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In vitro activity of sulbactam/durlobactam against global isolates of carbapenem-resistant *Acinetobacter baumannii*

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Objectives: To evaluate the activity of the novel broad-spectrum serine β-lactamase inhibitor durlobactam (ETX2514) combined with sulbactam against global isolates of carbapenem-resistant *Acinetobacter baumannii* with defined carbapenem resistance mechanisms compared with reference antimicrobials with known activity against *Acinetobacter* spp.

Methods: The susceptibility of 246 carbapenem-resistant non-duplicate *A. baumannii* isolates to sulbactam/durlobactam, amikacin, colistin, imipenem/sulbactam/durlobactam, imipenem, meropenem, minocycline and sulbactam was tested using broth microdilution. Isolates were obtained from various body sites from patients in 37 countries and from six world regions between 2012 and 2016. Identification of carbapenem resistance mechanisms and assignment to *A. baumannii* clonal lineages was based on WGS.

Results: Sulbactam/durlobactam showed excellent activity comparable to colistin but superior to amikacin, minocycline and sulbactam. The sulbactam/durlobactam $MIC_{50/90}$ values were 1/4 and 2/4 mg/L and the colistin $MIC_{50/90}$ values were 0.5 and 1 mg/L, respectively. Comparatively, amikacin, minocycline and sulbactam $MIC_{50/90}$ values were 256/≥512, 2/16 and 16/64 mg/L, respectively.

Conclusions: Sulbactam/durlobactam had excellent *in vitro* potency against *A. baumannii* isolates, including those that were resistant to imipenem/meropenem, amikacin, minocycline and colistin, compared with other compounds. Sulbactam/durlobactam has the potential to become a useful addition to the limited armamentarium of drugs that can be used to treat this problem pathogen.

Introduction

Acinetobacter baumannii is a nosocomial pathogen known for its MDR and propensity for epidemic spread.[1] Resistance to penicillins, cephalosporins, fluoroquinolones, aminoglycosides and tetracyclines is frequent and, in the past decade, resistance to carbapenems in *A. baumannii* has increased worldwide and is a cause of concern. Resistance to carbapenems in *A. baumannii* is primarily caused by carbapenem-hydrolysing class D β-lactamases and, less frequently, MBLs.[2,3] Carbapenem-resistant *A. baumannii* is considered as priority 1 ('critical') in the WHO priority pathogens list for research, discovery and development of new antibiotics (https://www.who.int/medicines/publications/global-priority-list-antibiotic-resistant-bacteria/en/) published in 2017 and has recently been upgraded to an urgent public health threat by the CDC (https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf).

Sulbactam is a penicillin derivative that is used widely as an inhibitor of β-lactamases. Furthermore, it has intrinsic activity against *A. baumannii*, due to inhibition of PBP3, but high MICs are usually seen among isolates showing resistance to carbapenems.[4–6] Sulbactam resistance determinants include the β-lactamases $bla_{TEM\text{-}1D}$ and bla_{ADC}, where the level of *ampC* expression was found to be related to the presence of the insertion element IS*Aba1* upstream of *ampC*.[5,7] In addition, sulbactam breakpoints are not available and this drug has only been used occasionally in combination with ampicillin for infections caused by *A. baumannii*.[8,9] Frequently, colistin is the only remaining therapeutic option for these infections, but, even with this drug, resistance has developed.[10,11]

The diazabicyclooctenone durlobactam (previously known as ETX2514) is a novel broad-spectrum serine β-lactamase inhibitor that restores sulbactam activity against resistant *A. baumannii*.[12,13] The combination sulbactam/durlobactam has promising *in vitro*

and *in vivo* activity against this organism.[13–15] Sulbactam/durlobactam has demonstrated favourable safety, tolerability and pharmacokinetic properties in Phase 1 and Phase 2 studies[16–18] and is currently being evaluated in a randomized, controlled Phase 3 study in patients with *A. baumannii* infections, including hospital-acquired bacterial pneumonia, ventilator-associated bacterial pneumonia and bacteraemia, as well as in patients with *A. baumannii* infections that are resistant to or have failed colistin treatment (https://clinicaltrials.gov/ct2/show/NCT03894046?term=ETX2514&draw=2&rank=7).

The purpose of this study was to evaluate the activity of the sulbactam/durlobactam combination in comparison with reference antimicrobials with known activity against *Acinetobacter* species against a collection of well characterized, non-duplicate, global isolates of carbapenem-resistant *A. baumannii* harbouring acquired oxacillinases, MBLs or an up-regulated intrinsic OXA-51-like carbapenemase.

Materials and methods

Antimicrobial susceptibility testing was performed by broth microdilution in freshly prepared CAMHB following CLSI recommendations.[19] Frozen, 96-well microdilution plates containing antibacterial agents in CAMHB were provided by JMI Laboratories (North Liberty, IA, USA). Two hundred and forty-six non-duplicate, carbapenem-resistant *A. baumannii* isolates were tested against amikacin, colistin, imipenem combined with sulbactam and durlobactam, imipenem, meropenem, minocycline, sulbactam combined with durlobactam, and sulbactam alone. Resistance to carbapenems has been previously confirmed by Etest (bioMérieux, Nürtingen, Germany). The concentration ranges tested in 2-fold dilutions were: amikacin, 0.125–256 mg/L; colistin, 0.06–128 mg/L; imipenem, 0.06–128 mg/L; imipenem/sulbactam/durlobactam (titrated at a fixed 1:1:2 ratio), 0.0625–128 mg/L; meropenem, 0.06–128 mg/L; minocycline, 0.03–64 mg/L; sulbactam, 0.06–128 mg/L; and sulbactam/durlobactam (fixed at 4 mg/L), 0.06–128 mg/L. MICs were interpreted following CLSI guidelines and susceptibility rates were determined using CLSI breakpoints where applicable.[20] *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853 and *A. baumannii* NCTC 13304 were used as quality control strains.

The isolates were subjected to WGS using the Illumina MiSeq platform and MLST types were derived from WGS data. Isolates had their carbapenem-resistance mechanisms determined as described previously. The presence of oxacillinase-encoding genes ($bla_{\text{OXA-51-like}}$, $bla_{\text{OXA-23-like}}$, $bla_{\text{OXA-40-like}}$, $bla_{\text{OXA-58-like}}$, $bla_{\text{OXA-143-like}}$ and $bla_{\text{OXA-235-like}}$) was investigated using a previously described multiplex PCR.[21,22] Two further multiplex PCRs were applied to detect bla_{VIM}, bla_{KPC}, bla_{NDM}, bla_{IMI}, bla_{GES}, bla_{GIM}, bla_{IMP} and IS*Aba1* upstream of $bla_{\text{OXA-51-like}}$.[23] In addition, ResFinder 3.1 (https://cge.cbs.dtu.dk/services/ResFinder/) was applied to determine the acquired resistome of each isolate from sequencing data with special interest in the distinct variants of the carbapenemase families identified by PCR. The raw sequencing reads generated in this project were submitted to the European Nucleotide Archive (https://www.ebi.ac.uk/ena/) under the study accession number PRJEB27899.

Results

The isolates were collected between 2012 and 2016 from various body sites in patients from 94 hospitals in 37 countries and from six world regions: Africa ($n = 25$), Asia and South Pacific (67), Europe (46), Latin America (66), Middle East (3) and North America (39). The average number of isolates per hospital was 3.8 with only 15% of hospitals contributing more than three isolates over the 5 year study period. Based on core genome MLST results, isolates represented the eight previously described major international clonal lineages [IC1 ($n = 21$), IC2 (150), IC3 (1), IC4 (4), IC5 (37), IC6 (3), IC7 (9) and IC8 (4)], while 17 isolates did not cluster with any of the international clonal lineages.[3] One hundred and eighty-three isolates harboured $bla_{\text{OXA-23-like}}$, 47 isolates harboured $bla_{\text{OXA-40-like}}$, 3 isolates harboured $bla_{\text{OXA-58-like}}$, 1 isolate harboured $bla_{\text{OXA-237}}$, 3 isolates harboured $bla_{\text{NDM-1}}$, 1 isolate co-harboured $bla_{\text{OXA-23}}$ and $bla_{\text{NDM-1}}$, 1 isolate harboured $bla_{\text{IMP-26}}$ and 7 isolates had no acquired carbapenemase but overexpressed their intrinsic $bla_{\text{OXA-51}}$.

Table 1 shows the MIC distributions, MIC_{50} and MIC_{90} values, MIC ranges and percentage susceptibility rates. All isolates were resistant to imipenem and meropenem, 69.5% of isolates were resistant to amikacin, 24.4% of isolates were resistant to

Table 1. MIC distributions, MIC_{50} and MIC_{90} values, MIC ranges and antimicrobial susceptibilities of 246 carbapenem-resistant *A. baumannii* isolates

	MIC																		
Antimicrobial agent	≤0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	≥256	MIC_{50}	MIC_{90}	MIC range	%S	%I	%R
Amikacin				3	9	14	6	9	**9**[d]	25	20	25	126	256	≥512	0.5 to ≥512	20.3	10.2	69.5
Colistin		3	52	159	20	**2**[d]		2		3	4		1	0.5	1	0.125 to ≥256	95.9	–	4.1
Imipenem						**0**[d]		8	5	49	121	57	6	64	128	8 to ≥256	0.0	0.0	100.0
Imipenem/sulbactam/durlobactam[a,b]			4	36	125	66	9	3		3				1	2	0.25–32	–	–	–
Meropenem						**0**[d]		2	10	55	99	58	22	64	128	8 to ≥256	0.0	0.0	100.0
Minocycline	4	6	24	38	29	23	**27**[d]	35	52	4	4			2	16	≤0.06–64	61.4	14.2	24.4
Sulbactam[a]						2	11	43	68	80	36	3	3	16	64	2 to ≥256	–	–	–
Sulbactam/durlobactam[a,c]			7	56	97	66	11	3	2	1	1	2		1	2	0.25–128	–	–	–

S, susceptible; I, intermediate; R, resistant.
MICs are given as mg/L.
[a]No CLSI breakpoint available.
[b]Imipenem MIC values are shown.
[c]Sulbactam MIC values are shown.
[d]Susceptible breakpoint values are indicated in bold.

minocycline, 4.1% of isolates were resistant to colistin and many isolates exhibited high sulbactam MICs (range = 2 to ≥256 mg/L).

The sulbactam/durlobactam $MIC_{50/90}$ values were 1/4 and 2/4 mg/L, respectively. Identical $MIC_{50/90}$ values of 1 and 2 mg/L were also observed for the imipenem/sulbactam/durlobactam (1:1:2) combination. Only nine isolates had a sulbactam/durlobactam MIC ≥8/4 mg/L. Among the 10 isolates that were resistant to colistin, all had low sulbactam/durlobactam MICs of ≤2/4 mg/L.

We did not find a correlation between the major bla_{OXA} types and MICs determined for sulbactam/durlobactam, as shown in Table 2. The sulbactam/durlobactam $MIC_{50/90}$ values were 1/4 and 2/4 mg/L, respectively, for isolates with OXA-23-like (n = 184) and 1/4 and 1/4 mg/L, respectively, for isolates with OXA-40-like (n = 47). Likewise, the sulbactam/durlobactam MIC values for isolates harbouring other serine carbapenemases (n = 11) ranged from 0.5 to 2 mg/L and the $MIC_{50/90}$ was 1/4 and 2/4 mg/L. Of note, all *A. baumannii* isolates exhibiting sulbactam/durlobactam MIC values ≥32 mg/L encoded the MBL bla_{NDM-1}. Isolates harbouring other carbapenemases were less frequently resistant to amikacin and to minocycline and they were all susceptible to colistin. Similarly, no impact of clonal strain type on sulbactam/durlobactam MICs was observed (Table 3). The sulbactam/durlobactam $MIC_{50/90}$ values were 0.5/4 and 2/4 mg/L, respectively, for IC1 isolates (n = 21), 1/4 and 2/4 mg/L for IC2 isolates (n = 150) and 1/4 and 1/4 mg/L for IC5 isolates (n = 37).

To analyse the correlation between sulbactam MICs and sulbactam/durlobactam activity, we compared sulbactam/durlobactam $MIC_{50/90}$ values for *A. baumannii* isolates with sulbactam MICs ≤16 mg/L (n = 124), 32–64 mg/L (n = 116) and ≥128 mg/L (n = 6). While the sulbactam/durlobactam MIC range for isolates with sulbactam MICs ≤16 mg/L was 0.25/4–4/4 and the $MIC_{50/90}$ values were 1/4 and 2/4 mg/L, the sulbactam/durlobactam MIC range was 0.25/4–16/4 mg/L for *A. baumannii* isolates with sulbactam MICs of 32 and 64 mg/L and their respective $MIC_{50/90}$ values were 1/4 and 4/4 mg/L. In contrast, *A. baumannii* isolates with sulbactam MICs ≥128 mg/L (n = 6), four of which expressed MBLs, had significantly higher sulbactam/durlobactam MICs, ranging from 1 to 128 mg/L, and their $MIC_{50/90}$ values were 32/4 and 128/4 mg/L, respectively.

Discussion

A. baumannii has recently been listed by the WHO among the critical-priority bacteria that urgently require discovery, research and development of new antimicrobials.[24] MDR *A. baumannii* is known for its propensity to cause hospital outbreaks around the globe and the majority of isolates recovered worldwide represent IC2.[3,25–27] Widespread resistance to carbapenems causes great concern and often leaves the clinician with few remaining treatment options.[28–30] In recent years, susceptibility of *A. baumannii* to carbapenems has declined to ∼20% in many geographical regions.[31] Frequently, colistin is the only compound showing measurable activity against carbapenem-resistant *A. baumannii*, but its therapeutic use is limited by toxicity and low serum and tissue concentrations.[28,30] In addition, colistin resistance is of increasing concern, in particular in countries where this drug is frequently used for the treatment of infections caused by carbapenem-resistant *A. baumannii*, Enterobacterales and *P. aeruginosa*.[10,30] Over the last decade, a number of new drugs

Table 2. MIC_{50} and MIC_{90} values and antimicrobial susceptibilities of 246 carbapenem-resistant *A. baumannii* isolates harbouring different carbapenemases

Antimicrobial agent	$bla_{OXA-23-like}$ (n = 184)						$bla_{OXA-40-like}$ (n = 47)						Other carbapenemases (n = 15)[d]					
	MIC_{50}	MIC_{90}	MIC range	%S	%I	%R	MIC_{50}	MIC_{90}	MIC range	%S	%I	%R	MIC_{50}	MIC_{90}	MIC range	%S	%I	%R
Amikacin	256	≥512	0.5 to ≥512	18.0	8.1	73.9	64	≥512	1 to ≥512	23.4	19.1	57.5	32	≥512	2 to ≥512	40.0	6.7	53.3
Colistin	0.5	1	0.5–6 4	96.7	-	3.3	0.5	32	0.25 to ≥256	91.5	-	8.5	0.5	0.5	0.125–1	100.0	-	0.0
Imipenem	64	128	16–128	0.0	0.0	100.0	128	≥256	64 to ≥256	0.0	0.0	100.0	8	≥256	8 to ≥256	0.0	0.0	100.0
Imipenem/ sulbactam/ durlobactam[a,b]	1	2	0.25–32	-	-	-	1	2	0.25–2	-	-	-	1	32	0.25–32	-	-	-
Meropenem	64	128	16 to ≥256	0.0	0.0	100.0	128	≥256	16 to ≥256	0.0	0.0	100.0	16	≥256	8 to ≥256	0.0	0.0	100.0
Minocycline	4	16	0.06–64	57.6	13.0	29.4	1	16	0.06–16	66.0	23.4	10.6	0.5	4	0.06–16	93.3	0.0	6.7
Sulbactam[a]	32	64	4 to ≥256	-	-	-	16	64	4–64	-	-	-	8	≥256	2 to ≥256	-	-	-
Sulbactam/ durlobactam[a,c]	1	2	0.25–128	-	-	-	1	1	0.25–8	-	-	-	1	64	0.5–128	-	-	-

S, susceptible; I, intermediate; R, resistant.
MICs are given as mg/L.
[a]No CLSI breakpoint available.
[b]Imipenem MIC values are shown.
[c]Sulbactam MIC values are shown.
[d]Other carbapenemases were $bla_{OXA-58-like}$ (3 isolates), $bla_{OXA-237}$ (1 isolate), bla_{NDM-1} (3 isolates), bla_{IMP-26} (1 isolate) and up-regulated bla_{OXA-51} (7 isolates).

Table 3. MIC_{50} and MIC_{90} values and antimicrobial susceptibilities of 208 carbapenem-resistant *A. baumannii* isolates representing international clonal lineages IC1, IC2 and IC5

Antimicrobial agent	IC1 (n = 21)						IC2 (n = 150)						IC5 (n = 37)					
	MIC_{50}	MIC_{90}	MIC range	%S	%I	%R	MIC_{50}	MIC_{90}	MIC range	%S	%I	%R	MIC_{50}	MIC_{90}	MIC range	%S	%I	%R
Amikacin	32	256	1 to ≥512	47.6	4.8	47.6	≥512	≥512	0.5 to ≥512	16.0	5.3	78.7	64	≥512	4 to ≥512	16.2	29.7	54.1
Colistin	0.5	1	0.25–1	100.0	–	0.0	0.5	0.5	0.25–64	96.0	–	4.0	0.5	2	0.25 to ≥256	91.9	–	8.1
Imipenem	32	128	8–128	0.0	0.0	100.0	64	128	8 to ≥256	0.0	0.0	100.0	64	128	16 to ≥256	0.0	0.0	100.0
Imipenem/ sulbactam/ durlobactam[a,b]	1	2	0.5–32	–	–	–	1	2	0.25–8	–	–	–	1	1	0.25–1	–	–	–
Meropenem	32	128	16 to ≥256	0.0	0.0	100.0	64	128	8 to ≥256	0.0	0.0	100.0	128	≥256	16 to ≥256	0.0	0.0	100.0
Minocycline	1	2	0.25–32	90.5	0.0	9.5	8	16	0.25–64	41.3	22.0	36.7	0.5	1	0.125–4	100.0	–	0.0
Sulbactam[a]	16	32	4 to ≥256	–	–	–	32	64	2–128	–	–	–	16	32	8–64	–	–	–
Sulbactam/ durlobactam[a,c]	0.5	2	0.25–128	–	–	–	1	2	0.25–16	–	–	–	1	1	0.25–1	–	–	–

S, susceptible; I, intermediate; R, resistant.
MICs are given as mg/L.
[a]No CLSI breakpoint available.
[b]Imipenem MIC values are shown.
[c]Sulbactam MIC values are shown.

with activity against MDR Gram-negative pathogens have found their way to the market, but most of these, including ceftolozane/tazobactam, ceftazidime/avibactam, plazomicin, imipenem/relebactam and meropenem/vaborbactam, have very poor activity against carbapenem-resistant *A. baumannii*.[12] Only eravacycline, the first fully synthetic fluorocycline antibiotic developed, and currently indicated for complicated intra-abdominal infections only, has shown promising *in vitro* activity against *A. baumannii*.[32] Therefore there is an urgent need to develop new drugs targeting serious infections caused by MDR *A. baumannii*.

Durlobactam is a potent inhibitor of class A, C and D β-lactamases.[13,14] In particular, the inhibition of OXA-type carbapenemases, which are commonly found in this species, make durlobactam a promising candidate to target MDR *A. baumannii*. It has intrinsic antibacterial activity against some Enterobacterales; however, it does not inhibit *A. baumannii* in the absence of a β-lactam partner. In preclinical studies, the combination of durlobactam with sulbactam has shown *in vitro* activity against *A. baumannii*, including carbapenem-resistant isolates.[13,33] It is currently in development as a narrow-spectrum agent in a fixed-dose combination with sulbactam, for the treatment of a variety of serious infections caused by MDR *A. baumannii*, including bacteraemia and ventilator-associated bacterial pneumonia.

In our study, we assessed the *in vitro* activity of sulbactam/durlobactam against a panel of carbapenem-resistant *A. baumannii* representing a unique collection of isolates. Their geographical origin from 94 hospitals in 37 countries and from six world regions ensures the greatest possible strain diversity in an organism that is known for its propensity for clonal epidemic spread. The number of isolates included was based on the population size of participating countries to optimally reflect the current global epidemiology of carbapenem-resistant *A. baumannii*. Molecular characterization of isolates using WGS was used to identify currently circulating international clonal lineages and carbapenem resistance mechanisms. We found that sulbactam/durlobactam had potent activity against carbapenem-resistant *A. baumannii* isolates irrespective of their assigned international clonal lineage as well as their oxacillinase type, with $MIC_{50/90}$ values of 1 and 2 mg/L, respectively. The addition of durlobactam lowered the MICs of sulbactam by 16- to 64-fold. Of note, the addition of imipenem to the sulbactam/durlobactam combination did not affect the activity of the combination alone. While the $MIC_{50/90}$ values of sulbactam/durlobactam were similar in isolates with lower (≤16 mg/L) and higher (32–64 mg/L) sulbactam MICs, isolates with sulbactam MICs of ≥128 mg/L had significantly higher sulbactam/durlobactam MICs. As expected, sulbactam/durlobactam was not active against *A. baumannii* isolates harbouring the MBL NDM-1, but this resistance mechanism was only rarely observed (1.2%). Our data concur with a previous study of 72 well-characterized *A. baumannii* isolates from the Walter Reed Army Medical Center (WRAMC), 17 of which were resistant to carbapenems.[14] In this study, Barnes *et al.*[14] reported sulbactam/durlobactam $MIC_{50/90}$ values of 1 and 2 mg/L, respectively. In 26 additional *A. baumannii* isolates collected from patients at the Brooke Army Medical Center as well as from two hospitals in Cleveland that were resistant to carbapenems, similar $MIC_{50/90}$ values of 2 and 2 mg/L, respectively, for sulbactam/durlobactam were found.[14] However, these isolates represented only a very limited geographical region in the USA and the finding that 70 of the 72 isolates from WRAMC possessed the intrinsic $bla_{OXA\text{-}69\text{-}like}$

suggests that the isolates represent a single clonal lineage. In another recent study of 1420 *A. baumannii* isolates collected worldwide, over 60% of which were carbapenem-resistant, comparable $MIC_{50/90}$ values of 1 and 4 mg/L, respectively, were reported.[33] However, no information regarding their epidemiological background or resistance mechanisms was provided, apart from a small subset of 39 isolates with sulbactam/durlobactam MICs >4 mg/L that were subjected to WGS. Of note, isolates with elevated sulbactam/durlobactam MICs were either NDM-1 producers ($n = 11$) or had amino acid changes in PBP3 ($n = 21$), the primary target of sulbactam.

In conclusion, sulbactam/durlobactam had excellent *in vitro* potency against *A. baumannii* isolates, including those that were resistant to imipenem/meropenem, amikacin, minocycline and colistin, compared with other compounds. The *in vitro* activity was similar against isolates possessing different oxacillinases and was not affected by *A. baumannii* clonal strain type or geographical region. Sulbactam/durlobactam is a promising therapeutic option for treatment of infections due to MDR *A. baumannii*.

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