

Treatment of Adults With Community-Acquired Respiratory Tract Infections: Results of a Multicentric Clinical Trial With Gatifloxacin

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Respiratory tract infections have an important clinical and economic impact and they are the most common indication for antibiotic use in outpatient practice. This prospective, multicenter non-controlled trial assessed the efficacy and safety of gatifloxacin in the treatment of community-acquired respiratory tract infections. Patients were treated with a daily oral dose of gatifloxacin 400 mg for 7-14 days. The diagnosis of respiratory infection was made based on the clinical condition and/or radiologic findings. A total of 5,044 adult patients with community-acquired respiratory infections was treated with gatifloxacin in different centers in Brazil between March 1, 2001, and October 31, 2001. Among the 5,044 patients treated, 1,501 patients (29.76%) had community-acquired pneumonia, 756 (14.99%) had acute exacerbation of chronic bronchitis and 2,787 (55.25%) had acute sinusitis. Of the total of patients treated, 3,607 (71.51%) were considered cured, 1,261 (25%) progressed with some clinical improvement, 28 (0.56%) presented a relapse, 56 (1.11%) failed to treatment and 92 (1.82%) were unable to be evaluated. Adverse events were described in 634 (12.57%) patients. The most common adverse events were: nausea (2.24%); dyspepsia (1.86%); diarrhea (0.79%); change in taste (0.46%); insomnia and irritability (0.22%); dizziness (0.77%); headache (0.42%); allergic reaction (0.18%); Central Nervous System alterations – insomnia, agitation, anxiety – (0.46%). This study showed that the treatment of respiratory tract infections with gatifloxacin was safe and efficient and had a low incidence of adverse events.

Key Words: Gatifloxacin, community-acquired pneumonia, acute sinusitis, acute exacerbation of chronic bronchitis, treatment of respiratory infections.

Community-acquired respiratory tract infections are responsible for the most part of morbidity and mortality and represent a serious public health problem. Community-acquired pneumonia remains an important cause of hospitalization and death. It is estimated that between 2 and 15/1,000 individuals become infected with pneumonia each year and about 20% to 40% need

to be hospitalized; 5% to 30% of those patients need to be treated in intensive care units [1-3]. In Brazil, pneumonia is the first cause of death due to pulmonary diseases with 40,000 deaths each year. Pneumonia is also responsible for almost half a million hospitalizations each year [2].

Treatment is often empirical and based on clinical and radiologic diagnosis directed to the most common organisms. An empiric regimen should take into account the important role of *Streptococcus pneumoniae* and *Haemophilus influenzae*, besides *M. pneumoniae*, *C. pneumoniae* and *L. pneumophila* in community-acquired bacterial pneumonias. It has recently been reported an increase of pneumococci strains moderately resistant to penicillin and more rarely some strains with

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a high level of resistance, a problem we now face in Brazil but in a smaller degree than in the United States, Asian and Latin American countries such as Mexico, Argentina, Chile e Uruguay [4-6]. In a similar way, there has been an increase in resistance of *Haemophilus influenzae* and *Staphylococcus aureus* to a number of antimicrobials [4]. Although a few domestic studies have determined the etiology of community-acquired pneumonia, *Mycoplasma pneumoniae*, *Legionella* spp. and *Chlamydia pneumoniae* are important organisms involved in community-acquired pneumonia in many countries [7,8]. Rocha, et al. (2000) evaluated 69 patients with a diagnosis of community-acquired pneumonia who were treated at a school hospital in São Paulo, Brazil, between March 1995 and January 1997. Of that total, 34 (50%) had an etiologic diagnosis of atypical pneumonia, with *Clamydia* spp. and *Mycoplasma pneumoniae* the most frequent agents [23].

In patients with exacerbation of chronic bronchitis, the attempts to isolate the etiologic agent are unsuccessful due to the frequent previous administration of antibiotics and because of bacterial colonization of tracheobronchial tree in these patients. Lower respiratory airways are almost always sterile in healthy, non-smoker individuals. A number of researches has shown that individuals with stable chronic bronchitis can be colonized by bacteria that are potentially pathogenic in the respiratory tree [9]. The main pathogens isolated from tracheobronchial secretions, in these cases, are *Haemophilus influenzae*, frequently the non-capsulated type, *Streptococcus pneumoniae* and *Moraxella catharrhalis* with satisfactory accordance between the expectorated samples and the specimens obtained from the lower respiratory airways by means of bronchoscopy or transtracheal aspiration [4,9]. Other potentially pathogenic bacteria include aerobic Gram-negative bacilli, but those are less common than *H. influenzae* and pneumococcus.

Sinusitis are among the most frequent community-acquired infections. The presence of mucopurulent secretion and facial pain suggest the occurrence of sinusitis, an inflammation of the lining of paranasal sinuses. The majority of cases occurs as a complication of

respiratory viral infections or other infections of the upper respiratory tract, and there are occasional cases caused by the extension of a periodontal infection underneath the maxillary sinus. The most frequent organism in acute sinusitis is *Streptococcus pneumoniae*. *Haemophilus influenzae* is more frequent in infants and children. The role of group A streptococcus, staphylococcus and *Moraxella catarrhalis* in acute sinusitis is a variable one. In many studies about community-acquired maxillary sinusitis in which the organisms were obtained from antral puncture and adequately cultured, more than 50% of bacteria isolated were *Streptococcus pneumoniae* or non-capsulated *H. influenzae* [10].

New quinolones (gatifloxacin – Tequin[®]; levofloxacin – Tavanic[®]/Levaquin[®] and moxifloxacin – Avalox[®]) have recently been launched for marketing in Brazil. These new quinolones, particularly gatifloxacin, a 8-metoxi fluorquinolone, show excellent activity against pneumococcus, including penicillin-resistant strains, as well as against *H. influenzae* and *M. catharrhalis* [4,11]. Besides this activity, gatifloxacin also presents good activity against Gram-negative bacilli and atypical organisms which are frequently involved in lower respiratory tract infections [12]. Gatifloxacin is bactericidal and has excellent pharmacokinetic properties. With an oral dose of 400 mg, peak serum concentration (C_{max}) reaches 3.7 mg/L after one to two hours (T_{max}) [12,13,17]. Its bioavailability is 96%, it is about 20% bound to protein and has a half-life of 8 hours [13,17]. As a result, it is used only once a day which favors the patient's compliance to treatment. Elimination is mainly urinary. Gatifloxacin has shown to be a safe medication with a low incidence of adverse effects. Only 3% of patients discontinue treatment because of adverse effects and this is the lowest rate when compared with levofloxacin, moxifloxacin and ciprofloxacin. The most frequent side effects include nausea, headache, dizziness and rarely diarrhea [12-14].

Many previous clinical trials with the objective of evaluating the efficacy of antimicrobials for the treatment of pneumonia are difficult to be assessed. In this current study we evaluated the efficacy, tolerability and safety of a new quinolone called

gatifloxacin in the treatment of community-acquired respiratory tract infections.

Materials and Methods

This prospective, open-label, noncomparative trial was performed in 1,208 Brazilian medical centers and comprised patients who were 18 years or older. The objective was to evaluate the efficacy of gatifloxacin in the treatment of community-acquired pneumonia, acute rhinosinusitis and acute exacerbation of chronic bronchitis. The following exclusion criteria were used: patient did not consent to participate in the study, history of hypersensitivity to quinolones, pregnancy and breastfeeding, inability to use appropriate contraceptives during the period of the study, patients with a history of chronic asthma or cystic fibrosis, clinical diagnosis of viral respiratory tract infection and malabsorption syndromes or other gastrointestinal disorders which may affect drug absorption.

Community-acquired pneumonia was defined as those cases in which the patients presented rales or egophony on pulmonary auscultation and at least two of the following signs or symptoms: fever (axillary temperature $> 100.4^{\circ}\text{F}$); chest pain; cough; purulent sputum; chills, malaise or radiological findings consistent with pneumonia. Patients with acute exacerbation of chronic bronchitis should present two or more of the following signs and symptoms: increase in sputum volume, purulent sputum, increase of cough and dyspnea. Sinusitis was diagnosed as the presence of two or more of the following signs or symptoms: facial pain/tenderness, pain in sinuses or teeth, purulence in nasal cavity, headache, fever (axillary temperature $> 100.4^{\circ}\text{F}$), postnasal discharge. Treatment was performed empirically and it did not require any material to be sent for microbiological exam.

The posology used consisted of 400 mg once daily for 7 to 14 days for community-acquired pneumonia, 7 to 10 days for acute bacterial exacerbation of chronic bronchitis and 10 days for acute sinusitis.

During the study, the patient was allowed to make use of antihistamines, anti-inflammatory drugs, bronchodilators and antipyretics.

Evaluation of efficacy and safety employed clinical and laboratorial parameters. Clinical response to therapeutics was evaluated according to the patient's evolution during the study. Clinical response was also analyzed by the researcher responsible for each medical center up to 48 hours after the end of treatment. Clinical responses were classified as cure (complete absence of all symptoms caused by the infection and no need of additional antibiotic treatment), improvement (clear reduction of symptoms of infection but there was an incomplete disappearance of all symptoms; there was no need to continue therapy), relapse (after an initial improvement, there was a relapse of symptoms during therapy and it was necessary to maintain antibiotic treatment) and unable to determine (patient who lost follow-up, did not conclude the cycle of evaluations or was not evaluated due to other diseases). All adverse events that occurred during treatment or up to 48 hours after the end of the study were recorded.

Results

During the period between March 1, 2001, and October 10, 2001, a total of 5,044 adult patients from 1,208 Brazilian hospitals and with community-acquired respiratory infections were treated with gatifloxacin. Of the 5,044 patients treated: 1,501 (29.76%) had community-acquired pneumonia; 756 (14.99%) had acute exacerbation of chronic bronchitis and 2,787 (55.25%) had acute sinusitis. Demographic data of the patient population with respiratory tract infections are shown in Table 1. There were 996 smokers among 5,018 patients (19.58%) and of the total of patients who had acute exacerbation of chronic bronchitis who were not smokers ($n=526$): 158 (30%) never smoked; 293 (55.7%) had smoked in the past and in 75 patients (14.3%) this information was impossible to be obtained.

Most of the patients studied had a previous history of respiratory tract infections: 1,807 (35.82%) patients had sinusitis, 964 (19.11%) patients had bronchitis, 542 (10.75%) patients had pneumonia, 781 (15.48%) patients had pharyngitis in the past. In the last 12 months as of the beginning of treatment of the current infection

Table 1. Characteristics of 5,044 patients with community-acquired respiratory infections treated with gatifloxacin

Variable	Community-acquired pneumonia (n=1,501)	Acute exacerbation of chronic bronchitis crônica (n=756)	Acute sinusitis (n=2,787)
Gender:			
Male	718 (47.9%)	403 (53.5%)	1,170 (42.1%)
Female	782 (52.1%)	350 (46.5%)	1,609 (57.9%)
Mean age (years) ± SD	49.15 ± 19.24	60.13 ± 15.69	37.92 ± 13.80
Mean weight (Kg) ± SD	67.79 ± 12.32	66.81 ± 13.30	67.79 ± 12.84
Smocking ^[1,2] :			
Yes	330 (22.1%)	226 (30.1%)	440 (15.9%)
No	1,166 (77.9%)	526 (69.9%)	2,330 (84.1%)
Information not available	5 (0.3%)	4 (0.5%)	17 (0.6%)
History of previous respiratory tract infections:			
Sinusitis	189 (12.6%)	94 (12.4%)	1,524 (54.7%)
Brochitis	231 (15.4%)	582 (77.0%)	151 (5.4%)
Pneumonia	270 (18.0%)	167 (22.1%)	105 (3.8%)
Pharyngitis	190 (12.7%)	59 (7.8%)	531 (19.1%)
Other	76 (5.1%)	30 (4.0%)	128 (4.6%)
Use of antibiotics in the last three months:			
Yes	447 (19.8%)	407 (53.8%)	1,017 (36.5%)
No	1,054 (70.2%)	349 (46.2%)	1,770 (63.5%)
Concomitant use of other medications with gatifloxacin:			
Steroid anti-inflammatory drug	155 (3.2%)	369 (48.8%)	914 (32.79%)
Non-steroid anti-inflammatory drug	313 (20.85%)	51 (6.74%)	750 (26.91%)
Antihistamine	67 (4.46%)	39 (5.16%)	471 (16.9%)
Bronchodilator	533 (35.5%)	623 (82.41%)	91 (3.26%)
Other	478 (31.84%)	156 (20.63%)	620 (22.25%)

[1] It was impossible to obtain information from all patients. [2] Of the total of patients with acute exacerbation of chronic bronchitis who reported to be non-smokers (n=526): 158 (30%) never smoked; 293 (55.7%) had been smokers in the past and in 75 patients (14.3%) this information was impossible to be obtained.

Tabela 2. Avaliação da eficácia e dos eventos adversos do tratamento com gatifloxacina

Variable	Community-acquired pneumonia (n=1,501)	Acute exacerbation of chronic bronchitis crônica (n=756)	Acute sinusitis (n=2,787)
Total duration (days) of gatifloxacin (400 mg/day) use:			
Mean ± SD	10.09 ± 2.78	9.51 ± 2.61	9.93 ± 1.88
Median	10.0	10.0	10.0
Clinical reponse:			
Cure	1,198 (79.8%)	350 (46.3%)	2,059 (73.9%)
Improvement	262 (17.5%)	375 (49.6%)	624 (22.4%)
Relapse	4 (0.3%)	7 (0.9%)	17 (0.6%)
Failure	14 (0.9%)	10 (1.3%)	32 (1.1%)
Not assessed	23 (1.5%)	14 (1.9%)	55 (2.0%)
Adverse events:			
Present	128 (8.5%)	91 (12%)	415 (14.9%)
Absent	1,373 (91.5%)	665 (88.0%)	2,372 (85.1%)

those patients had a mean ± standard deviation: 1.6 ± 1.1 sinusitis episodes; 2.13 ± 2.64 episodes of bronchitis; 1.29 ± 0.79 episodes of pneumonia and 1.64 ± 1.29 episodes of pharyngitis.

In terms of use of antimicrobials in the last three months, 1,871 patients of a total of 5,044 (37.09%) used some type of antimicrobial. The antimicrobials most commonly used were: amoxicillin (40.94%); macrolides (erythromycin and clarithromycin) (19.99%); first and second-generation cephalosporins (cephalexin, cefadroxil, cefaclor or cefuroxime) (22.92%); ciprofloxacin (8.33%).

Concomitant use of medication was observed in 4,025 (79.80%) patients, and the drugs used included: steroid anti-inflammatory drugs = 1,438 (35.73%) patients, non-steroid anti-inflammatory drugs = 1,114 (27.68%) patients; antihistamine = 577 (14.34%) patients, bronchodilators = 1,247 (30.98%) patients and other medications in 1,254 (31.16%) patients.

Table 2 shows the efficacy and adverse events related to treatment with gatifloxacin. The mean (±

standard deviation) duration of treatment was (in days) 9.91 ± 2.30, median of 10.

Of the total of patients treated, 3,607 (71.51%) were considered cured, 1,261 (25%) progressed with clinical improvement, 28 (0.56%) presented a relapse, 56 (1.11) failed to treatment and 92 (1.82%) were unable to be evaluated.

Adverse events were described in 634 (12.57%) patients. The most frequent adverse events were: nausea (2.24%); dyspepsia (1.86%); diarrhea (0.79%); change in taste (0.46%); insomnia and irritability (0.22%); dizziness (0.77%); headache (0.42%); allergic reaction (0.18%); alterations of Central Nervous System – insomnia, agitation, anxiety – (0.46%).

Discussion

Most treatments for both upper and lower respiratory tract infections are administered in an empirical way. Consequently, antimicrobial treatment

must take into account the microorganisms most frequently related to the sites of infection and their sensitivity to antimicrobials, their pharmacokinetic characteristics, adverse effects and costs of the therapeutic to be chosen [2,8]. With the advent of new antimicrobials of oral use with excellent efficacy against many community-acquired infections, many patients can be efficiently treated in the comfort of their homes. However, the biggest challenge is to choose an efficient therapy with less likelihood of inducing resistance.

The emergence of bacteria that are resistant to antibiotics is in general related to the excessive use of certain antimicrobials in clinical practice, although this relationship is not always confirmed by well-conducted epidemiologic studies. Some bacterial strains have gene complexes which are inter-correlated and as a consequence, the use of an antibiotic can induce the emergence of resistance to another similar compound. Although the episode of resistance to a certain antimicrobial is considered inevitable, the rational use of those drugs can delay that kind of occurrence. Therefore, for the treatment of a community-acquired infection or an infection acquired in a hospital setting we should use an antimicrobial with the least possibility of developing resistance and with the highest activity efficacy which can be determined by the pharmacokinetic characteristics as well minimum inhibitory concentration (MIC) that is enough to destroy the organism causing that infection.

Respiratory tract infection is the most frequent cause of antimicrobial use. Many of the respiratory infections have a viral etiology and are caused mainly by influenza virus, rhinovirus and adenovirus, and they do not need to be treated with antimicrobials. The excessive use of antimicrobials is directly related to the increase in resistance among respiratory pathogens.

A study carried out by Sader, et al. (2001) which evaluated the sensitivity [to antimicrobials] of bacteria isolated from the respiratory tract of patients with community-acquired infections in Brazil showed that among *S. pneumoniae* (176 isolates), 71.6% were sensitive to penicillin. High levels of resistance to penicillin and cefotaxime were found in 2.3% and 4.0%, respectively. The new quinolones – levofloxacin (MIC₉₀;

2 mg/L) and gatifloxacin (MIC₉₀; 0.5 mg/L) – were active against 100% of the isolates tested. Among other antimicrobials tested, the most active were (% of sensitivity): chloramphenicol (97.5%) > clindamycin (94%) > azithromycin (90.3%) > clarithromycin (89.4%) > tetracycline (76.4%) > sulfamethoxazole/trimethoprim (60.2%). The percentage of *Haemophilus influenzae* (101 isolates) resistant to amoxicillin was 90.1%, while only 9.0% of *Moraxella catarrhalis* (67 isolates) were sensitive. Clavulanic acid restored amoxicillin's activity against *H. influenzae* and *M. catarrhalis*. However, *H. influenzae* showed increased levels of resistance to sulfamethoxazole/trimethoprim (55.1% sensitivity), clarithromycin (80.4% sensitivity) and cefaclor (88.2% sensitivity). All isolates of *H. influenzae* and *M. catarrhalis* were sensitive to gatifloxacin (MIC₉₀; <0.06 mg/L for both) and showed very low MICs. The results of this study reveal that the prevalence of *S. pneumoniae* with a high level of resistance to penicillin is still low in Brazil; however, the prevalence of *S. pneumoniae* with intermediate resistance to penicillin and cross-reaction with other categories of antibiotics, especially macrolides, is relatively high in our country. On the other hand, new quinolones are highly active against *S. pneumoniae* and other pathogens responsible for community-acquired respiratory infections and gatifloxacin showed a better activity when compared to beta-lactamic antibiotics and other quinolones [4].

A number of studies and consensus produced by scientific societies have recommended the use of beta-lactamic antibiotics (with or without beta-lactamase inhibitor – such as amoxicillin associated with clavulanic acid), macrolides (clarithromycin and azithromycin) and fluorquinolones (levofloxacin, gatifloxacin and moxifloxacin) [2,15,16] for the treatment of respiratory infections. The definition of the best therapeutic regimen in our country is difficult especially because of the scarcity of studies that evaluate the etiology of community-acquired pneumonias.

Gatifloxacin was used in clinical trials mainly in upper and lower respiratory tract infections such as acute exacerbation of chronic bronchitis (7 to 10 days), community-acquired pneumonias (7 to 14 days), atypical pneumonias (14 days) and acute sinusitis (10

days) [14]. Gotfried et al (2001) evaluated the appropriate duration of treatment in cases of acute exacerbation of chronic bronchitis and they concluded that a short duration of treatment with gatifloxacin (5 days) resulted in clinical cure and microbiological eradication comparable to other treatments with a duration of 7 or 10 days [22].

Another important aspect that should be pointed out with the use of gatifloxacin is the possibility of sequential treatment (intravenous to oral) mainly in serious infections which require hospitalization. Dresser, et al. (2001) compared the use of single therapy with gatifloxacin (98 patients) versus ceftriaxone in association or not with a macrolide (105 patients) in the treatment of community-acquired pneumonia who required hospitalization. Sequential treatment was performed in 98% of patients in each group. Clinical cure and microbiological eradication were not statistically different among groups and those results were 98% and 97% with gatifloxacin versus 92% and 92% with ceftriaxone, respectively. The mean cost was US\$1,760.00 for patients treated with gatifloxacin and US\$2,125.00 for those treated with ceftriaxone ($p = 0,011$) [21].

In our study we had some problems related to structuring. Although we had the largest number of cases in the country for evaluating the treatment of respiratory tract infections and despite being a prospective and multicenter study, it was an open-label and noncomparative trial. Clinical response (cure or improvement) to treatment was excellent (96.5%). In patients with pneumonia, which is considered a potentially serious infection, cure was achieved in 79.8% and clinical improvement was observed in 17.5%. A similar study performed in Mexico by Casillas, et al. (2000) comprised 17,923 patients with community-acquired respiratory infections and showed cure or clinical improvement in 96.3% of patients treated with gatifloxacin. The most common adverse effects were nausea (2.76%) and headache (2.2%) [14].

In 756 patients treated for acute exacerbation of chronic bronchitis, cure or clinical improvement was observed in 725 individuals (95.9%). Among those treated for acute sinusitis, cure or clinical improvement was observed in 2,683 patients (96.3%). These findings are

similar to the ones in the study performed by Casillas, et al. (2000) [14].

The efficacy of gatifloxacin was also shown in other studies. Gatifloxacin administered once a day was just as effective as clarithromycin 500 mg administered twice daily or levofloxacin in patients with community-acquired pneumonia and it was more effective than cefuroxime axetil 250 mg administered twice a day in patients with acute exacerbation of chronic bronchitis [18-20].

Adverse events were not frequent; they occurred in 634 (12.57%) patients. The most common adverse events were: nausea (2.24%); dyspepsia (1.86%); diarrhea (0.79%); change in taste (0.46%); insomnia and irritability (0.22%); dizziness (0.77%); headache (0.42%); allergic reaction (0.18%); changes in the Central Nervous System – insomnia, agitation, anxiety – (0.46%). In other studies, gatifloxacin was also safe and showed few adverse effects [14,20-22].

This was a multicenter, prospective, open-label and noncomparative clinical trial in which gatifloxacin 400 mg was administered once a day for treating respiratory tract infection. The drug was considered safe and effective for the treatment of respiratory tract infections.

References

1. American Thoracic Society. Guidelines for initial management of adults with community acquired pneumonia: diagnosis, assessment of severity and initial antimicrobial therapy. *Am Rev Resp Dis* **1993**;148:1418-26.
2. Consenso Brasileiro de Pneumonias em Adultos Imunocompetentes. *J Pneumol*, 27(supl. 1):S3-S21, 2001.
3. Acute respiratory infections: the forgotten pandemic. *WHO Bull* **1998**;76:101-3.
4. Sader H.S., Gales A.C., Reis A.O., et al. Sensibilidade a antimicrobianos de bactérias isoladas do trato respiratório de pacientes com infecções respiratórias adquiridas na comunidade: resultados brasileiros do Programa SENTRY de Vigilância de Resistência a Antimicrobianos dos anos de 1997 e 1998. *J Pneumol* **2001**;27(1):25-34.
5. SENTRY Participants Group (Latin America), Gales A., Sader H.S., Jones R.N. Activities of BMS 284756 (T-3811) against *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae* isolates from SENTRY Antimicrobial Surveillance Program Medical Center in Latin America. *Antimicrob Agents Chemoter*, **2001**;45(5):1463-6.

6. Sader H.S., Gales A.C., Granacher T.L., et al. Prevalence of antimicrobial resistance among respiratory tract isolates in Latin America: Results from SENTRY Antimicrobial Surveillance Program (1997-98). *Braz J Infect Dis* **2000**;4:245-54.
7. MacFarlane J.T., Colville A., Guion A., et al. Prospective study of aetiology and outcome of adult lower-respiratory-tract infections in the community. *Lancet* **1993**;341:511-4.
8. Niederman M.S., Bass J.B., Campbell G.D., et al. Guidelines for the initial management of adults with community-acquired pneumonia: Diagnosis, assessment of severity, and initial antimicrobial therapy. *American Review of Respiratory Diseases* **1993**;148:1418-26.
9. Ball P. Epidemiology and treatment of chronic bronchitis and its exacerbations. *Chest* **1995**;108:43s-52s.
10. I Consenso Brasileiro sobre Rinossinusite da Sociedade Brasileira de Otorrinolaringologia. *Rev Bras Otorrinolaringol* **1999**;65(3)supl.9:5-30.
11. Blondeau J.M. A review of the comparative in vitro activities of 12 antimicrobial agents, with a focus on five new "respiratory quinolones". *J Antimicrob Chemother* **1999**;43(suppl. B):1-11.
12. Blondeau J.M. Gatifloxacin: a new fluoroquinolone. *Expert Opin. Investig. Drugs* **2000**;9(8):1877-95.
13. Fish D.N., North D.S. Gatifloxacin, na advanced 8-methoxy fluoroquinolone. *Pharmacotherapy* **2001**;21(1):35-59.
14. Casillas J.L., Rico G., Rodriguez-Parga D., et al. Multicenter evaluation of the efficacy and safety of gatifloxacin in mexican adult outpatients with respiratory tract infections. *Advances in Therapy* **2000**;17(6):263-271.
15. Bartlett J.G., Dowell S.F., Mandell L.A., et al. Practice guidelines for the management of community-acquired pneumonia in adults. *Clinical Infectious Diseases* **2000**;31:347-82.
16. Mandell L.A., Marrie T.J., Grossman R.F., et al. Canadian guidelines for the initial management of community-acquired pneumonia: an evidence-based update by the Canadian Infectious Diseases society and the Canadian Thoracic Society. *Clinical Infectious Diseases* **2000**;31:383-421.
17. Graziela D.M. Clinical pharmacology of gatifloxacin, a new fluoroquinolone. *Clin Infect Dis* **2000**;31(Suppl 2):51-8.
18. Ramirez J., Nguyen T.H., Tellier G., et al. Once-daily 400 mg oral gatifloxacin (GAT) vs twice-daily 500mg oral clarithromycin (CLA) in the treatment of community-acquired pneumonia (CAP). Presented at the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy; September 26-29, **1999**; San Francisco, California, Abstract 2242.
19. Gotfried M., Sullivan J.G., Mayer H., Plouffe J. A randomized, double-blind, multicenter, comparative study of gatifloxacin vs levofloxacin in the treatment of community-acquired pneumonia. Presented at the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy; September 26-29, **1999**; San Francisco, California, Abstract 2243.
20. DeAbate C.A., McIvor R.A., McElvaine P., et al. Gatifloxacin vs cefuroxime axetil in patients with acute exacerbations of chronic bronchitis. *J Respir Dis* **1999**;20:S23-S9.
21. Dresser L.D., Niederman M.S., Paladino J.Á. Cost-effectiveness of gatifloxacin vs ceftriaxone with a macrolide for the treatment of community-acquired pneumonia. *Chest* **2001**;119(5):1439-48.
22. Gotfried M.H., DeAbate C.A., Fogarty C., et al. Comparison of 5-day, short-course gatifloxacin therapy with 7-day gatifloxacin therapy and 10-day clarithromycin therapy for acute exacerbation of chronic bronchitis. *Clin Ther* **2001**;23(1):97-107.
23. Rocha R.T., Vital A.C., Silva C.O.S., et al. Pneumonia atípica na comunidade em pacientes tratados ambulatorialmente: aspectos epidemiológicos, clínicos e radiológicos das pneumonias atípicas e não típicas. *J Pneumol* **2000**;26(1):5-14.