Comparative Activities of Sitafloracin Against Recent Clinical Isolates in Hospitals Across China

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Original Article

Keywords: Sitafloracin, Antimicrobial susceptibility testing, Minimum inhibitory concentration, *Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus aureus*

Posted Date: February 9th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-173942/v1>

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Abstract

Sitafloxacin is one of the newer generation fluoroquinolones. Considering the ever-changing antimicrobial resistance, it is necessary to monitor the activities of sitafloxacin against recent pathogenic isolates. Therefore, we determined the minimum inhibitory concentrations (MICs) of sitafloxacin and comparators by broth microdilution or agar dilution method against 1101 clinical isolates collected from 2017 to 2019 in 31 hospitals across China. Sitafloxacin was highly active against gram-positive isolates evidenced by the MICs required to inhibit the growth of 50%/90% isolates (MIC_{50/90}): $\leq 0.03/0.25$, $\leq 0.03/0.125$, $\leq 0.03/2$, $0.125/0.25$, $0.25/2$, and $0.125/0.125$ mg/L for methicillin-susceptible *S. aureus* (MSSA), methicillin-susceptible coagulase-negative *Staphylococcus* (MSCNS), methicillin-resistant *S. aureus* (MRSA), methicillin-resistant CNS, *Enterococcus faecalis*, and *Streptococcus pneumoniae*, respectively. Sitafloxacin inhibited 82.8% of the MRSA strains and 97.5% of MRCNS strains. Sitafloxacin was also potent against ciprofloxacin-susceptible *Escherichia coli* (MIC_{50/90}: $\leq 0.03/0.06$ mg/L) and *Klebsiella pneumoniae* (MIC_{50/90}: $\leq 0.03/0.125$ mg/L), non-ESBL-producing *E. coli* (MIC_{50/90}: $\leq 0.03/1$ mg/L) and *K. pneumoniae* (MIC_{50/90}: $\leq 0.03/0.5$ mg/L), *Haemophilus influenzae* (MIC_{50/90}: $\leq 0.015/0.06$ mg/L), *Haemophilus parainfluenzae* (MIC_{50/90}: $0.125/0.5$ mg/L), *Moraxella catarrhalis* (MIC_{50/90}: $\leq 0.015/\leq 0.015$ mg/L), *Bacteroides fragilis* (MIC_{50/90}: $0.06/2$ mg/L), *Peptostreptococcus* (MIC_{50/90}: $0.125/4$ mg/L), and *Mycoplasma pneumoniae* ($\leq 0.03/\leq 0.03$ mg/L). However, sitafloxacin was less active for *E. faecium*, ciprofloxacin-resistant and/or ESBL-producing *E. coli* and *K. pneumoniae* strains. Sitafloxacin was superior or comparable to most of the comparators in activities against the above-mentioned isolates. So sitafloxacin is still highly active against most of the clinical isolates in hospitals across China, proving its utility in treatment of the above-mentioned susceptible strains.

Introduction

Sitafloxacin is one of the newer generation fluoroquinolones. It works by inhibiting the activity of bacterial DNA gyrase and topoisomerase IV. Even for the strains with mutations in quinolone resistance-determining region (QRDR), sitafloxacin still has potent inhibitory activity on the gyrase and topoisomerase IV. For this reason, sitafloxacin has relatively higher activity against the strains resistant to other quinolones. Sitafloxacin has been used to treat the respiratory and urinary tract infections caused by susceptible strains [1, 2], including gram-positive and -negative, aerobic organisms, atypical pathogens, and aerobes, such as *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Enterococcus*, *Proteus mirabilis*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophila* [3].

Sitafloxacin was approved in Japan in 2008 for treatment of the infections caused by sitafloxacin-susceptible bacterial strains. In 2019, the National Medical Products Administration (NMPA) of China approved the use of sitafloxacin to treat the pneumonia, infections secondary to chronic respiratory diseases, pyelonephritis, urethritis, and other respiratory and urinary tract infections caused by susceptible strains. A number of studies conducted in other countries have reported the activity of

sitafloxacin against clinically important pathogens [4–6]. However, few data are available regarding the activity of sitafloxacin against the recent clinical isolates in China. Considering the ever-changing antimicrobial resistance, this study was designed to evaluate the antimicrobial activities of sitafloxacin against recent clinical isolates collected from hospitals across China for better clinical use.

Materials And Methods

Bacterial isolates

A total of 1101 clinical isolates were collected from 31 hospitals across China (23 provinces, municipalities, and autonomous regions including Beijing, Shanghai, Zhejiang, Guangdong, Inner Mongolia) from 2017 to 2019. The isolates included aerobic gram-positive bacteria, specifically methicillin-resistant *Staphylococcus aureus* (MRSA, $n = 64$ strains) and methicillin-susceptible *S. aureus* (MSSA, $n = 47$), methicillin-susceptible coagulase-negative *Staphylococcus* (MSCNS, $n = 57$) and methicillin-resistant coagulase-negative *Staphylococcus* (MRCNS, $n = 80$), vancomycin-susceptible *Enterococcus faecalis* ($n = 40$), vancomycin-susceptible and -resistant *E. faecium* ($n = 53$), penicillin-susceptible *Streptococcus pneumoniae* (PSSP, $n = 44$) defined by penicillin minimum inhibitory concentration (MIC) ≤ 0.06 mg/L, penicillin-intermediate *S. pneumoniae* (PISP, $n = 14$) defined by penicillin MIC = 0.125–1 mg/L, penicillin-resistant *S. pneumoniae* (PRSP, $n = 56$) defined by penicillin MIC ≥ 2 mg/L; aerobic gram-negative bacteria such as *E. coli* ($n = 100$, ESBL-producers and non-ESBL-producers, ciprofloxacin-susceptible or -resistant), *K. pneumoniae* ($n = 95$, ESBL-producers and non-ESBL-producers, ciprofloxacin-susceptible or -resistant), *Pseudomonas aeruginosa* ($n = 88$), *Acinetobacter baumannii* ($n = 87$), *Haemophilus influenzae* and *Haemophilus parainfluenzae* ($n = 134$), and *Moraxella catarrhalis* ($n = 61$); anaerobes including *Bacteroides fragilis* ($n = 25$ strains), *Peptostreptococcus* ($n = 14$), and *Prevotella* spp. ($n = 11$); and *M. pneumoniae* ($n = 31$).

These isolates were obtained from various infection source. More than half (52.5%) of the isolates were identified from respiratory tract; 21.1% from urine; 9.2% from secretions including wound, ulcer, and vaginal secretions; 8.2% from blood; 0.7% from cerebrospinal fluid; and 8.4% of the isolates were recovered from other body sites. The duplicate strains isolated from the same patient were excluded. The strains were identified to species level using matrix assisted laser desorption ionization time-of-flight mass spectrometry technology (VITEK MS, bioMérieux). *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, *H. influenzae* ATCC 49766, *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, *S. pneumoniae* ATCC 49619, *B. fragilis* ATCC25285, and *M. pneumoniae* ATCC 29342 were included for quality control in antimicrobial susceptibility testing.

Antimicrobial susceptibility testing

The MICs of sitafloxacin and comparators against the above-listed clinical strains were determined in accordance with the standards described in the Clinical and Laboratory Standards Institute (CLSI) M100 (Edition 20) using broth microdilution method [7]. The anaerobes were tested by agar dilution method [8]. The MICs for *M. pneumoniae* were determined according to the standards of CLSI M43-A in 2011 [9]. The

antimicrobial agents tested in this study included sitafloxacin, levofloxacin, moxifloxacin, ciprofloxacin, nemonoxacin, oxacillin, cefazolin, cefuroxime, azithromycin, tetracycline, metronidazole, amoxicillin, clavulanic acid, clindamycin, imipenem, and erythromycin. The antimicrobial agents were tested in the concentration range from 0.06 mg/L to 64 mg/L for the nonfastidious organisms; 0.015 mg/L to 32 mg/L for the fastidious organisms; 0.015 mg/L to 128 mg/L for the anaerobic bacteria; and 0.03 mg/L to 32 mg/L for *Mycoplasma* strains.

Data analysis

The data of susceptibility testing were processed and analyzed using WHONET 5.6 software. The results were interpreted in accordance with the breakpoints of CLSI 2020 Edition.

Data availability

The relevant datasets generated and analysed during this study are available from the corresponding author on reasonable request

Results

Sitafloxacin showed MIC_{50/90} values of $\leq 0.03/0.25$ and $\leq 0.03/0.125$ mg/L against MSSA and MSCNS strains, $\leq 0.03/2$ and $0.125/0.25$ mg/L against MRSA and MRCNS, respectively. Sitafloxacin inhibited 82.8% of the MRSA strains and 97.5% of the MRCNS strains. Sitafloxacin also displayed MIC_{50/90} values of $0.25/2$ mg/L against vancomycin-susceptible *E. faecalis*; but MIC₅₀ range of 2–4 mg/L and MIC₉₀ range of 8–16 mg/L against *E. faecium* (including vancomycin-susceptible and -resistant strains). Sitafloxacin demonstrated MIC_{50/90} values of $0.125/0.125$ mg/L for all *S. pneumoniae* strains, whether PSSP, PISP, or PRSP (Table 1).

Table 1

The minimum inhibitory concentrations of sitafloxacin and comparators against 455 strains of aerobic gram-positive organisms

Organism (n)	Antimicrobial agent	MIC determination (mg/L)			R%	S%
		MIC Range	MIC ₅₀	MIC ₉₀		
Methicillin-resistant <i>S. aureus</i> (64)	Sitafloxacin	≤ 0.03–8	≤ 0.03	2	9.4	82.8
	Ciprofloxacin	0.25 - >64	1	> 64	42.2	53.1
	Levofloxacin	0.25 - >64	1	64	40.6	59.4
	Moxifloxacin	≤ 0.03–32	0.125	8	35.9	62.5
	Nemonoxacin	≤ 0.03–4	0.06	2	14.1	85.9
	Oxacillin	4 - >16	> 16	> 16	100	0
	Erythromycin	0.25 - >64	> 64	> 64	67.2	31.2
	Vancomycin	0.5–2	1	1	0	100
	Linezolid	1–4	2	2	0	100
Methicillin-susceptible <i>S. aureus</i> (47)	Sitafloxacin	≤ 0.03–1	≤ 0.03	0.25	0	100
	Ciprofloxacin	0.125–32	0.25	16	12.8	83
	Levofloxacin	0.25–8	0.25	8	12.8	87.2
	Moxifloxacin	≤ 0.03–2	0.06	0.5	2.1	93.6
	Nemonoxacin	≤ 0.03–1	≤ 0.03	0.25	0	100
	Oxacillin	0.125–2	1	2	0	100
	Erythromycin	0.25 - >64	> 64	> 64	59.6	36.2
	Vancomycin	≤ 0.125–2	1	1	0	100
	Linezolid	0.5–4	2	2	0	100
MSCNS (57)	Sitafloxacin	≤ 0.03–0.25	≤ 0.03	0.125	0	100
	Ciprofloxacin	0.06–32	0.25	4	15.8	80.7
MIC minimum inhibitory concentration, MRCNS methicillin-resistant coagulase-negative <i>Staphylococcus</i> , MSCNS methicillin-susceptible coagulase-negative <i>Staphylococcus</i> , NA not available, R% percentage resistant, S% percentage susceptible						

	Levofloxacin	$\leq 0.06-16$	0.25	4	17.5	80.7
	Moxifloxacin	$\leq 0.03-2$	0.06	1	5.3	87.7
	Nemonoxacin	$\leq 0.03-0.5$	≤ 0.03	0.125	0	100
	Oxacillin	$\leq 0.06-0.25$	0.125	0.25	0	100
	Erythromycin	$\leq 0.06 - >64$	4	> 64	49.1	47.4
	Vancomycin	0.25-2	1	2	0	100
	Linezolid	0.5-2	1	2	0	100
MRCNS (80)	Sitafloxacin	$\leq 0.03-2$	0.125	0.25	0	97.5
	Ciprofloxacin	0.125-64	2	64	48.8	47.5
	Levofloxacin	0.125 - >64	2	16	47.5	47.5
	Moxifloxacin	$\leq 0.03-32$	0.5	2	30	55
	Nemonoxacin	$\leq 0.03-2$	0.06	0.5	6.2	93.8
	Oxacillin	1 - >16	16	> 16	100	0
	Erythromycin	0.125 - >64	> 64	> 64	76.2	23.8
	Vancomycin	1-2	2	2	0	100
	Linezolid	$\leq 0.06-2$	1	2	0	100
Vancomycin-susceptible <i>E. faecalis</i> (40)	Sitafloxacin	$\leq 0.03-4$	0.25	2	2.5	67.5
	Ciprofloxacin	1 - >64	2	64	37.5	37.5
	Levofloxacin	0.5 - >64	2	64	35	62.5
	Moxifloxacin	0.25-16	0.5	16	32.5	65
	Nemonoxacin	0.25-8	0.5	4	NA	NA
	Ampicillin	1-8	1	2	0	100
	Erythromycin	0.125 - >64	> 64	> 64	72.5	5

MIC minimum inhibitory concentration, MRCNS methicillin-resistant coagulase-negative *Staphylococcus*, MSCNS methicillin-susceptible coagulase-negative *Staphylococcus*, NA not available, R% percentage resistant, S% percentage susceptible

	Vancomycin	1–4	1	2	0	100
Vancomycin-susceptible <i>E. faecium</i> (35)	Sitafloxacin	0.125–32	4	16	65.7	8.6
	Ciprofloxacin	1 - >64	64	> 64	97.1	2.9
	Levofloxacin	2 - >64	> 64	> 64	97.1	2.9
	Moxifloxacin	0.5–64	32	32	NA	NA
	Nemonoxacin	0.5–64	8	32	NA	NA
	Ampicillin	1 - >64	> 64	> 64	97.1	2.9
	Erythromycin	≤ 0.06 - >64	> 64	> 64	88.6	5.7
	Vancomycin	0.5–1	1	1	0	100
Vancomycin-resistant <i>E. faecium</i> (18)	Sitafloxacin	1–16	2	8	11.1	11.1
	Ciprofloxacin	32 - >64	32	> 64	100	0
	Levofloxacin	64 - >64	> 64	> 64	100	0
	Moxifloxacin	8–32	16	16	NA	NA
	Nemonoxacin	2–64	4	16	NA	NA
	Ampicillin	> 64 - >64	> 64	> 64	100	0
	Erythromycin	0.25 - >64	> 64	> 64	88.9	11.1
	Vancomycin	> 16 - >16	> 16	> 16	100	0
<i>S. pneumoniae</i> (penicillin MIC ≤ 0.06 mg/L) (44)	Sitafloxacin	≤ 0.03–0.125	0.125	0.125	0	100
	Ciprofloxacin	≤ 0.03–4	2	2	6.8	22.7
	Levofloxacin	0.5–2	1	1	0	100
	Moxifloxacin	≤ 0.03–0.25	0.25	0.25	0	100
	Nemonoxacin	≤ 0.03–0.25	0.125	0.125	0	100
	Penicillin	≤ 0.06–0.06	≤ 0.06	≤ 0.06	0	100
	Ceftriaxone	≤ 0.06–0.5	≤ 0.06	0.125	0	100

MIC minimum inhibitory concentration, *MRCNS* methicillin-resistant coagulase-negative *Staphylococcus*, *MSCNS* methicillin-susceptible coagulase-negative *Staphylococcus*, *NA* not available, *R%* percentage resistant, *S%* percentage susceptible

	Vancomycin	0.125–0.5	0.25	0.25	NA	100
	Erythromycin	≤ 0.06 - >64	> 64	> 64	84.1	15.9
<i>S. pneumoniae</i> (penicillin MIC = 0.125-1 mg/L) (14)	Sitafloxacin	0.06–0.125	0.125	0.125	0	100
	Ciprofloxacin	1–2	2	2	0	7.1
	Levofloxacin	0.5–1	1	1	0	100
	Moxifloxacin	0.125–0.25	0.25	0.25	0	100
	Nemonoxacin	0.06–0.125	0.125	0.125	0	100
	Penicillin	0.125–1	0.25	1	0	100
	Ceftriaxone	0.06–1	0.25	1	0	100
	Vancomycin	0.25–0.5	0.25	0.5	NA	100
	Erythromycin	32 - >64	> 64	> 64	100	0
<i>S. pneumoniae</i> (penicillin MIC ≥ 2 mg/L) (56)	Sitafloxacin	0.06–2	0.125	0.125	0	98.2
	Ciprofloxacin	0.25–64	2	2	7.1	12.5
	Levofloxacin	0.5–32	1	1	3.6	96.4
	Moxifloxacin	0.06–16	0.25	0.25	1.8	98.2
	Nemonoxacin	0.06–2	0.125	0.125	1.8	98.2
	Penicillin	2–8	4	4	100	0
	Ceftriaxone	0.5–16	2	8	44.6	37.5
	Vancomycin	0.125–0.5	0.25	0.5	NA	100
	Erythromycin	≤ 0.06 - >64	> 64	> 64	98.2	1.8
MIC minimum inhibitory concentration, <i>MRCNS</i> methicillin-resistant coagulase-negative <i>Staphylococcus</i> , <i>MSCNS</i> methicillin-susceptible coagulase-negative <i>Staphylococcus</i> , NA not available, R% percentage resistant, S% percentage susceptible						

The MIC_{50/90} values of sitafloxacin were ≤ 0.03/0.06 mg/L against ciprofloxacin-susceptible *E. coli* and ≤ 0.03/1 mg/L for non-ESBL-producing *E. coli*, but higher (MIC_{50/90}: 1/4 mg/L and 1/2 mg/L, respectively) for ciprofloxacin-resistant or ESBL-producing *E. coli*. Sitafloxacin displayed high activity against ciprofloxacin-susceptible or non-ESBL-producing *K. pneumoniae* (MIC_{50/90}: ≤ 0.03/0.06 and ≤

0.03/0.5 mg/L, respectively) and moderate activity against ciprofloxacin-resistant or ESBL-producing *K. pneumoniae* (MIC range: ≤ 0.008 -4 mg/L, MIC_{50/90}: 2/16 and 1/16 mg/L, respectively). For ciprofloxacin-susceptible or non-ESBL-producing *K. pneumoniae*, sitafloxacin was as highly active as most of the comparators; but for ciprofloxacin-resistant strains, sitafloxacin performed much better than other quinolones and cephalosporins, comparable to cefoperazone-sulbactam, and inferior to meropenem and amikacin. Sitafloxacin was not as good as meropenem and amikacin but was apparently better than other comparators in the activity against ESBL-producing *K. pneumoniae* strains (Table 2 and Fig. 1). Sitafloxacin demonstrated potent activity against *P. aeruginosa* and *A. baumannii* (MIC_{50/90}: 1/8 and 8/64 mg/L, respectively). Sitafloxacin was also highly active against *H. influenzae*, *H. parainfluenzae* and *M. catarrhalis*, evidenced by MIC_{50/90} values of $\leq 0.015/0.06$ mg/L for *H. influenzae*, 0.125/0.5 mg/L for *H. parainfluenzae*, and $\leq 0.015/\leq 0.015$ mg/L for *M. catarrhalis* (Table 3).

Table 2
The minimum inhibitory concentrations of sitafloxacin and comparators against 384 strains of Enterobacterales

Organism (<i>n</i>)	Antimicrobial agent	MIC determination (mg/L)			R%	S%
		MIC Range	MIC ₅₀	MIC ₉₀		
Ciprofloxacin-susceptible <i>E. coli</i> (48)	Sitafloxacin	≤ 0.03–0.125	≤ 0.03	0.06	0	100
	Ciprofloxacin	≤ 0.06–1	≤ 0.06	0.25	0	100
	Levofloxacin	≤ 0.03–1	≤ 0.03	0.25	2.1	100
	Moxifloxacin	≤ 0.03–1	0.06	0.25	0	97.9
	Nemonoxacin	≤ 0.03–1	0.125	0.5	0	100
	Cefoperazone/sulbactam	≤ 0.06/4–32/4	1/4	16/4	0	93.8
	Cefazolin	1- >64	2	> 64	31.2	68.8
	Cefuroxime	0.25 - >64	8	> 64	27.1	70.8
	Ceftazidime	≤ 0.06–32	0.25	8	6.2	85.4
	Ceftriaxone	≤ 0.06 - >64	≤ 0.06	> 64	25	75
	Ceftazidime/avibactam	≤ 0.06/4–0.25/4	≤ 0.06/4	0.25/4	0	100
	Cefepime	≤ 0.06 - >64	≤ 0.06	16	14.6	75
	Meropenem	≤ 0.06 - ≤0.06	≤ 0.06	≤ 0.06	0	100
	Amikacin	0.5–8	1	4	0	100
	Colistin	≤ 0.06–1	0.25	0.25	0	NA
Ciprofloxacin-resistant <i>E. coli</i> (50)	Sitafloxacin	0.25–16	1	4	12	62
ESBL extended-spectrum beta-lactamase, MIC minimum inhibitory concentration, NA not available, R% percentage resistant, S% percentage susceptible						

Ciprofloxacin	4 - >64	16	> 64	100	0
Levofloxacin	1 - >64	8	32	70	4
Moxifloxacin	1 - >64	8	64	90	2
Nemonoxacin	1 - >64	16	64	98	2
Cefoperazone/sulbactam	0.125/4 - >64/4	8/4	64/4	12	70
Cefazolin	1 - >64	> 64	> 64	66	34
Cefuroxime	1 - >64	> 64	> 64	68	24
Ceftazidime	0.125 - >64	4	32	30	54
Ceftriaxone	≤ 0.06 - >64	> 64	> 64	68	32
Ceftazidime/avibactam	≤ 0.06/4–4/4	0.125/4	0.25/4	0	100
Cefepime	≤ 0.06 - >64	16	64	54	36
Meropenem	≤ 0.06–0.125	≤ 0.06	≤ 0.06	0	100
Amikacin	0.5 - >64	2	8	2	98
Colistin	≤ 0.06–0.5	0.25	0.25	0	NA
Sitafloxacin	≤ 0.03 -16	≤ 0.03	1	7.5	90.6
Ciprofloxacin	≤ 0.06 - >64	≤ 0.06	16	32.1	69.8
Levofloxacin	≤ 0.03 - >64	0.06	16	22.6	69.8
Moxifloxacin	≤ 0.03 - >64	0.06	16	28.3	69.8
Nemonoxacin	≤ 0.03 - >64	0.125	16	30.2	69.8
Cefoperazone/sulbactam	≤ 0.06/4–16/4	1/4	4/4	0	100

ESBL extended-spectrum beta-lactamase, MIC minimum inhibitory concentration, NA not available, R% percentage resistant, S% percentage susceptible

	Cefazolin	0.125 - >64	2	8	18.9	56.6
	Cefuroxime	0.06 - >64	4	16	5.7	86.8
	Ceftazidime	≤ 0.06– 2	0.25	0.5	0	100
	Ceftriaxone	≤ 0.06– 0.25	≤ 0.06	0.125	0	100
	Ceftazidime/avibactam	≤ 0.06/4– 0.25/4	0.125/4	0.25/4	0	100
	Cefepime	≤ 0.06– 4	≤ 0.06	0.25	0	98.1
	Meropenem	≤ 0.06– 0.125	≤ 0.06	≤ 0.06	0	100
	Amikacin	0.25–8	2	4	0	100
	Colistin	≤ 0.06– 1	0.25	0.25	0	-
ESBL-producing <i>E. coli</i> (47)	Sitafloxacin	0.03–8	1	2	6.4	70.2
	Ciprofloxacin	0.06 - >64	8	> 64	76.6	23.4
	Levofloxacin	0.03–32	4	32	72.3	23.4
	Moxifloxacin	≤ 0.03– 64	8	32	63.8	27.7
	Nemonoxacin	0.06 - >64	8	64	72.3	27.7
	Cefoperazone/sulbactam	4/4 - >64/4	16/4	64/4	12.8	61.7
	Cefazolin	1 - >64	> 64	> 64	97.9	2.1
	Cefuroxime	1 - >64	> 64	> 64	95.7	2.1
	Ceftazidime	1 - >64	8	64	38.3	36.2
	Ceftriaxone	8 - >64	> 64	> 64	100	0
	Ceftazidime/avibactam	0.06/4– 4/4	0.125/4	0.25/4	0	100

ESBL extended-spectrum beta-lactamase, MIC minimum inhibitory concentration, NA not available, R% percentage resistant, S% percentage susceptible

	Cefepime	0.125 - >64	16	> 64	74.5	6.4
	Meropenem	0.06–0.125	0.064	0.064	0	100
	Amikacin	0.5 - >64	2	4	2.1	97.9
	Colistin	0.06–0.5	0.25	0.25	0	NA
Ciprofloxacin-susceptible <i>K. pneumoniae</i> (53)	Sitafloracin	≤ 0.03–0.25	≤ 0.03	0.125	0	100
	Ciprofloxacin	≤ 0.06–1	≤ 0.06	0.5	0	100
	Levofloxacin	≤ 0.03–1	0.064	0.5	0	100
	Moxifloxacin	0.06–2	0.125	0.5	0	100
	Nemonoxacin	0.125–8	0.25	1	3.8	96.2
	Cefoperazone/sulbactam	0.125/4 - >64/4	0.25/4	8/4	3.8	94.3
	Cefazolin	1 - >64	2	> 64	15.1	84.9
	Cefuroxime	1 - >64	2	> 64	11.3	84.9
	Ceftazidime	≤ 0.06 - >64	0.125	4	7.5	90.6
	Ceftriaxone	≤ 0.06 - >64	≤ 0.06	> 64	11.3	88.7
	Ceftazidime/avibactam	≤ 0.06/4 - >64/4	0.125/4	0.25/4	1.9	98.1
	Cefepime	≤ 0.06 - >64	≤ 0.06	4	7.5	88.7
	Meropenem	≤ 0.06 - >16	≤ 0.06	≤ 0.06	1.9	98.1
	Amikacin	0.25–2	1	1	0	100
	Colistin	0.125–2	0.25	0.5	0	NA
Ciprofloxacin-resistant <i>K. pneumoniae</i> (38)	Sitafloracin	0.25–64	2	32	31.6	36.8
	Ciprofloxacin	4 - >64	16	> 64	100	0
	Levofloxacin	0.5 - >64	8	> 64	73.7	15.8
ESBL extended-spectrum beta-lactamase, MIC minimum inhibitory concentration, NA not available, R% percentage resistant, S% percentage susceptible						

Moxifloxacin	2 - >64	16	> 64	76.3	5.3
Nemonoxacin	1 - >64	16	> 64	94.7	5.3
Cefoperazone/sulbactam	0.25/4 - >64/4	32/4	> 64/4	34.2	44.7
Cefazolin	2 - >64	> 64	> 64	84.2	15.8
Cefuroxime	8 - >64	> 64	> 64	92.1	5.3
Ceftazidime	0.25 - >64	32	> 64	73.7	21.1
Ceftriaxone	≤ 0.06 - >64	> 64	> 64	84.2	15.8
Ceftazidime/avibactam	0.125/4 - >64/4	0.5/4	0.5/4	2.6	97.4
Cefepime	≤ 0.06 - >64	16	> 64	63.2	13.2
Meropenem	≤ 0.06 - >16	≤ 0.06	0.25	5.3	94.7
Amikacin	0.5 - >64	1	4	5.3	94.7
Colistin	0.125–4	0.5	0.5	2.6	NA
Sitafloxacin	≤ 0.03–4	≤ 0.03	0.5	1.9	92.6
Ciprofloxacin	≤ 0.06–8	≤ 0.06	4	11.1	87
Levofloxacin	≤ 0.03–16	0.06	2	9.3	90.7
Moxifloxacin	0.06–32	0.125	4	9.3	87
Nemonoxacin	0.125–32	0.25	8	13	87
Cefoperazone/sulbactam	0.125/4 – 2/4	0.25/4	1/4	0	100
Cefazolin	1 - >64	2	4	3.7	96.3
Cefuroxime	1 ->64	2	16	5.6	88.9
Ceftazidime	≤ 0.06–64	0.125	0.5	3.7	96.3

ESBL extended-spectrum beta-lactamase, MIC minimum inhibitory concentration, NA not available, R% percentage resistant, S% percentage susceptible

	Ceftriaxone	$\leq 0.06-0.5$	≤ 0.06	0.125	0	100
	Ceftazidime/avibactam	$\leq 0.06/4 - 1/4$	0.125/4	0.25/4	0	100
	Cefepime	$\leq 0.06-4$	≤ 0.06	0.25	0	96.3
	Meropenem	$\leq 0.06- \leq 0.06$	≤ 0.06	≤ 0.06	0	100
	Amikacin	0.25-2	1	1	0	100
	Colistin	0.125-1	0.25	0.5	0	NA
ESBL-producing <i>K. pneumoniae</i> (41)	Sitafloxacin	$\leq 0.03-64$	1	16	26.8	51.2
	Ciprofloxacin	$\leq 0.06 - >64$	8	> 64	78	14.6
	Levofloxacin	$\leq 0.03 - >64$	8	> 64	56.1	34.1
	Moxifloxacin	0.06 - >64	16	> 64	58.5	26.8
	Nemonoxacin	0.125 - >64	8	> 64	78	22
	Cefoperazone/sulbactam	2/4 - >64/4	32/4	> 64/4	36.6	36.6
	Cefazolin	> 64 - >64	> 64	> 64	100	0
	Cefuroxime	16 - >64	> 64	> 64	97.6	0
	Ceftazidime	0.5 - >64	32	> 64	75.6	17.1
	Ceftriaxone	8 - >64	> 64	> 64	100	0
	Ceftazidime/avibactam	0.125/4 - >64/4	0.5/4	0.5/4	4.9	95.1
	Cefepime	2 - >64	16	> 64	70.7	4.9
	Meropenem	$\leq 0.06 - >16$	≤ 0.06	0.25	7.3	92.7
	Amikacin	0.5 - >64	1	4	4.9	95.1
	Colistin	0.125-4	0.5	0.5	2.4	NA
ESBL extended-spectrum beta-lactamase, MIC minimum inhibitory concentration, NA not available, R% percentage resistant, S% percentage susceptible						

Table 3
The minimum inhibitory concentrations of sitafloxacin and comparators against other gram-negative bacteria

Organism (<i>n</i>)	Antimicrobial agent	MIC determination (mg/L)			R%	S%
		MIC Range	MIC ₅₀	MIC ₉₀		
<i>P. aeruginosa</i> (88)	Sitafloxacin	≤ 0.03-64	1	8	23.9	54.5
	Ciprofloxacin	0.06->64	2	32	54.5	43.2
	Levofloxacin	≤ 0.03->64	8	32	56.8	43.2
	Moxifloxacin	0.06->64	4	64	NA	NA
	Nemonoxacin	0.06->64	4	64	46.6	53.4
	Ceftazidime	1->64	16	> 64	38.6	48.9
	Cefoperazone/sulbactam	1/4->64/4	32/4	> 64/4	NA	NA
	Meropenem	0.06-32	2	32	37.5	54.5
	Amikacin	1->64	4	> 64	12.5	85.2
	Ceftriaxone	16->64	> 64	> 64	NA	NA
	Ceftazidime/avibactam	0.5/4->64/4	2/4	64/4	29.5	70.5
	Cefepime	1->64	8	> 64	35.2	50
	Colistin	0.5–16	1	2	4.5	NA
<i>A. baumannii</i> (87)	Sitafloxacin	0.06 - >64	8	64	40.2	42.5
	Ciprofloxacin	1 - >64	64	> 64	59.8	40.2
	Levofloxacin	1 - >64	16	64	55.2	40.2
	Moxifloxacin	2 - >64	64	> 64	NA	NA
	Nemonoxacin	8 - >64	> 64	> 64	NA	NA
	Ceftazidime	1 - >64	32	> 64	59.8	39.1
	Cefoperazone/sulbactam	≤ 0.06/4 - >16/4	> 16/4	> 16/4	NA	NA
	Meropenem	0.125 - >64	> 64	> 64	58.6	41.4
	Amikacin	≤ 0.06 - >64	64	> 64	52.9	47.1
	Ceftriaxone	0.06 - >64	8	64	59.8	25.3
MIC minimum inhibitory concentration, NA not available, R% percentage resistant, S% percentage susceptible						

	Ceftazidime/avibactam	0.06/4 - >64/4	8/4	64/4	NA	NA
	Cefepime	≤ 0.03–16	2	8	57.5	40.2
	Colistin	0.125–4	0.5	0.5	0	NA
<i>H. influenzae</i> (107)	Sitafloxacin	≤ 0.015– 0.25	≤ 0.015	0.06	0	100
	Ciprofloxacin	≤ 0.015-16	0.03	1	NA	98.1
	Levofloxacin	≤ 0.06-8	≤ 0.06	1	NA	99.1
	Moxifloxacin	≤ 0.015-8	0.03	1	NA	98.1
	Nemonoxacin	≤ 0.015-1	0.03	0.5	0.9	99.1
	Ampicillin	≤ 0.06->64	4	64	55.1	38.3
	Cefuroxime	≤ 0.5–16	≤ 0.5	2	1.9	96.3
	Ceftriaxone	≤ 0.06-64	≤ 0.06	0.25	0	98.1
	Amoxicillin/clavulanic acid	≤ 0.5/0.25- 32/16	≤ 0.5/0.25	4/2	8.4	91.6
<i>H. parainfluenzae</i> (27)	Sitafloxacin	≤ 0.015-1	0.125	0.5	NA	NA
	Ciprofloxacin	≤ 0.015-32	2	16	NA	40.7
	Levofloxacin	≤ 0.06-8	1	8	NA	70.4
	Moxifloxacin	≤ 0.015-16	2	16	NA	44.4
	Nemonoxacin	≤ 0.015-8	1	4	NA	NA
	Ampicillin	≤ 0.06->64	1	64	29.6	55.6
	Cefuroxime	≤ 0.5-8	≤ 0.5	8	0	85.2
	Ceftriaxone	≤ 0.06-64	≤ 0.06	0.25	0	96.3
	Amoxicillin/clavulanic acid	≤ 0.5/0.25- 4/2	≤ 0.5/0.25	4/2	0	100
<i>M. catarrhalis</i> (61)	Sitafloxacin	≤ 0.015– 0.125	≤ 0.015	≤ 0.015	NA	NA
	Ciprofloxacin	≤ 0.015-0.5	0.06	0.06	NA	100
	Levofloxacin	≤ 0.06-1	≤ 0.06	≤ 0.06	NA	100
	Moxifloxacin	0.03–0.5	0.06	0.125	NA	NA

MIC minimum inhibitory concentration, NA not available, R% percentage resistant, S% percentage susceptible

Nemonoxacin	≤ 0.015 -8	1	4	NA	NA
Ampicillin	≤ 0.06 -16	2	8	NA	NA
Cefuroxime	≤ 0.5 -4	1	2	0	100
Ceftriaxone	≤ 0.06 -4	0.5	1	NA	98.4
Amoxicillin/clavulanic acid	$\leq 0.5/0.25$	$\leq 0.5/0.25$	$\leq 0.5/0.25$	0	100
<i>MIC</i> minimum inhibitory concentration, <i>NA</i> not available, <i>R</i> % percentage resistant, <i>S</i> % percentage susceptible					

Sitafloracin had high anti-aerobic activity, specifically active against *B. fragilis* (MIC_{50/90}: 0.06/2 mg/L), *Peptostreptococcus* (MIC_{50/90}: 0.125/4 mg/L) and *Prevotella* spp. (MIC_{50/90}: 4/8 mg/L) (Table 4). Sitafloracin was as active as imipenem and metronidazole, much better than other comparators against *B. fragilis*. For *Peptostreptococcus*, sitafloracin performed as well as imipenem and metronidazole, slightly weaker than ciprofloxacin, but better than other comparators. Sitafloracin was not as active as imipenem but more active than other comparators against *Prevotella* spp. based on lower MIC_{50/90} value.

Table 4

The minimum inhibitory concentrations of sitafloxacin and comparators against 50 strains of anaerobic clinical isolates

Organism (<i>n</i>)	Antimicrobial agent	MIC determination (mg/L)			R%	S%
		MIC Range	MIC ₅₀	MIC ₉₀		
<i>B. fragilis</i> (25)	Sitafloxacin	0.03–4	0.06	2	NA	NA
	Ciprofloxacin	0.125 - >128	8	>128	96	4
	Levofloxacin	1–128	2	32	28	56
	Moxifloxacin	0.25–32	0.5	16	40	56
	Nemonoxacin	1–64	4	32	NA	NA
	Imipenem	0.06–64	0.25	4	8	92
	Clindamycin	0.06 - >128	>128	>128	84	8
	Metronidazole	0.5–1	1	1	0	100
<i>Peptostreptococcus</i> (14)	Sitafloxacin	0.125–4	0.125	4	NA	NA
	Ciprofloxacin	≤ 0.015–1	0.064	0.5	NA	NA
	Levofloxacin	0.125–32	0.5	32	NA	NA
	Moxifloxacin	0.5–32	0.5	32	42.9	57.1
	Nemonoxacin	0.125–8	0.125	8	NA	NA
	Imipenem	0.03–0.5	0.032	0.5	0	0
	Clindamycin	0.5 - >128	16	16	64.3	28.6
	Metronidazole	0.5–8	1	1	0	100
<i>Prevotella</i> spp. (11)	Sitafloxacin	0.03–8	0.125	8	NA	NA
	Ciprofloxacin	0.125 - >128	2	>128	NA	NA
	Levofloxacin	0.125–128	2	128	NA	NA
	Moxifloxacin	0.125–128	0.5	128	45.5	54.5
	Nemonoxacin	0.06–128	0.5	128	NA	NA
	Imipenem	0.015–1	0.016	0.5	0	100
	Clindamycin	0.015 - >128	2	>128	45.5	54.5
	Metronidazole	0.5 - >128	8	>128	36.4	63.6

MIC minimum inhibitory concentration, NA not available, R% percentage resistant, S% percentage susceptible

Sitafloxacin was highly active against atypical pathogen *M. pneumoniae* based on MIC_{50/90} values ($\leq 0.03/\leq 0.03$ mg/L) (Table 5). It was superior to erythromycin and azithromycin and comparable to other comparators in the activity against *M. pneumoniae*.

Table 5
The minimum inhibitory concentrations of sitafloxacin and comparators against 31 strains of *Mycoplasma pneumoniae*

Organism (n)	Antimicrobial agent	Breakpoints (mg/L)		MIC Range (mg/L)	MIC ₅₀ (mg/L)	MIC ₉₀ (mg/L)	R%	S%
		S	R					
<i>M. pneumoniae</i> (31)	Sitafloxacin	NA	NA	≤ 0.03	≤ 0.03	≤ 0.03	NA	NA
	Ciprofloxacin	NA	NA	0.25–0.5	0.5	0.5	NA	NA
	Levofloxacin	≤ 1	NA	0.25–0.5	0.25	0.5	NA	100
	Moxifloxacin	≤ 0.5	NA	≤ 0.03 –0.06	0.06	0.06	NA	100
	Nemonoxacin	NA	NA	≤ 0.03 –0.06	0.06	0.06	NA	NA
	Erythromycin	≤ 0.5	≥ 1	32 - >32	> 32	> 32	100	0
	Azithromycin	≤ 0.5	≥ 1	1–16	8	8	100	0
	Tetracycline	≤ 2	NA	0.125–0.25	0.25	0.25	NA	100
MIC minimum inhibitory concentration, NA not available, R% percentage resistant, S% percentage susceptible								

Discussion

Bacterial resistance to quinolones is primarily due to target modification, active efflux via membrane - located pumps, and outer membrane porin loss. Sitafloxacin acts on both DNA gyrase and topoisomerase β to inhibit bacterial growth. Therefore, high-level resistance to sitafloxacin will not develop unless mutation emerges in both DNA gyrase and topoisomerase β . The modification of any one target, DNA gyrase or topoisomerase β , will not affect sitafloxacin susceptibility significantly. Ciprofloxacin works primarily by inhibiting the DNA gyrase of gram-negative organisms, and the topoisomerase of gram-positive organisms. Levofloxacin mainly inhibits bacterial DNA gyrase.

It is reported [10] that nearly 70% of *E. coli* isolates and about 50% of *K. pneumoniae* isolates are resistant to ciprofloxacin. We found in this study that sitafloxacin inhibited all (100%) the ciprofloxacin-susceptible *E. coli* and *K. pneumoniae* strains, 62% of the ciprofloxacin-resistant *E. coli* and 36.8% of the ciprofloxacin-resistant *K. pneumoniae* strains. Majority of the non-ESBL-producing *E. coli* (90.6%) and *K.*

pneumoniae (92.6%) strains were susceptible to sitafloxacin, while relatively lower percentage of ESBL-producing *E. coli* (70.2%) and *K. pneumoniae* (51.2%) were susceptible to sitafloxacin.

Sitafloxacin is very active against gram-negative organisms. In a large scale pharmacodynamic study of sitafloxacin [11], the MIC range was ≤ 0.008 -4 mg/L for *E. coli* (MIC_{50/90}: ≤ 0.008 /1 mg/L). In the present study, sitafloxacin also displayed potent activity against ciprofloxacin-resistant or ESBL-producing *E. coli* (MIC_{50/90}: 1/4 and 1/2 mg/L, respectively; MIC range: ≤ 0.25 -16 mg/L), but slightly higher MIC values because these are specified resistant strains. Sitafloxacin was also highly active against ciprofloxacin-susceptible or non-ESBL-producing *K. pneumoniae* (MIC_{50/90}: ≤ 0.03 /0.06 and ≤ 0.03 /0.5 mg/L), and active against ciprofloxacin-resistant or ESBL-producing *K. pneumoniae* (MIC_{50/90}: 2/16 and 1/16 mg/L). Other authors reported that for 445 strains of *K. pneumoniae*, sitafloxacin resulted in MIC range of ≤ 0.008 -8 mg/L (MIC_{50/90}: 0.015/0.12 mg/L). Our MIC_{50/90} values are relative higher, but MIC range remains the same.

Sitafloxacin is highly active against ciprofloxacin-resistant *E. coli* and *K. pneumoniae*. The underlying mechanism may be due to the fact that ciprofloxacin mainly acts on DNA gyrase, while sitafloxacin can inhibit both DNA gyrase and topoisomerase β . Even in case of QRDR mutation, sitafloxacin still has good inhibitory effect. Therefore, sitafloxacin remains powerful in inhibiting ciprofloxacin-resistant *Enterobacteriales* strains. Sitafloxacin was much more active than cephalosporins against ciprofloxacin-susceptible *E. coli*. Sitafloxacin performed much better than other quinolones and cephalosporins, comparable to cefoperazone-sulbactam, and inferior to meropenem and amikacin in the activity against ciprofloxacin-resistant *E. coli* strains. Sitafloxacin was better than other quinolones, and slightly weaker than third and fourth generation cephalosporins, cefoperazone-sulbactam, meropenem and amikacin in the activity against non-ESBL-producing *E. coli*.

For ESBL-producing *E. coli* strains, sitafloxacin had activity much higher other quinolones, slightly better than cefoperazone-sulbactam, but lower than meropenem and amikacin. For ciprofloxacin-susceptible or non-ESBL-producing *K. pneumoniae*, sitafloxacin was as highly active as most of the comparators; but for ciprofloxacin-resistant strains, sitafloxacin performed much better than other quinolones and cephalosporins, comparable to cefoperazone-sulbactam, and inferior to meropenem and amikacin. Sitafloxacin was not as good as meropenem and amikacin but was apparently better than other comparators in the activity against ESBL-producing *K. pneumoniae* strains.

Bacterial resistance surveillance network [10] reported that 16.7% of *P. aeruginosa* and 68.8% of *A. baumannii* strains were resistant to ciprofloxacin. In the present study, the prevalence of sitafloxacin-resistant *P. aeruginosa* was 23.9%, higher than the prevalence of ciprofloxacin-resistant *P. aeruginosa*. The prevalence of sitafloxacin-resistant *A. baumannii* was 40.2%, lower than the prevalence of ciprofloxacin-resistant *A. baumannii*. Sitafloxacin was comparable to nemonoxacin and meropenem, slightly better than other quinolones and ceftazidime, and poorer than amikacin in the activity against *P. aeruginosa*. Sitafloxacin inhibited about 40% of the *A. baumannii* strains, similar to any of the comparators.

Sitafloxacin was much more active than ampicillin and comparable to other comparators (inhibited > 90% of the strains) against *H. influenzae*. Sitafloxacin was comparable to ceftriaxone in the activity against *H. parainfluenzae* (MIC_{50/90}: 0.125/0.5 and $\leq$ 0.06/0.25 mg/L, respectively), and superior to other comparators. Sitafloxacin was highly active against *M. catarrhalis*, similar to most of the comparators.

According to the bacterial resistance surveillance network [10], about 50% of MRSA and 15% of MSSA strains were resistant to levofloxacin. In the present study, sitafloxacin inhibited 82.8% of MRSA and 100% of MSSA strains, 97.5% of MRCNS and 100% of MSCNS strains. Our MIC range of sitafloxacin for MRSA was $\leq$ 0.03-8 mg/L, higher than other reports ($\leq$ 0.008–0.03 mg/L) for *S. aureus*. Our MIC ranges of sitafloxacin for MSSA, MRCNS, and MSCNS are also higher than reported [12]. Sitafloxacin was superior to or apparently better than ciprofloxacin, levofloxacin, and moxifloxacin, but similar to nemonoxacin in the activity against *Staphylococcus* spp. including methicillin-susceptible and -resistant strains. Sitafloxacin was slightly poorer than vancomycin in the activity of against MRSA, but comparable to vancomycin and obviously better than erythromycin in the activity against MSSA, MSCNS, and MRCNS.

Sitafloxacin was active against vancomycin-susceptible *E. faecalis* (MIC_{50/90}: 0.25/2 mg/L), but showed poor activity against *E. faecium* (including vancomycin-susceptible and -resistant strains) with MIC₅₀ range of 2–4 mg/L and MIC₉₀ range of 8–16 mg/L. An overseas study on the *in vitro* activity of sitafloxacin [13] reported that the MIC₉₀ of sitafloxacin was 2 mg/L for *E. faecalis*, which is consistent with our result. Sitafloxacin was apparently better than ciprofloxacin, similar to other fluoroquinolones, and poorer than ampicillin and vancomycin in the activity against vancomycin-susceptible *E. faecalis*. Sitafloxacin was weaker than vancomycin in the activity against vancomycin-susceptible *E. faecium*, but comparable to other comparators against vancomycin-resistant *E. faecium*.

A study on the activity of sitafloxacin against 1531 clinical isolates found that the MIC range of sitafloxacin was $\leq$ 0.008–0.25 mg/L (MIC_{50/90}: 0.03/0.06 mg/L) for PSSP strains, $\leq$ 0.015–0.25 mg/L (MIC_{50/90}: 0.03/0.06 mg/L) for PISP strains, and MIC_{50/90} values of 0.03/0.06 mg/L for PRSP strains [14]. The corresponding results of sitafloxacin in our study were $\leq$ 0.03–0.125 mg/L (MIC_{50/90}: 0.125/0.125 mg/L) for PSSP, 0.06–0.125 mg/L (MIC_{50/90}: 0.125/0.125 mg/L) for PISP, and $\leq$ 0.06-2 mg/L (MIC_{50/90}: 0.125/0.125 mg/L) for PRSP, all higher than the above report [14]. Sitafloxacin inhibited 98.2% of the PRSP strains and 100% of the PSSP and PISP strains. Sitafloxacin was superior to ciprofloxacin and erythromycin and similar to other comparators in the activity against PSSP and PISP, and superior to ceftriaxone in the activity against PRSP.

A study on anaerobes [15] reported that sitafloxacin was active against anaerobes (MIC range: 0.06-16 mg/L, MIC_{50/90}: 0.5/2 mg/L). We also found that sitafloxacin was highly active against *B. fragilis* (MIC_{50/90}: 0.06/2 mg/L), and active against *Peptostreptococcus* and *Prevotella* spp. (MIC_{50/90}: 0.125/4 and 0.125/8 mg/L, respectively). Our MIC_{50/90} values are relatively higher than the above report. It is also reported that reduced susceptibility to other fluoroquinolones is found in *Bacteroides* spp., e.g., about 30%

of the strains are resistant to moxifloxacin, higher than the resistance rate to ciprofloxacin and levofloxacin.

Sitafoxacin was highly active against *M. pneumoniae* (MIC range: ≤ 0.03 mg/L; MIC_{50/90}: $\leq 0.03/\leq 0.03$ mg/L). It was superior to erythromycin and azithromycin and comparable to other comparators in the activity against *M. pneumoniae*.

In summary, a large number of clinical strains are tested for the susceptibility to sitafloxacin. However, the number of isolates for any one bacterial species is still not sufficient to completely reflect sitafloxacin activity against the common clinical isolates. Furthermore, increased MIC values of sitafloxacin are found for some bacteria. This highlights the necessity to implement subsequent *in vitro* activity studies and put in place surveillance program to monitor the changing pattern of sitafloxacin susceptibility in clinical settings.

Declarations

Funding information This work was supported by National Mega-project for Innovative Drugs (2019ZX09721001-006-004), and CHINET Antimicrobial Surveillance Network (grant number 2018QD099 and 2018QD100).

Conflicts of interest The authors declare that they have no conflicts of interest.

Ethics approval This study was approved by the Institutional Review Board of Huashan Hospital, Fudan University (Number: 2018-349).

Consent to participate Not applicable

Consent for publication Not applicable

Availability of data and material Data can be provided upon request

Code availability Not applicable

References

1. Asakura T, Suzuki S, Fukano H, et al (2019) Sitafoxacin-Containing Regimen for the Treatment of Refractory Mycobacterium avium Complex Lung Disease. Open Forum Infect Dis 6:ofz108.
2. Manosuthi W, Wiboonchutikul S (2016) Treatment outcomes of oral sitafloxacin in acute complicated urinary tract infection and pyelonephritis. Springerplus 5:410.
3. Keating GM (2011) Sitafoxacin: in bacterial infections. Drugs 71:731-744.
4. Hamasuna R, Ohnishi M, Matsumoto M, et al (2018) *In Vitro* Activity of Sitafoxacin and Additional Newer Generation Fluoroquinolones Against Ciprofloxacin-Resistant Neisseria gonorrhoeae Isolates.

Microb Drug Resist 24:30-34.

5. Tantisiriwat W, Linasmita P (2017) *In vitro* Activity of Sitafloracin and Other Antibiotics against Bacterial Isolates from HRH Princess Maha Chakri Sirindhorn Medical Center, Srinakharinwirot University and Samitivej Sukhumvit Hospital. J Med Assoc Thai 100:469-478.
6. Xu N, Wang G, Leng Y, et al (2018) Sulbactam enhances the *in vitro* activity of sitafloxacin against extensively-drug resistant *Acinetobacter baumannii*. Exp Ther Med 16:3485-3491.
7. Clinical and Laboratory Standards Institute (2020) Performance Standards for Antimicrobial Susceptibility Testing; M100 30th. Clinical and Laboratory Standards Institute.
8. CLSI (2018) M07, 11th Ed. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically. Wayne, PA: Clinical and Laboratory Standards Institute
9. CLSI (2011) Methods for Antimicrobial Susceptibility Testing for Human Mycoplasmas; Approved Guideline (M43-A). Wayne, PA: Clinical and Laboratory Standards Institute.
10. Hu F, Guo Y, Yang Y, et al (2019) Resistance reported from China antimicrobial surveillance network (CHINET) in 2018. Eur J Clin Microbiol Infect Dis 38:2275-2281.
11. Milatovic D, Schmitz FJ, Brisse S, Verhoef J, Fluit AC (2000) *In vitro* activities of sitafloxacin (DU-6859a) and six other fluoroquinolones against 8,796 clinical bacterial isolates. Antimicrob Agents Chemother 44:1102-1107.
12. Schmitz FJ, Fluit AC, Milatovic D, et al (2000) *In vitro* potency of moxifloxacin, clinafloxacin and sitafloxacin against 248 genetically defined clinical isolates of *Staphylococcus aureus*. J Antimicrob Chemother 46:109-113.
13. Amano A, Matsuzaki K, Kishi N, et al (2013) *In vitro* activity of sitafloxacin against clinical isolates in 2012. Jpn J Antibiot 66:311-30. [Japanese].
14. Doern GV, Heilmann KP, Huynh HK, et al (2001) Antimicrobial resistance among clinical isolates of *Streptococcus pneumoniae* in the United States during 1999–2000, including a comparison of resistance rates since 1994-1995. Antimicrob Agents Chemother 45:1721-1729.
15. Snyderman DR, Jacobus NV, McDermott LA, et al (2002) *In vitro* activities of newer quinolones against *Bacteroides* group organisms [Errata in Antimicrob Agents Chemother 2003;47(2):831]. Antimicrob Agents Chemother 46:3276-3279.

Figures

Figure 1

Distribution of minimum inhibitory concentrations of sitafloxacin against various gram-negative clinical isolates. CPFX sen, ciprofloxacin-sensitive; CPFX res, ciprofloxacin-resistant; ESBL, extended-spectrum beta-lactamase; ESBL+, ESBL-producing; ESBL-, non-ESBL-producing; AB, *A. baumannii*; PAE, *P. aeruginosa*; HIB, *H. influenzae* type B; HPI, *H. parainfluenzae*; MC, *M. pneumoniae*