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ORIGINAL RESEARCH

Susceptibility to ceftobiprole of respiratory-tract pathogens collected in the United Kingdom and Ireland during 2014–2015

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Purpose: Lower respiratory tract infections (LRTIs) can cause significant morbidity and mortality and are becoming increasingly difficult to treat because of the growing prevalence of resistance to conventional antimicrobial agents. This study aimed to assess the current in vitro susceptibility of respiratory tract pathogens collected from the UK and Ireland to ceftobiprole, an advanced-generation cephalosporin, as compared with other antibiotics.

Methods: Pathogens isolated from patients with LRTIs were analyzed as part of the British Society for Antimicrobial Chemotherapy Antimicrobial Resistance Surveillance Programme during 2014–2015. Antibiotic susceptibility was evaluated using European Committee on Antimicrobial Susceptibility Testing breakpoints, including the ceftobiprole pharmacokinetic/pharmacodynamic non-species-specific breakpoint when species-specific breakpoints were not available.

Results: One thousand one hundred and sixty-eight isolates from community-onset LRTIs and 1,264 isolates from hospital-onset LRTIs were analyzed. The ceftobiprole susceptibility rate was 99.8% (428/429) for *Streptococcus pneumoniae*, 100% (502/502) for *Haemophilus influenzae*, and 99.6% (236/237) for *Moraxella catarrhalis*. All *Staphylococcus aureus* isolates, including methicillin-susceptible *S. aureus* (MSSA; N=181) and methicillin-resistant *S. aureus* (MRSA; N=35), were susceptible to ceftobiprole. Overall, ceftobiprole susceptibility was observed in 88.1% (215/244) of *Escherichia coli* isolates, 83.4% (156/187) of *Klebsiella pneumoniae* isolates and 86.7% (98/113) of *Enterobacter* spp. isolates.

Conclusion: Ceftobiprole had in vitro activity against all *S. aureus* (both MSSA and MRSA) isolates, and almost all *S. pneumoniae* isolates, as well as against Gram-negative bacteria associated with community-onset or hospital-onset LRTIs. Based on this analysis, ceftobiprole is a good treatment option when broad-spectrum antibiotic coverage is needed for LRTIs.

Keywords: antibiotic, BSAC, cephalosporin, MIC, resistance, RTI

Introduction

Appropriate early empiric treatment is crucial in patients hospitalized for community-acquired lower respiratory tract infections (LRTIs),[1] and patients with hospital-acquired LRTIs.[2] Delayed or ineffective therapy in these settings incurs substantial morbidity and mortality.[3,4] The cephalosporin class of antibiotics is an important component of parenteral treatment algorithms in these settings;[1,2,5,6] however, as with all antibiotic classes, emerging resistance to broad-spectrum cephalosporins has become a major challenge in the treatment of these infections.[7] Antibiotic-resistant Gram-positive pathogens, particularly methicillin-resistant *Staphylococcus aureus* (MRSA), are a significant problem in pulmonary infections. Moreover, significant increases in pneumococcal

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resistance to commonly used beta-lactam agents have been documented in recent years.[8] Empiric selection of an antibiotic treatment with activity against likely causative pathogens is thus complicated not only by the wide range of possible bacteria, but also the growing prevalence of resistance to conventional agents.

Ceftobiprole medocaril is the prodrug of ceftobiprole, a parenteral cephalosporin with in vitro potency against a wide range of respiratory pathogens, including Gram-positive pathogens (methicillin-susceptible *S. aureus* [MSSA], MRSA, pneumococci resistant to penicillin or ceftriaxone) and Gram-negative pathogens (non-extended-spectrum beta-lactamase [ESBL]-producing Enterobacteriaceae, *Pseudomonas aeruginosa*).[9,10] *S. aureus* strains with reduced susceptibility to vancomycin, daptomycin, or linezolid have been shown to remain susceptible to ceftobiprole.[11,12] The results from randomized, double-blind, Phase III clinical trials have demonstrated that ceftobiprole monotherapy is non-inferior to combination therapy with ceftazidime and linezolid in patients with hospital-acquired pneumonia (HAP),[13] and non-inferior to ceftriaxone either as monotherapy or in combination with linezolid in community-acquired pneumonia (CAP).[14] Ceftobiprole is currently approved in around 20 European and non-European countries for the treatment of HAP (excluding ventilator-associated pneumonia [VAP]) and CAP in adults.

The mechanisms underlying development of resistance to cephalosporins are complex and vary among organisms. The main resistance mechanisms include mutation of the target genes (ie, genes encoding penicillin binding proteins [PBPs]), production of hydrolyzing enzymes (ie, beta-lactamases), and overexpression of multidrug efflux pumps.[15–18] In order to circumvent resistance to beta-lactams, ceftobiprole was specifically designed to have a high affinity for both PBP2a[19,20] of staphylococci, which confers the MRSA phenotype, and PBP2x of *Streptococcus pneumoniae* strains resistant to penicillin and ceftriaxone.[21,22] In addition, ceftobiprole has been shown to bind to and inhibit most of the essential PBPs in both Gram-positive and Gram-negative pathogens.[23] Although ceftobiprole has been shown to have a low propensity for resistance development,[24,25] regular monitoring of local ceftobiprole susceptibility rates is essential for informed therapy.

The British Society for Antimicrobial Chemotherapy (BSAC) Respiratory Resistance Surveillance Programme is designed to provide long-term surveillance data based on the in vitro activity of a range of antimicrobial agents against potential pathogens isolated from patients with LRTIs in the UK and Ireland. Data collected from the surveillance program during 2014–2015 were reviewed to assess the susceptibility of pathogens from LRTIs to ceftobiprole and other antimicrobial agents.

Methods

Isolate collection

The BSAC Respiratory Surveillance Programme is a collection of bacterial isolates provided by 40 sentinel laboratories in the UK and Ireland with wide geographical coverage and diversity between teaching vs non-teaching hospitals, urban vs rural settings, and more vs less socially deprived areas. The current analysis included isolates obtained during surveillance between October 2014 and October 2015.

As described in detail elsewhere,[26,27] each participating laboratory collected isolates annually (1 October–30 September). Isolates were from lower respiratory samples obtained from patients with community-onset or hospital-onset LRTIs, excluding patients with cystic fibrosis. Patients who tested positive for *S. pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis* were considered to have community-onset infections, unless they had been admitted to the hospital >48 hours before sampling, in which case they were excluded from the analysis. A patient was classified as having a hospital-onset infection if they had been admitted to the hospital >48 hours before sampling and had respiratory isolates of *S. aureus*, *Pseudomonas* spp., *Acinetobacter* spp., or Enterobacteriaceae. If the pathogen identified was not included in these predefined lists, it was excluded from the analysis (eg, an *S. aureus* isolate identified in a patient with a community-onset infection would be excluded).

Each center collected up to 14 consecutive isolates of *S. pneumoniae* and *H. influenzae*, up to seven consecutive isolates of *M. catarrhalis*, *S. aureus*, *Pseudomonas* spp., *Acinetobacter* spp., and 28 consecutive isolates of Enterobacteriaceae. Repeat isolates, defined as isolates of the same species obtained from the same patient within 14 days, were assumed to be from the same episode of infection and were excluded. It is important to note that isolates were not linked to a patient identifier and as such, samples from the same patient taken >14 days apart and isolates from polymicrobial infections in the same patient were considered separately. Therefore, patient numbers may include duplicate patients where multiple isolates were obtained from the same patient.

Isolates were frozen at –70°C in blood glycerol broth or other established methods and sent to the central laboratory (Public Health England, Colindale, London) for further analysis.

Microbiological testing

H. influenzae, *M. catarrhalis*, *S. aureus, Pseudomonas* spp., and Enterobacteriaceae spp. other than *Escherichia coli* were identified using matrix-assisted laser desorption time-of-flight mass spectrometry (MALDI-ToF MS). *E. coli* were identified as pink colored colonies on chromogenic media. *S. pneumoniae* were identified using optochin and bile solubility tests, followed by either classical serotyping or serotype prediction from genomic sequence data. *Acinetobacter baumannii* were identified using blaOXA-51 polymerase chain reaction; all other *Acinetobacter* spp. were identified using MALDI-ToF MS. Minimum inhibitory concentrations (MICs) of ceftobiprole and comparators were determined by the BSAC agar dilution method.[28] Categorization of isolates as susceptible/intermediate/resistant was based on susceptibility breakpoints from the European Committee on Antimicrobial Susceptibility Testing (EUCAST),[29] with which the BSAC breakpoints are harmonized.[30] When species-specific breakpoints were not available, pharmacokinetic/pharmacodynamic (PK/PD) breakpoints were applied. The EUCAST breakpoints for ceftobiprole susceptibility are 2 mg/L for *S. aureus*, 0.5 mg/L for *S. pneumoniae*, and 0.25 mg/L for Enterobacteriaceae. For interpretation of ceftobiprole MICs for all other species, the PK/PD non-species-specific breakpoint of 4 mg/L was used.[29]

Isolates of Enterobacteriaceae with ceftazidime or cefotaxime MICs ≥1 mg/L and isolates of *Klebsiella oxytoca* with a piperacillin/tazobactam MIC ≥128 mg/L (ie, at or above the susceptibility breakpoint for those antimicrobial agents) were tested for the production of ESBLs by BSAC agar dilution or Etest and then confirmed by polymerase chain reaction for the presence of CTX-M.[26]

Data analysis

MIC_{50}, MIC_{90}, and MIC ranges are presented by pathogen or pathogen group, and according to ESBL-producing phenotype where relevant. No statistical analyses were performed in this descriptive study.

Predicting antibiotic resistance in hospital-onset pneumonia

In a previous study of ceftobiprole activity against pathogens associated with pneumonia,[31] the authors conducted an experimental analysis to evaluate the clinical relevance of the in vitro susceptibility findings. In their analysis, the current prevalence of the pneumonia pathogens was estimated using data regarding isolates recovered from patients with HAP (excluding VAP) included in a large randomized, controlled, Phase III trial of ceftobiprole medocaril vs ceftazidime plus linezolid.[13] The data from the Phase III study were then cross-referenced to the susceptibility data obtained from the surveillance study to estimate the proportion of current clinical isolates that would be susceptible to ceftobiprole. In this study, this approach was replicated by cross-referencing the collected susceptibility data with isolate prevalence data reported for HAP/hospital-acquired LRTIs by the European Center for Disease Prevention and Control (ECDC) in its European point prevalence survey of healthcare-associated infections.[32] The data for ceftazidime–vancomycin in the current study were used as a surrogate to reproduce data reported for ceftazidime–linezolid in the previous study, as susceptibility data for linezolid were not available in the current study.

Results

Isolate numbers and patient demographics

In total, 2,440 isolates were collected. The majority of isolates were from patients who were male and aged 60 years or older (Table 1). The distribution of pathogens based on central laboratory identification is summarized in Table 1 and reflects the collection design. Overall, 47.9% of isolates (1,168/2,440) were from community-onset LRTIs, 51.8% of isolates (1,264/2,440) were from hospital-onset LRTIs (ie, collected from patients hospitalized for >48 hours), and 0.3% of isolates (8/2,440) were excluded from the analysis due to missing information or failing to meet the inclusion criteria. Of the isolates collected from patients with hospital-onset LRTIs, 36.4% (460/1,264) were from patients in the intensive care unit (ICU).

In vitro activity of ceftobiprole against community-onset pneumonia pathogens

In total, 429 *S. pneumoniae* isolates were assessed, of which 99.8% (428/429) were susceptible to ceftobiprole (MIC ≤0.5 mg/L, with $MIC_{50/90}$ 0.008/0.06 mg/L) (Table 2). The only remaining isolate had a ceftobiprole MIC of 1 mg/L. *S. pneumoniae* demonstrated susceptibility rates of 97.9% with cefotaxime, but ≤84.6% for the other agents tested, with 83.7% of isolates susceptible to penicillin (Table 3). No isolates of *S. pneumoniae* were inhibited by ciprofloxacin.

Using the PK/PD breakpoint, 100% (502/502) *H. influenzae* isolates were susceptible to ceftobiprole, as were 99.6% (236/237) of the *M. catarrhalis* isolates ($MIC_{50/90}$ 1/4 mg/L) (Table 2).

Table 1 Patient and isolate characteristics

	N (%)
Total number of isolates[a]	2,440
Gender, male	1,426 (58.4)
Age, years[b]	
0–4	110 (4.5)
5–19	53 (2.2)
20–39	169 (6.9)
40–49	199 (8.2)
50–59	301 (12.3)
60–69	619 (25.4)
70–79	634 (26.0)
≥80	354 (14.5)
Infection type	
Hospital-onset infection	1,264 (51.8)
ICU	460 (36.4)
Community-onset infection	1,168 (47.9)
Other[c]	8 (0.3)
Pathogen (central testing)	
Hospital-onset pneumonia	1,264 (51.8)
Escherichia coli	244 (19.3)
Non-ESBL	213
ESBL	31
Staphylococcus aureus	216 (17.1)
MSSA	181
MRSA	35
Pseudomonas aeruginosa	214 (16.9)
Klebsiella pneumoniae	187 (14.8)
Non-ESBL	159
ESBL	28
Enterobacter spp.	113 (8.9)[d]
Klebsiella oxytoca	63 (5.0)
Serratia spp.	56 (4.4)[e]
Acinetobacter baumannii	43 (3.4)
Citrobacter spp.	42 (3.3)[f]
Community-onset pneumonia	1,168 (47.7)
Haemophilus influenzae	502 (43.0)
Streptococcus pneumoniae	429 (36.7)
Moraxella catarrhalis	237 (20.3)

Notes: [a]As multiple isolates were collected from the same patient in a small proportion of patients with prolonged or polymicrobial infections, these values are estimates and are likely to be a slight overestimation of the number of patients included. [b]Age was not known for one patient. [c]Excluded from analysis; includes 1 *H. influenzae* isolate from a patient who was admitted for >48 hours when sample was taken, and 7 isolates for which information was incomplete. [d]68 *E. cloacae*, 23 *E. aerogenes*, 15 *E. cloacae* complex, 7 *E. asburiae* isolates, and 1 *E. gergoviae* isolate. [e]51 S. marcescens and 4 *S. liquefaciens* isolates. [f]34 *C. koseri* and 7 *C. freundii* isolates, and 1 *C. braakii* isolate.

Abbreviations: ESBL, extended-spectrum beta-lactamases; ICU, intensive care unit; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*.

In vitro activity of ceftobiprole against hospital-onset pneumonia pathogens

Of the 244 *E. coli* isolates collected, 87.3% (213/244) were non-ESBL producers and 12.7% (31/244) had an ESBL-positive phenotype. Overall, 88.1% (215/244) of *E. coli* isolates were susceptible to ceftobiprole, similar to the susceptibility rate for ceftazidime (86.1%; 210/244). Ceftobiprole was active against 98.6% (210/213) of non-ESBL-producing *E. coli* isolates, but had reduced activity against ESBL-producing isolates, with only 16.1% (5/31) of such isolates being susceptible to ceftobiprole (Table 2). Only meropenem was active against 100% of *E. coli* isolates (Table 3).

Other Enterobacteriaceae species isolated included *Klebsiella pneumoniae* and *Enterobacter* spp. From a total of 187 *K. pneumoniae* isolates examined, 83.4% (156/187) were susceptible to ceftobiprole. Ceftobiprole was active against 96.9% (154/159) of non-ESBL producing isolates of *K. pneumoniae*, while the 28 isolates with an ESBL-positive phenotype had a low rate of susceptibility (7.1% [2/28]; 26 of 28 had a ceftobiprole MIC ≤2 mg/L) (Table 2). The agent with the lowest rate of resistance for *K. pneumoniae* isolates was meropenem, with only 1.1% (2/187) of isolates displaying resistance. Resistance rates to the other agents ranged from 10.7% (20/187) for ceftazidime, gentamicin, and piperacillin/tazobactam, to 11.8% (22/187) for ciprofloxacin (Table 3).

A total of 113 *Enterobacter* isolates were assessed, of which 86.7% (98/113) were ceftobiprole-susceptible; MIC_{50} and MIC_{90} values were 0.06 and 2 mg/L, respectively (Table 2). Meropenem was the only agent with activity against all *Enterobacter* isolates; resistance rates for the other agents ranged from 1.8% (2/113) for gentamicin to 22.1% (25/113) for ceftazidime (Table 3).

Of the 216 *S. aureus* isolates, 83.8% (181/216) were MSSA and 16.2% (35/216) were MRSA. All *S. aureus* isolates, both MSSA and MRSA, were susceptible to ceftobiprole (MIC ≤2 mg/L), with $MIC_{50/90}$ values of 0.5/0.5 mg/L for MSSA and 1/2 mg/L for MRSA (Table 2). Among the other antimicrobial agents tested, 100% of *S. aureus* isolates were also susceptible to vancomycin (MIC ≤2 mg/L, with $MIC_{50/90}$ 1/1 mg/L). For ciprofloxacin and erythromycin, resistance was observed in 18.5% (40/216) and 20.8% (45/216) of *S. aureus* isolates, respectively (Table 3). For the MRSA isolates, the rate of resistance was 91.4% (32/35) for ciprofloxacin and 68.6% (24/35) for erythromycin.

Applying the ceftobiprole PK/PD breakpoint of 4 mg/L, ceftobiprole was active against 86.0% (184/214) of the *P. aeruginosa* isolates tested (Table 2). The highest rates of susceptibility were seen for colistin (98.6%; 211/214) and ceftolozane/tazobactam (99.1%; 212/214) (Table 3). Ceftazidime resistance was detected in 7.9% (17/214) of *P. aeruginosa* isolates, 9 of which were also ceftobiprole-resistant. Of the 197 ceftazidime-sensitive *P. aeruginosa* isolates, 10.7% (21/197) were ceftobiprole-resistant (Table 2). Resistance rates for *P. aeruginosa* against the other agents ranged from 3.7% (8/214) for gentamicin to 13.1% (28/214) for piperacillin/tazobactam (Table 3).

Table 2 Distribution of ceftobiprole MICs (mg/L) against bacterial isolates collected from the respiratory tract of hospitalized patients

	N	Number (%) of isolates inhibited by ceftobiprole at MIC														MIC_{50}	MIC_{90}	MIC range
		<0.03	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	≥128			
Hospital-onset pneumonia pathogens																		
Staphylococcus aureus	216					20 (9.3)	160 (83.3)	29 (96.8)	7 (100)							0.5	1	0.25–2
MSSA	181					20 (11.0)	159 (99.0)	2 (100)								0.5	0.5	0.25–1
MRSA	35						1 (2.9)	27 (80.0)	7 (100)							1	2	0.5–2
Enterobacteriaceae	762		78 (10.2)	386 (60.9)	150 (80.6)	49 (87.0)	19 (89.5)	7 (90.4)	3 (90.8)	9 (92.0)	5 (92.6)	1 (92.8)	3 (93.2)	12 (94.7)	40 (100)	0.06	1	0.03–128
Escherichia coli	244		32 (13.1)	133 (67.6)	41 (84.4)	9 (88.1)	6 (90.6)					1 (91.0)	1 (91.4)	7 (94.3)	14 (100)	0.06	0.5	0.03–128
ESBL	31			3 (9.7)		2 (16.1)	3 (25.8)					1 (29.0)	1 (32.3)	7 (54.8)	14 (100)	64	128	0.06–128
Non-EBSL	213		32 (15.0)	130 (76.1)	41 (95.3)	7 (98.6)	3 (100)									0.06	0.125	0.03–0.5
Klebsiella spp.	250		15 (6.0)		49 (71.2)	27 (82.0)	9 (85.6)	3 (86.8)		3 (88.0)	3 (88.8)		2 (89.6)	2 (90.4)	24 (100)	0.06	64	0.03–128
Klebsiella pneumoniae	187		15 (8.0)	105 (64.2)	28 (79.1)	8 (83.4)	5 (86.1)	2 (87.2)		2 (88.2)	2 (89.3)			1 (89.8)	19 (100)	0.06	128	0.03–128
ESBL	28			2 (7.1)			3 (17.9)	2 (25.0)		2 (32.1)	1 (35.7)			1 (39.3)	17 (100)	128	128	0.06–128
Non-ESBL	159		15 (9.4)	103 (74.2)	28 (91.8)	8 (96.9)	2 (98.1)				1 (98.7)				2 (100)	0.06	0.125	0.03–128
Klebsiella oxytoca	63			9 (14.3)	21 (47.6)	19 (77.8)	4 (84.1)	1 (85.7)		1 (87.3)			2 (90.5)	1 (92.1)	5 (100)	0.25	32	0.06–128
Enterobacter spp.	113		8 (7.1)	69 (68.1)	16 (82.3)	5 (86.7)	1 (87.6)	2 (89.4)	2 (91.1)	6 (96.5)	2 (98.2)			1 (99.1)	1 (100)	0.06	2	0.03–128
Serratia spp.	56		1 (1.8)	11 (21.4)	35 (83.9)	4 (91.1)	1 (92.9)	2 (96.4)	1 (98.2)						1 (100)	0.125	0.25	0.03–128
Citrobacter spp.	42		2 (4.8)	34 (85.7)	3 (92.9)	1 (95.2)	2 (100)									0.06	0.125	0.03–0.5
Pseudomonas spp.[a]	214						7 (3.3)	35 (19.6)	91 (62.1)	51 (86.0)	23 (96.7)	4 (98.6)	1 (99.1)	1 (99.5)	1 (100)	2	8	0.5–>64
Ceftazidime R	17							1 (5.9)	1 (11.8)	6 (47.1)	3 (64.7)	3 (82.4)	1 (88.2)	1 (94.1)	1 (100)	8	64	1–>64
Ceftazidime S	197						7 (3.6)	34 (20.8)	90 (66.5)	45 (89.3)	20 (99.5)	1 (100)				2	8	0.5–16

(*Continued*)

Table 2 (*Continued*)

	N	Number (%) of isolates inhibited by ceftobiprole at MIC											MIC_{50}	MIC_{90}	MIC range
		<0.03	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	≥128			
Acinetobacter spp.	72		1 (1.4)	3 (5.6)	3 (9.7)	20 (37.5)	21 (66.7)	10 (80.6)		1 (81.9)	1 (83.3)		6 (91.7)	5 (98.6)	1 (100)	0.5	32	0.03–128
Acinetobacter baumannii	43				1 (2.3)	9 (23.3)	16 (60.5)	3 (67.4)		1 (70.0)	1 (72.1)		6 (86.0)	5 (97.7)	1 (100)	0.5	64	0.125–128
Community-onset pneumonia pathogens																		
Haemophilus influenzae	502	25 (5.0)	129 (30.7)	238 (78.1)	88 (95.6)	20 (99.6)	2 (100)									0.06	0.125	0.004–0.5
Streptococcus pneumoniae	429	358 (83.5)	20 (88.1)	10 (90.4)	12 (93.2)	15 (96.7)	13 (99.8)	1 (100)								0.008	0.06	0.004–1
Moraxella catarrhalis	237	6 (2.5)		1 (3.0)	2 (3.8)	9 (7.6)	47 (27.4)	79 (60.8)	54 (83.5)	38 (99.6)	1 (100)					1	4	0.015–>4

Notes: [a]Includes 2 *P. fluorescens* isolates and 1 *P. putida* isolate.

Abbreviations: ESBL, extended-spectrum beta-lactamases; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; R, resistant; S, susceptible.

Amongst *A. baumannii* isolates, 69.8% (30/43) were susceptible to ceftobiprole, with $MIC_{50/90}$ values of 0.5/64 mg/L (Table 2). The susceptibility rates for *A. baumannii* for meropenem (69.8%; 30/43), gentamicin (69.8%; 30/43), and piperacillin/tazobactam (65.1%; 28/43) were similar or identical to the rate observed for ceftobiprole, but there was a low rate of susceptibility (34.9%; 15/43) to ceftazidime in this species (Table 3).

Predicting antibiotic resistance in hospital-onset pneumonia

An exploratory analysis was carried out to predict the proportion of healthcare-associated respiratory pathogens in the UK likely to be susceptible to the different antimicrobial agents. Using an approach replicated from a previous study,[31] susceptibility rates observed in the current study were cross-referenced with prevalence data reported in the ECDC European point prevalence survey of healthcare-associated respiratory infections.[32]

The proportion of susceptible isolates from HAP/hospital-onset LRTIs in the UK was predicted to be 87.8% for ceftobiprole, 89.4% for meropenem, 82.1% for piperacillin/tazobactam, and 92.9% for ceftazidime-vancomycin (Table 4).

Discussion

The data presented here from the BSAC Surveillance Programme during the 2014–2015 season confirm the continued potent activity of ceftobiprole against the key respiratory pathogens associated with community-onset or hospital-onset LRTIs in the UK and Ireland. In CAP, *S. pneumoniae, H. influenzae*, and *M. catarrhalis* are the primary causative pathogens.[33] All *H. influenzae* isolates were susceptible to ceftobiprole. Susceptibility to ceftobiprole was also high in *S. pneumoniae* and *M. catarrhalis,* with susceptibility rates of 99.8% and 99.6%, respectively. These data suggest that ceftobiprole is a good empirical treatment choice for patients with CAP, given its comprehensive activity against the most common causative Gram-positive and Gram-negative pathogens.

In HAP, *S. aureus, P. aeruginosa,* and Enterobacteriaceae (including *E. coli* and *K. pneumoniae*) account for the majority of infections.[32,34] Ceftobiprole demonstrated potent in vitro activity against all *S. aureus* isolates tested, including both MSSA and MRSA isolates. Ceftobiprole also showed in vitro activity against *S. aureus* isolates that were resistant to other antimicrobial agents, such as ciprofloxacin and erythromycin. Only vancomycin demonstrated similar susceptibility rates against all *S. aureus* isolates.

Table 3 In vitro activity of ceftobiprole and comparators against bacterial isolates collected from the respiratory tract of hospitalized patients

	MIC (mg/L)			% Susceptible/resistant
	MIC_{50}	MIC_{90}	Range	EUCAST[a]
Hospital-onset pneumonia pathogens				
***Staphylococcus aureus* (N=216)**				
Ceftobiprole	0.5	1	0.25–2	100/0
Oxacillin	0.5	128	0.125–>128	83.8/16.2
Tetracycline	0.5	0.5	≤0.06–>128	95.8/4.2
Trimethoprim	1	2	0.125–>128	92.6/7.4
Vancomycin	1	1	0.5–2	100/0
Ciprofloxacin	0.5	128	0.125–>128	81.5/18.5[b]
Erythromycin	0.5	>128	0.125–>128	79.2/20.8[c]
Gentamicin	0.25	0.25	0.06–32	97.2/2.8
Enterobacteriaceae (N=762)				
Ceftobiprole	0.06	1	0.03–128	87.0/13.0
Ciprofloxacin	0.03	1	0.004–>256	87.1/11.3
Ceftazidime	0.25	4	0.03–>256	86.4/9.1
Meropenem	0.03	0.06	0.015–>256	99.7/0.3
Piperacillin/tazobactam	2	16	0.06–>256	85.3/9.3
Gentamicin	0.5	1	≤0.125–>256	93.6/6.2
***Escherichia coli* (N=244)**				
Ceftobiprole	0.06	0.5	0.03–128	88.1/11.9
Ciprofloxacin	0.015	32	0.004–256	78.7/20.1
Ceftazidime	0.25	4	0.06–256	86.1/7.0
Meropenem	0.015	0.03	0.015–0.06	100/0
Piperacillin/tazobactam	2	16	1–>256	87.3/8.6
Gentamicin	0.5	4	0.25–64	89.7/9.4
***Klebsiella pneumoniae* (N=187)**				
Ceftobiprole	0.06	128	0.03–128	83.4/16.6
Ciprofloxacin	0.03	1	0.008–>256	85.6/11.8
Ceftazidime	0.25	8	0.06–>256	84.0/10.7
Meropenem	0.03	0.03	0.015 –>256	98.9/1.1
Piperacillin/tazobactam	4	32	0.5–>256	82.4/10.7
Gentamicin	0.25	16	≤0.125–>256	89.3/10.7
***Enterobacter* spp. (N=113)**				
Ceftobiprole	0.06	2	0.03–128	86.7/13.3
Ciprofloxacin	0.015	0.06	0.008–128	93.8/3.5
Ceftazidime	0.25	64	0.125–>256	75.2/22.1
Meropenem	0.03	0.125	0.015–0.5	100/0
Piperacillin/tazobactam	4	32	1–256	78.8/15.0
Gentamicin	0.25	0.5	≤0.125–64	98.2/1.8
***Pseudomonas aeruginosa* (N=214)[d]**				
Ceftobiprole	2	8	0.5–>64	86.0/14.0[e]
Ciprofloxacin	0.125	2	0.015–32	85.0/15.0
Ceftazidime	2	8	0.25–>256	92.1/7.9
Piperacillin/tazobactam	4	32	≤0.125–>256	86.9/13.1
Meropenem	0.25	8	≤0.03–>32	83.2/7.0
Colistin	1	1	0.06–>32	98.6/1.4
Gentamicin	1	2	≤0.125–128	96.3/3.7
Ceftolozane/tazobactam	0.5	1	≤0.06–>256	99.1/0.9
***Acinetobacter* spp. (N=72)**				
Ceftobiprole	0.5	32	0.03–128	81.9/18.1[e]
Ciprofloxacin	0.25	256	0.03–>256	80.6/19.4
Ceftazidime	8	256	1–>256	40.3/20.8[e]
Meropenem	0.25	32	0.06–64	80.6/18.1

(*Continued*)

Table 3 (*Continued*)

	MIC (mg/L)			% Susceptible/resistant
	MIC_{50}	MIC_{90}	Range	EUCAST[a]
Piperacillin/tazobactam	0.06	256	≤0.015–>256	70.8/18.1[e]
Gentamicin	0.25	>256	0.03–>256	77.8/22.2
***Acinetobacter baumannii* (N=43)**				
Ceftobiprole	0.5	64	0.125–128	69.8/30.2[e]
Ciprofloxacin	0.5	>256	0.125–>256	67.4/32.6
Ceftazidime	8	256	1–>256	34.9/30.2[e]
Meropenem	0.25	64	0.125–64	69.8/30.2
Piperacillin/tazobactam	1	256	0.03–>256	62.8/30.2[e]
Gentamicin	0.25	>256	0.03–>256	69.8/30.2
Community-onset pneumonia pathogens				
***Haemophilus influenzae* (N=502)**				
Ceftobiprole	0.06	0.125	0.004–0.5	100/0[e]
Amoxicillin	0.5	64	0.06–>256	74.3/25.7
Ampicillin	0.5	128	0.03–>256	69.9/30.1
Ciprofloxacin	0.008	0.015	≤0.001–4	98.8/1.2
Amoxicillin-clavulanate (2:1 ratio)	0.5	1	0.03–8	97.6/2.4
Cefotaxime	0.015	0.06	≤0.001–0.5	97.4/2.6
Tetracycline	0.5	0.5	0.06–16	96.8/1.0
***Streptococcus pneumoniae* (N=429)**				
Ceftobiprole	0.008	0.06	0.004–1	99.8/0.2
Clindamycin	0.125	>128	0.03–>128	84.6/15.4
Erythromycin	0.125	>128	0.06–>128	78.8/21.2
Cefotaxime	0.015	0.125	≤0.004–2	97.9/0
Ciprofloxacin	1	2	0.5–64	0.0/94.4[e]
Penicillin	0.015	0.25	0.004–2	83.7/0
Tetracycline	0.25	32	0.06–64	81.1/18.6[f]
***Moraxella catarrhalis* (N=237)**				
Ceftobiprole	1	4	0.015–>4	99.6/0.4[e]
Amoxicillin-clavulanate (2:1 ratio)	0.06	0.25	≤0.001–0.25	100/0
Cefotaxime	0.5	1	0.06–2	98.7/0
Erythromycin	0.06	0.06	0.015–0.25	100/0
Tetracycline	0.5	1	0.25–1	100/0

Notes: [a]Species-related clinical breakpoint set by EUCAST. [b]94.3% of MRSA were resistant to ciprofloxacin. [c]68.6% of MRSA were resistant to erythromycin. [d]Includes 2 *P. fluorescens* isolates and 1 *P. putida* isolate. [e]Susceptibility based on the EUCAST pharmacokinetic/pharmacodynamic breakpoint. [f]Based on clinical breakpoint for benzylpenicillin in indications other than meningitis.

Abbreviations: EUCAST, European Committee on Antimicrobial Susceptibility Testing; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *S. aureus*.

Rates of resistance in *S. aureus* were as follows: gentamicin, 2.8%; tetracycline, 4.2%; trimethoprim, 10.2%; oxacillin, 16.3%; ciprofloxacin, 20.8%; and erythromycin, 20.8%.

Gram-negative bacteria associated with HAP also showed high susceptibility to ceftobiprole, with rates of 83.4% and 88.1% in *K. pneumoniae* and *E. coli* isolates, respectively. As observed in previous studies, susceptibility to ceftobiprole was notably lower for ESBL-producing strains. The activity of ceftobiprole against *P. aeruginosa* was good (susceptibility rate: 86.0%), while activity against *A. baumannii* was moderate (susceptibility rate: 69.8%). However, these data are based on the EUCAST non-species-specific PK/PD breakpoint for ceftobiprole, and therefore additional data will be needed to confirm the correlation of these in vitro results with patient outcomes.

Notably, *A. baumannii* had the lowest ceftobiprole susceptibility rates of any of the bacterial species tested, a trend also observed with the other antimicrobials included in the study, with overall *A. baumannii* susceptibility rates ranging from 69.8% for ceftobiprole, meropenem, and gentamicin, to 65.0% for piperacillin/tazobactam and only 35.4% for ceftazidime. This pattern of reduced antibiotic susceptibility rates for *A. baumannii* isolates has also been observed in other surveillance studies in Europe.[35]

The high rates of susceptibility to ceftobiprole among MSSA, MRSA, and *S. pneumoniae* isolates observed in

Table 4 Predicted susceptibility to ceftobiprole and comparator therapies among the six bacterial species most frequently recovered from patients with healthcare-associated pneumonia/lower respiratory tract infections in Europe. Prevalence data were obtained from the ECDC European point prevalence study of healthcare-associated respiratory infections[32]

	S. aureus	*P. aeruginosa*	*Klebsiella* spp.[a]	*E. coli*	*Acinetobacter* spp.	*Enterobacter* spp.	Total
Percentage of isolates recovered from HAP/LRTIs in Europe (ECDC), %[b]	12.6	17.4	11.4	8.8	8.7	5.0	63.9
Adjusted percentage[c]	19.7	27.2	17.8	13.8	13.6	7.8	100
Ceftobiprole							
Susceptible (%)[d]	100	86.0	82.0	88.1	81.9	86.7	NA
Predicted % susceptible	19.7	23.4	14.6	12.2	11.1	6.8	87.8
Piperacillin/tazobactam							
Susceptible (%)[d]	83.8[e]	86.9	83.6	87.3	65.0	78.8	NA
Predicted % susceptible	16.5	23.7	15.0	12.0	8.8	6.1	82.1
Ceftazidime + vancomycin							
Susceptible (%)[d]	100[f]	92.1[g]	87.6[g]	86.1[g]	34.9[g]	75.2[g]	NA
Predicted % susceptible	19.7	25.1	15.6	11.9	4.7	5.9	92.9
Meropenem							
Susceptible (%)[d]	83.8[e]	83.2	99.2	100	80.6	100	NA
Predicted % susceptible	16.5	22.6	17.7	13.8	11.0	7.8	89.4

Notes: [a]Data not shown in Table 3. [b]Approximately 1/3 of patients were intubated within the 48 hours prior to infection onset. [c]Percentages adjusted to represent the percentage value if these 6 species represented 100% of the species. In fact, other species were isolated. [d]Values taken from Table 3 above. Susceptibility is based on species-related clinical breakpoint set by EUCAST or pharmacokinetic/pharmacodynamic breakpoint set by EUCAST. [e]For *S. aureus* spp., susceptibility to piperacillin/tazobactam or to meropenem is inferred from the oxacillin susceptibility. [f]Vancomycin susceptibility. [g]Ceftazidime susceptibility.

Abbreviations: ECDC, European Center for Disease Prevention and Control; EUCAST, European Committee on Antimicrobial Susceptibility Testing; HAP, hospital-acquired pneumonia; LRTI, lower respiratory tract infection; NA, not applicable.

this study are similar to ceftobiprole susceptibility rates reported in a previous study of 9,067 pathogens collected from hospitalized patients across the EU and Middle East in 2008 (CLASS study).[36] In the CLASS study, ceftobiprole susceptibility rates of 100%, 99.9%, and 100% were observed for MSSA, MRSA, and *S. pneumoniae*, respectively,[36] which align very closely with the ceftobiprole susceptibility rates observed in the current study (100%, 100%, and 99.8% for MSSA, MRSA, and *S. pneumoniae*, respectively). This suggests that the in vitro activity of ceftobiprole against these prevalent Gram-positive pathogens has not changed in almost a decade.

The results of the current study also align well with a recent surveillance study of 12,240 bacterial pathogens collected from Europe, Turkey, and Israel during 2015, in which ceftobiprole susceptibility rates of 100%, 96.5%, and 99.3% were observed for MSSA, MRSA, and *S. pneumoniae*, respectively.[37] These results suggest that the activity of ceftobiprole against these pathogens is similar in the UK and Ireland compared with the EU as a whole. It is notable, however, that this same previous study reported a lower rate of susceptibility to ceftobiprole in *P. aeruginosa* isolates (70.4%)[37] compared with the current study (86.0% susceptibility). It is unknown whether this shift is a result of regional susceptibility differences between the UK/Ireland and the EU, as is observed with other cephalosporins,[38] or as a result of differences in testing methods between the studies; BSAC agar dilution testing was used in the current study, while the Clinical and Laboratory Standards Institute (CLSI) broth microdilution method was used for the previous study.

In another surveillance study by Kresken et al, isolates from respiratory or blood samples from hospitalized patients with pneumonia were collected from 25 laboratories in Austria, Germany, and Switzerland in 2010.[31] In that analysis, susceptibility to ceftobiprole was similar to the current analysis for MSSA (100%) and *S. pneumoniae* (98.8%). However, only 90.0% (27/30) susceptibility to ceftobiprole was noted among the MRSA isolates, although the significance of this latter finding may be limited due to the low number of isolates assessed. In addition, two of the three non-susceptible isolates were subsequently classified as susceptible when using alternative testing methodology.

To validate the findings of the present study and assess their applicability to clinical practice, an exploratory analysis was conducted, which was designed to estimate the activity of ceftobiprole against the most commonly encountered pathogens causing HAP/hospital-acquired LRTIs in Europe. In this analysis, the susceptibility data presented here from the UK and Ireland were cross-referenced with European pathogen prevalence data in these infections.[32] European data

were used due to a lack of available data specific to the UK and Ireland. This analysis predicted that ceftobiprole would be active against 87.8% of isolates observed in HAP/hospital-acquired LRTIs, which is comparable to the predicted activity of meropenem (89.4%), and slightly higher than the predicted activity of piperacillin/tazobactam (82.1%). While this analysis had some limitations, including the assumption that the relative prevalence of causative pathogens observed in HAP in the UK and Ireland is comparable to that observed in Europe, the data support the efficacy of ceftobiprole as an empiric treatment for patients with hospital-acquired respiratory infections in the UK and Ireland and suggest its activity is similar to that of meropenem or piperacillin/tazobactam.

Ceftobiprole may be a valuable treatment option preferable to meropenem or piperacillin/tazobactam in certain countries or healthcare systems that have adopted programs for antibiotic stewardship. These programs often promote carbapenem-sparing strategies to try to reduce the emergence and subsequent spread of antibiotic resistance in Gram-negative pathogens.[39,40] In the UK, for example, the Commission for Quality and Innovation initiative put in place by NHS England provides financial incentives to reduce the use of meropenem and piperacillin/tazobactam.

Empiric treatment in patients with HAP or hospital-acquired LRTIs is particularly common in the UK, as diagnostic workup is frequently limited (sputum cultures are frequently not representative and bronchial alveolar lavage is too invasive a procedure for most patients); causative respiratory pathogens are thus difficult to obtain and identify. In countries where it is licensed, empiric use of ceftobiprole monotherapy in patients with HAP is also recommended in the 2016 Infectious Diseases Society of America guidelines.[2] Ceftobiprole may also be a useful option in patients with HAP who are at risk of Gram-negative infection, or at increased risk of mortality, in whom the guidelines recommend combination therapy with antibiotics from two different classes with activity against *P. aeruginosa.*

A limitation in the design of this study is the use of a predefined species collection list. Because of this, the epidemiology of infection in community-onset vs hospital-onset pneumonia could not be investigated. This is a common limitation with antibiotic resistance surveillance studies, which usually feature a similar design to this study. However, an epidemiological analysis of LRTIs was not the key aim of this study. Instead, this study aimed to evaluate the resistance rates against relevant antibiotic agents in a selected range of species known to be commonly associated with LRTIs. The main limitation of the exploratory analysis was the assumption that a comparable prevalence of HAP/hospital-acquired LRTIs would be observed in the UK and Ireland as in the EU.

Conclusion

As shown by this contemporary data set, ceftobiprole has good in vitro activity against the most clinically relevant Gram-positive and Gram-negative respiratory pathogens, including *P. aeruginosa* and *Enterobacter* spp. in the UK and Ireland. Therefore, ceftobiprole is an effective alternative option for the empirical treatment of both community- and hospital-onset respiratory infections in the UK and Ireland, due to its broad-spectrum in vitro activity.

Data sharing statement

The data sets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Disclosure

ASH is a former employee of Basilea Pharmaceutica International Ltd. JIS and KH are employees of Basilea Pharmaceutica International Ltd. The authors report no other conflicts on interest in this work.

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