbone of antibiotic therapy and it wasn't until the 1960s that development and research (basic and clinical) led to extended-spectrum agents with broader ranges of antibacterial activity, including cephalosporins, monobactams, cephamycins, carbapenems, improved tetracyclines and macrolides/azalides and quinolones.

The quinolones are a unique class of molecules in that they act against both typical and 'atypical' bacterial pathogens by inhibiting DNA gyrase, an enzyme that is necessary for the replication of nucleic acid. These agents were first described by Lescher *et al.*[2] Since then, over 10,000 quinolone derivatives have been synthesized worldwide, although few have entered into clinical development and, currently, fewer than ten have been approved for clinical use.[3]

The original quinolone was 1,8-naphthyridine-nalidixic acid and the 4-quinolone synthetic compounds are analogues of this original molecule.[4] Nalidixic acid possesses limited in-vitro activity against Gram-negative bacteria and its use was restricted to oral treatment of patients with urinary tract infections.

Modifications to this drug in the 1970s gave rise to similar compounds (oxolinic acid, rosoxacin, cinoxacin and flumequine) which were also available only for use in patients with urinary tract infections, but it was not until a piperazine substitution at position 7 of the naphthyridine core and fluorination at position 6 that molecules with improved activities against Gram-negative and -positive

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pathogens respectively were produced; fluorination produced the fluoroquinolones.

Norfloxacin was the first of the fluoroquinolones and possessed increased activity against Gram-negative bacteria, including *Pseudomonas aeruginosa*.[5] As with earlier compounds, however, the use of norfloxacin was restricted to the treatment of patients with urinary tract infections. Two major pathways of quinolone development followed from the original 1, 8-naphthyridine nucleus and with the 6-fluoro, 7-piperazinyl modifications. The first pathway involved substitution of a carbon atom for nitrogen, thereby resulting in ciprofloxacin, a 1-cyclopropanyl, and ofloxacin and levofloxacin, both 1, 8-cyclo compounds—all three of which were classified as second-generation fluoroquinolones. Sparfloxacin and clinafloxacin, with improved activities and pharmacokinetics,[6] followed as extended-spectrum second-generation agents and moxofloxacin, resulting from a 7-azabicyclo modification which endowed the molecule with enhanced antibacterial activity and pharmacokinetic properties, is a third-generation quinolone. Moxifloxacin also possesses an 8-methoxy side-chain—a property it shares with gatifloxacin. Grepafloxacin is classified as a second-generation agent. The second major pathway involved modification of the naphthyridine core, giving rise to enoxacin and rosafloxacin, and a 7-azabicyclo modification produced trovafloxacin—a third-generation agent with enhanced antibacterial activity. It was not until ciprofloxacin came on to the market that a broad-spectrum quinolone became available for systemic use—initially as an oral formulation and later an iv one. Ofloxacin and levofloxacin were also subsequently released for systemic use.

Third-generation quinolones have enhanced activities against Gram-positive bacteria and prolonged serum half-lives, thereby permitting od dosing. Current third-generation quinolones include moxifloxacin and trovafloxacin. Clinafloxacin, gatifloxacin and grepafloxacin, which are regarded as second-generation agents, have slightly weaker potencies against *Streptococcus pneumoniae* isolates, but also possess more favourable pharmacokinetic properties than earlier fluoroquinolones.[7]

Respiratory pathogens, antimicrobial resistance and the need for new agents

Antimicrobial resistance is a global concern. Resistant bacterial isolates have emerged and spread throughout the world because of the genetic plasticity of microorganisms, the selective pressures of antimicrobial use and the mobility of the world population.[8] As a consequence, the emergence of multidrug-resistant pathogens has fuelled the continual search for new compounds that are stable against known mechanisms of resistance. Unfortunately, many such compounds are closely related because they are members of the same class of agents or have similar basic structures. While resistance to virtually all human pathogens and to at least one antimicrobial agent have been recognized, the full impact of this emerging resistance has not yet been fully appreciated.

Antimicrobial resistance amongst bacterial respiratory tract pathogens is an area of particular concern. The predominant causes of lower respiratory tract infections are: *Haemophilus influenzae*, *Moraxella catarrhalis* and *S. pneumoniae* and much emphasis has recently been placed on these three pathogens and the increasing incidences of resistance amongst them to antimicrobial agents commonly used in the outpatient setting. The following is a review of the roles of the three pathogens in respiratory tract infections and current levels of antimicrobial resistance.

Woodhead[9] recently reviewed the incidences of microbial pathogens in community-acquired pneumonia and reported the following: *S. pneumoniae*, 30–75%; *Mycoplasma pneumoniae*, 5–18%; *H. influenzae*, 4–5%; and others, including *Legionella pneumophila*, *Staphylococcus aureus*, *Chlamydia* spp., *Coxiella burnetii* and *M. catarrhalis*, 0–10%. Similarly, Mandel[10] suggested that the incidence of pneumococcal pneumonia is decreasing, but that *S. pneumoniae* is still the single most common pathogen, with rates ranging from 8 to 34%. Differences in reported incidences may arise from the use of pneumococcal polysaccharide capsular antigen testing in some studies, the ability to obtain appropriate sputum samples and whether or not patients were taking antimicrobials at the time of specimen collection.

Ball[11] reviewed the prevalences of major respiratory pathogens in patients with acute exacerbations of chronic bronchitis. Evaluation of seven studies revealed that the prevalences of *H. influenzae* were 30–58%, *M. catarrhalis* 3.3–22.5% and *S. pneumoniae* 15–25%. Collectively, *H. influenzae*, *M. catarrhalis* and *S. pneumoniae* account for 70% of all exacerbations and 85–95% of all bacterial exacerbations.

Gwaltney[12] recently reviewed the aetiology of community-acquired sinusitis and reported that *S. pneumoniae* was associated with 26–31% of episodes, *H. influenzae* with 21–26%, *S. aureus* with 4% and *M. catarrhalis* and *Streptococcus pyogenes* with 2% each.

M. catarrhalis was, for many years, an under-recognized pathogen in patients with respiratory tract infections. Catlin[13] reviewed its role as a disease-causing microorganism and, in the past few years, numerous surveillance studies have characterized the susceptibilities of this pathogen to amoxycillin and many broad-spectrum agents. Figure 1 illustrates the percentages of β-lactamase-producing *M. catarrhalis* strains isolated in Canada, Europe and the USA. Currently, >85% of all strains produce β-lactamase, this being the principal mechanism of resistance in this bacterium.

H. influenzae is one of the commonest respiratory tract pathogens. β-Lactamase-producing strains were first recog-

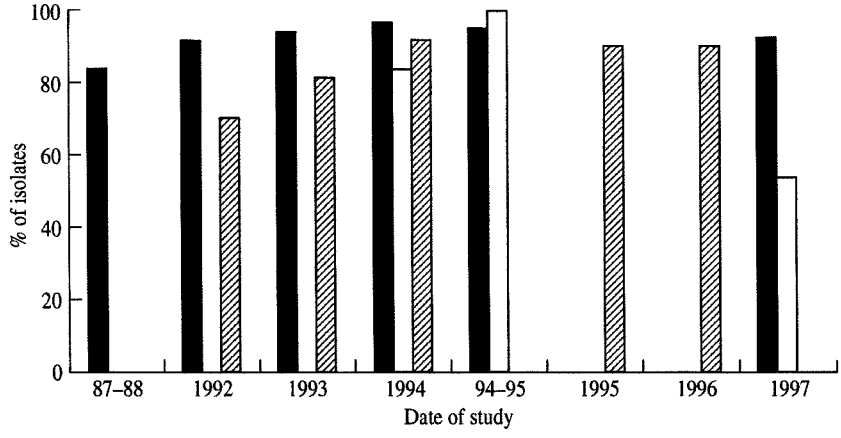

Figure 1. Percentages of *M. catarrhalis* isolates producing β-lactamase in studies from the USA (■), Europe (▨) and Canada (□).

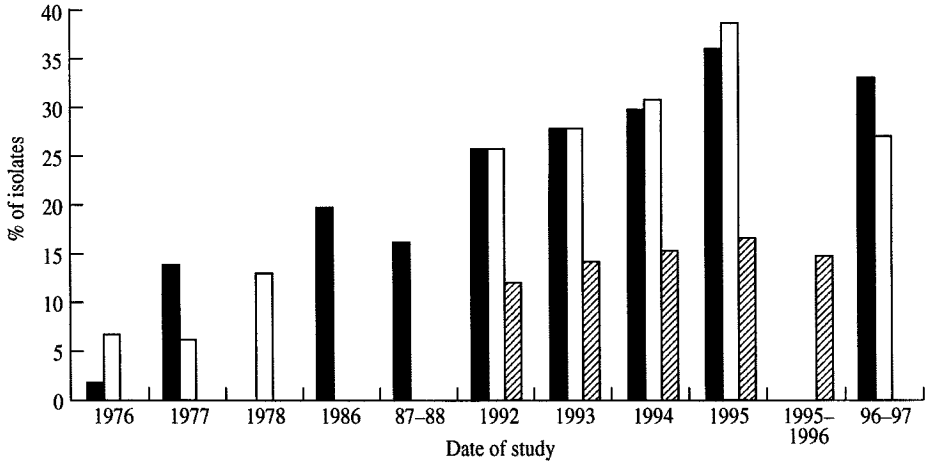

Figure 2. Percentages of *H. influenzae* isolates producing β-lactamase in studies from the USA (■), Europe (▨) and Canada (□) between 1976 and 1997.

nized in the mid-1970s and, since then, their incidences have increased to >30–35% of isolates in North America and >15–20% in Europe. Unlike *M. catarrhalis*, for which little regional variation in susceptibility to amoxycillin has been observed, *H. influenzae* isolates have exhibited wide geographical variation in terms of resistance to this drug.[14] Figure 2 shows the percentages of β-lactamase-producing *H. influenzae* isolates in studies carried out in Canada, Europe and the USA. Doern *et al*.[15] studied *H. influenzae* isolated from 30 medical centres in the USA and found that the percentage of β-lactamase-positive strains varied from 17 to 68.3%. Similarly, Scriver *et al.*[16] reported that the incidence of β-lactamase-positive isolates from nine Canadian provinces varied from 11 to 45.5% and Felmingham *et al.*[17] described regional variation of 4.3% to 23.4% in 12 regions of the UK. Regional variation has also been observed in Europe, with incidences ranging from 1.8 to 26% (Felmingham, D., personal communication).

Doern *et al.*[15] also identified strains of *H. influenzae* that were β-lactamase-positive, but resistant to co-amoxiclav. These isolates also exhibited increased MICs when their susceptibilities to cefaclor, loracarbef, cefprozil, cefuroxime and cefpodoxime were determined, thereby demonstrating cross-resistance. A subsequent evaluation of the same isolates by Jacobs & Bajaksouzian[18] showed that the higher MICs of co-amoxiclav could be accounted for by variations in inoculum, the presence of spheroplasts and/or a difference in the potency of amoxycillin and/or clavulanic acid. Our laboratory (unpublished data) investigated 10–12 isolates of *H. influenzae* with increased MICs of co-amoxiclav. Should *H. influenzae* isolates resistant to co-amoxiclav emerge and spread, there would be considerable implications for the future use of many currently available oral antimicrobial agents, particularly the cephalosporins. In a further worrying development, Vali *et al*.[19] described an enzyme, VAT-1, in isolates of *H. influenzae* which exhibited cephalosporinase activity and resistance to β-lactamase inhibitors such as clavulanic acid, sulbactam and tazobactam.

The dramatic increase in the incidence of isolates of *S. pneumoniae* with reduced susceptibility to penicillin is a cause of particular concern. Until 1991, the incidence of such strains was <5% in Canada and 5–10% in the USA, while in Europe, rates varied from <1% to >30%; most of

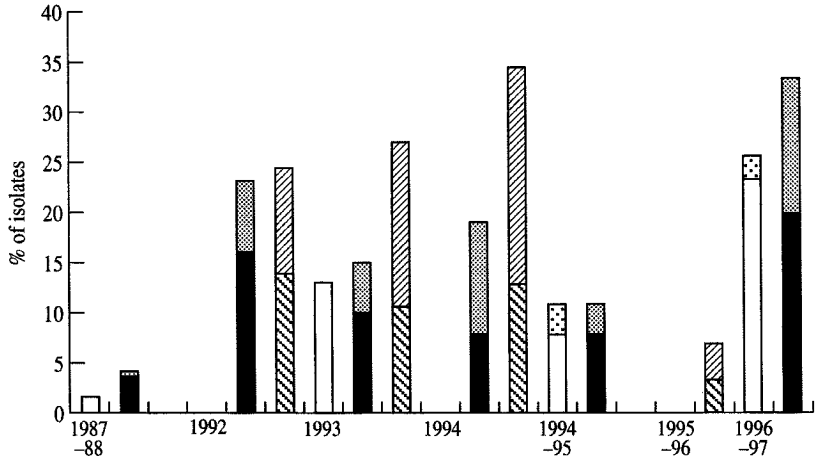

Figure 3. Percentages of *S. pneumoniae* isolates exhibiting intermediate (I) or high-level (HL) resistance to penicillin in studies carried out in the USA (I, ■; HL, ▩), Europe (I, ▧; HL, ▨) and Canada (I, □; HL, ⊡) between 1987 and 1997.

these isolates exhibited intermediate susceptibility. Today, however, the picture is very different (Figure 3). Simor *et al.*[20] recently reported that 11.7% of 1089 pneumococcal isolates from across Canada exhibited reduced susceptibility to penicillin: 8.4% intermediate susceptibility and 3.3% resistance. Resistance rates varied from 7.4% in Atlantic Canada to 10.3% and 16.1% in central and western Canada respectively. Doern *et al.*[21] reported that 23.6% of pneumococcal isolates from 30 medical centres in the USA showed reduced susceptibility to penicillin: 14.1% intermediate susceptibility and 9.5% resistance; overall rates amongst the centres varied from 2.1% to 52.9%, with rates of intermediate susceptibility and resistance varying from 2.1% to 29.5% and from 0% to 23.5% respectively. Thornsberry *et al.*[22] reported that 33.5% of 9190 pneumococcal isolates exhibited reduced susceptibility to penicillin (19.9% intermediate susceptibility and 13.6% resistance, with regional variation ranging from 28.6% to 40.4%. Felmingham *et al.*[17] investigated the incidence of reduced susceptibility to penicillin amongst pneumococci in the UK and identified 7.1% of isolates as falling into this category: 3.4% intermediate susceptibility and 3.7% resistance. Regional variation ranged from 0 to 38.5% overall and from 0 to 18.7% and 0 to 23.1% for isolates showing intermediate susceptibility and resistance respectively. For Europe, the ranges for strains exhibiting intermediate susceptibility and resistance were 0.2% to 20.4% and 0 to 47.5%, respectively for 1995 and 4% to 18.4% and 0 to 32.1%, respectively for 1996. Resistance rates in France and Spain were higher than those in Italy, Germany and the UK (Felmingham, D., personal communication).

The increasing incidence of penicillin resistance amongst pneumococci is clearly a major cause of concern, but equally or more worrying is the marked cross-resistance to other agents. Based on data from Simor *et al.*[20] and Doern *et al.*[21], as well as breakpoints recommended by the National Committee for Clinical Laboratory Standards (NCCLS),[23] 36% of isolates exhibiting intermediate susceptibility were resistant to cefuroxime, 1–8% to cefotaxime/ceftriaxone, 8–20% to macrolides, 17–21% to tetracycline and 40–54% to co-trimoxazole. Similarly, for isolates that were fully resistant to penicillin, 100% were resistant to cefuroxime, 32–78% to cefotaxime/ceftriaxone, 17–49% to macrolides, 25–43% to tetracycline and 80–97% to co-trimoxazole. While the results of in-vitro susceptibility tests do not invariably correlate with clinical outcome, the trend toward higher resistance rates suggests that the incidences of therapeutic failure will also increase in the future.

To date, resistance to vancomycin amongst pneumococci has not been described. Another important observation is that the MICs of the quinolones—both current and investigational—are unaffected by the reduced susceptibility of pneumococci to penicillin. This status has implications for the future use of quinolones, particularly those with enhanced potencies against pneumococci, as treatment of patients with respiratory tract infections.

In-vitro activities of new quinolones

Tables I–III summarize the in-vitro activities of six quinolones (ciprofloxacin, gatifloxacin, grepafloxacin, levofloxacin, moxifloxacin and trovafloxacin) and six non-quinolone antibiotics (azithromycin, clarithromycin, amoxycillin, co-amoxiclav, cefuroxime and co-trimoxazole) against Gram-negative, Gram-positive and 'atypical' human pathogens respectively. The MIC data were extracted from studies published in peer-reviewed journals or from the abstracts of papers presented at recent international meetings. The data have not been standardized in terms of methodology, but, in general, the techniques used to determine in-vitro susceptibility included the microbroth dilution, agar dilution and Etest methods.

Table I. Comparative in-vitro activities of 12 antibiotics against Gram-negative bacteria[a]

	MIC_{90} (mg/L)											
Bacterium	Cip	Gati	Grepa	Levo	Moxi	Trova	Azi	Clar	Amox	A/C	Cefur	Cot
Escherichia coli	0.125–0.5	0.06	0.06–0.12	0.06–<0.5	0.06–1	0.12–1	4–16	NT	16–1024	4–16	4–16	>16
Enterobacter spp.	0.03	1	0.12–0.25	0.06–<0.5	0.06	0.03–1	32	NT	>128	8	>16	2
H. influenzae												
β-lactamase +	0.015–0.03	<0.03	0.03	0.03–0.47	0.03–0.06	0.015	1–2	8–16	8–128	1–2	2–4	<0.05
β-lactamase −	0.015–0.03	<0.03	0.03	0.03–0.32	0.03–0.06	0.015	1–2	8–24	1	1–2	2–8	<0.05
Klebsiella pneumoniae	0.25	0.06–0.25	0.12–0.25	0.12–0.25	0.12–0.25	0.5	64	NT	32–1024	8	8–16	>4
Klebsiella spp.	0.03–0.25	0.5	0.06	<0.015–0.25	0.5	0.06–1	64	NT	>128	8	4–64	8–>64
M. catarrhalis												
β-lactamase +	0.015–0.06	<0.03	0.015–0.06	0.06–0.094	0.012–0.06	0.03	<0.06	<0.06–0.38	>16	0.38	3	0.25–0.5
β-lactamase −	0.015–0.06	<0.03	0.015–0.06	0.06	0.012–0.06	0.03	<0.06	0.06–4	0.25	0.38	2	0.25–0.5
Morganella morganii	2	4	NT	2	0.25	>4	>128	NT	512	32–512	64–128	>16
Neisseria spp.	0.004	0.008	0.008–0.6	0.008	0.015	0.008	0.12–0.5	0.5–1	0.12–>32	0.12–1	<0.06–0.25	NT
Proteus spp.	<0.015–0.03	1	0.25	0.03–<0.5	0.025	0.125–0.5	>64	NT	1–1024	<0.5–8	1–>32	16
P. aeruginosa	0.25–4	>4	1–4	0.5–>4	8	0.25–8	NT	NT	2048	>128	⩾128	>16
Stenotrophomonas maltophilia	8	4	NT	4	1–2	2–4	NT	NT	NT	>128	NT	NT
Serratia spp.	1	4	1–25	2	4	4	64	NT	32–2048	32–256	128–>256	8
Citrobacter spp.	<0.015	0.016–0.5	0.12	<0.015	0.12	0.03	NT	NT	32–1024	16	2–>32	>16

Abbreviations: Cip, ciprofloxacin; Gati, gatifloxacin; Grepa, grepafloxacin; Levo, levofloxacin; Moxi, moxifloxacin; Trova, trovafloxacin; Azi, azithromycin; Clar, clarithromycin; Amox, amoxycillin; A/C, co-amoxiclav; Cefur, cefuroxime; Cot, co-trimoxazole; NT, not tested.

[a] Data summarized from references 16, 22, 24–60 and 93–95.

Gram-negative pathogens (Table I)

Of the quinolones tested, ciprofloxacin is the most active overall against Enterobacteriaceae, with MIC_{90}s ranging from <0.15 mg/L to 2 mg/L. Azithromycin and clarithromycin are not, for the most part, active against Enterobacteriaceae and all of the quinolones are more potent than amoxycillin, co-amoxiclav, cefuroxime and co-trimoxazole. Ciprofloxacin is the quinolone with the most potent activity against *P. aeruginosa* (MIC_{90}s 0.25–4 mg/L), followed by levofloxacin (MIC_{90}s 0.5–>4 mg/L). The MIC_{90}s of the remaining quinolones for the *P. aeruginosa* isolates range from 0.25 to 8 mg/L; the non-quinolones tested have no activity against this bacterium. Against the more fastidious bacteria (*H. influenzae*, *M. catarrhalis* and *Neisseria* spp.), all of the quinolones are highly active (MIC_{90}s for *H. influenzae*, 0.015–0.47 mg/L, for *M. catarrhalis*, 0.015–0.094 mg/L and for *Neisseria* spp., 0.004–0.06 mg/L) and are unaffected by β-lactamase production. Azithromycin is four- to 24-fold more active than clarithromycin against the *H. influenzae* isolates and up to 64-fold more active against the *M. catarrhalis* isolates. β-Lactamase-positive strains are resistant to amoxycillin (MIC_{90}s, 8–128 mg/L), but susceptible to the other drugs tested.

Gram-positive pathogens (Table II)

Ciprofloxacin is the least active of the six quinolones against the Gram-positive pathogens; the MIC_{90}s of this drug for all but the *Enterococcus* spp., *Staphylococcus epidermidis* and methicillin-resistant *S. aureus* (MRSA) isolates ranged from 0.5 to 2 mg/L. All of the agents tested were uniformly active against the *S. pyogenes* strains.

The methicillin-susceptible *S. aureus* (MSSA) isolates are highly susceptible to the quinolones, with MIC_{90}s of all but ciprofloxacin of 0.06–0.25 mg/L. The MIC_{90}s of the macrolides and β-lactams ranged from 0.05 to 8 mg/L. Moxifloxacin and trovafloxacin are two-fold more active then gatifloxacin and grepafloxacin and eight-fold and up to 64-fold more active than levofloxacin and ciprofloxacin respectively against the MRSA isolates.

Gatifloxacin, grepafloxacin, moxifloxacin and trovafloxacin are all more active against the *S. pneumoniae* isolates (MIC_{90}s 0.06–0.5 mg/L) than ciprofloxacin and levofloxacin (MIC_{90}s 1–2 mg/L). The MICs of the quinolones are unaffected by reduced susceptibility to penicillin, the MIC_{90}s being the same, irrespective of whether the isolates are susceptible, of intermediate susceptibility or resistant to penicillin. However, this does not apply to the other antibiotics tested, with the MIC_{90}s for the isolates exhibiting intermediate susceptibility to penicillin being higher than those for the isolates that are susceptible and those for the resistant isolates being higher still. Overall, the activities of moxifloxacin and trovafloxacin were equivalent and slightly greater than those of grepafloxacin and gatifloxacin.

Table II. Comparative in-vitro activities of 12 antibiotics against Gram-positive bacteria[a]

Bacterium	MIC_{90} (mg/L)											
	Cip	Gati	Grepa	Levo	Moxi	Trova	Azi	Clar	Amox	A/C	Cefur	Cot
E. faecalis	2–64	0.5–>4	0.37–4	0.5–2	0.5–8	0.5	8–>64	>64	2	0.5	0.03–256	2
E. faecium	4–>128	4–>64	4–12.5	2–32	2	2	NT	NT	NT	16	NT	NT
S. aureus												
MSSA	0.5–1	0.12	0.25	0.25	0.12	0.06	1–>8	0.25–>8	4	0.05–1	1–4	1–2
MRSA	32–128	4	4	16	2	2	>128	>64	>64	>128	>128	3.37–>64
S. epidermidis	8	2	0.25	0.5–1	2	4	32–>128	8–>64	4	2	0.5–2	4
S. pneumoniae												
Pen S	1–2	0.5	0.25–0.5	1–2	0.06–0.25	0.12–0.25	0.06–0.12	0.03–0.25	0.03–0.06	0.03	0.06–0.25	1
Pen I	1–2	0.5	0.25–0.5	1–2	0.12–0.25	0.12–0.25	4–8	4–64	1–2	1	2–4	8–16
Pen R	1–2	0.5	0.25–0.5	1–2	0.12–0.25	0.12–0.25	>64	32–>256	8	4	8–16	8–16
S. pyogenes	1–2	0.5	0.25	1	0.25	0.25	0.12–0.25	0.03	<0.12	0.015	<0.12	1–4

Abbreviations: See subscript to Table I, and Pen S, susceptible to penicillin; Pen I, intermediate susceptibility to penicillin; Pen R, resistant to penicillin.
[a] Data summarized from references 20–22, 24–26, 28–30, 32, 34, 37–42, 44, 51–52, 54–56, 61–72, 93–95 and Blondeau, J. M., unpublished data.

Enterococcus spp. are becoming increasingly important pathogens. Against *Enterococcus faecalis*, ciprofloxacin is the least active quinolone (MIC_{90}s of 2–64 mg/L, compared with MIC_{90}s of 0.05–8 mg/L for the other five). Moxifloxacin and trovafloxacin are up to six-fold more active than grepafloxacin against *Enterococcus faecium* and two- to >32-fold more active than gatifloxacin. The quinolones evaluated here are unlikely to make significant contributions to the therapeutic dilemma resulting from the emergence of vancomycin-resistant enterococci.

Atypical pathogens (Table III)

Gatifloxacin, grepafloxacin, moxifloxacin, trovafloxacin, azithromycin and clarithromycin are highly active against *Chlamydia* spp. and *M. pneumoniae*, with MIC_{90}s ranging from 0.008 to 1 mg/L. Levofloxacin is slightly less active, followed by ciprofloxacin. All of the quinolones are highly active against *L. pneumophila* (MIC_{90}s 0.008–0.12 mg/L).

Discussion

The development and release on to the market of the fluoroquinolones in the late 1980s represented a landmark in antimicrobial therapy. These compounds offer a unique mechanism of action, favourable side-effect and safety profiles, favourable pharmacokinetic properties (some agents being available as both oral and iv formulations) and broad-spectrum activity against Gram-negative and -positive pathogens. Early fluoroquinolones possess enhanced activities *in vitro* against Gram-negative bacteria and although less potent against Gram-positives, the MIC_{90}s of these drugs are still within ranges that make them useful for treating patients with clinically important infections caused by *S. aureus* and *S. pneumoniae*; same atypical pathogens are also susceptible.

Newer fluoroquinolones represent advances in the evolution of this class of compounds. Agents such as gatifloxacin, grepafloxacin, moxifloxacin and trovafloxacin have enhanced activities against Gram-positive and atypical pathogens and anaerobes, while retaining potencies and broad-spectrum cover against Gram-negative organisms that are comparable to those of their earlier congeners

While β-lactamase production by *M. catarrhalis* and *H. influenzae* isolates has limited the efficacies of first-line β-lactams, there are several agents (co-amoxiclav, cephalosporins, extended-spectrum macrolides, co-trimoxazole and quinolones) that retain activity against these organisms. This is not the case, however, with penicillin-resistant pneumococci, against which all of the aforementioned drugs, with the exception of the quinolones, exhibit marked degrees of resistance. Given that most antibiotics are prescribed empirically and given the prominent role of the pneumococcus in respiratory tract infections, novel fluoroquinolones are likely to assume increasing importance in

Table III. Comparative in-vitro activities of 12 antibiotics against atypical pathogens[a]

Bacterium	MIC_{90} (mg/L)											
	Cip	Gati	Grepa	Levo	Moxi	Trova	Azi	Clar	Amox	A/C	Cefur	Cot
Chlamydia pneumoniae	1–2	0.06–0.25	0.06–0.05	0.25–0.05	0.03–1	0.12–7[b]	0.25	0.03	NT	NT	NT	NT
Chlamydia trachomatis	2	0.06–0.25	0.06–0.12	0.25–0.5	0.03–0.125	0.12[b]	0.12	NT	NT	NT	NT	NT
L. pneumophila	0.12	0.016–0.03	0.008–0.05[c]	0.03[c]	0.015	0.06	0.25	0.03–0.06	NT	NT	NT	NT
M. pneumoniae	0.78–8	0.05–0.13	0.06–0.5	NT	0.06–0.12	0.06–0.25	0.002	0.008–0.03	NT	NT	NT	NT

[a] Data summarized from references 25, 43, 44, 69, 73–93, 95 and 96.
[b] For all *Chlamydia* spp.
[c] For all *Legionella* spp.

the treatment of patients with infections caused by these bacteria.

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