

Effect of Culture Conditions on MICs of Ceftobiprole (BAL9141), Representing a New Class of Cephalosporins Active against MRSA

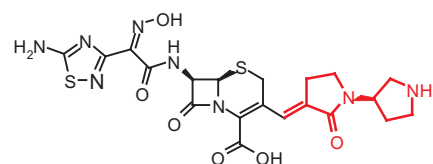
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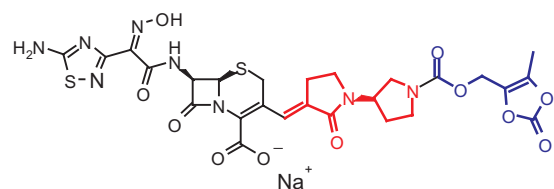
Background

- Ceftobiprole (formerly BAL9141) is a new cephalosporin, now in Phase III development, with strong affinity for the *mecA* product, PBP-2a (PBP-2') and potent activity against methicillin-resistant staphylococci in routine susceptibility tests.
- Strong induction of *mecA* (e.g. at 30°C on Columbia agar with 2% NaCl) increases the resistance of methicillin-resistant staphylococci to other β-lactams, revealing their vulnerability to this mechanism of resistance.
- We tested whether ceftobiprole's activity was significantly reduced under strongly *mecA*-inducing conditions.

Figure 1: Molecular structure of ceftobiprole



BAL9141 / Ceftobiprole



BAL5788 / Ceftobiprole medocaril

Methods

- The BSAC Bacteraemia Resistance Surveillance Programme collected 235 isolates of *S. aureus* and 212 coagulase-negative staphylococci associated with blood-stream infections from 25 laboratories in the UK and Ireland in 2003 (www.bsacsurv.org).
- MICs were measured centrally on Iso-Sensitest agar (the standard susceptibility test medium in the UK) at 37°C, and on Columbia agar with 2% NaCl at 30°C.

Results

- MIC distributions for the isolates on each medium are shown in the figures.
- MICs of ceftobiprole on Columbia agar with 2% NaCl at 30°C were increased, compared with values on Iso-Sensitest agar at 37°C, for 49% of 140 MSSA, 93% of 95 MRSA, 32% of 90 methicillin-susceptible CoNS, and 43% of 122 methicillin-resistant CoNS.
- MIC increases on Columbia agar were usually of one doubling dilution, sometimes two, rarely three (Table 1).
- For a few isolates (3 - 15%) MICs were lower on Columbia than Iso-Sensitest agar, probably owing to low salt tolerance (Table 1).

MIC shifts on different media	Percentage of isolates with indicated change in MIC on Columbia agar + 2% NaCl at 30°C compared with Iso-Sensitest agar (Doubling dilutions)						
	Decrease in MIC			No change	Increase in MIC		
	≤ -3	-2	-1	0	+1	+2	≥ +3
MSSA	3	2	5	41	49	0	0
MRSA	2	1	0	4	83	9	0
Methicillin-susceptible CoNS	0	0	7	61	20	10	2
Methicillin-resistant CoNS	0	2	12	42	37	6	1

Abbreviations

MSSA methicillin-susceptible *S. aureus*
MRSA methicillin-resistant *S. aureus*
CoNS coagulase-negative staphylococci

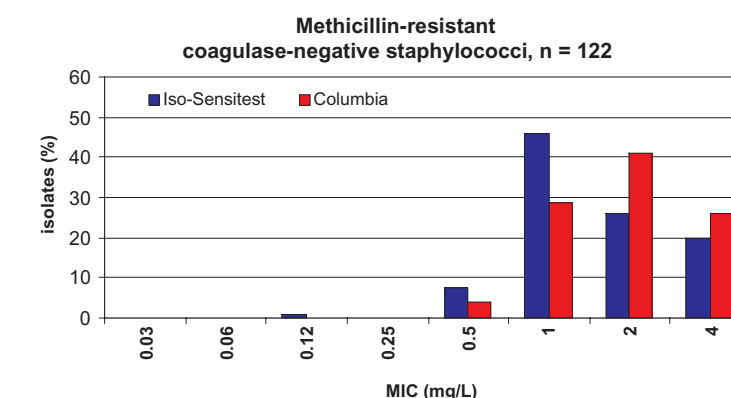
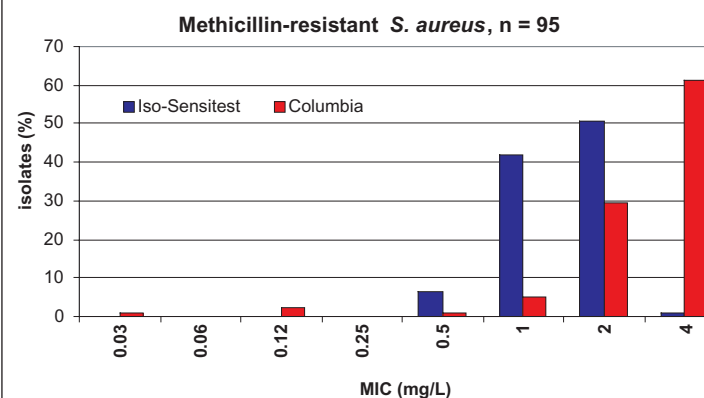
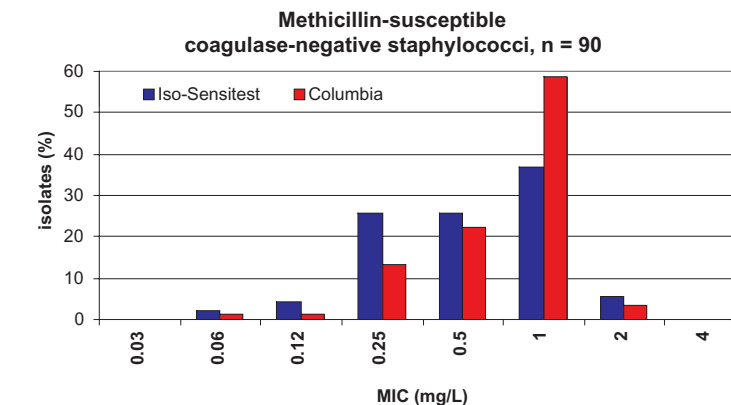
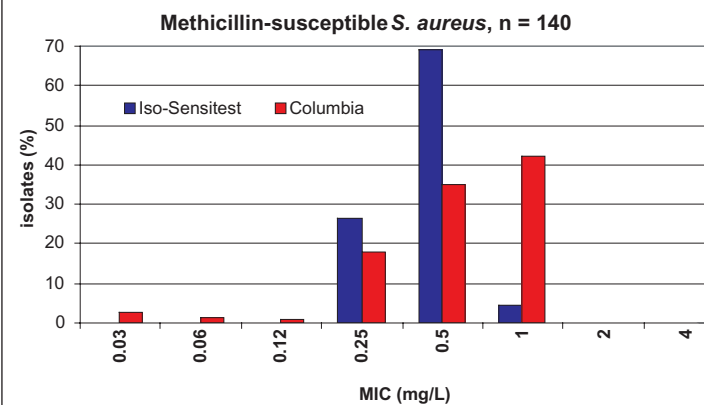
- Geometric mean MICs of ceftobiprole were increased on Columbia agar by 1.2-fold for MSSA, 1.9-fold for MRSA, and 1.3-fold for both methicillin-susceptible and -resistant CoNS (Table 2).
- The maximum recorded MICs were 1 mg/L for MSSA, 2 mg/L for methicillin-susceptible CoNS, and 4 mg/L for MRSA and methicillin-resistant CoNS, irrespective of medium.

MIC summary measures on different media	Number of isolates	MIC summary measure (mg/L)			
		MIC ₅₀	MIC ₉₀	Maximum	Geometric Mean
MSSA Iso-Sensitest	140	0.5	0.5	1	0.43
MSSA Columbia + 2% NaCl at 30°C	140	0.5	1	1	0.52
MRSA Iso-Sensitest	95	2	2	4	1.38
MRSA Columbia + 2% NaCl at 30°C	95	4	4	4	2.62
Methicillin-susceptible CoNS Iso-Sensitest	90	0.5	1	2	0.52
Methicillin-susceptible CoNS Columbia + 2% NaCl at 30°C	90	1	1	2	0.69
Methicillin-resistant CoNS Iso-Sensitest	122	1	4	4	1.47
Methicillin-resistant CoNS Columbia + 2% NaCl at 30°C	122	2	4	4	1.86

Conclusions

- Use of Columbia agar +2% NaCl at 30°C increased ceftobiprole MICs, typically by one doubling dilution for MRSA, and by less than one dilution on average for MSSA and for CoNS (irrespective of methicillin resistance).
- Ceftobiprole MICs were consistently ≤4mg/L, even under strongly *mecA*-inducing conditions.
- Thus ceftobiprole, unlike available β-lactams, should achieve anti-MRSA activity at clinically relevant concentrations.
- It does not appear necessary to use special culture conditions such as Columbia agar plus salt, or low temperature, for routine testing of staphylococci with ceftobiprole.

Figure 2— MIC distributions of ceftobiprole for staphylococci on Iso-Sensitest agar and on Columbia agar + 2% NaCl at 30°C



Acknowledgements

Collecting Laboratories: *England:* William Harvey Hospital, Kent; Birmingham City Hospital; Bristol Royal Infirmary; West Suffolk Hospital, Bury St. Edmunds; Addenbrooke's Hospital, Cambridge; Countess of Chester Hospital, Chester; Coventry & Warwickshire Hospital, Coventry; Royal Infirmary, Leicester; St Mary's Hospital, London; University College Hospital, London; Wythenshawe Hospital, Manchester; Freeman Hospital, Newcastle; Northern General Hospital, Sheffield; Royal Shrewsbury Hospital; Southampton General Hospital; Sunderland Royal Hospital; Treliske Hospital, Truro. *Ireland:* Cork University Hospital; Beaumont Hospital, Dublin. *N. Ireland:* Belfast City Hospital; Altnagelvin Area Hospital, Londonderry. *Scotland:* Glasgow Royal Infirmary; Victoria Hospital, Kirkcaldy. *Wales:* Ysbyty Gwynedd, Bangor; University Hospital of Wales, Cardiff.

Central Laboratory: HPA, London.

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