POTENTIATION OF IMIPENEM BY RELEBACTAM FOR *PSEUDOMONAS AERUGINOSA* FROM BACTERAEMIA AND RESPIRATORY INFECTIONS

Carolyne Horner[1], Shazad Mushtaq[2], David M Livermore[2,3] and the BSAC Resistance Surveillance Standing Committee
[1]British Society of Antimicrobial Chemotherapy, Birmingham, UK; [2]Public Health England, London, UK; [3]University of East Anglia, Norwich, UK

BSAC BRITISH SOCIETY FOR ANTIMICROBIAL CHEMOTHERAPY
RESISTANCE SURVEILLANCE PROGRAMME
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INTRODUCTION

- Imipenem resistance in *Pseudomonas aeruginosa* can result from either:[1]
  - Loss of OprD, a 'carbapenem-specific' porin
  - Acquired carbapenemases
- Imipenem resistance mediated by OprD loss is more common and requires continued expression of AmpC β-lactamase.[2]
- Relebactam (MK-7655, Merck) is a developmental diazabicyclooctane inhibitor with a spectrum including pseudomonal AmpC (Fig. 1).[3]

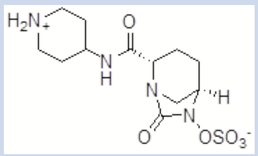

FIGURE 1
Structure of relebactam (MK-7655).[4]

Objective:

- To determine the effects of relebactam on imipenem MICs for *P. aeruginosa* isolates.

METHODS

- Consecutive *P. aeruginosa* isolates causing bacteraemia or hospital-onset lower respiratory tract infection submitted to the BSAC Resistance Surveillance Programme were tested.[5]
- Isolates were submitted from laboratories (n=24-38) throughout the UK and Ireland (Fig. 2).
- MICs were determined centrally by agar dilution,[6] with relebactam fixed at 4 mg/L.
- Current imipenem EUCAST breakpoints were used. Breakpoints for imipenem-relebactam have not been established yet.[7]
- β-Lactamase genes were identified by PCR.

FIGURE 2
Distribution of participating laboratories throughout the UK and Ireland (n=24-38).

RESULTS

Surveillance		Bacteraemia		Respiratory	
Season		2015	2016	2014-15	2015-16
Isolates (n)		216	217	211	207
Centres (n)		38	25	36	24
Sex (%)	Male	63	68	62	62
	Female	37	32	38	38
	NK	0	4	0	0
Age range (years %)	0-9	3	2	6	7
	10-19	2	1	2	8
	20-29	1	1	3	5
	30-39	2	3	4	3
	40-49	5	9	4	4
	50-59	13	11	14	11
	60-69	19	19	23	20
	70+	55	53	43	41
	NK	1	1	0	1

TABLE 1
Demographic details of the *P. aeruginosa* isolates tested (n=851) (NK: not known).

- 851 *P. aeruginosa* isolates were tested from a 26-month period (Table 1).
- 89% isolates were imipenem-susceptible (IMI-S).
- Of the 92 imipenem-non-susceptible (IMI-NS) isolates:
  - 2 had ESBLs
  - 5 had metallo-carbapenemases (MBLs)
- MIC ranges of imipenem (IMI) alone vs. imipenem with relebactam (IMI-REL) are shown in Table 2.
- MIC distributions of imipenem alone vs. imipenem-relebactam are shown in Figure 3.

Resistance Phenotype	*n*	MIC (mg/L)	
		IMI	IMI-REL
IMI-S (MIC≤4mg/L)	759	0.5-2	0.25-0.5
IMI-NS (MIC>4mg/L)	92	8-16	1-2
ESBL (VEB=1; PER=1)	2	8-16	2-4
MBL (VIM=4; NDM=1)	5	32->256	16->256

TABLE 2
Summary of MIC parameters by resistance type. (MIC90 values: IMI: 8mg/L; IMI-REL, 1mg/L).

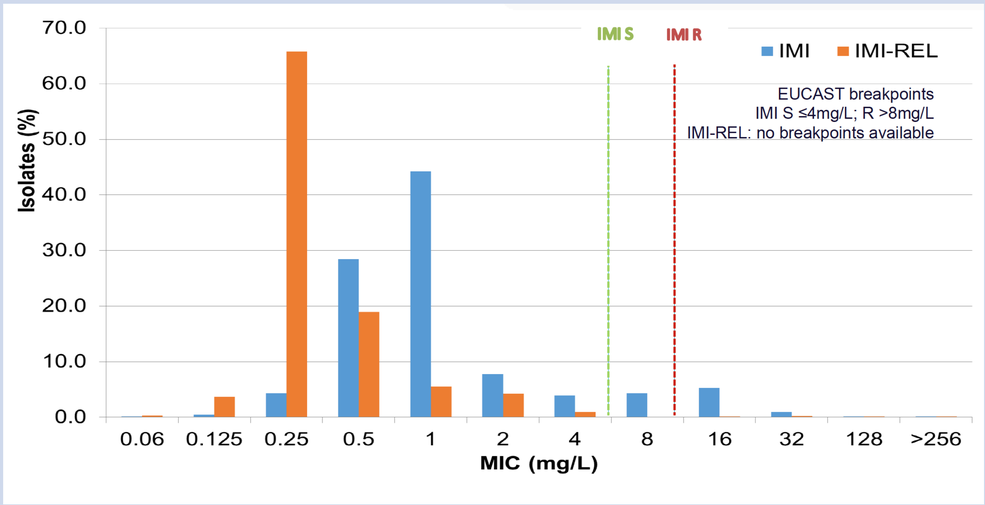

FIGURE 3
Susceptibility of *P. aeruginosa* tested against imipenem and imipenem with relebactam. The green dotted line indicates the IMI-S EUCAST breakpoint (≤4mg/L), the red dotted line the IMI-R EUCAST breakpoint (>8mg/L).

CONCLUSIONS

- Potentiation of imipenem by relebactam was almost universal for *P. aeruginosa*, which supports the view that endogenous AmpC, where inducible or derepressed, protects *P. aeruginosa* against imipenem.[2]
- The modal MIC reduction with relebactam for IMI-S *P. aeruginosa* was 4-fold.
- The modal MIC reduction with relebactam for IMI-NS *P. aeruginosa* lacking MBLs was 8-fold.
- Relebactam 4 mg/L brought imipenem MICs to the EUCAST breakpoint or below for 87/92 (95%) IMI-NS *P. aeruginosa*.
- Potentiation of two IMI-NS ESBL producers probably reflected inhibition of co-produced AmpC.
- MBL-producing *P. aeruginosa* remained resistant; MBLs are not inhibited by diazabicyclooctanes.[3]

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PROGRAMME CO-ORDINATOR

Programme Co-ordinator: Dr Carolyne Horner.
Email: rs@bsac.org.uk.