Activity of Gatifloxacin Tested Against Isolates from Children Less Than 7 Years of Age: Report from the SENTRY Antimicrobial Surveillance Program (North America, 1998 - 2003)

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AMENDED ABSTRACT

Background: Ciprofloxacin (CIP) has been recently approved (FDA) for the treatment of complicated UTI in children and gatifloxacin (GAT) may be applied to the treatment of selected children with severe or refractory otitis media. We evaluated the activity of GAT against strains isolated in North American medical centers from children < 7 years old (y-o) in comparison with the general population using the SENTRY Program database.

Methods: Isolates were consecutively collected from 1998 to 2003 from > 30 medical centers located in the US and Canada. A total of 59,826 isolates were tested (4,641 from children < 7 y-o) by NCCLS broth microdilution methods.

Results: The table presents GAT susceptibility percentages among 2 patient populations and 10 pathogens.

	Children < 7 y-o/general population	
Organism (n)	% susceptible (S)	% resistant (R)
S. pneumoniae (SPN; 1,382/9,248)	100.0/99.2	0.0/0.7
S. aureus (747/17,260)	94.1/72.0	1.7/13.5
CoNS (749/4,951)	97.2/85.4	0.9/8.1
E. faecalis (EF; 244/3,514)	94.7/58.4	4.1/40.6
E. coli (513/10,356)	98.8/93.5	0.6/5.2
K. pneumoniae (272/4,251)	99.3/95.5	0.4/2.9
Enterobacter spp. (258/2,838)	99.2/95.5	0.4/2.9
Acinetobacter spp. (ASP; 84/1,044)	97.6/64.8	1.2/28.7
P. aeruginosa (PSA; 338/5,517)	95.0/69.1	1.2/21.6
S. maltophilia (54/847)	100.0/83.7	0.0/6.7

In contrast with the data from the general population, GAT-R rates were very low among isolates from younger children. GAT-S rates were > 94% for all pathogens evaluated. All SPN strains from children were S to GAT. GAT-S among Enterobacteriaceae was > 98%. The greatest difference in S rates between children and the general population was detected among non-fermentative Gram-negative bacilli and EF. S for PSA and ASP from children were ≥ 95% (≥ 97% for CIP).

Conclusions: GAT remains very active against bacterial strains isolated from children that are naive to fluoroquinolone therapy. Continued surveillance is necessary to monitor the activity of the fluoroquinolones as they are introduced into the pediatric age groups, especially among SPN and PSA.

INTRODUCTION

Gatifloxacin is a broad-spectrum fluoroquinolone with a methoxy side chain at the C-8 position. This side chain and other characteristics of the chemical structure of gatifloxacin minimize the rate at which bacteria can acquire antimicrobial resistance. At least two mutations of the QRDR are necessary for gatifloxacin resistance to occur.

Ciprofloxacin has been recently approved by the US-FDA for the treatment of complicated UTI in children, and gatifloxacin has been applied in clinical trials to the treatment of selected children with severe otitis media failing therapy with current agents such as Augmentin® (amoxicillin/clavulanate).

The SENTRY Antimicrobial Surveillance Program has monitored susceptibility rates and trends of pathogens worldwide since 1997. The purpose of this study was to evaluate the activity of gatifloxacin tested against strains isolated in North American medical centers from children less than seven years of age and compare those results to the general population of patients using the SENTRY Program database.

MATERIALS AND METHODS

A total of 59,826 isolates were collected by the SENTRY Program in North America from 1998 - 2003. Among these isolates, 4,641 were from children under seven years of age. The rank order of pathogens in these children was: *Streptococcus pneumoniae* (1,382 isolates) > coagulase-negative staphylococci (CoNS; 749 isolates) > *Staphylococcus aureus* (747 isolates) > *Escherichia coli* (513 isolates) > *Pseudomonas aeruginosa* (338 isolates), *Klebsiella pneumoniae* (272 isolates) > *Enterobacter* spp. (258 isolates) > *Enterococcus faecalis* (244 isolates) > *Acinetobacter* spp. (84 isolates) > *Stenotrophomonas maltophilia* (54 isolates).

Susceptibility tests were performed at the JMI Laboratories (North Liberty, Iowa, USA). The isolates were tested by NCCLS reference broth microdilution methods against greater than 30 antimicrobial agents including gatifloxacin, levofloxacin and ciprofloxacin. Quality control (QC) tests and inoculum colony counts were routinely performed with *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, *Haemophilus influenzae* ATCC 49247, *E. coli* ATCC 25922 and 35218 and *P. aeruginosa* ATCC 27853.

RESULTS

- The tables list the activity and potency of gatifloxacin for two patient populations (age < seven years, all patients) and 10 pathogens.
- In contrast with the data from the general all patient population, gatifloxacin resistance rates were very low among isolates from younger children (susceptibility was > 94% for all pathogens evaluated).

Table 1. In vitro activity of gatifloxacin against isolates from children < seven years of age.

	MIC (µg/ml)				
Organism/antimicrobial agent (no. tested)	50%	90%	Range	% susceptible	% resistant
S. pneumoniae (1,382)					
Gatifloxacin	0.25	0.5	≤0.03-1	100.0	0.0
Penicillin	0.03	2	≤0.03->4	54.9	26.0
Ceftriaxone	≤0.25	1	≤0.25-16	92.8	3.6
Erythromycin	≤0.25	>8	≤0.25->8	65.7	33.8
Clindamycin	≤0.25	>2	≤0.25->2	89.6	10.4
Tetracycline	≤4	>8	≤4->8	80.0[a]	20.0
Trimethoprim/Sulfamethoxazole	≤0.5	>1	≤0.5->1	54.6	37.8
S. aureus (747)					
Gatifloxacin	0.06	0.25	≤0.03->4	94.1	1.7
Levofloxacin	0.12	2	≤0.03->4	90.0	7.1
Ciprofloxacin	0.25	1	≤0.25->2	90.4	8.8
Oxacillin	0.5	>2	≤0.25->2	81.0	19.0
Erythromycin	0.5	>8	≤0.06->8	61.8	36.3
Clindamycin	0.12	0.5	≤0.06->8	91.0	8.4
CoNS (749)					
Gatifloxacin	0.12	2	≤0.03->4	97.2	0.9
Levofloxacin	0.25	>4	0.06->4	84.6	10.7
Ciprofloxacin	0.25	>2	≤0.25->2	83.7	15.8
Oxacillin	>2	>2	≤0.25->2	17.1	82.9
Erythromycin	>8	>8	≤0.06->8	14.6	84.8
Clindamycin	0.25	>8	≤0.06->8	52.6	46.9
E. faecalis (244)					
Gatifloxacin	0.5	0.5	0.12->4	94.7[b]	4.1[b]
Levofloxacin	1	2	0.5->4	92.8	6.6
Ciprofloxacin	1	2	0.5->2	85.2	6.6
Ampicillin	≤2	2	≤2->16	99.6	0.4
Vancomycin	1	2	0.5-4	100.0	0.0
Linezolid	2	2	0.25-8	96.7	0.4
E. coli (513)					
Gatifloxacin	≤0.03	0.06	≤0.03->4	98.8	0.6
Ciprofloxacin	≤0.25	≤0.25	≤0.25->2	98.6	1.4
Cefepime	≤0.12	≤0.12	≤0.12->16	99.8	0.2
Piperacillin/Tazobactam	2	4	≤0.5->64	98.4	0.6
Imipenem	≤0.5	≤0.5	≤0.5-4	100.0	0.0
Gentamicin	≤2	≤2	≤2->8	95.5	3.1
K. pneumoniae (272)					
Gatifloxacin	0.06	0.12	≤0.03->4	99.3	0.4
Ciprofloxacin	≤0.25	≤0.25	≤0.25->4	98.9	0.7
Cefepime	≤0.12	0.25	≤0.12-16	99.3	0.0
Piperacillin/Tazobactam	4	8	≤0.5->64	94.4	2.6
Imipenem	≤0.5	≤0.5	≤0.5->8	99.6	0.4
Gentamicin	≤2	≤2	≤2->8	94.1	3.3
Enterobacter spp. (258)					
Gatifloxacin	≤0.03	0.12	≤0.03->4	99.2	0.4
Ciprofloxacin	≤0.25	≤0.25	≤0.25->2	98.4	0.8
Cefepime	≤0.12	1	≤0.12->16	99.2	0.4
Piperacillin/Tazobactam	2	64	≤0.5->64	80.9	9.4
Imipenem	≤0.5	1	≤0.5-4	100.0	0.0
Gentamicin	≤2	≤2	≤2->8	93.4	5.0
Acinetobacter spp. (84)					
Gatifloxacin	0.06	0.12	≤0.03->4	97.6[c]	1.2[c]
Ciprofloxacin	≤0.25	0.5	≤0.25->4	97.6	2.4
Cefepime	2	8	0.25->16	92.9	2.4
Piperacillin/Tazobactam	2	32	≤0.5->64	85.5	4.8
Imipenem	≤0.5	≤0.5	≤0.5->8	98.8	1.2
P. aeruginosa (338)					
Gatifloxacin	0.5	2	0.12->4	95.0[b]	1.2[b]
Ciprofloxacin	≤0.25	0.5	≤0.25->2	97.9	1.5
Cefepime	2	8	0.5->16	92.0	1.2
Piperacillin/Tazobactam	4	64	≤0.5->64	93.2	6.8
Imipenem	1	2	≤0.5->8	95.6	0.9
S. maltophilia (54)					
Gatifloxacin	0.5	2	≤0.03-2	100.0[b]	0.0[b]
Ciprofloxacin	1	>2	0.25->2	50.0	29.6
Cefepime	16	>16	2->16	35.2	37.0
Imipenem	>8	>8	4->8	1.9	98.1
Trimethoprim/Sulfamethoxazole	≤0.5	≤0.5	≤0.5-1	100.0	0.0

a. Includes isolates susceptible and intermediate.
b. This breakpoint applies to UTI only.

- In children less than seven years, all *S. pneumoniae* strains were susceptible to gatifloxacin while 0.7% resistance was observed in the general population (0.7% resistance for levofloxacin). This is markedly different when compared to other drug classes, where greater resistance in pneumococci was observed in the younger patients.
- Gatifloxacin was at least 16-fold more potent against *S. aureus* in children < seven years old (MIC_{90}, 0.25 µg/ml) than in the general population (MIC_{90}, > 4 µg/ml). Similarly, among the coagulase-negative staphylococci, gatifloxacin was two-fold more potent against pediatric patient isolates.

Table 2. In vitro activity of gatifloxacin against isolates from the general population.

	MIC (µg/ml)				
Organism/antimicrobial agent (no. tested)	50%	90%	Range	% susceptible	% resistant
S. pneumoniae (9,248)					
Gatifloxacin	0.25	0.5	≤0.03->4	99.2	0.7
Penicillin	≤0.03	2	≤0.03->4	69.9	15.2
Ceftriaxone	≤0.25	1	≤0.25->16	96.5	1.5
Erythromycin	≤0.25	8	≤0.25->8	76.6	22.5
Clindamycin	≤0.25	≤0.25	≤0.25->2	92.7	7.0
Tetracycline	≤4	>8	≤4->8	85.9[a]	14.1
Trimethoprim/Sulfamethoxazole	≤0.5	>1	≤0.5->1	70.0	23.7
S. aureus (17,260)					
Gatifloxacin	0.12	>4	≤0.03->4	72.0	13.5
Levofloxacin	0.25	>4	≤0.03->4	60.2	32.5
Ciprofloxacin	0.5	>2	≤0.25->2	61.7	37.2
Oxacillin	0.5	>2	≤0.25->2	63.0	37.0
Erythromycin	4	>8	≤0.06->8	48.5	50.0
Clindamycin	>8	>8	≤0.06->8	69.4	30.4
CoNS (4,951)					
Gatifloxacin	0.25	4	≤0.03->4	85.4	8.1
Levofloxacin	2	>4	≤0.03->4	53.7	35.5
Ciprofloxacin	1	>2	≤0.25->2	50.4	48.0
Oxacillin	>2	>2	≤0.25->2	23.8	76.2
Erythromycin	>8	>8	≤0.06->8	28.6	70.8
Clindamycin	0.12	>8	≤0.06->8	60.0	39.5
E. faecalis (3,514)					
Gatifloxacin	0.5	>4	≤0.03->4	58.4[b]	40.6[b]
Levofloxacin	2	>4	≤0.03->4	55.0	44.5
Ciprofloxacin	2	>2	≤0.25->2	48.7	43.2
Ampicillin	≤2	2	≤2->16	99.2	0.8
Vancomycin	1	2	≤0.12->16	96.1	3.5
Linezolid	2	2	≤0.25->8	98.5	0.1
E. coli (10,356)					
Gatifloxacin	≤0.03	0.12	≤0.03->4	93.5	5.2
Ciprofloxacin	≤0.25	≤0.25	≤0.25->2	93.1	6.7
Cefepime	≤0.12	≤0.12	≤0.12->16	99.7	0.2
Piperacillin/Tazobactam	2	4	≤0.5->64	97.2	1.1
Imipenem	≤0.5	≤0.5	≤0.5-4	100.0	0.0
Gentamicin	≤2	≤2	≤2->8	96.0	3.3
K. pneumoniae (4,251)					
Gatifloxacin	0.06	0.5	≤0.03->4	95.5	2.9
Ciprofloxacin	≤0.25	0.5	≤0.25->2	93.9	4.7
Cefepime	≤0.12	0.25	≤0.25->16	99.3	0.4
Piperacillin/Tazobactam	2	8	≤0.5->64	95.3	2.6
Imipenem	≤0.5	≤0.5	≤0.5->8	99.9	0.1
Gentamicin	≤2	≤2	≤2->8	94.3	4.3
Enterobacter spp. (2,838)					
Gatifloxacin	≤0.03	0.5	≤0.03->4	95.5	2.9
Ciprofloxacin	≤0.25	0.5	≤0.25->2	93.6	4.6
Cefepime	≤0.12	2	≤0.12->16	99.0	0.4
Piperacillin/Tazobactam	2	64	≤0.5->64	83.5	6.7
Imipenem	≤0.5	1	≤0.5->8	99.9	0.1
Gentamicin	≤2	≤2	≤2->8	93.7	5.0
Acinetobacter spp. (1,044)					
Gatifloxacin	0.12	>4	≤0.03->4	64.8[c]	28.7[c]
Ciprofloxacin	≤0.25	>2	≤0.25->2	60.8	37.7
Cefepime	4	>16	≤0.12->16	63.1	22.5
Piperacillin/Tazobactam	8	>64	≤0.5->64	63.2	20.3
Imipenem	≤0.5	4	≤0.5->8	92.4	4.7
P. aeruginosa (5,517)					
Gatifloxacin	1	>4	≤0.03->4	69.1[b]	21.6[b]
Ciprofloxacin	≤0.25	>2	≤0.25->2	75.2	19.0
Cefepime	4	16	≤0.12->16	85.2	5.5
Piperacillin/Tazobactam	8	>64	≤1->64	89.1	10.9
Imipenem	1	8	≤0.5->8	86.9	7.6
S. maltophilia (847)					
Gatifloxacin	1	4	≤0.03->4	83.7[c]	6.7[c]
Ciprofloxacin	2	>2	≤0.25->2	27.2	43.0
Cefepime	16	>16	≤0.12->16	30.5	37.3
Imipenem	>8	>8	0.5->8	0.9	98.0
Trimethoprim/Sulfamethoxazole	≤0.5	≤0.5	≤0.5->1	97.8	2.2

a. Includes isolates susceptible and intermediate.
b. This breakpoint applies to UTI only.

- In pediatric patient isolates, gatifloxacin (MIC_{90}, ≤ 0.12 µg/ml) susceptibility among the Enterobacteriaceae was > 98% (lower rates for ciprofloxacin, see tables).
- Among the *E. faecalis*, the gatifloxacin (MIC_{90}, 0.5 µg/ml) susceptibility rate was 94.7% for strains from younger children. In contrast, gatifloxacin susceptibility rates (MIC_{90}, ≥ 4 µg/ml; 58.4% susceptible) in the general population was almost half that observed in younger children.
- Gatifloxacin susceptibility for *P. aeruginosa* (MIC_{50}, 0.5 µg/ml) and *Acinetobacter* spp. (MIC_{50}, 0.06 µg/ml) isolated from children less than seven years old was ≥ 95% (≥ 97% for ciprofloxacin, MIC_{50}, ≤ 0.25 µg/ml). However, in the general population, fluoroquinolone susceptibility rates were generally 20% lower.

CONCLUSIONS

- The greatest difference in susceptibility rates of gatifloxacin between children and the general population was detected among the non-fermentative Gram-negative bacilli and *E. faecalis*.
- Gatifloxacin remains very active against bacterial strains isolated from children overall that are naive to fluoroquinolone therapy and selection toward resistance.
- Gatifloxacin activities versus *S. pneumoniae* isolated from children show no significant resistance and continued potential for use for organisms resistant to contemporary regimens from refractory otitis media infections.
- Continued surveillance will be necessary to monitor the activity of the fluoroquinolones as they are introduced into the pediatric age groups and as a component of a comprehensive risk management plan.

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