

# Susceptibility of ceftobiprole and comparators against *Staphylococcus aureus* from hospital-acquired respiratory tract infections in the UK and Ireland: 2011/2012 and 2012/2013

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## Introduction and purpose

- Hospital-acquired pneumonia (HAP) is one of the most common hospital-acquired respiratory tract infections and accounts for 25% of all infections in intensive care units.<sup>1</sup>
- The most common bacterial species to cause HAP include *Staphylococcus aureus*, members of the *Enterobacteriaceae* and *Pseudomonas aeruginosa*. Pathogens that are resistant to antibiotics, such as methicillin-resistant *S. aureus* (MRSA), are associated with poor patient outcomes and high treatment costs.<sup>1</sup>
- Ceftobiprole medocartil is a novel parenteral cephalosporin with broad-spectrum *in vitro* activity against Gram-positive bacteria, including MRSA, and Gram-negative bacteria.<sup>2</sup> Ceftobiprole, the active moiety of ceftobiprole medocartil, exerts its antimicrobial activity against strains such as MRSA by inhibiting the transpeptidase activity of bacterial penicillin-binding proteins, which are essential for bacterial cell-wall synthesis.<sup>1</sup>
- In Europe, ceftobiprole medocartil (500 mg i.v. every 8 hours) is approved for the treatment of HAP (excluding ventilator-associated pneumonia) and community-acquired pneumonia in adults.<sup>2</sup>
- This study assesses the activity of ceftobiprole and comparator antimicrobial agents against *S. aureus* isolates recovered from patients with hospital-acquired respiratory tract infections, using data from the UK and Ireland (2011–2013) collected during the British Society for Antimicrobial Chemotherapy (BSAC) Resistance Surveillance Project.<sup>3,4</sup>

## Methods

- As part of the ongoing BSAC Resistance Surveillance Project, isolates were collected from a total of 45 laboratories in the UK (n = 41) and Ireland (n = 4) during 2011–2013, and each isolate was tested for resistance to a selection of antibiotics. This collection includes *S. aureus* isolates from patients with hospital-acquired respiratory tract infections.<sup>4</sup>
- The respiratory programme of BSAC runs from 1 October each year to 30 September in the following year. The current analysis assessed data for 209 *S. aureus* isolates collected in the year 2011/2012, and 199 isolates collected in 2012/2013.
- In the BSAC Resistance Surveillance Project, minimum inhibitory concentrations (MICs) were measured by the BSAC agar dilution method using iso-Sensitest medium (Oxoid, Basingstoke, UK).<sup>4,5</sup>
- The BSAC/European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints were used to categorize isolates as susceptible or resistant (Table 1).

## Results

- Ceftobiprole demonstrated potent activity against *S. aureus* (MRSA: 95/408 [23%]; methicillin-susceptible *S. aureus* [MSSA]: 313/408 [77%]) (Figure 1).
- All 408 *S. aureus* isolates were fully susceptible to ceftobiprole, and overall MICs ranged from 0.25 mg/L to 2 mg/L.
- All MSSA isolates were inhibited at a concentration of 1 mg/L or lower, and all MRSA isolates were inhibited at a concentration of 2 mg/L or lower.

- The MIC<sub>50/90</sub> for ceftobiprole against all *S. aureus* isolates was 0.5/1 mg/L for both 2011/2012 (Table 2) and 2012/2013 (Table 3).
- For MRSA isolates, the MIC range for ceftobiprole was 0.5–2 mg/L in 2011/2012 and 0.25–2 mg/L in 2012/2013. The MIC<sub>50/90</sub> was 1/2 mg/L in both collection periods.
- For MSSA isolates, the MIC range for ceftobiprole was 0.25–1 mg/L in both collection periods. The MIC<sub>50</sub> was 0.5 mg/L in both collection periods, and the MIC<sub>90</sub> was 1 mg/L and 0.5 mg/L in 2011/2012 and 2012/2013, respectively.

- All *S. aureus* isolates were also fully susceptible to linezolid, tigecycline and vancomycin (Tables 2 and 3). Other antimicrobial agents had less activity against *S. aureus* than ceftobiprole.
- Over 90% of MRSA and MSSA isolates were also susceptible to gentamicin, rifampicin, minocycline and tetracycline in both collection periods.
- For all isolates, susceptibility was less than 90% with ciprofloxacin and erythromycin in both collection periods (Tables 2 and 3).

- Rates of resistance to ciprofloxacin in 2011/2012 were 23% for *S. aureus* overall, 89% for MRSA and 6% for MSSA, and in 2012/2013 were 26% overall, 86% for MRSA and 6% for MSSA.
- Rates of resistance to erythromycin in 2011/2012 were 21% for *S. aureus* overall, 62% for MRSA and 9% for MSSA. In 2012/2013, the rates of resistance were noticeably higher: 32% overall, 72% for MRSA and 19% for MSSA.
- For clindamycin, the proportion of susceptible isolates was above 90% for *S. aureus* overall (Tables 2 and 3).
- For MRSA isolates, rates of resistance to clindamycin were 16% in 2011/2012, but much lower at 4% in 2012/2013.

## Conclusions

- Ceftobiprole had potent *in vitro* antimicrobial activity against all *S. aureus* isolates causing hospital-acquired respiratory tract infections in the UK and Ireland between 2011 and 2013.
- Notably, 100% of MRSA isolates were fully susceptible to ceftobiprole.
- Ceftobiprole was also fully active against isolates that were resistant to other antimicrobial agents, such as clindamycin, ciprofloxacin and erythromycin.
- Ceftobiprole is approved in Europe for the treatment of adults with HAP (excluding ventilator-associated pneumonia) and community-acquired pneumonia. Our analysis confirms that ceftobiprole should be efficacious against *S. aureus* associated with HAP, and is especially suitable when MRSA infection is suspected.

## References

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## Disclosures

IM and SH are employees of IHMA Europe Sàrl; MJ and ASH are employees of Basilea Pharmaceutica International Ltd; RR declares no conflict of interest.

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Figure 1. Ceftobiprole activity against *Staphylococcus aureus* isolates recovered from patients with hospital-acquired respiratory tract infections in the UK and Ireland during the time periods (a) 2011/2012 and (b) 2012/2013.

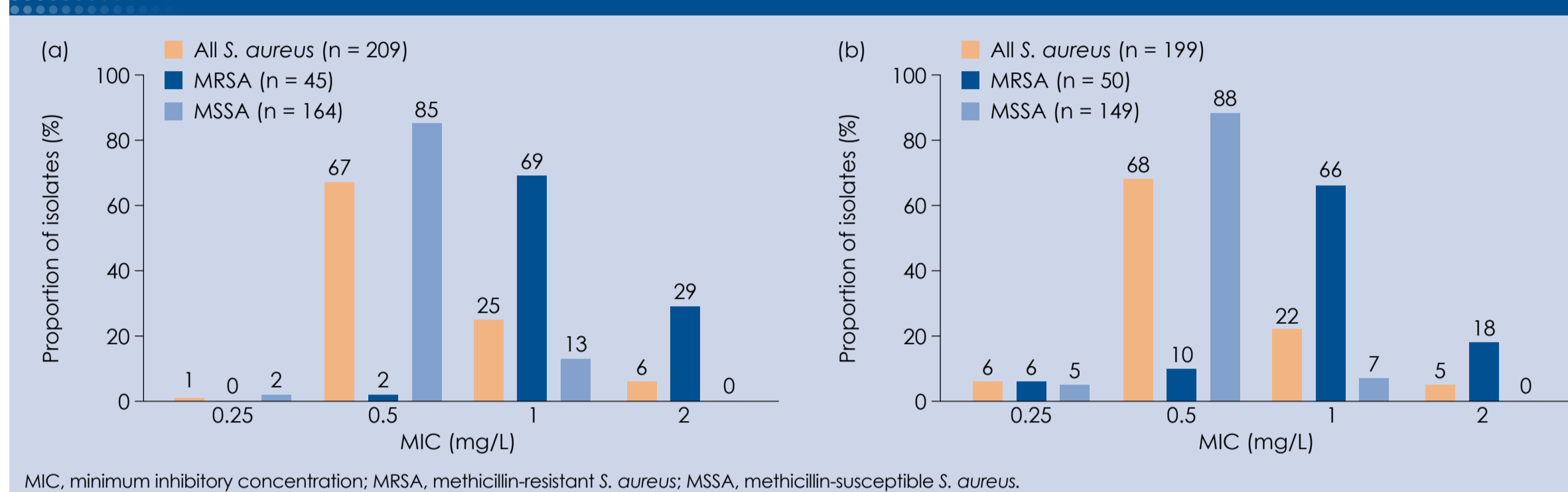


Table 2. Activity of ceftobiprole and comparator antimicrobial agents against *Staphylococcus aureus* isolates recovered from patients with hospital-acquired respiratory tract infections in the UK and Ireland during the time period 2011/2012.

2011/2012	Antibiotic concentration (mg/L)				Proportion of isolates by sensitivity category (%) <sup>a</sup>		
	Min.	MIC <sub>50</sub>	MIC <sub>90</sub>	Max.	Susceptible <sup>b</sup>	Intermediate	Resistant
<b>All <i>S. aureus</i> (n = 209)</b>							
Ceftobiprole	0.25	0.5	1	2	100	0	0
Ciprofloxacin	0.12	0.5	128	≥ 512	77	0	23
Clindamycin	≤ 0.03	0.06	0.12	≥ 256	97	0	3
Erythromycin	≤ 0.12	0.25	≥ 256	≥ 256	77	2	21
Gentamicin	0.12	0.25	0.25	32	100	0	1
Linezolid	0.25	2	2	2	100	0	0
Minocycline	0.03	0.12	0.12	≥ 4	98	0	2
Rifampicin	0.008	0.008	0.015	≥ 4	100	0	1
Tetracycline	0.12	0.5	0.5	128	96	0	4
Tigecycline	0.06	0.12	0.25	0.5	100	0	0
Trimethoprim	≤ 0.06	0.25	1	≥ 256	96	0	4
Vancomycin	≤ 0.5	1	1	1	100	0	0
<b>MRSA (n = 45)</b>							
Ceftobiprole	0.5	1	2	2	100	0	0
Ciprofloxacin	0.25	128	256	≥ 512	11	0	89
Clindamycin	≤ 0.03	0.12	≥ 256	≥ 256	84	0	16
Erythromycin	≤ 0.12	≥ 256	≥ 256	≥ 256	36	2	62
Gentamicin	0.12	0.25	0.25	32	98	0	2
Linezolid	1	2	2	2	100	0	0
Minocycline	0.06	0.12	0.12	≥ 4	96	0	4
Rifampicin	0.008	0.008	0.015	≥ 4	98	0	2
Tetracycline	0.25	0.5	0.5	128	91	0	9
Tigecycline	0.12	0.25	0.25	0.5	100	0	0
Trimethoprim	0.12	0.25	8	32	84	0	16
Vancomycin	≤ 0.5	≤ 0.5	1	1	100	0	0
<b>MSSA (n = 164)</b>							
Ceftobiprole	0.25	0.5	1	1	100	0	0
Ciprofloxacin	0.12	0.5	1	128	95	0	6
Clindamycin	≤ 0.03	0.06	0.06	0.12	100	0	0
Erythromycin	≤ 0.12	0.25	2	≥ 256	88	2	9
Gentamicin	0.12	0.25	0.25	0.5	100	0	0
Linezolid	0.25	2	2	2	100	0	0
Minocycline	0.03	0.12	0.12	≥ 4	99	0	1
Rifampicin	0.008	0.008	0.015	0.015	100	0	0
Tetracycline	0.12	0.5	0.5	128	98	0	2
Tigecycline	0.06	0.12	0.25	0.25	100	0	0
Trimethoprim	≤ 0.06	0.25	1	≥ 256	99	0	1
Vancomycin	≤ 0.5	1	1	1	100	0	0

<sup>a</sup>Sensitivity categories defined by MIC breakpoint according to EUCAST. <sup>b</sup>Susceptibility rates below 90% are highlighted in bold. EUCAST, The European Committee on Antimicrobial Susceptibility Testing; Max., maximum; MIC, minimum inhibitory concentration; Min., minimum; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*.

Table 3. Activity of ceftobiprole and comparator antimicrobial agents against *Staphylococcus aureus* isolates recovered from patients with hospital-acquired respiratory tract infections in the UK and Ireland for the time period 2012/2013.

2012/2013	Antibiotic concentration (mg/L)				Proportion of isolates by sensitivity category (%) <sup>a</sup>		
	Min.	MIC <sub>50</sub>	MIC <sub>90</sub>	Max.	Susceptible <sup>b</sup>	Intermediate	Resistant
<b>All <i>S. aureus</i> (n = 199)</b>							
Ceftobiprole	0.25	0.5	1	2	100	0	0
Ciprofloxacin	0.06	0.5	64	≥ 1024	74	0	26
Clindamycin	0.06	0.06	0.12	≥ 256	96	0	4
Erythromycin	≤ 0.12	0.25	≥ 256	≥ 256	67	1	32
Gentamicin	0.03	0.25	0.5	64	97	0	3
Linezolid	0.5	2	2	2	100	0	0
Minocycline	0.03	0.12	0.12	≥ 4	99	0	2
Rifampicin	≤ 0.004	0.008	0.015	≥ 4	99	0	1
Tetracycline	0.12	0.5	0.5	128	94	0	6
Tigecycline	0.06	0.12	0.25	0.5	100	0	0
Trimethoprim	≤ 0.06	0.5	0.5	≥ 256	94	0	7
Vancomycin	≤ 0.5	≤ 0.5	1	1	100	0	0
<b>MRSA (n = 50)</b>							
Ceftobiprole	0.25	1	2	2	100	0	0
Ciprofloxacin	0.12	64	≥ 1024	≥ 1024	14	0	86
Clindamycin	0.06	0.06	0.12	≥ 256	96	0	4
Erythromycin	0.25	≥ 256	≥ 256	≥ 256	28	0	72
Gentamicin	0.03	0.25	0.5	64	92	0	8
Linezolid	0.5	2	2	2	100	0	0
Minocycline	0.03	0.12	0.12	≥ 4	98	0	2
Rifampicin	≤ 0.004	0.008	0.015	0.015	100	0	0
Tetracycline	0.25	0.5	0.5	128	92	0	8
Tigecycline	0.06	0.12	0.25	0.5	100	0	0
Trimethoprim	0.12	0.25	8	≥ 256	84	0	16
Vancomycin	≤ 0.5	≤ 0.5	1	1	100	0	0
<b>MSSA (n = 149)</b>							
Ceftobiprole	0.25	0.5	0.5	1	100	0	0
Ciprofloxacin	0.06	0.5	1	≥ 1024	94	0	6
Clindamycin	0.06	0.06	0.12	≥ 256	96	0	4
Erythromycin	≤ 0.12	0.25	≥ 256	≥ 256	80	1	19
Gentamicin	0.06	0.25	0.5	32	99	0	1
Linezolid	0.5	2	2	2	100	0	0
Minocycline	0.06	0.12	0.12	≥ 4	99	0	1
Rifampicin	≤ 0.004	0.008	0.015	≥ 4	99	0	1
Tetracycline	0.12	0.5	0.5	128	95	0	5
Tigecycline	0.06	0.12	0.25	0.5	100	0	0
Trimethoprim	≤ 0.06	0.5	0.5	≥ 256	97	0	3
Vancomycin	≤ 0.5	≤ 0.5	1	1	100	0	0

<sup>a</sup>Sensitivity categories defined by MIC breakpoint according to EUCAST. <sup>b</sup>Susceptibility rates below 90% are highlighted in bold. EUCAST, The European Committee on Antimicrobial Susceptibility Testing; Max., maximum; MIC, minimum inhibitory concentration; Min., minimum; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*.