Management of community-acquired lower respiratory tract infections: gemifloxacin, a new economic paradigm

Gary Patou, Glenn Tillotson & Joseph Blondeau[†]

[†]*Author for correspondence*
University of Saskatchewan, Royal University Hospital and the Saskatoon Health Region and the Departments of Microbiology and Immunology and Pathology, 103 Hospital Drive, Saskatoon, Saskatchewan, S7N 0W8 Canada
Tel.: +1 306 655 6943
Fax: +1 306 655 6947
joseph.blondeau@saskatoonhealthregion.ca

Lower respiratory tract infections account for over 50 million deaths each year globally. They exert a growing clinical and financial burden on healthcare systems and employers. The increasing prevalence of antimicrobial resistance among usual bacterial pathogens over the past 10 years further drives this burden of disease. Typically, species such as *Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis* exhibit differing, but still growing, resistance phenotypes. The impact of resistance has only recently been fully appreciated, with clinical failures to many first-line agents being reported, as well as eminent groups acknowledging the financial impact of bacterial resistance. As resistance continues to emerge, it is recognized that a successful clinical outcome depends upon several factors including the patient, selection of appropriate drug and local epidemiology of the likely pathogen. Treatment failures will lead to repeat physician visits, extra diagnostic and laboratory tests, further therapies and, possibly, hospitalization. The latter has been shown to be a major driver of infectious disease healthcare costs. Targeting the pathogen with the most effective antimicrobial in an appropriately selected patient should optimize both clinical and microbiological success while maximizing economic outcomes. The new fluoroquinolones have been developed to meet these new demands. Gemifloxacin is the latest fluoroquinolone to be approved for the treatment of community-acquired respiratory tract infections and acute bacterial exacerbations of chronic bronchitis. Gemifloxacin is a dual-targeting fluoroquinolone with *in vitro* activity against DNA gyrase (topoisomerase II) and topoisomerase IV, and has been shown to have potent *in vitro* activity against *S. pneumoniae*, including both multidrug-resistant phenotypes and many fluoroquinolone-resistant strains. Additionally, gemifloxacin is active against other clinically important Gram-positive cocci, Gram-negative and atypical human pathogens.

Keywords: community, gemifloxacin, health economics, respiratory tract infections

Community-acquired respiratory tract infections (RTIs) remain a frequent and important clinical entity. Despite significant advances in antimicrobial therapy and the development of treatment algorithms (guidelines), patients with community-acquired pneumonia (CAP) continue to suffer significant morbidity and, depending on a number of comorbidities, significant mortality. Similarly, patients suffering from chronic obstructive pulmonary disease (COPD) may suffer from repeated acute bacterial exacerbations of chronic bronchitis.

Community-acquired infections of the lower respiratory tract continue to account for significant proportions of antimicrobial use, hospitalization, morbidity and mortality [1]. Data compiled by the US Centers for Disease Control and Prevention (CDC) for the year 2000 showed that there were over 120,000 deaths from chronic lower respiratory tract disease and deaths from pneumonia and influenza exceeded 65,000 [2]. Chronic lower respiratory tract disease was the fourth leading cause of death, while pneumonia was the seventh [2]. Mannino and colleagues reported data collected in the USA from 1971 to 2000 and summarized it for the year 2000. Results demonstrated that COPD accounted for 8 million physician and hospital outpatient visits, 1.5 million emergency-room visits and 726,000 hospitalizations [3]. Hall and Owings reported that pneumonia was responsible for 1.3 million hospital admissions in the year 2000, with almost 60% of the pneumonia patients being aged 65 years or over [4]. Niederman and colleagues estimated the financial and clinical burden of caring for patients with lower RTIs [5,6]. Costs associated with treating patients were US$8 billion versus $6 billion for the treatment of CAP patients. Clearly, therapy that can minimize the requirement for hospitalization or shorten the stay, when admitted, is essential.

10.2217/14750708.2.3.357 © 2005 Future Medicine Ltd ISSN 1475-0708

As age is repeatedly identified as a risk factor for having more severe infections and since COPD is more pronounced with increased age, RTIs will increase dramatically over the next 10 years or so (especially in North America) as a significant percentage of the population ages, that is, as the so-called 'baby boomers' move closer to and exceed the age of 65 years.

Spencer and colleagues indicated that COPD is one of the five leading causes of death world wide. Indeed, chronic bronchitis may affect up to 13 million individuals – some 4 to 6% of adults in the USA – and is associated with considerable morbidity and mortality [7]. These authors confirmed the direct impact of COPD/acute exacerbation of chronic bronchitis (AECB) on the individual patient by using validated assessment systems, such as the St George's Respiratory Questionnaire, to compare two antibiotics in their effect on patient's daily life and well being.

Kupronis and colleagues reported on invasive pneumococcal disease in older patients residing in long-term care facilities and in the community, and summarized data indicating that, despite advances in antimicrobial therapy, 20% of elderly patients hospitalized for bacteremic pneumococcal infections die – this value increases to 38% for patients aged 85 years or older – and that older adults have the highest incidence of multidrug-resistant *S. pneumoniae* infection [8].

O'Brien and colleagues studied the costs of treating CAP in patients aged 18 years and older [9]. The cost profile for in- and outpatients were created and weighted so as to determine the average cost for CAP cases per episode, and considered by age and selected comorbidity. The costs associated with the treatment of an elderly patient with an episode of CAP were twice those of treating younger patients. The main reason was that more elderly patients required hospitalization. The weighted averaged cost for treating an episode of CAP (all CAP cases) was estimated to range between US$3455 and 2306 (2001 values) for younger patients versus $5316 for elderly patients; for hospitalized patients, the costs were $14,383 and compiled from a database of 278,550 patients from 480 hospitals in five states.

Loeb reviewed pneumonia in older people and reported that CAP is the fifth leading cause of death in patients aged 65 years or over, and that some 60,000 seniors die annually – with the vast majority of excess deaths and hospitalizations occuring in people aged 65 years or over [10,11]. Age-specific incidence data increased from 15.4 to 34.2 in a group of 1000 individuals for those aged 60 to 74 and 75 years or over, respectively.

Etiology of RTIs in the elderly was studied by Jokinen and colleagues by comparing paired serum samples from patients in Finland with CAP. *Streptococcus pneumoniae* was found in 48% of patients aged 60 years or over, compared with *Chlamydia* spp. (12%), *Mycoplasma pneumoniae* (10%), *Haemophilus influenzae* (4%) and respiratory viruses (10%) [12]. The study by Jokinen and colleagues confirmed that *S. pneumoniae* is an important cause of CAP in both younger and older patients [12] and that atypical pathogens may also be associated with the disease in the elderly, but are more common in younger patients [13].

Risk factors from pneumonia in the elderly (>60 years) were reported by Ruiz and colleagues from patients in Finland and reported that the following were independent risk factors for pneumonia [13]:

- Alcoholism
- Bronchial asthma
- Immunosuppression
- Lung disease
- Heart disease
- Institutionalization
- Increased age

Farr and colleagues reported that increased age and COPD were also risk factors [14].

Robinson and colleagues reported that *S. pneumoniae* was the most commonly identified cause of CAP in patients aged 65 years as well as being a frequent cause of bacteremia, with older patients more likely to be infected with multidrug-resistant pneumococcal strains [15].

Streptococcus pneumoniae & antimicrobial resistance

Extensive data are available on the susceptibility of community-acquired respiratory pathogens to commonly prescribed antimicrobial compounds. Of the respiratory bacterial pathogens, penicillin and multidrug-resistant *S. pneumoniae* (MDRSP) has attracted the greatest interest – especially those strains showing high-level (minimum inhibitory concentration [MIC] of 2 µg/ml) penicillin resistance [16]. For *S. pneumoniae* strains that are susceptible to penicillin, MIC values are 0.06 µg/ml or less; intermediate-resistant strains have MIC values between 0.1 and 1µg/ml. As such, any strain with an MIC of 0.1 µg/ml or more can be

considered nonsusceptible, whereas those with MIC values over 2 µg/ml are considered highly resistant. High-level penicillin-resistant strains are more likely to be co- or crossresistant to other β-lactam compounds (including cephalosporins), macrolide/azalide compounds, trimethoprim/sulfamethoxazole and tetracyclines. Felmingham and colleagues reported on antibacterial resistance of respiratory tract pathogens [17]. Data were reported from a number of geographical locations with data for penicillin and macrolide nonsusceptibility or resistance. Data from over 2800 pneumococcal isolates from around the world indicated that over 30% of strains (20–39% in North America) for patients aged 13 to 65 years were not susceptible to penicillin, with 19% being highly resistant (9–27% in North America) and of patients aged over 65 years, more than 36% were nonsusceptible (24–25% in North America) with 26% being highly resistant (15–20% in North America). For other areas of the world, penicillin-resistant *S. pneumoniae* rates were variable, with the highest resistance rates occurring in several countries/regions in South-East Asia and substantially lower in some European countries. Worldwide rates of macrolide resistance ranged from 28% (patients 13–65 years) to over 37% (patients >65 years) and in North America fluctuated between 20 and 28% in the younger and 15 and 27%, in the older age groups. Similar to penicillin-resistance rates, rates for macrolide resistance were higher in South-East Asia and variable throughout Europe. Additional susceptibility data from the Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin (PROTEKT) study in the USA was provided by Doern and Brown, who reported penicillin and macrolide resistance from over 10,000 clinical isolates of *S. pneumoniae*, and observed that over 38% were not susceptible to penicillin [18]. They also found that 26% were highly resistant and that 31% were macrolide resistant. Overall resistance to quinolones ranged from under 1 to 1.2%. Finally, the PROTEKT data showed that MDRSP levels were 30% in the USA, and data from Jacobs and colleagues showed MDRSP to account for 25.8% of pneumococci isolated in the USA; however, these strains were resistant to three or more classes, which is more stringent than the US Food and Drug Administration (FDA) definition of two or more class-resistance mechanisms [19].

The development and introduction of the fluoroquinolones represented a significant evolution in anti-infective therapy for both in- and outpatient populations. For example, norfloxacin (urinary tract only), ciprofloxacin and ofloxacin/levofloxacin were approved and clinically useful for treating Gram-negative and some Gram-positive infections; however, while clinically efficacious, the aforementioned quinolones are best characterized as having potent *in vitro* activity against Gram-negative and atypical bacilli, and with borderline (near breakpoint) *in vitro* activity against clinically important Gram-positive cocci such as *S. pneumoniae*. Subsequently, fluoroquinolones with enhanced *in vitro* activity against Gram-positive pathogens, most notably *S. pneumoniae*, enhanced *in vitro* activity against atypical pathogens and broad-spectrum anti-Gram-negative activity (not *Pseudomonas aeruginosa*) were developed. These latter compounds included agents such as trovafloxacin and grepafloxacin, both of which were withdrawn due to toxicity issues. Subsequently, more potent antipneumococcal agents, such as gatifloxacin and moxifloxacin, were approved for community-acquired RTIs. The newest and most potent *in vitro* antipneumococcal fluoroquinolone is gemifloxacin. This review will discuss the microbiologic, pharmacologic, clinical and safety characteristics of gemifloxacin in the context of an agent that, not only provides high levels of efficacy, but also confers health–economic and possible societal advantages in two common and costly infections.

Gemifloxacin

As a fluoroquinolone, gemifloxacin is derived from the antimicrobial compound nalidixic acid. The addition of a nitrogen atom at the 8-position of the molecule gave rise to the naphthyridine compounds of which gemifloxacin is one [20]. In addition, gemifloxacin has a 1-cyclopropanyl group at position 1 and a pyrrolidine substituent at the C7-position and that latter moiety may be associated with reduced CNS side effects [21]; the presence of a C-8 methoxyamino group may contribute to the enhanced activity against *S. pneumoniae* [22]. Ball recently reviewed the fluoroquinolone compounds and provided the following characteristics of gemifloxacin [20]:

- Highest antipneumococcal activity
- Retained activity against ciprofloxacin-resistant pneumococcal strains
- Marked antiatypical activity

Table 1. Comparison of the *in vitro* activity of various antimicrobials against three respiratory tract pathogens collected by the Alexander Project, 1999–2001 [1].

Antimicrobial	*Streptococcus pneumoniae*			*Haemophilus influenzae*			*Moraxella catarrhalis*		
	n	MIC_{50} (mg/l)	MIC_{90} (mg/l)	*n*	MIC_{50} (mg/l)	MIC_{90} (mg/l)	*n*	MIC_{50} (mg/l)	MIC_{90} (mg/l)
Gemifloxacin	8882	0.015	0.03	8523	0.004	0.015	874	0.008	0.015
Amoxacillin	8882	0.03	2.0	8523	0.05	>16	874	8.0	16.0
Amoxacillin/ clavulanate	8882	0.03	2.0	8523	0.05	1.0	874	≤0.12	0.25
Cefuroxime axetil	8882	0.06	8.0	8523	1.0	2.0	874	1.0	2.0
Ceftriaxone	8882	0.03	1.0	8523	≤0.004	0.008	874	0.12	1.0
Erythromycin	8882	0.06	>32	8523	4.0	8.0	874	≤0.5	≤0.5
Clarithromycin	8882	0.03	>32	8523	8.0	16.0	874	≤0.5	≤0.5
Azithromycin	8882	0.12	>32	8523	1.0	2.0	874	0.06	0.12
Ciprofloxacin	8882	1.0	2.0	8523	0.015	0.003	874	0.03	0.06
Levofloxacin	6512	1.0	1.0	5651	0.015	0.015	421	0.03	0.06
Gatifloxacin	3414	0.25	0.5	2764	0.008	0.015	250	0.03	0.03
Moxifloxacin	3414	0.12	0.25	2764	0.015	0.03	250	0.036	0.06

- Active against Gram-negative pathogens
- Favorable pharmacokinetics, once daily dosing, balanced elimination
- Very little need for dosage adjustments and few drug–drug interactions
- Predominantly high efficacy for RTIs based on pharmacokinetics
- Favorable adverse drug-reaction profile

In vitro activity

Gemifloxacin has been investigated, *in vitro*, against a wide range of bacterial pathogens and atypical pathogens (extensively reviewed but not exclusively in [23–34]). The activity against organisms associated with community-acquired RTIs is summarized in Tables 1 & 2. Against penicillin-susceptible, penicillin-resistant and multidrug-resistant pneumococci (not including quinolone-resistant), the MIC_{90} values for gemifloxacin have been reported to range from between 0.015 and 0.031 µg/ml. For *S. pneumoniae* isolates resistant to either ciprofloxacin or levofloxacin, gemifloxacin MIC_{90} values ranged between 0.03 and 1 µg/ml; values exceeded by achievable total and free-drug concentrations in serum and pulmonary and sinus tissues; however, it is likely that the free-drug fraction is most important. Susceptibility testing of clinical isolates of *H. influenzae*, *Moraxella catarrhalis* and *H. parainfluenzae*, yielded MIC_{90} values, ranging from less than 0.008 to 0.06 µg/ml, and these values were not influenced by β-lactamase-producing or macrolide-resistant strains. MIC_{90} values of 0.016 to 0.25 µg/ml were reported against *M. pneumoniae*, *Chlamydia (Chlamydophila) pneumoniae* and *Legionella pneumophila*. Against methicillin-susceptible strains of *S. aureus*, MIC_{90} values ranged from 0.03 to 0.063 µg/ml but were higher against methicillin- (1–8 µg/ml) and ciprofloxacin-resistant strains (8 µg/ml).

Drug–drug interactions

Gemifloxacin has been investigated for its potential interaction with various other substances. Gemifloxacin can be taken with or without food [35], either 2 h before sucralfate or ferrous sulfate, or at least 3 h after ferrous sulfate [36]. It can be coadministered with digoxin without the need for dosage adjustment [37] and should be administered over 2 h prior to or 3 h or more after maalox or other cation-containing compounds [38]. In addition, gemifloxacin could be coadministered with theophylline without any theophylline dosage adjustment, due to the fact that it is not affected by cytochrome P450 metabolism [39]. Dosage adjustments were not necessary in renal insufficiency patients with CrCl levels over 40 ml/min, Child–Pugh classes A, B or C or

Table 2. Comparison of *in vitro* activity of various antimicrobial agents against atypical respiratory tract pathogens [1].

Compound	*L. pneumophila*		*M. pneumoniae*		*C. pneumoniae*	
	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	MIC_{50} (μg/ml)	MIC (μg/ml)	MIC_{50} (μg/ml)	MIC (μg/ml)
Gemifloxacin	0.015	0.03	0.06	0.012	0.25	0.25
Ciprofloxacin	0.03	0.03	1	2	1	2
Levofloxacin	0.008	0.015	0.5	0.5	0.5	1
Gatifloxacin	0.015	0.015	0.06	0.12	0.12	0.25
Moxifloxacin	0.015	0.015	0.12	0.12	0.5	1

hepatic insufficiency or the elderly [40]. Dosage adjustment (160 mg once daily) is only necessary in patients with impaired renal function (creatinine clearance $\leq$ 40 ml/min).

Pharmacokinetic & pharmacodynamic properties

The pharmacologic properties of gemifloxacin are following a single daily oral dose of 320 mg, yielding a peak plasma concentration of 1.48 to 1.6 mg/l, with a time to peak plasma concentration of 1 h. The area under the serum concentration curve is 9.30 mg/l/h, with a renal clearance of 9.06 l/h and a half-life of 6.65 h [29]. Seo and colleagues investigated serum protein binding for gemifloxacin is between 60 to 70% [40,41].

Gemifloxacin, like other fluoroquinolones, acts as a concentration-dependent killing agent [23] against bacteria within its spectrum and, as such, parameters such as maximum concentration (C_{max})/MIC ratios and area under the curve (AUC)/MIC are reliable predictors of antibacterial effect and prevention of resistance. The MIC_{90} for gemifloxacin ranges from 0.03 to -0.06 and, with a C_{max} of 1.6 μg/ml and AUC of 9.3 mg/l.h, would yield C_{max}/MIC ratios of 53.3 to 26.6 (total drug) and 18.7 to 9.3 (free drug at 65% protein bound) and AUC/MIC ratios of 310 to 155. The pharmacodynamic parameters of currently available fluoroquinolones against *S. pneumoniae* are shown in Table 3, with gemifloxacin exceeding the two thresholds of 25 [42] and 100 [43,44] for AUC:MIC for healthy and immunocompromised patients, respectively. The highest value of currently available fluoroquinolones is 96. Two previous studies with β-lactam compounds suggest that it is the free-drug fraction that is important for the antibacterial effect [45,46].

Gee and colleagues studied the tissue penetration and pharmacokinetics of oral gemifloxacin (320 mg) in healthy males and determined the plasma, blister fluid and urine concentrations. Peak plasma concentration was 2.33 ± 0.5 μg/ml at 1.2 ± 0.4 h. Inflammatory fluid concentration was 61.19 ± 10.4% of serum drug concentrations (peak concentration 0.74 ± 0.3 μg/ml) at a mean time of 3.40 ± 1.7 h [47]. Finally, urinary excretion of the drug was 36.11% of the total dose. Gee and colleagues concluded that gemifloxacin reaches sufficient concentrations in inflammatory fluid to inhibit many pathogens [47].

Postantibiotic effects

The postantibiotic effect (PAE) can be defined as the continued suppression of bacterial growth after the drug concentration has dropped below the MIC of the organism. In studies where organisms were exposed to drug based on multiples of the MIC, Moore and colleagues and MacKenzie and colleagues investigated the PAE of gemifloxacin and reported that, at 4 × MIC, the PAE was 0.1 greater than at 6 h against *S. aureus*, *M. catarrhalis*, *H. influenzae*, *Escherichia coli*, *P. aeruginosa*, *Klebsiella pneumoniae* and *P. vulgaris* [48,49]. A PAE of 1.5 and 2.7 h at 4 × MIC was observed for *S. pneumoniae* and, at 10 × MIC, a PAE of 3.8 h was seen for both penicillin-susceptible and -resistant pneumococci. In the experiments by Moore and colleagues, organisms were exposed to a drug for 1 h then removed by ultrafiltration. Following drug removal, viable counts were carried out for 6 h [48].

Dual targeting

Newer fluoroquinolones such as gemifloxacin [23], gatifloxacin and moxifloxacin, have been reported to have enhanced *in vitro* activity against clinically important Gram-positive cocci [50] – specifically *S. pneumoniae* – when compared with older quinolone compounds such as ciprofloxacin and levofloxacin [34]. For *S. pneumoniae*, gemifloxacin attacks both DNA gyrase

Table 3. Pharmacodynamic parameters for *Streptococcus pneumoniae* [1].

Compound	Dose (mg)	Median MIC_{90}	Mean AUC_{0-24}	AUC_{0-24}: MIC_{90}	Protein binding (%)	$fAUC_{0-24}$	$fAUC_{0-24}$: MIC_{90}
Gemifloxacin	320	0.03	9.93	331	65*	3.47	116
Moxifloxacin	400	0.25	48.0	192	50	24.0	96
Gatifloxacin	400	0.5	34.4	68.8	20	27.5	55
Levofloxacin	500	1.0	47.5	47.5	31*	32.8	32.8
Levofloxacin	750	1.0	90.7	90.7	31*	62.6	62.6

*Median protein-binding value

and topoisomerase IV, while older compounds preferentially target topoisomerase-IV [51,52]. Furthermore, Fisher and colleagues [53] indicate that gemifloxacin exhibits dual activity based on the minimal effects that either a *parC* or *gyrA* mutations have on resistance; however, strains with mutations in both genes demonstrate lower levels of susceptibility, with MIC values of 0.2 over 0.5 µg/ml, compared with 0.03 for fluoroquinolone-susceptible strains. These data have been corroborated by Gillespie and colleagues [54], Chen and colleagues [55] and Perez-Trallero and colleagues [56], all of whom have shown gemifloxacin to possess activity against a range of single- and, more importantly, double-step mutants of *S. pneumoniae*. Gemifloxacin is the only flouroquinolone approved by the US Food and Drug Administration (FDA) to be active at both target sites at therapeutically achievable drug concentrations.

Selection of resistant mutants

The development of resistance to gemifloxacin *in vitro* has been studied by Rittenhouse and colleagues [57], where mutational frequencies ranging from less than 1.1×10^{-9} to less than 9.0×10^{-8} were reported for *S. aureus, S. saprophyticus, S. pyogenes, S. pneumoniae, M. catarrhalis, H. influenzae, E. coli*, and *P. aeruginosa* and 4.6×10^{-7} for *K. pneumoniae*.

Gillespie and colleagues compared the spontaneous mutation rate of ciprofloxacin and gemifloxacin in *S.pneumoniae* and noted a 400-fold lower rate for gemifloxacin against the pneumococcus [54]. First- and second-step mutation rates for ciprofloxacin and gemifloxacin to *S. pneumoniae* were 1.1×10^{-9}, 1.3×10^{-8} and 1.6×10^{-11} and 7.2×10^{-9}, respectively. Thus, the mutation rate for gemifloxacin is 400-times lower than that for ciprofloxacin.

The mutant-prevention concentration (MPC) for fluoroquinolones defines the antimicrobial drug concentration that would require an organism to simultaneously possess two mutations to grow in the presence of the drug or the MIC of the most resistant first-step mutant present a the heterogeneous bacterial population [58]. The MPC concept has been best studied for quinolones and only applies to those bacterial populations that have been deemed susceptible to the antimicrobial agent by traditional antimicrobial susceptibility testing, using a standardized inoculum of 10^5 CFU/ml, such as that recommended by the National Committee for Clinical Laboratory Standards.

Fluoroquinolones with a dual mechanism of action may not only be the most potent agents *in vitro* but they may also minimize the selection of resistant *S. pneumoniae*. With *S. pneumoniae*, the frequency with which a single mutation occurs ranges from 10^{-7} to 10^{-9} [59]. Thus, if a double mutation were to occur simultaneously, it would need a mutation rate of 1 in more than 10^{14} bacteria ($10^{-7} \times 10^{-7}$) to develop two concurrent fluoroquinolone-resistant mutations [59]. Fluoroquinolone compounds that target only one intracellular target (i.e., either DNA gyrase or DNA topoisomerase IV) may select for a first-step (one mutation) resistant mutant when exposed to a bacterial inoculum of 10^9 or more cells. Such inocula are attainable in human infections [60–62]. More specifically, Frisch and colleagues reported that, in pneumococcal pneumonia, bacterial loads in the lung may be as high as 10^{10} to 10^{12} organisms [63]. For truly dual-acting compounds, more than 10^{14} bacterial cells would be required to find one organism containing two concurrent mutations that would allow growth in the presence of the drug. A logical conclusion from this argument would be that potent dual-acting fluoroquinolones, such as gemifloxacin, would be less likely to select for quinolone-resistant *S. pneumoniae* than would the less avidly bound compounds.

Current data confirm some important observations:

- Gemifloxacin exerts rapid concentration dependent bactericidal activity against *S. pneumoniae*.
- Gemifloxacin is rapidly bactericidal over a range of inocula – including high bacterial inocula typically found at the site of pulmonary or sinus infection.
- Gemifloxacin has the lowest overall resistance selection potential based on MIC_{90} and MPC_{90} *in vitro* studies.

Achieving and maintaining drug concentrations above the MPC drug concentration for prolonged periods (≥4 h) are important for ensuring bacterial killing of high density inocula and preventing selection of resistant mutants.

In vivo animal studies

Gemifloxacin has been investigated in several animal models including a rat model of RTI [64], pyelonephritis and wound infection [65], guinea-pig pneumonia model [66] and a rabbit meningitis model [67,68]. Berry and colleagues tested the *in vivo* efficacy of gemifloxacin in a rat RTI model following infection with either of *S. pneumoniae* (MIC values to gemifloxacin of <0.03 µg/ml) or *H. influenzae* (MIC values to gemifloxacin of <0.008 µg/ml) strains that showed differential susceptibilities to other antimicrobial compounds [64]. A total of 24 h after intrabronchial infection and the establishment of pneumonia, animals were treated with gemifloxacin (240 mg/kg to simulate the 320-mg dose in humans) therapy was continued for 3 days and the lungs excised for bacterial enumeration 17 h after the end of therapy. For *S. pneumoniae*-infected rats, gemifloxacin resulted in 3 to 5 log reductions compared with untreated controls, and was as effective as amoxicillin/clavulanic acid (350/50 mg/kg to simulate 875/125-mg dose in humans) and more potent than ciprofloxacin (200 mg/kg in simulating a 750-mg dose in humans), trovafloxacin (40 mg/kg to simulate 200 mg dose in humans), grepafloxacin (200 mg/kg to simulate 600-mg dose in humans) and levofloxacin (125 mg/kg to simulate 500-mg dose in humans) which resulted in log reduction values of under log 3 when compared with untreated controls. Against *H. influenzae*-treated rats, gemifloxacin resulted in a significant reduction in bacterial numbers ($p < 0.01$) when compared with untreated controls and was similar to responses seen with ciprofloxacin, grepafloxacin, levofloxacin and trovafloxacin but was more potent than either cefuroxime (70 mg/kg to simulate 250-mg dose in humans) or azithromycin (40/20 mg/kg to simulate 1000/500-mg doses in humans). Berry concluded that gemifloxacin may be of significant benefit in the treatment of RTIs.

Society guidelines for the management of acute exacerbation of chronic bronchitis and community-acquired pneumonia in 2003/2004

For CAP, the Infectious Diseases Society of America (IDSA) published updated guidelines in light of recent changes such as growing resistance and new etiologic agents [69], while the Canadian Thoracic Society and the Canadian Infectious Disease Society also published their AECB management guidelines in 2003 with a similar stratified approach using certain risk factors as a guide for when to turn to potent agents such as the new fluoroquinolones [70]. The criteria for 'at-risk' patients in the two sets of guidelines are described in Box 1. At-risk patients are those that are at a higher risk of infection than the general population and is influenced by factors such as age, smoking, alcoholism and various comorbidities. Agents such as gemifloxacin and other new fluoroquinolones play an important role in the management of these patients, especially in patients with pathogens resistant to other antimicrobial classes.

Clinical experience with gemifloxacin in community-acquired respiratory infections

Clinical data on gemifloxacin is derived from 14 studies, 12 of which were randomized (nine summarized in this manuscript) comparative trials designed to show 'noninferiority', unusually, six studies showed gemifloxacin to be superior for some important end points.

Ball and colleagues reported on the efficacy and safety with 7 days of gemifloxacin (320 mg once daily) for treatment of adult lower RTIs [71]. Patients with acute exacerbations of chronic bronchitis (n = 261) and 216 patients with CAP were enrolled into an open label, noncomparative trial to assess clinical and bacteriologic efficacy. Clinical success at follow-up (21–28 days) (intent-to-treat) was 83.1% in AECB patients and 82.9% in CAP patients. Bacteriologic success rates (intent-to-treat) were 91.2% in AECB patients and 77.9% in CAP patients. Isolated pathogens recovered included: *H. influenzae, H. parainfluenzae, M. catarrhalis, S. aureus, K. pneumoniae, P. aeruginosa, C. pneumoniae, M. pneumoniae*

Box 1. Society guideline criteria for 'at-risk' patients with acute exacerbations of chronic bronchitis [70] and community-acquired pneumonia [69].

Acute exacerbations of chronic bronchitis

Any one of the following:

- >4 exacerbations per year
- Smoking, or history of
- Genetic predisposition
- Environmental pollution
- Repeated viral respiratory infections

Community-acquired pneumonia

Any one of the following:

- Age >65 years
- Any antimicrobial therapy including β-lactams during the last 3 months
- Alcoholism
- Multiple medical comorbidities including cardio–pulmonary conditions, diabetes and renal disease
- Immunosuppressed patients
- Exposure to a child at a daycare center or nursing home

and *C. psittaci*. *S. pneumoniae* and *C. pneumoniae* were eradicated with high success – *S. pneumoniae* eradication occurred in eight out of eight AECB patients and 12 out of 18 CAP patients regardless of penicillin or macrolide resistance. *C. pneumoniae* eradication was 15 out of 16 from CAP patients. Overall eradication rates exceeded 90% (n = 159). Where failures to gemifloxacin were noted, they could not be explained by organism MIC values as these were generally low against the initial pathogen and for most failures, the initial pathogen was not re-isolated at the time of failure. Of the few cases where there was documentation of recurrence of the initial pathogen, the increases in MIC values were within the experimental error for the test. Gemifloxacin therapy was well tolerated and the most frequent side effects were diarrhea (1.9–2.8%), nausea (1.1–1.9%) and headache (1.1–1.4%). Oral gemifloxacin (320-mg dose once daily for 7 days) was associated with high clinical and bacteriological success in patients with lower RTIs [71].

Community-acquired pneumonia studies

Gemifloxacin was compared with β-lactam alone or with or without a macrolide and a fluoroquinolone in patients with CAP.

Oral gemifloxacin (320 mg once daily) was compared with sequential therapy with intravenous ceftriaxone/oral cefuroxime with or without a macrolide for the treatment of patients hospitalized with CAP in a randomized open-label multicenter study for both clinical efficacy and tolerability [72]. Hospitalized adult patients with clinical or radiological evidence of pneumonia were randomized to receive either oral gemifloxacin for 7 to 14 days versus 2 g intravenous ceftriaxone once daily for 1 to 7 days followed by oral cefuroxime 500 mg for 1 to 13 days for a total of less than 14 days. Patients receiving the cephalosporin regimen were also allowed concomitant macrolide therapy at the discretion of the investigator. This dose of ceftriaxone is twice that typically administered in most hospitals. A total of 341 patients were enrolled (gemifloxacin, 169 out of 172; ceftriaxone/cefuroxime 172 out of 173). Clinical success in clinically evaluable patients at follow-up (day 21–28 post therapy) were 107 out of 116 (92.2%) for gemifloxacin-treated patients versus 113 out of 121 (93.4%) for those receiving ceftriaxone/cefuroxime plus a macrolide group. For patients classified as Fine risk Classes IV and V, the clinical efficacy was 87% (20 out of 23) (gemifloxacin) versus 83.3% (20 out of 24) (ceftriaxone/cefuroxime) and macrolide addition did not affect clinical response at follow-up. For bacteriologically evaluable patients, bacteriologic success rates were 90.6% (58 out of 64) for those receiving gemifloxacin versus 87.3% (55 out of 63) for those receiving ceftriaxone/cefuroxime.

Of 132 patients in the end-of-therapy bacteriologic evaluable population, 26 were bacteremic (19.7%) (gemifloxacin: 16, ceftriaxone/cefuroxime: 10). *S. pneumoniae* was isolated from 75% (12 out of 16) of those that received gemifloxacin compared with 50% (five out of ten) of those who received ceftriaxone/cefuroxime therapy. All bacteremic patients in the bacteriological evaluable populations were clinical successes at end of therapy and there were no bacteriologic failures following gemifloxacin therapy and one for those receiving ceftriaxone/cefuroxime treatment. All 25 bacteriologic evaluable patients bacteremic at screening were a clinical success at follow-up and all pathogens were eliminated from the blood. Clinical success based on the pretherapy pathogen ranged from 90 to 100% for both treatment regimens for *S. pneumoniae*, *M. pneumoniae*, *C. pneumoniae* and *Legionella pneumophila*.

The authors concluded that 320 mg of gemifloxacin was clinically equivalent to intravenous ceftriaxone/oral cefuroxime (plus macrolide) for the treatment of hospitalized adult patients with moderate-to-severe CAP, and

that both regimens were effective in bacteremic patients and those at an increased risk of mortality. The time to hospital discharge for those receiving oral gemifloxacin was 8 days (median range: 1–32 days) versus 9 days (median range: 1–45 days) for ceftriaxone/cefuroxime-treated patients. The importance of this finding was that oral therapy was equivalent to intravenous therapy and, as such, is cheaper for many reasons (i.e., reduced pharmacy preparation time, reduced nursing time for administration and monitoring, and reduced ancillary costs of intravenous bags and needles) better for patients and, in theory, initial PO treatment on diagnosis could enable more prompt therapy. It has been demonstrated that treatment administered in less than 4 h leads to a lower mortality. This prompt treatment is a new key continuous quality improvement indicator for CAP.

Gemifloxacin was studied for efficacy and safety (vs. trovafloxacin) in patients with CAP, in a randomized, double-blind study [73]. A total of 571 patients were randomized to receive either gemifloxacin (320 mg once daily) or trovafloxacin (200 mg once daily) for 7 to 14 days and approximately two-thirds of the patients were treated for 7 days. Both gemifloxacin and trovafloxacin treatment resulted in high clinical success rates at follow-up (95.8 vs. 93.6%, respectively in the per-protocol population). For the intent-to-treat populations, clinical success at follow-up was significantly superior for gemifloxacin (87.6%) versus trovafloxacin treatment (81.1%: 95% CI 0.5, 12.4). For gemifloxacin-treated patients, eradication rates were: 93% for *M. pneumoniae* isolates, 100% for *S. pneumoniae*, *C. pneumoniae*, *C. burnetii*, *S. aureus*, *H. influenzae*, *L. pneumophila* and 94% of all pathogens were eradicated. Adverse events were similar between treatment groups, with the most frequent side effects reported for gemifloxacin-treated patients being rash (5.2%), headache (3.4%) and diarrhea (2.8%). For trovafloxacin-treated patients, the most frequently reported side effects were dizziness (5.0%), nausea (4.6%), headache (2.5%) and rash (1.8%).

Gemifloxacin (320 mg once daily for 7 days) was compared with 10 days' high-dose amoxicillin/clavulanic acid (1 g/125 mg three-times daily) for the treatment of 324 patients with CAP of suspected pneumococcal origin. The study was a randomized, multicenter, double-blind, double-dummy, parallel group Phase III trial. Outcome measures were clinical, bacteriologic and radiologic responses at end-of-therapy (days 12–14) and at follow-up (days 24–30) [74].

The rates of clinical resolution at follow-up were 88.7% for gemifloxacin (n = 228 per protocol) treated patients and 87.6% for those who received high dose amoxicillin/clavulanic acid (95% confidence interval [CI]: 7.3, 9.5). For patients evaluated at end-of-therapy (n = 249 per protocol), clinical resolution was similar for both groups (95.3% for 7 days of gemifloxacin vs. 90.1% for 10 days of high-dose amoxicillin/clavulanic acid, 95% CI: 1.2, 11.7).

Bacteriologic response rates (per protocol) at end-of-therapy were 96.3% for gemifloxacin-treated patients versus 91.8% for the high-dose amoxicillin/clavulanic acid-treated group (95% CI: 4.7, 13.6) and at follow-up 87.2 versus 89.1%, respectively (95% CI: 15.0, 11.2). *S. pneumoniae* was eradicated from gemifloxacin-treated patients, including those strains resistant to penicillin and macrolides. The pathogens recovered were *S. pneumoniae*, *M. pneumoniae* (by serology), *H. influenzae*, *L. pneumophilia* (urine antigen positive or serology), *C. pneumoniae* (by serology), *M. catarrhalis* and *S. aureus*, and no differences in eradication rates were shown between gemifloxacin or high-dose amoxicillin/clavulanate-treated patients at either end-of-therapy or follow-up visits. Statistically fewer withdrawals due to lack of therapeutic effect were seen in gemifloxacin-treated patients than those receiving high-dose amoxicillin/clavulanic acid (95% CI: 8.8, 0.6; p = 0.03).

Gemifloxacin (320 mg once daily) therapy was found to be clinically, bacteriologically and radiologically as effective as 10 days of high-dose amoxicillin/clavulanate (1 g/125 mg) three-times daily for the treatment of suspected pneumococcal CAP.

File and colleagues summarized that ciprofloxacin-resistant pneumococci have emerged recently in some countries [73] including Canada, Hong Kong and Spain [55,75,76]. According to the authors, the appearance of these strains may be related to the ability of different quinolones to select for quinolone-resistant mutants and that resistance to the older quinolones appears to occur in a single step, while resistance to the newer agents, such as gemifloxacin, required two mutations to induce high-level resistance, an occurrence unlikely to be a frequent event [77]. Reports of levofloxacin failures in patients

treated for CAP have been noted. With some of these reported cases, organisms susceptible to the drug at the start of therapy were found to have reduced susceptibility or resistance (by MIC measurements and DNA sequence analysis) to the treatment drug following therapeutic failure [78,79] Quinolones with the greatest potency were initially expected to retain activity against mutants that had been selected for use by older quinolones [80]. In theory, the initial use of the most potent agent is likely to prevent or decrease selection of resistance [43,50]. File and colleagues indicated that once-daily dosing may improve compliance and as such, might reduce the risk of antibiotic resistance from developing. Bacteriologic and clinical data on the efficacy of gemifloxacin against ciprofloxacin-intermediate and ciprofloxacin-resistant *S. pneumoniae* showed 19 out of 22 and four out of four successes, respectively, thus clinically corroborating *in vivo* the dual targeting activity of gemifloxacin against pneumococci observed *in vitro* [40].

Acute exacerbations of chronic bronchitis

Oral gemifloxacin administered for 5 days was compared with a fluoroquinolone, a macrolide, a β-lactam/β-lactamase inhibitor combination as well as a parenteral β-lactam agent in AECB.

Gemifloxacin (320 mg once daily for 5 days) was compared with clarithromycin (500 mg twice daily for 7 days) for therapy (efficacy and safety) in patients with acute exacerbations of chronic bronchitis. Long-term follow-up and clinical outcomes were also recorded [81]. Clinical and bacteriologic response rates were assessed at end-of-therapy (days 8–12), the 2- to 3-week follow-up visit (days 13–24), the 4- to 5-week follow-up visit (days 25–38) and the long-term phase of follow-up at 26 weeks.

Patients were randomized from 73 North American and 20 European centers in seven countries to receive either gemifloxacin (n = 351) or clarithromycin (n = 361). Clinical response (per protocol groups) at the 2- to 3-week follow-up visit was 85.4% (gemifloxacin-treated patients) versus 84.6% (clarithromycin-treated patients); for the intent-to-treat population 79.5 versus 78.2%, respectively. *H. influenzae* was the single most common pathogen from patients in both groups: n = 20 (35.1% of gemifloxacin-treated patients); n = 18 (27.3% for clarithromycin-treated patients). Other pathogens were *H. parainfluenzae*, *M. catarrhalis*, *S. aureus* and *S. pneumoniae* occurring in 10.5 to 15.8% (n = 6–9) of patients who received gemifloxacin and 9.1 to 12.1% (n = 6–8) of those receiving clarithromycin. Bacteriologic success was statistically higher (per protocol) for gemifloxacin treated patients than for those who received clarithromycin (36 out of 44 [81.8%] vs. 31 out of 50 [62%], respectively; 95% CI: 2.2–37.5) at the 4 to 5 week follow-up visit. Higher eradication rates in favor of gemifloxacin over clarithromycin were also seen at the end of therapy (per protocol) (93.6 vs. 81.5) and at the 2- to 3-week follow-up visit (86.7 vs. 73.1); however, none of these differences were statistically different.

Wilson and colleagues evaluated the time to eradication of *H. influenzae* by both gemifloxacin and clarithromycin, considering that this organism is an important pathogen in AECB patients [81]. A total of 24 out of 193 patients agreed to have daily sputum cultures (12 in each group) collected and all 24 patients originally had *H. influenzae* isolated from their presentation visit sputum. Gemifloxacin therapy resulted in a significantly shorter time to *H. influenzae* eradication then did clarithromycin treatment ($p < 0.02$) (mean eradication time: 1 vs. 2 days, respectively).

Long-term outcome for patients treated with either of gemifloxacin and clarithromycin were also assessed by Wilson and colleagues [81]. A total of 438 patients (214 gemifloxacin-treated and 224 clarithromycin-treated) were enrolled from centers in the USA and Canada. More patients (intent-to-treat) treated with gemifloxacin (at all visits) had fewer recurrences of acute exacerbations of chronic bronchitis over the 26 week follow-up period than those given clarithromycin (71 vs. 58.5%; 95% CI: 2.46–22.59; $p = 0.016$ for 26 week follow-up visits). There was a trend towards reduced hospitalization, with fewer patients who received gemifloxacin admitted during the 26-week assessment (2.3 vs. 6.3%; 95% CI: 7.76 to -0.15; $p = 0.059$). Wilson and colleagues suggested that the long-term benefits seen with gemifloxacin may relate to superior antimicrobial efficacy and that decreased rates of hospitalization for RTIs related conditions in gemifloxacin treated patients likely has significant economic implications.

Sethi and colleagues compared gemifloxacin (320-mg once daily for 5 days) therapy with that of levofloxacin (500 mg once daily for 7 days) for treating patients with AECB in a randomized, double-blind, double-dummy, multicenter

parallel-group study and was conducted in 60 different medical centers in the USA, the UK and Germany [82]. The primary efficacy measurement was a clinical response at follow-up (days 14–21). Clinical success at follow-up (per protocol) was 88.2% in the gemifloxacin-treated group versus 85.1% for those treated with levofloxacin. Significant differences were not seen in the intent-to-treat population (85.2 vs. 78.1%, respectively) and clinical success at end of therapy (per protocol day 9–11) was 97.5% for those receiving gemifloxacin and 93.5% for those given levofloxacin; 94 versus 88.8%, respectively for the intent-to-treat population. For long-term follow-up (day 28–35), clinical success in the per protocol population was 83.7% (gemifloxacin-treated) versus 78.4% (levofloxacin-treated) and for the intent-to-treat population 80.8% versus 70.8%, respectively – a statistically different observation in favor of gemifloxacin (95% CI: 1.18, 18.78).

The bacteriologic success rate for gemifloxacin-treated patients was similar to that seen in patients treated with levofloxacin at the end of therapy, respectively (per protocol 87.5 vs. 90.4%; intent-to-treat 81.8 vs. 86.7%); at follow-up, respectively (per protocol 78.4 vs. 85.7; intent-to-treat 75 vs. 80%) at long-term follow-up, respectively (per protocol 77.8 vs. 70.5%; intent-to-treat 75 vs. 65%). No significant differences in the eradication of the three major pathogens (*H. influenzae*, *M. catarrhalis* and *S. pneumoniae*) were seen between the two treatment groups.

Sethi and colleagues concluded that the clinical efficacy of gemifloxacin therapy (320 mg once daily for 5 days) was as good as levofloxacin (500 mg once daily for 7 days) for the treatment of AECB. Fewer withdrawals were also seen amongst gemifloxacin-treated patients. Gemifloxacin was statistically better than levofloxacin at long-term follow-up (intent-to-treat population) [82].

File and colleagues compared 5 days of once-daily 320 mg gemifloxacin with 625 mg coamoxicllin–clavulanate three-times daily for 7 days for the treatment of AECB [83]. The two drugs were shown to be equally effective with clinical success rates of 93.6 and 93.2%, respectively. Bacteriologic success favored gemifloxacin, but was not quite statistically significant, 90.9 versus 79.5% (95% CI: 3.9; 4.6). Once-daily gemifloxacin was considered to be as effective and more convenient for the treatment of AECB.

Ball and colleagues compared gemifloxacin with trovafloxacin for the treatment of AECB [84]. Both drugs were administered once daily for 5 days. Over 600 patients were enrolled in the study, 303 gemifloxacin and 314 trovafloxacin. Clinical success at follow-up was 91.5% with gemifloxacin and 87.6% with trovafloxacin. For the intention-to-treat (empirical or real-world) cohort, the clinical efficacy of gemifloxacin was statistically superior to that of trovafloxacin; 89.4 versus 83.1% (95% CI: 0.9, 11.7). A similar finding was reported at long-term follow-up as well. Bacteriologic outcomes were also better with gemifloxacin 86.8% compared with 82.4% [83].

Wilson and colleagues compared 5 days of once-daily gemifloxacin with 1 to 3 days of intravenous ceftriaxone followed by 3 to 7 days of oral cefuroxime for the treatment of AECB in hospitalized patients [85]. Although both regimens showed similar clinical outcomes, those who received 5 days of gemifloxacin were discharged form hospital 2 days earlier than the ceftriaxone/oral cefuroxime cohort. This 2-day difference was statistically significant, $p = 0.04$. The likely cost savings related to this observation are probably high due to reduced 'daily hotel' costs.

Safety & tolerability

The safety of gemifloxacin has previously been determined from a number of clinical trials and following administration to healthy volunteers. Data summarized by File and Iannini [1] and in the prescribing information approved by the FDA [40] has indicated that 6775 patients received 320 mg oral doses of gemifloxacin in clinical trials, and that 1797 healthy volunteers and 81 patients with renal or hepatic impairment received either single or repeat oral doses in pharmacolic studies. Two approaches for evaluating drug safety include the reporting of any adverse events and/or to compare rates of discontinuation of therapy. File and Iannini reported that 44.7% of patients ($n = 6775$) reported at least one adverse event and this was not significantly different than the rate reported for patients ($n = 5248$) treated with all comparator compounds (47.5%) [1]. For data in the product label for gemifloxacin-treated patients, the most frequently reported adverse events (classified as possible or probable), compared with comparator agents, respectively (β-lactams, macrolides and fluoroquinolones)

were as follows: diarrhea (3.6 vs. 4.6%), headache (1.2 vs. 1.5%), nausea (2.7 vs. 3.2%), rash (2.8 vs. 0.6%), abdominal pain (0.9 vs. 1.1%), vomiting (0.9 vs. 1.1%), dizziness (0.8 vs. 1.52.6%) and taste perversion (0.3 vs. 1.9%). Most adverse events were considered to be of mild-to-moderate severity.

Gemifloxacin has a low potential for photosensitivity as demonstrated by Vousden and colleagues where they compared 160- and 320-mg doses of gemifloxacin with 500 mg of ciprofloxacin or placebo in healthy male and female volunteers [86]. Skin reactions were assessed at 0 to 30 min for immediate erythema and at 24 and 48 h for delayed erythema after irradiation. Both drugs were associated with mild phototoxicity following 7 days of drug administration, and the phototoxicity observed with the 160-mg dose of gemifloxacin was lower than with the 320-mg dose. The authors concluded that 320 mg of gemifloxacin given for 7 days has a low potential to cause mild photosensitivity and this was similar to that seen with the 500-mg dose of ciprofloxacin. The low potential for gemifloxacin-related phototoxicity was confirmed from clinical trials, where treatment-related photosensitivity occurred in 0.039% (three out of 7659) of patients.

Liver-enzyme elevations (increased ALT and/or AST) occurred in patients receiving gemifloxacin (320 mg once daily) at rates comparable to those in patients receiving comparator compounds (i.e., ciprofloxacin, levofloxacin/ofloxacin, clarithromycin, cefuroxime axetil or amoxicillin/clavulanic acid). No clinical symptoms were associated with the elevated liver enzymes and the raised values returned to normal at the end of therapy. Higher dosages resulted in increased elevations in liver enzymes and, as such, the recommended dosage of 320 mg once daily should not be exceeded (gemifloxacin PI). Dosage adjustment to 160 mg once daily is only necessary in patients with impaired renal function (creatinine clearance of under 40 ml/min).

Rash has been reported from patients in gemifloxacin clinical trials. According to clinical studies, the overall incidence of rash was 2.8% and was most commonly described as maculopapular and generally of mild-to-moderate intensity [40]. The rash was usually noticed after 8 to 10 days of therapy and resolved in 60% of patients within 7 days and 80% with 14 days. No phototoxicity, vasculitis or necrosis was associated with the rash and by histology was described as an uncomplicated exanthematous skin reaction. The incidence of rash associated with gemifloxacin varied by age and gender [40] and was, more commonly, observed in female patients aged under 40 years, as well as postmenopausal female patients taking hormone-replacement therapy. Duration of therapy longer than 7 days resulted in an increase in the incidence of rash in all subgroups, with the exception of men over the age of 40 years. Therapy with gemifloxacin for 5 days demonstrated a rash rate of 1.2 to 1.5%. Patients treated with gemifloxacin who develop a rash should discontinue therapy. There appears to be no cross-sensitization with gemifloxacin. Volunteers who developed a rash were exposed to either ciprofloxacin or placebo; 5.9% developed a rash on ciprofloxacin and 2.0% on placebo. The characteristics of the rashes were similar among these cases to those occurring with ciprofloxacin alone. There was no evidence of subclinical sensitization to gemifloxacin, moreover, there was no relationship between the incidence of rash and systemic exposure to either gemifloxacin or its major metabolite, *N*-acetyl gemifloxacin.

Drug tolerability may also be evaluated by comparing discontinuation rates. The rates in clinical trials for patients receiving gemifloxacin were compared with those from patients receiving comparator agents, 2.2 versus 2.1%. Previous recent fluoroquinolone discontinuation rates were as follows [40,87]:

- Trovafloxacin (7%)
- Grepafloxacin (6.4%)
- Sparfloxacin (2.8–3%)
- Levofloxacin (3.7%)
- Gatifloxacin (3.1%)
- Moxifloxacin (3.0%)
- Gemifloxacin (2.1%)

Notably, these clinical-trial dossiers were developed at the same time period as gemifloxacin in many of the same sites and patient types, thus, comparison is reasonable. The reasons for discontinuation (possibly or probably drug related) in gemifloxacin-treated patients were rash (0.9%), nausea (0.3%), diarrhea (0.3%), urticaria (0.3%) and vomiting (0.2%), while for comparator agents, diarrhea (0.5%), nausea (0.3%), vomiting (0.3%) and rash (0.3%) were most frequent.

Economic & societal considerations of antimicrobial therapy for community-acquired lower RTIs

Birnbaum and colleagues recently reported the financial impact of RTIs to the employer [88]. Overall, these infections cost an estimated US$112 billion in 1997, including medical treatment and lost productivity costs. Although there is wide variation in the estimated costs of some infections – pneumonia is estimated to cost $11,544 per patient compared with $5874 for a patient with chronic bronchitis – it is clear that the overall burden of cost for these very common conditions is increasing as the patient population ages and expands.

The cost–effectiveness of gemifloxacin therapy in AECB has been investigated. Halpern and colleagues compared the cost–effectiveness of oral gemifloxacin versus oral clarithromycin therapy in patients treated for acute exacerbations of chronic bronchitis [89]. Specifically, economic outcomes were assessed in the Gemifloxacin Long-term Outcomes in Bronchitis Exacerbations (GLOBE) study. This was a prospective double-blind, comparative, health-outcomes study that compared health resource utilization and clinical outcomes in patients randomized to receive the following: gemifloxacin group received either of 320 mg once daily for 5 days or 500 mg of clarithromycin twice daily for 7 days. Base-case analysis from the third-party payor perspective considered the costs of RTI/related medical care and treatment effectiveness was measured as the proportion of patients without recurrences requiring antimicrobial therapy following recovery form the initial exacerbation that required therapy. Societal costs included lost productivity. Data sources used included the outcomes study itself and standard US cost sources.

Gemifloxacin therapy resulted in significantly more patients without exacerbation recurrences requiring antimicrobial therapy after 26 weeks when compared with clarithromycin (73.8 vs. 63.8%; $p = 0.024$) and fewer patients receiving gemifloxacin (five out of 214) were hospitalized than those receiving clarithromycin (14 out of 224) ($p = 0.059$). In addition, fewer patients receiving gemifloxacin (8.3 days) had less time off from usual activities than those receiving clarithromycin (10.1 days). The direct cost per patient (mean) was $247.00 versus 374.00 for gemifloxacin versus clarithromycin-treated patients, respectively: mean direct plus indirect costs $1413 versus 1742, respectively, suggesting that gemifloxacin dominated clarithromycin in cost–effective analysis. Finally, the data suggested that from a payor's perspective, gemifloxacin was (over the study period) more clinically effective and cost–effective than clarithromycin, and the authors concluded that for AECB, gemifloxacin was more cost effective and improved AECB outcomes than was clarithromycin.

In addition to this exhaustive analysis of gemifloxacin in ambulatory AECB, the drug has also been compared with intravenous ceftriaxone in both hospitalized AECB and CAP patients. Indeed, the latter patients could also receive a macrolide in addition to the standard intravenous β-lactam. In both studies, oral gemifloxacin was at least as effective and superior by certain end points to the 'gold-standard' therapy [72,73]. Wilson and colleagues compared 5 days of oral gemifloxacin with sequential intravenous to oral therapy with ceftriaxone/cefuroxime for a maximum of 10 days for the treatment of hospitalized patients with acute exacerbations of chronic bronchitis [85]. While a cost analysis of therapy was not included in this report, the authors reported that the median time to hospital discharge in gemifloxacin-treated patients was 9 days versus 11 for those receiving ceftriaxone/cefuroxime ($p < 0.04$), suggesting a range of marked savings associated with the shorter course of an oral agent.

In the CAP study, oral gemifloxacin was shown to be superior in clinical outcomes at the ITT follow-up assessment. It is well accepted that oral therapy is preferred over parenteral agents due to cost-acquisition savings, no administration or giving costs, easier for the nursing and medical staff to oversee and control and significantly lower injection-site adverse events, such as phlebitis. Oral gemifloxacin has been shown to be as effective as the intravenous best-practice choice and will carry significant cost savings.

Furthermore, it has been suggested that the knowledge that an oral drug that can achieve these results may also enable physicians to initiate therapy within 4 h of diagnosis, a new quality marker for best practice in CAP to improve patient outcomes.

The direct effect of an antibiotic on the patient's daily well being has also been assessed within one of these studies. Spencer and colleagues investigated the time course of recovery of health status following an infective exacerbation of chronic bronchitis by studying patients enrolled in a with clarithromycin in

Table 4. Outcomes from clinical trials of gemifloxacin in lower respiratory tract infections (statistically significant observations favoring gemifloxacin).

Community-acquired pneumonia		
Comparator	***Outcome***	***Ref.***
Trovafloxacin (200 mg q.d. 7–14 days)	Clinical success ITT Radiological success ITT	[73]
Coamoxicilin–clavulanic acid (1000/125 g t.i.d. 7–10 days)	Lower withdrawal rate due to poor efficacy in ITT	[74]
AECB		
Trovafloxacin (200 mg q.d 5 days)	Clinical success at follow up = long term follow up in ITT	[84]
Clarithromycin (500 mg b.i.d 7 days)	Superior bacteriological eradication Fewer recurrences after 6 months Fewer RTI related hospitalizations	[81]
Levofloxacin (500 mg q.d 7 days)	Superior clinical success at long term follow up	[82]
Ceftriaxone (1 mg q.d 7–10 days)	Clinical success at follow up in ITT Shorter hospitalization (9 versus 11days, p = 0.04)	[85]

All other outcomes were noninferior. Gemifloxacin dosed at 320 mg q.d. for 5 days AECB or 7 days community-acquired pneumonia.
AECB: Acute exacerbation of chronic bronchitis; b.i.d: Twice daily; ITT: Intent to treat; q.d: Once daily; t.i.d: Three-times daily.

patients with acute infectious exacerbations of chronic bronchitis [7]. Patients were followed and evaluated using the St Georges Respiratory Questionnaire (SGRQ) at baseline and after 4, 12 and 26 weeks. The time course for recovery (12–26 weeks) appeared to occur in two phases: a fast improvement over the first 4 weeks, followed by a slower phase that occurred over several months and the level of improvement was thought to be large, provided that the patient remained free from further exacerbations. Additional exacerbations within 6 months impacted significantly on the time to recovery such that differences in SGRQ scores between patients with or without additional exacerbations was both clinically and statistically significant after 4 weeks and continued to widen such that at 6 months was more than twice what was required for a clinically significant difference. Data from this study clearly suggest that prolonging the disease-free interval has a profound effect on health status and that any treatments that can reduce exacerbation frequency could have a significant impact on health status.

In clinical trials investigating gemifloxacin for the therapy of patients with CAP and acute infectious exacerbations of chronic bronchitis, clinical and bacteriologic outcomes were equivalent to those observed with comparator agents and, by some end points, statistically superior in favor of gemifloxacin. For patients with AECB, gemifloxacin-treated patients had lower recurrences, lower hospitalization rates and lower costs (both direct and indirect). The various superiority outcomes are shown in Table 4.

Expert opinion

In the face of growing antibiotic resistance among respiratory pathogens and escalating healthcare costs, gemifloxacin was designed to be an enhanced affinity fluoroquinolone with high *in vitro* potency against pathogens associated with community-acquired lower RTIs to provide a high degree of efficacy and low potential for resistance selection. Specifically, gemifloxacin has the lowest MIC values against *S. pneumoniae* (MIC_{90} 0.03–0.06 µg/ml) isolates and the these are not influenced by pneumococcal resistance to nonfluoroquinolone antimicrobial agents. In today's environment, of increasing resistance rates of key respiratory pathogens, an appropriate antimicrobial agent is one that has the 'appropriate empiric' spectrum of activity, be shown to be highly efficacious in clinical trials and be active against pathogens that are resistant to currently available antimicrobial agents, such as multiply drug-resistant *S. aureus* and fluoroquinolone-resistant *S. pneumoniae*. Additionally, an oral administered agent which is at best equal to or in some end points superior to current intravenous standards should confer a range of health economic outcomes benefits.

Outlook

If prescribers do not adjust their ingrained habits, then rates of morbidity, hospital admission, lower productivity and possibly mortality will all probably increase. The past 10 years has seen exponential increases in antimicrobial resistance – often co- or crossresistance in particularly virulent species. Thus, it is timely to review and change how we prescribe antibiotics. It is not merely enough to give a course of 'old and inexpensive' drugs to keep the patient happy, it is essential that the societal cost of such actions is now reckoned and a different approach taken. There is no such thing as a 'benign antibiotic' as

all compounds are associated with beneficial or potentially harmful consequences. The silo mentality of many prescribers and health-care providers does not recognize the impending and growing issue of antibiotic resistance. Attempting management once antimicrobial resistance has become a nonreversible reality may not be the best approach: rather, resistance prevention in an attempt to delay or minimize the escalation of resistance is worthy of consideration, given that existing strategies have had a minimal impact on resistance prevention. Some conventional thinking suggests that the appropriate use of more potent agents will, not only lead to good or better clinical outcomes, but can also slow or possibly reverse the emergence of resistance. As long as the patient is not harmed, this approach can be cost effective in the long term as there will be fewer callbacks, office revisits and hospital admissions. We must think of the 'bigger picture' while we wait for academia, the pharmaceutical industry and government bodies to agree on the best strategy for the development and approval of new antibiotics.

Highlights

- Growing bacterial resistance requires new approaches in the light of few novel agents, application of mutant-prevention concentrations and use of more potent drugs can help slow down the emergence of resistance.
- More potent drugs are as well tolerated and safe as older agents.
- Gemifloxacin is among the most potent drugs against today's resistant respiratory pathogens and may provide benefits in addition to expected clinical and microbiologic outcomes.

Bibliography

1. File TM Jr, Iannini PB. A profile of gemifloxacin, a new respiratory fluoroquinolone. *Today's Ther. Trends* 21, 415–435 (2003).
2. Minino AM, Arias E, Kochanek KD *et al.* Deaths: final data for 2000. *Natl Vital Stat. Rep.* 50, (2002).
3. Mannino DM, Homa DM, Akinbami LJ *et al.* Chronic obstructive pulmonary disease surveillance – USA, 1971–2000. *Respir. Care* 47, 1184–1189 (2002).
4. Hall MJ, Owings MF. Advanced data from vital and health statistics. In: *2000 National Hospital Discharge Survey.* National Center for Health Statistics, MD, USA 1–18 (2002).
5. Niederman MS, McCombs JS, Unger AN *et al.* The cost of treating community-acquired pneumonia. *Clin. Ther.* 20, 820–837 (1998).
6. Niederman MS, McCombs JS, Unger AN *et al.* Treatment cost of acute exacerbations of chronic bronchitis. *Clin. Ther.* 21, 576–591 (1999).
7. Spencer S, Jones PW, GLOBE Study Group: Time course of recovery of health status following an infective exacerbation of chronic bronchitis. *Thorax* 58, 589–593 (2003).
8. Kupronis BA, Richards Jr. CL, Whitney CG and the Active Bacterial Core Surveillance Team. Invasive pneumococcal disease in older adults residing in long-term care facilities and in the community. *J. Am. Geriatr. Soc.* 51, 1520–1525 (2003).
9. O'Brien JA, Patrick AR, Caro JJ. Community-acquired pneumonia: costs of managing CAP are double for elderly patients. *Drug Benefit Trends* 32–47 (2003).
10. Loeb M. Pneumonia in older persons. *Clin. Infect. Dis.* 37, 1335–1339 (2003).
11. Pneumonia and influenza death rates: United States, 1979–1994. *MMWR Morbid. Mortal. Wkly Rep.* 44, 535–537 (1995).
12. Jokinen C, Heiskanen L, Jouvonen H *et al.* Microbial etiology of community-acquired pneumonia in the adultu population of 4 municipalities in eastern Finland. *Clin. Infect. Dis.* 32, 1141–1154 (2001).
13. Ruiz M, Ewig S, Marcos M *et al.* Etiology of community-acquired pneumonia: impact of age, comorbidity and severity. *Am. J. Resp. Clin. Care Med.* 160, 397–405 (1999).
14. Farr BM, Woodhead MA, MacFarlane JT *et al.* Risk factors for community-acquired pneumonia diagnosed by general practitioners in the community. *Resp. Med.* 94, 422–427 (2000).
15. Robinson KA, Baughman W, Rothrock G *et al.* Epidemiology of invasive *Streptococcus pneumoniae* infections in the United States. *J. Am. Med. Assoc.* 285, 1729–1735 (2001).
16. Whitney CG, Farley MM, Hadler J *et al.* Increasing prevalence of multidrug resistant *Streptococcus pneumoniae*. *N. Engl. J. Med.* 343, 1917–1924 (2000).
17. Felmingham D, Farrell DJ, Reinert R, Rene, Morrissey I. Antibacterial resistance among children with community-acquired respiratory tract infections (PROTEKT 1999–2000). *J. Infect.* 48, 39–55 (2004).
18. Doern GV, Brown SD. Antimicrobial susceptibility among community-acquired respiratory tract pathogens in the USA: data from PROTEKT US 2000–01. *J. Infect.* 48, 56–65 (2004).
19. Jacobs MR, Felmingham D, Appelbaum PC, Gruneberg RN, The Alexander Project Group: The Alexander Project 1998–2000: susceptibility of pathogens isolated from community-acquired respiratory tract infection to commonly used antimicrobial agents. *J. Antimicrob. Chemother.* 52, 229–246 (2003).
20. Ball P. Quinolone generations: natural history or natural selection? *J. Antimicrob. Chemother.* 46, 17–24 (2000).
21. Domagala J. Structure-activity and structure-side effect relationships for the quinolone antibacterials. *J. Antimicrob. Chemother.* 33, 685–706 (1994).
22. Garcia I, Pascual A, Ballesta S, Joyanes P, Perea EJ. Intracellular penetration and activity of gemifloxacin in human polymorphonuclear leukocytes. *Antimicrob. Agents Chemother.* 44, 3193–3195 (2000).
23. Blondeau JM, Missaghi B. Gemifloxacin: a new fluoroquinolone. *Expert opinion Pharmacother.* 5, 1117–1152 (2004).
24. King A, May J, French G, Phillips I. Comparative *in vitro* activity of gemifloxacin. *J. Antimicrob. Chemother.* 45, 1–12 (2000).
25. McCloskey L, Moore T, Niconovich N *et al.* *In vitro* activity of gemifloxacin against a broad range of recent clinical isolates from the USA. *J. Antimicrob. Chemother.* 45, 13–21 (2000).

26. Rittenhause S, McCloskey L, Broskey J et al. *In vitro* antibacterial activity of gemifloxacin and comparator compounds against common respiratory pathogens. *J. Antimicrob. Chemother.* 45, 23–27 (2000).
27. Duffy LB, Crabb D, Searcey K *et al.* Comparative potency of gemifloxacin, new quinolones, macrolides, tetracycline and clindamycin against *Mycoplasma* spp.. *J. Antimicrob. Chemother.* 43, 29–33 (2000).
28. Hammerschlag MR. Activity of gemifloxacin and other new quinolones against *Chlamydia pneumoniae*: a review. *J. Antimicrob. Chemother.* 45, 35–39 (2000).
29. Dubois J, Saint-Pierre C. Comparative *in vitro* activity and post-antibiotic effect of gemifloxacin against *Legionella* spp. *J. Antimicrob. Chemother.* 45, 41–46 (2000).
30. Mortensen JE, Rodgers GL. *In vitro* activity of gemifloxacin and other antimicrobial agents against isolates of *Bordetella pertussis* and *Bordetella parapertussis*. *J. Antimicrob. Chemother.* 45, 47–49 (2000).
31. Ieven M, Goossens W, De Wit S, Goossens H. *In vitro* activity of gemifloxacin compared with other antimicrobial agents against recent clinical isolates of streptococci. *J. Antimicrob. Chemother.* 45, 51–53 (2000).
32. Goldstein EJC. Review of the *in vitro* activity of gemifloxacin against Gram-positive and Gram-negative anaerobic pathogens. *J. Antimicrob. Chemother.* 45, 55–65 (2000).
33. Jones RN, Deshpande LM, Erwin M *et al.* Antigonococcal activity of gemifloxacin against fluoroquinolone-resistant strains and a comparison of agar dilution and E-test methods. *J. Antimicrob. Chemother.* 45, 67–70 (2000).
34. Blondeau JM, Hansen G, Borsos S, Irvine L, Blanco L. *In vitro* susceptibility of 4903 bacterial isolates of gemifloxcin - an advanced fluoroquinolone. *Int. J. Antimicrob. Agents* 9, 44–49 (2003).
35. Allen A, Bygate E, Clark D, Lewis A, Pay V. The effect of food on the bioavailability of oral gemifloxacin in healthy volunteers. *Int. J. Antimicrob. Agents* 16, 45–50 (2000).
36. Allen A, Bygate E, Faessel H, Isaac L, Lewis A. The effect of ferrous sulfate and sucralfate on the bioavailability of oral gemifloxacin in healthy volunteers. *Int. J. Antimicrob. Agents* 15, 283–289 (2000).
37. Vousden M, Allen A, Lewis A *et al.* Lack of pharmacokinetic interaction between gemifloxacin and digoxin in healthy elderly volunteers. *Chemother. Basel* 45, 485–490 (1999).
38. Allen A, Vousden M, Porter A, Lewis A. Effect of Maalox on the bioavailability of oral gemifloxacin in healthy volunteers. *Chemotherapy* 45, 504–522 (1999).
39. Davy M, Allen A, Bird N, Rost KL, Fuder H. Lack of effect of gemifloxacin on the steady-state pharmacokinetics of theophylline in healthy volunteers. *Chemotherapy* 45, 478–484 (1999).
40. Gemifloxacin (FACTIVE), prescribing information. Oscient Pharmaceuticals, MA, USA (2004).
41. Seo SM, Lee SH, Choi YJ *et al.* Pharmacokinetics of LB20304, a new fluoroquinolone in rats and dogs. *Arch. Pharmacol. Res.* 19, 359–367 (1996).
42. Drusano GL, Preston SL, Owens RC, Jr., Ambrose PG. Fluoroquinolone pharmacodynamics (Correspondence). *Clin. Infect. Dis.* 33, 2091–2092 (2001).
43. Schentag JJ, Gilliland KK, Paladino JA. Fluoroquinolone Pharmacodynamics (Reply). *Clin. Infect. Dis.* 33, 2092–2096 (2001).
44. Schentag JJ, Gilliland KK, Paladino JA. What have we learned from pharmacokinetic and pharmacodynamic theories? *Clin. Infect. Dis.* 32, S39–S46 (2001).
45. Wise R. Protein binding of β-lactams; the effects on activity and pharmacology, particularly tissue penetration, part I. *J. Antimicrob. Chemother.* 12, 1–18 (1983).
46. Wise R. Protein binding of beta-lactams: the effects on activity and pharmacology, particularly tissue penetration, part II. *J. Antimicrob. Chemother.* 12, 105–118 (1983b).
47. Gee T, Andrews JM, Ashby JP, Marshall G, Wise R. Pharmacokinetics and tissue penetration of gemifloxacin following a single oral dose. *J. Antimicrob. Chemother.* 47, 431–434 (2001).
48. Moore T, Kershner K, Donald B *et al.* Post-antibiotic effect (PAE) of gemifloxacin (SP-265805) and ciprofloxacin against Gram-positive and Gram-negative organisms. *39th Interscience Conference on Antimicrobial Agents and Chemotherapy* CA, USA (1999).
49. MacKenzie H, Forward K, de Azavedo J *et al.* Post-antibiotic effect (PAE) of gemifloxacin (SB-265805) in *S. pneumoniae* with diminished susceptibility to ciprofloxacin., in *39th Interscience Conference on Antimicrobial Agents and Chemotherapy* CA, USA (1999).
50. Blondeau JM, Hansen G, Metzler KL, Hedlin P. The role of PK/PD parameters to avoid selection and increase of resistance: mutant prevention concentration. *J. Chemother.* 16, 1–19 (2004).
51. Heaton VJ, Ambler J, Fisher LM. Potent antipneumococcal activity of gemifloxacin is associated with dual targeting of gyrase and topoisomerase IV, an *in vivo* target preference for gyrase, and enhanced stabilization of cleavable complexes *in vitro*. *Antimicrob. Agents Chemother.* 44, 3112–3117 (2000).
52. Hooper DC. Mechanisms of fluoroquinolone resistance. *Drug Resist. Updates* 2, 38–55 (1999).
53. Fisher LM, Gould KA, Pan X-S, Patel S, Heaton VJ. Analysis of dual active fluoroquinolones in *Streptococcus pneumoniae*. *J. Antimicrob. Chemother.* 52, 312–316 (2003).
54. Gillespie SH, Voelker LL, Dickens A. Evolutionary barriers to quinolone resistance in *Streptococcus pneumoniae*. *Microb. Drug Resist.* 8, 79–84 (2002).
55. Chen DK, McGeer A, De Azavedo J, Low DE, The Canadian Bacterial Surveillance Network: Decreased susceptibility of *Streptococcus pneumoniae* to fluoroquinolones in Canada. *N. Engl. J. Med.* 341, 233–239. (1999).
56. Perez-Trallero E, Garcia-Rey C, Martin-Sanchez AM, Aguilar L, Garcia-de-Lomas J, Ruiz J, Spanish Surveillance Group for Respiratory Pathogens S. Activities of six different quinolones against clinical respiratory isolates of *Streptococcus pneumoniae* with reduced susceptibility to ciprofloxacin in Spain. *Antimicrob. Agents Chemother.* 46, 2665–2667 (2002).
57. Rittenhause S, Donald B, Niconovich N *et al.* Effect of gemifloxacin and comparator quinolones on the development of *in vitro* bacterial resistance. *21st International Congress of Chemotherapy* Birmingham, UK (1999).
58. Dong Y, Zhao X, Domagala J, Drlica K. Effect of fluoroquinolone concentration on selection of resistant mutants of *Mycobacterium bovis* BCG and *Staphylococcus aureus*. *Antimicrob. Agents Chemother.* 43, 1756–1758 (1999).
59. Blondeau J, Zhao X, Hansen GT, Drlica K. Mutant prevention concentrations (MPC) for fluoroquinolones with clinical isolates of *Streptococcus pneumoniae*. *Antimicrob. Agents Chemother.* 45, 433–438 (2001).

60. Bingen E, Lambert-Zechovsky N, Mariani-Kurkdjian P *et al*. Bacterial counts in cerebrospinal fluid of children with meningitis. *Eur.J. Clin.Microbiol. Infect. Dis.* 9, 278–281. (1990).
61. Feldman W. Concentrations of bacteria in cerebrospinal fluid of patients with bacterial meningitis. *J. Pediatr.* 88, 549–552 (1976).
62. Mitchison DA. Drug resistance in mycobacteria. *Br. J. Bull.* 50, 84–90 (1984).
63. Frisch AW, Tripp JT, Barrett Jr. CD, Pidgeon BE. Specific polysaccaride content of pneumonic lungs. *J. Exp. Med.* 76, 505–510 (1942).
64. Berry V, Page R, Satterfield J, Singley C, Straub R, Woodnutt G. Comparative *in vivo* activity of gemifloxacin in a rat model of respiratory tract infection. *J. Antimicrob. Chemother.* 45, 79–85 (2000).
65. Berry V, Page R, Satterfield J, Singley C, Straub R, Woodnutt G. Comparative efficacy of gemifloxacin in experimental models of pyelonephritis and wound infection. *J. Antimicrob. Chemother.* 45, 87–93 (2000).
66. Edelstein PH, Shinzato T, Doyle E, Edelstein MA. *In vitro* activity of gemifloxacin (SB-265805, LB20304a) against *Legionella pneumophila* and its pharmacokinetics in guinea-pigs with *L. pneumophila* pneumonia. *Antimicrob. Agents Chemother.* 45, 2204–2209 (2001).
67. Cottagnoud P, Acosta F, Cottagnoud M, Tauber MG. Gemifloxacin is efficacious against penicillin-resistant and quinolone-resistasnt pneumococci in experimental meningitis. *Antimicrob. Agents Chemother.* 46, 1607–1609 (2002).
68. Smirnov A, Wellmer A, Gerber J, Maier K, Henne S, Nau R. Gemifloxacin is effective in experimental pneumococcal meningitis. *Antimicrob. Agents Chemother.* 44, 767–770 (2000).
69. Mandell LA, Bartlett JG, Dowell SF, File Jr. TM, Musher DM. Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. *Clin. Infect. Dis.* 37, 1405–1433 (2003).
70. Balter MS, La Forge J, Low DE, Mandell LA, Grossman RF, Chronic Bronchitis Working Group: Canadian guidelines for the management of acute exacerbations of chronic bronchitis. *Can. Respir. J.* 10, 3B–32B (2003).
71. Ball P, File Jr. TM, Twynholm M, Henkel T, 061 Study Group: Efficacy and safety of gemifloxacin 320 mg once-daily for 7 days in the treatment of adult lower respiratory tract infections. *Int. J. Antimicrob. Agents* 18, 19–27 (2001).
72. Lode H, File Jr. TM, Mandell LA, Ball P, Pypstra R, Thomas M, 185 Gemifloxacin Study Group: Oral gemifloxacin versus sequential therapy with intravenous ceftriaxone/oral cefuroxime with or without a macrolide in the treatment of patients hospitalized with community-acquired pneumonia: a randomized, open-label, multicenter study of clinical efficacy and tolerability. *Clin. Ther.* 24, 1915–1936 (2002).
73. File Jr. TM, Schlemmer B, Garau J, Cupo M, Young C, 049 Clinical Study Group. Efficacy and safety of gemifloxacin in the treatment of community-acquired pneumonia: a randomized, double-blind comparison with trovafloxacin. *J. Antimicrob. Chemother.* 48, 67–74 (2001).
74. Leophonte P, File Jr. TM, Feldman C. Gemifloxacin once daily for 7 days compared to amoxicillin/clavulanic acid thrice daily for 10 days for the treatment of community-acquired pneumonia of suspected pneumococcal origin. *Resp. Med.* 98, 708–720 (2004).
75. Ho PL, Que TL, Tsang DN, Ng TK, Chow KH, Seto WH. Emergence of fluoroquinolone resistance among multiple resistant strains of *Streptococcus pneumoniae* in Hong Kong. *Antimicrob. Agents Chemother.* 43, 1310–1313 (1999).
76. Linares J, de la Campa AG, Pallares R. Fluoroquinolone resistance in *Streptococcus pneumoniae. N. Engl. J. Med.* 341, 1546–1547. (1999).
77. Drlica K. Mechanism of fluoroquinolone action. *Curr. Opin. Microbiol.* 2, 504–508 (1999).
78. Davidson RJ, Cavalcanti R, Brunton JL *et al*. Resistance to levofloxacin and failure of treatment of pneumococcal pneumonia. *N. Engl. J. Med.* 346, 747–750 (2002).
79. Anderson KB, Tan JS, File Jr. TM, DiPersio JR, Willey BM, Low DE. Emergence of levofloxacin-resistant pneumococci in immunocompromised adults after therapy for community-acquired pneumonia. *Clin. Infect. Dis.* 37, 376–381 (2003).
80. Davies TA, Kelly LM, Pankuch GA, Credito KL, Jacobs MR, Appelbaum PC. Antipneumococcal activities of gemifloxacin compared with those of nine other agents. *Antimicrob. Agents Chemother.* 44, 304–310 (2000).
81. Wilson R, Schentag JJ, Ball P, Mandell LA, 068 Study Group. A comparison of gemifloxacin and clarithromycin in acute exacerbations of chronic bronchitis and long-term clinical outcomes. *Clin. Ther.* 24, 639–652 (2002).
82. Sethi S, Fogarty C, Fulambarker A. A randomized, double-blind study comparing 5 days oral gemifloxacin with 7 days' oral levofloxacin in patients with acute exacerbation of chronic bronchitis. *Resp. Med.* 98, 697–707 (2004).
83. File Jr. TM, Sclemmer B, Garau J, Lode H, Lynch S, Young C, 070 Clinical Study Group. Gemifloxacin versus amoxicillin/clavulanate in the treatment of acute exacerbations of chronic bronchitis. *J. Chemother.* 12, 314–325 (2000).
84. Ball P, Wilson R, Mandell LA, Brown J, Henkel T, 069 Clinical Study Group. Efficacy of gemifloxacin in acute exacerbations of chronic bronchitis: a randomized, double-blind comparison with trovafloxacin. *J. Chemother.* 13, 288–298 (2001).
85. Wilson R, Langan C, Ball P, Bateman K, Pypstra R, Gemifloxacin 207 Clinical Study Group: Oral gemifloxacin once daily for 5 days compared with sequential therapy with intravenous ceftriaxone/oral cefuroxime (maximum of 10 days) in the treatment of hospitalized patients with acute exacerbations of chronic bronchitis. *Resp. Med.* 97, 242–249 (2003).
86. Vousden M, Ferguson J, Richards JG *et al*. Evaluation of phototoxic potential of gemifloxacin in healthy volunteers compared with ciprofloxacin. *Chemother. Basel* 45, 512–520 (1999).
87. Ball P. Adverse drug reactions: implications for the development of fluoroquinolones. *J. Antimicrob. Chemother.* 51, 21–27 (2003).
88. Birnbaum HG, Morley M, Greenberg PE, Colice GL. Economic burden of respiratory infections in an employed population. *Chest* 122, 603–611 (2002).
89. Halpern MT, Palmer CS, Zodet M, Kirsch J. Cost-effectiveness of gemifloxacin: results from the GLOBE Study. *Am J. Health Syst. Pharm.* 59, 1357–1365 (2002).

Affiliations

Gary Patou
Oscient Pharmaceuticals,
Waltham, MA 02435, USA
Glenn Tillotson
Oscient Pharmaceuticals,
Waltham, MA 02435, USA

Joseph Blondeau
University of Saskatchewan,
Royal University Hospital and the
Saskatoon Health Region and the
Departments of Microbiology and
Immunology and Pathology, 103 Hospital Drive,
Saskatoon, Saskatchewan, S7N 0W8, Canada
Tel.: +1 306 655 6943
Fax: +1 306 655 6947
joseph.blondeau@saskatoonhealthregion.ca