Antimicrobial activity of ceftobiprole and comparator agents when tested against gram-positive and -negative organisms collected across China (2016–2018)

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Abstract

Background: Ceftobiprole is a fifth-generation cephalosporin which has been reported to have broad antibacterial spectrum when tested against bacteria collected from other countries except China. This study evaluated the in vitro activity of ceftobiprole in comparison with other comparators against clinically significant isolates collected across from China.

Results: Susceptibility testing of ceftobiprole and comparators against 1163 clinically isolated Gram-positive and Gram-negative bacteria was performed with broth micro dilution method following the CLSI guidelines. All 110 S. aureus were susceptible to ceftobiprole with MIC50/90 of 1/2 mg/L for MRSA and 0.5/1 mg/L for MSSA. For Coagulase-negative staphylococci (CNS), MIC50/90 of ceftobiprole for MRCNS and MSCNS was 1/2 mg/L and 0.25/0.5 mg/L. Ceftobiprole demonstrated good potency against E. faecalis (MIC50/90 of 0.5/1 mg/L) but limited activity against E. faecium (MIC50/90 of > 32/ > 32 mg/L). Ceftobiprole demonstrated potent activity against all 39 β-hemolytic Streptococcus spp. with MIC50/90 ≤ 0.015/≤ 0.015–2 mg/L and 110 of PSSP with 98.2% susceptibility. Ceftobiprole inhibited all isolates of H. influenzae and M. catarrhalis at ≤ 1 mg/L. 91.8% and 98.2% of the ESBL-negative E. coli and K. pneumoniae were susceptible to ceftobiprole, but most of the ESBL-positive or carbapenem-resistant strains were also resistant to ceftobiprole. Ceftobiprole inhibited 84.2% of carbapenem-susceptible P. aeruginosa and 94.1% of carbapenem-susceptible A. baumannii at ≤ 8 mg/L, but only 52.6% of carbapenem-resistant P. aeruginosa and 5.3% of carbapenem-resistant A. baumannii.

Conclusion: Ceftobiprole demonstrated good in vitro activity against a broad range of clinically relevant contemporary Gram-positive and Gram-negative bacterial isolates.

Keywords: S. aureus, E. faecalis, H. influenzae, Streptococcus spp, M. catarrhalis, E. coli, K. pneumoniae, Ceftobiprole, Minimal inhibitory concentration

Background

Antimicrobial resistance has been a public health threat in recent years, with an increase of multi-drug resistant bacteria, such as extended-spectrum β-lactamase positive Enterobacterales, methicillin-resistant Staphylococcus aureus (MRSA), Vancomycin-resistant E. faecium and penicillin-non-susceptible S. pneumoniae (PRSP), which are listed as the important pathogens for new...
antibiotics by WHO [1]. Ceftobiprole is a fifth-generation parenteral cephalosporin demonstrating potent in vitro activity against Gram-positive pathogens, including MRSA and PRSP, as well as some non-carbapenemase or ESBL-producing Gram-negative pathogens commonly associated with pneumonia [2, 3]. It has obtained regulatory approval in Europe and several non-European countries for the treatment of hospital-acquired pneumonia excluding ventilator-associated pneumonia and community-acquired pneumonia in adults [4, 5]. It has been reported that ceftobiprole is generally β-lactamase stable and has a strong affinity for essential penicillin-binding proteins, including those responsible for β-lactam resistance in staphylococci and pneumococci [6]. Several studies have been reported on the spectrum and potency of ceftobiprole against Gram-positive and Gram-negative pathogens collected from Europe and surrounding countries in a variety of infection types [2–4, 7, 8]. In this present study, we expand upon those observations by reporting the activity of ceftobiprole and comparators against bacterial isolates obtained and tested during the 2016–2018 CHINET Antimicrobial Surveillance Network in China.

Results
Ceftobiprole and comparator antibiotics activity against gram-positive bacteria
Ceftobiprole was active against 110 S. aureus (MIC range, 0.25–2 mg/L, 100% susceptibility) and 80 Coagulase-negative Staphylococci (CNS, MIC range, ≤0.015–4 mg/L). All S. aureus and CNS were susceptible to vancomycin and linezolid. For MRSA, susceptibility to ciprofloxacin, clindamycin, and erythromycin was 54.5%, 23.6%, and 12.7%, which was less than that of methicillin-susceptible S. aureus (MSSA), 83.6%, 72.7%, and 43.6%, respectively. Ceftobiprole was twice as active against MSSA strains with MIC_{50/90} of 0.5/1 mg/L than on MRSA strains with MIC_{50/90} of 1/2 mg/L. For methicillin-resistant Coagulase-negative Staphylococci (MRCNS), ciprofloxacin, clindamycin, and erythromycin susceptibility were 17.5%, 57.5%, and 12.5%, which were all less than that of methicillin-susceptible Coagulase-negative Staphylococci (MSCNS), 67.5%, 85%, and 32.5%, respectively. Ceftobiprole was two-fold more active on MSCNS strains with MIC_{50/90} of 0.25/0.5 mg/L than on MRCNS strains with MIC_{50/90} of 1/2 mg/L (Table 1).

Ceftobiprole was also active against 24 E. faecalis with MIC_{50/90} of 0.5/1 mg/L but showed no clinically relevant activity against 24 E. faecium with both MIC_{50} and MIC_{90} > 32 mg/L. All E. faecium were susceptible to vancomycin and linezolid, but 8.3% of E. faecalis was intermediate to linezolid. For E. faecalis, the resistance rate to ampicillin, ciprofloxacin, and erythromycin was much less than that for E. faecium (8.3%, 29.2%, and 62.5% VS 82.6%, 87%, and 91.3%) (Table 2).

Ceftobiprole demonstrated good activity against PSSP (susceptibility of 98.2%), which was similar to linezolid and vancomycin, whereas only half of the PISP and PRSP were susceptible to it. Erythromycin showed poor activity against all S. pneumoniae. Ceftobiprole demonstrated potent activity against all 39 Streptococcus with

| Antimicrobial agents | MIC Range | MIC_{50} | MIC_{90} | R% | S% |
|----------------------|-----------|----------|----------|----|----|
| Methicillin-resistant Staphylococcus aureus (MRSA) (55) |
| Ceftobiprole         | 0.25–2    | 1        | 2        | 0  | 100|
| Linezolid            | 0.25–2    | 0.5      | 1        | 0  | 100|
| Vancomycin           | 0.25–1    | 0.5      | 1        | 0  | 100|
| Penicillin           | 0.015–32  | >32      | >32      | 0  | 100|
| Oxacillin            | 0.015–4   | >4       | >4       | 0  | 100|
| Ciprofloxacin        | 0.25–32   | >0.25    | >0.25    | 0  | 100|
| Clindamycin          | ≤0.06–128 | >128     | >128     | 76.4| 23.6|
| Erythromycin         | 0.125–128 | >128     | >128     | 85.5| 12.7|
| Methicillin-susceptible Staphylococcus aureus (MSSA) (40) |
| Ceftobiprole         | 0.25–2    | 0.5      | 1        | 0  | 100|
| Linezolid            | 0.25–2    | 0.5      | 1        | 0  | 100|
| Vancomycin           | 0.25–1    | 0.5      | 1        | 0  | 100|
| Penicillin           | 0.015–32  | >32      | >32      | 0  | 100|
| Oxacillin            | 0.015–4   | >4       | >4       | 0  | 100|
| Ciprofloxacin        | 0.125–32  | >0.25    | >0.25    | 0  | 100|
| Clindamycin          | ≤0.06–128 | >128     | >128     | 76.4| 23.6|
| Erythromycin         | 0.125–128 | >128     | >128     | 85.5| 12.7|
| Methicillin-susceptible Coagulase negative Staphylococci (MRCNS) (40) |
| Ceftobiprole         | ≤0.015–1  | 0.25     | 0.5      | –  | –  |
| Linezolid            | 0.05–2    | 0.5      | 1        | 0  | 100|
| Vancomycin           | 0.05–2    | 0.25     | 0.5      | 0  | 100|
| Penicillin           | ≤0.015–32 | 0.25     | 8        | 65 | 35 |
| Oxacillin            | ≤0.015    | ≤0.25    | ≤0.25    | 0  | 100|
| Ciprofloxacin        | 0.125–16  | 0.25     | 4        | 15 | 67.5|
| Clindamycin          | ≤0.06–128 | ≤0.06    | >128     | 15 | 85 |
| Erythromycin         | ≤0.06–128 | >64      | >128     | 67.5| 32.5|
Table 2 Activity of ceftobiprole and comparator antimicrobial agents when tested against *Enterococcus* isolated from China (mg/L)

| Antimicrobial agents | MIC Range | MIC50 | MIC90 | R% | S% |
|----------------------|-----------|-------|-------|----|----|
| *Enterococcus faecalis* (24) | | | | | |
| Ceftobiprole | 0.06–>32 | 0.5 | 1 | – | – |
| Linezolid | 0.5–4 | 0.5 | 2 | 0 | 91.7 |
| Vancomycin | 0.5–2 | 0.5 | 1 | 0 | 100 |
| Ampicillin | 1–>128 | 1 | 4 | 83.3 | 17.7 |
| Ciprofloxacin | 0.25–>32 | 1 | >32 | 29.2 | 70.8 |
| Erythromycin | 1–>128 | >128 | >128 | 62.5 | 0 |
| *Enterococcus faecium* (23) | | | | | |
| Ceftobiprole | 0.5–>32 | >32 | >32 | – | – |
| Linezolid | 0.25–1 | 0.5 | 0.5 | 0 | 100 |
| Vancomycin | 0.25–4 | 0.5 | 0.5 | 0 | 100 |
| Ampicillin | 1–>128 | >128 | >128 | 82.6 | 17.4 |
| Ciprofloxacin | 1–>32 | >32 | >32 | 87.8 | 12.2 |
| Erythromycin | 0.125–>128 | >128 | >128 | 91.3 | 8.7 |

MIC50/90 ≤ 0.015/≤ 0.015–2 mg/L, which is far better than that of linezolid and vancomycin (both MIC50/90 are 0.25/0.25–0.5 mg/L). All 13 *Streptococcus pyogenes* were resistant to erythromycin, while 35.7% of *Streptococcus agalactiae* and 33.3% of *Streptococcus mitis* remained susceptible to it (Table 3).

Ceftobiprole and comparator antibiotics activity against gram-negative bacteria

Ceftobiprole exhibited potent activity against *Haemophilus influenzae* (MIC50/90 ≤ 0.015/0.5 mg/L). Ceftobiprole also showed good activity against *Moraxella catarrhalis* with MIC50/90 of 0.25/0.5 mg/L. All *H. influenzae* and *M. catarrhalis* were inhibited at MIC of ≤ 1 mg/L ceftobiprole, and highly susceptible to ampicillin-sulbactam, ceftazidine, ceftriaxone, cefoperazone-sulbactam, imipenem, amikacin, colistin, and tigecycline, but against ESBL-producers, ceftobiprole performed worse than these other cephalosporins. Ceftobiprole also showed no activity against carbapenem-resistant *K. pneumoniae* (MIC50/90 > 128/128 mg/L), some of which were susceptible to amikacin (40%), colistin (91.1%), and tigecycline (100%). Ceftobiprole showed moderate activity against *E. aerogenes*, *C. freundii*, *P. mirabilis*, and *M. morganella*, with over 50% of strains inhibited at ≤ 0.06 mg/L. For *E. cloacae* and *S. marcescens*, over 50% of strains were inhibited at 0.25–0.5 mg/L.
Ceftobiprole had little activity against *P. vulgaris*, with MIC<sub>50</sub>/90 of 32/ > 128 mg/L (Table 5a-c).

Ceftobiprole also had limited activity against *P. aeruginosa*, independent of susceptibility to carbapenems, with MIC<sub>50</sub>/90 8/64- > 128 mg/L. Interestingly, for carbapenem-susceptible *A. baumannii*, 94.1% of strains were inhibited at ≤ 4 mg/L, showing the potency of ceftobiprole which was comparable to that of amikacin, cefoperazone-sulbactam, imipenem, colistin and tigecycline (MIC<sub>50</sub>/90 was 1/4, 0.125/0.25 and 0.5/1 mg/L, respectively). However, for the carbapenem-resistant *A. baumannii*, ceftobiprole had negligible activity with a MIC<sub>50</sub>/90 of > 128 mg/L. For all *P. aeruginosa* and *A. baumannii*, colistin retained excellent in vitro activity (MIC<sub>50</sub>/90, 0.5–1/1–2 mg/L) (Table 6).

The MIC distribution of ceftobiprole is presented in Table 7a-b.

**Discussion**

As one of the limited new effective antibiotics approved for treating infection caused by resistant Gram-positive and Gram-negative bacteria, ceftobiprole has been evaluated in several studies in different medical centers around the world [7, 9, 10]. However, the published literature for its efficacy against contemporary clinical isolates from China is limited. In this study, we report on the activity of ceftobiprole and comparators against recent clinical isolates collected from hospitalized patients from...
### Table 5 (continued)

| Antimicrobial agents | MIC Range | MIC50 | MIC90 | R%  | S%  |
|----------------------|-----------|-------|-------|-----|-----|

#### Enterobacter cloacae (49)
- Ceftobiprole: 0.06 – >128
- Ceftazidime: 0.125 – 128
- Ceftriaxone: 0.06 – >128
- Ceferazone-Sulbactam: 0.125 – 128
- Imipenem: 0.06 – 64
- Amikacin: 0.125 – >128
- Colistin: 32 – >128
- Tigecycline: 0.25 – >128

#### Enterobacter aerogenes (55)
- Ceftobiprole: 0.06 – >128
- Ceftazidime: 0.125 – 128
- Ceftriaxone: 0.06 – >128
- Ceferazone-Sulbactam: 0.125 – 128
- Imipenem: 0.06 – 64
- Amikacin: 0.125 – >128
- Colistin: 32 – >128
- Tigecycline: 0.25 – >128

#### Citrobacter freundii (53)
- Ceftobiprole: 0.06 – >128
- Ceftazidime: 0.25 – >128
- Ceftriaxone: 0.06 – >128
- Ceferazone-Sulbactam: 0.125 – >128
- Imipenem: 0.06 – 64
- Amikacin: 0.125 – >128
- Colistin: 32 – >128
- Tigecycline: 0.25 – >128

#### Proteus mirabilis (52)
- Ceftobiprole: 0.06 – >128
- Ceftazidime: 0.06 – 2
- Ceftriaxone: 0.06 – >128
- Ceferazone-Sulbactam: 0.25 – 4
- Imipenem: 0.06 – 2
- Amikacin: 0.5 – 32
- Colistin: 32 – >32
- Tigecycline: 1 – 8

#### Proteus vulgaris (35)
- Ceftobiprole: 0.06 – >128
- Ceftazidime: 0.06 – >128
- Ceftriaxone: 0.06 – >128
- Ceferazone-Sulbactam: 0.5 – 64
- Imipenem: 0.25 – 32
- Amikacin: 0.15 – 16
- Colistin: 32 – >32
- Tigecycline: 0.5 – 4

#### Morganella morganella (53)
- Ceftobiprole: 0.06 – 64
- Ceftazidime: 0.06 – >128
- Ceftriaxone: 0.06 – >128

### Table 5 (continued)

| Antimicrobial agents | MIC Range | MIC50 | MIC90 | R%  | S%  |
|----------------------|-----------|-------|-------|-----|-----|

#### Serratia marcescens (53)
- Ceftobiprole: 0.06 – >128
- Ceftazidime: 0.06 – >128
- Ceftriaxone: 0.06 – >128
- Ceferazone-Sulbactam: 0.5 – >128
- Imipenem: 0.125 – 1
- Amikacin: 0.5 – >128
- Colistin: >32 – >32
- Tigecycline: 0.5 – 2

2016–2018 in China through the China Antimicrobial Surveillance Program. Our study suggest that ceftobiprole has high antibacterial activity against *Staphylococcus* (including MRSA) similar to the results from Europe and the United States [11]. We observed that MSSA strains were more susceptible to ceftobiprole than MRSA strains with one-fold lower MIC90. When compared to the earlier studies, the data reported in our study are comparable for ceftobiprole concerning the target gram-positive pathogens, such as *Staphylococcus*, *E. faecalis*, *Streptococcus*, supporting that ceftobiprole has a high susceptibility [9]. Ceftobiprole's in vitro activity demonstrates potent binding against PBPs of gram-positive bacteria, including those with decreased β-lactam sensitivity, such as PBP2x and PBP2b in PRSP and, PBPa, which confers methicillin resistance to *S. aureus* strains [12]. Besides gram-positive bacteria, ceftobiprole also has good antibacterial activity against non-MDR gram-negative bacteria. Ceftobiprole exhibits a high affinity for PBPs in Enterobacteriales but is labile to hydrolysis by common extended spectrum β-lactamases and carbapenemases. ESBL-negative *E. coli* and *K. pneumoniae*, MICs50/90 were both 0.03/0.25 mg/L in the current study. Previous MIC results, including the SENTRY Antimicrobial Surveillance Program in the U.S. (2016) and in Europe (2015), demonstrated the potency of ceftobiprole against *Pseudomonas aeruginosa* (MIC50/90, >16 mg/L) and had limited activity against Acinetobacter spp. (MIC50/90, >16/ >16 mg/L) [11, 13]. The data reported here showed a little difference in these two non-fermentative gram-negative bacteria with MICs50/90 were 8/ >128 mg/L for carbapenem-susceptible *P. aeruginosa* and 0.5/4 mg/L for carbapenem-susceptible *A. baumannii*. 
Table 6 Activity of ceftobiprole and comparator antimicrobial agents when tested against Pseudomonas aeruginosa and Acinetobacter baumannii isolated from China (mg/L)

| Antimicrobial agents | MIC Range | MIC<sub>50</sub> | MIC<sub>90</sub> | R% | S% |
|---------------------|-----------|-----------------|-----------------|----|----|
| **Carbapenem-susceptible Pseudomonas aeruginosa (19)** | | | | | |
| Ceftobiprole       | 1 –> 128 | 8               | >128            | –  | –  |
| Ceftazidime        | 1 –> 128 | 4               | >128            | 10.5| 68.4|
| Cefoperazone-Sulbactam | 0.25 –> 128 | 4 | 64 | 10.5| 84.2|
| Imipenem           | 0.25 – 4 | 0.5             | 4               | 0   | 84.2|
| Amikacin           | 0.5 –> 128 | 2 | >128 | 10.5| 89.5|
| Colistin           | 0.5 – 2  | 1               | 2               | 0   | 100 |
| **Carbapenem-resistant Pseudomonas aeruginosa (19)** | | | | | |
| Ceftobiprole       | 4 –> 128 | 8               | 64              | –  | –  |
| Ceftazidime        | 8 – 64   | 16              | 64              | 36.8| 26.3|
| Cefoperazone-Sulbactam | 1 – 128 | 64 | 128 | 52.6| 36.8|
| Imipenem           | 4 – 64   | 4               | 32              | 47.4| 0   |
| Amikacin           | 1 –> 128 | 2               | 16              | 53  | 94.7|
| Colistin           | 0.5 – 1  | 1               | 1               | 0   | 100 |
| **Carbapenem-susceptible Acinetobacter baumannii (17)** | | | | | |
| Ceftobiprole       | 0.25 –> 128 | 0.5 | 4 | – | –|
| Ceftazidime        | 2 – 64  | 8               | 8               | 5.9 | 94.1|
| Cefoperazone-Sulbactam | 1 – 128 | 1 | 2 | 5.9 | 94.1|
| Imipenem           | ≤0.06 – 0.5 | 0.125 | 0.25 | 0 | 100 |
| Amikacin           | 0.25 – 1  | 1               | 4               | 0   | 100 |
| Colistin           | 0.25 – 2  | 0.5             | 1               | 0   | 100 |
| Tigecycline        | 0.25 – 1  | 0.25            | 1               | 0   | 100 |
| **Carbapenem-resistant Acinetobacter baumannii (19)** | | | | | |
| Ceftobiprole       | 4 –> 128 | >128            | >128            | –  | –  |
| Ceftazidime        | 32 –> 128 | 128 | >128 | 100 | 0 |
| Cefoperazone-Sulbactam | 16 – 128 | 64 | 64 | 52.6| 36.8|
| Imipenem           | 4 – 128  | 16               | 32              | 89.5| 0   |
| Amikacin           | 1 –> 128 | >128            | >128            | 84.2| 15.8|
| Colistin           | 0.5 – 2  | 0.5             | 2               | 0   | 100 |
| Tigecycline        | 0.5 – 4  | 1               | 2               | 0   | 94.7|

There were some limitations to our study. Firstly, ceftobiprole is approved for the treatment of community-acquired pneumonia and hospital-acquired pneumonia except for ventilator-associated pneumonia, but there is no relevant clinical disease information for the strains in our study. Secondly, there are a few strains of some Streptococcus spp, which may not fully demonstrate the antibacterial activity of cefpirome against such Streptococcus spp.

**Conclusion**

Our study indicated that ceftobiprole showed potent in vitro activity against clinical significant pathogens including MRSA, MRCNS, E. faecalis, PRSP, H. influenzae, M. catarrhalis, ESBL-negative Enterobacteriales, even carbapenem-susceptible A. baumannii, which could be a considerable choice for treating infections caused by those pathogens in healthcare facilities.

**Materials and Methods**

**Clinical strains**

A total of 1163 strains were selected randomly from 49 hospitals across China from 2016-to 2018, relying on the China Antimicrobial Surveillance Network (CHINET). Strains included methicillin-resistant S. aureus (MRSA, n=55), methicillin-susceptible S. aureus (MSSA, n=55), methicillin-resistant Coagulase negative Staphylococci (MRCNS, n=40), methicillin-susceptible Coagulase negative Staphylococci (MSCNS, n=40), E. faecalis (n=24), E. faecium (n=23), Streptococcus pyogenes (n=13), Streptococcus agalactiae (n=14), Streptococcus mitis (n=12), Streptococcus pneumonia (MIC of Penicillin ≤ 2 mg/L, PSSP, n=110), Streptococcus pneumonia (MIC of Penicillin = 4 mg/L, PISP, n=25), Streptococcus pneumonia (MIC of Penicillin ≥ 8 mg/L, PRSP, n=13), Haemophilus influenzae (n=53), Moraxella catarrhalis (n=49), Escherichia coli (ESBL-, n=49), Escherichia coli (ESBL+, n=50), Klebsiella pneumoniae (ESBL-, n=56), Klebsiella pneumoniae (ESBL+, n=58), Enterobacter cloacae (n=49), Enterobacter aerogenes (n=55), Citrobacter freundii (n=53), Proteus mirabilis (n=52), Proteus vulgaris (n=35), Morganella morganella (n=53), Serratia marcescens (n=53), Pseudomonas aeruginosa (n=38) and Acinetobacter baumannii (n=36). Species identification was performed at the microbial laboratory of Huashan Hospital by the matrix-assisted laser desorption ionization-time-of-flight mass spectrometry (MALDI-TOF, Vitek MS; bioMérieux). E. coli ATCC 25,922, P. aeruginosa ATCC 27,853, S. pneumoniae ATCC 49,619, H. influenzae ATCC 49,766 and ATCC 49,247, S. aureus ATCC29213 and E. faecalis ATCC 29,212 were used as the quality control strains in antimicrobial susceptibility testing.

**Antimicrobial susceptibility testing**

MICs were determined by the reference broth microdilution method recommended by the Clinical and Laboratory Standards Institute (CLSI) [14]. Ceftobiprole, linezolid, vancomycin, ampicillin, penicillin, oxacillin, ciprofloxacin, clindamycin, and erythromycin were tested for all Gram-positive bacteria; Ceftobiprole, ampicillin, ampicillin-sulbactam, cefuroxime, ceftazidime, ceftriaxone, ciprofloxacin, azithromycin, cefoperazone-sulbactam, imipenem, amikacin, colistin, and tigecycline were tested for Gram-negative
bacteria as needed. Quality control and interpretation of the results were based on 2019 CLSI break-points for all the antimicrobial agents except tigecycline, for which CLSI criteria are not available [14]. Tigecycline MICs were interpreted using U.S. FDA MIC break-points for Enterobacterales (susceptible, ≤ 2 g/ml; resistant, ≥ 8 g/ml) [https://www.fda.gov/drugs/development-resources/tigecycline-injection-products].

Table 7  The minimal inhibitory concentration (MIC) distribution of ceftobiprole when tested against different clinically isolated strains in China

| Organisms (no.) | Cumulative percentage of isolates at MIC (mg/L, %) |
|-----------------|---------------------------------------------|
|                 | ≤ 0.015 0.03 0.06 0.125 0.25 0.5 1 2 4 8 16 32 64 128 > 128 |
| MRSA (55)       | 0.0 0.0 0.0 0.0 5.5 27.3 80.0 100.0 – – – – – – |
| MSSA (55)       | 0.0 0.0 0.0 0.0 1.8 69.1 98.2 100.0 – – – – – – |
| MRCNS (40)      | 10.0 10.0 10.0 10.0 12.5 40.0 87.5 95.0 100.0 – – – – – – |
| MSCNS (40)      | 5.0 5.0 15.0 32.5 65.0 97.5 100.0 – – – – – – – – – – – – |
| E. faecalis (24) | 0.0 0.0 4.2 4.2 25.0 66.7 91.7 91.7 91.7 91.7 91.7 91.7 100.0 – – – – – – |
| E. faecium (23) | 0.0 0.0 0.0 0.0 0.0 4.3 8.7 17.4 17.4 17.4 17.4 17.4 100.0 – – – – – – |
| S. pyogenes (13) | 100.0 – – – – – – – – – – – – – – – – – – |
| S. agalactiae (14) | 100.0 – – – – – – – – – – – – – – – – – – |
| S. mitis (12)   | 58.3 58.3 75.0 75.0 75.0 83.3 83.3 100.0 – – – – – – |
| PSSP (110)      | 24.5 28.2 40.0 55.5 74.5 98.2 100.0 – – – – – – |
| PISP (25)       | 0.0 0.0 0.0 4.0 8.0 52.0 100.0 – – – – – – – – – – – – |
| PRSP (13)       | 0.0 0.0 0.0 0.0 0.0 53.8 84.6 92.3 92.3 92.3 92.3 92.3 100.0 – – – – – – |
| H. influenzae (53) | 71.2 76.9 76.9 82.7 86.5 96.2 100.0 – – – – – – |
| M. catarrhalis (49) | 0.0 0.0 18.4 38.8 71.4 98.0 100.0 – – – – – – |
| E. coli (ESBL-) (49) | – – 59.2 89.8 91.8 95.9 95.9 100.0 – – – – – – |
| E. coli (ESBL+) (50) | – – 0.0 0.0 0.0 0.0 4.0 4.0 4.0 4.0 6.0 8.0 8.0 8.0 100.0 – – – – – – |
| K. pneumonia (ESBL-) (56) | – – 80.4 87.5 98.2 98.2 98.2 98.2 98.2 98.2 98.2 98.2 100.0 – – – – – – |
| K. pneumonia (ESBL+) (58) | – – 5.2 5.2 6.9 6.9 6.9 6.9 8.6 10.3 12.1 12.1 13.8 100.0 – – – – – – |
| CR-KPN (45)     | – – 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.0 0.0 100.0 – – – – – – |
| E. cloacae (49) | – – 40.8 49.0 49.0 57.1 61.2 61.2 63.3 67.3 67.3 69.4 69.4 100.0 – – – – – – |
| E. aerogenes (55) | – – 54.5 74.5 80.0 83.6 85.5 85.5 87.3 87.3 87.3 87.3 87.3 87.3 89.1 100.0 – – – – – – |
| C. freundii (53) | – – 50.9 58.5 64.2 64.2 66.0 69.8 71.7 71.7 71.7 71.7 73.6 100.0 – – – – – – |
| P. mirabilis (52) | – – 55.8 65.4 65.4 65.4 65.4 67.3 67.3 67.3 69.2 69.2 69.2 71.2 100.0 – – – – – – |
| P. vulgaris (35) | – – 17.1 17.1 17.1 17.1 20.0 25.7 31.4 34.3 54.3 60.0 80.0 88.6 100.0 – – – – – – |
| M. morganella (53) | – – 65.5 78.2 80.0 83.6 85.5 87.3 87.3 87.3 87.3 96.4 100.0 – – – – – – |
| S. marcescens (53) | – – 9.6 38.5 71.2 80.8 84.6 88.5 88.5 90.4 90.4 90.4 90.4 90.4 100.0 – – – – – – |
| CS-PAE (19)     | – – 0.0 0.0 0.0 0.0 10.5 26.3 47.4 84.2 89.5 89.5 89.5 89.5 100.0 – – – – – – |
| CR-PAE (19)     | – – 0.0 0.0 0.0 0.0 0.0 0.0 10.5 52.6 84.2 89.5 94.7 94.7 100.0 – – – – – – |
| CS-ABA (17)     | – – 0.0 0.0 41.2 64.7 88.2 88.2 94.1 94.1 94.1 94.1 94.1 94.1 100.0 – – – – – – |
| CR-ABA (19)     | – – 0.0 0.0 0.0 0.0 0.0 0.0 5.3 5.3 5.3 5.3 10.5 26.3 100.0 – – – – – – |

MRSA Methicillin-resistant Staphylococcus aureus, MSSA Methicillin-susceptible Staphylococcus aureus, MRCNS Methicillin-resistant Coagulase negative Staphylococci, MSCNS Methicillin-susceptible Coagulase negative Staphylococci, PSSP Streptococcus pneumonia with MIC of Penicillin ≤ 2 mg/L, PISP Streptococcus pneumonia with MIC of Penicillin = 4 mg/L, ESBL- Extended spectrum β-Lactamases negative, ESBL+ Extended spectrum β-Lactamases positive, CR-KPN Carbapenem-resistant Klebsiella pneumonia, CS-PAE Carbapenem-susceptible Pseudomonas aeruginosa, CR-PAE Carbapenem-resistant Pseudomonas aeruginosa, CS-ABA Carbapenem-susceptible Acinetobacter baumannii, CR-ABA Carbapenem-resistant Acinetobacter baumannii

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Authors' contributions
WS and ZYG performed the major work of antibiotics susceptibility testing, GY and YY performed the major work of strains collection; YDD analyzed and interpreted the susceptibility data and was a major contributor in writing the manuscript; ZDM and HFP contributed to the study design and the manuscript review. All authors read and approved the final manuscript.
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Availability of data and materials
All data involved in this study are available from the corresponding author by email if needed.

Declarations

Ethics approval and consent to participate
We confirmed that all methods were carried out in accordance with relevant guidelines and regulations; all experimental protocols were approved by the Institutional Review Board of Huashan Hospital, Fudan University (No.2017–321). None of human participants were directly involved in the study, so the informed consent was not applicable here.

Competing interests
The authors declare that they have no competing interests.

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