Comparative activities of sitafloxacin against recent clinical isolates in hospitals across China

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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): ≤0.03/0.25, ≤0.03/0.125, ≤0.03/0.125 mg/L for methicillin-susceptible Staphylococcus aureus (MSSA), methicillin-susceptible coagulase-negative Staphylococcus (MSCNS), methicillin-resistant Staphylococcus 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: ≤0.03/0.06 mg/L) and Klebsiella pneumoniae (MIC 50/90: ≤0.03/0.125 mg/L), non-ESBL-producing E. coli (MIC 50/90: ≤0.03/1 mg/L) and K. pneumoniae (MIC 50/90: ≤0.03/0.5 mg/L), Haemophilus influenzae (MIC 50/90: ≤0.015/0.06 mg/L), Haemophilus parainfluenzae (MIC 50/90: 0.125/0.5 mg/L), Moraxella catarrhalis (MIC 50/90: ≤0.015/0.015 mg/L), Bacteroides fragilis (MIC 50/90: 0.06/2 mg/L), Peptostreptococcus (MIC 50/90: 0.125/4 mg/L), and Mycoplasma pneumoniae (≤0.03/0.03 mg/L). However, sitafloxacin was less active for Enterococcus 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 abovementioned isolates, so sitafloxacin is still highly active against most of the clinical isolates in hospitals across China, proving its utility in treatment of the abovementioned susceptible strains.

Keywords Sitafloxacin · Antimicrobial susceptibility testing · Minimum inhibitory concentration · Escherichia coli · Klebsiella pneumoniae · Staphylococcus aureus

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 gram-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 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**

This study was designed to evaluate the antimicrobial activities of sitafloxacin and selected comparators against recent clinical isolates, which did not involve the confidential personal data of patients. In this case, it is acceptable for the Institutional Review Board (IRB) waiver of informed consent. This study was approved by the Institutional Review Board of Huashan Hospital, Fudan University (number: 2019-572).

**Bacterial isolates**

All the strains were isolated from the patients suspected of infection. The strains collected from screening or surveillance programs were not included. The duplicate strains isolated from the same patient were excluded. The resistant phenotypes (e.g., ciprofloxacin-resistant or ciprofloxacin-susceptible *Enterobacteriales*, methicillin-resistant or methicillin-susceptible *Staphylococcus*) of the strains were characterized by conventional susceptibility testing methods.

A total of 1101 clinical isolates were collected from 31 hospitals across China from 2017 to 2019, including Anhui (n = 37 strains), Beijing (n = 85), Fujian (n = 32), Shanghai (n = 239), Gansu (n = 30), Guizhou (n = 4), Heilongjiang (n = 17), Hebei (n = 21), Henan (n = 28), Hubei (n = 50), Jilin (n = 9), Jiangxi (n = 19), Yunnan (n = 30), Liaoning (n = 8), Inner Mongolia (n = 18), Ningxia (n = 78), Shandong (n = 5), Shanxi (n = 22), Shaanxi (n = 19), Guangdong (n = 62), Sichuan (n = 64), Tianjin (n = 38), Zhejiang (n = 76), Xinjiang (n = 8), Jiangsu (n = 7), and Hunan (n = 95).

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-resistant and vancomycin-resistant *Enterococcus faecium* (n = 53), penicillin-susceptible *Streptococcus pneumoniae* (PISP, n = 14) defined by penicillin minimum inhibitory concentration (MIC) ≤ 0.06 mg/L, penicillin-intermediate *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 ciprofloxacin-resistant, *K. pneumoniae* (n = 95), ESBL producers and non-ESBL producers, ciprofloxacin-susceptible or ciprofloxacin-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). The resistant phenotypes of the test strains are based on prior susceptibility testing results.

These isolates were obtained from various infection sources. 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 strains were identified to species level using matrix-assisted laser desorption ionization time-of-flight mass spectrometry technology (VITEK MS, bioMérieux).

*Escherichia 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 to 64 mg/L for the nonfastidious organisms; 0.015-32 mg/L for the fastidious organisms; 0.015-128 mg/L for the anaerobic bacteria; and 0.03-32 mg/L for *Mycoplasma* strains.

**Data analysis**

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

Data availability

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

Results

Sitafloxacin showed MIC_{50/90} values of ≤0.03/0.25 and ≤0.03/0.125 mg/L against MSSA and MSCNS strains, ≤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 MIC_{50} range of 2-4 mg/L and MIC_{90} range of 8-16 mg/L against E. faecium (including vancomycin-susceptible and vancomycin-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).

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-resistant 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 to 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 ≤0.015/0.06 mg/L for H. influenzae, 0.125/0.5 mg/L for H. parainfluenzae, and ≤0.015/0.015 mg/L for M. catarrhalis (Table 3).

Sitafloxacin 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). Sitafloxacin was as active as imipenem and metronidazole, much better than other comparators against B. fragilis. For Peptostreptococcus, sitafloxacin performed as well as imipenem and metronidazole, slightly weaker than ciprofloxacin, but better than other comparators. Sitafloxacin was not as active as imipenem but more active than other comparators against Prevotella spp. based on lower MIC_{50/90} value.

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

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 IV to inhibit bacterial growth. Therefore, high-level resistance to sitafloxacin will not develop unless mutation emerges in both DNA gyrase and topoisomerase IV. The modification of any one target, DNA gyrase or topoisomerase IV, 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 to 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 to 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 to 8 mg/L (MIC_{50/90}: 0.015/0.12 mg/L). Our MIC_{50/90} values are relatively higher, but MIC range remains the same.
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               | MIC₅₀ | MIC₉₀ |
| Methicillin-resistant S. aureus  (64) | Sitafloxacin       | ≤0.03 to 8               | ≤0.03 | 2   | 9.4  | 82.8 |
|                                   | Ciprofloxacin      | 0.25 to >64              | 1   | >64 | 42.2  | 53.1 |
|                                   | Levofloxacin       | 0.25 to >64              | 1   | 64  | 40.6  | 59.4 |
|                                   | Moxifloxacin       | ≤0.03 to 32              | 0.125 | 8  | 35.9  | 62.5 |
|                                   | Nemonoxacin        | ≤0.03 to 4               | 0.06 | 2   | 14.1  | 85.9 |
|                                   | Oxacillin          | 4 to >16                 | >16 | >16 | 100   | 0    |
|                                   | Erythromycin       | 0.25 to >64              | >64 | >64 | 67.2  | 31.2 |
|                                   | Vancomycin         | 0.5-2                    | 1   | 1   | 0     | 100  |
|                                   | Linezolid          | 1-4                      | 2   | 2   | 0     | 100  |
| Methicillin-susceptible S. aureus (47) | Sitafloxacin       | ≤0.03 to 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 to 2               | 0.06 | 0.5 | 2.1   | 93.6 |
|                                   | Nemonoxacin        | ≤0.03 to 1               | ≤0.03 | 0.25 | 0   | 100  |
|                                   | Oxacillin          | 0.125-2                  | 1   | 2   | 0     | 100  |
|                                   | Erythromycin       | 0.25 to >64              | >64 | >64 | 59.6  | 36.2 |
|                                   | Vancomycin         | ≤0.125 to 2              | 1   | 1   | 0     | 100  |
|                                   | Linezolid          | 0.5-4                    | 2   | 2   | 0     | 100  |
| MSCNS (57)                        | Sitafloxacin       | ≤0.03 to 0.25            | ≤0.03 | 0.125 | 0   | 100  |
|                                   | Ciprofloxacin      | 0.06-32                  | 0.25 | 4   | 15.8  | 80.7 |
|                                   | Levofloxacin       | ≤0.06 to 16              | 0.25 | 4   | 17.5  | 80.7 |
|                                   | Moxifloxacin       | ≤0.03 to 2               | 0.06 | 1   | 5.3   | 94.7 |
|                                   | Nemonoxacin        | ≤0.03 to 0.5             | ≤0.03 | 0.125 | 0   | 100  |
|                                   | Oxacillin          | ≤0.06 to 0.25            | 0.125 | 0.25 | 0   | 100  |
|                                   | Erythromycin       | ≤0.06 to >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       | ≤0.03 to 2               | 0.125 | 0.25 | 0   | 97.5 |
|                                   | Ciprofloxacin      | 0.125 to 64              | 2   | 64  | 48.8  | 47.5 |
|                                   | Levofloxacin       | 0.125 to >64             | 2   | 16  | 47.5  | 47.5 |
|                                   | Moxifloxacin       | ≤0.03 to 32              | 0.5 | 2   | 30    | 55   |
|                                   | Nemonoxacin        | ≤0.03 to 2               | 0.06 | 0.5 | 6.2   | 93.8 |
|                                   | Oxacillin          | 1 to >16                 | 16  | >16 | 100   | 0    |
|                                   | Erythromycin       | 0.125 to >64             | >64 | >64 | 76.2  | 23.8 |
|                                   | Vancomycin         | 1-2                      | 2   | 2   | 0     | 100  |
|                                   | Linezolid          | ≤0.06 to 2               | 1   | 2   | 0     | 100  |
| Vancomycin-susceptible E. faecalis (40) | Sitafloxacin       | ≤0.03 to 4               | 0.25 | 2   | 2.5   | 67.5 |
|                                   | Ciprofloxacin      | 1 to >64                 | 2   | 64  | 37.5  | 37.5 |
|                                   | Levofloxacin       | 0.5 to >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 to >64             | >64 | >64 | 72.5  | 5    |
|                                   | Vancomycin         | 1-4                      | 1   | 2   | 0     | 100  |
| Vancomycin-susceptible E. faecium (35) | Sitafloxacin       | 0.125-32                 | 4   | 16  | 65.7  | 8.6  |
|                                   | Ciprofloxacin      | 1 to >64                 | 64  | >64 | 97.1  | 2.9  |
|                                   | Levofloxacin       | 2 to >64                 | >64 | >64 | 97.1  | 2.9  |
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 IV. Even in case of QRDR mutation, sitafloxacin still has good inhibitory effect. Therefore,

| Organism (n) | Antimicrobial agent | MIC determination (mg/L) | R% | S% |
|--------------|---------------------|--------------------------|----|----|
|              |                     | MIC range | MIC<sub>50</sub> | MIC<sub>90</sub> |          |
|              | Moxifloxacin        | 0.5-64     | 32       | 32       | NA       | NA       |
|              | Nemonoxacin         | 0.5-64     | 8        | 32       | NA       | NA       |
|              | Ampicillin          | 1 to >64   | >64       | >64       | 97.1     | 2.9      |
|              | Erythromycin        | ≤0.06 to >64 | >64 | >64       | 88.6     | 5.7      |
|              | Vancomycin          | 0.5-1      | 1        | 1        | 0        | 100      |
| Vancomycin-resistant *E. faecium* (18) | Sitaflaxin        | 1-16       | 2        | 8        | 11.1     | 11.1     |
|              | Ciprofloxacin       | 32 to >64  | 32       | >64       | 100      | 0        |
|              | Levofloxacin        | 64 to >64  | >64       | >64       | 100      | 0        |
|              | Moxifloxacin        | 8-32       | 16       | 16       | NA       | NA       |
|              | Nemonoxacin         | 2-64       | 4        | 16       | NA       | NA       |
|              | Ampicillin          | >64 to >64 | >64       | >64       | 100      | 0        |
|              | Erythromycin        | 0.25 to >64 | >64 | >64       | 88.9     | 11.1     |
|              | Vancomycin          | >16 to >16 | >16       | >16       | 100      | 0        |
| *S. pneumoniae* (penicillin MIC ≤ 0.06 mg/L) (44) | Sitaflaxin        | ≤0.03 to 0.125 | 0.125 | 0.125 | 0       | 100      |
|              | Ciprofloxacin       | ≤0.03 to 4 | 2        | 2        | 6.8      | 22.7     |
|              | Levofloxacin        | 0.5-2      | 1        | 1        | 0        | 100      |
|              | Moxifloxacin        | ≤0.03 to 0.25 | 0.25 | 0.25 | 0       | 100      |
|              | Nemonoxacin         | ≤0.03 to 0.25 | 0.125 | 0.125 | 0       | 100      |
|              | Penicillin          | ≤0.06 to 0.06 | ≤0.06 | ≤0.06 | 0       | 100      |
|              | Ceftriaxone         | ≤0.06 to 0.5 | ≤0.06 | 0.125 | 0       | 100      |
|              | Vancomycin          | 0.125-0.5  | 0.25     | 0.25     | NA       | 100      |
|              | Erythromycin        | ≤0.06 to >64 | >64 | >64       | 84.1     | 15.9     |
| *S. pneumoniae* (penicillin MIC = 0.125-1 mg/L) (14) | Sitaflaxin        | 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 to >64  | >64       | >64       | 100      | 0        |
| *S. pneumoniae* (penicillin MIC ≥ 2 mg/L) (56) | Sitaflaxin        | 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      |

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

| Organism (n)                          | Antimicrobial agent | MIC determination (mg/L) | R%  | S%  |
|---------------------------------------|---------------------|--------------------------|-----|-----|
|                                       |                     | MIC range | MIC<sub>50</sub> | MIC<sub>90</sub> |
| Ciprofloxacin-susceptible E. coli (48) | Sitafloxacin        | ≤0.03 to 0.125 | ≤0.03 | 0.06  | 0  | 100 |
|                                       | Ciprofloxacin       | ≤0.06 to 1    | ≤0.06 | 0.25  | 0  | 100 |
|                                       | Levofloxacin        | ≤0.03 to 1    | ≤0.03 | 0.25  | 2.1 | 100 |
|                                       | Moxifloxacin        | ≤0.03 to 1    | 0.06  | 0.25  | 0  | 97.9 |
|                                       | Nemonoxacin         | ≤0.03 to 1    | 0.125 | 0.5   | 0  | 100 |
|                                       | Cefoperazone/sulbactam | ≤0.06/4 to 32/4 | 1/4  | 16/4  | 0  | 93.8 |
|                                       | Cefazolin           | 1 to >64      | 2     | >64   | 31.2 | 68.8 |
|                                       | Cefuroxime          | 0.25 to >64   | 8     | >64   | 27.1 | 70.8 |
|                                       | Cefazidime          | ≤0.06 to 32   | 0.25  | 8     | 6.2 | 85.4 |
|                                       | Ceftriaxone         | ≤0.06 to >64  | ≤0.06 | >64   | 25  | 75  |
|                                       | Cefazidime/avibactam | ≤0.06/4 to 0.25/4 | ≤0.06/4 | 0.25/4 | 0  | 100 |
|                                       | Cefepime            | ≤0.06 to >64  | ≤0.06 | 16    | 14.6 | 75  |
|                                       | Meropenem           | ≤0.06 to ≤0.06 | ≤0.06 | ≤0.06 | 0  | 100 |
|                                       | Amikacin            | 0.5-8         | 1     | 4     | 0  | 100 |
|                                       | Colistin            | ≤0.06 to 1    | 0.25  | 0.25  | 0  | NA  |
| Ciprofloxacin-resistant E. coli (50)  | Sitafloxacin        | 0.25-16       | 1     | 4     | 12  | 62  |
|                                       | Ciprofloxacin       | 4 to >64      | 16    | >64   | 100 | 0   |
|                                       | Levofloxacin        | 1 to >64      | 8     | 32    | 70  | 4   |
|                                       | Moxifloxacin        | 1 to >64      | 8     | 64    | 90  | 2   |
|                                       | Nemonoxacin         | 1 to >64      | 16    | 64    | 98  | 2   |
|                                       | Cefoperazone/sulbactam | 0.125/4 to >64/4 | 8/4  | 64/4  | 12  | 70 |
|                                       | Cefazolin           | 1 to >64      | >64   | >64   | 66  | 34  |
|                                       | Cefuroxime          | 1 to >64      | >64   | >64   | 68  | 24  |
|                                       | Cefazidime          | 0.125 to >64  | 4     | 32    | 30  | 54  |
|                                       | Ceftriaxone         | ≤0.06 to >64  | >64   | >64   | 68  | 32  |
|                                       | Cefazidime/avibactam | ≤0.06/4 to 4/4 | 0.125/4 | 0.25/4 | 0  | 100 |
|                                       | Cefepime            | ≤0.06 to >64  | 16    | 64    | 54  | 36  |
|                                       | Meropenem           | ≤0.06 to 0.125 | ≤0.06 | ≤0.06 | 0  | 100 |
|                                       | Amikacin            | 0.5 to >64    | 2     | 8     | 2   | 98  |
|                                       | Colistin            | ≤0.06 to 0.5  | 0.25  | 0.25  | 0  | NA  |
| Non-ESBL-producing E. coli (47)       | Sitafloxacin        | ≤0.03 to 16   | ≤0.03 | 1     | 7.5 | 90.6 |
|                                       | Ciprofloxacin       | ≤0.06 to >64  | ≤0.06 | 16    | 32.1 | 69.8 |
|                                       | Levofloxacin        | ≤0.03 to >64  | 0.06  | 16    | 22.6 | 69.8 |
|                                       | Moxifloxacin        | ≤0.03 to >64  | 0.06  | 16    | 28.3 | 69.8 |
|                                       | Nemonoxacin         | ≤0.03 to >64  | 0.125 | 16    | 30.2 | 69.8 |
|                                       | Cefoperazone/sulbactam | ≤0.06/4 to 16/4 | 1/4  | 4/4   | 0  | 100 |
|                                       | Cefazolin           | 0.125 to >64  | 2     | 8     | 18.9 | 56.6 |
|                                       | Cefuroxime          | 0.06 to >64   | 4     | 16    | 5.7  | 86.8 |
|                                       | Cefazidime          | ≤0.06 to 2    | 0.25  | 0.5   | 0  | 100 |
|                                       | Ceftriaxone         | ≤0.06 to 0.25 | ≤0.06 | 0.125 | 0   | 100 |
|                                       | Cefazidime/avibactam | ≤0.06/4 to 0.25/4 | 0.125/4 | 0.25/4 | 0  | 100 |
|                                       | Cefepime            | ≤0.06 to >64  | ≤0.06 | 0.25  | 0   | 98.1 |
|                                       | Meropenem           | ≤0.06 to 0.125 | ≤0.06 | ≤0.06 | 0  | 100 |
|                                       | Amikacin            | 0.25-8        | 2     | 4     | 0   | 100 |
|                                       | Colistin            | ≤0.06 to 1    | 0.25  | 0.25  | 0  | 100 |
| ESBL-producing E. coli (47)            | Sitafloxacin        | 0.03-8        | 1     | 2     | 6.4  | 70.2 |
|                                       | Ciprofloxacin       | 0.06 to >64   | 8     | >64   | 76.6 | 23.4 |
| Organism (n)                        | Antimicrobial agent       | MIC determination (mg/L) | R%  | S%  |
|------------------------------------|---------------------------|--------------------------|-----|-----|
|                                    |                           | MIC range | MIC<sub>50</sub> | MIC<sub>90</sub> |
| Levofoxacin                         |                           | 0.03-32  | 4              | 32             | 72.3 | 23.4 |
| Moxifloxacin                        |                           | ≤0.03 to 64 | 8     | 32     | 63.8 | 27.7 |
| Nemonoxacin                         |                           | 0.06 to >64 | 8     | 64     | 72.3 | 27.7 |
| Cefoperazone/sulbactam              |                           | 4/4 to >64/4 | 16/4 | 64/4   | 12.8 | 61.7 |
| Cefazolin                           |                           | 1 to >64 | >64             | >64            | 97.9 | 2.1 |
| Cefuroxime                          |                           | 1 to >64  | >64             | >64            | 95.7 | 2.1 |
| Ceftazidime                         |                           | 1 to >64  | 8               | 64             | 38.3 | 36.2 |
| Ceftiraxone                         |                           | 8 to >64  | >64             | >64            | 100  | 0   |
| Ceftazidime/avibactam               |                           | 0.06/4-4/4 | 0.125/4 | 0.25/4 | 0   | 100 |
| Cefepime                            |                           | 0.125 to >64 | 16  | >64 | 74.5 | 6.4 |
| Meropenem                           |                           | 0.06-0.125 | 0.064 | 0.064 | 0   | 100 |
| Amikacin                            |                           | 0.5 to >64 | 2     | 4     | 2.1  | 97.9 |
| Colistin                            |                           | 0.06-0.5  | 0.25            | 0.25           | 0   | NA  |
|                                    | Ciprofloxacin-susceptible \( K. pneumoniae \) (53) | | | |
| Sitafloxacin                        |                           | ≤0.03 to 0.25 | ≤0.03 | 0.125 | 0   | 100 |
| Ciprofloxacin                       |                           | ≤0.06 to 1 | ≤0.06 | 0.5 | 0   | 100 |
| Levofoxacin                         |                           | ≤0.03 to 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 to >64/4 | 0.25/4 | 8/4 | 3.8 | 94.3 |
| Cefazolin                           |                           | 1 to >64  | 2               | >64            | 15.1 | 84.9 |
| Cefuroxime                          |                           | 1 to >64  | 2               | >64            | 11.3 | 84.9 |
| Ceftazidime                         |                           | ≤0.06 to >64 | 0.125 | 4     | 7.5  | 90.6 |
| Ceftiraxone                         |                           | ≤0.06 to >64 | ≤0.06 | >64 | 11.3 | 88.7 |
| Ceftazidime/avibactam               |                           | ≤0.06/4 to >64/4 | 0.125/4 | 0.25/4 | 1.9 | 98.1 |
| Cefepime                            |                           | ≤0.06 to >64 | ≤0.06 | 4     | 7.5  | 88.7 |
| Meropenem                           |                           | ≤0.06 to >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 \( K. pneumoniae \) (38) | | | |
| Sitafloxacin                        |                           | 0.25-64    | 2               | 32             | 31.6 | 36.8 |
| Ciprofloxacin                       |                           | 4 to >64 | 16               | >64            | 100  | 0   |
| Levofoxacin                         |                           | 0.5 to >64 | 8               | >64            | 73.7 | 15.8 |
| Moxifloxacin                        |                           | 2 to >64 | 16               | >64            | 76.3 | 5.3 |
| Nemonoxacin                         |                           | 1 to >64  | 16               | >64            | 94.7 | 5.3 |
| Cefoperazone/sulbactam              |                           | 0.25/4 to >64/4 | 32/4 | >64/4  | 34.2 | 44.7 |
| Cefazolin                           |                           | 2 to >64  | >64             | >64            | 84.2 | 15.8 |
| Cefuroxime                          |                           | 8 to >64  | >64             | >64            | 92.1 | 5.3 |
| Ceftazidime                         |                           | 0.25 to >64 | 32 | >64 | 73.7 | 21.1 |
| Ceftiraxone                         |                           | ≤0.06 to >64 | >64 | >64 | 84.2 | 15.8 |
| Ceftazidime/avibactam               |                           | 0.125/4 to >64/4 | 0.5/4 | 0.5/4 | 2.6 | 97.4 |
| Cefepime                            |                           | ≤0.06 to >64 | 16 | >64 | 63.2 | 13.2 |
| Meropenem                           |                           | ≤0.06 to >16 | ≤0.06 | 0.25 | 5.3 | 94.7 |
| Amikacin                            |                           | 0.5 to >64 | 1               | 4 | 5.3 | 94.7 |
| Colistin                            |                           | 0.125-4    | 0.5 | 0.5 | 2.6 | NA  |
|                                    | Non-ESBL-producing \( K. pneumoniae \) (54) | | | |
| Sitafloxacin                        |                           | ≤0.03 to 4 | ≤0.03 | 0.5 | 1.9 | 92.6 |
| Ciprofloxacin                       |                           | ≤0.06 to 8 | ≤0.06 | 4 | 11.1 | 87 |
| Levofoxacin                         |                           | ≤0.03 to 16 | 0.06 | 2 | 9.3 | 90.7 |
| Moxifloxacin                        |                           | 0.06-32    | 0.125 | 4 | 9.3 | 87 |
sitafloxacin remains powerful in inhibiting ciprofloxacin-resistant Enterobacterales 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. 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.

For ESBL-producing E. coli strains, sitafloxacin had activity much higher than 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.

### Table 2 (continued)

| Organism (n) | Antimicrobial agent | MIC determination (mg/L) | R% | S% |
|--------------|---------------------|--------------------------|----|----|
|              |                     | MIC range | MIC<sub>50</sub> | MIC<sub>90</sub> |          |
| 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 to >64            | 2          | 4             | 3.7         | 96.3     |
| Cefuroxime   | 1 to >64            | 2          | 16            | 5.6         | 88.9     |
| Ceftazidime  | ≤0.06 to 64         | 0.125      | 0.5           | 3.7         | 96.3     |
| Ceftriaxone  | ≤0.06 to 0.5        | ≤0.06      | 0.125         | 0           | 100      |
| Cefepime     | ≤0.06 to >4         | 0.125/4    | 0.25/4        | 0           | 100      |
| Meropenem    | ≤0.06 to ≤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 K. pneumoniae (41) | | | | |
| Sitafloxacin | ≤0.03 to 64         | 1          | 16            | 26.8        | 51.2     |
| Ciprofloxacin| ≤0.06 to >64        | 8          | >64           | 78          | 14.6     |
| Levofoxacin  | ≤0.03 to >64        | 8          | >64           | 56.1        | 34.1     |
| Moxifloxacin | 0.06 to >64         | 16         | >64           | 58.5        | 26.8     |
| Nemonoxacin  | 0.125 to >64        | 8          | >64           | 78          | 22       |
| Cefoperazone/sulbactam | 2/4 to >64/4 | 32/4 | >64/4 | 36.6 | 36.6 |
| Cefazolin    | >64 to >64          | >64        | >64           | 100         | 0        |
| Cefuroxime   | 16 to >64           | >64        | >64           | 97.6        | 0        |
| Ceftazidime  | 0.5 to >64          | 32         | >64           | 75.6        | 17.1     |
| Ceftriaxone  | 8 to >64            | >64        | >64           | 100         | 0        |
| Cefazidime/avibactam | 0.125/4 to >64/4 | 0.5/4 | 0.5/4 | 4.9 | 95.1 |
| Cefepime     | 2 to >64            | 16         | >64           | 70.7        | 4.9      |
| Meropenem    | ≤0.06 to >16        | ≤0.06      | 0.25          | 7.3         | 92.7     |
| Amikacin     | 0.5 to >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**
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*, 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 ≤ 0.03 to 8 mg/L, higher than other reports (≤ 0.008 to 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 methicillin-resistant strains. Sitafloxacin was slightly poorer than vancomycin in the activity 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<sub>50/90</sub>: 0.25/2 mg/L), but showed poor activity against *E. faecium* (including vancomycin-susceptible and vancomycin-resistant strains) with MIC<sub>50</sub> range of 2-4 mg/L and MIC<sub>90</sub> range of 8-16 mg/L. An overseas study on the

**Fig. 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*
# Table 3

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

| Organism (n)          | Antimicrobial agent     | MIC determination (mg/L) | R%  | S%  |
|-----------------------|-------------------------|--------------------------|-----|-----|
|                       |                         | MIC range                | MIC\textsubscript{50} | MIC\textsubscript{90} |     |
| **P. aeruginosa (88)**| Sitafloxacin            | ≤0.03 to 64              | 1   | 8   | 23.9 | 54.5 |
|                       | Ciprofloxacin           | 0.06 to >64              | 2   | 32  | 54.5 | 43.2 |
|                       | Levofloxacin            | ≤0.03 to >64             | 8   | 32  | 56.8 | 43.2 |
|                       | Moxifloxacin            | 0.06 to >64              | 4   | 64  | NA   | NA   |
|                       | Nemonoxacin             | 0.06 to >64              | 4   | 64  | 46.6 | 53.4 |
|                       | Ceftazidine             | 1 to >64                 | 16  | >64 | 38.6 | 48.9 |
|                       | Cefoperazone/sulbactam  | 1/4 to >64/4             | 32/4| >64/4| NA   | NA   |
|                       | Meropenem               | 0.06-32                  | 2   | 32  | 37.5 | 54.5 |
|                       | Amikacin                | 1 to >64                 | 4   | >64 | 12.5 | 85.2 |
|                       | Ceftriaxone             | 16 to >64                | >64 | >64 | NA   | NA   |
|                       | Ceftazidine/avibactam   | 0.5/4 to >64/4           | 2/4 | 64/4| 29.5 | 70.5 |
|                       | Cefepime                | 1 to >64                 | 8   | >64 | 35.2 | 50   |
|                       | Colistin                | 0.5-16                   | 1   | 2   | 4.5  | NA   |
| **A. baumannii (87)**| Sitafloxacin            | 0.06 to >64              | 8   | 64  | 40.2 | 42.5 |
|                       | Ciprofloxacin           | 1 to >64                 | 64  | >64 | 59.8 | 40.2 |
|                       | Levofloxacin            | 1 to >64                 | 16  | 64  | 55.2 | 40.2 |
|                       | Moxifloxacin            | 2 to >64                 | 64  | >64 | NA   | NA   |
|                       | Nemonoxacin             | 8 to >64                 | >64 | >64 | NA   | NA   |
|                       | Ceftazidine             | 1 to >64                 | 32  | >64 | 59.8 | 39.1 |
|                       | Cefoperazone/sulbactam  | ≤0.06/4 to >16/4         | >16/4| >16/4| NA   | NA   |
|                       | Meropenem               | 0.125 to >64             | >64 | >64 | 58.6 | 41.4 |
|                       | Amikacin                | ≤0.06 to >64             | 64  | >64 | 52.9 | 47.1 |
|                       | Ceftriaxone             | 0.06 to >64              | 8   | >64 | 59.8 | 25.3 |
|                       | Ceftazidine/avibactam   | 0.06/4 to >64/4          | 8/4 | 64/4| NA   | NA   |
|                       | Cefepime                | ≤0.03 to 16              | 2   | 8   | 57.5 | 40.2 |
|                       | Colistin                | 0.125-4                  | 0.5 | 0.5 | 0    | NA   |
| **H. influenzae (107)**| Sitafloxacin            | ≤0.015 to 0.25           | ≤0.015| 0.06 | 0    | 100  |
|                       | Ciprofloxacin           | ≤0.015 to 16             | 0.03| 1   | NA   | 98.1 |
|                       | Levofloxacin            | ≤0.06 to 8               | ≤0.06| 1   | NA   | 99.1 |
|                       | Moxifloxacin            | ≤0.015 to 8              | 0.03| 1   | NA   | 98.1 |
|                       | Nemonoxacin             | ≤0.015 to 1              | 0.03| 0.5 | 0.9  | 99.1 |
|                       | Ampicillin              | ≤0.06 to >64             | 4   | 64  | 55.1 | 38.3 |
|                       | Cefuroxime              | ≤0.5 to 16               | ≤0.5| 2   | 1.9  | 96.3 |
|                       | Ceftriaxone             | ≤0.06 to 64              | ≤0.06| 0.25| 0    | 98.1 |
|                       | Amoxicillin/clavulanic acid| ≤0.5/0.25 to 32/16| ≤0.5/0.25| 4/2| 8.4 | 91.6 |
| **H. parainfluenzae (27)**| Sitafloxacin            | ≤0.015 to 1              | 0.125| 0.5 | NA   | NA   |
|                       | Ciprofloxacin           | ≤0.015 to 32             | 2   | 16  | NA   | 40.7 |
|                       | Levofloxacin            | ≤0.06 to 8               | 1   | 8   | NA   | 70.4 |
|                       | Moxifloxacin            | ≤0.015 to 16             | 2   | 16  | NA   | 44.4 |
|                       | Nemonoxacin             | ≤0.015 to 8              | 1   | 4   | NA   | NA   |
|                       | Ampicillin              | ≤0.06 to >64             | 1   | 64  | 29.6 | 55.6 |
|                       | Cefuroxime              | ≤0.5 to 8                | ≤0.5| 8   | 0    | 85.2 |
|                       | Ceftriaxone             | ≤0.06 to 64              | ≤0.06| 0.25| 0    | 96.3 |
|                       | Amoxicillin/clavulanic acid| ≤0.5/0.25 to 4/2| ≤0.5/0.25| 4/2| 0   | 100  |
| **M. catarrhalis (61)**| Sitafloxacin            | ≤0.015 to 0.125          | ≤0.015| ≤0.015| NA   | NA   |
|                       | Ciprofloxacin           | ≤0.015 to 0.5            | 0.06| 0.06| NA   | 100  |
|                       | Levofloxacin            | ≤0.06 to 1               | ≤0.06| ≤0.06| NA   | 100  |
in vitro activity of sitafloxacin [13] reported that the MIC 90 of sitafloxacin was 2 mg/L for \textit{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 \textit{E. faecalis}. Sitafloxacin was weaker than vancomycin in the activity against vancomycin-susceptible \textit{E. faecium}, but comparable to other comparators against vancomycin-resistant \textit{E. faecium}.

A study on the activity of sitafloxacin against 1531 clinical isolates found that the MIC range of sitafloxacin was \leq 0.008 to 0.25 mg/L (MIC 50/90: 0.03/0.06 mg/L) for PSSP strains, \leq 0.015 to 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 to 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 to 2 mg/L (MIC 50/90: 0.125/0.125 mg/L) for PRSP strains.

### Table 3 (continued)

| Organism (n) | Antimicrobial agent | MIC determination (mg/L) | R% | S% |
|--------------|---------------------|--------------------------|----|----|
|              | MIC range           | MIC 50 | MIC 90 |    |    |
|              |                     |    |    | NA | NA |
| \textit{B. fragilis} (25) | Sitafloxacin | 0.03-4 | 0.06 | 2 | NA | NA |
|               | Ciprofloxacin 0.125 to >128 | 8 | \textgreater 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 to >128 | \textgreater 128 | \textgreater 128 | 84 | 8 |
|               | Metronidazole 0.5-1 | 1 | 1 | 0 | 100 |

| \textit{Peptostreptococcus} (14) | Sitafloxacin 0.125-4 | 0.125 | 4 | NA | NA |
|                                      | Ciprofloxacin \leq 0.015 to 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 to >128 | 16 | 16 | 64.3 | 28.6 |
|                                      | Metronidazole 0.5-8 | 1 | 1 | 0 | 100 |

| \textit{Prevotella} spp. (11) | Sitafloxacin 0.03-8 | 0.125 | 8 | NA | NA |
|                                | Ciprofloxacin 0.125 to >128 | 2 | \textgreater 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 to >128 | 2 | \textgreater 128 | 45.5 | 54.5 |
|                                | Metronidazole 0.5 to >128 | 8 | \textgreater 128 | 36.4 | 63.6 |

\textit{MIC} minimum inhibitory concentration; \textit{NA} not available; \textit{R\%} percentage resistant; \textit{S\%} percentage susceptible
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 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.

These in vitro pharmacodynamic results are promising and support the clinical use of sitafloxacin in the treatment of various infections. According to a pharmacokinetics and pharmacodynamics (PK/PD) analysis in patients with community-acquired respiratory tract infections (RTIs), the authors examined the correlation between pharmacokinetics and bacteriological efficacy. They simulated the clinical efficacy of sitafloxacin after various dosing regimens. It was found that the eradication rate was 96.4% for \( \frac{fAUC_{(0-24\ h)}}{MIC} \geq 30 \) and 96.3% for \( \frac{C_{max}}{MIC} \geq 2 \). The PK/PD target values of sitafloxacin were \( fAUC_{(0-24\ h)}/MIC \geq 30 \) and \( C_{max}/MIC \geq 2 \) for the treatment of mild to moderate RTIs. The dosing regimen of 50 or 100 mg twice daily reached these PK/PD target values in patients with RTIs. And a 100 mg once-daily regimen also showed similar efficacy based on PK/PD simulations [16].

Sitafloxacin has been used in Japan in the treatment of a number of bacterial infections. Randomized, double-blind, multicenter, noninferiority trials have indicated that the clinical efficacy of oral sitafloxacin was noninferior to oral levofloxacin in the treatment of complicated urinary tract infections, noninferior to oral tosufloxacin in the treatment of community-acquired pneumonia, and noninferior to oral levofloxacin in the treatment of community-acquired pneumonia or an infectious exacerbation of chronic respiratory tract disease. Non-controlled studies also proved the efficacy of oral sitafloxacin in urethritis in men, Chlamydia trachomatis-associated cervicitis in women, otolaryngological infections, and odontogenic infections [3].

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.

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### Code availability
Not applicable.

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This work was supported by National Mega-project for Innovative Drugs (2019ZX09721001-006-004), and CHINET Antimicrobial Surveillance Network (grant number WI207259).

### Data availability
Data can be provided upon request.

### Declarations

#### Ethics approval
This study was approved by the Institutional Review Board of Huashan Hospital, Fudan University (number: 2019-572).

#### Consent to participate
Not applicable.

#### Consent for publication
Not applicable.

#### Conflict of interest
The authors declare no competing interests.

| Organism (n) | Antimicrobial agent | Breakpoints (mg/L) | MIC range (mg/L) | MIC 50 (mg/L) | MIC 90 (mg/L) | R% | S% |
|-------------|---------------------|--------------------|------------------|--------------|--------------|----|----|
| M. pneumoniae (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 to 0.06 | 0.06 | 0.06 | NA 100 |
| Nemonoxacin | NA NA | ≤0.03 to 0.06 | 0.06 | 0.06 | NA NA |
| Erythromycin | ≤0.5 ≥1 | 32 to >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.
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