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Comparative activity of ceftobiprole against Gram-positive and Gram-negative isolates from Europe and the Middle East: the CLASS study

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Objectives: To assess the *in vitro* activity of ceftobiprole and comparators against a recent collection of Gram-positive and Gram-negative pathogens, in order to detect potential changes in susceptibility patterns, and to evaluate the Etest assay for ceftobiprole susceptibility testing.

Methods: Contemporary Gram-positive and Gram-negative isolates (excluding extended-spectrum β-lactamase-producing isolates) from across Europe and the Middle East were collected, and their susceptibility to ceftobiprole, vancomycin, teicoplanin, linezolid, ceftazidime and cefepime was assessed using the Etest method. Quality testing [using Etest and broth microdilution (BMD)] was conducted at a central reference laboratory.

Results: Some 5041 Gram-positive and 4026 Gram-negative isolates were included. Against Gram-positive isolates overall, ceftobiprole had the lowest MIC_{50} (0.5 mg/L), compared with 1 mg/L for its comparators (vancomycin, teicoplanin and linezolid). Against methicillin-resistant *Staphylococcus aureus*, all four agents had a similar MIC_{90} (2 mg/L), but ceftobiprole had a 4-fold better MIC_{90} (0.5 mg/L) against methicillin-susceptible strains. Only 38 Gram-positive isolates were confirmed as ceftobiprole resistant. Among Gram-negative strains, 86.9%, 91.7% and 95.2% were susceptible to ceftobiprole, ceftazidime and cefepime, respectively. *Pseudomonas aeruginosa* was less susceptible to all three antimicrobials than any other Gram-negative pathogen. There was generally good agreement between local Etest results and those obtained at the reference laboratory (for ceftobiprole: 86.8% with Gram-negatives; and 94.7% with Gram-positives), as well as between results obtained by BMD and Etest methods (for ceftobiprole: 98.2% with Gram-negatives; and 98.4% with Gram-positives).

Conclusions: Ceftobiprole exhibits *in vitro* activity against a wide range of Gram-positive and Gram-negative pathogens, including multidrug-resistant strains. No changes in its known susceptibility profile were identified.

Keywords: cephalosporins, MRSA, Etest, broad spectrum, surveillance

Introduction

Ceftobiprole is a novel cephalosporin with bactericidal activity against a wide range of clinically relevant pathogens. Its broad *in vitro* spectrum encompasses both Gram-positive and most Gram-negative bacteria, including methicillin-susceptible *Staphylococcus aureus* (MSSA), methicillin-resistant *S. aureus* (MRSA), community-acquired (CA)-MRSA, vancomycin-resistant *S. aureus*, methicillin-resistant coagulase-negative staphylococci (MR-CoNS), penicillin-resistant *Streptococcus pneumoniae* (PRSP), *Enterococcus faecalis*, *Clostridium perfringens*, *Pseudomonas aeruginosa* and ~85% of Enterobacteriaceae. Ceftobiprole has only moderate activity against *Acinetobacter* spp. and is not active against *Proteus vulgaris*, ceftazidime-non-susceptible *P. aeruginosa*, *Bacteroides* spp. and

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some extended-spectrum β-lactamase (ESBL)-producing isolates.[1–8] Ceftobiprole has been evaluated in Phase II and Phase III clinical studies, particularly in complicated skin and skin-structure infections (cSSSIs; including diabetic foot infection) and nosocomial pneumonia,[9] due to both Gram-positive and Gram-negative pathogens. Antimicrobial surveillance studies are essential not only to support continuing clinical development of ceftobiprole, but also to detect potential changes in susceptibility patterns. Furthermore, it is necessary to evaluate local pathogen susceptibility to ceftobiprole in comparison with the general activity of this agent. These aspects become particularly important when considering that ceftobiprole is likely to be used in a clinical environment in which multidrug-resistant (MDR) bacteria are already common; thus, further emphasizing the importance of continued monitoring of ceftobiprole activity.[5]

An Etest assay for ceftobiprole susceptibility testing has recently been developed. While this approach constitutes a fairly rapid and simple assessment methodology, its use in the clinical setting remains to be validated through prospective studies.

To address these issues, the Ceftobiprole Local Antibiotic Susceptibility Surveillance (CLASS) study evaluated the *in vitro* activity of ceftobiprole and comparator antimicrobials against selected Gram-positive and Gram-negative, contemporary, clinical isolates from a large number of centres across Europe and the Middle East, employing the Etest method at the participating study sites. Quality control and additional susceptibility testing were conducted at a central reference laboratory to verify the robustness of the locally collected data.

Materials and methods

Clinical isolates were collected in two regional phases of identical design from a total of 108 centres in 19 countries across Europe and the Middle East between May 2008 and June 2009. Participating countries comprised Austria (2 centres), Bulgaria (2 centres), the Czech Republic (1 centre), Egypt (1 centre), France (9 centres), Germany (12 centres), Greece (3 centres), Ireland (1 centre), Israel (2 centres), Italy (14 centres), Poland (5 centres), Portugal (3 centres), Russia (10 centres), Slovakia (1 centre), Switzerland (4 centres), Spain (17 centres), the Netherlands (3 centres), Turkey (10 centres) and the UK (8 centres). The specific period of isolate collection varied between centres, depending on which study phase the respective country participated in and when the individual centre was initiated into the study. Pathogens were isolated from hospitalized patients (including intensive care unit patients) with bloodstream infections, cSSSIs and nosocomial pneumonia (including ventilator-associated pneumonia). Isolates from urinary tract infections were not collected. Centres determined the susceptibility of isolates to ceftobiprole and comparator agents using Etest strips following the manufacturer's guidelines and established susceptibility breakpoints;[10,11] the breakpoints for ceftobiprole were recommended by the study sponsor based on previous data. Breakpoints used to determine the susceptibility of isolates to ceftobiprole and comparator agents are shown in Tables 1 and 2. For analysis purposes, each Etest MIC was rounded up to the nearest doubling dilution.

The *in vitro* activity of ceftobiprole against Gram-positive pathogens was compared with that of vancomycin, teicoplanin and linezolid. Each centre aimed to collect a target of 55 Gram-positive isolates, including 3–10 MSSA and 6–12 MRSA isolates per centre. Other Gram-positive species that were permitted for inclusion into the study were: methicillin-susceptible (MS) CoNS (target: 3–10 isolates) and MR-CoNS (target: 6–12 isolates); vancomycin-resistant (target: 1–5 isolates) and vancomycin-susceptible *E. faecalis* (target: 3–10 isolates); MDR *S. pneumoniae* (resistant to two or more of the following antibiotics: penicillin; second-generation cephalosporins; macrolides; tetracyclines; and trimethoprim/sulfamethoxazole) or PRSP (target: 3–10 isolates); *Streptococcus* spp. of groups A, B, C and G (target: 1–5 isolates per group); and 'viridans group' streptococci (target: 3–10 isolates).

The *in vitro* activity of ceftobiprole against Gram-negative pathogens was compared with that of cefepime and ceftazidime. Each centre aimed to collect a target of 45 Gram-negative isolates from the following pathogens: *Haemophilus influenzae* (target: 3–10 isolates per centre); *Escherichia coli* (target: 6–12 isolates); *Klebsiella pneumoniae* (target: 3–10 isolates); *Enterobacter* spp. (target: 3–10 isolates); and *P. aeruginosa* (target: 3–10 isolates). Isolates that were confirmed ESBL producers were excluded.

Isolates were sent in one batch from each collecting centre to Quotient Bioresearch (Microbiology) Ltd (Fordham, UK) and stored at −70°C in undiluted horse serum. At this central reference laboratory, confirmation of species identification and a quality-control check of the centres' Etest results were conducted. For this quality-control check, the MICs of ceftobiprole and comparators agents were retested for all isolates found resistant to any of the study agents at the collecting centre and for 10% of all non-resistant isolates (randomly selected) from each centre. Retesting was conducted by both broth microdilution (BMD) and Etest, using standardized methodologies.[10,12]

Isolates that were obtained from patients with infections other than those defined in the protocol, that were repeat isolates from a single patient or that were not submitted with the required clinical and demographic data specified in the protocol (where permitted by local

Table 1. Susceptibility breakpoints (in mg/L) for ceftobiprole (manufacturer recommendation) and comparator antibiotics (from CLSI M100-S19[11]) against Gram-positive pathogens evaluated in this study

	Ceftobiprole			Vancomycin			Linezolid			Teicoplanin		
	S	I	R	S	I	R	S	I	R	S	I	R
S. aureus	≤4	—	≥8	≤2	4–8	≥16	≤4	—	—	≤8	16	≥32
CoNS	≤4	—	≥8	≤4	8–16	≥32	≤4	—	—	≤8	16	≥32
E. faecalis	≤2	4	≥8	≤4	8–16	≥32	≤2	4	≥8	≤8	16	≥32
S. pneumoniae	≤2	4	≥8	≤1	—	—	≤2	—	—	—	—	—
β-Haemolytic streptococci	≤0.5	—	≥1	≤1	—	—	≤2	—	—	—	—	—
Viridans group streptococci	≤0.5	—	≥1	≤1	—	—	≤2	—	—	—	—	—

S, susceptible; I, intermediate susceptible; R, resistant.

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Table 2. Susceptibility breakpoints (in mg/L) for ceftobiprole (manufacturer recommendation) and comparator antibiotics (from CLSI M100-S19[11]) against Gram-negative pathogens evaluated in this study

	Ceftobiprole			Ceftazidime			Cefepime		
	S	I	R	S	I	R	S	I	R
Enterobacteriaceae	≤1	2–4	≥8	≤8	16	≥32	≤8	16	≥32
H. influenzae	≤2	4	≥8	≤2	—	—	≤2	—	—
P. aeruginosa	≤4	—	≥8	≤8	16	≥32	≤8	16	≥32

S, susceptible; I, intermediate susceptible; R, resistant.

regulations) were excluded from the study. Isolates that were non-viable on arrival at the central reference laboratory or were subcultured but subsequently non-viable and were not available again from the collecting centre were also excluded, as were isolates that did not belong to the protocol-defined Gram-positive or Gram-negative target species or that were confirmed to be ESBL producers. All Gram-negative isolates that had both ceftobiprole and ceftazidime MICs of ≥2 mg/L confirmed by the central reference laboratory were retrospectively tested at the reference laboratory to identify any potential ESBL producers that may have been originally misidentified as ESBL-negative isolates at the collecting centre. ESBL screening was carried out using recommended screening agents (cefotaxime, cefotaxime/clavulanate, ceftazidime, ceftazidime/clavulanate, ceftriaxone and ceftriaxone/clavulanate), in addition to performing an extended antibiogram (with ceftobiprole, ceftobiprole/clavulanate, cefepime, cefepime/clavulanate, ciprofloxacin, levofloxacin, imipenem, doripenem, meropenem and tigecycline) for each isolate by BMD using standardized methods.[11,12] All ESBL-positive isolates thus identified were excluded from the analyses.

Results

Gram-positive organisms

A total of 5041 eligible Gram-positive isolates were included in the study. The majority of these were obtained from patients with bloodstream infections (46.2%) or cSSSIs (43.9%); the remainder were from patients with nosocomial pneumonia (9.9%). Of these isolates, 39.4% were *S. aureus* (50.7% of which were MRSA), 23.9% were CoNS (66.7% of which were methicillin-resistant), 23.1% were streptococci and 13.6% were *E. faecalis* (4.4% of which were vancomycin-resistant). Of the 1207 CoNS isolates, 61.9% were *Staphylococcus epidermidis*, 12.2% were *Staphylococcus haemolyticus*, 12.1% were *Staphylococcus hominis*, 5.5% were *Staphylococcus capitis*, 3.2% were *Staphylococcus warnerii*, 1.7% were *Staphylococcus lugdunensis* and <1% of each were *Staphylococcus simulans*, *Staphylococcus xylosus*, *Staphylococcus caprae*, *Staphylococcus saprophyticus*, *Staphylococcus cohnii*, *Staphylococcus schleiferi*, *Staphylococcus kloosii*, *Staphylococcus sciuri* or *Staphylococcus equorum*. A total of 101 *S. pneumoniae* isolates were collected, 37.6% of which were MDR, with the remainder identified as PRSP (i.e. penicillin MIC ≥0.12 mg/L). Other collected streptococcal isolates included β-haemolytic streptococci (n=757) and viridans group streptococci (n=304; 49.7% of which were *Streptococcus mitis*, 17.4% *Streptococcus constellatus*, 12.2% *Streptococcus oralis*, 7.9% *Streptococcus salivarius*, 6.3% *Streptococcus bovis*, 3.0% *Streptococcus sanguinis*, 1.3% *Streptococcus equinus* and <1% each of *Streptococcus intermedius*, *Streptococcus dysgalactiae*, *Streptococcus anginosus* or *Streptococcus thermophillus*).

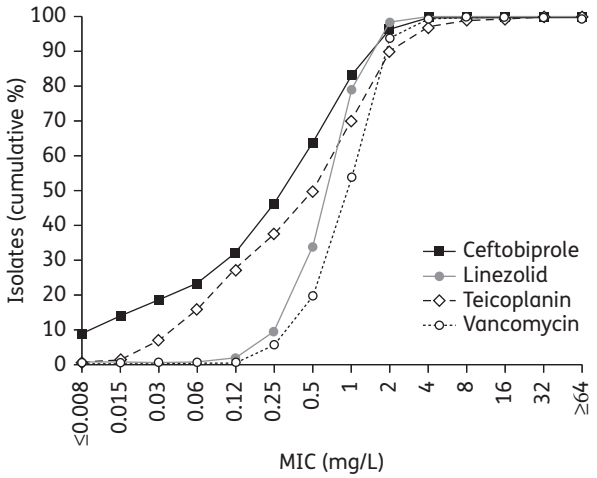

Figure 1. Cumulative percentage MIC distribution of ceftobiprole in comparison with vancomycin, linezolid and teicoplanin against Gram-positive isolates overall.

There was low overall resistance to all study antibiotics among Gram-positive isolates. In total, only 86 (1.7%) isolates were resistant to at least one of ceftobiprole, vancomycin, teicoplanin or linezolid, based on the Etest results obtained at the respective study centres. Against Gram-positive isolates combined, all four antibiotics had MICs in the range ≤0.008 to ≥64 mg/L and all had an MIC_{90} of 2 mg/L. Ceftobiprole had the lowest MIC_{50} (0.5 mg/L), compared with 1 mg/L for vancomycin, teicoplanin and linezolid (Figure 1). Against *S. aureus* isolates, all agents had an MIC_{90} of 2 mg/L, while the ceftobiprole MIC_{50} (0.5 mg/L) was 2-fold lower than that of its comparators (all 1 mg/L). Figure 2(a) shows the cumulative MIC distributions of the four agents, indicating that ceftobiprole was more active than linezolid and the glycopeptides against the *S. aureus* isolates collected in this study. Against MRSA, ceftobiprole had similar activity to vancomycin, teicoplanin and linezolid, with an MIC_{50} of 1 mg/L and an MIC_{90} of 2 mg/L. However, against MSSA, the MIC_{90} of ceftobiprole was 0.5 mg/L, compared with 2 mg/L for the other three agents. Among *S. aureus* isolates, 847 (42.7%) had a vancomycin MIC of ≥2 mg/L; 806 (40.6%) of these had an MIC of 2 mg/L and 41 (2.1%) had an MIC of 4 mg/L. Seven of these vancomycin-intermediate *S. aureus* isolates were retested at the central reference laboratory due to reported resistance to one of the other study antibiotics, and were actually found vancomycin susceptible through both Etest and BMD methods. Ceftobiprole was as effective against isolates with a vancomycin MIC of ≥2 mg/L as it was against those isolates with a vancomycin MIC of <2 mg/L (Figure 2b). For *S. aureus* isolates with a vancomycin MIC of ≥2 mg/L, ceftobiprole, teicoplanin and linezolid all showed similar activity against MRSA; however, against MSSA, ceftobiprole was more active than the other two agents.

Ceftobiprole was slightly less active than linezolid ($MIC_{50/90}$=1/2 mg/L and 0.5/1 mg/L, respectively) against MR-CoNS, but was 2- to 4-fold more active than linezolid against MS-CoNS ($MIC_{50/90}$=0.12/0.5 mg/L and 0.5/1 mg/L,

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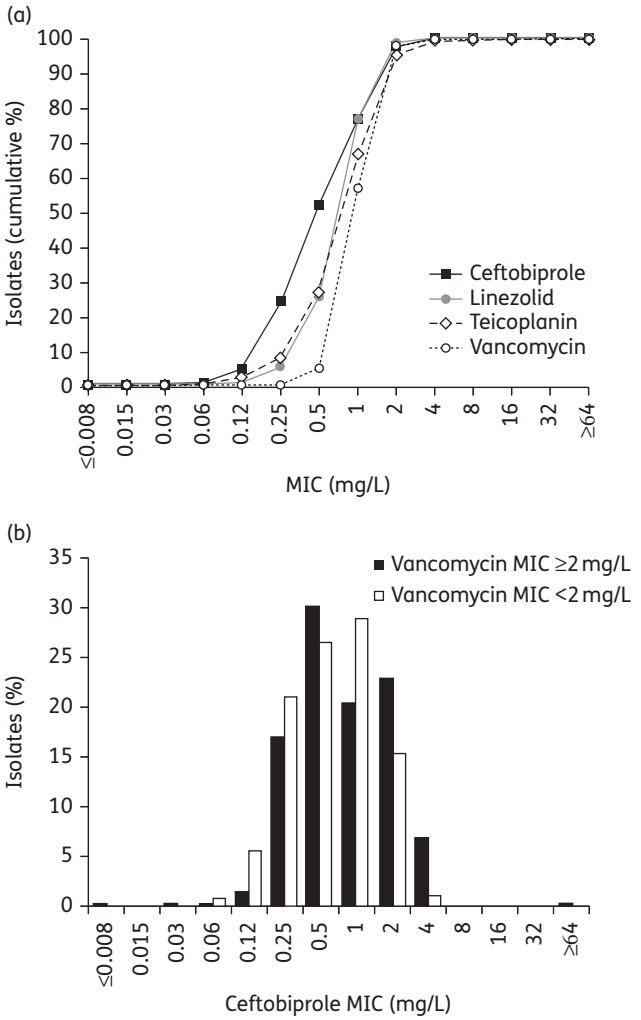

Figure 2. Activity of ceftobiprole against *S. aureus* in comparison with other antibiotics (a) and against *S. aureus* strains according to vancomycin MIC (b).

respectively). Vancomycin and teicoplanin were 2- to 4-fold less active than linezolid and 4- to 8-fold less active than ceftobiprole against both MR- and MS-CoNS. Five staphylococcal isolates (one MRSA and four CoNS) were reported as linezolid non-susceptible and confirmed as such by the central reference laboratory, with respective MICs ranging from 8 to >16 mg/L, as determined by BMD; all of these isolates were found susceptible to ceftobiprole and vancomycin. Three of the four CoNS were from Spain and one was from Italy, and all were from separate centres.

Against *E. faecalis*, ceftobiprole and teicoplanin had similar activity, with $MIC_{50/90}$ values of 0.25/2 mg/L, compared with 2/2 mg/L for linezolid and 2/4 mg/L for vancomycin. Against the β-haemolytic streptococci, ceftobiprole ($MIC_{50/90}$= 0.008/0.03 mg/L) was the most active of the four agents (0.06/0.25 mg/L for teicoplanin, 0.5/1 mg/L for vancomycin and 1/2 mg/L for linezolid).

Against *S. pneumoniae*, ceftobiprole ($MIC_{50/90}$=0.25/0.5 mg/L) was less active than teicoplanin ($MIC_{50/90}$=0.06/0.12 mg/L), but was 2-fold more active than both vancomycin and linezolid based on $MIC_{50/90}$ values. Against the viridans group streptococci, ceftobiprole, linezolid and vancomycin had an MIC_{90} of 1 mg/L, whereas teicoplanin had an MIC_{90} of 0.25 mg/L. However, the respective MIC_{50} of ceftobiprole (0.03 mg/L) was 2-fold lower than that of teicoplanin (0.06 mg/L), and 16-fold lower than both vancomycin and linezolid. Ceftobiprole had the lowest MIC of the four agents against ~70% of viridans group streptococci.

Table 3 shows the non-susceptibility rates of Gram-positive isolates to each study antibiotic, as reported by the participating centres. A total of 57 isolates were originally found resistant to ceftobiprole: 31 (54.4%) of these belonged to the viridans group streptococci (mostly *S. mitis*); 18 (31.6%) were *E. faecalis*; 4 (7.0%) were β-haemolytic streptococci; 3 (5.3%) were methicillin-resistant CoNS; and 1 (1.8%) was MRSA. Two of the ceftobiprole-resistant isolates (both enterococci) were also resistant to vancomycin and teicoplanin. Notably, only 1 of 1985 *S. aureus* and 2 of 1207 CoNS isolates were reported as ceftobiprole resistant (i.e. MIC >4 mg/L); the central reference laboratory confirmed ceftobiprole resistance for only one of these isolates

Table 3. Proportion of isolates non-susceptible (i.e. either resistant or intermediate susceptible) to the study antibiotics among 5041 Gram-positive isolates, as determined by Etest at the study centres

	Ceftobiprole non-susceptible	Vancomycin non-susceptible	Teicoplanin non-susceptible	Linezolid non-susceptible
S. aureus (*n*=1985)	<0.1%	2.1%	0.1%	<0.1%
methicillin resistant (*n*=1007)	0.1%	2.5%	0.2%	0.1%
methicillin susceptible (*n*=978)	0.0%	1.6%	<0.1%	0.0%
CoNS (*n*=1207)	0.2%	0.7%	2.8%	0.3%
methicillin resistant (*n*=805)	0.4%	1.0%	3.8%	0.5%
methicillin susceptible (*n*=402)	0.0%	0.2%	0.7%	0.0%
S. pneumoniae (*n*=101)	0.0%	1.0%	NA	0.0%
β-Haemolytic streptococci (*n*=757)	0.5%	2.6%	NA	1.2%
Viridans group streptococci (*n*=304)	10.2%	6.9%	NA	0.0%
E. faecalis (*n*=687)	2.6%	4.8%	3.6%	4.1%

NA, not applicable.

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Table 4. Proportion of isolates non-susceptible (i.e. either resistant or intermediate susceptible) to the study antibiotics among 4026 Gram-negative isolates (ESBL-positives excluded), as determined by Etest at the study centres

	Ceftobiprole non-susceptible	Ceftazidime non-susceptible	Cefepime non-susceptible
Enterobacteriaceae ($n=2560$)	4.9%	6.1%	1.0%
E. coli ($n=1139$)	1.8%	1.2%	0.4%
K. pneumoniae ($n=686$)	3.1%	2.2%	0.9%
Enterobacter spp. ($n=735$)	11.6%	17.4%	2.2%
H. influenzae ($n=404$)	0.2%	0.2%	0.0%
P. aeruginosa ($n=1062$)	37.6%	16.6%	15.6%

(i.e. an *S. capitis* isolate from Italy). Ceftobiprole resistance could not be confirmed by the central reference laboratory for 19 isolates, 17 of which were actually found to be ceftobiprole susceptible. Of the 28 vancomycin-resistant isolates (all vancomycin-resistant enterococci), 24 (85.7%) were susceptible to ceftobiprole.

Gram-negative organisms

Of all collected Gram-negative isolates, 4026 were eligible for inclusion into the study; a total of 214 isolates were retrospectively identified as ESBL-positive at the central reference laboratory and, therefore, excluded. More isolates were obtained from patients with bloodstream infections (40.2%) than with cSSSIs (29.6%) or nosocomial pneumonia (30.2%). Species distribution was as follows: *E. coli*, 28.3%; *P. aeruginosa*, 26.4%; *K. pneumoniae*, 17.0%; *Enterobacter* spp., 18.3%; and *H. influenzae*, 10.0%. The most frequently collected *Enterobacter* spp. were *Enterobacter cloacae* (81.1%) and *Enterobacter aerogenes* (15.9%); the remaining species were isolated at a frequency of $<2\%$.

The majority of isolates (86.9%) were susceptible to ceftobiprole (excluding ESBL-positive isolates), compared with 91.7% to ceftazidime and 95.2% to cefepime. *P. aeruginosa* was less susceptible to all three antimicrobials than any other Gram-negative pathogen group (Table 4). Against Gram-negative pathogens combined (excluding ESBL-positive isolates), the MIC_{50} for ceftobiprole and cefepime was lower (0.06 mg/L) than that for ceftazidime (0.25 mg/L). Cefepime had the lowest MIC_{90} (4 mg/L), compared with ceftobiprole and ceftazidime (8 mg/L) (Figure 3). Comparative activities against Enterobacteriaceae, *K. pneumoniae* and *P. aeruginosa* are shown in Figure 4. Based on the centre Etest results, 13.7% of the Gram-negative isolates were resistant to at least one of the comparator antibiotics: 11.5% of isolates were resistant to ceftobiprole; 6.0% to ceftazidime; and 2.6% to cefepime, respectively.

Of the 465 ceftobiprole-resistant isolates (11.5% of all Gram-negative bacteria collected), 16.1% were also resistant to both ceftazidime and cefepime, 17.6% were resistant to ceftazidime but not to cefepime, and 4.7% were resistant to cefepime but not to ceftazidime. *P. aeruginosa* and Enterobacteriaceae (mainly *Enterobacter* spp.) comprised 85.8% and 13.8%, respectively, of the ceftobiprole-resistant species collected in this study. Overall, 266 isolates were deemed to be resistant to ceftazidime and/or cefepime. Of these, 29.3% were resistant to both ceftazidime and cefepime, 65.0% were resistant to ceftazidime only, and 9.4% were resistant to cefepime only.

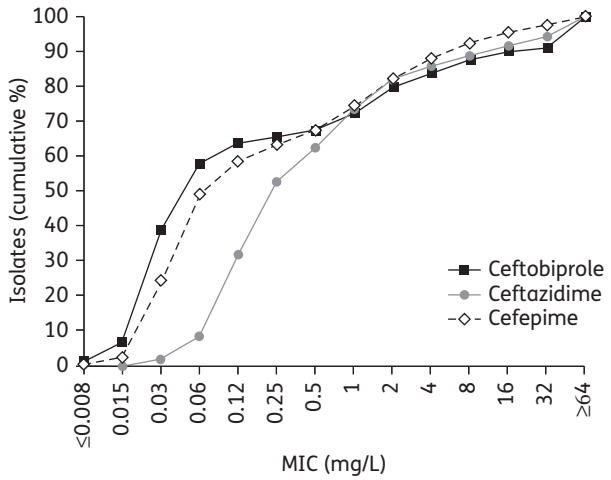

Figure 3. Cumulative percentage MIC distribution of ceftobiprole in comparison with ceftazidime and cefepime against Gram-negative pathogens overall.

Etest validation

A total of 619 Gram-positive isolates were selected for quality-control purposes. Overall, there was generally good agreement between Etest susceptibility results from the study sites and those obtained at the central reference laboratory: 94.7% for ceftobiprole; 91.9% for vancomycin; 95.8% for teicoplanin; and 97.3% for linezolid. Notably, Etest MICs at the study centres were the same or within one doubling dilution of the reference laboratory MIC in 88.4% of cases. Centres falsely interpreted 14% of ceftobiprole non-susceptible isolates as susceptible. Conversely, centres also incorrectly interpreted some susceptible isolates as non-susceptible; this was the case for 4.0% of ceftobiprole, 8.1% of vancomycin and 2.0% of teicoplanin and linezolid non-susceptible isolates. There was also a high correlation between susceptibility results obtained by BMD and Etest methods when conducted at the central reference laboratory. Agreement in the susceptibility category between the two methodologies was 98.4% for ceftobiprole, 99.7% for vancomycin, 98.4% for teicoplanin and 99.5% for linezolid.

Similar observations were made for the Gram-negative quality-control isolates ($n=929$). Again, there was generally good agreement between Etest susceptibility results from the study sites and those obtained at the central reference laboratory: 86.8% for ceftobiprole; 85.6% for ceftazidime; and 82.7%

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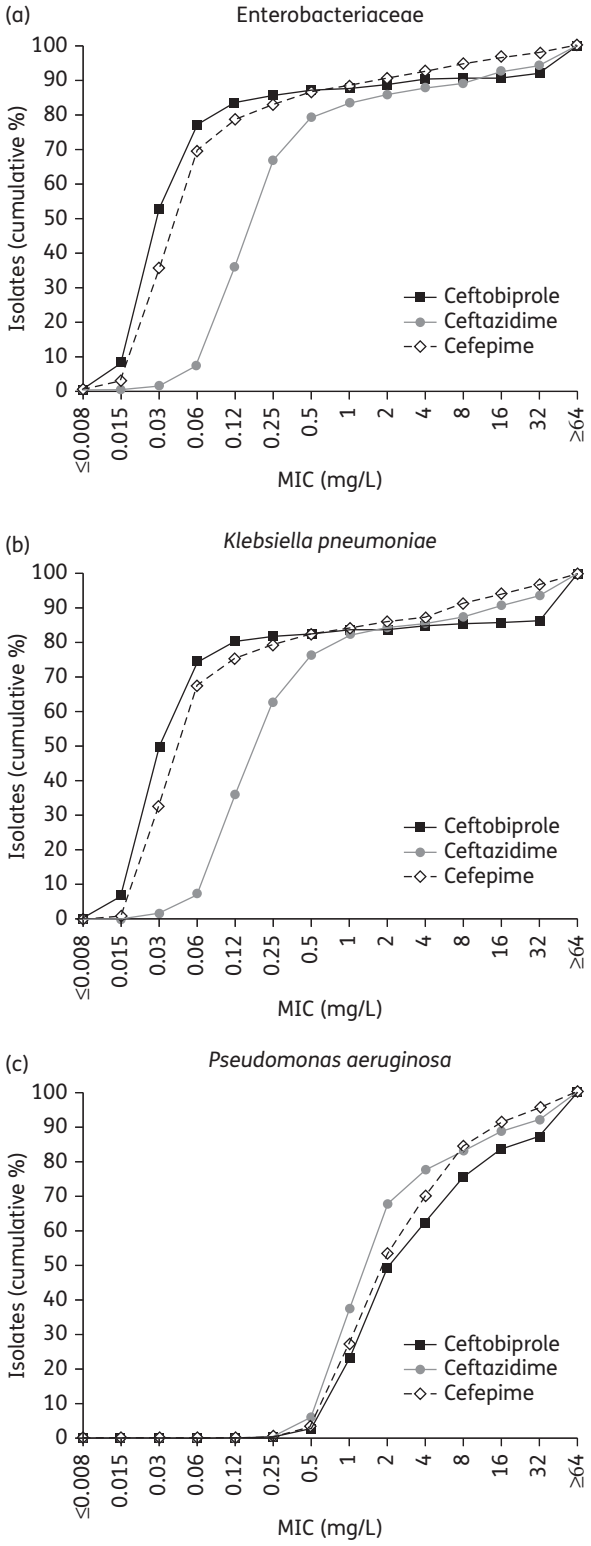

Figure 4. Cumulative percentage MIC distribution of ceftobiprole in comparison with ceftazidime and cefepime against Enterobacteriaceae overall (a), *K. pneumoniae* (b) and *P. aeruginosa* (c).

for cefepime. For the three cephalosporins overall, Etest MICs at the study centres were the same or within one doubling dilution of the reference laboratory MIC in 79.5% of cases. Centres falsely interpreted ceftobiprole susceptible isolates as non-susceptible in 18.0% of cases, compared with 4.6% for ceftazidime and 4.2% for cefepime. As with Gram-positives, there was a high correlation between the BMD and Etest methods when conducted at the central reference laboratory. Agreement in susceptibility between the two methodologies was 98.2% for ceftobiprole, 93.6% for ceftazidime and 91.9% for cefepime.

Discussion

In this large antibiotic surveillance study conducted across Europe and the Middle East, ceftobiprole showed potent *in vitro* activity that was comparable to or higher than that of vancomycin, teicoplanin and linezolid against the major groups of Gram-positive pathogens causing serious infections in hospitalized patients. Furthermore, ceftobiprole showed similar activity to ceftazidime and cefepime against a range of clinically relevant Gram-negative pathogens causing cSSSIs, bloodstream infections and nosocomial pneumonia. These results are particularly encouraging given that the evaluated isolates comprised a significant proportion of MDR strains and that the comparator agents are generally accepted as first-line treatment for various MDR bacterial infections. Ceftobiprole may therefore contribute towards fulfilling the current need for new agents active against both Gram-positive and Gram-negative bacteria, including MDR strains (e.g. MRSA, MR-CoNS and MDR *S. pneumoniae* and *P. aeruginosa*), which pose an increasing threat in many clinical settings.[13–16]

Ceftobiprole is under investigation as a broad-spectrum, intravenous therapy for severe bacterial infections (in particular, in cSSSIs, including diabetic foot infections, and nosocomial pneumonia) in hospitalized patients, with encouraging results. These infections may potentially involve MDR and/or mixed Gram-positive and Gram-negative pathogens.[16–20] In addition, the results of this study support the use of the Etest as a reliable and convenient method for assessing susceptibility to ceftobiprole.

The main aim of the CLASS study was to expand current knowledge on the susceptibility of common pathogens that cause serious infections in hospitalized patients to the novel cephalosporin ceftobiprole, in comparison with other antibiotics. Unlike global surveillance studies, which often only collect data from a few centres per country, this particular study was designed to collect local susceptibility data from a larger number of centres within Europe and the Middle East only.

It should be noted that ~2% of all *S. aureus* isolates had vancomycin MICs above the susceptibility breakpoint for this agent (i.e. ≤2 mg/L), a higher proportion than that recorded in other recent European and worldwide surveillance studies.[5,21–24] These studies, which utilized BMD methods, found nearly 100% of all collected *S. aureus* isolates to be fully susceptible to vancomycin. This difference may be due to the fact that the conventional Etest method, as used in the CLASS study, has been known to overestimate vancomycin MICs.[25,26] While site-level

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results indicating only intermediate susceptibility to vancomycin were not routinely verified at the central reference laboratory, all retested *S. aureus* isolates (due to cross-resistance with another study antibiotic) were found to be vancomycin susceptible. This suggests that the actual number of vancomycin-intermediate isolates may be considerably lower than reported by the study centres and, thus, more in line with previous reports.

There are concerns that some *S. aureus* isolates with a vancomycin MIC of 2 mg/L, although susceptible according to current breakpoints, may be heteroresistant and, thus, more likely to fail therapy with vancomycin. In this context, it should be noted that our study found ceftobiprole to be as effective against isolates with a vancomycin MIC of ≥2 mg/L as against those with an MIC of <2 mg/L.

Against other staphylococci, ceftobiprole was the most active agent against MS-CoNS and comparable to linezolid against MR-CoNS, both being more active than the glycopeptides against the latter group of isolates. Of note, ceftobiprole was active against all linezolid non-susceptible staphylococcal isolates in this study, a significant finding in light of recent reports of linezolid-resistant MRSA and CoNS strains.[27,28] Ceftobiprole resistance was reported for only ~1% of Gram-positive isolates; the majority of these were viridans group streptococci (mostly *S. mitis*) and *E. faecalis*.

Ceftobiprole showed better activity at MIC_{50} than the comparator antimicrobials for most of the Gram-negative pathogen groups analysed, except for *Enterobacter* spp., where ceftobiprole and cefepime MIC values were identical, and for *P. aeruginosa*, where ceftobiprole had slightly less activity. At MIC_{90}, ceftobiprole showed better activity than ceftazidime and cefepime against the Enterobacteriaceae overall (*E. coli* and *K. pneumoniae* in particular) and *H. influenzae*, but was less active than the comparator antimicrobials against *P. aeruginosa*. Approximately 1.9% of cephalosporin-resistant isolates were resistant to all three cephalosporins tested. In order to increase the likelihood of detecting ESBL-producing strains, all isolates that were judged as ESBL-negative by the centres, but had both ceftobiprole and ceftazidime MICs of ≥2 mg/L confirmed by the central reference laboratory, were retrospectively tested for ESBL production. This was not part of the original study protocol, but was conducted in retrospect due to the unusually high MICs for many Gram-negative strains that were initially recorded as ESBL-negative.

Our study utilized the CLSI breakpoints current at the time of data analysis;[11] European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints were not employed, as some study centres were outside Europe. However, given that the vast majority of isolates ended up coming from European countries, it may be useful to evaluate our results in light of current EUCAST breakpoints[29]—in particular, since cephalosporin breakpoints for the Enterobacteriaceae are considerably lower than those proposed by the CLSI. It should be noted that no consensus breakpoints for ceftobiprole are currently available; the ceftobiprole susceptibility breakpoints used in this study were determined based on previous data. According to the 2010 EUCAST breakpoints, almost 10% of all CoNS would have been considered non-susceptible to vancomycin, while almost all streptococci would have been classed as susceptible to this agent. Similarly, all *E. faecalis* isolates would have been considered susceptible to linezolid. Notably, current European breakpoints for teicoplanin are 2- to 4-fold lower than those used in our comparisons across all pathogen groups; this would have resulted in ~3% of all Gram-positive isolates being classed as teicoplanin non-susceptible, including >5% of MRSA. Current EUCAST susceptibility breakpoints for ceftazidime and cefepime are lower than the CLSI breakpoints that were used at the time of our study. Therefore, more Gram-negative isolates would have been classified as non-susceptible to these comparator antibiotics; this would have had a particularly strong effect on *Enterobacter* spp., with only 74% and 89% being susceptible to ceftazidime and cefepime, respectively. Furthermore, >15% of *P. aeruginosa* isolates would have been classed as resistant to each comparator antibiotic, since current EUCAST breakpoints do not recognize the existence of cefepime and ceftazidime intermediate-susceptible strains of this organism.

The results obtained by the CLASS study are generally consistent with those from other surveillance and *in vitro* susceptibility studies of ceftobiprole, and are in line with the known antimicrobial activity of this agent.[1–7,30] This assumption is supported by antimicrobial surveillance data, with no cases of ceftobiprole resistance among *S. aureus* (both MSSA and MRSA) reported to date.

The Etest was an effective predictor of susceptibility to ceftobiprole, as well as to the other study antibiotics. The respective susceptibility results for ceftobiprole correlated strongly (>98%) with those obtained by BMD when both methods were compared at the central reference laboratory. In general, the individual study sites accurately determined isolate susceptibility, judging from the high correlation between Etest results obtained at the site level and those from quality controls (95% for Gram-positives and 91% for Gram-negatives). The Etest therefore appears to be an accurate as well as fairly rapid and convenient method for determining ceftobiprole MICs. Furthermore, the high correlation between centre Etest results and quality-control samples indicates the strength of the overall data collected in this study.

In summary, this surveillance study across 19 countries further demonstrates the *in vitro* activity of ceftobiprole against a wide range of Gram-positive and Gram-negative pathogens, including MDR strains such as MRSA. No changes in the known susceptibility profile of ceftobiprole were identified. Its broad-spectrum bactericidal activity potentially makes ceftobiprole a useful new agent for the first-line treatment of serious infections in hospitalized patients, such as cSSSIs and nosocomial pneumonia, including mixed infections.

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G. M. R. has served in the speakers' bureau of and attended advisory board meetings organized by Janssen-Cilag. M. S. D. has received speaker honoraria from Bayer, Novartis, Pfizer and Wyeth, participated

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as a clinical investigator and as a data reviewer in a number of studies involving antibiotics mentioned in this article, and participated in advisory board meetings for Bayer, Janssen-Cilag, Novartis, Pfizer and Wyeth. R. S. K. has no relevant conflicts of interest to report. A. Q. and R. K. F. are full-time employees of Johnson & Johnson. J. M. L. is a full-time employee of Janssen-Cilag EMEA, a subsidiary of Johnson & Johnson. A. Q., R. K. F. and J. M. L. hold stock and options with Johnson & Johnson. E. L. is a full-time employee of Janssen Pharmaceutica, a subsidiary of Johnson & Johnson. I. M. is a full-time employee of Quotient Bioresearch, which was a paid consultant in regards to the conduct of this study; Quotient Bioresearch also conducts research for other pharmaceutical companies. I. M. holds stocks and options in Quotient Bioresearch Ltd.

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