694

In vitro Antibacterial Activity of Sulbactam-Durlobactam (ETX2514) against 121 Recent *Acinetobacter baumannii* Isolates from Patients in India

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Abstract

Background

The incidence of infections caused by multidrug-resistant *Acinetobacter baumannii* is increasing at an alarming rate in Southeast Asia and other parts of the world. Sulbactam (SUL) has intrinsic antibacterial activity against *A. baumannii*; however, the prevalence of β-lactamases in this species has limited its therapeutic use. Durlobactam (ETX2514, DUR) is a novel β-lactamase inhibitor with broad spectrum activity against Ambler class A, C and D β-lactamases. DUR restores SUL *in vitro* activity against multidrug-resistant *A. baumannii*. Against >3,600 globally diverse clinical isolates from 2012-2017, addition of 4 mg/L durlobactam reduced the SUL MIC_{90} from >32 to 2 mg/L. SUL-durlobactam (SUL-DUR) is currently in Phase 3 clinical development for the treatment of infections caused by *A. baumannii*. The goal of this study was to determine the activity of SUL-DUR and comparator agents amikacin (AMK), ampicillin-sulbactam (AMP-SUL), sulbactam-cefoperazone (SUL-CFP) and meropenem (MEM) against *A. baumannii* isolated from hospitalized patients in India.

Methods

A total of 121 clinical MDR *A. baumannii* isolates from multiple hospital settings and infection sources were collected between 2016 and 2019 from six geographically diverse hospitals in India. Species identification was performed by MALDI-TOF. Susceptibility of these isolates to SUL-DUR (10μg/10μg) and comparator antibiotics was determined by disk diffusion using CLSI methodology, except for SUL-CFP, for which resistance was defined using the SUL-CFP package insert.

Results

As shown in Table 1, resistance of this collection of isolates to marketed agents was extremely high. In contrast, based on preliminary breakpoint criteria, only 11.5% of isolates were resistant to SUL-DUR.

Table 1. Percent Resistant *A. baumannii*

SUL-DUR	AMP-SUL	MEM	AMK	SUL-CFP
11.6	90.9	95.9	88.4	78.5

Conclusions

The *in vitro* antibacterial activity of SUL-DUR was significantly more potent than comparator agents against multidrug-resistant *A. baumannii* isolates collected from diverse sites in India. These data support the continued development of SUL-DUR for the treatment of antibiotic-resistant infections caused by *A. baumannii*.

Introduction

Durlobactam (DUR, ETX2514) is a novel, diazabicyclooctenone β-lactamase inhibitor (BLI) with best-in-class broad spectrum activity against class A, C and D β-lactamases[1]. Sulbactam (SUL) is an approved BLI with antibacterial activity against *Acinetobacter* spp. due to its inhibition of PBP3, an enzyme required for cell wall biosynthesis[2]. SUL-DUR is active against >98% of *Acinetobacter baumannii calcoaceticus* complex (ABC) clinical isolates tested to date in longitudinal, global surveillance studies, with an MIC_{90} of 2 mg/L (N > 3,600). SUL-DUR is currently in Phase 3 clinical development for the treatment of infections caused by drug-resistant ABC organisms.

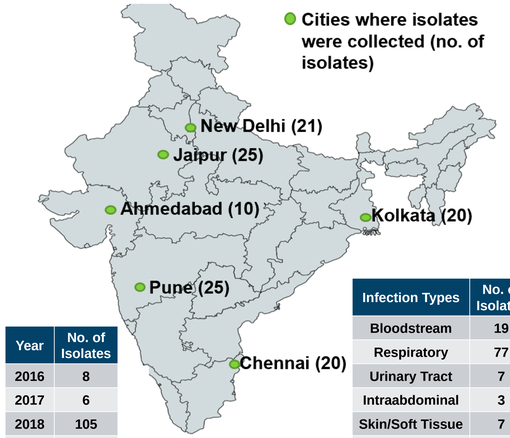
Although surveillance systems to monitor multi-drug resistance in India are currently being established[3], quantitative, prevalence-based data are not yet available. We therefore sought to determine rates of antibiotic resistance in recent, MDR *A. baumannii* clinical isolates from six geographically distinct hospitals using both disk diffusion and broth microdilution methods. Because Class B metallo-β-lactamases are likely to be common in India, we also performed PCR to determine the percentage of isolates bearing genes for these enzymes.

Methods

Broth microdilution and disk diffusion susceptibility testing was conducted according to CLSI guidelines[4], including assessment of QC strains. Susceptibility testing by disk diffusion was performed by IHMA-India, in which a SUL-DUR 10μg/10μg disk was used. All other assays were performed at IHMA-US. For susceptibility testing by broth MIC, SUL-DUR was assayed by dilution of sulbactam in the presence of a fixed concentration of 4 mg/L durlobactam. Genomic DNA was extracted from all isolates, and PCR was performed to screen for the presence of metallo-β-lactamase genes.

Study Design

121 MDR *A. baumannii* were collected during 2016-2019 from Indian medical centers in 6 cities. Isolates represent a variety of infection types including bloodstream, pneumonia and skin and soft tissue in hospitalized patients.
Each isolate was profiled for sulbactam-durlobactam (SUL-DUR) susceptibility by disk diffusion and broth MIC. Each isolate was also profiled by PCR for the presence of genes encoding metallo-β-lactamases VIM, GIM, IMP, SPM and NDM.



Year	No. of Isolates
2016	8
2017	6
2018	105
2019	2

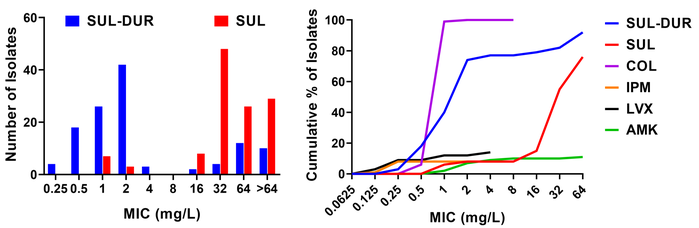
Infection Types	No. of Isolates
Bloodstream	19
Respiratory	77
Urinary Tract	7
Intraabdominal	3
Skin/Soft Tissue	7
Other	8

Susceptibility to Sulbactam-Durlobactam by Disk Diffusion

Antimicrobial Agent	Range (mm)	Interpretive Criteria*		
		%S	%I	%R
Sulbactam-Durlobactam	6 – 34	81.0	7.4	11.6
Meropenem	6 – 35	3.3	0.8	95.9
Amikacin	6 – 28	10.7	0.8	88.4
Ampicillin-Sulbactam	6 – 34	5.8	3.3	90.9
Sulbactam-Cefoperazone	6 – 36	6.6	14.9	78.5

*Based on 2019 CLSI breakpoint criteria[5] except for cefoperazone-sulbactam, which is based on the package insert for sulperazone®[6], and sulbactam-durlobactam, which is based on the working MIC-disk correlates using the preliminary breakpoint of S/I/R of 4/8/16 mg/L. %S=percent susceptible, %I=percent intermediate, %R=percent resistant.

Susceptibility to Sulbactam-Durlobactam by Broth Microdilution



Antimicrobial Agent	N	mg/L				Interpretive Criteria*		
		Min	Max	MIC_{50}	MIC_{90}	%S	%I	%R
SUL-DUR	121	0.25	>64	2	64	76.9	0	23.1
SUL	121	1	>64	32	>64	8.3	0	91.7
SUL-CFP	121	1	>32	>32	>32	10.7	26.4	62.9
IPM	121	0.12	>8	>8	>8	8.3	0	91.7
MEM	121	0.06	>8	>8	>8	8.3	0	91.7
FEP	121	1	>16	>16	>16	8.3	0.8	90.9
LVX	121	≤0.06	>4	>4	>4	6.6	1.7	91.7
COL	121	0.5	2	1	1	100	NA	0
AMK	121	1	>64	>64	>64	9.9	0	90.1

*Based on 2019 CLSI breakpoint criteria[5] except for sulbactam-cefoperazone, which is based on the package insert for sulperazone®[6], and sulbactam-durlobactam, which is based on the preliminary breakpoint of 4/8/16 mg/L (S/I/R). %S=percent susceptible, %I=percent intermediate, %R=percent resistant. SUL-DUR=sulbactam-durlobactam; SUL=sulbactam; SUL-CFP=sulbactam-cefoperazone (1:2); IPM=imipenem; MEM=meropenem; FEP=cefepime; LVX=levofloxacin; COL=colistin; AMK=amikacin.

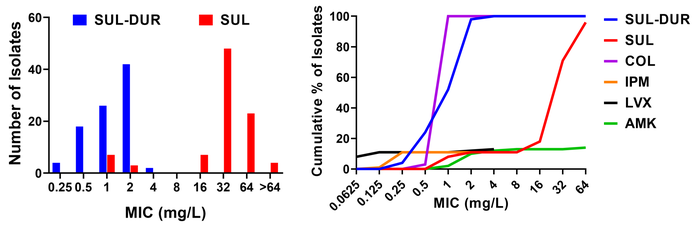
- **Over 90% of these MDR isolates are carbapenem-resistant.**
- **SUL-DUR was significantly more active than comparator agents against these isolates (except for colistin).**
- **28 MDR isolates had SUL-DUR MIC > 4 mg/L.**

PCR Screen for Metallo-β-lactamases in all 121 *A. baumannii* Isolates

All 121 *A. baumannii* isolates were profiled by multiplex PCR for the presence of genes encoding the following metallo-β-lactamases (MBLs): VIM, GIM, IMP, SPM and NDM.

- 29 of the 121 isolates were positive for the presence of bla_{NDM}.
- No other MBL genes were detected.
- 28 of the 29 NDM⁺ isolates had SUL-DUR MIC values > 4 mg/L, suggesting that most of the bla_{NDM} genes were expressed.
- Each of the isolates with elevated SUL-DUR MIC values was positive for bla_{NDM}.

Activity of Sulbactam-Durlobactam vs. non-MBL⁺ *A. baumannii*



Antimicrobial Agent	N	mg/L				Interpretive Criteria*		
		Min	Max	MIC_{50}	MIC_{90}	%S	%I	%R
SUL-DUR	92	0.25	4	1	2	100	0	0
SUL	92	1	>64	32	64	10.9	0	89.1
SUL-CFP	92	1	>32	>32	>32	13.0	33.7	53.3
IPM	92	0.12	>8	>8	>8	10.9	0	89.1
MEM	92	0.06	>8	>8	>8	10.9	0	89.1
FEP	92	1	>16	>16	>16	10.9	1.1	88.0
LVX	92	≤0.06	>4	>4	>4	12.0	1.1	86.9
COL	92	0.5	1	1	1	100	NA	0
AMK	92	1	>64	>64	>64	13.0	0	87.0

*Based on 2019 CLSI breakpoint criteria[5] except for sulbactam-cefoperazone, which is based on the package insert for sulperazone®[6], and sulbactam-durlobactam, which is based on the preliminary breakpoint of 4/8/16 mg/L (S/I/R). %S=percent susceptible, %I=percent intermediate, %R=percent resistant. SUL-DUR=sulbactam-durlobactam; SUL=sulbactam; SUL-CFP=sulbactam-cefoperazone (1:2); IPM=imipenem; MEM=meropenem; FEP=cefepime; LVX=levofloxacin; COL=colistin; AMK=amikacin.

- **100% of isolates lacking MBLs were susceptible to sulbactam-durlobactam.**
- **89% of this subset of isolates was carbapenem-resistant.**
- **The SUL-DUR MIC_{90} against this subset is consistent with results from ongoing, global surveillance studies.**

Conclusions

- **Durlobactam effectively restored sulbactam antibacterial activity against a collection of recent *A. baumannii* clinical isolates from six cities across India.**
- **Sulbactam-durlobactam was significantly more active against these MDR isolates than all the comparator antibiotics except colistin.**
- **Every isolate with an elevated SUL-DUR MIC encoded the gene for the metallo-β-lactamase NDM, which is not inhibited by durlobactam.**
- **NDM⁺ ABC may be more common in India than in other parts of the world; a recent global study found less that than 2% of carbapenemase-producing *A. baumannii* were NDM⁺ [7].**

References

1. Durand-Réville, T. *et al.,* (2017) *Nature Microbiol*. 2:17104. **2.** Penwell, W., *et al.,* (2015) *AAC* 59:1680-89. **3.** Veeraraghavan, B. & Walia, K., (2019) *Indian J. Med. Res.* 149: 87-96. **4.** CLSI M07-A10. 2015; CLSI M02-A13. 2019; **5.**CLSI M100, 29th ed. 2019 **6.** Sulperazone® package insert (2009). Available at https://www.thefilipinodoctor.com/brand_pdf/Sulperazone.pdf. **7.** Müller, C. *et al.*, (2018) Poster P1527, ECCMID 2018, Madrid, Spain.

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