

In vitro* Activity of Fluoroquinolones (Gatifloxacin, Levofloxacin and Trovafloxacin) and Seven Other Antibiotics Against *Streptococcus pneumoniae

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In recent years, the level of resistance of *S. pneumoniae* to beta-lactam and/or macrolides has increased around the world including some countries in South America. Because of this resistance, it is necessary to test the therapeutic alternatives for treating this pathogen, including the newer quinolones. This study was carried out in order to compare the *in vitro* activity of fluoroquinolones gatifloxacin, levofloxacin and trovafloxacin, to penicillin G, amoxicillin, amoxicillin-clavulanate, cefuroxime sodium, ceftriaxone, azithromycin and clarithromycin, against 300 strains of *S. pneumoniae*. Of the 300 samples tested, 18.6% were not susceptible to penicillin (56 strains) and 7% (21 strains) were resistant to the second generation cephalosporin. Among the macrolides, resistance ranged from 6.7% for clarithromycin to 29.6% for azithromycin. Susceptibility to the newer quinolones was 100% including the 56 strains not susceptible to penicillin. Among the 10 antibiotics evaluated, the fluoroquinolones gatifloxacin, levofloxacin, and trovafloxacin displayed high levels of *in vitro* activity against *S. pneumoniae*.

Key Words: *S. pneumoniae* antimicrobial resistance, susceptibility testing *in vitro*, respiratory tract infections, pneumococci.

The new fluoroquinolones are the result of a significant improvement in the basic chemical structure of this class of synthetic antibiotics. The resulting improvement in antimicrobial activity and pharmacokinetic features make these drugs useful as monotherapy for the treatment of upper and lower community-acquired respiratory tract infections [1]. The use of these drugs is particularly useful in countries where there is a high incidence of respiratory tract infections due to beta-lactam and/or macrolide antibiotic resistant strains.

The resistance of *S. pneumoniae* to penicillin and other antimicrobial drugs was first noted in Australia and Papua, New Guinea in the 1960s, spread to South

Africa in the 1970s, and then to many countries in Europe, specially Eastern Europe, Africa and Asia in the 1980s [2]. Resistant *S. pneumoniae* greatly increased in the United States during the last decade [3-6], and has been observed in some Latin American countries [7], including Brazil [8, 9]. The treatment of serious diseases caused by *S. pneumoniae* is now a considerable challenge to clinicians.

In this study, we evaluated the *in vitro* minimum inhibitory concentration (MIC) of gatifloxacin, levofloxacin, trovafloxacin and 7 other antimicrobial agents including penicillin G, amoxicillin, amoxicillin-clavulanate, cefuroxime sodium, ceftriaxone, azithromycin and clarithromycin, against 300 strains of clinical specimens isolated from the respiratory tract, blood, and other usually sterile sites or fluids.

Material and Methods

Strains confirmed as *S. pneumoniae*, according to standard procedures [10], were screened to verify their susceptibility to penicillin by using 1 µg oxacillin disks.

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Table 1.

Antimicrobial agent	Breakpoints		Number of strains	% R	% I	% S	MIC ₅₀	MIC ₉₀	Variation of MIC (Range)
Penicillin	S≤0.06	R≥2	300	2.0	16.6	81.3	0.094	0.750	0.002-2
Amoxicillin	S≤0.5	R≥2	300	0.0	1.0	99.0	0.008	0.047	0.008-0.75
Amoxicillin-Clavulanate	S≤0.5	R≥2	300	0.0	1.3	98.7	0.008	0.064	0.008-0.75
Cefuroxime	S≤0.5	R≥2	300	6.7	0.3	93.0	0.016	0.250	0.008-3
Ceftriaxone	S≤0.5	R≥2	300	0.3	0.0	99.7	0.008	0.094	0.002-32
Azithromycin	S≤0.5	R≥2	300	7.3	22.3	70.3	0.38	1.000	0.023-256
Clarithromycin	S≤0.25	R≥1	300	6.7	0.0	93.3	0.032	0.064	0.008-256
Levofloxacin	S≤2	R≥8	300	0.0	0.0	100.0	0.38	0.750	0.047-1
Trovafloxacin	S≤1	R≥4	300	0.0	0.0	100.0	0.064	0.094	0.012-0.25
Gatifloxacin	S≤1	R≥4	300	0.0	0.0	100.0	0.125	0.190	0.016-0.5

The strains identified as having diminished susceptibility to penicillin (halos ≤ 19 mm) were submitted to E-test (AB Biodisk, Sweden) assays to determine the minimal inhibitory concentration (MIC) to penicillin. Samples with results of ≤ 0.06 µg/ml were considered susceptible, samples with results from 0.06 µg/ml to 1.0 µg/ml were considered of intermediate susceptibility, and samples with results of ≥ 2 µg/ml were considered penicillin-resistant (high level). The susceptibility categorization followed the National Committee for Clinical Laboratory Standards (NCCLS) guidelines [11].

The E-test method was also used to evaluate the 9 other antimicrobial agents selected for this study (amoxicillin, amoxicillin-clavulanate, cefuroxime sodium, ceftriaxone, azithromycin, clarithromycin, levofloxacin, trovafloxacin and gatifloxacin). The concentration of the antimicrobial agents available in the E-test varies from 0.002 µg/ml to 256 µg/ml.

Results

The *in vitro* activities of penicillin G, amoxicillin, amoxicillin-clavulanate, cefuroxime sodium, ceftriaxone, azithromycin, clarithromycin, levofloxacin, trovafloxacin,

and gatifloxacin against the 300 strains of *S. pneumoniae* are summarized in Table 1 and the results are expressed as MIC₅₀ and MIC₉₀ (µg/ml).

The MIC₉₀ for gatifloxacin for the 300 analyzed strains was 0.19 µg/ml ranging from 0.016 µg/ml to 0.5 µg/ml. The susceptibility for penicillin using 1 µg oxacillin disks demonstrated that 103 of 300 strains were not susceptible (halo ≤ 19 mm). The E-test of these 103 strains showed that 47 were susceptible to penicillin (MIC ≤ 0.06 µg/ml), 50 strains presented intermediated level resistance (MIC 0.1 µg/ml to 1.0 µg/ml), and 6 strains presented high level resistance (MIC ≥ 2 µg/ml); thus, 56 (18.6%) of the strains were considered penicillin resistant. We verified 7% of resistance to the second generation cephalosporin, and only 1 strain was not susceptible to ceftriaxone. Regarding the macrolides, resistance ranged from 6.7% for clarithromycin to 29.6% for azithromycin. The susceptibility to the new quinolones was 100%, including the 56 strains not susceptible to penicillin, with both MIC₅₀ and MIC₉₀ lower for trovafloxacin and gatifloxacin, respectively, when compared to levofloxacin. Among the 10 antibiotics evaluated gatifloxacin, levofloxacin and trovafloxacin displayed enhanced *in vitro* activity against *S. pneumoniae*.

Discussion

The results of this study, as summarized in Table 1, are in accordance with other studies [12, 13] and support the inclusion of the newest quinolones as monotherapy for the treatment of respiratory and other invasive infections caused by *S. pneumoniae*. Their use should be considered mainly in countries with a high frequency of respiratory tract infections due to resistant strains.

The improved pharmacokinetic profile of this generation of quinolones permits the use of a single daily dose and a switch of therapy. However, the fluoroquinolones should be chosen for situations in which they offer a clear therapeutic advantage over other classes of antibiotics, rather than being selected for routine empirical use because of their broad spectrum of action [14]. The rational and appropriate use of these drugs is important in order to minimize the development of resistance and to ensure the maximum benefit from this class of antibiotics.

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