In Vitro Activity of Eravacycline against Gram-Positive Bacteria Isolated in Clinical Laboratories Worldwide from 2013 to 2017

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Running title: Activity of eravacycline against Gram-positive cocci (52 characters and spaces)

Keywords: eravacycline, Gram-positive, MRSA, VRE, streptococci

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Word counts: Abstract (245 words); Text (1401 words)
Eravacycline is a novel, fully-synthetic fluorocycline antibiotic being developed for the treatment of serious infections, including those caused by resistant Gram-positive pathogens. Herein, we evaluated the in vitro activities of eravacycline and comparator antimicrobial agents against a recent global collection of frequently encountered clinical isolates of Gram-positive bacteria. The CLSI broth microdilution method was used to determine in vitro MIC data for isolates of Enterococcus spp. (n=2,807), Staphylococcus spp. (n=4,331), and Streptococcus spp. (n=3,373) isolated primarily from respiratory, intra-abdominal, urinary, and skin specimens by clinical laboratories in 37 countries on three continents from 2013 to 2017. Susceptibilities were interpreted using both CLSI and EUCAST breakpoints. There were no substantive differences (>1 doubling increase or decrease) in eravacycline MIC90 values for different species/organism groups over time or by region. Eravacycline showed MIC90 and MIC90 results of 0.06 and 0.12 μg/ml when tested against Staphylococcus aureus, regardless of methicillin susceptibility. Staphylococcus epidermidis and Staphylococcus haemolyticus demonstrated equal MIC90 values for eravacycline (0.5 μg/ml). The eravacycline MIC90s for Enterococcus faecalis and Enterococcus faecium were 0.06 μg/ml, and were within one doubling-dilution regardless of vancomycin susceptibility profile. Eravacycline exhibited MIC90 results of ≤0.06 μg/ml when tested against Streptococcus pneumoniae, β-hemolytic, and viridans group streptococci isolates. In this surveillance study eravacycline demonstrated potent in vitro activity against frequently isolated clinical isolates of Gram-positive bacteria (Enterococcus, Staphylococcus, and Streptococcus spp.), including isolates collected over a 5-year period (2013-2017), underscoring its potential benefit in treatment of infections caused by common Gram-positive pathogens.
Multidrug-resistant (MDR) Gram-positive organisms are major human pathogens, causing both healthcare and community-acquired infections. Clinically important antimicrobial-resistant Gram-positive pathogens include methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and *Streptococcus pneumoniae*. In fact, all three have recently been highlighted among Gram-positive pathogens classified as serious or high public health threats by the CDC and WHO agencies (1, 2).

Eravacycline is a novel, fully-synthetic fluorocycline antibiotic recently approved by the FDA and EMA for the treatment of complicated intra-abdominal infections (cIAI), including those caused by MDR pathogens (3-5). Additionally, eravacycline has demonstrated *in vivo* efficacy in treating murine systemic, thigh, lung, and pyelonephritis infection models (4, 6, 7).

Eravacycline is comprised of a tetracycline core with two novel modifications: a fluorine atom at the C-7 position and a pyrrolidinoacetamido group at the C-9 position, both on the D-ring (4, 8). These novel modifications confer enhanced *in vitro* activity compared to other tetracyclines against resistant Gram-negative and Gram-positive bacteria, and the pyrrolidinoacetamido group allows for increased ribosomal binding and steric hindrance to avoid ribosome protection-based tetracycline resistance.

Eravacycline inhibits bacterial protein synthesis (i.e., acyl-tRNA transfer) by binding to the 30S ribosomal subunit (9). Eravacycline demonstrates potent broad-spectrum activity against Gram-positive cocci, Gram-negative bacilli (except *Pseudomonas aeruginosa* and *Burkholderia* spp.), and anaerobes, as well as atypical bacterial pathogens and *Neisseria gonorrhoeae* (3, 10-15) and does not exhibit loss of antibacterial activity against isolates expressing tetracycline ribosomal protection genes or most tetracycline efflux resistance genes (9, 10, 13).
The objective of the current study was to determine the *in vitro* activity of eravacycline, relative to other antimicrobial agents, using a representative global collection of clinical isolates of Gram-positive bacteria.

RESULTS AND DISCUSSION

A total of 10,511 Gram-positive aerobic isolates collected between 2013 and 2017 were included in this study. The MIC distributions and the cumulative percentage of isolates inhibited by concentrations of eravacycline for selected isolates of Gram-positive bacteria tested are shown in Table 1. The concentration of eravacycline inhibiting 90% of isolates (MIC$_{90}$) of isolates of *S. aureus* was 0.12 μg/ml irrespective of whether the isolates were MRSA or methicillin-susceptible *S. aureus* (MSSA). Coagulase-negative staphylococci demonstrated eravacycline MIC$_{90}$ values of ≤0.5 μg/ml for both *Staphylococcus epidermidis* and *Staphylococcus haemolyticus*, including the methicillin-resistant subsets. The eravacycline MIC$_{90}$ for *Enterococcus faecalis* was 0.06 μg/ml with a one-dilution shift for vancomycin resistant *E. faecalis*. The eravacycline MIC$_{90}$ for *Enterococcus faecium* was 0.06 μg/ml regardless of vancomycin susceptibility. Eravacycline exhibited MIC$_{90}$ results of ≤0.06 μg/ml when tested against β-hemolytic and viridans group streptococci isolates as well as an MIC$_{90}$ of 0.015 μg/ml for *Streptococcus pneumoniae*.

Tables 2, 3, and 4 provide detail on the *in vitro* activity of eravacycline and comparator agents against staphylococci, enterococci, and streptococci, respectively, including percent susceptibility by CLSI and EUCAST breakpoints. The highest rates of non-susceptibility in MRSA were reported for azithromycin, clindamycin, and levofloxacin (75.9%, 38.3% and 65.9% respectively by CLSI criteria) while resistance rates were <1% for linezolid, daptomycin and...
vancomycin, (Table 2). For the tetracycline class compounds, tigecycline and minocycline, resistance rates were approximately 2-12% across FDA/CLSI and EUCAST breakpoints.

Comparatively, due to overall lower breakpoints for eravacycline the non-susceptible rate was nearly 20% by the FDA criteria and 4.5% by EUCAST, but the MIC<sub>90</sub> value of eravacycline was 2-fold lower than that of tigecycline. Similarly, for E. faecalis the non-susceptibility rate to linezolid was <1% and 5.6% for daptomycin, while they were 2% and 53%, respectively, for E. faecium (Table 3). Vancomycin retained activity against E. faecalis, with a resistance rate of 4.9% but was generally ineffective against E. faecium where resistance exceeded 40%. Both species of enterococci were resistant to minocycline, with non-susceptibility rates from 49-72%.

While eravacycline and tigecycline non-susceptibility rates were around 1-5%, the MIC<sub>90</sub> of tigecycline was two doubling-dilutions higher than that of eravacycline. Notably, the rates of resistance for the comparators in this study are similar to those seen in other global surveillance studies (16, 17).

When isolates were allocated to their respective geographic regions, eravacycline MIC<sub>90</sub>s were within one doubling-dilution for all Gram-positive genera/species (Supplemental Table 3). Similarly, there were no significant (>1 doubling-dilution increase or decrease in MIC<sub>90</sub>s) differences observed in the in vitro activity of eravacycline for any genera/species of Gram-positive bacteria stratified by study period (2013-2014, 2015, 2016, 2017) (Supplemental Table 4) or stratified by specimen source (Supplemental Table 5). A detailed trend analysis could not be conducted given there were changes in participating laboratories and the panel of antimicrobial agents tested over the time period studied (2013-2017). Overall, eravacycline activity was similar over time and across geographic regions and specimen sources.
Eravacycline consistently demonstrated 2- to 4-fold lower MIC₉₀ values compared with tigecycline for populations of Gram-positive pathogens. Previous *in vitro* studies comparing eravacycline and tigecycline have reported similar 2- to 4-fold improvements in the MIC₉₀ (4, 6, 7, 15). Susceptibility rates, due to a difference in breakpoints, were similar between these two antibiotics. As tigecycline EUCAST breakpoints have been recently lowered for gram-negative organisms, perhaps a review of gram-positive breakpoints is also warranted for this agent.

This global surveillance investigation highlights the broad-spectrum potency of eravacycline against Gram-positive bacteria, including resistant isolates. As cIAI are well-known to be polymicrobial, involving synergistic gram-positive, gram-negative and anaerobic organism interactions, this study underscores the potential benefit of eravacycline for empiric treatment of cIAI. Furthermore, eravacycline may have a role in treatment of other infections caused predominantly by gram-positive pathogens, but the clinical utility in such disease states should be investigated.

**MATERIALS AND METHODS**

**Bacterial isolates.** From 2013 to 2017, 10,511 clinical isolates of *Enterococcus* spp. (n=2,807), *Staphylococcus* spp. (n=4,331), and *Streptococcus* spp. (n=3,373) were collected by laboratories in 37 countries on three continents (Asia/Pacific, Europe, North America). The identity of each isolate was confirmed using matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry (Bruker Biotyper, Bruker Daltonics, Bremen, Germany).

Supplemental Table 1 summarizes the numbers of isolates collected in each of the four study periods (2013-2014, 2015, 2016, and 2017) by geographic region. Overall, approximately
54% of the isolates came from Europe, 35% of the isolates came from North America, and 10% from the Asia/Pacific region. In total, there were 3,180, 2,082, 3176, 956, and 1,117 isolates, respectively, from respiratory, intra-abdominal, urinary, skin, and other specimen sources (Supplemental Table 2).

Isolates were limited to one per patient, determined by the participating laboratory algorithms to be clinically significant, and collected irrespective of their antimicrobial susceptibility profile and independent of patient gender or age. The study was not designed to directly compare the prevalence of antimicrobial resistant pathogens across specific geographic locations but rather to evaluate the \textit{in vitro} activities of eravacycline and comparator antimicrobial agents against a global collection of frequently encountered clinical isolates of Gram-positive bacteria from 2013 to 2017.

\textbf{Antimicrobial susceptibility testing.} \textit{In vitro} susceptibilities of isolates were determined using the CLSI-defined broth microdilution method in 96-well broth microdilution panels (18, 19). The antimicrobial agents used in panel production were acquired as laboratory-grade powders from their respective manufacturers or from a commercial source. The list of antimicrobial agents tested in each of the four study periods varied slightly, for example, in that some agents, in addition to those tested in the 2013-2014 period, were included in the 2015, 2016, and 2017 testing periods. Of note, ampicillin, clindamycin, meropenem, and oxacillin were only tested in 2015, 2016, and 2017. Eravacycline MICs for Gram-positive bacteria were read following the current CLSI standard for dilution method testing; MIC endpoints were read following panel incubation at 35°C in ambient air for 16-20 hours (\textit{Enterococcus} and \textit{Staphylococcus} spp.) or 35°C in ambient air for 20-24 hours (\textit{Streptococcus} spp.) (19). Quality control testing for eravacycline and other antimicrobial agents was performed on each day of
testing as specified by the CLSI using the CLSI-defined control strains: *E. faecalis* ATCC 29212, *S. aureus* ATCC 29213, and *S. pneumoniae* ATCC 49619 (19).

MICs were interpreted using 2019 CLSI MIC breakpoints (19) and 2019 EUCAST MIC breakpoints (20) with the following exceptions. FDA MIC interpretative breakpoints were used for tigecycline (21) and eravacycline in place of CLSI MIC breakpoints, which are not currently published for these agents. Additionally, tigecycline breakpoints for vancomycin-susceptible *Enterococcus faecalis* were applied to vancomycin-resistant isolates and to *Enterococcus faecium*; EUCAST eravacycline breakpoints for *S. anginosus* group were applied to β-haemolytic streptococci; EUCAST tigecycline breakpoints for β-haemolytic streptococci were applied to *S. anginosus* group; EUCAST eravacycline breakpoints for *S. aureus* were applied to coagulase-negative *Staphylococcus* species.
ACKNOWLEDGEMENTS

The authors thank all laboratories participating in this eravacycline global surveillance study for their contributions, as well as Sophie Magnet for her coordination of the laboratory work.

Funding for this research was provided by Tetraphase Pharmaceuticals, Inc., Watertown, MA, USA, which also included compensation fees for services in relation to preparing this manuscript. CF and MO are employees of Tetraphase Pharmaceuticals. JN is a former employee of Tetraphase Pharmaceuticals.

IM and SH are employees of IHMA Europe Sàrl. SHL works for IHMA, Inc. Both IHMA laboratories have received research funding from Tetraphase Pharmaceuticals, Inc. JAK is a consultant to IHMA, Inc. The IHMA authors and JAK do not have personal financial interests in the sponsor of this paper (Tetraphase Pharmaceuticals, Inc.).

MB has participated in advisory boards and/or received speaker honoraria from Achaogen, Angelini, Astellas, AstraZeneca, Bayer, Basilea, Cidara, Gilead, Menarini, MSD, Nabriva, Paratek, Pfizer, The Medicine Company, Tetraphase and Vifor. GRC has received consulting fees from Cempra Pharmaceuticals, PRA International, Furiex Pharmaceuticals, Inimex Pharmaceuticals, Dr Reddy’s Laboratories, Cerexa/Forest Laboratories, AstraZeneca, GlaxoSmithKline, Merck, ContraFect, Theravance, and Astellas; has received research grants from Theravance, Innocoll, and The Medicines Company; and has served on advisory boards of Pfizer, Polymedix, Tetraphase Pharmaceuticals, Seachaid Pharmaceuticals, BioCryst Pharmaceuticals, Durata, Achaogen, ContraFect, and Nabriva.
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| Organism                     | n  | ≤0.001 | 0.002 | 0.004 | 0.008 | 0.015 | 0.03  | 0.06  | 0.12  | 0.25  | 0.5   | 1     | 2     |
|------------------------------|----|--------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| All isolates                 |    |        |       |       |       |       |       |       |       |       |       |       |       |
| S. aureus                   | 2588 | 0.4   | 3.8   | 33.4 | 84.5  | 94.8  | 97.6  | 99.4  | 100   |       |       |       |       |
| S. aureus, MR               | 1304 | 0.2   | 4.1   | 32.8 | 80.8  | 91.6  | 95.5  | 98.8  | 100   |       |       |       |       |
| S. aureus, MS               | 1284 | 0.5   | 3.5   | 34.0 | 88.3  | 98.0  | 99.8  | 100   |       |       |       |       |       |
| S. epidermidis              | 1012 | 1.4   | 11.5  | 28.2 | 45.7  | 63.4  | 84.6  | 92.1  | 99.8  | 100   |       |       |       |
| S. epidermidis, MR          | 480  | 1.9   | 10.8  | 30.8 | 43.8  | 66.7  | 90.4  | 97.9  | 99.8  | 100   |       |       |       |
| S. epidermidis, MS          | 255  | 2.0   | 24.3  | 47.8 | 59.6  | 75.7  | 98.9  | 99.6  | 99.6  | 100   |       |       |       |
| S. haemolyticus             | 731  | 1.2   | 13.5  | 34.6 | 45.6  | 64.8  | 89.9  | 96.0  | 98.8  | 100   |       |       |       |
| S. haemolyticus, MR         | 440  | 0.5   | 11.4  | 30.9 | 36.8  | 60.2  | 90.0  | 95.2  | 98.0  | 100   |       |       |       |
| S. haemolyticus, MS         | 134  | 5.2   | 35.8  | 76.9 | 85.8  | 94.8  | 97.8  | 99.3  | 100   |       |       |       |       |
| E. faecalis                 | 1586 | 0.2   | 2.6   | 28.9 | 94.5  | 99.4  | 99.7  | 100   |       |       |       |       |       |
| E. faecalis, VR             | 59   |       | 23.7  | 89.8 | 98.3  |       |       |       |       |       |       |       |       |
| E. faecalis, VS             | 1505 | 0.2   | 2.7   | 29.4 | 94.8  | 99.5  | 99.7  | 100   |       |       |       |       |       |
| E. faecium                  | 1221 | 0.6   | 4.3   | 60.2 | 95.0  | 97.7  | 99.1  | 99.8  | 100   |       |       |       |       |
| E. faecium, VR              | 510  | 0.6   | 3.7   | 54.9 | 93.1  | 96.1  | 98.0  | 99.6  | 100   |       |       |       |       |
| E. faecium, VS              | 702  | 0.6   | 4.6   | 63.8 | 96.3  | 98.9  | 99.9  | 100   |       |       |       |       |       |
| S. pneumonia                 | 596  | 0.8   | 2.0   | 14.8 | 73.0  | 97.8  | 100   |       |       |       |       |       |       |
| S. agalactiae               | 1239 | 0.7   | 13.4  | 70.5 | 98.0  | 99.8  | 100   |       |       |       |       |       |       |
| S. pyogenes                 | 1192 | 0.2   | 3.6   | 47.8 | 96.0  | 100   |       |       |       |       |       |       |       |
| S. anginosus group           | 346  | 5.2   | 5.5   | 8.7  | 19.9  | 46.5  | 86.4  | 99.1  | 100   |       |       |       |       |

**Table 1** Cumulative percent inhibited by eravacycline MICs for clinical isolates of staphylococci, enterococci, and streptococci, cumulative 2013-2017 data

- **MIC** (μg/ml) indicates the lowest dilution of eravacycline tested was 0.008 μg/ml.
- **MR**, methicillin-resistant; **MS**, methicillin-susceptible; **VR**, vancomycin-resistant; **VS**, vancomycin-susceptible.
- **S. anginosus group** includes *S. anginosus* (n=302), *S. constellatus* (n=36), *S. intermedius* (n=7), and *S. intermedius/milleri* (n=1).
- MR, methicillin-resistant; MS, methicillin-susceptible; VR, vancomycin-resistant; VS, vancomycin-susceptible.
**TABLE 2** In vitro activity of eravacycline and comparator agents against staphylococci, cumulative 2013-2017 data

| Organism | Drug | n  | MIC<sub>50</sub> | MIC<sub>90</sub> | MIC range | CLSI | EUCAST |
|----------|------|----|------------------|------------------|-----------|------|--------|
| **S. aureus** | Eravacycline | 2588 | 0.06 | 0.12 | ≤0.008 - 1 | 84.5<sup>a</sup> | 97.0 |
| | Amoxicillin-clavulanate | 2588 | >1 | >1 | ≤0.12 - >1 | NA | NA |
| | Azithromycin | 2588 | >4 | >4 | ≤0.25 - >4 | 49.3 | 47.8 |
| | Cefaroline | 1076 | 0.5 | 1 | ≤0.06 - 4 | 94.1 | 94.1 |
| | Ceftriaxone | 980 | 16 | >64 | 1 - >64 | NA | NA |
| | Clindamycin | 1608 | 0.12 | >2 | ≤0.03 - >2 | 78.3 | 78.2 |
| | Daptomycin | 2588 | 0.5 | 1 | ≤0.06 - 4 | 99.8 | 99.8 |
| | Gentamicin | 532 | 0.25 | 0.5 | ≤0.06 - 8 | 92.5 | 92.1 |
| | Levofloxacin | 2588 | 0.25 | >4 | ≤0.03 - >4 | 62.1 | 62.1 |
| | Linezolid | 2588 | 2 | 2 | ≤0.5 - 2 | 100 | 100 |
| | Minocycline | 2587 | 0.12 | 0.25 | ≤0.06 - >8 | 95.2 | 93.2 |
| | Oxacillin | 1608 | >2 | >2 | ≤0.12 - >2 | 13.4 | 13.4 |
| | Penicillin | 2588 | 0.25 | >16 | ≤0.06 - >16 | 87.6 | 86.1 |
| | Tetracycline | 2588 | 0.12 | >16 | ≤0.03 - >2 | 98.6<sup>a</sup> | 98.6 |
| | Vancomycin | 1608 | 1 | 1 | ≤0.25 - 2 | 100 | 100 |
| **S. aureus, MR** | Eravacycline | 1304 | 0.06 | 0.12 | ≤0.008 - 1 | 80.8<sup>a</sup> | 95.5 |
| | Amoxicillin-clavulanate | 1304 | >1 | >1 | ≤0.5 - >1 | NA | NA |
| | Azithromycin | 1304 | >4 | >4 | ≤0.25 - >4 | 24.1 | 23.1 |
| | Cefaroline | 548 | 1 | 2 | 0.12 - >4 | 88.3 | 88.3 |
| | Ceftriaxone | 493 | >64 | >64 | 4 - >64 | NA | NA |
| | Clindamycin | 811 | 0.12 | >2 | ≤0.03 - >2 | 61.7 | 61.7 |
| | Daptomycin | 1304 | 0.5 | 1 | ≤0.06 - 4 | 99.6 | 99.6 |
| | Gentamicin | 263 | 0.25 | >8 | 0.12 - >8 | 85.6 | 85.2 |
| | Levofloxacin | 1304 | >4 | >4 | ≤0.06 - >4 | 34.1 | 34.1 |
| | Linezolid | 1304 | 2 | 2 | ≤0.5 - 2 | 100 | 100 |
| | Minocycline | 1303 | 0.12 | >4 | ≤0.06 - >4 | 91.7 | 88.2 |
| | Oxacillin | 811 | >2 | >2 | ≤0.12 - >2 | 0.1 | 0.1 |
| | Penicillin | 1304 | >2 | >2 | ≤0.12 - >2 | 0.2 | 0.2 |
| | Tetracycline | 1304 | 0.25 | >16 | ≤0.06 - >16 | 82.0 | 79.8 |
| | Tigecycline | 1304 | 0.12 | 0.25 | ≤0.03 - >2 | 97.5<sup>a</sup> | 97.5 |
| | Vancomycin | 811 | 1 | 1 | ≤0.25 - 2 | 100 | 100 |
| **S. aureus, MS** | Eravacycline | 1284 | 0.06 | 0.12 | ≤0.008 - 0.5 | 88.3<sup>a</sup> | 99.8 |
| | Amoxicillin-clavulanate | 1284 | >1 | >1 | ≤0.12 - >1 | NA | NA |
| | Azithromycin | 1284 | >4 | >4 | ≤0.25 - >4 | 74.9 | 73.0 |
| | Cefaroline | 528 | 0.25 | 0.25 | ≤0.06 - 0.5 | 100 | 100 |
| Antibiotic         | ID  | MIC (μg/mL) | Zone (mm) | Breakpoint |
|-------------------|-----|-------------|-----------|------------|
| Ceftriaxone       | 487 | 4           | 8         | 1 - >64    |
| Clindamycin       | 797 | 0.06 0.12   | <0.03 - >2| NA NA      |
| Daptomycin        | 1284| 0.5 0.5     | 0.12 - 2  | 99.9 99.9  |
| Gentamicin        | 269 | 0.25 0.5    | <0.06 - >8| 99.3 98.9  |
| Levofloxacin      | 1284| 0.25 1      | <0.03 - >4| 90.5 90.5  |
| Linezolid         | 1284| 2 2        | <0.5 - 2  | 100 100    |
| Minocycline       | 1284| 0.12 0.12   | <0.06 - >8| 98.7 98.3  |
| Oxacillin         | 797 | 0.25 0.5    | <0.06 - >2| 99.9 99.9  |
| Penicillin        | 1284| 2 2        | <0.12 - >2| 26.8 26.8  |
| Tetracycline      | 1284| 0.25 0.5    | <0.06 - >16| 93.4 92.5 |
| Tigecycline       | 1284| 0.12 0.25   | 0.03 - 1  | 99.7 99.7  |
| Vancomycin        | 797 | 1 1        | <0.25 - 2 | 100 100    |

**S. epidermidis**

| Antibiotic         | ID  | MIC (μg/mL) | Zone (mm) | Breakpoint |
|-------------------|-----|-------------|-----------|------------|
| Eravacycline      | 1012| 0.12 0.5    | <0.008 - 2| 45.7 84.0  |
| Amoxicillin-clavulanate | 1012| >1 >1      | <0.12 - >1| NA NA      |
| Azithromycin      | 1012| >4 >4      | <0.25 - >4| 37.2 36.9  |
| Ceftriaxone       | 277 | 16 >64     | <0.5 - >64| NA NA      |
| Clindamycin       | 735 | 0.06 >2    | <0.03 - >2| 72.0 68.6  |
| Daptomycin        | 1012| 0.5 1      | <0.06 - 4 | 99.5 99.5  |
| Gentamicin        | 206 | 0.12 >8    | <0.06 - >8| 62.6 55.8  |
| Levofloxacin      | 1012| 2 >4       | 0.06 - >4 | 45.6 45.6  |
| Linezolid         | 1012| 1 2        | <0.5 - >8 | 98.5 98.5  |
| Minocycline       | 1012| 0.12 0.5   | <0.06 - >8| 99.6 98.7  |
| Oxacillin         | 735 | 2 >2       | <0.06 - >2| 34.7 34.7  |
| Penicillin        | 1012| >2 >2      | <0.12 - >2| 11.1 NA    |
| Tetracycline      | 1012| 1 >16      | <0.06 - >16| 85.7 66.5 |
| Tigecycline       | 1012| 0.12 0.5   | <0.015 - 1| 97.5 97.5  |
| Vancomycin        | 735 | 1 2        | 0.5 - 2   | 100 100    |

**S. epidermidis, MR**

| Antibiotic         | ID  | MIC (μg/mL) | Zone (mm) | Breakpoint |
|-------------------|-----|-------------|-----------|------------|
| Eravacycline      | 480 | 0.12 0.25   | <0.008 - 2| 43.8 90.4  |
| Amoxicillin-clavulanate | 480| >1 >1  | <0.12 - >1| NA NA      |
| Azithromycin      | 480 | >4 >4      | <0.25 - >4| 30.6 30.4  |
| Ceftriaxone       | 326 | 0.5 1      | <0.06 - >4| NA NA      |
| Clindamycin       | 480 | 0.12 >2    | <0.03 - >2| 61.7 57.7  |
| Daptomycin        | 480 | 0.5 0.5    | <0.06 - >8| 52.0 44.2  |
| Gentamicin        | 154 | 4 >8       | <0.06 - >8| 26.3 26.3  |
| Levofloxacin      | 480 | 0.5 1      | <0.5 - >4 | 97.7 97.7  |
| Linezolid         | 480 | >0.5 1     | <0.5 - >4 | 99.4 98.8  |
| Minocycline       | 480 | 0.12 0.5    | <0.06 - >8| 99.4 98.8  |
| Oxacillin         | 480 | >2 >2      | <0.12 - >2| 1.3 NA     |
| Penicillin        | 480 | >2 >2      | <0.12 - >2| 0.0 NA     |
| Antibiotic          | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavulanate | Minimum | Maximum |stromicillin-clavu
| Antibiotic         | MIC Interpretation | Minimum | Maximum | Minimum | Maximum |
|--------------------|--------------------|---------|---------|---------|---------|
| Gentamicin         | G 8               | ≤0.06   | >8      | 30.1    | 17.9    |
| Levofloxacin       | G 8               | 0.06    | >8      | 13.0    | 13.0    |
| Linezolid          | 1                 | ≤0.5    | 2       | 100     | 100     |
| Minocycline        | ≤0.25             | ≤0.06   | >8      | 88.0    | 84.0    |
| Oxacillin          | >2                | 0.06    | >16     | 82.3    | 71.8    |
| Penicillin         | ≤0.12             | ≤0.12   | >2      | 74.6    | NA      |
| Tetracycline       | ≤0.25             | ≥0.25   | <2      | 100     | 100     |
| Vancomycin         | ≤0.5              | ≤0.06   | ≤0.5    | 99.8    | 97.5    |

| MIC Interpretation | Minimum | Maximum |
|--------------------|---------|---------|
| Gentamicin         | ≥0.06   | >8      |
| Levofloxacin       | >2      | >2      |
| Linezolid          | >2      | >2      |
| Minocycline        | >2      | >2      |
| Oxacillin          | >2      | >2      |
| Penicillin         | >2      | >2      |
| Tetracycline       | >2      | >2      |
| Vancomycin         | >2      | >2      |

*S. haemolyticus, MS*  
Eravacycline 143 0.03 0.12 ≤0.008 ≤1 265 266 85.8 97.8

Amoxicillin-clavulanate 143 ≤0.12 0.5 <0.12 >1 NA NA

Azithromycin 134 0.5 >4 ≤0.25 >4 54.5 53.0

Ceftriaxone 109 0.25 0.25 ≤0.06 ≤2 NA NA

Clindamycin 134 0.06 0.25 <0.03 >2 96.3 96.3

Daptomycin 134 0.25 0.5 0.12 ≤0.5 100 100

Gentamicin 25 ≤0.06 8 <0.06 >8 88.0 84.0

Levofloxacin 134 0.12 4 0.06 >4 85.1 85.1

Linezolid 134 ≤0.5 1 ≤0.5 ≤2 100 100

Minocycline 134 ≤0.06 0.25 ≤0.06 ≤0.5 100 100

Oxacillin 134 0.12 0.25 ≤0.06 ≤0.25 100 100

Penicillin 134 ≤0.12 1 ≤0.12 >2 74.6 NA

Tetracycline 134 0.25 >16 <0.06 >16 79.1 78.4

Tigecycline 134 0.12 0.25 0.06 ≤0.5 100 100

Vancomycin 134 ≥0.5 1 ≤0.25 ≤2 100 100

**S. haemolyticus, MS**

**Eravacycline** 143 0.03 0.12 ≤0.008 ≤1 85.8 97.8

**Amoxicillin-clavulanate** 143 ≤0.12 0.5 <0.12 >1 NA NA

**Azithromycin** 134 0.5 >4 ≤0.25 >4 54.5 53.0

**Ceftriaxone** 109 0.25 0.25 ≤0.06 ≤2 NA NA

**Clindamycin** 134 0.06 0.25 <0.03 >2 96.3 96.3

**Daptomycin** 134 0.25 0.5 0.12 ≤0.5 100 100

**Gentamicin** 25 ≤0.06 8 <0.06 >8 88.0 84.0

**Levofloxacin** 134 0.12 4 0.06 >4 85.1 85.1

**Linezolid** 134 ≤0.5 1 ≤0.5 ≤2 100 100

**Minocycline** 134 ≤0.06 0.25 ≤0.06 ≤0.5 100 100

**Oxacillin** 134 0.12 0.25 ≤0.06 ≤0.25 100 100

**Penicillin** 134 ≤0.12 1 ≤0.12 >2 74.6 NA

**Tetracycline** 134 0.25 >16 <0.06 >16 79.1 78.4

**Tigecycline** 134 0.12 0.25 0.06 ≤0.5 100 100

**Vancomycin** 134 0.5 1 ≤0.25 ≤2 100 100

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265 United States Food and Drug Administration (FDA) MIC interpretative breakpoints were used for eravacycline (≤0.06 μg/ml) and tigecycline (≤0.5 μg/ml) (21) in place of CLSI MIC breakpoints as none currently exist. FDA eravacycline and tigecycline breakpoints for *S. aureus* were applied to the tested coagulase-negative *Staphylococcus* species.

267 EUCAST eravacycline breakpoints for *S. aureus* (≤0.25 μg/ml) were applied to the tested coagulase-negative *Staphylococcus* species.

268 Defined using oxacillin MICs, which were only available for 2015-2017.

269 NA, MIC breakpoint not available.
| Organism | Drug                      | MIC<sub>50</sub> | MIC<sub>90</sub> | MIC range       | CLSI % Susceptible | EUCAST % Susceptible |
|----------|---------------------------|------------------|------------------|------------------|---------------------|----------------------|
| E. faecalis | Eravacycline              | 0.06             | 0.06             | 0.008 - 0.5     | 94.5%               | 99.5%                |
|           | Amoxicillin-clavulanate   | 1586             | 1                | 0.12 - >1       | NA                  | 99.9%                |
|           | Ampicillin                | 1085             | 1                | 0.25 - >8       | 99.3%               | 99.3%                |
|           | Azithromycin              | 501              | >8               | 0.12 - >8       | NA  NA              |
|           | Ceftriaxone               | 501              | >64              | 0.5 - >64       | NA  NA              |
|           | Daptomycin                | 1586             | 1                | 0.06 - >8       | 94.4%               | NA                   |
|           | Levofloxacin              | 1586             | >8               | 0.03 - >8       | 69.1%  69.5%       |
|           | Linezolid                 | 1586             | 2                | 0.5 - >4        | 99.4%  99.9%       |
|           | Minocycline               | 1586             | >8               | 0.015 - 8       | 94.8%               | 94.8%                |
|           | Vancomycin                | 1582             | 1                | 0.12 - >32      | 95.1%  95.1%       |
| E. faecalis, VR | Eravacycline          | 59               | 0.06             | 0.12 - >0.25    | 89.8%  98.3%       |
|           | Amoxicillin-clavulanate   | 59               | 1                | 0.5 - >1        | NA  98.3%           |
|           | Ampicillin                | 34               | 2                | 1 - >8          | 97.1%  97.1%       |
|           | Azithromycin              | 25               | >8               | 2 - >8          | NA  NA              |
|           | Ceftriaxone               | 25               | >64              | 4 - >64         | NA  NA              |
|           | Daptomycin                | 59               | 1                | 0.5 - >4        | 96.6%               | NA                   |
|           | Levofloxacin              | 59               | >8               | 0.5 - >8        | 5.1%  5.1%          |
|           | Linezolid                 | 59               | 1                | >0.5 - 2        | 100%  100%          |
|           | Minocycline               | 59               | >8               | 0.06 - >8       | 15.3%               | NA                   |
|           | Penicillin                | 59               | 4                | 1 - >8          | 96.6%               | NA                   |
|           | Tetracycline              | 59               | >32              | >0.015 - >32    | 8.5%  8.5%          |
|           | Tigecycline               | 59               | 0.12             | 0.25 - >0.67    | 94.9%  94.9%       |
|           | Vancomycin                | 59               | >16              | >16 - >32       | 0.0%  0.0%          |
| E. faecalis, VS  | Eravacycline          | 1505             | 0.06             | 0.06 - >0.5     | 94.8%  95.5%       |
|           | Amoxicillin-clavulanate   | 1505             | 1                | 0.12 - >1       | NA  100%            |
|           | Ampicillin                | 1046             | 1                | 0.25 - >8       | 99.3%  99.3%       |
|           | Azithromycin              | 459              | >8               | 0.12 - >8       | NA  NA              |
|           | Ceftriaxone               | 459              | >64              | 0.5 - >64       | NA  NA              |
|           | Daptomycin                | 1505             | 1                | 0.06 - >8       | 94.3%               | NA                   |
|           | Levofloxacin              | 1505             | >8               | 0.03 - >8       | 71.8%  72.2%       |
|           | Linezolid                 | 1505             | 2                | 0.5 - >4        | 99.5%  99.9%       |
|           | Minocycline               | 1505             | >8               | 0.03 - >8       | 28.1%               | NA                   |
|           | Penicillin                | 1505             | 2                | >0.12 - >8      | 97.7%               | NA                   |
| Antibiotic       | MIC         | MIC         | MIC         | MIC         | MIC         | MIC         | MIC         |
|------------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| Tetracycline 1505| >32 >32 >32 | ≤0.06 - >32 | 22.6 NA     |              |              |              |              |
| Tigecycline 1505 | 0.12 0.25 0.12 - 4 | 0.12 - 4 22.6 | 94.8 NA     | 94.8 NA     | 11.2 NA     |              |              |
| Vancomycin 1505  | 1 2 0.12 - 4 | 0.12 - 4 22.6 | 94.8 NA     | 94.8 NA     | 11.2 NA     |              |              |

**E. faecium**

| Antibiotic       | MIC         | MIC         | MIC         | MIC         | MIC         | MIC         | MIC         |
|------------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| Eravacycline     | 0.03 0.06 0.008 - 1 | 0.008 - 1 22.6 | 51.4 NA     | 97.7 NA     |              |              |              |
| Amoxicillin-clavulanate | 49 >64 >64 >64 | >64 - >64 22.6 | 94.8 NA     | 94.8 NA     | 94.8 NA     |              |              |
| Ampicillin 256    | >8 >8 >8 >8 | >8 - >8 22.6 | 94.8 NA     | 94.8 NA     | 94.8 NA     |              |              |
| Azithromycin 499  | >8 >8 >8 >8 | >8 - >8 22.6 | 94.8 NA     | 94.8 NA     | 94.8 NA     |              |              |
| Ceftaxone 499     | >64 >64 >64 >64 | >64 - >64 22.6 | 94.8 NA     | 94.8 NA     | 94.8 NA     |              |              |
| Daptomycin 1221   | 4 4 0.12 - 4 | 0.12 - 4 22.6 | 94.8 NA     | 94.8 NA     | 94.8 NA     |              |              |
| Levofloxacin 1221 | >8 >8 >8 >8 | >8 - >8 22.6 | 94.8 NA     | 94.8 NA     | 94.8 NA     |              |              |
| Linezolid 1221    | 2 2 >0.5 >0.5 | >0.5 - >0.5 22.6 | 94.8 NA     | 94.8 NA     | 94.8 NA     |              |              |
| Minocycline 1221  | 4 >8 >0.5 >0.5 | >0.5 - >0.5 22.6 | 94.8 NA     | 94.8 NA     | 94.8 NA     |              |              |
| Penicillin 1221   | >8 >8 >0.5 >0.5 | >0.5 - >0.5 22.6 | 94.8 NA     | 94.8 NA     | 94.8 NA     |              |              |
| Tetracycline 1221 | 0.12 0.25 0.03 - 0.25 | 0.03 - 0.25 22.6 | 94.8 NA     | 94.8 NA     | 94.8 NA     |              |              |
| Vancomycin 1219   | 1 >32 >0.12 >0.12 | >0.12 - >0.12 22.6 | 94.8 NA     | 94.8 NA     | 94.8 NA     |              |              |

**E. faecium, VR**

| Antibiotic       | MIC         | MIC         | MIC         | MIC         | MIC         | MIC         | MIC         |
|------------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| Eravacycline     | 0.03 0.06 0.008 - 1 | 0.008 - 1 22.6 | 51.4 NA     | 97.7 NA     |              |              |              |
| Amoxicillin-clavulanate | 49 >64 >64 >64 | >64 - >64 22.6 | 94.8 NA     | 94.8 NA     | 94.8 NA     |              |              |
| Ampicillin 256    | >8 >8 >8 >8 | >8 - >8 22.6 | 94.8 NA     | 94.8 NA     | 94.8 NA     |              |              |
| Azithromycin 499  | >8 >8 >8 >8 | >8 - >8 22.6 | 94.8 NA     | 94.8 NA     | 94.8 NA     |              |              |
| Ceftaxone 499     | >64 >64 >64 >64 | >64 - >64 22.6 | 94.8 NA     | 94.8 NA     | 94.8 NA     |              |              |
| Daptomycin 1221   | 2 2 >0.5 >0.5 | >0.5 - >0.5 22.6 | 94.8 NA     | 94.8 NA     | 94.8 NA     |              |              |
| Levofloxacin 1221 | >8 >8 >0.5 >0.5 | >0.5 - >0.5 22.6 | 94.8 NA     | 94.8 NA     | 94.8 NA     |              |              |
| Linezolid 1221    | 2 2 >0.5 >0.5 | >0.5 - >0.5 22.6 | 94.8 NA     | 94.8 NA     | 94.8 NA     |              |              |
| Minocycline 1221  | >8 >8 >0.5 >0.5 | >0.5 - >0.5 22.6 | 94.8 NA     | 94.8 NA     | 94.8 NA     |              |              |
| Penicillin 1221   | >8 >8 >0.5 >0.5 | >0.5 - >0.5 22.6 | 94.8 NA     | 94.8 NA     | 94.8 NA     |              |              |
| Tetracycline 1221 | 0.12 0.25 0.03 - 0.25 | 0.03 - 0.25 22.6 | 94.8 NA     | 94.8 NA     | 94.8 NA     |              |              |
| Vancomycin 1219   | 1 >32 >0.12 >0.12 | >0.12 - >0.12 22.6 | 94.8 NA     | 94.8 NA     | 94.8 NA     |              |              |

**E. faecium, VS**

| Antibiotic       | MIC         | MIC         | MIC         | MIC         | MIC         | MIC         | MIC         |
|------------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| Eravacycline     | 0.03 0.06 0.008 - 0.5 | 0.008 - 0.5 22.6 | 963 NA     | 96.9 NA     |              |              |              |
| Amoxicillin-clavulanate | 49 >64 >64 >64 | >64 - >64 22.6 | 94.8 NA     | 94.8 NA     | 94.8 NA     |              |              |
| Ampicillin 504    | >8 >8 >8 >8 | >8 - >8 22.6 | 94.8 NA     | 94.8 NA     | 94.8 NA     |              |              |
| Azithromycin 198  | >8 >8 >8 >8 | >8 - >8 22.6 | 94.8 NA     | 94.8 NA     | 94.8 NA     |              |              |
| Ceftaxone 198     | >64 >64 >64 >64 | >64 - >64 22.6 | 94.8 NA     | 94.8 NA     | 94.8 NA     |              |              |
| Daptomycin 702    | 4 4 >0.5 >0.5 | >0.5 - >0.5 22.6 | 94.8 NA     | 94.8 NA     | 94.8 NA     |              |              |
| Levofloxacin 702  | >8 >8 >0.5 >0.5 | >0.5 - >0.5 22.6 | 94.8 NA     | 94.8 NA     | 94.8 NA     |              |              |
| Linezolid 702     | 2 2 >0.5 >0.5 | >0.5 - >0.5 22.6 | 94.8 NA     | 94.8 NA     | 94.8 NA     |              |              |
| Minocycline 702   | 1 >8 >0.5 >0.5 | >0.5 - >0.5 22.6 | 94.8 NA     | 94.8 NA     | 94.8 NA     |              |              |
| Penicillin 702    | >8 >8 >0.5 >0.5 | >0.5 - >0.5 22.6 | 94.8 NA     | 94.8 NA     | 94.8 NA     |              |              |
| Tetracycline 702  | 1 >32 >0.06 >0.06 | >0.06 - >0.06 22.6 | 94.8 NA     | 94.8 NA     | 94.8 NA     |              |              |
|              | MIC (μg/ml) | Interpretation |
|--------------|-------------|----------------|
| Tigecycline  | 0.12        | 0.12 ≤0.015 - 8 |
| (≤0.25 μg/ml)|             | 96.2*           |
| Vancomycin   | 1           | 1 ≤0.12 - 4     |
| (≤0.06 μg/ml)|             | 100             |

*a United States Food and Drug Administration (FDA) MIC interpretative susceptible breakpoints were used for eravacycline (≤0.06 μg/ml) and tigecycline (≤0.25 μg/ml) in place of CLSI MIC breakpoints as none currently exist. FDA tigecycline breakpoints for vancomycin-susceptible *E. faecalis* were also applied to vancomycin-resistant isolates and to *E. faecium*.

EUCAST breakpoints were applied for amoxicillin-clavulanate, although these are based on susceptibility testing using a fixed concentration of clavulanic acid of 2 μg/ml, while for this study amoxicillin-clavulanate was tested with a 2:1 ratio.

NA, MIC breakpoint not available.
| Organism  | Drug                   | n   | MIC<sub>50</sub> | MIC<sub>90</sub> | MIC range | CLSI (%) | EUCAST (%) |
|-----------|------------------------|-----|-------------------|-------------------|-----------|----------|------------|
|           |                        |     | μg/ml             | μg/ml             | ≤0.001 - 0.03 |          |            |
| S. pneumoniae | Eravacycline            | 596 | 0.008            | 0.015            | NA        | NA       |
|           | Amoxicillin-clavulanate | 491 | 0.06             | 0.015 - 0.03      | 83.5      | NA       |
|           | Azithromycin            | 596 | 0.12             | ≥2                | 58.9      | 58.4     |
|           | Cefaroline              | 105 | 0.008            | 0.12             | ≥0.004 - 0.5 | 100      | 98.1     |
|           | Ceftriaxone             | 596 | 0.03             | 1                 | 92.3      | 82.4     |
|           | Clindamycin             | 105 | 0.03             | ≥1                | 74.3      | 74.3     |
|           | Daptomycin              | 595 | 0.12             | 0.25              | ≤0.015 - 1 | NA       | NA        |
|           | Linezolid               | 596 | 1                | ≥0.12             | 99.0      | 99.0     |
|           | Meropenem               | 105 | ≤0.03            | >0.5              | 78.1      | --       |
|           | Minocycline             | 596 | ≤0.06            | 8                 | ≤0.03 - 8 | NA       | 75.8      |
|           | Penicillin              | 596 | ≤0.12            | 2                 | 48.0<sup>3</sup> | 48.0<sup>3</sup> | 100 | NA |
|           | Tigecycline             | 596 | 0.12             | >4                | 74.8      | 74.8     |
|           | Vancomycin              | 105 | 0.25             | 0.5               | 100       | 100      |
| S. agalactiae | Eravacycline           | 1239| 0.03             | 0.06              | 0.008 - 0.25 | 98.0<sup>4</sup> | 99.8<sup>4</sup> |
|           | Amoxicillin-clavulanate | 598 | 0.12             | 0.12              | 0.03 - 0.5 | 63.7     | 63.6      |
|           | Azithromycin            | 1239| 0.12             | >1                | 63.7      | 63.6     |
|           | Cefaroline              | 641 | 0.015            | 0.015             | ≥0.004 - 0.12 | 100      | NA       |
|           | Ceftriaxone             | 1239| 0.06             | 0.12              | ≥0.015 - 0.5 | 100      | NA       |
|           | Clindamycin             | 1040| 0.06             | >1                | 74.5      | 75.9     |
|           | Daptomycin              | 1239| 0.25             | 0.5               | 100       | 100      |
|           | Linezolid               | 1239| 1                | ≥0.25             | 96.5      | 96.5     |
|           | Meropenem               | 1040| 0.06             | 0.12              | ≥0.03 - 0.25 | 100      | NA       |
|           | Minocycline             | 1239| >8               | >8                | ≥0.06 - >8 | NA       | 19.9      |
|           | Penicillin              | 1239| ≤0.12            | ≤0.12             | ≥0.12 - 0.5 | 99.6     | 99.8      |
|           | Tigecycline             | 1239| 0.06             | 0.06              | 100<sup>5</sup> | 99.8<sup>5</sup> | 100 | NA |
|           | Vancomycin              | 1040| 0.5              | 0.5               | 100       | 100      |
| S. pyogenes | Eravacycline           | 1192| 0.03             | 0.03              | 0.008 - 0.03 | 100      | 100<sup>6</sup> |
|           | Amoxicillin-clavulanate | 665 | 0.03             | 0.03              | ≥0.015 - 0.25 | NA       | NA       |
|           | Azithromycin            | 1192| 0.12             | 0.5               | ≥0.03 - >2 | 90.1     | 89.9      |
|           | Cefaroline              | 527 | ≤0.004            | 0.008             | ≥0.004 - 0.003 | 100      | NA       |
|           | Ceftriaxone             | 1192| 0.03             | 0.03              | ≥0.015 - 1 | 99.9      | NA       |
|           | Clindamycin             | 869 | 0.06             | 0.06              | <0.015 - >1 | 94.8     | 94.9      |
Daptomycin 1192 0.06 0.06 ≤0.03 - 0.25 100 100
Levofoxacin 1192 0.5 1 ≤0.25 - 4 99.6 99.6
Lincomycin 1192 1 2 ≤0.12 - 2 100 100
Meropenem 869 ≤0.03 ≤0.03 ≤0.03 - 0.12 100 NA
Minocycline 1192 0.12 4 ≤0.06 - 8 NA 86.9
Penicillin 1192 ≤0.12 ≤0.12 ≤0.12 - 0.12 100 100
Tetracycline 1192 0.25 4 ≤0.03 - 4 86.9 86.7
Tigecycline 1192 0.03 0.06 ≤0.008 - 0.12 100 100
Vancomycin 869 0.5 0.5 ≤0.06 - 1 100 100

S. anginosus group
Eravacycline 346 0.03 0.06 ≤0.001 - 0.12 99.1 100
Aminocillin-clavulanate 138 0.06 0.25 ≤0.015 - 2 NA NA
Azithromycin 346 0.06 >1 ≤0.03 - 2 81.2 NA
Cefaroline 208 0.015 0.03 ≤0.004 - 0.25 NA NA
Ceftriaxone 346 0.12 0.25 ≤0.015 - 2 99.4 99.1
Clindamycin 266 0.03 0.06 ≤0.015 - 1 91.0 91.0
Daptomycin 346 0.25 0.5 ≤0.03 - 1 100 NA
Levofoxacin 346 0.5 1 ≤0.25 - 4 99.4 NA
Lincomycin 346 1 2 ≤0.12 - 2 100 NA
Meropenem 266 ≤0.03 0.12 ≤0.03 - 0.5 100 100
Minocycline 346 ≤0.06 8 ≤0.06 - 8 NA NA
Penicillin 346 ≤0.12 ≤0.12 ≤0.12 - 1 95.4 98.0
Tetracycline 346 0.25 4 ≤0.03 - 4 69.9 NA
Tigecycline 346 0.03 0.06 ≤0.008 - 0.5 99.1 99.1
Vancomycin 266 0.5 1 ≤0.06 - 1 100 100

1 United States Food and Drug Administration (FDA) MIC interpretative breakpoints for eravacycline (≤0.06 μg/ml) were applied to β-haemolytic streptococci.
2 Using CLSI susceptible breakpoint for oral penicillin and EUCAST susceptible breakpoint for benzylpenicillin indications other than meningitis (≤0.06 μg/ml).
3 United States Food and Drug Administration (FDA) MIC interpretative susceptible breakpoints were used for eravacycline (≤0.06 μg/ml) and tigecycline (≤0.25 μg/ml) in place of CLSI MIC breakpoints as none currently exist. FDA eravacycline susceptible breakpoint for S. anginosus was applied to β-haemolytic streptococci.
4 EUCAST eravacycline susceptible breakpoint for S. anginosus (≤0.12 μg/ml) was applied to β-haemolytic streptococci.
5 Other than meningitis (n=346), S. constellatus (n=36), S. intermedius (n=7), and S. intermedius/milleri (n=1).
6 EUCAST tigecycline breakpoints for β-haemolytic streptococci (≤0.12 μg/ml) were applied to S. anginosus group.
7 NA, MIC breakpoint not available; –, not evaluable as the tested MIC range did not extend high enough for the EUCAST susceptible breakpoint for S. pneumoniae.

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