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Activity of ceftaroline versus ceftobiprole against staphylococci and pneumococci in the UK and Ireland: analysis of BSAC surveillance data

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Short running head: Comparative activity of ceftaroline and ceftobiprole

Background: Ceftaroline and ceftobiprole inhibit most MRSA and MDR pneumococci. Few direct comparisons of their activity have been published, but in several years (2008, 2013, 2017 and 2018) both were tested in parallel in the BSAC Resistance Surveillance Programme, giving paired results. These are reviewed.

Methods: Isolates included were bloodstream *Staphylococcus aureus* [*n*=1884 (MRSA, *n*=234)], bloodstream CoNS, (*n*=813, 574 methicillin resistant) and bloodstream (*n*=852) and respiratory (*n*=670) *Streptococcus pneumoniae*. MICs were determined by BSAC agar dilution and reviewed against EUCAST breakpoints; *S. aureus* breakpoints were assumed for CoNS.

Results: Ceftaroline MICs were mostly 2-fold lower than those of ceftobiprole, but, for all groups, MICs of both agents were strongly inter-related. Methicillin-susceptible staphylococci were universally susceptible to both agents; all MRSA were susceptible to ceftobiprole, whereas 10/234 had intermediate/high dose susceptibility to ceftaroline. Among methicillin-resistant CoNS, 88% were susceptible to both agents, but reduced ceftaroline susceptibility and ceftobiprole resistance were frequent (65%) among methicillin-resistant *Staphylococcus haemolyticus*. One *S. pneumoniae* was resistant to both ceftaroline (MIC 0.5 mg/L) and ceftobiprole (MIC 1 mg/L) and seven others were only resistant to ceftobiprole (MIC 1 mg/L); seven of these eight pneumococci belonged to serotype 19A or 19F. No time trend in susceptibility was seen for either cephalosporin.

Conclusions: Ceftaroline and ceftobiprole have similarly good activity against staphylococci and pneumococci. Therapeutic choices between these agents should be predicated on other differentiating factors, including licensed indications, clinical experience and need for Gram-negative coverage.

Introduction

Ceftaroline fosamil (Pfizer Inc.)[1] and ceftobiprole medocaril (Correvio Pharma Corp.)[2] are cephalosporins active against most MRSA and penicillin-resistant *Streptococcus pneumoniae.* This reflects their ability to target the supplementary PBP2' of methicillin-resistant staphylococci and the modified PBPs of penicillin-resistant pneumococci. Licensing and post-marketing trials have demonstrated the efficacy of ceftaroline fosamil in skin and skin structure infection, including against MRSA, and in community-acquired pneumonia. Ceftobiprole medocaril has had a more chequered development pathway, with initial rejection of skin and skin structure infection trials by the FDA on a data quality issue,[3] but the drug has since been licensed by the EMA for community-acquired pneumonia and hospital-acquired pneumonia, again with anti-MRSA activity demonstrated.[4]

Although there are many publications on each of these cephalosporins individually, there are few direct comparisons. Both have, however, been included for several years in the BSAC Resistance Surveillance Programme, yielding paired results for staphylococci and pneumococci causing clinically significant bacteraemia and for pneumococci causing community-onset lower respiratory tract infection (LRTI). These data are reviewed.

Materials and methods

The BSAC Surveillance Programme has been detailed previously.[5] It collects fixed quotas of isolates, by species, from bacteraemias and LRTIs across a panel of UK and Irish microbiology laboratories. According to the year, between 23 and 39 sites have participated. Collection of bacteraemia isolates runs by calendar year, while that of LRTI isolates runs from October in one year to September of the next year, capturing isolates from a 'respiratory season'. Results were reviewed whenever ceftobiprole and ceftaroline were both tested in parallel during a collection year. This applied for *Staphylococcus aureus*, CoNS and *S. pneumoniae* bloodstream isolates in 2008, 2013, 2017 and 2018, and for respiratory *S. pneumoniae* isolates in 2016/17 and 2017/18.

Staphylococci were categorized by their coagulase reaction and, except in 2008 CoNS were identified to species level by MALDI-TOF MS. Methicillin resistance was defined by the presence of *mecA*, as determined by PCR.[6] Pneumococci were identified by appearance and optochin susceptibility; they were serotyped as previously described.[7]

BSAC agar dilution was used to determine MIC,[5] with each isolate only tested once. Breakpoints followed EUCAST criteria (Version 10.0, 2020),[8] with *S. aureus* values adopted for CoNS (ceftaroline, indications other than pneumonia, ≤1/>2 mg/L; ceftobiprole ≤2/>2 mg/L).

Results

Both agents were tested against a total of 4219 isolates in the four bacteraemia years and two respiratory seasons. MIC distributions are shown in Table 1, whilst Figure 1 cross-plots MIC data for the two cephalosporins.

The staphylococci comprised: (i) 1884 *S. aureus*, of which 234 (12%) were MRSA; and (ii) 813 CoNS, of which 574 (71%) were methicillin resistant. Six hundred and thirty-three CoNS were identified to species level, comprising *Staphylococcus epidermidis* (*n*=424), *Staphylococcus hominis* (*n*=84), *Staphylococcus haemolyticus* (*n*=55), *Staphylococcus capitis* (*n*=46), *Staphylococcus warneri* (*n*=13) and others (*n*=11). Proportions of the major CoNS species did not change over the seasons studied (*P*=0.06). The *S. pneumoniae* panel comprised 1522 isolates, 852 from bacteraemias and 670 from LRTI.

MICs of the two cephalosporins were inter-related across the susceptibility spectrum, with ceftaroline generally around 2-fold more active than ceftobiprole on a gravimetric basis (Figure 1). All the methicillin-susceptible staphylococci were susceptible to both compounds, with MICs for methicillin-susceptible CoNS generally lower than those for MSSA. MICs for methicillin-resistant staphylococci were raised above those for their methicillin-susceptible counterparts; nonetheless, MICs for all 234 MRSA remained within the susceptible range for ceftobiprole (≤2 mg/L) and in the susceptible (≤1 mg/L) or, in 10/234 cases, high-dose susceptible/intermediate range for ceftaroline (2 mg/L) (no genotyping data for these isolates are available).

The behaviour of methicillin-resistant CoNS was species related. Among 574 such isolates tested, 518 were susceptible, by *S. aureus* breakpoints, to ceftaroline, 55 were intermediate/high-dose susceptible and 1, with a ceftaroline MIC of 4 mg/L, was resistant. Forty-three of the 56 isolates that were not fully susceptible were identified to species level [33 (77%) were *S. haemolyticus*, 5 were *S. capitis*, 3 were *S. hominis* and 2 were *S. epidermidis*]. For ceftobiprole, 519 methicillin-resistant CoNS isolates were susceptible and 55 were resistant, with MICs of 4–8 mg/L (EUCAST has no intermediate category here); 41 of these 55 isolates were identified to species level, comprising 34 *S. haemolyticus* (83%), 4 *S. hominis*, 2 *S. epidermidis* and 1 *S. capitis*. There was near total overlap between the isolates with intermediate susceptibility to ceftaroline and those with resistance to ceftobiprole. Overall, 32/55 identified methicillin-resistant *S. haemolyticus* were resistant or intermediate to both cephalosporins compared with 1/424 methicillin-resistant *S. epidermidis*, 1/84 methicillin-resistant *S. hominis*, 1/46 methicillin-resistant *S. capitis*, 0/13 methicillin-resistant *S. warneri* and 0/11 among methicillin-resistant isolates of other species; the excess of resistance in *S. haemolyticus* was highly significant (P<0.001). Geometric mean MICs of ceftaroline and ceftobiprole followed a similar relationship to species, being highest for methicillin-resistant *S. haemolyticus* at 1.18 and 2.13 mg/L, respectively, and lowest for methicillin-resistant *S. epidermidis* at 0.27 and 0.89 mg/L, respectively. At the opposite end of the MIC spectrum, it is notable that 15/26 methicillin-susceptible CoNS isolates with ceftobiprole MICs ≤0.06 mg/L were identified as *S. capitis*; these comprised one-third of all the *S. capitis* included and 68% (15/22) of all the methicillin-susceptible *S. capitis* (P<0.001).

Among the 1522 *S. pneumoniae* isolates, 1384 were fully susceptible to penicillin (with MICs ≤0.06 mg/L), 135 were in the high-dose susceptible/intermediate range (with MICs between 0.12 and 2 mg/L) and three were resistant (with MICs >2 mg/L). The rate of full susceptibility to penicillin among bloodstream isolates decreased insignificantly from 97% in 2008 to 94% in 2018 (P=0.3), but was significantly lower among respiratory isolates (574/670, 86%) compared with bloodstream isolates (810/852, 95%) (P<0.001). MICs of the two cephalosporins tracked with the penicillin values; thus, the geometric mean MICs of ceftaroline and ceftobiprole for the penicillin-susceptible isolates were 0.007 and 0.013 mg/L, respectively, the geometric mean MICs of ceftaroline and ceftobiprole for the penicillin-intermediate isolates were 0.05 and 0.12 mg/L, respectively, and the geometric mean MICs of ceftaroline and ceftobiprole for the penicillin-resistant isolates were 0.2 and 1 mg/L, respectively. Only one *S. pneumoniae* isolate, from blood in 2008 and

belonging to serotype 19F, was resistant to both ceftaroline (MIC=0.5 mg/L) and ceftobiprole (MIC=1 mg/L). Seven further isolates [all respiratory; 2016/17 (*n*=2) and 2017/18 (*n*=5); serotypes 19F (*n*=3),19A (*n*=3) and 6B (*n*=1)] were only resistant to ceftobiprole (MIC=1 mg/L). Six isolates were MDR (resistant to at least penicillin, erythromycin and tetracycline).

Mode and geometric mean MICs did not change significantly over time within the MSSA, MRSA, methicillin-susceptible CoNS, methicillin-resistant CoNS or pneumococci groups (Table 1), though the proportion of MRSA among *S. aureus* was higher in 2008 (25%) than in the three later years (range 12 - 6%).

Discussion

Ceftaroline and ceftobiprole had similarly good activity as each other against *S. aureus*, including MRSA, and pneumococci, with only tiny proportions of isolates showing reduced susceptibility or resistance. At this level, our findings corroborate those of larger surveillances for the individual compounds in the USA,[9] Canada[10] and Europe.[11] Resistance has been described in MRSA and is associated with PBP2' mutations, but these are extremely rare in the UK, Europe or the USA, though more frequent in the Far East.[12–14] In the case of pneumococci, as also found previously in the UK[15] and Canada,[16] resistance or reduced susceptibility was largely associated with serotypes (19F and 19A) that are covered by conjugate vaccines that are now widely deployed, meaning that their prevalence has diminished.

CoNS present a more complex picture, with raised ceftaroline and ceftobiprole MICs frequent among methicillin-resistant *S. haemolyticus*, as also found previously in the UK[17] and the USA.[18] This species accounted for 65% (32/44) of CoNS isolates found resistant to ceftobiprole and resistant or (mostly) intermediate/high dose susceptible to ceftaroline, but for only 8.7% (55/633) of all CoNS identified to species level. At the other end of the MIC spectrum, extreme susceptibility to ceftobiprole (not ceftaroline) was a trait of methicillin-susceptible *S. capitis.* It should also be re-stressed here that CoNS lack formal breakpoints from EUCAST. We adopted *S. aureus* breakpoints, as have others,[11] though a higher non-species-specific pharmacokinetic/pharmacodynamic breakpoint of ≤4 mg/L has also been used[9] and would have recategorized as susceptible all but one of the CoNS isolates categorized here as resistant to ceftobiprole.

Given the similar microbiological performance of these two agents, with the lower MICs of ceftaroline partly offset by a higher susceptible breakpoint for ceftobiprole, we conclude that clinical choice of which agent to prefer in a given patient should be predicated on other factors, specifically: licensed indications, clinical experience and any need for concurrent Gram-negative activity. Anti-Enterobacterales coverage is more extensive for ceftobiprole, which has a degree of stability to AmpC enzymes,[19] though not to ESBLs. Surveillance of Enterobacterales in Canadian hospitals found resistance to ceftaroline was more prevalent than to ceftobiprole, particularly in species where derepression of AmpC is frequent, e.g. *Enterobacter cloacae*.[10] According to the BNF, the per vial NHS cost for each of the two agents is similar (£37.50 for ceftaroline and £39.60 for ceftobiprole), though total costs will depend on whether ceftaroline is administered as 600 mg q8h or 600 mg q12h; ceftobiprole is licensed only for a 500 mg q8h regimen.

Continued collection of surveillance data is crucial for our understanding of emergence of resistance to or increase in MIC of newer antimicrobial agents over time, particularly for those organisms where limited national surveillance exists (e.g. CoNS).

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Members of the BSAC Resistance Surveillance Standing Committee

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Transparency declarations

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Table 1. MIC distributions, mode MICs and geometric mean MICs of ceftaroline and ceftobiprole for staphylococci and pneumococci

		MIC (mg/L)													Geometric mean MIC (mg/L)			
Organism (*n*)	Agent	0.002	0.004	0.008	0.015	0.03	0.06	0.125	0.25	0.5	1	2	4	8	2008	2013	2017	2018
Bacteraemia																		
S. aureus (1884)																		
MRSA (234)	ceftaroline	-	-	-	-	-	-	-	6	81	137	10	-	-	0.54	0.35	0.48	0.48
	ceftobiprole	-	-	-	-	-	-	-	-	8	140	86	-	-	1.51	0.95	1.13	1.19
MSSA (1650)	ceftaroline	-	-	-	-	-	8	140	**1361**	111	30	-	-	-	0.3	0.22	0.25	0.25
	ceftobiprole	-	-	-	-	-	5	12	330	1182	113	8	-	-	0.95	0.66	0.68	0.68
CoNS (813)																		
methicillin-resistant CoNS (574)	ceftaroline	1	-	1	-	-	3	57	**276**	121	59	55	1	-	0.39	0.35	0.39	0.37
	ceftobiprole	-	-	-	1	-	-	-	6	118	**287**	107	54	1	1.2	0.92	1.15	1.17
methicillin-susceptible CoNS (239)	ceftaroline	-	-	-	6	29	**105**	80	18	1	-	-	-	-	0.09	0.08	0.07	0.07
	ceftobiprole	-	-	-	2	5	18	45	**131**	33	4	1	-	-	0.3	0.18	0.2	0.19
S. pneumoniae (852)																		
penicillin MIC ≤0.06 mg/L (810)	ceftaroline	10	236	483	51	27	3	-	-	-	-	-	-	-	0.01	0.01	0.01	0.01
	ceftobiprole	-	12	225	509	56	7	1	-	-	-	-	-	-	0.02	0.01	0.01	0.01
penicillin MIC 0.12–2 mg/L (41)	ceftaroline	-	-	-	9	12	12	8	-	-	-	-	-	-	0.05	0.04	0.05	0.03
	ceftobiprole	-	-	1	5	10	4	3	9	9	-	-	-	-	0.17	0.1	0.15	0.05
penicillin MIC >2 mg/L (1)	ceftaroline	-	-	-	-	-	1	-	-	-	-	-	-	-	1	-	-	-
	ceftobiprole	-	-	-	-	-	-	-	-	-	1	-	-	-	0.06	-	-	-
																	2016/17	2017/18
Respiratory																		
S. pneumoniae (670)																		
penicillin MIC ≤0.06 mg/L (574)	ceftaroline	1	106	382	72	12	1	-	-	-	-	-	-	-	-	-	0.01	0.01
	ceftobiprole	-	-	117	427	22	8	-	-	-	-	-	-	-	-	-	0.01	0.01
penicillin MIC 0.12–2 mg/L (94)	ceftaroline	-	-	-	14	24	29	24	3	-	-	-	-	-	-	-	0.06	0.05
	ceftobiprole	-	-	-	6	26	9	6	16	26	5	-	-	-	-	-	0.11	0.14
penicillin MIC >2 mg/L (2)	ceftaroline	-	-	-	-	-	-	-	1	1	-	-	-	-	-	-	0.5	0.25
	ceftobiprole	-	-	-	-	-	-	-	-	-	2	-	-	-	-	-	1	1

EUCAST breakpoints for ceftaroline: *S. aureus*, ≤1/>2 mg/L; and *S. pneumoniae*, ≤0.25/>0.2 5 mg/L. EUCAST breakpoints for ceftobiprole: *S. aureus*, ≤2/>2 mg/L; and *S. pneumoniae*, ≤0.5/>0.5 mg/L. *S. aureus* breakpoints were assumed for CoNS.

Mode MICs are indicated in bold.

Figure 1. MICs of ceftobiprole in relation to those of ceftaroline for *S. aureus*, CoNS and *S. pneumoniae*. EUCAST breakpoints for ceftaroline: *S. aureus*, ≤1/>2 mg/L; and *S. pneumoniae*, ≤0.25/>0.25 mg/L. EUCAST breakpoints for ceftobiprole: *S. aureus*, ≤2/>2mg/L; and *S. pneumoniae*, ≤0.5/>0.5 mg/L. *S. aureus* breakpoints were assumed for CoNS. *S. aureus* isolates in the high-dose susceptible/intermediate range for ceftaroline (MIC 2 mg/L) are indicated with light grey shading, while isolates with an MIC value above the resistance breakpoint for either agent are indicated with dark grey shading.

		Ceftobiprole MIC (mg/L)												
	Ceftaroline MIC (mg/L)	0.004	0.008	0.015	0.03	0.06	0.125	0.25	0.5	1	2	4	8	Total
S. aureus	0.002	-	-	-	-	-	-	-	-	-	-	-	-	-
	0.004	-	-	-	-	-	-	-	-	-	-	-	-	-
	0.008	-	-	-	-	-	-	-	-	-	-	-	-	-
	0.015	-	-	-	-	-	-	-	-	-	-	-	-	-
	0.03	-	-	-	-	-	-	-	-	-	-	-	-	-
	0.06	-	-	-	-	-	4	3	1	-	-	-	-	8
	0.125	-	-	-	-	2	7	107	24	-	-	-	-	140
	0.25	-	-	-	-	3	1	218	1101	44	-	-	-	1367
	0.5	-	-	-	-	-	-	2	64	118	8	-	-	192
	1	-	-	-	-	-	-	-	-	91	76	-	-	167
	2	-	-	-	-	-	-	-	-	-	10	-	-	10
	4	-	-	-	-	-	-	-	-	-	-	-	-	-
	8	-	-	-	-	-	-	-	-	-	-	-	-	-
	Total	-	-	-	-	5	12	330	1190	253	84	10	-	1884
CoNS	0.002	-	-	-	-	-	-	-	-	1	-	-	-	1
	0.004	-	-	-	-	-	-	-	-	-	-	-	-	-
	0.008	-	-	1	-	-	-	-	-	-	-	-	-	1
	0.015	-	-	-	1	2	0	2	1	-	-	-	-	6
	0.03	-	-	2	3	7	9	8	0	-	-	-	-	29
	0.06	-	-	-	1	8	30	64	4	1	-	-	-	108
	0.125	-	-	-	-	1	6	59	66	5	-	-	-	137
	0.25	-	-	-	-	-	-	4	71	216	3	-	-	294
	0.5	-	-	-	-	-	-	-	9	65	48	-	-	122
	1	-	-	-	-	-	-	-	-	3	45	11	-	59
	2	-	-	-	-	-	-	-	-	-	12	42	1	55
	4	-	-	-	-	-	-	-	-	-	-	1	-	1
	8	-	-	-	-	-	-	-	-	-	-	-	-	-
	Total	-	-	3	5	18	45	137	151	291	108	54	1	813
S. pneumoniae	0.002	4	7	-	-	-	-	-	-	-	-	-	-	11
	0.004	8	222	112	-	-	-	-	-	-	-	-	-	342
	0.008	-	111	740	14	-	-	-	-	-	-	-	-	865
	0.015	-	3	89	44	9	1	-	-	-	-	-	-	146
	0.03	-	-	6	52	15	2	-	-	-	-	-	-	75
	0.06	-	-	-	4	4	7	19	11	1	-	-	-	46
	0.125	-	-	-	-	-	-	6	24	2	-	-	-	32
	0.25	-	-	-	-	-	-	-	-	4	-	-	-	4
	0.5	-	-	-	-	-	-	-	-	1	-	-	-	1
	1	-	-	-	-	-	-	-	-	-	-	-	-	-
	2	-	-	-	-	-	-	-	-	-	-	-	-	-
	4	-	-	-	-	-	-	-	-	-	-	-	-	-
	8	-	-	-	-	-	-	-	-	-	-	-	-	-
	Total	12	343	947	114	28	10	25	35	8	-	-	-	1522