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Quinolone, Beta-lactam and Macrolide Activity Against *S. pneumoniae* from Hospitalized Patients in the United States Irrespective of Regional Resistance Patterns

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ABSTRACT

Background: The prevalence of penicillin (Pen)- and macrolide (azithromycin)- resistant(R) *S. pneumoniae* (SPN) varies by country and region. Earlier studies have documented U.S. regional variations in PenR SPN only. The purpose of this study was to determine regional variations of Pen and macrolide (Mac) R and non-susceptible (NS) strains of SPN, and to determine the activity of gatifloxacin[a] (Gat) and ceftriaxone (Cfx), ciprofloxacin (Cip), levofloxacin (Lev), azithromycin (Azi) and Pen to resistant isolates.

Methods: Up to 50 clinically relevant isolates of SPN were collected from patients in 108 hospitals. MIC's to all agents tested were determined using Etest strips and interpreted following manufacturer's instructions and NCCLS guidelines. The CDC Regions were defined as: East North Central (ENC), East South Central (ESC), Mid-Atlantic (MA), Mountain (Mt), New England (NE), Pacific (P), South Atlantic (SA), West North Central (WNC), and West South Central (WSC).

Results: Incidence of PenR and MacR was 21% and 27% respectively. AziR/AziNS (>0.5µg/ml) strains of SPN were highest in the ESC, 41.7%/42.2% and lowest in the NE, 17.2%/20.7%. PenR/PenNS (>0.06µg/ml) strains of SPN were highest in the ESC, 33.67%/53.3% and lowest in the NE, 9.7%/26.1%. Regional comparisons of PenR and AziR are listed below and expressed in MIC_{90} µg/ml/% Resistant:

Region	Pen/Mac Res (n)	Azi	Cfx	Cip[a]	Gat	Lev	Pen
ENC	PenR (177)	>256/77	4/34	2/7	0.38/0.6	1/0.6	8/100
	MacR (214)	>256/100	2/24	2/10	0.38/0.5	1/0.5	8/64
ESC	PenR (67)	>256/79	4/30	2/7	0.38/0	2/0	8/100
	MacR (83)	>256/100	2/22	2/7	0.38/0	2/0	4/64
M A	PenR (107)	>256/65	2/24	2/3	0.38/2	2/2	8/100
	MacR (126)	>256/100	2/13	2/6	0.38/2	2/3	8/56
Mt	PenR (69)	>256/69	2/19	2/3	0.38/0	1/0	8/100
	MacR (77)	>256/100	2/13	2/3	0.38/0	1/0	4/61
NE	PenR (34)	>256/40	4/35	2/10	0.38/0	2/0	8/100
	MacR (44)	>256/100	1/7	4/16	0.38/5	2/5	4/27
P	PenR (74)	>256/71	2/14	4/11	0.38/0	2/0	8/100
	MacR (97)	>256/100	1/6	4/10	0.38/1	2/1	4/48
S A	PenR (265)	>256/75	2/21	2/4	0.38/0.4	2/0.8	8/100
	MacR (327)	>256/100	2/14	2/6	0.38/0	2/0.3	4/59
WNC	PenR (67)	>256/61	2/16	4/10	0.38/3	2/3	8/100
	MacR (83)	>256/100	2/12	2/10	0.38/2	2/4	4/49
WSC	PenR (121)	>256/73	2/13	2/3	0.38/0	2/0	4/100
	MacR (180)	>256/100	1/8	2/4	0.38/0	2/0	4/49

[a] Breakpoints defined as susceptible ≤1 µg/ml, intermediate = 2 µg/ml, resistant ≥4 µg/ml.

Conclusions: Gatifloxacin was >95% active *in vitro* against SPN irrespective of observed regional variation for PenR or MacR *SPN* and >99% active *in vitro* overall.

INTRODUCTION

Resistance among common Gram-positive pathogens, notably *Streptococcus pneumoniae*, has compromised the therapeutic effectiveness of commonly employed antimicrobials. Since first reported in 1965, there has been a significant rise of penicillin resistance in *S. pneumoniae*. This is a significant problem since both multiple drug resistance and increased mortality are associated with high levels of penicillin drug resistance (>4µg/ml). Likewise Penicillin nonsusceptible *S. pneumoniae* have increased rapidly over the last 8 years from 10.9% to as high as 46.9% in controlled surveillance studies and have been shown to vary from country to country and region to region. There has been a concurrent rise in macrolide resistance but regional distribution within the United States has not been widely published. While quinolone MICs have typically remained low, surveillance studies are beginning to show a rise in *S. pneumoniae* isolates with ciprofloxacin nonsusceptible and resistant MICs.

The *in vitro* activity of six comparative antimicrobial agents were tested against 4,751 *Streptococcus pneumoniae* collected by 108 medical centers within the United States. Regional *in vitro* activity and susceptibility differences were recorded for gatifloxacin, ciprofloxacin, levofloxacin, ceftriaxone, azithromycin and penicillin.

MATERIALS & METHODS

- Isolates were collected between July 1999 and May 2000 from 108 study centers within 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).

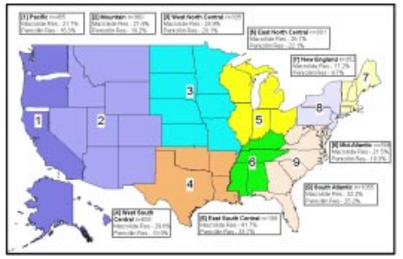
ANTIMICROBIAL SUSCEPTIBILITY TESTING

- 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. *S. pneumoniae* was incubated in the presence of 5% carbon dioxide.
- The antimicrobial breakpoints used for data analysis were those recommended by the NCCLS (M100-S11, 2001) for broth dilution susceptibility testing. Azithromycin breakpoints are those for Etest with *S. pneumoniae* incubated in CO_2 (AB Biodisk, Solna Sweden). Ciprofloxacin used a breakpoint of susceptible ≤1 µg/ml, intermediate = 2 µg/ml, resistant ≥4 µg/ml.
- 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-S11, 2001).

RESULTS

Results are shown in the following Tables and Graphs.

Figure 1. Geographic Map of Penicillin and Macrolide[a] Percent Resistance (%) of 4,751 Isolates of *Streptococcus pneumoniae* from 108 Centers in the United States Categorized by CDC Regions



[a] Macrolide resistance determined by Etest breakpoints for azithromycin and *S. pneumoniae* incubated in CO_2 (MIC ≥ 16 µg/ml)

Table 1. *In Vitro* Activity (MIC µg/ml) of Six Comparative Agents Against 4,751 Isolates of *Streptococcus pneumoniae* from 109 Centers in the United States Categorized by CDC Regions.

CDC Region	Antimicrobial	%Sus	%Int	%Res	%NS	MIC_{50}	MIC_{90}
All Regions	Gatifloxacin	99.3	0.2	0.5	0.7	0.25	0.38
(n=4,751)	Ciprofloxacin [a]	71.0	22.9	6.1	29.0	1	2
	Levofloxacin	98.7	0.7	0.6	1.3	1	1.5
	Azithromycin [b]	71.3	2.0	26.7	28.7	1.5	256
	Ceftriaxone	81.2	13.7	5.1	18.8	0.032	1
	Penicillin	59.0	20.3	20.7	41.0	0.047	2
East	Gatifloxacin	99.5	0.1	0.4	0.5	0.25	0.38
North	Ciprofloxacin [a]	72.8	22.5	4.7	27.2	1	2
Central	Levofloxacin	99.4	0.1	0.5	0.6	0.75	1.5
(n=801)	Azithromycin [b]	71.5	1.7	26.7	28.5	1.5	256
	Ceftriaxone	79.5	12.9	7.6	20.5	0.032	1
	Penicillin	61.3	16.6	22.1	38.7	0.047	3
East	Gatifloxacin	100.0	0.0	0.0	0.0	0.25	0.38
South	Ciprofloxacin [a]	73.4	21.1	5.5	26.6	1	2
Central	Levofloxacin	99.5	0.5	0.0	0.5	0.75	1.5
(n=199)	Azithromycin [b]	57.8	0.5	41.7	42.2	2	>256
	Ceftriaxone	66.3	20.6	13.1	33.7	0.125	1.5
	Penicillin	46.7	19.6	33.7	53.3	0.19	3
Mid-Atlantic	Gatifloxacin	99.1	0.2	0.7	0.9	0.25	0.38
(n=586)	Ciprofloxacin [a]	82.4	14.1	3.5	17.6	0.75	1.5
	Levofloxacin	98.6	0.7	0.7	1.4	0.75	1.5
	Azithromycin [b]	76.8	1.7	21.5	23.2	1.5	256
	Ceftriaxone	82.4	13.1	4.4	17.6	0.023	1
	Penicillin	63.1	18.6	18.3	36.9	0.032	2
Mountain	Gatifloxacin	100.0	0.0	0.0	0.0	0.25	0.38
(n=360)	Ciprofloxacin [a]	81.7	14.4	3.9	18.3	0.75	1.5
	Levofloxacin	99.7	0.3	0.0	0.3	0.75	1.5
	Azithromycin [b]	77.2	1.4	21.4	22.8	1.5	256
	Ceftriaxone	82.5	13.6	3.9	17.5	0.032	1
	Penicillin	58.9	21.9	19.2	41.1	0.047	2
New	Gatifloxacin	98.6	0.6	0.9	1.4	0.25	0.38
England	Ciprofloxacin [a]	63.7	31.7	4.6	36.3	1	2
(n=352)	Levofloxacin	98.3	0.3	1.4	1.7	1	1.5
	Azithromycin [b]	79.3	3.5	17.2	20.7	1.5	128
	Ceftriaxone	92.0	4.5	3.4	8.0	0.023	0.5
	Penicillin	73.9	16.5	9.7	26.1	0.032	1
Pacific	Gatifloxacin	98.9	0.2	0.9	1.1	0.25	0.5
(n=455)	Ciprofloxacin [a]	52.2	30.4	17.4	47.8	1	3
	Levofloxacin	96.7	2.2	1.1	3.3	1	2
	Azithromycin [b]	75.8	2.5	21.7	24.2	1.5	256
	Ceftriaxone	84.6	13.2	2.2	15.4	0.023	0.75
	Penicillin	65.4	18.3	16.3	34.6	0.032	2
South	Gatifloxacin	99.5	0.2	0.3	0.5	0.25	0.38
Atlantic	Ciprofloxacin [a]	71.5	22.7	5.8	28.5	0.75	2
(n=1055)	Levofloxacin	98.6	1.0	0.5	1.4	1	1.5
	Azithromycin [b]	65.8	2.1	32.2	34.2	1.5	256
	Ceftriaxone	77.8	16.5	5.7	22.2	0.047	1
	Penicillin	52.1	22.7	25.2	47.9	0.064	3
West	Gatifloxacin	98.8	0.3	0.9	1.2	0.25	0.38
North	Ciprofloxacin [a]	62.4	28.7	9.0	37.6	1	2
Central	Levofloxacin	97.9	0.9	1.2	2.1	1	1.5
(n=335)	Azithromycin [b]	72.5	2.7	24.9	27.5	1.5	256
	Ceftriaxone	84.2	11.3	4.5	15.8	0.023	1
	Penicillin	62.9	17.1	20.1	37.1	0.032	2
West	Gatifloxacin	99.5	0.2	0.3	0.5	0.25	0.38
South	Ciprofloxacin [a]	72.4	25.0	2.6	27.6	1	2
Central	Levofloxacin	99.5	0.2	0.3	0.5	0.75	1.5
(n=608)	Azithromycin [b]	68.6	1.8	29.6	31.4	1.5	>256
	Ceftriaxone	81.7	15.1	3.1	18.3	0.047	0.75
	Penicillin	52.5	27.6	19.9	47.5	0.064	2

[a] Breakpoints defined as susceptible ≤1 µg/ml, intermediate = 2 µg/ml, resistant ≥4 µg/ml.

[b] Breakpoints for azithromycin and *S. pneumoniae* in CO_2 using Etest are: susceptible ≤4 µg/ml, intermediate = 8, resistant ≥8 µg/ml.

Table 2. *In Vitro* Activity (MIC µg/ml) of Six Comparative Agents against Penicillin and Macrolide Non-Susceptible Isolates of *Streptococcus pneumoniae* from 108 Centers in the United States

Phenotype (n)	Antimicrobial	%Sus	%Int	%Res	MIC_{50}	MIC_{90}
Penicillin	Gatifloxacin	99.1	0.3	0.6	0.25	0.38
Non-Susceptible	Ciprofloxacin [a]	76.5	18.0	5.5	0.75	2
(n=1,946)	Levofloxacin	98.5	0.7	0.8	0.75	1.5
	Azithromycin [b]	39.7	4.0	56.3	16	>256
	Ceftriaxone	54.3	33.3	12.4	0.5	1.5
	Penicillin	0.0	49.6	50.4	1.5	4
Macrolide	Gatifloxacin	98.9	0.3	0.8	0.25	0.38
Non-Susceptible	Ciprofloxacin [a]	75.5	17.2	7.3	0.75	2
(n=1,322)	Levofloxacin	97.9	1.1	1.1	0.75	1.5
	Azithromycin [b]	0.0	6.9	93.1	192	>256
	Ceftriaxone	49.5	36.6	13.8	0.75	1.5
	Penicillin	13.2	31.5	55.3	1.5	4

[a] Breakpoints defined as susceptible ≤1 µg/ml, intermediate = 2 µg/ml, resistant ≥4 µg/ml.

[b] Breakpoints for azithromycin and *S. pneumoniae* in CO_2 using Etest are: susceptible ≤4 µg/ml, intermediate = 8, resistant ≥8 µg/ml.

Table 2. Frequency Distribution (N) and Cumulative Percent Inhibited (%) Data on 1,307 Ciprofloxacin Non-Susceptible *Streptococcus pneumoniae* (MIC >1 µg/ml) from 108 Centers in the United States.

MICs (µg/ml)		0.032	0.125	0.25	0.5	1	2	4	8	16	32	>32
Ciprofloxacin	n						378	56	19	5	2	34
	%						79.0	93.3	96.3	97.2	97.4	100.0
Gatifloxacin [a]	n	1	8	331	233	3	5	2	2	2		5
	%	0.1	0.8	29.1	95.2	97.8	98.4	98.6	98.9	99.4		100.0
Levofloxacin [b]	n				15	398	163	4	5	5		17
	%				1.2	37.3	95.4	97.9	98.3	98.7		100.0

[a] Gatifloxacin breakpoints, susceptible ≤ 1 µg/ml, intermediate = 2 µg/ml, resistant ≥ 4 µg/ml

[b] Levofloxacin breakpoints, susceptible ≤ 2 µg/ml, intermediate = 4 µg/ml, resistant ≥ 8 µg/ml

CONCLUSIONS

- Gatifloxacin was >99% active in vitro against all *S. pneumoniae* tested.
- Gatifloxacin demonstrated the lowest *in vitro* MIC_{90} at 0.38 µg/ml of all antimicrobial agents in all regions and regardless of resistant phenotype.
- Penicillin and macrolide resistance were more prevalent in the South Eastern Regions: East South Central and South Atlantic.
- Penicillin and macrolide resistance is lowest in the New England region.
- Over 25% of all *Streptococcus pneumoniae* isolates tested had a ciprofloxacin non-susceptible MIC >1 µg/ml and 6% had an MIC ≥4 µg/ml.
- Resistant patterns vary at local, regional, and national levels and require the structured monitoring of controlled surveillance studies for the benefit of therapeutic regimes and the research and development of antimicrobial agents.

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