In vitro activities of Eravacycline against 336 isolates collected from 2012 to 2016 from 11 teaching hospitals in China

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Abstract

Background: In China multidrug-resistant bacteria pose a considerable threat to public health. Antimicrobial resistance has weakened the effectiveness of many medicines widely used today. Thus, discovering new antibacterial drugs is paramount in the effort to treat emerging drug-resistant bacteria.

Methods: Eravacycline, tigecycline and other clinical routine antibiotics were tested by reference broth micro-dilution method against 336 different strains collected from 11 teaching hospitals in China between 2012 and 2016. These isolates included Enterobacteriaceae, non-fermentative, Staphylococcus spp., Enterococcus, and a number of fastidious organisms. The strains involved in this study possess the most important drug resistance characteristics currently known in China. Drug resistant bacteria such as those producing extended spectrum β-lactamases (ESBL) and carbapenemases (KPC-2 and NDM-1), and those exhibiting colistin resistance (mcr-1) and tigecycline were included in this study. Additionally, methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant enterococci (VRE), β-lactamase positive Haemophilus influenzae, and penicillin resistant Streptococcus pneumoniae (PRSP) were also included.

Results: Eravacycline exhibited good efficacy against all the strains tested, especially for organisms with ESBLs, carbapenemases, and mcr-1 gene compared with tigecycline and other antibiotics tested. The MIC values of eravacycline against carbapenemase producing Enterobacteriaceae and OXA-23-producing A. baumannii were much lower than the MIC values of other antibiotics. MRSA, VRE, β-lactamase positive Haemophilus influenzae, and PRSP were sensitive to eravacycline in every strain tested. Furthermore, in most strains tested, the MICs of eravacycline were two to four-fold lower than the MICs of tigecycline.

Conclusions: Eravacycline has shown potent antibacterial activity against common and clinically important antibiotic-resistant pathogens. The MIC distribution of eravacycline was generally lower than that of tigecycline which demonstrates that this new drug is potentially more effective than the existing medications.

Keywords: Eravacycline, Tigecycline, Carbapenem resistant Enterobacteriaceae bacteria, Acinetobacter baumannii, Antibiotic resistance

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Background
In China, microbial resistance to presently administered antimicrobial agents is increasing steadily owing to the emergence of novel resistance mechanisms in the microbes [1, 2]. Multidrug-resistant bacterium causes a considerable threat to public health. Antimicrobial resistance weakened the effectiveness of many medicines widely used today [3]. Thus discovering new antibacterial drugs are required to combat the threat of these emerging resistant bacteria. Eravacycline (TP-434 or 7-fluoro-9-pyrrolidinoacetamido-6-demethyl-6-deoxytetra-cycline) is a novel broad-spectrum synthetic tetracycline antibiotic being developed for the treatment of severe life-threatening infections, including those that are resistant to current broad-spectrum antibiotics [4]. Eravacycline has already been proven effective against some clinically important antibiotic-resistant pathogens, including gram-positive and gram-negative aerobic and anaerobic pathogens [5, 6]. Moreover, eravacycline was found to be safer and more effective than carbapenems in patients with complicated intra-abdominal infection (cIAI) during global phase 3 clinical trials (NCT01844856 and NCT02784704) [5, 7]. Additionally, there is a clinical development plan in place to introduce it into China to address bacterial drug resistance. The targets of eravacycline include complicated intra-abdominal infection (cIAI), complicated urinary tract infection (cUTI), and pulmonary infections caused by other susceptible pathogens. Tigecycline is a relatively new competing drug for eravacycline, imipenem, meropenem and colistin in the treatment of carbapenem-resistant Enterobacteriaceae. The present study was designed to evaluate the in vitro activities of eravacycline against panels of clinical bacterial pathogens, with or without remarkable resistance factors, which were collected in recent years and were similar to pathogenic bacteria that this drug was designed to treat. This study was designed to prove the in-vitro efficacy of eravacycline (presented by minimum inhibitory concentration, MIC) against major target pathogens in China, which will be used to support further clinical development of eravacycline within China.

Methods
In the present study, a total of 336 different clinical isolates, were routinely collected from 11 teaching hospitals representing the south, north, northwest, east, and middle regions of mainland China between 2012 and 2016, and tested (list of the hospitals can be found in Additional file 1). After re-identification with the typical biochemical reaction of each organism, the strains were stored in a Microbank tube and placed in a refrigerator at −80 degrees Celsius before test. All organisms and their associated drug resistance factors are detailed in Table 1. MIC measurements were performed via the reference broth microdilution method as described by the Clinical and Laboratory Standards Institute (CLSI) M7-A9 (2012) [8]. Escherichia coli ATCC 25922 and Pseudomonas aeruginosa ATCC 27853 were utilized as quality controls in MIC testing of gram-negative bacteria. Staphylococcus aureus ATCC 29213 and Enterococcus faecalis ATCC 29212 were utilized as quality controls in MIC testing of gram-positive bacteria. Streptococcus pneumoniae ATCC 49619, Haemophilus influenzae ATCC 49247 and Haemophilus influenzae ATCC 49766 were used as quality controls during MIC testing of the fastidious organisms. Tigecycline, the major comparator for eravacycline, imipenem, meropenem and colistin to treat carbapenem-resistant Enterobacteriaceae and Acinetobacter bauman-nii, were selected in the panel of antibiotics to be tested. We evaluated eravacycline with a gradient concentration of 0.002–16 mg/L against common clinical gram-negative bacilli, gram-positive cocci, and fastidious organisms collected from our previous studies [9–13], including Enterobacteriaceae (Klebsiella pneumoniae, Escherichia coli, Enterobacter cloacae), Acinetobacter bauman-nii, Stenotrophomonas maltophilia, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus haemolyticus, Staphylococcus malthophilia, Staphylococcus faecalis, Enterococcus faecium, Streptococcus pneumoniae and Haemophilus influenzae. Antibiotic solutions for susceptibility testing were freshly prepared according to the manual of CLSI [8]. A scatter plot of eravacycline versus tigecycline was drawn for each species of bacteria, to reveal the relationship between the two antibiotics in different organisms. All the results related to resistant genes were readily available, directly from our previous researches [12–14]. Statistical analyses and data visualization were done with R (version 3.4.4) and ggplot2 package (version 2.2.1).

Results
In vitro activity of eravacycline was evaluated against 336 strains of clinically significant species, with many exhibiting resistance factors (Table 1). In most of the strains tested, the MIC_{50} and MIC_{90} values for eravacycline were lower than that of tigecycline and other comparable antibiotics tested for each organism/phenotypic group. Furthermore, eravacycline was highly effective against all of the organisms tested, regardless of resistance factors.

For Enterobacteriaceae bacteria, the MIC values of eravacycline varied with the resistance characteristics, especially for K. pneumoniae. The MIC_{50} values of eravacycline against E. cloacae and E. coli were much lower than the values of other comparable drugs, especially in strains with resistance phenotypes (Table 2). For K. pneumoniae, the MIC distribution of eravacycline differed depending on the drug resistance features. K. pneumoniae strains which were ESBL-positive (n = 10),
**Table 1** The strains involved in this study and antibiotic resistance characteristics of the strains

| Group                        | Identification                  | Resistance features                  | Number |
|------------------------------|----------------------------------|--------------------------------------|--------|
| Enterobacteriaceae           | Klebsiella pneumoniae             | ESBL                                 | 10     |
|                              |                                  | Tigecycline resistant                 | 13     |
|                              |                                  | kpc-2 positive                        | 9      |
|                              |                                  | NDM-1 positive                        | 3      |
|                              |                                  | mcr-1 positive                        | 4      |
|                              |                                  | Sensitive a                           | 10     |
|                              | Escherichia coli                  | ESBL                                 | 10     |
|                              |                                  | mcr-1, NDM-5                         | 5      |
|                              |                                  | Carbapenem resistant                  | 10     |
|                              |                                  | Sensitive a                           | 10     |
|                              | Enterobacter cloacae              | ESBL                                 | 6      |
|                              |                                  | Carbapenem resistant                  | 1      |
|                              |                                  | Sensitive a                           | 22     |
|                              | Non-fermentive                    | Acinetobacter baumannii              |        |
|                              |                                  | OXA-23 positive                      | 21     |
|                              |                                  | Tigecycline resistant                 | 9      |
|                              |                                  | Sensitive a                           | 9      |
|                              | Stenotrophomonas maltophilia      | Sensitive a                          | 29     |
| Staphylococcus sp.           | Staphylococcus aureus             | MRSA                                 | 15     |
|                              |                                  | MSSA                                 | 6      |
|                              | Staphylococcus epidermidis        | MRCoNS                               | 10     |
|                              |                                  | MSCoNS                               | 10     |
|                              | Staphylococcus haemolyticus       | MRCoNS                               | 8      |
|                              |                                  | MSCoNS                               | 1      |
|                              | Staphylococcus hominis            | MRCoNS                               | 6      |
|                              |                                  | MSCoNS                               | 4      |
|                              | Enterococcus                     | Enterococcus faecalis                | 10     |
|                              |                                  | Sensitive a                          |        |
|                              |                                  | Enterococcus faecium                 | 3      |
|                              |                                  | VRE                                  |        |
|                              |                                  | Sensitive a                          | 8      |
|                              | Fastidious                       | Haemophilus influenzae               |        |
|                              |                                  | β-lactamase negative                 | 10     |
|                              |                                  | β-lactamase positive                 | 10     |
|                              |                                  | Streptococcus pneumoniae             |        |
|                              |                                  | PRSP                                 | 10     |
|                              |                                  | PSSP                                 | 10     |

* a: Sensitive strains referred to strains do not have specific resistance characteristics such as ESBL, carbapenem resistance, polymyxin resistance and glycopeptide resistance.

**kpc-2-positive** (*n* = 9) and **NDM-1-positive** (*n* = 3), had similar MIC distributions. The MIC$_{50}$ value of eravacycline against strains with the above three resistance mechanisms is 0.5 mg/L, and the MIC90 values were 1 mg/L, 2 mg/L and 1 mg/L respectively.

*K. pneumoniae* strains resistant to tigecycline were susceptible to eravacycline at higher MIC$_{50}$ values of 8 mg/L, while the MIC$_{90}$ was equivalent to that of tigecycline at 16 mg/L. For **mcr-1** positive strains, the MIC$_{50}$ of eravacycline was 1 mg/L compared with 16 mg/L for tigecycline, while the MIC$_{90}$ of eravacycline and tigecycline was equivalent at 16 mg/L. The MIC$_{50}$ (0.5 mg/L) and MIC$_{90}$ (2 mg/L) values of eravacycline against carbapenem-resistant *K. pneumoniae*, were much lower than those of other antibiotics such as imipenem, meropenem, cephalosporins, and fluoroquinolones. The MIC distributions for *K. pneumoniae* of different resistant phenotypes to eravacycline, tigecycline, and other clinically common antibiotics are presented in Table 3.

MIC distributions for *A. baumannii* also varied by resistance characteristics. *A. baumannii* isolates were tigecycline resistant and showed slightly elevated MIC$_{50}$ and MIC$_{90}$ for eravacycline at 2 mg/L. OXA-23-producing *A. baumannii* isolates have a MIC$_{50}$ of 1 mg/L and MIC$_{90}$
of 2 mg/L for eravacycline, and these values were much lower than the MIC\textsubscript{50} and MIC\textsubscript{90} of tigecycline (4 mg/L, 4 mg/L), imipenem (64 mg/L, 64 mg/L), and meropenem (32 mg/L, 64 mg/L). The MIC distributions for \textit{A. baumannii} with different resistant phenotypes to eravacycline, tigecycline, and other clinically relevant antibiotics such as imipenem, meropenem, and colistin are presented in Table 4.

For \textit{S. maltophilia} there is no breakpoints available for tigecycline, the MIC distributions of tigecycline and eravacycline against \textit{S. maltophilia} were evaluated. The MIC\textsubscript{50} and MIC\textsubscript{90} for eravacycline were both 1 mg/L, at the same time the MIC\textsubscript{50} and MIC\textsubscript{90} for tigecycline were 0.5 mg/L and 1 mg/L.

For \textit{Staphylococcus} spp., the results indicated that MIC\textsubscript{50} and MIC\textsubscript{90} of eravacycline were 0.25 mg/L and 0.5 mg/L,
Table 3 MIC distribution of eravacycline and relevant antibiotics against *K. pneumoniae* of different resistance characteristics

| Antibiotics                  | Sensitive, n=10 | ESBL, n=10 | *kpc*-2 positive, n=9 | NDM-1 positive, n=3 | mcr-1 positive, n=4 | Tigecycline resistant, n=13 |
|------------------------------|-----------------|------------|-----------------------|---------------------|---------------------|-----------------------------|
|                              | MIC<sub>50</sub> | MIC<sub>90</sub> | Range | MIC<sub>50</sub> | MIC<sub>90</sub> | Range | MIC<sub>50</sub> | MIC<sub>90</sub> | Range | MIC<sub>50</sub> | MIC<sub>90</sub> | Range | MIC<sub>50</sub> | MIC<sub>90</sub> | Range |
| Eravacycline                 | 0.25            | 0.5        | 0.125-0.5            | 0.5                 | 0.125               | 0.25-4          | 0.5             | 1               | 0.5-1                | 1               | 16                  | 0.5-16           | 8               | 16                  | 2-16 |
| Tigecycline                  | 0.5             | 1          | 0.5-2                | 1                   | 4                   | 0.5-4            | 1               | 4               | 0.125                | 1               | 2                   | 1-2              | 16              | 16                  | 2-16 |
| Piperacillin/Tazobactam      | 2               | 4          | 2-4                  | 4                   | 256                 | 2-256            | 256             | 256             | 256-256              | 4               | 4                   | 4-4              | 16              | 32                  | 4-32 |
| Cefoxitin                    | 4               | 8          | 2-16                 | 8                   | 16                  | 2-32             | 256             | 256             | 256-256              | 8               | 8                   | 2-8              | 32              | 64                  | 8-128 |
| Ceftazidime                  | 0.125           | 0.25       | 0.125-0.25           | 64                  | 256                 | 16-256           | 64              | 256             | 32-256               | 1               | 1                   | 0.125-1         | 1               | 64                  | 0.5-64 |
| Cefoperazone/Sulbactam       | 0.25            | 0.25       | 0.125-0.25           | 16                  | 64                  | 8-64             | 256             | 256             | 256-256              | 1               | 1                   | 0.5-1           | 2               | 32                  | 1-128 |
| Ceftriaxone                  | 0.064           | 0.064      | 0.032-0.125          | 256                 | 256                 | 256             | 256             | 256             | 256-256              | 0.125           | 0.125               | 0.032-0.125     | 0.5             | 128                 | 0.125-256 |
| Cefotaxime                   | 0.032           | 0.125      | 0.032-0.125          | 256                 | 256                 | 256             | 256             | 256             | 256-256              | 0.125           | 0.125               | 0.032-0.125     | 0.5             | 128                 | 0.125-256 |
| Cefepime                     | 0.032           | 0.064      | 0.032-0.064          | 32                  | 64                  | 4-128            | 64              | 256             | 32-256               | 128            | 256                 | 128-256         | 2               | 2                   | 0.032-2 |
| Ertapenem                    | 0.016           | 0.016      | 0.016-0.016          | 0.25                | 0.05                | 0.032-0.05      | 32              | 32              | 32-32                | 32              | 32                  | 32-32           | 0.016           | 0.016               | 0.032-0.016 |
| Imipenem                     | 0.125           | 0.25       | 0.125-1              | 0.125               | 0.025               | 0.125-0.25      | 8               | 32              | 8-32                 | 8               | 32                  | 8-32            | 0.125           | 0.125               | 0.125-0.125 |
| Meropenem                    | 0.016           | 0.082      | 0.016-0.032          | 0.032               | 0.0064              | 0.032-0.015     | 16              | 32              | 8-32                 | 0.032           | 0.064               | 0.032-0.064     | 0.032           | 0.064               | 0.016-0.064 |
| Colistin                     | 0.25            | 0.25       | 0.125-0.25           | 0.25                | 0.25                | 0.125-0.25      | 0.25            | 0.25             | 0.125-0.25           | 32              | 64                  | 16-64           | 0.25           | 32                  | 0.125-32 |
| Amikacin                     | 1               | 1          | 0.5-1                | 1                   | 4                   | 0.5-32           | 1               | 256             | 0.5-256              | 2               | 2                   | 1-2             | 1               | 1                   | 1-1             | 1               | 2                   | 0.5-256 |
| Minocycline                  | 2               | 4          | 2-8                  | 16                  | 32                  | 2-32             | 32              | 32              | 4-32                 | 32              | 32                  | 4-32            | 32              | 128                 | 16-256 |
| Ciprofloxacin                | 0.016           | 0.082      | 0.016-0.25           | 2                   | 0.016-0.64          | 32               | 64              | 64              | 64-64                | 32              | 32                  | 0.032-32        | 32              | 64                  | 0.25-64 |
| Levofloxacin                 | 0.004           | 0.125      | 0.004-0.05           | 2                   | 0.004-0.64          | 16               | 64              | 16-64           | 32              | 32                  | 16-32           | 16              | 16                  | 0.064-16 |

<sup>a</sup> Sensitive strains referred to strains do not have ESBL, carbapenem resistance and polymyxin resistance
respective, for MRSA (methicillin-resistant \textit{S. aureus}), for MSSA (methicillin-sensitive \textit{S. aureus}) the MIC\textsubscript{50} of eravacycline was as low as 0.064 mg/L, and MIC\textsubscript{50} remained the same as that of MRSA. MIC\textsubscript{50} and MIC\textsubscript{90} of eravacycline for methicillin-resistant coagulase-negative \textit{staphylococci} (MRCoNS) were 0.25 mg/L and 1 mg/L, respectively, and for MSCoNS (methicillin-sensitive coagulase-negative \textit{staphylococci}) the values of eravacycline were lower at 0.016 mg/L and 0.25 mg/L, respectively. For other antibiotics, the values are presented in Table 5.

In the results obtained for \textit{Enterococcus} spp. it was found that MIC\textsubscript{50} and MIC\textsubscript{90} of eravacycline for \textit{E. faecalis} were both 0.032 mg/L. The MIC\textsubscript{50} and MIC\textsubscript{90} of eravacycline for \textit{E. faecium} were 0.016 mg/L and 0.032 mg/L. For Vancomycin-Resistant \textit{Enterococci} (VRE) strains, the MIC\textsubscript{50} and MIC\textsubscript{90} were identical with that of vancomycin-susceptible \textit{E. faecium} strains. For other antibiotics, the values are presented in Table 6. In general, for gram-positive bacteria with varying resistance factors, eravacycline demonstrated substantial antibacterial activity.

### Table 4 MIC distribution of Eravacycline and relevant antibiotics against \textit{A. baumannii} of different resistance characteristics

| Antibiotics          | Sensitive \(^a\), n = 9 | OXA-23 positive, n = 21 | Tigecycline resistant, n = 9 |
|----------------------|--------------------------|--------------------------|-----------------------------|
|                      | MIC\textsubscript{50} | MIC\textsubscript{90} | Range          | MIC\textsubscript{50} | MIC\textsubscript{90} | Range          | MIC\textsubscript{50} | MIC\textsubscript{90} | Range          |
| Eravacycline         | 0.125          | 0.25       | 0.016–0.25 | 1          | 2       | 0.5–2          | 2          | 2       | 2–4          |
| Tigecycline          | 0.25           | 0.5        | 0.25–0.5  | 4          | 4       | 4–8           | 8          | 8       | 8–8          |
| Piperacillin/Tazobactam | 2             | 4          | 0.016–8  | 256        | 256     | 256–256       | 256        | 256     | 256–256      |
| Cefazidime           | 2             | 8          | 0.125–32 | 256        | 256     | 64–256        | 256        | 256     | 256–256      |
| Cefepime             | 1             | 4          | 0.032–32 | 64         | 256     | 32–256        | 256        | 256     | 128–256      |
| Imipenem             | 0.125          | 1          | 0.125–1  | 64         | 64      | 16–64         | 64         | 64      | 16–64        |
| Meropenem            | 0.032          | 1          | 0.016–1  | 32         | 64      | 16–64         | 64         | 64      | 32–128       |
| Colistin             | 0.125          | 0.25       | 0.125–0.25 | 0.25       | 0.25   | 0.125–0.25 | 0.25    | 0.25 | 0.25–0.25 |
| Amikacin             | 4             | 4          | 1–4      | 256        | 256     | 256–256       | 256        | 256     | 256–256      |
| Minocycline          | 0.125          | 16         | 0.064–16 | 8          | 16      | 4–16          | 8          | 8       | 8–16         |
| Ciprofloxacin        | 0.125          | 0.5        | 0.032–32 | 32         | 32      | 32–32         | 32         | 32      | 32–32        |
| Levofloxacin         | 0.125          | 1          | 0.064–32 | 16         | 32      | 8–32          | 16         | 16      | 16–32        |

\(^a\) Sensitive strains referred to strains do not have carbapenem resistance and tigecycline resistance

### Table 5 MIC distribution of Eravacycline and relevant antibiotics against \textit{Staphylococcus} spp. of different resistance characteristics

| Antibiotics          | MRSA\(^b\), N = 15 | MSSA\(^b\), N = 6 | MRCoNS\(^b\), N = 24 | MSCoNS\(^b\), N = 15 |
|----------------------|---------------------|-------------------|----------------------|----------------------|
|                      | MIC\textsubscript{50} | MIC\textsubscript{90} | Range          | MIC\textsubscript{50} | MIC\textsubscript{90} | Range          | MIC\textsubscript{50} | MIC\textsubscript{90} | Range          |
| Eravacycline         | 0.25           | 0.5        | 0.032–1       | 0.064       | 0.5       | 0.016–2       | 0.25          | 0.25   | 0.16–2       |
| Tigecycline          | 0.25           | 0.5        | 0.125–0.5     | 0.25        | 0.25      | 0.125–0.25   | 0.25          | 0.25   | 0.125–0.25  |
| Oxacillin            | 64             | 64         | 2–64          | 0.25        | 0.5       | 0.25–0.5     | 2             | 64      | 0.5–25       |
| Cefoxitin            | 256            | 256        | 32–256        | 4           | 4         | 2–4          | 16           | 256     | 2–256        |
| Vancomycin           | 1              | 1          | 0.5–1         | 0.5         | 0.5       | 0.5–0.5      | 1             | 2       | 0.5–2        |
| Teicoplanin          | 2              | 2          | 0.5–2         | 0.5         | 0.5       | 0.5–1        | 2             | 4       | 0.064–8      |
| Erythromycin         | 256            | 256        | 0.25–256      | 256         | 256       | 0.25–256     | 64            | 256     | 0.125–256   |
| Minocycline          | 4              | 16         | 0.064–32      | 0.064       | 0.125     | 0.064–0.125  | 0.25          | 0.25   | 0.064–8     |
| Ciprofloxacin        | 64             | 64         | 0.25–64       | 0.5         | 0.5       | 0.25–0.5     | 16            | 64      | 0.125–64    |
| Levofloxacin         | 32             | 64         | 0.25–64       | 0.25        | 0.25      | 0.125–0.25   | 4             | 128     | 0.25–128    |
| Moxifloxacin         | 8              | 16         | 0.016–32      | 0.064       | 0.064     | 0.016–0.064  | 1             | 16      | 0.064–32    |
| Trimethoprim/Sulfamethoxazole | 0.125   | 16         | 0.032–16      | 0.032       | 0.064     | 0.032–0.25   | 4             | 32      | 0.064–64    |
| Chloramphenicol      | 8              | 8          | 4–32          | 8           | 8         | 4–64         | 4             | 8       | 2–64        |
| Rifampin             | 256            | 256        | 0.004–256     | 0.008       | 0.016     | 0.004–0.016  | 0.008         | 0.008  | 0.004–0.016 |
| Clindamycin          | 128            | 256        | 0.064–256     | 0.064       | 256       | 0.064–256    | 0.125         | 256     | 0.064–256   |
| Linezolid            | 1              | 2          | 0.5–2         | 2           | 2         | 1–2          | 1             | 1       | 0.5–1       |

\(^b\) Methicillin-resistant \textit{Staphylococcus aureus}, \(^b\) Methicillin-sensitive \textit{Staphylococcus aureus}, \(^b\) Methicillin-resistant coagulase-negative \textit{staphylococci}, \(^b\) Methicillin-sensitive coagulase-negative \textit{staphylococci}
For fastidious strains, including 20 *S. pneumoniae* isolates and 20 *H. influenzae* isolates, eravacycline showed high antimicrobial activities against *S. pneumoniae* with MIC50 (0.008 mg/L) and MIC90 (0.008 mg/L), there was no difference with eravacycline distribution between PRSP (Penicillin-resistant *S. pneumoniae*) and PSSP (Penicillin-sensitive *S. pneumoniae*) strains (Table 7). For *H. influenzae* the MIC50 and MIC90 were 0.064 mg/L and 0.125 mg/L, and they were the same in both β-lactamase-positive and β-lactamase-negative strains (Table 8).

A jittered scatter plot was drawn using the MIC values of eravacycline and tigecycline involving all the strains tested. A clear pattern was found showing that most of the MIC values of tigecycline are higher than the corresponding MIC values of eravacycline (in many cases by 2 to 4 fold). For all of the clinical isolates tested, except for *Staphylococcus* spp. and *S. maltophilia*, more points are located above the diagonal y = x line, suggesting that eravacycline has lower MIC distribution than tigecycline (Fig. 1). For *Staphylococcus* spp. and *S. maltophilia* the points were distributed on both sides of the diagonal.


Table 8 MIC distribution of Eravacycline and relevant antibiotics against H. influenza of different resistance characteristics

| Antibiotics                      | β-lactamases negative, n = 10 |          | β-lactamases positive, n = 10 |          |
|----------------------------------|--------------------------------|----------|-----------------------------|----------|
|                                  | MIC50  | MIC90  | Range                      | MIC50  | MIC90  | Range                      |
| Eravacycline                     | 0.064  | 0.125  | 0.064-0.125                | 0.064  | 0.125  | 0.032-0.125                |
| Tigecycline                      | 0.25   | 0.5    | 0.125-0.5                  | 0.125  | 0.25   | 0.064-0.5                  |
| Ampicillin                       | 0.125  | 0.5    | 0.125-1                    | 16     | 64     | 0.064-64                   |
| Amoxicillin/Clavulanic acid      | 0.125  | 0.5    | 0.125-0.5                  | 1      | 1      | 0.5-1                      |
| Penicillin                       | 16     | 32     | 0.032-32                   | 16     | 32     | 1-64                       |
| Cefadroxil                       | 2      | 8      | 0.5-8                      | 4      | 16     | 1-32                       |
| Cefuroxime                       | 1      | 2      | 0.25-4                     | 1      | 4      | 0.25-16                    |
| Azithromycin                     | 1      | 4      | 0.064-4                    | 2      | 64     | 0.25-64                    |
| Clarithromycin                   | 4      | 16     | 0.5-16                     | 4      | 64     | 1-64                       |
| Levofloxacin                     | 0.032  | 1      | 0.016-1                    | 0.032  | 0.125  | 0.016-0.5                  |
| Moxifloxacin                     | 0.032  | 1      | 0.016-1                    | 0.032  | 0.25   | 0.016-0.5                  |
| Trimethoprim/Sulfamethoxazole    | 16     | 32     | 0.032-32                   | 16     | 32     | 1-64                       |
| Tetracycline                     | 1      | 4      | 0.064-4                    | 2      | 64     | 0.25-64                    |
| Chloramphenicol                  | 0.5    | 1      | 0.25-1                     | 1      | 8      | 0.5-8                      |

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bacterial isolates is required. For fastidious strains, eravacycline demonstrated excellent potency despite resistance characteristics of the strains. From the scatter plot, we can see that although MIC values of eravacycline were generally lower than those of tigecycline, the MIC values of eravacycline were also rising with the MIC values of tigecycline proportionally, thus, we need to be alert to the possible cross-resistance potential of eravacycline and tigecycline, especially in strains with higher MIC values of tigecycline.

Limitation and suggestion
The clinical isolates tested were limited by country as they were exclusively collected in China and within this country, these isolates were only obtained from 11 teaching hospitals. No strains from other hospitals were utilized. Therefore, many different clinical isolates remain untested. Thus, it is important that researchers reproduce our work in other countries with different isolates in order to understand the full spectrum of this new antibiotics’ efficacy. The results of this study show
that eravacycline has a positive application potential for the treatment of current drug-resistant bacterial infections. Considering the relatively small number of each organism and limited types of resistant phenotypes, the result of this study only partially represent the resistant phenotype encountered in real clinical practice, and additional studies are needed for a more comprehensive assessment of the antibacterial activity of eravacycline.

Conclusions
The results of this study proved that eravacycline possesses a broad spectrum of activity against a variety of gram-positive and gram-negative bacteria, including multi-drug resistant strains such as *A. baumannii* and carbapenem-resistant *Enterobacteriaceae*.

Additional file

Additional file 1: The list of committee and the institute to which it belongs for all hospitals that provided Administrative Consent to access or receive samples. This additional file list the committee (and the institute to which it belongs) for all hospitals that provided Administrative Consent to access or receive samples/data (DOCX 13 kb)

Abbreviations
CLSI: Clinical and Laboratory Standards Institute; CRAB: Carbapenem resistant *Acinetobacter baumannii*; CRE: Carbapenem resistant *Enterobacteriaceae*; cUTI: complicated urinary tract infections; ESBL: extended-spectrum-lactamases; MIC: minimum inhibitory concentration; MRSA: methicillin-resistant *Staphylococcus aureus*; MSCoNS: Methicillin-sensitive coagulase-negative *Staphylococci*; PCR: polymerase chain reaction; PRSP: penicillin resistant *Streptococcus pneumoniae*; VRE: Vancomycin-resistant enterococci

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Authors’ contributions
HW, CZ conceived and designed experiments. CZ, XW, YZ, RW, QW and HL performed antibiotic susceptibility testing. HW, CZ wrote the manuscript. CZ performed the data processing and data visualization. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate
Study protocols were reviewed and granted by the Ethical Committee of Peking University People’s Hospital (No. 2017/PHB163). For the hospitals participated, administrative permissions to access the raw samples were granted by the Research Department of the hospitals participated.

Consent for publication
Not applicable as no human subjects.

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

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