

# Activity of Gatifloxacin Against Penicillin-, Macrolide- and Ciprofloxacin-Resistant *S. pneumoniae* Isolated from Pediatric, Adult and Elderly Hospitalized Patients in the United States

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## ABSTRACT

**Background:** Gatifloxacin is a newly marketed fluoroquinolone with enhanced activity against Gram-positive pathogens including *S. pneumoniae* (SPN) exhibiting varying resistance phenotypes. The purpose of this study was to examine the activities of gatifloxacin<sup>a</sup> (G) and comparators: levofloxacin (L), ciprofloxacin (C), penicillin (P), azithromycin (A) and ceftriaxone (CT) against clinical isolates of SPN resistant to penicillin, azithromycin or ciprofloxacin<sup>a</sup>. Isolates were collected from pediatric (< 18 yr.), adult (18-65 yr.) and elderly (> 65 yr.) patients in the United States in 1999/2000.

**Method:** A total of 108 centers geographically dispersed across the U.S. collected up to 50 isolates each from hospitalized patients with SPN that were deemed clinically significant. Susceptibilities to gatifloxacin and comparators were determined using Etest strips and interpreted following manufacturer's instructions and NCCLS guidelines as appropriate.

**Results:** : MIC<sub>90</sub> expressed as mcg/ml and % Susceptible (PenR/MacroR/CiproR)

Age Group	Drug	N	G <sup>a</sup>	L	C <sup>a</sup>	P	A	CT
Pediatric	PenR	349	0.38/100	2/100	2/79	8/0	>256/17	2/19
	MacroR	402	0.38/100	1/99	2/83	4/7	>256/0	2/38
	CiproR	37	0.5/100	4/86	16/0	8/65	>256/66	1/84
Adult	PenR	368	0.38/99	2/98	2/77	8/0	>256/27	2/26
	MacroR	493	0.38/99	2/97	2/75	4/14	>256/0	2/55
	CiproR	128	2/89	8/78	>32/0	4/61	>256/66	1/83
Elderly	PenR	234	0.38/99	2/97	2/70	8/0	>256/32	2/19
	MacroR	292	0.38/98	2/97	4/71	4/19	>256/0	2/51
	CiproR	91	1/90	4/82	>32/0	4/64	>256/67	1/81

<sup>a</sup> Breakpoints defined as susceptible ≤1, intermediate =2, resistant >2µg/ml

**Conclusions:** Gatifloxacin was more active in vitro against *Streptococcus pneumoniae* than all comparators irrespective of all resistance phenotypes.

## INTRODUCTION

Streptococci pathogens cause a wide range of infections in humans. More specifically, infections from *Streptococcus pneumoniae* rank among the top 10 leading causes of all deaths in the United States even in the post-antibiotic era. Morbidity and mortality from pneumococcal infections occur more frequently in populations at the extremes of the age continuum, the very young and very old, those with underlying diseases, and more recently, in those with high-level penicillin resistance to *S. pneumoniae*. The precipitous use of antibiotics since their discoveries has led to mutations in *S. pneumoniae* affecting the effectiveness of the penicillins

(penicillin binding proteins), macrolides (methylase and mefA genes) and now even the quinolones (parC, parE and pmrA genes). Current resistant rates in the United States have been reported as high as 29.5% for penicillin, 30% for macrolides and 0.3% for quinolones with wide variations from region to region.

In this study, gatifloxacin and comparative antimicrobial agents were tested against 4,751 *Streptococcus pneumoniae* collected by 108 medical centers within the United States between July 1999 and May 2000. The *in vitro* activities of gatifloxacin and five comparative agents were determined from respiratory isolates and the data presented below.

## MATERIALS & METHODS

- Isolates were collected between July 1999 and May 2000 from 108 study centers from the United States.
- Each center collected up to 50 pathogens of *Streptococcus pneumoniae* associated with respiratory tract infections.
- Each isolate was identified and determined to be the causative agent of a recent respiratory infection using local laboratory criteria. Only one isolate per patient was accepted.
- Organism collection, transport, storage and antimicrobial susceptibility testing, as well as construction and management of a centralized database, was coordinated by International Health Management Associates, Inc. (IHMA, Rolling Meadows, IL).

## ANTIMICROBIAL SUSCEPTIBILITY TESTING

- Gatifloxacin, levofloxacin, ciprofloxacin, azithromycin, ceftriaxone and penicillin minimum inhibitory concentrations (MICs) were determined using Etest strips (AB Biodisk, Solna, Sweden) according to the manufacturer's recommendations.
- Plates were inoculated with bacterial suspensions equivalent to a 0.5 McFarland standard and incubated at 35°C for 18-24 hours. All *S. pneumoniae* were incubated in the presence of 5% carbon dioxide.
- The antimicrobial breakpoints used for data analysis were those recommended by the NCCLS (M100-S10, 2000) for broth dilution susceptibility testing. Azithromycin breakpoints are those for Etest with *S. pneumoniae* incubated in CO<sub>2</sub> (AB Biodisk, Solna Sweden). Ciprofloxacin used breakpoints of susceptible ≤1 µg/ml, intermediate = 2 µg/ml, resistant ≥4 µg/ml were used.
- Control strains used were *S. pneumoniae* ATCC 49619 and *S. aureus* ATCC 29213. Test isolate results were accepted into the final analysis only if the quality control isolate MICs were within the acceptable range defined by NCCLS guidelines (M100-S10, 2001).

## RESULTS

Results are shown in the following Tables and Graphs.

Table 1. *In Vitro* Activity (µg/mL) of Gatifloxacin and 5 Comparators Against 4,751 Isolates of *Streptococcus pneumoniae* from 108 Centers in the United States

Antimicrobial	MIC <sub>50</sub>	MIC <sub>90</sub>	Range	%Sus <sup>a</sup>	%Int	%Res
Gatifloxacin	0.25	0.38	0.016 ->32	99.3	0.2	0.5
Ciprofloxacin <sup>b</sup>	1	2	0.008 ->32	71.0	22.9	6.1
Levofloxacin	1	1.5	0.016 ->32	98.7	0.7	0.6
Azithromycin <sup>c</sup>	1.5	256	0.016 ->256	71.3	2.0	26.7
Ceftriaxone	0.032	1	0.003 ->32	81.2	13.7	5.1

<sup>a</sup> Breakpoints derived from NCCLS publication M100-S11, 2001.

<sup>b</sup> Breakpoints defined as susceptible ≤1µg/ml, intermediate =2µg/ml resistant >2µg/ml

<sup>c</sup> Breakpoints for azithromycin and *S. pneumoniae* in CO<sub>2</sub> using Etest are: susceptible ≤4 µg/ml, intermediate = 8µg/ml, resistant >8 µg/ml.

Table 2. *In Vitro* Activity (µg/mL) of Gatifloxacin and 5 Comparators Against 4,746 Isolates of *Streptococcus pneumoniae* from the United States categorized by Susceptible, Intermediate and Resistant Penicillin Phenotypes

Phenotype (n)	Antimicrobial	MIC <sub>50</sub>	MIC <sub>90</sub>	Range	%Sus <sup>a</sup>	%Int	%Res
Penicillin (n = 2800)	Gatifloxacin	0.25	0.38	0.016 ->32	99.5	0.1	0.4
	Susceptible Ciprofloxacin <sup>b</sup>	1	2	0.008 ->32	67.1	26.3	6.5
	Levofloxacin	1	1.5	0.016 ->32	98.9	0.7	0.5
	Azithromycin <sup>c</sup>	1	2	0.016 ->256	93.5	0.5	6.0
	Ceftriaxone	0.016	0.047	0.003 -1.5	99.9	0.1	0.0
Intermediate (n = 965)	Penicillin	0.023	0.047	0.002 -0.064	100.0	0.0	0.0
	Gatifloxacin	0.25	0.38	0.023 ->32	99.0	0.4	0.6
	Ciprofloxacin <sup>b</sup>	0.75	2	0.023 ->32	76.7	18.1	5.2
	Levofloxacin	0.75	1.5	0.023 ->32	98.4	0.6	0.9
	Azithromycin <sup>c</sup>	2	>256	0.016 ->256	55.8	3.7	40.5
Resistant (n = 981)	Ceftriaxone	0.25	0.75	0.016 -24	87.2	10.9	2.0
	Penicillin	0.38	1	0.094 -1	0.0	100.0	0.0
	Gatifloxacin	0.25	0.38	0.016 ->32	99.3	0.1	0.6
	Ciprofloxacin <sup>b</sup>	0.75	2	0.016 ->32	76.2	18.0	5.8
	Levofloxacin	0.75	1.5	0.016 ->32	98.6	0.7	0.7
Resistant (n = 981)	Azithromycin <sup>c</sup>	48	>256	0.016 ->256	24.0	4.3	71.8
	Ceftriaxone	1	2	0.008 ->32	21.9	55.3	22.8
	Penicillin	2	6	1.5 ->256	0.0	0.0	100.0

<sup>a</sup> Breakpoints derived from NCCLS publication M100-S11, 2001.

<sup>b</sup> Breakpoints defined as susceptible ≤1µg/ml, intermediate=2µg/ml, resistant >2µg/ml

<sup>c</sup> Breakpoints for azithromycin and *S. pneumoniae* in CO<sub>2</sub> using Etest are: susceptible ≤4 µg/ml, intermediate = 8µg/ml, resistant >8 µg/ml.

Table 3. *In Vitro* Activity (µg/mL) of Gatifloxacin and 5 Comparators Against 1,506 Isolates of *Streptococcus pneumoniae* from the United States Resistant to Macrolides and Ciprofloxacin

Phenotype (n)	Antimicrobial	MIC <sub>50</sub>	MIC <sub>90</sub>	Range	%Sus <sup>b</sup>	%Int	%Res
Macrolide <sup>a</sup> (n = 1231)	Gatifloxacin	0.25	0.38	0.016 ->32	99.0	0.2	0.7
	Resistant Ciprofloxacin <sup>b</sup>	0.75	2	0.023 ->32	76.1	16.6	7.3
	Levofloxacin	0.75	1.5	0.016 ->32	98.0	1.1	1.0
	Azithromycin <sup>c</sup>	256	>256	12 ->256	0.0	0.0	100.0
	Ceftriaxone	0.75	1.5	0.008 ->32	48.7	37.2	14.1
Ciprofloxacin (n = 275)	Penicillin	1.5	4	0.002 -192	13.1	31.0	56.0
	Gatifloxacin	0.5	0.75	0.125 ->32	90.5	1.8	7.6
	Resistant Ciprofloxacin <sup>b</sup>	4	>32	3 ->32	0.0	0.0	100.0
	Levofloxacin	1.5	4	0.5 ->32	79.9	10.2	9.9
	Azithromycin <sup>c</sup>	1.5	>256	0.064 ->256	66.1	2.2	31.8
Resistant (n = 275)	Ceftriaxone	0.023	1	0.008 ->32	83.3	9.1	7.6
	Penicillin	0.032	3	0.008 -64	62.9	17.1	20.0

<sup>a</sup> Macrolide resistance determined by Etest breakpoints for azithromycin and *S. pneumoniae* incubated in CO<sub>2</sub> (MIC=8 µg/ml)

<sup>b</sup> Breakpoints derived from NCCLS publication M100-S11, 2001.

<sup>c</sup> Breakpoints for azithromycin and *S. pneumoniae* in CO<sub>2</sub> using Etest are: susceptible ≤4 µg/ml, intermediate = 8µg/ml, resistant >8 µg/ml.

Graph 1. Frequency distribution by age of 4,486 *Streptococcus pneumoniae* isolates collected from 108 centers in the United States from July 1999 to May 2000.

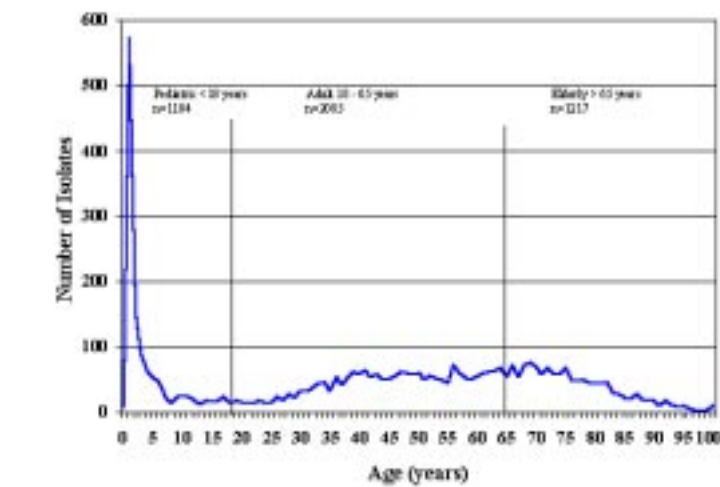


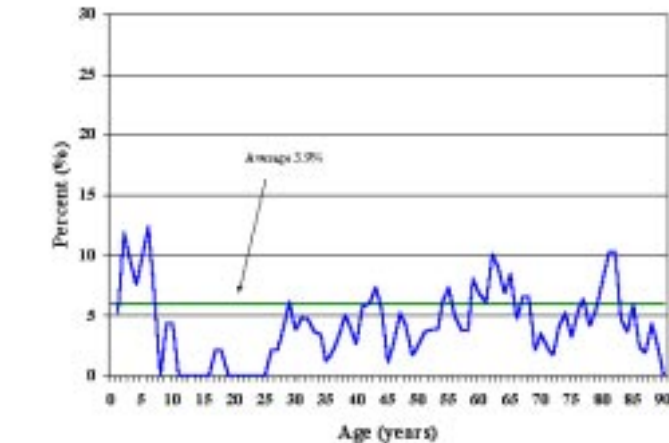
Table 4. *In Vitro* Activity (µg/mL) of Gatifloxacin and 5 Comparators Against 4,486 Isolates of *Streptococcus pneumoniae* from the United States Categorized by Age Groups

Age Group	Antimicrobial	MIC <sub>50</sub>	MIC <sub>90</sub>	Range	%Sus <sup>a</sup>	%Int	%Res
Pediatric <18 years	Gatifloxacin	0.25	0.38	0.032 - 0.75	100	0	0
	Ciprofloxacin <sup>b</sup>	0.75	2	0.023 ->32	74.9	21.8	3.2
	Levofloxacin	0.75	1.5	0.047 -4	99.5	0.5	0
Adult 18 to 65 years	Azithromycin <sup>c</sup>	1.5	>256	0.016 ->256	63.4	2.5	34.2
	Ceftriaxone	0.064	1	0.003 ->32	72.4	19.7	7.9
	Penicillin	0.094	3	0.003 -256	48.6	21.9	29.5
	Gatifloxacin	0.25	0.38	0.016 ->32	99.2	0.2	0.5
	Ciprofloxacin <sup>b</sup>	1	2	0.008 ->32	69.8	23.8	6.4
Elderly >65 years	Levofloxacin	1	1.5	0.016 ->32	98.6	0.8	0.7
	Azithromycin <sup>c</sup>	1.5	256	0.016 ->256	74.4	1.8	23.8
	Ceftriaxone	0.023	0.75	0.003 ->32	84.7	11.2	4.1
	Penicillin	0.032	2	0.002 -192	61.1	21.2	17.7
	Gatifloxacin	0.25	0.38	0.016 ->32	99.1	0.2	0.7
>65 years	Ciprofloxacin <sup>b</sup>	1	2	0.023 ->32	71.1	21.2	7.7
	Levofloxacin	1	1.5	0.023 ->32	98.5	0.7	0.8
	Azithromycin <sup>c</sup>	1.5	256	0.016 ->256	73.7	2	24.3
	Ceftriaxone	0.023	1	0.004 ->32	82	13.3	4.8

<sup>a</sup> Breakpoints derived from NCCLS publication M100-S11, 2001.

<sup>b</sup> Breakpoints defined as susceptible ≤1µg/ml, intermediate =2µg/ml, resistant >2µg/ml

Graph 2. Percentage (%) of *S. pneumoniae* isolates at each age where Penicillin MICs ≥ 4 µg/ml\*



\* Percentage calculations were omitted for any age where n < 20.

## CONCLUSIONS

- Gatifloxacin was more active *in vitro* against *Streptococcus pneumoniae* than all comparators irrespective of penicillin-, macrolide-, ciprofloxacin-resistant phenotypes or age demographics.
- Cross-resistance is seen less frequently with gatifloxacin than levofloxacin among ciprofloxacin resistant *Streptococcus pneumoniae*.
- High-level penicillin resistance (≥ 4 µg/ml) is more frequent in the very young and elderly.
- Ciprofloxacin resistance (MICs ≥ 4µg/ml) appear to be rising significantly, 6.1% up from 0.3% in 1996-1997,<sup>4,5</sup> among Streptococcus pneumoniae species within the United States.

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