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# Antimicrobial activity of ceftobiprole and comparator agents when tested against contemporary Gram-positive and -negative organisms collected from Europe (2015)

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## ABSTRACT

Susceptibility testing of ceftobiprole and comparators against 12,240 isolates was performed following CLSI/EUCAST guidelines. The percentage of susceptible MRSA isolates was higher for ceftobiprole (96.5% susceptible) than for ceftaroline (86.2% susceptible). Both ceftobiprole (MIC<sub>50/90</sub>, 0.5/2 mg/L) and ceftaroline (MIC<sub>50/90</sub>, 0.25/1 mg/L) demonstrated potent activity against coagulase-negative staphylococci. Ceftobiprole demonstrated good potency against *Enterococcus faecalis* (MIC<sub>50/90</sub> values of 0.5/2 mg/L); ceftaroline (MIC<sub>50/90</sub>, 2/8 mg/L) was 4-fold less active against these strains. Ceftobiprole activity was comparable to that of the other  $\beta$ -lactam agents tested against *S. pneumoniae* (MIC<sub>90</sub>, 0.5 mg/L vs 0.12–2 mg/L [other  $\beta$ -lactams]), viridans-group streptococci (MIC<sub>90</sub>, 0.25 mg/L vs 0.006–1 mg/L [other  $\beta$ -lactams]), and  $\beta$ -hemolytic streptococci (MIC<sub>90</sub>, 0.03 mg/L vs 0.015–0.06 mg/L [other  $\beta$ -lactams]). Overall, 73.8% of *Enterobacteriaceae* isolates tested were susceptible to ceftobiprole. Ceftobiprole inhibited 70.4% of *P. aeruginosa* at  $\leq 4$  mg/L and all isolates of *Haemophilus influenzae* and *Moraxella catarrhalis* at  $\leq 0.5$  mg/L. Ceftobiprole was active in vitro against a broad range of clinically-relevant contemporary Gram-positive and Gram-negative bacterial isolates.

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## 1. Introduction

Antimicrobial resistance (AMR) is a global problem that requires a coordinated response to address established and emerging threats to human health (Queenan et al., 2016). In a global report commissioned by the United Kingdom, it has been estimated that infections with drug-resistant pathogens will account for 10 million deaths per year by 2050, with lost economic outputs totaling \$100 trillion (Queenan et al., 2016). Modern medical care, including cancer therapy, organ transplantation, and management of the critically ill, would not be possible without safe and effective antibacterial therapeutic agents (Boucher et al., 2009; Laxminarayan et al., 2016; Spellberg et al., 2008). Failure to address AMR could compromise such medical advances (Cosgrove, 2006; Denning et al., 2017; Laxminarayan et al., 2016).

Collecting AMR surveillance data is essential to define the scope of the resistance problem and to develop interventions that improve appropriate antibiotic use and decrease resistance selection pressure (Perez and Villegas, 2015; Queenan et al., 2016). Gaining a better understanding of the mechanisms of resistance is also important as this

information can be used to develop new agents, or to modify older agents, to have or regain potent activity against key target pathogens (Brogan and Mossialos, 2013; Ling et al., 2015; Spellberg et al., 2008).

Ceftobiprole is an advanced-generation parenteral cephalosporin with potent expanded-spectrum bactericidal activity (Farrell et al., 2014; Fritsche et al., 2008; Rossolini et al., 2011; Walkty et al., 2011) that has obtained regulatory approval in Europe and several non-European countries for the treatment of hospital-acquired pneumonia (HAP; excluding ventilator-associated pneumonia [VAP]) and community-acquired pneumonia (CAP) in adults (Awad et al., 2014; Liapikou et al., 2015; Nicholson et al., 2012; Syed, 2014; Zhanel et al., 2008). Ceftobiprole is generally  $\beta$ -lactamase stable and has a strong affinity for essential penicillin binding proteins, including those responsible for  $\beta$ -lactam resistance in staphylococci and pneumococci (Davies et al., 2007; Zhanel et al., 2008). It has also been shown to have a low propensity for resistance development (Bogdanovich et al., 2005; Chan et al., 2015; Davies et al., 2007). This agent demonstrates potent in vitro activity against Gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant coagulase-negative staphylococci (MR-CoNS), and penicillin-resistant *Streptococcus pneumoniae* (PRSP), in addition to activity against Gram-negative pathogens commonly associated with pneumonia (Farrell et al., 2014; Fritsche et al., 2008; Rossolini et al., 2011;

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Walkty et al., 2011). This, in combination with its potent bactericidal action, make ceftobiprole an attractive therapeutic candidate.

The spectrum and potency of ceftobiprole against Gram-positive and Gram-negative pathogens, collected during the period of 2005 through 2010 from medical centers in Europe and surrounding countries has been documented for a variety of infection types (Farrell et al., 2014; Rossolini, et al., 2011). In the present survey, we expand upon those observations by reporting the activity of ceftobiprole and comparators against bacterial isolates obtained and tested during the 2015 SENTRY Antimicrobial Surveillance Program in Europe, Turkey, and Israel.

## 2. Materials and methods

### 2.1. Bacterial strains tested

From the ceftobiprole SENTRY Antimicrobial Surveillance Program (described at <https://www.jmilabs.com/sentry-surveillance-program/>) in Europe (2015), a total of 12,240 non-duplicate, consecutive clinical isolates were submitted from 37 medical centers in the following countries (number of sites): Belgium (1), Czech Republic (1), France (4), Germany (5), Greece (1), Hungary (1), Ireland (2), Israel (1), Italy (4), Poland (1), Portugal (1), Romania (1), Russia (3), Slovenia (1), Spain (3), Sweden (2), Turkey (2), and the United Kingdom (3). All organisms were isolated from documented infections and only 1 strain per patient infection episode was included in the surveillance collection. Isolates were derived primarily from hospitalized patients with bloodstream infections, skin and skin structure infections (SSSI), pneumonias, urinary tract infections, and intra-abdominal infections, according to a common surveillance design (Jones and Masterton, 2001). Species identification was performed at the participant medical centers and confirmed at the monitoring laboratory (JMI Laboratories, North Liberty, IA, USA) using the Vitek 2 System (bioMérieux, Hazelwood, MO, USA) and matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker, Billerica, MA, USA) when necessary.

### 2.2. Susceptibility testing methods

All isolates were tested by the Clinical Laboratories Standards Institute (CLSI) broth microdilution method (M07-A10, 2015) (CLSI, 2015) using validated commercially-prepared panels (ThermoFisher Scientific, Cleveland, OH, USA) in cation-adjusted Mueller-Hinton broth (with 5% lysed horse blood added for testing fastidious streptococci, or Haemophilus Test Medium (HTM) for testing *H. influenzae*) against ceftobiprole and comparator antimicrobial agents. All tested agents were provided as reagent-grade formulations of the active compounds by the respective manufacturers. Susceptibility interpretations were based upon the EUCAST breakpoints (EUCAST, 2017), including the EUCAST breakpoints recently established for ceftobiprole: *S. aureus* (susceptible  $\leq 2$  mg/L, resistant  $> 2$  mg/L), *S. pneumoniae* (susceptible  $\leq 0.5$  mg/L, resistant  $> 0.5$  mg/L), *Enterobacteriaceae* (susceptible  $\leq 0.25$  mg/L, resistant  $> 0.25$  mg/L), and non-species specific breakpoint (susceptible  $\leq 4$  mg/L, resistant  $> 4$  mg/L) (Zevtera, 2013). *S. aureus* strains were classified as MRSA according to their level of oxacillin resistance (MIC  $\geq 4$  mg/L) *Escherichia coli*, *Klebsiella pneumoniae*, *K. oxytoca* and *Proteus mirabilis* were grouped as ESBL screen-positive (SP) phenotype based on the CLSI screening criteria for potential ESBL production, i.e., ceftazidime, ceftriaxone, or aztreonam MIC  $\geq 2$  mg/L (CLSI, 2017). Results are reported as MIC distributions (ceftobiprole only), MIC<sub>50/90</sub> values (MIC encompassing 50% and 90% of isolates tested), and % susceptible (S) and resistant (R) according to EUCAST interpretive criteria.

Concurrently tested ATCC quality control (QC) strains included: *S. aureus* ATCC 29213; *E. faecalis* ATCC 29212; *E. coli* ATCC 25922 and ATCC 35218; *P. aeruginosa* ATCC 27853; *S. pneumoniae* ATCC 49619; and *H. influenzae* ATCC 49247. All QC results were within published limits (Anderegg et al., 2004; CLSI, 2017).

## 3. Results

### 3.1. Ceftobiprole activity against staphylococci

Ceftobiprole was active against 2,588 *S. aureus* (MIC<sub>50/90</sub>, 0.5/2 mg/L; all MIC results at  $\leq 4$  mg/L, 99.2% susceptible; Tables 1 and 2). All *S. aureus* were susceptible to vancomycin (MIC<sub>50/90</sub>, 0.5/1 mg/L), linezolid (MIC<sub>50/90</sub>, 1/1 mg/L), tigecycline (MIC<sub>50/90</sub>, 0.12/0.25 mg/L), and daptomycin (MIC<sub>50/90</sub>, 0.25/0.5 mg/L) (Table 2). In addition to ceftobiprole, susceptibility to ceftaroline, clindamycin, gentamicin, tetracycline, and trimethoprim-sulfamethoxazole was  $> 90\%$  (range 91.6–99.2%). Among 2,009 methicillin-susceptible *S. aureus* (MSSA), the ceftobiprole susceptibility rate was 100.0% (Table 1).

The overall frequency of MRSA was 22.4% (579/2,588; Table 1). As expected, all  $\beta$ -lactams displayed higher MIC values when tested against MRSA (579 isolates; Table 2). Ceftobiprole (MIC<sub>50/90</sub>, 2/2 mg/L; 96.5% susceptible) and ceftaroline (MIC<sub>50/90</sub>, 1/2 mg/L; 86.2% susceptible) were at least 8-fold more potent (by MIC<sub>90</sub>) than ceftriaxone and were 2-fold less potent than linezolid and vancomycin, 4-fold less potent than daptomycin, and 16-fold less potent than tigecycline (Table 2). Among the 20 MRSA isolates that were resistant to ceftobiprole (MIC, 4 mg/L), all were resistant to ceftaroline and 14 were submitted from 3 different medical centers in Italy, suggesting possible nosocomial transmission. These MRSA isolates were highly resistant to levofloxacin (83.4%), erythromycin (68.0%), and clindamycin (31.3%). Greatest coverage of all *S. aureus* (MSSA and MRSA) was provided by vancomycin, daptomycin, linezolid, and tigecycline (all 100.0% susceptible), trimethoprim-sulfamethoxazole (99.8% susceptible), ceftobiprole (99.2% susceptible), and ceftaroline (96.9% susceptible; Table 2).

The activity of ceftobiprole against 526 coagulase-negative staphylococci (CoNS) isolates was similar to that against MRSA, reflecting the greater proportion of CoNS that were oxacillin-resistant compared to *S. aureus* (63.9% versus 22.4%, respectively, Table 1). All methicillin-susceptible CoNS were susceptible to ceftobiprole at an MIC of  $< 1$  mg/L, and 85.7% of MR-CoNS were inhibited at the *S. aureus* susceptible breakpoint of  $< 2$  mg/L (Table 1). All (100.0%) CoNS isolates were susceptible to daptomycin, tigecycline, and vancomycin; 99.4% were susceptible to linezolid (Table 2). Of the 3 isolates resistant to linezolid, all were MR-CoNS from Italy, the ceftobiprole MICs were 1 mg/L for 1 isolate and 2 mg/L for 2 isolates (data not shown).

### 3.2. Ceftobiprole activity against enterococci

Ceftobiprole demonstrated good activity against 411 *Enterococcus faecalis* (MIC<sub>50/90</sub>, 0.5/2 mg/L; 95.9% inhibited at MIC  $< 4$  mg/L), while ceftaroline (MIC<sub>50/90</sub>, 2/8 mg/L) was 4-fold less active against these strains. Neither ceftobiprole (MIC<sub>50</sub>,  $> 4$  mg/L, Table 1) nor ceftaroline (MIC<sub>50</sub>,  $> 8$  mg/L, data not shown) were active against the 235 isolates of *Enterococcus faecium* (Table 1). This pattern was similar to that of ampicillin where 100.0% of *E. faecalis* and only 8.9% of *E. faecium* were susceptible (data not shown). Vancomycin resistance was low for *E. faecalis* (1.5%, EUCAST) but much higher for *E. faecium* (16.2%). There was no cross-resistance between ceftobiprole and vancomycin among *E. faecalis* isolates. Susceptibility rates of 93.2–100.0% were found for linezolid, teicoplanin, tigecycline, and vancomycin tested against *Enterococcus* spp. (Table 2).

### 3.3. Ceftobiprole activity against *S. pneumoniae*

Ceftobiprole was active against *S. pneumoniae* with MIC<sub>50</sub>, and MIC<sub>90</sub> values of 0.015 and 0.5 mg/L, respectively. All isolates were inhibited at a ceftobiprole MIC of  $\leq 2$  mg/L and 99.3% were susceptible to ceftobiprole at the EUCAST-approved breakpoint of  $\leq 0.5$  mg/L (Tables 1 and 2). Ceftaroline (99.9% susceptible), imipenem (100.0%), levofloxacin (98.1%), linezolid (100.0%), and vancomycin (100.0%) were all active

**Table 1**  
Antimicrobial activity of ceftibiprole tested against the main organisms and organism groups of isolates included as part of 2015 European surveillance studies.

| Organism/organism group (no.)                       | No. of isolates at MIC (mg/L; cumulative %) |          |           |             |             |              |             |             |             |               |             |             |             |            |             |              | MIC <sub>50</sub> | MIC <sub>90</sub> |
|-----------------------------------------------------|---------------------------------------------|----------|-----------|-------------|-------------|--------------|-------------|-------------|-------------|---------------|-------------|-------------|-------------|------------|-------------|--------------|-------------------|-------------------|
|                                                     | 0.001                                       | 0.002    | 0.004     | 0.008       | 0.015       | 0.03         | 0.06        | 0.12        | 0.25        | 0.5           | 1           | 2           | 4           | 8          | 16          | >            |                   |                   |
| <i>Staphylococcus aureus</i> (2,588)                |                                             |          |           |             |             | 4 (0.2%)     | 2 (0.2%)    | 7 (0.5%)    | 729 (28.7%) | 1301 (78.9%)  | 234 (88.0%) | 291 (99.2%) | 20 (100.0%) |            |             |              | 0.5               | 2                 |
| MSSA (2,009)                                        |                                             |          |           |             |             | 4 (0.2%)     | 2 (0.3%)    | 7 (0.6%)    | 729 (36.9%) | 1267 (100.0%) |             |             |             |            |             |              | 0.5               | 0.5               |
| MRSA (579)                                          |                                             |          |           |             |             |              |             |             | 0 (0.0%)    | 34 (5.9%)     | 234 (46.3%) | 291 (96.5%) | 20 (100.0%) |            |             |              | 2                 | 2                 |
| Coagulase-negative staphylococci (526) <sup>a</sup> |                                             |          |           |             |             | 13 (2.5%)    | 20 (6.3%)   | 72 (20.0%)  | 64 (32.1%)  | 97 (50.6%)    | 164 (81.7%) | 48 (90.9%)  | 45 (99.4%)  | 3 (100.0%) |             |              | 0.5               | 2                 |
| MS-CoNS (190)                                       |                                             |          |           |             |             | 12 (6.3%)    | 20 (16.8%)  | 72 (54.7%)  | 57 (84.7%)  | 27 (98.9%)    | 2 (100.0%)  |             |             |            |             |              | 0.12              | 0.5               |
| MR-CoNS (336)                                       |                                             |          |           |             |             | 1 (0.3%)     | 0 (0.3%)    | 0 (0.3%)    | 7 (2.4%)    | 70 (23.2%)    | 162 (71.4%) | 48 (85.7%)  | 45 (99.1%)  | 3 (100.0%) |             |              | 1                 | 4                 |
| <i>Enterococcus</i> spp. (646)                      |                                             |          |           |             |             |              |             | 60 (9.3%)   | 108 (26.0%) | 165 (51.5%)   | 18 (54.3%)  | 37 (60.1%)  | 28 (64.4%)  |            |             | 230 (100.0%) | 0.5               | >4                |
| <i>Enterococcus faecalis</i> (411)                  |                                             |          |           |             |             |              |             | 60 (14.6%)  | 107 (40.6%) | 161 (79.8%)   | 13 (83.0%)  | 32 (90.8%)  | 21 (95.9%)  |            |             | 17 (100.0%)  | 0.5               | 2                 |
| <i>Enterococcus faecium</i> (235)                   |                                             |          |           |             |             |              |             | 0 (0.0%)    | 1 (0.4%)    | 4 (2.1%)      | 5 (4.3%)    | 5 (6.4%)    | 7 (9.4%)    |            |             | 213 (100.0%) | >4                | >4                |
| <i>Streptococcus pneumoniae</i> (833)               |                                             |          | 12 (1.4%) | 290 (36.3%) | 280 (69.9%) | 55 (76.5%)   | 17 (78.5%)  | 22 (81.2%)  | 55 (87.8%)  | 96 (99.3%)    | 3 (99.6%)   | 3 (100.0%)  |             |            |             |              | 0.015             | 0.5               |
| Viridans group streptococci (264) <sup>b</sup>      | 0 (0.0%)                                    | 2 (0.8%) | 13 (5.7%) | 62 (29.2%)  | 48 (47.3%)  | 72 (74.6%)   | 28 (85.2%)  | 17 (91.7%)  | 9 (95.1%)   | 9 (98.5%)     |             | 4 (100.0%)  |             |            |             |              | 0.06              | 0.25              |
| Beta-hemolytic streptococci (498) <sup>c</sup>      | 0 (0.0%)                                    | 2 (0.4%) | 5 (1.4%)  | 206 (42.8%) | 122 (67.3%) | 160 (99.4%)  | 2 (99.8%)   | 1 (100.0%)  |             |               |             |             |             |            |             |              | 0.015             | 0.03              |
| <i>Enterobacteriaceae</i> (4,646) <sup>d</sup>      |                                             |          |           | 55 (1.2%)   | 589 (13.9%) | 1912 (55.0%) | 585 (67.6%) | 190 (71.7%) | 99 (73.8%)  | 67 (75.3%)    | 40 (76.1%)  | 48 (77.2%)  | 40 (78.0%)  | 19 (78.4%) | 24 (78.9%)  | 978 (100.0%) | 0.03              | >16               |
| <i>Escherichia coli</i> (2,123)                     |                                             |          |           | 20 (0.9%)   | 314 (15.7%) | 1006 (63.1%) | 254 (75.1%) | 59 (77.9%)  | 23 (78.9%)  | 15 (79.7%)    | 5 (79.9%)   | 7 (80.2%)   | 3 (80.4%)   | 5 (80.6%)  | 7 (80.9%)   | 405 (100.0%) | 0.03              | >16               |
| ESBL screen-positive (467)                          |                                             |          |           | 0 (0.0%)    | 1 (0.2%)    | 7 (1.7%)     | 7 (3.2%)    | 8 (4.9%)    | 8 (6.6%)    | 9 (8.6%)      | 4 (9.4%)    | 4 (10.3%)   | 3 (10.9%)   | 5 (12.0%)  | 7 (13.5%)   | 404 (100.0%) | >16               | >16               |
| ESBL screen-negative (1,656)                        |                                             |          |           | 20 (1.2%)   | 313 (20.1%) | 999 (80.4%)  | 247 (95.4%) | 51 (98.4%)  | 15 (99.3%)  | 6 (99.7%)     | 1 (99.8%)   | 3 (99.9%)   | 0 (99.9%)   | 0 (99.9%)  | 0 (99.9%)   | 1 (100.0%)   | 0.03              | 0.06              |
| <i>Klebsiella pneumoniae</i> (853)                  |                                             |          |           | 4 (0.5%)    | 96 (11.7%)  | 247 (40.7%)  | 64 (48.2%)  | 21 (50.6%)  | 5 (51.2%)   | 6 (51.9%)     | 1 (52.1%)   | 5 (52.6%)   | 3 (53.0%)   | 2 (53.2%)  | 4 (53.7%)   | 395 (100.0%) | 0.12              | >16               |
| ESBL screen-positive (421)                          |                                             |          |           |             | 0 (0.0%)    | 2 (0.5%)     | 2 (1.0%)    | 3 (1.7%)    | 1 (1.9%)    | 6 (3.3%)      | 1 (3.6%)    | 4 (4.5%)    | 3 (5.2%)    | 2 (5.7%)   | 3 (6.4%)    | 394 (100.0%) | >16               | >16               |
| ESBL screen-negative (432)                          |                                             |          |           | 4 (0.9%)    | 96 (23.1%)  | 245 (79.9%)  | 62 (94.2%)  | 18 (98.4%)  | 4 (99.3%)   | 0 (99.3%)     | 0 (99.3%)   | 1 (99.5%)   | 0 (99.5%)   | 0 (99.5%)  | 1 (99.8%)   | 1 (100.0%)   | 0.03              | 0.06              |
| <i>Klebsiella oxytoca</i> (188)                     |                                             |          |           | 0 (0.0%)    | 2 (1.1%)    | 24 (13.8%)   | 31 (28.2%)  | 39 (44.7%)  | 21 (65.4%)  | 9 (81.4%)     | 0 (81.4%)   | 0 (81.4%)   | 1 (81.9%)   | 1 (82.4%)  | 33 (100.0%) | 33 (100.0%)  | 0.25              | >16               |
| ESBL screen-positive (35)                           |                                             |          |           |             |             |              |             |             |             |               |             |             | 0 (0.0%)    | 1 (2.9%)   | 1 (5.7%)    | 33 (100.0%)  | >16               | >16               |
| ESBL screen-negative (153)                          |                                             |          |           | 0 (0.0%)    | 2 (1.3%)    | 24 (17.0%)   | 27 (34.6%)  | 31 (54.9%)  | 39 (80.4%)  | 21 (94.1%)    | 9 (100.0%)  |             |             |            |             |              | 0.12              | 0.5               |
| <i>Enterobacter</i> spp. (501)                      |                                             |          |           | 2 (0.4%)    | 29 (6.2%)   | 207 (47.5%)  | 88 (65.1%)  | 22 (69.5%)  | 9 (71.3%)   | 4 (72.1%)     | 11 (74.3%)  | 23 (78.8%)  | 26 (84.0%)  | 6 (85.2%)  | 6 (86.4%)   | 68 (100.0%)  | 0.06              | >16               |
| <i>Citrobacter</i> spp. (198)                       |                                             |          |           | 0 (0.0%)    | 21 (10.6%)  | 122 (72.2%)  | 19 (81.8%)  | 4 (83.8%)   | 0 (83.8%)   | 3 (85.4%)     | 7 (88.9%)   | 8 (92.9%)   | 2 (93.9%)   | 1 (94.4%)  | 2 (95.5%)   | 9 (100.0%)   | 0.03              | 2                 |
| <i>Proteus mirabilis</i> (325)                      |                                             |          |           | 6 (1.8%)    | 73 (24.3%)  | 177 (78.8%)  | 20 (84.9%)  | 9 (87.7%)   | 2 (88.3%)   | 7 (90.5%)     | 5 (92.0%)   | 2 (92.6%)   | 4 (93.8%)   | 3 (94.8%)  | 1 (95.1%)   | 16 (100.0%)  | 0.03              | 0.5               |
| Indole-positive <i>Proteus</i> spp. (202)           |                                             |          |           | 22 (10.9%)  | 48 (34.7%)  | 82 (75.2%)   | 6 (78.2%)   | 0 (78.2%)   | 0 (78.2%)   | 1 (78.7%)     | 1 (79.2%)   | 0 (79.2%)   | 1 (79.7%)   | 0 (79.7%)  | 3 (81.2%)   | 38 (100.0%)  | 0.03              | >16               |
| <i>Serratia</i> spp. (203)                          |                                             |          |           | 0 (0.0%)    | 4 (2.0%)    | 34 (18.7%)   | 98          | 37          | 13          | 7 (95.1%)     | 1 (95.6%)   | 0 (95.6%)   | 0 (95.6%)   | 1 (96.1%)  | 0           | 8 (100.0%)   | 0.06              | 0.25              |

(continued on next page)

Table 1 (continued)

| Organism/organism group<br>(no.)             | No. of isolates at MIC (mg/L; cumulative %) |       |          |            |             |             |            |            |            |            |             |             |             |             |            |              | MIC <sub>50</sub> | MIC <sub>90</sub> |
|----------------------------------------------|---------------------------------------------|-------|----------|------------|-------------|-------------|------------|------------|------------|------------|-------------|-------------|-------------|-------------|------------|--------------|-------------------|-------------------|
|                                              | 0.001                                       | 0.002 | 0.004    | 0.008      | 0.015       | 0.03        | 0.06       | 0.12       | 0.25       | 0.5        | 1           | 2           | 4           | 8           | 16         | >            |                   |                   |
| <i>Pseudomonas aeruginosa</i><br>(1,064)     |                                             |       |          |            |             |             | (67.0%)    | (85.2%)    | (91.6%)    |            |             |             |             |             | (96.1%)    |              | 2                 | >16               |
| <i>Acinetobacter</i> spp. (356)              |                                             |       |          |            |             |             |            | 2 (0.2%)   | 8 (0.9%)   | 46 (5.3%)  | 315 (34.9%) | 243 (57.7%) | 135 (70.4%) | 127 (82.3%) | 45 (86.6%) | 143 (100.0%) | >16               | >16               |
| <i>Stenotrophomonas maltophilia</i><br>(159) |                                             |       |          |            |             |             |            | 29 (8.1%)  | 30 (16.6%) | 18 (21.6%) | 6 (23.3%)   | 1 (23.6%)   | 2 (24.2%)   | 2 (24.7%)   | 9 (27.2%)  | 259 (100.0%) | >16               | >16               |
| <i>Haemophilus influenzae</i><br>(428)       |                                             |       | 0 (0.0%) | 36 (8.4%)  | 202 (55.6%) | 144 (89.3%) | 40 (99.8%) | 5 (100.0%) |            |            |             |             |             |             |            |              | 0.03              | 0.12              |
| Beta-lactamase-positive<br>(61)              |                                             |       | 0 (0.0%) | 3 (4.9%)   | 40 (70.5%)  | 13 (91.8%)  | 4 (98.4%)  | 1 (100.0%) |            |            |             |             |             |             |            |              | 0.03              | 0.06              |
| Beta-lactamase-negative<br>(367)             |                                             |       | 0 (0.0%) | 33 (9.0%)  | 162 (53.1%) | 131 (88.8%) | 36 (99.7%) | 4 (100.0%) |            |            |             |             |             |             |            |              | 0.03              | 0.12              |
| <i>Haemophilus parainfluenzae</i><br>(6)     |                                             |       | 0 (0.0%) | 1 (16.7%)  | 3 (66.7%)   | 0 (66.7%)   | 1 (83.3%)  | 1 (100.0%) |            |            |             |             |             |             |            |              | 0.03              | --                |
| <i>Moraxella catarrhalis</i> (226)           |                                             |       |          | 37 (16.4%) | 36 (32.3%)  | 59 (58.4%)  | 74 (91.2%) | 19 (99.6%) | 1 (100.0%) |            |             |             |             |             |            |              | 0.06              | 0.12              |

<sup>a</sup> Organisms include: *Staphylococcus auricularis* (1), *S. capitis* (29), *S. caprae* (1), *S. cohnii* (1), *S. epidermidis* (277), *S. haemolyticus* (87), *S. hominis* (60), *S. intermedius* (1), *S. lugdunensis* (38), *S. pasteurii* (2), *S. pettenkoferi* (1), *S. saprophyticus* (7), *S. schleiferi* (1), *S. simulans* (6), *S. warneri* (14).

<sup>b</sup> Organisms include: *Streptococcus anginosus* (70), *S. anginosus* group (7), *S. bovis* group (1), *S. constellatus* (6), *S. cristatus* (4), *S. gallolyticus* (18), *S. gordonii* (4), *S. infantis* (4), *S. intermedius* (2), *S. lutetiensis* (1), *S. massiliensis* (1), *S. mitis* (8), *S. mitis* group (9), *S. mitis/oralis* (39), *S. mutans* (4), *S. oralis* (38), *S. parasanguinis* (15), *S. salivarius* (13), *S. salivarius* group (9), *S. sanguinis* (7), *S. vestibularis* (4).

<sup>c</sup> Organisms include: *Streptococcus agalactiae* (186), *S. dysgalactiae* (100), *S. pyogenes* (212).

<sup>d</sup> Organisms include: *Citrobacter amalonaticus* (4), *C. amalonaticus/farmeri* (1), *C. braakii* (7), *C. freundii* (72), *C. freundii* species complex (22), *C. koseri* (89), *C. werkmanii* (2), *C. youngae* (1), *Enterobacter aerogenes* (108), *E. asburiae* (13), *E. cancerogenus* (2), *E. cloacae* (269), *E. cloacae* species complex (105), *E. gergoviae* (3), *E. radicincitans* (1), *Escherichia coli* (2,123), *E. hermannii* (1), *E. vulneris* (1), *Hafnia alvei* (24), *Klebsiella oxytoca* (188), *K. pneumoniae* (853), *K. variicola* (7), *Morganella morganii* (133), *Pantoea agglomerans* (4), *Proteus mirabilis* (325), *P. penneri* (3), *P. vulgaris* (40), *Providencia rettgeri* (14), *P. stuartii* (15), *Raoultella ornithinolytica* (3), *R. planticola* (3), *Serratia liquefaciens* (11), *S. marcescens* (192), unspiciated *Cedecea* (1), unspiciated *Pantoea* (2), unspiciated *Raoultella* (4).

**Table 2**

Activity of ceftobiprole and comparator antimicrobial agents when tested against Gram-positive pathogens from Europe, Turkey, and Israel (2015).

| Organism (no.) Antimicrobial agent            | MIC <sub>50</sub> | MIC <sub>90</sub> | EUCAST <sup>a</sup> |                   |
|-----------------------------------------------|-------------------|-------------------|---------------------|-------------------|
|                                               |                   |                   | %S                  | %R                |
| <b><i>S. aureus</i> (2,588)</b>               |                   |                   |                     |                   |
| Ceftobiprole                                  | 0.5               | 2                 | 99.2                | 0.8               |
| Ceftaroline                                   | 0.25              | 1                 | 96.9                | 3.1               |
| Ceftriaxone                                   | 4                 | >8                | - <sup>b</sup>      | -                 |
| Clindamycin                                   | ≤0.25             | ≤0.25             | 91.6                | 8.1               |
| Daptomycin                                    | 0.25              | 0.5               | 100.0               | 0.0               |
| Erythromycin                                  | 0.25              | >8                | 71.4                | 27.2              |
| Gentamicin                                    | ≤1                | ≤1                | 94.7                | 5.3               |
| Levofloxacin                                  | 0.25              | >4                | 77.6                | 22.0              |
| Linezolid                                     | 1                 | 1                 | 100.0               | 0.0               |
| Oxacillin                                     | 0.5               | >2                | 77.6                | 22.4              |
| Tetracycline                                  | ≤0.5              | ≤0.5              | 92.2                | 7.7               |
| Tigecycline                                   | 0.06              | 0.12              | 100.0               | 0.0               |
| Trimethoprim-sulfamethoxazole                 | ≤0.5              | ≤0.5              | 99.8                | 0.1               |
| Vancomycin                                    | 0.5               | 1                 | 100.0               | 0.0               |
| <b>MRSA (579)</b>                             |                   |                   |                     |                   |
| Ceftobiprole                                  | 2                 | 2                 | 96.5                | 3.5               |
| Ceftaroline                                   | 1                 | 2                 | 86.2                | 13.8              |
| Ceftriaxone                                   | >8                | >8                | -                   | -                 |
| Clindamycin                                   | ≤0.25             | >2                | 68.6                | 31.3              |
| Daptomycin                                    | 0.25              | 0.5               | 100.0               | 0.0               |
| Erythromycin                                  | >8                | >8                | 30.3                | 68.0              |
| Gentamicin                                    | ≤1                | >8                | 85.7                | 14.3              |
| Levofloxacin                                  | >4                | >4                | 16.1                | 83.4              |
| Linezolid                                     | 1                 | 1                 | 100.0               | 0.0               |
| Tetracycline                                  | ≤0.5              | >8                | 85.8                | 14.2              |
| Tigecycline                                   | 0.12              | 0.12              | 100.0               | 0.0               |
| Trimethoprim-sulfamethoxazole                 | ≤0.5              | ≤0.5              | 99.3                | 0.3               |
| Vancomycin                                    | 0.5               | 1                 | 100.0               | 0.0               |
| <b>Coagulase-negative staphylococci (526)</b> |                   |                   |                     |                   |
| Ceftobiprole                                  | 0.5               | 2                 | -                   | -                 |
| Ceftaroline                                   | 0.25              | 1                 | -                   | -                 |
| Ceftriaxone                                   | >8                | >8                | -                   | -                 |
| Clindamycin                                   | ≤0.25             | >2                | 75.1                | 23.6              |
| Daptomycin                                    | 0.5               | 0.5               | 100.0               | 0.0               |
| Erythromycin                                  | >8                | >8                | 39.2                | 59.9              |
| Gentamicin                                    | ≤1                | >8                | 55.5                | 44.5              |
| Levofloxacin                                  | 2                 | >4                | 49.6                | 45.2              |
| Linezolid                                     | 0.5               | 1                 | 99.4                | 0.6               |
| Oxacillin                                     | >2                | >2                | 36.1                | 63.9              |
| Tetracycline                                  | ≤0.5              | >8                | 82.5                | 16.0              |
| Tigecycline                                   | 0.06              | 0.25              | 100.0               | 0.0               |
| Trimethoprim-sulfamethoxazole                 | ≤0.5              | >4                | 70.7                | 13.3              |
| Vancomycin                                    | 1                 | 2                 | 100.0               | 0.0               |
| <b><i>Enterococcus</i> spp. (646)</b>         |                   |                   |                     |                   |
| Ceftobiprole                                  | 0.5               | >4                | -                   | -                 |
| Ampicillin                                    | 1                 | >8                | 66.9                | 33.1              |
| Ceftaroline                                   | 2                 | >8                | -                   | -                 |
| Daptomycin                                    | 1                 | 2                 | -                   | -                 |
| Levofloxacin                                  | 2                 | >4                | 51.9                | 48.1 <sup>b</sup> |
| Linezolid                                     | 1                 | 2                 | 99.7                | 0.3               |
| Teicoplanin                                   | ≤2                | ≤2                | 94.0                | 6.0               |
| Tigecycline                                   | 0.06              | 0.12              | 100.0               | 0.0               |
| Vancomycin                                    | 1                 | 2                 | 93.2                | 6.8               |
| <b><i>Streptococcus pneumoniae</i> (833)</b>  |                   |                   |                     |                   |
| Ceftobiprole                                  | 0.015             | 0.5               | 99.3                | 0.7               |
| Ceftaroline                                   | ≤0.008            | 0.12              | 99.9                | 0.1               |
| Ceftriaxone                                   | 0.03              | 1                 | 86.4                | 0.7               |
| Clindamycin                                   | ≤0.12             | >1                | 82.2                | 17.8              |
| Erythromycin                                  | 0.03              | >2                | 75.0                | 24.8              |
| Imipenem                                      | ≤0.015            | 0.25              | 100.0               | 0.0               |
| Levofloxacin                                  | 1                 | 1                 | 98.1                | 1.9               |
| Linezolid                                     | 1                 | 1                 | 100.0               | 0.0               |
| Penicillin                                    | ≤0.06             | 2                 | 70.9                | 29.1 <sup>c</sup> |
|                                               |                   |                   | 70.9                | 4.0 <sup>d</sup>  |
| Tetracycline                                  | 0.25              | >4                | 76.1                | 23.5              |
| Trimethoprim-sulfamethoxazole                 | ≤0.5              | 4                 | 77.9                | 18.0              |
| Vancomycin                                    | 0.25              | 0.25              | 100.0               | 0.0               |
| <b>β-hemolytic streptococci (498)</b>         |                   |                   |                     |                   |
| Ceftobiprole                                  | 0.015             | 0.03              | -                   | -                 |
| Ceftaroline                                   | ≤0.008            | 0.015             | 100.0               | 0.0               |
| Ceftriaxone                                   | ≤0.03             | 0.06              | 100.0               | 0.0               |
| Clindamycin                                   | 0.06              | 0.25              | 90.6                | 9.4               |

(continued on next page)

Table 2 (continued)

| Organism (no.) Antimicrobial agent | MIC <sub>50</sub> | MIC <sub>90</sub> | EUCAST <sup>a</sup> |      |
|------------------------------------|-------------------|-------------------|---------------------|------|
|                                    |                   |                   | %S                  | %R   |
| Daptomycin                         | 0.12              | 0.25              | 100.0               | 0.0  |
| Erythromycin                       | ≤0.03             | 4                 | 83.3                | 15.9 |
| Levofloxacin                       | 0.5               | 1                 | 97.0                | 1.4  |
| Linezolid                          | 1                 | 1                 | 100.0               | 0.0  |
| Meropenem                          | ≤0.008            | 0.06              | 100.0               | 0.0  |
| Penicillin                         | ≤0.03             | 0.06              | 100.0               | 0.0  |
| Tetracycline                       | ≤0.25             | >8                | 52.8                | 47.0 |
| Vancomycin                         | 0.25              | 0.5               | 100.0               | 0.0  |
| <b>Viridans streptococci (264)</b> |                   |                   |                     |      |
| Ceftobiprole                       | 0.06              | 0.25              | -                   | -    |
| Ceftaroline                        | 0.015             | 0.06              | -                   | -    |
| Ceftriaxone                        | 0.12              | 0.5               | 92.4                | 7.6  |
| Clindamycin                        | ≤0.015            | 0.5               | 90.2                | 9.8  |
| Daptomycin                         | 0.25              | 0.5               | -                   | -    |
| Erythromycin                       | ≤0.03             | >4                | -                   | -    |
| Levofloxacin                       | 1                 | 2                 | -                   | -    |
| Linezolid                          | 0.5               | 1                 | -                   | -    |
| Meropenem                          | 0.03              | 0.25              | 100.0               | 0.0  |
| Penicillin                         | 0.06              | 1                 | 82.6                | 3.4  |
| Vancomycin                         | 0.5               | 0.5               | 100.0               | 0.0  |

<sup>a</sup> Criteria as published by EUCAST (EUCAST, 2017).<sup>b</sup> No interpretive criteria.<sup>c</sup> Meningitis breakpoints used.<sup>d</sup> Non-meningitis breakpoints used.

against *S. pneumoniae* (Table 2). Overall, penicillin non-susceptibility/resistance was 29.1/4.0% by EUCAST criteria (EUCAST, 2017). Furthermore, ceftriaxone non-susceptibility/resistance was 13.6/0.7% by EUCAST; ceftobiprole susceptibility was 94.7% against the 113 ceftriaxone non-susceptible strains (data not shown). Erythromycin, clindamycin, tetracycline, and trimethoprim-sulfamethoxazole resistances were 24.8%, 17.8%, 23.5%, and 18.0%, respectively.

### 3.4. Ceftobiprole activity against other streptococci

Ceftobiprole was active against all 498 isolates of  $\beta$ -hemolytic streptococci, with MIC<sub>50/90</sub> values at 0.015/0.03 mg/L. All isolates were inhibited at a ceftobiprole MIC ≤0.12 mg/L (Tables 1 and 2). All isolates were susceptible to penicillin, ceftaroline, ceftriaxone, daptomycin, linezolid, meropenem, and vancomycin. Levofloxacin resistance was 1.4% (applying EUCAST criteria). Resistance to erythromycin and clindamycin was 15.9 and 9.4%, respectively.

Ceftobiprole (MIC<sub>50/90</sub>, 0.06/0.25 mg/L) was 2-fold more active than ceftriaxone (MIC<sub>90</sub>, 0.5 mg/L) and 4-fold more active than penicillin (MIC<sub>50/90</sub>, 0.06/1 mg/L, 17.4% nonsusceptible) against 264 viridans-group streptococci (Table 2). Penicillin and levofloxacin resistances were 3.4% (14.0% intermediate by EUCAST criteria) and 2.7% (CLSI criteria), respectively. Resistance to clindamycin and erythromycin was 9.8% (EUCAST criteria) and 39.8% (CLSI criteria), respectively. Daptomycin (99.6% susceptible [CLSI criteria]), linezolid (100.0% susceptible [CLSI criteria]), and vancomycin (100.0% susceptible [EUCAST criteria]) showed the broadest coverage for this pathogen group.

### 3.5. Ceftobiprole activity against Enterobacteriaceae and non-fermentative Gram-negative bacilli

The activity of ceftobiprole against *Enterobacteriaceae* had a bimodal distribution, with 73.8% of isolates being inhibited at an MIC value ≤0.25 mg/L (the EUCAST susceptibility breakpoint) and 21.1% (978/4,646 isolates) having MIC values of ≥8 mg/L (Table 1). This susceptibility rate was comparable to EUCAST rates for cefepime (78.2%), piperacillin-tazobactam (81.7%), ceftazidime (74.2%), and ceftriaxone (73.3%); the EUCAST susceptibility rate for ceftaroline was lower, at 66.1% (Table 3). This pattern, shown for all cephalosporin agents tested, reflects the agents' limited activity against

extended-spectrum  $\beta$ -lactamase (ESBL) screen-positive strains of *Escherichia coli* and *Klebsiella* spp.

Susceptibility rates for *E. coli* (2,123 isolates, of which 467/2,123 [22.0%] were ESBL-screen positive, Table 1), are presented in Table 3. Against all isolates, meropenem (99.8% susceptible), imipenem (99.8% susceptible), and tigecycline (99.8% susceptible) were the most active agents tested (Table 3). Rates of *E. coli* resistance (applying EUCAST criteria) were 12.8%, 31.5%, and 36.9% for gentamicin, levofloxacin, and trimethoprim-sulfamethoxazole, respectively. Cefepime, ceftriaxone, ceftazidime, ceftaroline and ceftobiprole (Table 2) demonstrated bimodal activity against these strains (Tables 1 and 3). The *E. coli* MIC<sub>50/90</sub> values for ceftobiprole were 0.03/>16 mg/L, with 78.9% of isolates being susceptible.

Among the 467 *E. coli* isolates with the ESBL-phenotype, potencies for all agents tested were markedly decreased, with the exception of the carbapenems and tigecycline (data not shown). Ceftobiprole had limited activity (6.6% susceptible) against most ESBL-producers, in contrast to a susceptibility rate of 99.3% found against non-ESBL *E. coli* (Table 1).

Ceftobiprole activity against *Klebsiella pneumoniae* (853 isolates) is displayed in Tables 1 and 3. After tigecycline (93.0%), the carbapenems provided the best overall susceptibility rates (85.6%–86.8%) (EUCAST interpretive criteria). As observed for *E. coli*, the activity of ceftobiprole against *K. pneumoniae* was bimodal (Table 1), with MIC<sub>50/90</sub> values of 0.12/>16 mg/L. However, in contrast to *E. coli* (78.9% susceptible to ceftobiprole), and similar to other  $\beta$ -lactams, only 51.2% of *K. pneumoniae* were susceptible to ceftobiprole (Table 3). *K. pneumoniae* isolates showing an ESBL phenotype (49.4%, 421 isolates) displayed higher resistance rates against most antimicrobial agents tested (data not shown), including ceftobiprole (1.9% susceptible) (Table 1). Ceftobiprole was active however, against non-ESBL *K. pneumoniae* (432 isolates, 99.3% susceptible; Table 1).

In contrast to the *K. pneumoniae* results, ceftobiprole susceptibility was higher against 188 *K. oxytoca* isolates (65.4% vs. 51.2%, respectively; Table 1), because of the higher ESBL rate in *K. pneumoniae* (49.4%) compared to *K. oxytoca* (18.6%). Carbapenem susceptibility was also high for this group (100.0% by EUCAST criteria for meropenem and imipenem; data not shown).

Ceftobiprole activity against isolates of *Enterobacter* spp. (71.3% susceptible), *Citrobacter* spp. (83.8% susceptible), *Proteus mirabilis* (88.3%

**Table 3**

Activity of ceftobiprole and comparator antimicrobial agents when tested against Gram-negative pathogens from Europe, Turkey, and Israel (2015).

| Organism (no.)                               | Antimicrobial agent | MIC <sub>50</sub> | MIC <sub>90</sub> | EUCAST <sup>a</sup> |      |
|----------------------------------------------|---------------------|-------------------|-------------------|---------------------|------|
|                                              |                     |                   |                   | %S                  | %R   |
| <b><i>Haemophilus influenzae</i> (428)</b>   |                     |                   |                   |                     |      |
| Ceftobiprole                                 |                     | 0.03              | 0.12              | - <sup>b</sup>      | -    |
| Amoxicillin-clavulanic acid                  |                     | 0.5               | 2                 | 98.4                | 1.6  |
| Azithromycin                                 |                     | 0.5               | 1                 | 1.4                 | 0.2  |
| Cefepime                                     |                     | 0.06              | 0.12              | 99.5                | 0.5  |
| Ceftaroline                                  |                     | 0.008             | 0.015             | 98.6                | 1.4  |
| Ceftriaxone                                  |                     | ≤0.015            | ≤0.015            | 100.0               | 0.0  |
| Imipenem                                     |                     | 0.5               | 1                 | 97.4                | 2.6  |
| Levofloxacin                                 |                     | ≤0.015            | ≤0.015            | 100.0               | 0.0  |
| Piperacillin-tazobactam                      |                     | ≤0.015            | 0.03              | 98.4                | 1.6  |
| Tetracycline                                 |                     | 0.5               | 0.5               | 99.8                | 0.2  |
| Trimethoprim-sulfamethoxazole                |                     | 0.06              | >4                | 70.1                | 26.9 |
| <b><i>Enterobacteriaceae</i> (4,646)</b>     |                     |                   |                   |                     |      |
| Ceftobiprole                                 |                     | 0.03              | >16               | 73.8                | 26.2 |
| Aztreonam                                    |                     | ≤0.12             | >16               | 74.6                | 22.8 |
| Cefepime                                     |                     | 0.06              | >64               | 78.2                | 18.0 |
| Ceftaroline                                  |                     | 0.25              | >32               | 66.1                | 33.9 |
| Ceftazidime                                  |                     | 0.25              | >32               | 74.2                | 21.8 |
| Ceftriaxone                                  |                     | ≤0.06             | >8                | 73.3                | 26.0 |
| Gentamicin                                   |                     | 0.5               | >8                | 85.7                | 13.8 |
| Imipenem                                     |                     | ≤0.12             | 1                 | 96.3                | 1.4  |
| Levofloxacin                                 |                     | 0.06              | >4                | 73.6                | 24.5 |
| Meropenem                                    |                     | 0.03              | 0.06              | 97.1                | 1.9  |
| Piperacillin-tazobactam                      |                     | 2                 | 64                | 81.7                | 14.4 |
| Tigecycline                                  |                     | 0.25              | 1                 | 92.2                | 1.7  |
| Trimethoprim-sulfamethoxazole                |                     | ≤0.5              | >4                | 68.4                | 30.7 |
| <b><i>Escherichia coli</i> (2,123)</b>       |                     |                   |                   |                     |      |
| Ceftobiprole                                 |                     | 0.03              | >16               | 78.9                | 21.1 |
| Aztreonam                                    |                     | ≤0.12             | >16               | 78.8                | 18.9 |
| Cefepime                                     |                     | 0.06              | 64                | 79.5                | 17.0 |
| Ceftaroline                                  |                     | 0.12              | >32               | 72.2                | 27.8 |
| Ceftazidime                                  |                     | 0.25              | 16                | 79.7                | 15.5 |
| Ceftriaxone                                  |                     | ≤0.06             | >8                | 79.0                | 20.7 |
| Gentamicin                                   |                     | 0.5               | >8                | 87.1                | 12.8 |
| Imipenem                                     |                     | ≤0.12             | ≤0.12             | 99.8                | 0.0  |
| Levofloxacin                                 |                     | ≤0.03             | >4                | 68.0                | 31.5 |
| Meropenem                                    |                     | ≤0.015            | 0.03              | 99.8                | 0.1  |
| Piperacillin-tazobactam                      |                     | 2                 | 16                | 88.2                | 8.5  |
| Tigecycline                                  |                     | 0.12              | 0.25              | 99.8                | 0.0  |
| Trimethoprim-sulfamethoxazole                |                     | ≤0.5              | >4                | 62.4                | 36.9 |
| <b><i>Klebsiella pneumoniae</i> (853)</b>    |                     |                   |                   |                     |      |
| Ceftobiprole                                 |                     | 0.12              | >16               | 51.2                | 48.8 |
| Aztreonam                                    |                     | 0.25              | >16               | 52.1                | 46.9 |
| Cefepime                                     |                     | 0.25              | >64               | 53.5                | 45.0 |
| Ceftaroline                                  |                     | 2                 | >32               | 48.5                | 51.5 |
| Ceftazidime                                  |                     | 1                 | >32               | 51.3                | 47.0 |
| Ceftriaxone                                  |                     | 0.25              | >8                | 51.9                | 47.6 |
| Gentamicin                                   |                     | 0.25              | >8                | 72.8                | 27.0 |
| Imipenem                                     |                     | ≤0.12             | 8                 | 86.8                | 7.6  |
| Levofloxacin                                 |                     | 0.5               | >4                | 62.0                | 34.9 |
| Meropenem                                    |                     | 0.03              | 8                 | 85.6                | 9.7  |
| Piperacillin-tazobactam                      |                     | 4                 | >128              | 61.3                | 32.9 |
| Tigecycline                                  |                     | 0.25              | 1                 | 93.0                | 0.8  |
| Trimethoprim-sulfamethoxazole                |                     | ≤0.5              | >4                | 56.9                | 42.0 |
| <b><i>Pseudomonas aeruginosa</i> (1,064)</b> |                     |                   |                   |                     |      |
| Ceftobiprole                                 |                     | 2                 | >16               | -                   | -    |
| Amikacin                                     |                     | 4                 | 32                | 84.2                | 10.2 |
| Aztreonam                                    |                     | 4                 | >16               | 5.7                 | 16.6 |
| Cefepime                                     |                     | 2                 | 16                | 82.6                | 17.4 |
| Ceftaroline                                  |                     | 16                | >32               | -                   | -    |
| Ceftazidime                                  |                     | 2                 | 32                | 77.0                | 23.0 |
| Colistin                                     |                     | ≤0.5              | 1                 | 99.9                | 0.1  |
| Gentamicin                                   |                     | 2                 | >8                | 78.8                | 21.2 |
| Imipenem                                     |                     | 1                 | >8                | 72.4                | 13.8 |
| Levofloxacin                                 |                     | 0.5               | >4                | 60.9                | 30.8 |
| Piperacillin-tazobactam                      |                     | 4                 | >64               | 72.9                | 27.1 |
| Trimethoprim-sulfamethoxazole                |                     | 4                 | >4                | -                   | -    |

<sup>a</sup> Criteria as published by EUCAST (EUCAST, 2017).

<sup>b</sup> No interpretive criteria.

susceptible), indole-positive *Proteus* spp. (78.2% susceptible), and *Serratia* spp. (91.6% susceptible) was generally comparable to activity of other advanced-spectrum cephalosporins (applying EUCAST criteria; Table 1 and data not shown).

The potency of ceftobiprole against *Pseudomonas aeruginosa* (MIC<sub>50/90</sub>, 2/>16 mg/L; 70.4% susceptible by EUCAST non-species specific susceptibility breakpoint of 4 mg/L) was comparable to those of cefepime (MIC<sub>50/90</sub>, 2/16 mg/L; 82.6% susceptible) and ceftazidime (MIC<sub>50/90</sub>, 2/32 mg/L; 77.0% susceptible) (Table 3). Notably, the activity of ceftobiprole against *P. aeruginosa* is not predictive for ceftazidime and vice versa, as 22% of ceftazidime-resistant isolates showed MIC values of <4 mg/L for ceftobiprole and 39.4% of isolates for which the ceftobiprole MIC was >4 mg/L were susceptible to ceftazidime. Ceftobiprole had limited activity against *Acinetobacter* spp. (MIC<sub>50</sub>, >16 mg/L; 23.6% with an MIC ≤4 mg/L) and *Stenotrophomonas maltophilia* (MIC<sub>50</sub>, >16 mg/L) (Table 1).

### 3.6. Ceftobiprole activity against *Haemophilus* spp. and *M. catarrhalis*

Ceftobiprole exhibited potent activity against *Haemophilus influenzae* (MIC<sub>90</sub>, 0.12 mg/L) and *Haemophilus parainfluenzae* (MIC<sub>50</sub>, 0.03 mg/L) by inhibiting all isolates at ≤0.5 mg/L (Table 1). Ceftobiprole was also very active against *Moraxella catarrhalis* with MIC<sub>50/90</sub> values of 0.06/0.12 mg/L; all isolates were inhibited at MIC values of ≤0.5 mg/L (Table 1).

## 4. Conclusions

The in vitro results from an extensive European surveillance study evaluating 12,240 isolates confirm earlier reports on the broad-spectrum activity of ceftobiprole against both Gram-positive and Gram-negative pathogens. Specifically, these results complement findings from an extensive European study conducted by Rossolini et al. (Rossolini, et al., 2011) in 2008 and 2009 and from the European SENTRY Program from 2005 through 2010 (Farrell et al., 2014). When compared to the earlier studies, the data reported here are comparable for ceftobiprole with respect to the target pathogens, supporting previous reports that ceftobiprole may have a low propensity for resistance development (Bogdanovich et al., 2005; Chan et al., 2015; Davies et al., 2007). Ceftobiprole offers several advantages in terms of potency, spectrum, and β-lactamase stability when compared to third-generation cephalosporins and other β-lactams, especially with its enhanced coverage of *E. faecalis*, *S. aureus* and CoNS, including methicillin-resistant strains. The unique spectrum of this agent is especially promising (Liapikou et al., 2015) given its current indications for its use in Europe and several non-European countries to treat CAP and HAP (excluding VAP) and the potential for using this agent in infections where Gram-positive and Gram-negative pathogens may be present.

In conclusion, the activity of ceftobiprole against target pathogens in Europe has not changed in over a decade of in vitro surveillance encompassing 18 countries. Increasing multidrug-resistance (resistance to >3 different classes of agents) has complicated empirical antibiotic therapy, especially in patients with risk factors for AMR pathogens, often necessitating a combination therapy approach (Cosgrove, 2006; Nicholson et al., 2012). Monotherapy has been recommended whenever possible to reduce the risk of multidrug-resistance development and adverse outcomes (Brogan and Mossialos, 2013; Cosgrove, 2006; Laxminarayan et al., 2016; Spellberg et al., 2008). In this study, ceftobiprole exhibited excellent coverage of Gram-positive pathogens, including MRSA and PRSP, and has a spectrum of activity against Gram-negative bacilli comparable to third- and fourth-generation cephalosporins.

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