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In Vitro Activity of Gemifloxacin Against Multiple-drug-resistant Strains of *Streptococcus pneumoniae* Isolated From 42 Countries in North America, Latin America, Europe, Asia, South Pacific and Africa/Middle East

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Abstract

Background: While penicillin and macrolide antibiotics have been the mainstay of therapy against *Streptococcus pneumoniae* (*Sp*) for decades, the prevalence of penicillin-, macrolide- and trimethoprim/sulfamethoxazole (T/S)-resistant *Sp* has increased. In addition, a large number of these strains are multiple-drug resistant (three or more drug classes). Respiratory quinolones have shown potential to effectively treat *Sp* including penicillin- and macrolide-resistant strains. **Methods:** Gemifloxacin, an enhanced-affinity quinolone, was tested against more than 3500 *Sp,* including penicillin-susceptible *Sp* (PSSP), penicillin-resistant (PRSP), macrolide-resistant (MRSP), T/S-resistant (T/SRSP) and multiple-drug-resistant (MDRSP) strains collected worldwide. Testing centers performed broth microdilution determinations on each isolate under a standardized protocol and reporting system, following NCCLS recommended procedures, using Sensititre or MicroScan panels and ancillary products. **Results:** The MIC_{90}s (µg/ml) of PSSP, PRSP, MRSP, T/SRSP and MDRSP were as follows:

Agent	MIC_{90} (µg/ml)				
	PSSP (n = 2026)	PRSP (n = 597)	MRSP (n = 1037)	T/SRSP (n = 981)	MDRSP[a] (n = 317)
Gemifloxacin	0.03	0.06	0.06	0.06	0.06
Grepafloxacin	0.25	0.25	0.25	0.25	0.25
Levofloxacin	1	1	1	1	1
Trovafloxacin	0.12	0.12	0.12	0.12	0.12
Clarithromycin	2	16	16	16	16
T/S	2	16	8	16	16
Cefuroxime	0.12	8	8	8	8

[a]Resistant to penicillin, macrolides and trimethoprim/sulfamethoxazole

Conclusions: Gemifloxacin demonstrated greater potency than levofloxacin, grepafloxacin, trovafloxacin, clarithromycin, T/S and cefuroxime against all resistant groups including MDRSP. Gemifloxacin offers an alternative to other therapies against MDRSP.

Introduction

The rapid emergence of penicillin-, macrolide-, trimethoprim/sulfamethoxazole (T/S)- and multidrug-resistant *Streptococcus pneumoniae* over the past 10 years has encouraged the development of new, highly potent compounds to combat this growing therapeutic problem.

Gemifloxacin is an enhanced-affinity quinolone that demonstrates a higher affinity for topoisomerase IV than other quinolones. In previous studies, gemifloxacin has shown excellent *in vitro* activity against a variety of pathogens, especially those found in respiratory infections, such as *S. pneumoniae*. In repeated studies, gemifloxacin has sustained potent activity against *S. pneumoniae* harboring target site mutations (GyrA, GyrB, ParC, ParE) and/or efflux mechanisms that may significantly elevate MICs to other quinolones.

Objectives

The current study, *The Gemifloxacin Global Surveillance Study*, provides a comprehensive view of the *in vitro* activity of gemifloxacin and comparative antimicrobials against *S. pneumoniae* resistant to penicillin, macrolides and T/S in countries and regions worldwide. In addition, the *in vitro* activity of gemifloxacin against multidrug-resistant *S. pneumoniae* was determined and compared with other antimicrobials with similar activity spectra.

Materials and Methods

S. pneumoniae Isolates

- Isolates were collected between September 1997 and April 2000. Most sites (n = 130) in 42 countries contributed up to 50 isolates of *S. pneumoniae* for the study.
- Each isolate was identified as *S. pneumoniae* and deemed by local laboratory criteria to be a significant pathogen.
- The *S. pneumoniae* isolates described in this poster are a component of a larger prospective international surveillance study of the activity of gemifloxacin against selected aerobic Gram positive and Gram negative pathogens.
- Isolate collection, processing, transport and antimicrobial susceptibility testing methods as well as the construction of a centralized database to record worldwide antimicrobial susceptibility testing results were coordinated by Laboratories International for Microbiology Studies, International Health Management Associates (IHMA) (Rolling Meadows, IL, USA).
- Available demographic information included patient age, specimen source and in- *versus* outpatient information.

Antimicrobial Susceptibility Testing

- MICs were determined by the NCCLS recommended broth microdilution testing method.[1] The microdilution panels used in this study were purchased from Sensititre® (Trek Diagnostics Inc., Westlake, OH) and MicroScan® (Dade Behring Inc., Sacramento, CA) and utilized identical antimicrobial dilution configurations. Gemifloxacin was supplied by SmithKline Beecham (Collegeville, PA) and comparative antimicrobials by their respective manufacturers or the panel manufacturer. Appropriate broth media were also provided directly by the panel manufacturers.[1]
- MICs were determined in each participating country at one or more designated laboratories.
- Gemifloxacin disk testing (5 and 10 µg disks) was conducted by most testing sites in Europe and North America.
- The antimicrobial breakpoints used for data analysis were those recommended by the NCCLS for broth dilution susceptibility testing.[2]
- Each designated testing laboratory performed quality controls each day of testing using *S. pneumoniae* ATCC 49619. 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.[2]

Participating Study Centers

The number of isolates and collecting sites per region are shown in Table 1.

Table 1. Number of Countries, Sites and *S. pneumoniae* Isolates Per Region

Region	No. of countries	No. of sites	No. of isolates
Europe	16	61	2019
North America	2	15	417
Latin America	3	19	181
Asia	13	17	693
Africa/Middle East	6	11	132
South Pacific	2	7	85

Results

See Tables 2–7.

Table 2. *In Vitro* Activity (MIC µg/ml) of Gemifloxacin and Comparative Antimicrobials Against 3527 Isolates of *S. pneumoniae* From Six Global Regions

Antimicrobial	Europe (n = 2019)		North America (n = 417)		Latin America (n = 181)		Asia (n = 693)		Africa/Middle East (n = 132)		South Pacific (n = 85)	
	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Penicillin	0.015	2	0.03	2	0.03	1	0.25	2	0.12	1	0.03	2
Cefuroxime	<0.06	4	0.06	8	<0.06	4	0.5	8	0.12	2	0.06	4
Azithromycin	<0.06	>64	0.06	16	<0.06	16	4	>64	0.12	8	0.06	8
Clarithromycin	0.03	>16	0.03	8	<0.015	2	2	>16	0.03	2	0.03	1
T/S[a]	0.25	4	0.25	8	0.5	8	1	8	1	4	0.25	>64
Ciprofloxacin	1	2	1	2	1	2	1	2	1	1	1	2
Grepafloxacin	0.12	0.25	0.12	0.25	0.25	0.5	0.12	0.25	0.12	0.25	0.25	0.5
Levofloxacin	0.5	1	1	1	1	1	1	1	1	1	1	2
Ofloxacin	2	2	2	2	2	2	2	2	1	2	2	2
Trovafloxacin	0.12	0.25	0.12	0.12	0.06	0.12	0.06	0.12	0.06	0.12	0.12	0.25
Gemifloxacin	0.015	0.03	0.015	0.03	0.03	0.06	0.03	0.06	0.03	0.06	0.03	0.06

[a]T/S, trimethoprim/sulfamethoxazole, ratio tested was 1:19

Table 3. Global *In Vitro* Activity (MIC µg/ml) of Gemifloxacin and Comparative Antimicrobials Against 3527 Isolates of *S. pneumoniae* from 42 Countries and 130 Sites

Antimicrobial	MIC_{50}	MIC_{90}	Range	% S[a]	% I[a]	% R[a]
Penicillin	0.06	2	<0.015–>16	57.4	25.7	16.9
Cefuroxime	0.06	4	<0.06–>64	72.4	4.4	23.2
Azithromycin	0.06	>64	<0.06–>64	67.4	1.9	30.7
Clarithromycin	0.03	>16	<0.015–>16	67.1	1.6	31.3
T/S[b]	0.25	8	<0.06–>64	59.7	12.5	27.8
Ciprofloxacin	1	2	<0.015–>16	NC[c]	NC	NC
Grepafloxacin	0.12	0.25	<0.015–16	99.2	0.5	0.3
Levofloxacin	1	1	<0.015–>16	99.7	0.1	0.2
Ofloxacin	2	2	<0.06–32	96.4	3.2	0.4
Trovafloxacin	0.12	0.12	<0.015–>16	99.8	0.1	0.1
Gemifloxacin	0.015	0.06	0.001–0.5	NC	NC	NC

[a]NCCLS recommended breakpoints (µg/ml) were used to group isolates into % susceptible (% S), % intermediate (% I) and % resistant (% R) categories[2]
[b]Trimethoprim/sulfamethoxazole, ratio tested was 1:19
[c]NA, breakpoints have not been established by NCCLS

Table 4. *In Vitro* Activity (MIC µg/ml) of Gemifloxacin and Comparative Antimicrobial Agents Against Isolates of *S. pneumoniae* Susceptible, Intermediate and Resistant to Penicillin

Phenotype	Antimicrobial	MIC_{50}	MIC_{90}	Range	% S[a]	% I[a]	% R[a]
PSSP[b] (n = 2026)	Penicillin	0.015	0.06	<0.015–0.06	100	0	0
	Cefuroxime	0.06	0.12	<0.06–8	99.5	0.3	0.2
	Azithromycin	0.06	2	<0.06–>64	88.9	0.6	10.5
	Clarithromycin	0.03	2	<0.015–>16	88.1	0.8	11.1
	T/S[c]	0.25	2	<0.06–>64	84.7	8.2	7.1
	Ciprofloxacin	1	2	<0.015–>16	NA[d]	NA	NA
	Grepafloxacin	0.12	0.25	<0.015–8	99.3	0.5	0.2
	Levofloxacin	1	1	<0.015–8	99.7	0.2	0.1
	Ofloxacin	2	2	<0.06–32	97.4	2.3	0.3
	Trovafloxacin	0.12	0.12	<0.015–4	99.9	0	0.1
	Gemifloxacin	0.015	0.03	0.001–0.25	NA	NA	NA
PISP[b] (n = 904)	Penicillin	0.5	1	0.12–1	0	100	0
	Cefuroxime	1	4	<0.06–>64	58.0	13	29.0
	Azithromycin	0.1	64	<0.06–>64	48.2	4.0	47.8
	Clarithromycin	0.5	16	0.015–>16	49.2	3.1	47.7
	T/S[c]	2	8	<0.06–>64	35.0	21.5	43.5
	Ciprofloxacin	1	2	<0.015–16	NA	NA	NA
	Grepafloxacin	0.12	0.25	<0.015–8	99.3	0.6	0.1
	Levofloxacin	1	1	<0.015–8	99.7	0	0.3
	Ofloxacin	2	2	<0.06–32	94.7	4.9	0.4
	Trovafloxacin	0.12	0.12	<0.015–4	99.9	0	0.1
	Gemifloxacin	0.03	0.06	0.002–0.5	NA	NA	NA
PRSP[b] (n = 597)	Penicillin	2	4	2–>16	0	0	100
	Cefuroxime	4	8	<0.06–>64	2.5	5.2	92.3
	Azithromycin	64	64	<0.06–>64	23.3	3.2	73.5
	Clarithromycin	16	16	<0.015–>16	23.3	1.8	74.9
	T/S[c]	4	16	<0.06–>64	12.4	13.4	74.2
	Ciprofloxacin	1	2	<0.015–>16	NA	NA	NA
	Grepafloxacin	0.12	0.25	<0.015–16	98.8	0.5	0.7
	Levofloxacin	1	1	<0.015–16	99.7	0.2	0.1
	Ofloxacin	2	2	<0.06–32	95.3	4.0	0.7
	Trovafloxacin	0.12	0.12	<0.015–>16	99.5	0.2	0.3
	Gemifloxacin	0.03	0.06	0.002–0.5	NA	NA	NA

[a]NCCLS recommended breakpoints (µg/ml) were used to group isolates into % susceptible (% S), % intermediate (% I) and % resistant (% R) categories[2]
[b]Penicillin susceptible (PSSP) = ≤0.06 µg/ml; penicillin intermediate (PISP) = 0.12–1.0 µg/ml; penicillin resistant (PRSP) = ≥2.0 µg/ml
[c]T/S, trimethoprim/sulfamethoxazole, ratio tested was 1:19
[d]NA, breakpoints have not been established by NCCLS

Table 5. *In Vitro* Activity (MIC µg/ml) of Gemifloxacin and Comparative Antimicrobial Agents Against Isolates of *S. pneumoniae* Susceptible and Resistant to Macrolides

Phenotype	Antimicrobial	MIC_{50}	MIC_{90}	Range	% S[a]	% I[a]	% R[a]
MSSP[b] (n = 2330)	Penicillin	0.03	1	<0.015–>16	76.2	18.1	5.7
	Cefuroxime	0.06	2	<0.06–>64	88.6	2.5	8.9
	Azithromycin	0.06	0.12	<0.06–0.5	100	0	0
	Clarithromycin	0.03	0.06	<0.015–0.25	100	0	0
	T/S[c]	0.25	4	<0.06–>64	74.0	10.6	15.4
	Ciprofloxacin	1	2	<0.015–>16	NA[d]	NA	NA
	Grepafloxacin	0.12	0.25	<0.015–8	99.6	0.3	0.1
	Levofloxacin	1	1	<0.015–8	99.9	0.1	0
	Ofloxacin	2	2	<0.06–32	96.8	3.1	0.1
	Trovafloxacin	0.12	0.12	<0.015–4	99.9	0	0.1
	Gemifloxacin	0.015	0.03	0.001–0.25	NA	NA	NA
MRSP[b] (n = 1037)	Penicillin	1	2	<0.015–>16	19.3	39.4	41.3
	Cefuroxime	4	8	<0.06–>64	38.0	7.5	54.5
	Azithromycin	64	64	2–>64	0	0	100
	Clarithromycin	16	16	1–>16	0	0	100
	T/S[b]	4	8	0.06–>64	30.4	15.3	54.3
	Ciprofloxacin	1	2	<0.015–>16	NA	NA	NA
	Grepafloxacin	0.12	0.25	<0.015–16	98.7	0.8	0.5
	Levofloxacin	1	1	<0.015–16	99.3	0.2	0.5
	Ofloxacin	2	2	<0.06–32	95.8	3.4	0.8
	Trovafloxacin	0.12	0.12	<0.015–>16	99.5	0.2	0.3
	Gemifloxacin	0.03	0.06	0.001–0.5	NA	NA	NA

[a]NCCLS recommended breakpoints (µg/ml) were used to group isolates into % susceptible (% S), % intermediate (% I) and % resistant (% R) categories[2]
[b]Macrolide susceptible (MSSP) = azithromycin breakpoint ≤0.5 µg/ml and clarithromycin breakpoint ≤0.25 µg/ml. Macrolide resistant (MRSP) = azithromycin breakpoint ≥2.0 µg/ml and clarithromycin breakpoint ≥1.0 µg/ml
[c]T/S, trimethoprim/sulfamethoxazole, ratio tested was 1:19
[d]NA, breakpoints have not been established by NCCLS

Table 6. *In Vitro* Activity (MIC µg/ml) of Gemifloxacin and Comparative Antimicrobial Agents Against Isolates of *S. pneumoniae* Susceptible and Resistant to Trimethroprim/Sulfamethoxazole

Phenotype	Antimicrobial	MIC_{50}	MIC_{90}	Range	% S[a]	% I[a]	% R[a]
T/SSP[b] (n = 2105)	Penicillin	0.03	0.25	<0.015–>16	81.4	15.1	3.5
	Cefuroxime	0.06	0.5	<0.06–>64	93.0	2.0	5.0
	Azithromycin	0.06	64	<0.06–>64	83.4	1.0	15.6
	Clarithromycin	0.03	16	<0.015–>16	82.5	1.0	16.5
	T/S[c]	0.25	0.5	<0.06–0.5	100	0	0
	Ciprofloxacin	1	2	<0.015–>16	NA[d]	NA	NA
	Grepafloxacin	0.12	0.25	<0.015–8	99.3	0.5	0.2
	Levofloxacin	1	1	<0.015–8	99.7	0.1	0.2
	Ofloxacin	2	2	<0.06–32	96.8	2.9	0.3
	Trovafloxacin	0.12	0.12	<0.015–4	99.9	0	0.1
	Gemifloxacin	0.015	0.03	0.001–0.25	NA	NA	NA
T/SRSP[b] (n = 981)	Penicillin	1	4	<0.015–>16	14.7	40.1	45.2
	Cefuroxime	4	8	<0.06–>64	30.3	8.3	61.4
	Azithromycin	8	64	<0.06–>64	37.2	3.3	59.5
	Clarithromycin	4	16	<0.015–>16	37.7	2.4	59.9
	T/S[c]	4	16	4–>64	0	0	100
	Ciprofloxacin	1	2	0.03–>16	NA	NA	NA
	Grepafloxacin	0.12	0.25	<0.015–>16	99.1	0.6	0.3
	Levofloxacin	1	1	<0.015–16	99.8	0.1	0.1
	Ofloxacin	2	2	0.06–32	95.7	3.9	0.4
	Trovafloxacin	0.12	0.12	<0.015–>16	99.7	0.1	0.2
	Gemifloxacin	0.03	0.06	0.001–0.5	NA	NA	NA

[a]NCCLS recommended breakpoints (µg/ml) were used to group isolates into % susceptible (% S), % intermediate (% I) and % resistant (% R) categories[2]
[b]T/S susceptible (T/SSP) = ≤0.5/9.5 µg/ml; T/S resistant (T/SRSP) = ≥4/76 µg/ml
[c]T/S, trimethoprim/sulfamethoxazole, ratio tested was 1:19
[d]NA, breakpoints have not been established by NCCLS

Table 7. *In Vitro* Activity (MIC µg/ml) of Gemifloxacin and Comparative Antimicrobial Agents Against Multidrug-resistant *S. pneumoniae* Isolates

Phenotype	Antimicrobial	MIC_{50}	MIC_{90}	Range	% S[a]	% I[a]	% R[a]
MDRSP[b] (n = 317)	Penicillin	2	4	2–>16	0	0	100
	Cefuroxime	4	8	0.5–>64	0.3	2.2	97.5
	Azithromycin	64	64	2–>64	0	0	100
	Clarithromycin	16	16	1–>16	0	0	100
	T/S[c]	4	16	4–>64	0	0	100
	Ciprofloxacin[c]	1	2	0.25–>16	NA[d]	NA	NA
	Grepafloxacin	0.12	0.25	<0.015–16	98.1	0	1.9
	Levofloxacin	1	1	0.25–16	98.4	0.3	1.3
	Ofloxacin	2	2	0.12–32	94.3	4.1	1.6
	Trovafloxacin	0.06	0.12	<0.015–>16	98.1	0.3	1.6
	Gemifloxacin	0.03	0.06	0.002–0.5	NA	NA	NA

[a]NCCLS recommended breakpoints (µg/ml) were used to group isolates into % susceptible (% S), % intermediate (% I) and % resistant (% R) categories[2]
[b]Multidrug-resistant isolates determined by the following: penicillin resistant = ≥2.0 µg/ml; and macrolide resistant = azithromycin MIC ≥2.0 µg/ml and clarithromycin MIC ≥1.0 µg/ml; and T/S resistant = ≥4/76 µg/ml
[c]T/S, trimethoprim/sulfamethoxazole, ratio tested was 1:19
[d]NA, breakpoints have not been established by NCCLS

Conclusions

- Gemifloxacin demonstrated the lowest MIC_{90} against *S. pneumoniae* when compared with all other antimicrobials tested.
- Gemifloxacin demonstrated greater potency than levofloxacin, grepafloxacin, trovafloxacin and cefuroxime against all resistant groups, including MDRSP.
- The prevalence of resistance to penicillin (16.9%), azithromycin (30.7%), clarithromycin (31.3%) and T/S (27.8%) for *S. pneumoniae* was considerably higher than that seen with the quinolone group of antimicrobials.
- The activity of newer quinolones, such as gemifloxacin, against resistant isolates of *S. pneumoniae*, a major cause of respiratory infections, suggests a promising role for this new quinolone in the physician's therapeutic regimen.

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