Respiratory Medicine (2004) **98**, 708–720

respiratoryMEDICINE

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

P. Léophonte[a,*], T. File[b,c], C. Feldman[d]

[a]*Hôpital Larrey, TSA 30300; 24 Chemin de Pouvourville; 31059 Toulouse, Cedex 9, France*
[b]*Northeastern Ohio Universities College of Medicine, Rootstown, OH, USA*
[c]*Summa Health System, 75 Arch Street, Suite 105, Akron, OH 44304, USA*
[d]*Department of Medicine, Division of Pulmonology, Johannesburg Hospital and University of the Witwatersrand, Johannesburg, South Africa*

Received 13 February 2004; accepted 15 April 2004

KEYWORDS
Community-acquired pneumonia;
Pneumococcal pneumonia;
Gemifloxacin;
Fluoroquinolone

Summary *Context*: Community-acquired pneumonia (CAP) is common among adults and contributes considerably to morbidity and mortality.

Objective: To compare the safety and efficacy of gemifloxacin to high-dose amoxicillin/clavulanate for the treatment of CAP of suspected pneumococcal origin.

Design: Randomized, multicentre, double-blind, double-dummy, parallel group Phase III study.

Setting and participants: From September 1998 to July 1999, 324 patients with CAP were randomized at 102 centers in France, Poland and the Republic of South Africa.

Intervention: Patients were double-blind randomized to receive either oral gemifloxacin 320 mg once daily for 7 days or oral amoxicillin/clavulanate 1 g/125 mg three times daily for 10 days.

Main outcome measures: The main outcome measures were clinical, bacteriological, and radiological responses at the end of therapy (day 12–14) and follow-up (day 24–30) visits.

Results: In 228 PP patients, clinical resolution at follow-up was 88.7% for 7-day gemifloxacin and 87.6% for 10-day amoxicillin/clavulanate [95% CI, −7.3, 9.5]. In 249 PP patients, clinical resolution at end of therapy was 95.3% for 7-day gemifloxacin vs. 90.1% for 10-day amoxicillin/clavulanate [95% CI, −1.2, 11.7]. Bacteriologic response rates for the PP patients at end of therapy were 96.3% for 7-day gemifloxacin and 91.8% for the amoxicillin/clavulanate group [95% CI, −4.7, 13.6]. Bacteriologic response rates at follow-up were 87.2% for 7-day gemifloxacin and 89.1% for the amoxicillin/clavulanate group [95% CI, −15.0, 11.2]. Specifically gemifloxacin eradicated 95.7% of *Streptococcus pneumoniae* including penicillin and macrolide resistant strains. Radiological response rates for the PP patients at end of therapy were 89.1% for 7-day gemifloxacin and 87.6% for the amoxicillin/clavulanate group. The most frequently reported drug-related events were in the gemifloxacin

*Corresponding author. Tel.: +39-0567771832.
E-mail address: leophonte.p@chu-toulouse.fr (P. Léophonte).

0954-6111/$ - see front matter
doi:10.1016/j.rmed.2004.04.007

group, diarrhea (6.0%) and rash (3.0%) and in the amoxicillin/clavulanate group, diarrhea (11.1%) and fungal infection, vaginitis and vomiting (each 2.0%). Overall there were statistically fewer withdrawals due to lack of therapeutic effect in the gemifloxacin group compared with the amoxicillin/clavulanate cohort, (95% CI, −8.8;0.6; $P = 0.03$).

Conclusion: Gemifloxacin 320 mg once daily for 7 days was found to be clinically, bacteriologically, and radiologically as effective as 10 days of amoxicillin/clavulanate 1 g/125 mg three times daily for the treatment of suspected pneumococcal CAP.

Introduction

Community-acquired pneumonia (CAP) remains an important disease and severe CAP has been shown to be associated with considerable morbidity, mainly as hospitalization and mortality, particularly among the elderly and those with co-morbidities.[1,2] For this reason, early diagnosis and early empiric antimicrobial therapy are essential to the effective management of CAP. A diagnosis of CAP is based on signs and symptoms such as fever, increased cough, dyspnoea, rapid respiratory rate and sputum production, as well as clinical signs of consolidation demonstrated by radiological evidence.

The most common bacterial causes of CAP are *Streptococcus pneumoniae*, and atypical pathogens, such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Legionella* species, in addition to a mixed etiology in up to 30% of infections.[3–6] The changing susceptibility patterns of these pathogens, in particular that of *S. pneumoniae*, have raised concerns about the efficacy of currently available therapies and have prompted the development and evaluation of new agents. Penicillin-resistant strains of *S. pneumoniae* have been identified world-wide,[7] and resistance to other antibacterials such as cephalosporins and macrolides is high among isolates of *S. pneumoniae* expressing high-level penicillin resistance.[8,9] Accordingly, the specific recognition and treatment of CAP caused by *S. pneumoniae* has become increasingly important.

Many currently available antimicrobials must be given more than once a day, which can lead to compliance issues.[10] The need for a convenient, shorter course, once-daily agent with broad-spectrum activity is thus apparent.

Gemifloxacin is a new quinolone antibacterial agent with such a broad spectrum of antibacterial activity. It has excellent activity against both Gram-positive and Gram-negative organisms, including potent antibacterial activity against *Streptococcus* species (spp) and methicillin-susceptible *Staphylococcus* spp. In vitro studies using clinical isolates have shown gemifloxacin to be highly active against penicillin- and macrolide-resistant strains of *S. pneumoniae*. In contrast to other reference quinolones gemifloxacin, due to its dual mode of action, retained good activity against clinical isolates of *S. pneumoniae* that were resistant to other members of the quinolone class.[11] Gemifloxacin acts by the simultaneous inhibition of both bacterial DNA gyrase and DNA Topoisomerase IV at therapeutically achievable tissue concentrations, thereby interfering with bacterial DNA replication.[11] Gemifloxacin has also demonstrated excellent activity against β-lactamase-producing and macrolide-resistant isolates of *Haemophilus influenzae* in addition to all the respiratory atypical pathogens.

Based on the in vitro activity of gemifloxacin against respiratory pathogens and its pharmacokinetic profile,[11] a dose of 320 mg once daily provides serum levels for adequate bactericidal activity for patients with CAP. Hence, the purpose of the current study was to assess the clinical, bacteriological, and radiological efficacy of gemifloxacin 320 mg once daily for seven days with that of amoxicillin/clavulanate 1 g/125 mg three times daily for 10 days in the treatment of CAP of suspected pneumococcal origin. The rationale for comparing gemifloxacin to 1 g amoxicillin in a fixed combination was that the study was conducted primarily in France where there is a high rate of penicillin-resistant *S. pneumoniae*. This dosing of β-lactam is currently approved by the French authorities and would ensure that the comparator agent was not at a disadvantage during the study. The relative safety and tolerability of these two agents were also compared.

Methods

Study design

This was a double-blind, randomized, active controlled, parallel-group trial designed to compare

gemifloxacin using a 7-day regimen to 10-day amoxicillin/clavulanate in the treatment of CAP of suspected pneumococcal origin. The trial format was conducted according to the guidelines described by the Committee on the Consolidation of Standards for Reporting Trials.[12]

Study population

Patients eligible for inclusion in the study were 18 years or older with a clinical diagnosis of community-acquired bacterial pneumonia characterized by fever and at least two of the following signs and symptoms: new or increased cough, purulent sputum or a change in sputum characteristics, rales and/or evidence of pulmonary consolidation, or dyspnoea.

In order to be eligible for study participation, the patient must have had a chest radiograph showing the presence of new or progressive infiltrate(s), consolidation, or pleural effusion consistent with pneumonia. In addition, the pneumonia was to be of suspected pneumococcal origin based on at least two of the following: sudden onset (i.e. <48 h), chills, pleuritic chest pain, localized alveolar consolidation on chest radiograph, or Gram-positive cocci on respiratory sample smear on direct examination. Patients were excluded for the following reasons: allergy or severe adverse reactions to carboxyquinolone derivatives or penicillin or other beta-lactam derivatives; pregnancy or lactating; history of tendonitis while taking fluoroquinolones; phenylketonuria or sensitivity to aspartame; severe respiratory tract infections requiring parenteral antimicrobial therapy; pre-therapy chest radiograph negative for chest infiltrates, or inconsistent with a CAP diagnosis; patients with hospital-acquired or aspiration pneumonia; patients with localized bronchial obstruction or a history of post-obstructive pneumonia; patients with cystic fibrosis, active tuberculosis, bronchiectasis, or active pulmonary malignancies or any other complicating infection or disease that would compromise treatment evaluation of the study medication; evidence of significant liver or renal impairment; or needed a concomitant antibacterial agent with a spectrum of activity similar to the study drugs. Prospective patients were also excluded if they were HIV positive or otherwise immunocompromised, if they were taking concomitant sucralfate, probenecid or systemic steroids; or received previous therapy with a systemic antibiotic for more than 24 h prior to enrollment. The study was approved by each investigator's institutional review board and all patients gave written informed consent prior to enrollment.

Study drugs and laboratory assessments

Patients were randomized in blinded fashion at the first visit in a 1:1 ratio to gemifloxacin 320 mg once daily for 7 days or amoxicillin/clavulanate 1 g/125 mg three times daily for 10 days. Following random assignment to treatment and to preserve the study blind, patients received both active and dummy tablets and sachets as indicated:

Treatment Group A: Oral gemifloxacin 320 mg once daily for 7 days and oral amoxicillin/clavulanate-placebo three times daily for 10 days.

Treatment Group B: Oral amoxicillin/clavulanate 1 g/125 mg three times daily for 10 days and oral gemifloxacin-placebo once daily for 7 days.

At the end of therapy, each patient was questioned regarding the number of tablets and sachets taken during the study in order to document patient compliance.

Standardized clinical assessment and bacteriologic evaluation (Gram stain and sputum culture) were performed pre-therapy, during therapy (day 2–4), at the end of therapy visit (days 12–14) and at the follow-up visit (days 24–30). Blood cultures for bacteriological evaluation were taken at screening, prior to the first dose of study medication and at follow-up (day 24–30). Acute and convalescent phase serological tests for atypical pathogens *C. pneumoniae* [MIF; MRL Diagnostics, California, USA] *Legionella pneumophila* [IFA, Zeus Scientific Inc. Raritan, NJ, USA] "definite" a 4-fold increase in IgG titers to $>1:256$; "possible" a single IgG titer of $>1:512$ or specific IgM anti-Chlamydia $>1:16$. *Coxiella burnetii* [IFA, MRL Diagnostics, California, USA], "definite", a four-fold increase in phase II IgG titers or a single phase II IgM titer of $>1:80$ and, *M. pneumoniae* [ELISA,CTLLAB,California, USA] "possible", detection of IgM and were conducted by the central laboratory, as was an assay for *L. pneumophila* sero-group 1 antigen using urine samples collected from the patients prior to the first dose of study medication (day 0). Susceptibility testing was performed according to NCCLS guidelines.[13,14] *Haemophilus* spp. and *M. catarrhalis* also were tested for beta-lactamase production. *S. pneumoniae* was tested for penicillin susceptibility, either by oxacillin disk or by penicillin *E*-test strip. ECGs were performed prior to initiation of study drug therapy and once during therapy on day 2–4.

Two populations were evaluated in this trial patients for whom drug efficacy could be evaluated

(per protocol (PP) population; see below) and all randomized patients who received study drug (intent-to-treat (ITT) population) for drug safety evaluation. Two additional populations were also defined: Bacteriologic PP and Bacteriologic ITT, which represented patients in the PP and ITT populations who also had a pre-therapy pathogen identified (some by isolation and some, atypicals, by serological methods).

Efficacy/safety measurements

The primary objective of this study was to demonstrate the non-inferiority of gemifloxacin relative to amoxicillin/clavulanate with respect to clinical response and safety at follow-up. Secondary objectives were to compare gemifloxacin and amoxicillin/clavulanate with respect to clinical response at end of therapy, bacteriologic response at end of therapy and follow-up, and radiological response at end of therapy and follow-up. The end points were radiological, bacteriologic and clinical response at the end of therapy (days 12–14) and at follow-up (days 24–30).

Clinical response was based on serial examinations of the patient using objective signs of auscultatory findings (rales, rhonchi, wheezing, breath sounds and subjective symptoms). At the end of therapy, clinical response was graded as *Clinical Success* (sufficient improvement or resolution of the signs and symptoms of CAP recorded at baseline such that no additional antibacterial therapy was required for CAP), *Clinical Failure* (insufficient improvement or deterioration of signs and symptoms of CAP such that additional antibacterial therapy was required for CAP), or *Unable to Determine* (clinical assessment was not possible to determine for any reason). The clinical response at the follow-up visit was reported as: *Follow-up Clinical Success* (sufficient improvement or resolution of signs and symptoms of CAP for patients who were clinical successes at the end of therapy visit, such that no additional antibacterial therapy was required for CAP), *Clinical Recurrence* (reappearance of signs and symptoms of CAP for patients who were clinical successes at the end of therapy, such that additional antibacterial therapy was required for CAP), or *Unable to Determine* (patients in whom a clinical assessment was not possible to determine).

Bacteriological response was based on the results of cultures taken before and after therapy. At the end of therapy, the bacteriological responses were graded as eradication, presumed eradication (if no material was available due to a clinical success), persistence, presumed persistence (no material was available in a patient considered a clinical failure), or indeterminate (if bacteriological response to the study drug was not evaluable for any reason). In addition, super-infection was defined as the presence of pathogen different from the pre-therapy organism in a symptomatic patient and requiring additional antimicrobial therapy. Colonization was defined as the presence of pathogen different from the pre-therapy organism in an asymptomatic patient and not requiring additional antimicrobial therapy. For patients with an end of therapy response of eradication or presumed eradication, follow-up bacteriologic eradication was defined as: follow-up eradication, follow-up presumed eradication, recurrence (original causative organism present), presumed recurrence (clinical recurrence but no follow-up sputum or respiratory sample) and unable to determine (not evaluable for any reason).

For *L. pneumophila*, only sputum/respiratory samples were considered as appropriate forms of culture. Respiratory samples collected by alternative methods (e.g. bronchoscopy with protected specimens [protected brush or telescopic plugged catheter], transtracheal aspiration, percutaneous lung or pleural fluid aspiration, or physiotherapy) were acceptable for other organisms. Patients were considered positive for this pathogen if *L. pneumophila* antigen was detected in urine or, if by serology, there was at least a four-fold rise in *L. pneumophila* antibody titre between screening and follow-up. For *M. pneumoniae*, *C. pneumoniae*, and *C. psittaci*, there were no possible sources of culture, i.e., only serology was used for identification, and the bacteriological outcome was presumed on the basis of clinical response. Patients were considered positive for this pathogen if *M. pneumoniae* IgM was detected by serology at screening and/or follow-up with an immune status ratio (ISR) $\geqslant$1.1, or *M. pneumoniae* IgG detected at follow-up with an ISR $\geqslant$1.1 and with a rise in *M. pneumoniae* IgG of $\geqslant$46% between screening and follow-up. Patients were considered positive for *C. pneumoniae* or *C. psittaci* if either were detected by serology and met one or more of the following criteria: there was at least a four-fold rise in *C. pneumoniae* or *C. psittaci* IgG titre between the screening and follow-up visits and/or there was a *C. pneumoniae* or *C. psittaci* IgM titre of $\geqslant$1:10 at screening and/or at the follow-up visit.

Radiological outcome was based on the investigator assessment of the posterior–anterior and lateral chest radiographs obtained at the end of therapy (day 12–14) and at follow-up (day 24–30) relative to those obtained at screening. The

outcome was reported as *Improved* (improvement or resolution of radiological signs of CAP), *Unchanged* (no improvement in the baseline radiological signs of CAP), *Worse* (worsening of baseline radiological signs of CAP or appearance of new radiological signs of CAP) or *Unable to Determine* (a valid assessment of radiological outcome could not be made [e.g. the patient was lost to follow-up]). The radiological response was then defined on the basis of the radiological outcome as *Success* (the derived radiological outcome was 'improved' or 'presumed improved'), *Failure* (the derived radiological outcome was 'unchanged' or 'worse'), or *Unable to Determine* (the derived radiological outcome was 'unable to determine').

All patients receiving at least one dose of study drug were evaluable for safety (intent-to-treat population). Safety was evaluated on the basis of physical examination findings, ECGs, adverse events, intercurrent illness and laboratory tests, including routine hematology, blood chemistry, and urinalysis tests. Investigators rated each adverse event subjectively according to relationship to study drug (probable, possible, remote, or none) and severity (mild, moderate, severe, or serious or life threatening).

Statistical analyses

The primary goal of the study was to determine whether gemifloxacin, given for 7 days was non-inferior to 10 days of amoxicillin/clavulanate in patients with CAP. For each evaluation of clinical, bacteriological and radiological response, a two-sided 95% confidence interval for the weighted difference between treatment groups was constructed based on the formula of Makuch and Simon.[15] Non-inferiority was defined as the lower limit of the two-sided 95% confidence interval (CI) for the difference between groups being greater than −15%. With the sample size of 240 per-protocol patients enrolled, the study had a power of 90% to test the null hypothesis of non-inferiority, assuming a failure rate of 15% for each treatment group. An alpha level of 5% was used to assess significance of main effects and a level of 10% was used for treatment-covariate interactions. All CIs for differences in proportions were calculated using the normal approximation to the binomial distribution.

Comparisons of the incidence rates of adverse events between the two study drug groups were done descriptively. Adverse event reporting was performed using the World Health Organization (WHO) coding system. Events were tabulated by type (according to the COSTART glossary) and by frequency for all adverse events and for those events considered to be related to drug treatment.

Results

Of the 324 patients randomized, 320 (99%) patients comprised the intent-to-treat (ITT) population. Four patients were excluded from the intent-to-treat analysis (one in the gemifloxacin group and three in the amoxicillin/clavulanate group) because they were withdrawn from the study before the first dose of study medication had been administered. Two hundred fifty-four patients completed the study (134 in the gemifloxacin group, 120 in the amoxicillin/clavulanate group). Among those patients who failed to receive a full course of study drug, adverse events were the main reason for premature discontinuation of treatment (gemifloxacin: 9.6%; amoxicillin/clavulanate: 9.8%; see safety section below). A further 71 patients (39 gemifloxacin; 32 amoxicillin/clavulanate) were excluded from the Clinical PP populations as a result of poor visit compliance, treatment with another systemic antibacterial for inter-current illnesses, poor study medication compliance, and a clinical outcome of unable to determine. A total of 185 patients (95 in the gemifloxacin group and 90 in the amoxicillin/clavulanate group) were excluded from the Bacteriology ITT population as they did not have at least one respiratory pathogen identified at screening. The remaining 72 patients in the gemifloxacin group and 63 patients in the amoxicillin/clavulanate group comprised the Bacteriology ITT population. One hundred three patients with a pre-therapy organism identified at pre-therapy were valid for the efficacy analysis (54 in the gemifloxacin group, 49 in the amoxicillin/clavulanate group). These patients comprise the Bacteriology PP population. The most common reasons for exclusion from the efficacy analysis were again poor visit compliance, a clinical or bacteriological outcome of unable to determine, or prohibited antibacterial therapy for an intercurrent illness.

As shown in Table 1, both treatment groups were well matched with respect to demographic and clinical characteristics. Although the data presented are from the ITT population, similar data were obtained from the Clinical PP follow-up population. In the ITT population, the mean age for patients was 53.3 years in the gemifloxacin group and 55.3 years in the amoxicillin/clavulanate group. In both treatment groups there were more

Table 1 Demographics and baseline medical characteristics.

Variable	Intent-to-treat population	
	7-day gemifloxacin 320 mg qd (*N* = *167*)	10-day amox/clav 1 g/125 mg tid (*N* = *153*)
Age, years		
Mean (SD)	53.3 (20.4)	55.3 (19.8)
Range	18–97	18–86
Sex, *n* (%) male	107 (64.1)	96 (62.7)
Race, *n* (%) caucasian	138 (82.6)	120 (78.4)
History of cigarette smoking		
Current smoker, *n* (%)	45 (28.7)	47 (30.7%)
Smoked regularly in last month, *n* (%)	59 (35.3)	56 (36.6)
CAP severity*		
Non-severe low risk	70 (41.9)	54 (35.3)
Non-severe moderate risk	71 (42.5)	73 (47.7)
Severe	26 (15.6)	26 (17.0)

*Based on ATS guidelines.[16]

males (over 62%) than females, and most patients were white (at least 78% overall). Approximately one-third of patients in both groups were regular cigarette smokers. Based on the ATS guideline stratification,[16] not more than 17% of patients in each treatment group were classified as having a severe risk of mortality from CAP.

A high proportion of patients were hospitalized at screening in both the ITT and Clinical PP populations. Slightly more patients were in-patients at screening in the amoxicillin/clavulanate group than the gemifloxacin group (Clinical PP follow-up population, gemifloxacin: 103/115 patients, 89.6%; amoxicillin/clavulanate: 111/113 patients, 98.2%). Overall, in the Bacteriology PP follow-up population, eight gemifloxacin-treated patients (17.0%) and 11 amoxicillin/clavulanate-treated patients (23.9%) were bacteremic at screening. Proportions of bacteremic patients were similar in the ITT population. Most bacteremic patients had *S. pneumoniae* isolated (e.g., in the Bacteriology PP follow-up population, gemifloxacin: 6/8 patients, 75.0%; amoxicillin/clavulanate: 10/11 patients, 90.9%).

Clinical response

Table 2 illustrates the clinical success rates for patients treated with either regimen and analyzed at the various time points assessed during the study. The primary efficacy parameter was clinical response at follow-up. As shown in the table, the clinical success rates at follow-up for the PP population were 88.7% (102/115) in the gemifloxacin group, and 87.6% (99/113) in the amoxicillin/clavulanate group (95% CI for the treatment difference: −7.3, 9.5). In the ITT population, the clinical success rates at follow-up were 77.2% (129/167) in the gemifloxacin group, and 79.1% (121/153) in the amoxicillin/clavulanate group (95% CI for the treatment difference: −10.9, 7.2). Thus, gemifloxacin, in both populations, was found to be at least as clinically effective as amoxicillin/clavulanate, as the lower limit of the 95% CI for the treatment difference (gemifloxacin–amoxicillin/clavulanate) was no less than the tolerable limit set for this study (−15%). The success rates at follow-up in the Bacteriology PP population (i.e., patients who were clinically valid and had a pre-therapy pathogen) were 87.2% (41/47) in the gemifloxacin group and 89.1% (41/46) in the amoxicillin/clavulanate group (95% CI, −15.0,11.2), indicating that gemifloxacin was also at least as clinically effective as amoxicillin/clavulanate in this population. In the Bacteriology ITT, similar results were noted, with therapeutic success rates at follow-up similar between treatment groups (gemifloxacin: 75.0%; amoxicillin/clavulanate: 76.2%).

The clinical success rates at end of therapy were 95.3% (122/128) in the gemifloxacin group and 90.1% (109/121) in the amoxicillin/clavulanate group for the Clinical PP population. In the ITT population, clinical success rates at end of therapy were 85.6% (143/167) and 83.7% (128/153) in the

Table 2 Clinical success rates at follow-up and end of therapy.

	7-day gemifloxacin 320 mg qd *n*/*N* (%)		10-day amox/clav 1 g/125 mg tid *n*/*N* (%)
Follow-up			
Clinical PP population	102/115 (88.7)		99/113 (87.6)
95% CI		−7.3, 9.5	
ITT population	129/167 (77.2)		121/153 (79.1)
95% CI		−10.9, 7.2	
Bacteriology PP population	41/47 (87.2)		41/46 (89.1)
95% CI		−15.0, 11.2	
Bacteriology ITT population	54/72 (75.0)		48/63 (76.2)
95% CI		−15.7, 13.3	
End of therapy			
Clinical PP population	122/128 (95.3)		109/121 (90.1)
95% CI		−1.2, 11.7	
ITT population	143/167 (85.6)		128/153 (83.7)
95% CI		−5.9, 9.9	
Bacteriology PP population	52/54 (96.3)		45/49 (91.8)
95% CI		−4.7, 13.6	
Bacteriology ITT population	61/72 (84.7)		51/63 (81.0)
95% CI		−9.0, 16.5	

gemifloxacin and amoxicillin/clavulanate treatment groups, respectively. Thus, gemifloxacin in both of these populations was also shown to be at least as clinically effective as amoxicillin/clavulanate. The success rates at this time point in the Bacteriology PP populations were 96.3% (52/54) in the gemifloxacin group and 91.8% (45/49) in the amoxicillin/clavulanate group. In the Bacteriology ITT, success rates were higher in the gemifloxacin group than the amoxicillin/clavulanate group (gemifloxacin: 84.7%; amoxicillin/clavulanate: 81%). Gemifloxacin and amoxicillin/clavulanate were both clinically effective in patients with *S. pneumoniae* (clinical success rates of 86.4% and 96.4%, respectively).

There were no clinical failures among the gemifloxacin-treated patients at end of therapy with persistence or presumed persistence of *S. pneumoniae* alone. Two patients isolated *S. pneumoniae* on entry to the study failed therapy, the initial pathogens were eradicated but no subsequent pathogens were isolated on follow-up.

When severity of CAP (mortality risk) or bacteremia at screening were considered, in the Clinical PP follow-up population, gemifloxacin produced a higher response rate than amoxicillin/clavulanate. In this population, patients at severe risk of mortality from CAP achieved success rates of 100% in the gemifloxacin group and 88% in the amoxicillin/clavulanate group. In bacteremic patients, clinical success rates were 100% in the gemifloxacin group and 91% in the amoxicillin/clavulanate group.

Bacteriologic response

Consistent with the design of this study, *S. pneumoniae* was the most common pathogen isolated, being identified in 42% of gemifloxacin-treated patients and 41% of amoxicillin/clavulanate-treated patients. A relatively high number of *M. pneumoniae* infections were also identified serologically (28% in the gemifloxacin group, 32% in the amoxicillin/clavulanate group). Infection with *L. pneumophila* was identified in 11% of patients and infection with *C. pneumoniae* 8% of patients. Most bacteraemic patients had *S. pneumoniae* isolated (gemifloxacin: 6/8 patients, 75.0%; amoxicillin/clavulanate: 10/11 patients, 90.9%). Mixed populations of bacteria occurred in 7.8% of gemifloxacin patients and 10.5% of amoxicillin/clavulanic acid cases. Patients with two or more pathogens tended to have infections with both an atypical organism and typical pathogen (gemifloxacin: 8/13 patients; amoxicillin/clavulanate: 12/16 patients). Overall both therapies performed well in these infections. Only two patients infected with atypical organisms in mixed populations failed on gemifloxacin [one case of *L. pneumophila* + *S. aureus* and one case of *M. pneumoniae* + *H. influenzae* + *S. pneumoniae*] while four patients

Table 3 Eradication rates for the most common pre-treatment organisms isolated should indicate this is mostly presumed eradication.

	7-day gemifloxacin *n*/*N* (%)	10-day amox/clav *n*/*N* (%)
Follow-up		
S. pneumoniae	17/19 (89)	18/19 (95)
H. influenzae	7/9 (78)	5/5 (100)
L. pneumophilia	3/3 (100)	5/5 (100)
M. catarrhalis	3/3 (100)	0/0
S. aureus	2/2 (100)	1/1 (100)
End of therapy		
S. pneumoniae	22/23 (96)	21/21 (100)
H. influenzae	11/12 (92)	5/5 (100)
L. pneumophilia	4/5 (80)	5/6 (83)
M. catarrhalis	3/3 (100)	0/0
S. aureus	2/2 (100)	1/1 (100)

with atypicals failed on amoxicillin/clavulanate therapy [*L. pneumophila* 2; *M. pneumoniae* 2]. In all other mixed aetiologies clinical and bacteriological success was reported.

In the Bacteriology PP populations, overall eradication rates were high, with 92.6% (50/54) of all pathogens in the gemifloxacin group and 96.2% (51/53) of all pathogens in the amoxicillin/clavulanate group being eradicated or presumed eradicated. Individual eradication rates for the key pathogens associated with CAP are shown in Table 3. Eradication rates of *M. pneumoniae* at end of therapy were 94% and 83% for the gemifloxacin group and amoxicillin/clavulanate group, respectively, and the eradication rates of *C. pneumoniae* at end of therapy were 100% for both the gemifloxacin and amoxicillin/clavulanate groups.

Eradication rates of *S. pneumoniae* at end of therapy were also high (95.7% and 100% for the gemifloxacin group and amoxicillin/clavulanate group, respectively), including against penicillin-intermediate and resistant strains of *S. pneumoniae*. Of the 19 *S. pneumoniae* isolates in each treatment group, 17 isolates (89.5%) in the gemifloxacin group and 18 isolates (94.7%) in the amoxicillin/clavulanate group were either eradicated or presumed eradicated at follow-up.

Six bacteraemic patients (Bacteriology PP follow-up population) in the gemifloxacin group had *S. pneumoniae* isolated from blood at screening. Gemifloxacin showed a 100% eradication rate in these bacteraemic patients.

The bacteriological outcomes at follow-up for the key pathogens associated with CAP were similar in the Bacteriology ITT population to those of the Bacteriology PP follow-up population, with a bacteriological response of eradication or presumed eradication of 89.2% in the gemifloxacin group and 92.4% in the amoxicillin/clavulanate group.

There were no pathogens associated with new infection at follow-up in either Bacteriology follow-up populations.

Susceptibility testing

A total of four *S. pneumoniae* isolates (of the 69 isolated) were resistant to penicillin and nine were of intermediate susceptibility. All isolates had an MIC to gemifloxacin of <0.03 mg/l with all but one being either eradicated or presumed eradicated. One patient experienced clinical and bacteriological failure with an isolate of *S. pneumoniae* penicillin MIC 4 mg/l. All of the isolates with an elevated penicillin MIC were eradicated by amoxicillin/clavulanate. Four *H. influenzae* isolates (of the 20 isolated) showed intermediate susceptibility to clarithromycin. One *H. influenzae* isolate and one *S. pneumoniae* isolate were resistant to clarithromycin, and 16 *S. pneumoniae* isolates were resistant to both clarithromycin and azithromycin. Nine *S. pneumoniae* isolates were resistant to cefuroxime, and of these seven isolates were resistant to both macrolides and cefuroxime. A total of 5/20 isolates of *H. influenzae*, 3/3 isolates of *M. catarrhalis* and 4/5 isolates of *S. aureus* were beta-lactamase positive. In contrast, no isolates recovered in this study showed evidence of resistance to ofloxacin at screening.

Radiological response

The radiological success rates at follow-up for the Clinical PP populations were 90.4% in the gemifloxacin group and 87.6% in the amoxicillin/clavulanate group. In the ITT population, success rates were 79.6% in the gemifloxacin and 79.1% in the amoxicillin/clavulanate group (see Table 4). Thus, in both populations gemifloxacin was shown to be at least as effective as amoxicillin/clavulanate in terms of radiological response at follow-up. Similarly, the radiological success rates at end of therapy for both the ITT and PP populations showed gemifloxacin to be at least as effective as amoxicillin/clavulanate (see Table 4).

Safety

The safety population comprised 320 patients (167 gemifloxacin and 153 amoxicillin/clavulanate).

Table 4 Radiologic success rates at follow-up and end of therapy.

	7-day gemifloxacin 320 mg qd *n*/*N* (%)		10-day amox/clav 1 g/125 mg tid *n*/*N* (%)
Follow-up			
Clinical PP population	104/115 (90.4)		99/113 (87.6)
95% CI		−5.3, 10.9	
ITT population	133/167 (79.6)		121/153 (79.1)
95% CI		−8.3, 9.4	
End of therapy			
Clinical PP population	114/128 (89.1)		106/121 (87.6)
95% CI		−6.5, 9.4	
ITT population	133/167 (79.6)		122/153 (79.7)
95% CI		−8.9, 8.7	

Withdrawals, reported as an adverse event, from the study occurred in the two cohorts, 33 in each group, of those withdrawn due to an insufficient response to therapy two were in the gemifloxacin group and nine in the amoxicillin/clavulanate cohort, $P = 0.03$ (95% CI, −8.8;0.6), a statistically significant difference Amoxicillin/clavulanate-treated patients reported more treatment-emergent events (62.1%) than did the gemifloxacin (58.7%) group. The most frequently reported adverse events (⩾5%) were insomnia, diarrhea and headache for gemifloxacin-treated patients (11.4%, 8.4% and 5.4%, respectively) and diarrhea and insomnia for amoxicillin/clavulanate-treated patients (13.1% and 5.2%). There were no statistically significant differences between the treatment groups for any of these events. More patients in the amoxicillin/clavulanate group were prematurely discontinued from the study due to adverse events: 8.4% of the gemifloxacin-treated and 9.8% of those given amoxicillin/clavulanate.

Drug-related events were reported by 18.6% of patients in the gemifloxacin group and 22.9% of patients in the amoxicillin/clavulanate group. Events occurring in at least 1% of the study population and considered to be drug-related are summarized in Table 5. Among these patients, in the gemifloxacin group, the adverse events most frequently reported as being of suspected or probable relationship to study medication were diarrhea (6.0%) and rash (3.0%). In the amoxicillin/clavulanate group, the adverse events most frequently reported as being of suspected or probable relationship to study medication were diarrhea (11.1%) and fungal infection, vaginitis and vomiting (all 2.0%). Of note, the incidence of diarrhea of suspected or probable relationship to study medication was higher in the amoxicillin/clavulanate group (11.1%) compared with the gemifloxacin group (6.0%). Rash was reported in five gemofloxacin treated patients and three amoxicillin/clavulanate treated subjects.

Table 5 Drug-related adverse occurring in at least 1% of patients.

	7-day gemifloxacin *n* (%)	10-day amox/clav *n* (%)
Adverse event	*N* = 167	*N* = 153
Diarrhea	10 (6%)	17 (11%)
Rash	5 (3%)	3 (2%)
Vomiting	4 (2%)	3 (2%)
Pneumonia	4 (2%)	3 (<2%)
Erythematous rash	2 (1%)	0
Pruritus	2 (1%)	0
Headache	1 (<1%)	2 (1%)
Hepatocellular damage	1 (<1%)	2 (1%)
Moniliasis	1 (<1%)	2 (1%)
Nausea	1 (<1%)	2 (1%)
Fungal infection	0	3 (2%)
Vaginitis	0	3 (2%)
Therapeutic response increased	0	2 (1%)

Nine gemifloxacin-treated patients (5.4%) and 12 amoxicillin/clavulanate-treated patients (7.8%) had treatment emergent increases of potential clinical concern (⩾3 fold upper limits of normal) for one or more liver function parameters at the on-therapy visit, but only two patients (1.3%) in the amoxicillin/clavulanate group had such elevated values by the end of therapy. The majority of elevated liver function parameters were transient, with lower values being recorded at end of therapy compared with on-therapy. No patients had abnormal values for total bilirubin at either time point.

A total of seven patients died during the study, of whom 3 were classified as having severe pneumonia (Fine class IV or V): four in the gemifloxacin group and three in the amoxicillin/clavulanate group. None of the adverse events associated with the deaths was considered by the investigator to be of suspected or probable relationship to study medication, and none of the deaths was considered related to study treatment. In total, 24 gemifloxacin-treated patients (14.4%) and 31 amoxicillin/clavulanate-treated patients (20.3%) reported at least one serious adverse event. Two serious adverse events occurred in more than two patients from each treatment group—pneumonia (six patients in the gemifloxacin group) and pulmonary carcinoma (three patients in each treatment group). Serious adverse events considered by the investigator to be related to study medication occurred for five patients in the gemifloxacin group: pneumonia and respiratory insufficiency (one patient), granulocytopenia, pharyngitis (one patient each) and pneumonia (two patients), and in four patients in the amoxicillin/clavulanate group: hallucination, diarrhea (one patient each) and therapeutic response increased (two patients).

Discussion

This was a randomized, double-blind, double-dummy, parallel group study designed to evaluate the efficacy and safety of oral gemifloxacin 320 mg once daily for 7 days versus oral amoxicillin/clavulanate 1 g/125 mg three times daily for 10 days in the treatment of patients with CAP of suspected pneumococcal origin. The dose of amoxicillin/clavulanate used is higher than the typical dose historically prescribed in the USA. The primary end point of the study was the clinical response at follow-up (day 23–37), and the secondary efficacy parameters were clinical response rates at the end of therapy (day 11–16), the bacteriologic response rates at end of therapy and at follow-up, and the radiological response rates at end of therapy and at follow-up.

The objective of the study was to show that gemifloxacin was at least as efficacious as high-dose amoxicillin/clavulanate, that is, that the lower limit of the 95% CI for the treatment difference was within a pre-specified non-inferiority margin. The margin stated in this protocol was −15%, and was based on an overall projected clinical success rate for the study of 85% at follow-up. Two additional randomized clinical trials of gemifloxacin in CAP,[16,17] for which the entry criteria did not specifically target pneumococcal pneumonia, each used a margin of −10% with a projected success rate of 90% at follow-up. The wider non-inferiority margin used in this study was selected because of the increased variability associated with the lower overall response rate expected for a group of patients with CAP of suspected pneumococcal origin.

The two treatment groups were well matched with respect to demographic and clinical characteristics at baseline. In the ITT population, the mean age for patients was 53 years in the gemifloxacin group and 55 years in the amoxicillin/clavulanate group. In both treatment groups there were more males (over 62%) than females, and most patients were white (at least 78% overall). In these patients with suspected pneumococcal pneumonia, 17% of patients in each treatment group or less were classified as having severe risk of mortality from CAP, as based on the ATS guidelines.[18] Over 91% of patients in each group were hospitalized at the time of randomization.

The results of this study indicated that oral gemifloxacin 320 mg once daily for 7 days is at least as effective as high-dose oral amoxicillin/clavulanate 1 g/125 mg three times daily for 10 days for the treatment of CAP of suspected pneumococcal origin. The clinical success rates in the Clinical PP follow-up population were 89% in the gemifloxacin group and 88% in the amoxicillin/clavulanate group (95% CI for the treatment difference: −7.3, 9.5). Using the non-inferiority criteria set for the concurrent gemifloxacin trials (−10%), the conclusion of non-inferior efficacy is maintained for the Clinical PP follow-up population, which is the primary population of interest. The clinical success rate at follow-up in the ITT population was 77% for the gemifloxacin group and 79% for the amoxicillin/clavulanate group (95% CI for the treatment difference: −10.9, 7.2).

The finding that gemifloxacin was at least as effective as amoxicillin/clavulanate in the treatment of CAP was supported by the analysis of the secondary efficacy parameters. In the Clinical PP follow-up population, clinical success rates at end of therapy were 95% and 90% in the gemifloxacin and amoxicillin/clavulanate groups, respectively. In the Bacteriology PP populations, bacteriological success rates for the gemifloxacin and amoxicillin/clavulanate groups were 96% and 92% at end of therapy and 87% and 89% at follow-up, respectively. In the Clinical PP populations, radiological success rates were 89% in the gemifloxacin group and 88% in the amoxicillin/clavulanate group at end of therapy, and 90% and 88% in the gemifloxacin and

amoxicillin/clavulanate groups, respectively, at follow-up.

When severity of CAP (mortality risk) or bacteremia on entry were considered, in the Clinical PP follow-up population, gemifloxacin and amoxicillin/clavulanate both had high response rates. In patients at severe risk of mortality from CAP the success rates were 100% in gemifloxacin-treated patients and 88% in amoxicillin/clavulanate-treated patients. In bacteraemic patients, clinical success rates were 100% in the gemifloxacin group and 91% in the amoxicillin/clavulanate group. It should be noted, however, that other studies have shown that addition of a macrolide to a beta-lactam-based regimen can improve the mortality rate for bacteremic pneumococcal pneumonia leading to the suggestion that monotherapy for these infections may be suboptimal.[19,20]

A review of recently published literature on trials with quinolones and high-dose amoxicillin in CAP indicates that the results observed in this study are similar to those reported previously. In such studies, clinical success rates in evaluable patients ranged from 81% to 91%.[21–23] In our study, patients were treated with gemifloxacin once a day for seven days. In published studies of a comparator treatment versus an oral quinolone with fixed dosage duration, patients received 10 days of quinolone antibacterial therapy,[22,23] and in studies where the dosage or duration was variable, patients were elected by the physician to receive on average 10–13 days of an oral quinolone.[22,24] Gemifloxacin was also shown after 7 days treatment to be clinically superior to 7 days of oral trovafloxacin therapy at some endpoints.[17] The high clinical success rates observed in the current study with gemifloxacin indicate that good efficacy can be maintained with a shorter, once-daily, oral treatment regimens.

The growing incidence of beta lactam and/or macrolide resistance among *S. pneumoniae*, *H. influenzae*, *M. catarrhalis* and *S. aureus*, all of which were isolated in this study, has limited the use of some traditional antibacterial agents.[7,9] Indeed, recent results of *S. pneumoniae* susceptibility testing from the TRUST surveillance program show that from 1998 to 2002, the prevalence of azithromycin resistance increased by 4.8% to 27.5%, the prevalence of penicillin resistance increased by 3.7% to 18.4%, the prevalence of ceftriaxone resistance increased by 0.5% to 1.7%, and the prevalence of levofloxacin resistance increased by 0.3% to 0.9%.[25] In this context, a number of key initial pathogens showed evidence of resistance to beta-lactams or to macrolides in this study: 5.8% (4/69) *S. pneumoniae* isolates were resistant to penicillin and 13% (9/69) were of intermediate susceptibility; 1.4% (1/69) were resistant to clarithromycin alone, and 23% (16/69) were resistant to both clarithromycin and azithromycin; 13% (9/69) were resistant to cefuroxime, of which 77.8% (7/9) were resistant to both macrolides and cefuroxime. Additional data from both Doern et al. and Jacobs et al. from US-isolated strains of *S. pneumoniae* showed an increasing incidence of multi-drug resistant isolates with around 25% having resistance to three or more antimicrobials in 2000.[26,27] However, caution must be shown due to the recent cases of levofloxacin therapy failure among isolates of *S. pneumoniae* in which clinical failure has been accompanied by emergence of levofloxacin resistance. To date over 25 such cases have been reported and in most tested strains gemifloxacin has retained activity at concentrations achievable in respiratory tissues.[28,29] Given this worrying trend, it has been suggested that the newer RTI fluoroquinolones (e.g., gemifloxacin, moxifloxacin) should only be considered empiric treatment options for adults with CAP of suspected drug-resistant pneumococcal origin.[30] Current data and opinion suggest that if a quinolone antimicrobial is to be prescribed then the initial selection of the most potent agent should provide optimal clinical and microbiological outcomes as well as minimize the selection of resistance.[28]

Both antibacterial treatments were highly effective in the eradication of the key pathogens of CAP, with overall eradication rates of 94% for gemifloxacin and 93% for amoxicillin/clavulanate treatment groups at end of therapy, in the Bacteriology PP end of therapy population. This suggests that gemifloxacin can provide appropriate coverage when used as an empirical therapy in CAP, as cover for both the typical pathogens and atypical organisms was provided. Eradication rates of *S. pneumoniae* at end of therapy were high (95.7% and 100% for the gemifloxacin group and amoxicillin/clavulanate group, respectively), and gemifloxacin was also seen to be highly effective in penicillin-intermediate and resistant strains of *S. pneumoniae*. Six bacteraemic patients (Bacteriology PP follow-up population) in the gemifloxacin group had *S. pneumoniae* isolated from blood at screening. Gemifloxacin showed a 100% eradication rate in these bacteraemic patients. This is particularly encouraging in light of data from Kelley et al. describing breakthrough pneumococcal bacteremia in patients treated with azithromycin and clarithromycin.[31]

Consistent with the published literature and the design of this study, *S. pneumoniae* was the most common pathogen isolated (40% of patients overall,

where a causative pathogen was identified). Of interest was the relatively high number of *M. pneumoniae* infections detected by serology (28% in the gemifloxacin group, 32% in the amoxicillin/clavulanate group), and patients with *L. pneumophila* and *C. pneumoniae* (11% and 8% overall, respectively). This would indicate that, while the inclusion criteria used for this study increased the likelihood of pneumococcal pneumonia, they do not exclude patients with atypical pathogens. This could have been a concern, given the comparator's historically weak activity against atypical pathogens, yet both drugs fared well against these organisms. This may reflect that the patients suffered for a mild form of pneumonia or that legionellosis (such as with *M.* and *C. pneumoniae*) may be self-limiting. We should further acknowledge that our study design was limited by the fact that our definition of a "typical" pneumococcal syndrome has not been definitively demonstrated in the literature. Treatment failures could not be explained in terms of underlying CAP mortality risk and the interaction between treatment and this covariate was not statistically significant. Moreover, it was not possible to draw conclusions on an association between MIC and treatment failure, because the range of gemifloxacin MICs at screening was generally low. In some patients, treatment failures could be explained on the basis of the patient's underlying co-morbidities (e.g., emphysema, COPD).

From a safety perspective, gemifloxacin was well tolerated. The most frequently reported adverse events ($\geqslant$5% incidence) in the gemifloxacin group were insomnia, diarrhea and headache (11.4%, 8.4% and 5.4%, respectively). In the amoxicillin/clavulanate group, the most frequently reported adverse events were diarrhea and insomnia (13.1% and 5.2%, respectively). There were no statistically significant differences between the treatment groups for any adverse events with an incidence of $\geqslant$5%. The numbers of patients with transiently elevated liver function tests or other laboratory values of potential clinical concern were low and similar in both treatment groups. There was an incidence of 3% rash and 1% erythematous rash in the gemifloxacin arm. The rash is mild to moderate in severity and has been more commonly observed in patients under the age of 40 years and who took drug for more than 7 days and the rash resolves within 7 days. The rash shows no evidence of phototoxicity, vasculitis, or necrosis. Seven deaths were reported during the study (four in the gemifloxacin group and three in the amoxicillin/clavulanate group); none of the adverse events associated with the deaths were considered to be related to study medication. Serious adverse events were reported for 24 patients (14.4%) in the gemifloxacin group and 31 patients (20.3%) in the amoxicillin/clavulanate group. However, these adverse events were considered by the investigator to be drug-related for only five patients (3.0%) in the gemifloxacin group and four (2.6%) in the amoxicillin/clavulanate group. The proportion of discontinuations due to adverse events was lower in the gemifloxacin group (gemifloxacin: 8.4%, amoxicillin/clavulanate: 9.8%).

In summary, this study has shown that oral gemifloxacin 320 mg once daily for 7 days is at least as effective clinically, bacteriologically, and radiologically as oral, high-dose amoxicillin/clavulanate 1 g/125 mg three times daily for 10 days in the treatment of patients with CAP of suspected pneumococcal origin. Given the comparable adverse experience profiles for gemifloxacin and amoxicillin/clavulanate, these data suggest that gemifloxacin is an effective alternative to amoxicillin/clavulanate and offers a more convenient dosing regimen.

Acknowledgements

The authors would like to thank the 011 investigator group: France—F. Bart, L. Boudoux, P. Canton, C. Chidiac, F. Bonnaud, D. Debieuvre, B. Duvert, D. Elkharrat, J.-M. Estavoyer, E. Fournier, P. Granier, D. Hermann, H. Jullian, P. Kieffer, P. Laurent, B. Lechevalier, M. Micoud, D. Mottier, Y. Mouton, R. Pelet, R. Poirier, A. Proust, A. Prudhomme, Y. Rogeau, J. Seigneur, G. Simmonneau, P. Dellamonica, P. Veyssier, P. Vinceneux, L. Vivet, P. Vivet, C. Wallaert, E. Weitzenlum, J.M. Zipper, P. Astoul, H. Berard, P. Bernard, G.R. Boyer, P. Carles, J.P. Derenne, P. Gayard, P. Godard, C. Hermant, O.J. Lambert, I. Caby, J.P. Labaan, M.E. Lamouliate, F.X. Lebas, F. Leconte, Y. Lierman, A. Marceau, J.C. Meurice, J.L. Meynard, J.F. Muir, F. Natali, G. Nouvet, C. Brousse, J.M. Pone, J.C. Saltiel, J. Sauvaget, G. Thomas, L. Vincent, D. Wahl, S. Salmeron, F. Poubeau, A. Gerards, J.P. Chevalier, V. Robert, G. Dien, D. Braun, D. Jeandeau, Z. Bavele, R. Lamaze, J. Virally, Y. Curran, T. Prazuck, R. Riou, P. Abueguen, H. Mouawad, B. Lemmens, B. Maury, J. Arpillange, F. Bricaire, C. Paradis, N. Abenhaim, J.Y. Vogel, J.F. Wilmann, F. Paganin. Poland—A. Horban.

South Africa—P.Wilcox, J. Thomson, N. van Rensburg, J. Smit, S. Moola, P. Matthews.

References

1. Meyer RD, Finch RG. Community-acquired pneumonia. *J Hosp Infect* 1992;**22**(Suppl A):51–9.
2. Bartlett JG, Mundy LM. Community-acquired pneumonia. *N Engl J Med* 1995;**333**:1618–24.
3. Massachussets Medical Society. Pneumonia and influenza death rates—United States, 1979–1994. *Morbid Mortal Weekly Rep* 1995;**44**:535–7.
4. Fang GD, Fine M, Orloff J, et al. New and emerging aetiologies for community-acquired pneumonia with implications for therapy. *Medicine* 1990;**69**:307–16.
5. Fass RJ. Aetiology and treatment of community-acquired pneumonia in adults: an historical perspective. *J Antimicrob Chemother* 1993;**32**(Suppl A):17–27.
6. Bartlett JG, Breiman RF, Mandell LA, et al. Community-acquired pneumonia in adults: guidelines for management. *Clin Infect Dis* 1998;**26**:811–38.
7. Doern GV. Trends in antimicrobial susceptibility of bacterial pathogens of the respiratory tract. *Am J Med* 1995;**99**(Suppl 6B):3S–7S.
8. Appelbaum PC. Antimicrobial resistance in *Streptococcus pneumoniae*: an overview. *Clin Infect Dis* 1992;**15**:77–83.
9. Doern GV, Bruggemann A, Holley Jr. HP, et al. Antimicrobial resistance of *Streptococcus pneumoniae* recovered from outpatients in the United States during the winter months of 1994 to 1995: results of a 30 center national surveillance study. *Antimicrobial Agents Chemother* 1996;**40**:1208–13.
10. Greenberg RN. Overview of patient compliance with medication dosing: a literature review. *Clin Ther* 1994;**6**:592–9.
11. SB-265805/RSD-100M9R/4. *FACTIVE* (*Gemifloxacin*) *Investigator Brochure*, 4th ed. 16 January 1999.
12. Begg C, Mildred C, Eastwood S, et al. Improving the quality of reporting of randomized clinical trials. The CONSORT statement. *JAMA*, 1996;**276**(8):637–9.
13. Performance Standards for Antimicrobial Disk Susceptibility Tests. *Approved Standard*, M2-A5. 5th ed. National Committee for Clinical Laboratory Standards, Villanova, PA, 1993.
14. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically. *Approved Standard*. M7-A3. 3rd ed. National Committee for Clinical Laboratory Standards. Villanova, PA, 1993.
15. Makuch R, Simon R. Sample size requirements for evaluating a conservative therapy. *Cancer Treat Rep* 1978;**62**:1037–40.
16. File TM, Schlemmer B, Garau J, Cupo M, Young C. Efficacy and safety of gemifloxacin in the treatment of community-acquired pneumonia: a randomized, double-blind comparison with trovafloxacin. *J Antimicrob Chemother* 2001;**48**:67–74.
17. Stevenson K, Davies JT, Gilson M, et al. A randomised, double-blind, double-dummy, multicentre, parallel group study to assess the efficacy and safety of oral gemifloxacin 320 mg once daily versus oral cefuroxime 500 mg plus clarithromycin 500 mg twice daily for 7 or 14 days in the treatment of bacterial community acquired pneumonia (CAP) in adults. SB-265805/RSD-100ZW2/l. SB-265805/012. 1999.
18. Niederman MS, Bass JB, Campbell GD, et al. Guidelines for the initial management of adults with community-acquired pneumonia: diagnosis, assessment of severity, and initial antimicrobial therapy. American Thoracic Society, Medical Section of the American Lung Association. *Am Rev Respir Dis* 1993;**148**:1418–26.
19. Martinez JA. Addition of a macrolide to a beta-lactam-based empirical antibiotic regimen is associated with lower in-hospital mortality for patients with bacteremic pneumococcal pneumonia. *Clin Infect Dis* 2003;**36**(4):389–95.
20. Waterer GW. Monotherapy may be suboptimal for severe bacteremic pneumococcal pneumonia. *Arch Intern Med* 2001;**161**(15):1837–42.
21. Tremolieres F, DE Kock F, Pluck N, et al. Trovafloxacin versus high-dose amoxicillin (1 g three times daily) in the treatment of community-acquired bacterial pneumonia. *Eur J Clin Microbiol Infect Dis* 1998;**17**:447–53.
22. Aubier M, Verster R, Regamey C, et al. Once-daily sparfloxacin versus high dosage amoxicillin in the treatment of community-acquired, suspected pneumococcal pneumonia in adults. *Clin Infect Dis* 1998;**26**:1312–20.
23. Petipretz P, Branco Pines J, Dosedel J, et al. Moxifloxacin (MFX) versus amoxycillin (AMOX) in the treatment of community-acquired suspected pneumococcal pneumonia: a multinational double-blind randomized study. *Clin Microbiol Infect* 1999;**5**(Suppl 3):P207.
24. Fogarty CM, Sullivan JG, Chattman MS, et al. Once a day levofloxacin in the treatment of mild to moderate and severe community-acquired pneumonia in adults. *Infect Dis Clin Pract* 1998;**7**:400–7.
25. Karlowsky JA, Thornsberry CT, Jones ME, et al. Factors associated with relative rates of antimicrobial resistance among *Streptococcus pneumoniae* in the United States: results from the TRUST surveillance program (1998–2002). *Clin Infect Dis* 2003;**36**:963–70.
26. Doern GV, Heilmann KP, Hyunh HK, Rhomberg PR, Coffman SK, Bruggemann AB. Antimicrobial resistance among clinical isolates of *Streptococcus pneumoniae* in the US during 1999–2000 including a comparison of rates since 1994–1995. *Antimicrob Agents Chemother* 2001;**45**:1721–9.
27. 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 infections to commonly used antimicrobials. *J Antimicrob Chemother* 2003;**52**:229–46.
28. Scheld WM. Maintaining fluoroquinolone class efficacy: review of the influencing factors. *Emerg Infect Dis* 2003;**8**:1–9.
29. Anderson KB, Tan JS, File TM, DiPersio JR, Willey BM, Low DE. Emergence of levofloxacin-resistant pneumococci in immunocompromised adults after therapy for community-acquired pneumonia. *Clin Infect Dis* 2003;**37**:376–81.
30. Appelbaum PC. Resistance among *Streptococcus pneumoniae*: implications for drug selection. *Clin Infect Dis* 2002;**34**:1613–20.
31. Kelley MA, Weber DJ, Gilligan P, Cohen MS. Breakthrough pneumococcal bacteremia in patients being treated with azithromycin and clarithromycin. *Clin Infect Dis* 2000;**31**:1008–11.