Friday - Poster 3114

In Vitro Activity of Sulbactam-Durlobactam Against Recent Clinical *Acinetobacter baumannii-calcoaceticus* Complex Isolates from the United States

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Abstract

Background: *Acinetobacter baumannii-calcoaceticus* complex (ABC) causes severe infections that are difficult to treat due to increasing antibiotic resistance. Sulbactam (SUL) has intrinsic antibacterial activity against ABC, but its clinical utility has been compromised by the prevalence of serine β-lactamases. Durlobactam (DUR) is a diazabicyclooctane β-lactamase inhibitor with potent activity against Ambler classes A, C and D serine β-lactamases that effectively restores SUL activity against ABC isolates. SUL-DUR is an antibiotic designed to treat serious ABC infections, including multidrug-resistant strains, which recently demonstrated noninferiority to colistin in a Phase 3 clinical trial with the endpoint of 28-day all-cause mortality. The potency of SUL-DUR was measured against 1,271 ABC isolates from various infection types collected in the United States between 2016 and 2020.

Methods: The strains, including 884 *A. baumannii*, 215 *A. pittii*, 145 *A. nosocomialis* and 27 *A. calcoaceticus*, were collected from 23 states distributed broadly across the US. Susceptibility testing was performed according to CLSI guidelines. Susceptibility was defined by CLSI breakpoints, where available. SUL-DUR susceptibility was defined using a preliminary breakpoint of ≤4 mg/L. SUL-DUR-resistant isolates were subjected to whole genome sequencing.

Results: Among 1,271 US ABC isolates collected between 2016 and 2020, the SUL-DUR MIC_{90} was 2 mg/L with 99.3% susceptibility, compared with 32 mg/L for sulbactam alone with 66.2% susceptibility. Susceptibilities to imipenem and meropenem were 67.6 and 65.7% of isolates, respectively. Susceptibilities to amikacin, cefepime, ciprofloxacin and minocycline were 78.1, 59.9, 60.8 and 87.1% of isolates, respectively. The isolates were 97.1% susceptible to colistin. The SUL-DUR susceptibility by year was consistent, between 98.8 and 99.6% of isolates. Among the 450 multidrug-resistant (MDR) and 297 extremely drug-resistant (XDR) isolates, 98% and 97%, respectively, were susceptible to SUL-DUR. Whole genome sequencing of the 8 unique SUL-DUR-resistant isolates showed that 7 contained either the NDM-1 metallo-β-lactamase gene or one or two mutations in the gene encoding penicillin-binding protein-3 (PBP3), the target of sulbactam.

Conclusions: Over 99% of 1271 recent US clinical isolates of ABC, including MDR and XDR isolates, were susceptible to SUL-DUR. These data support the potential utility of SUL-DUR for the treatment of antibiotic-resistant infections caused by ABC.

Introduction

The Gram-negative organisms collectively named the *Acinetobacter baumannii-calcoaceticus* complex (ABC) have emerged as serious pathogens[1]. The ABC complex includes *A. baumannii*, *A. nosocomialis*, *A. pittii, A. dijkshoorniae, A. seifertii* and *A. calcoaceticus. A. baumannii* is considered the most clinically important species of the complex due to its frequent association with nosocomial infections. Globally, the susceptibility of ABC to all antimicrobial agents has declined over the last 20 years[2].

Sulbactam-durlobactam (SUL-DUR) recently completed a Phase 3 clinical trial for the treatment of infections caused by carbapenem-resistant ABC organisms. SUL is an approved β-lactamase inhibitor (BLI) with antibacterial activity against *Acinetobacter* spp. due to its inhibition of PBP3, an enzyme required for cell wall biosynthesis[3]. However, degradation of SUL by the β-lactamases present in most contemporary ABC isolates limits its clinical use. DUR is a diazabicyclooctane BLI with potent activity against class A, C and D serine β-lactamases[4]. DUR protects SUL from degradation, restoring antibacterial activity against ABC organisms. Here we profile the activity of SUL-DUR and other antibiotics against 1,271 ABC isolates collected in the United States between 2016 and 2020.

Durlobactam Restores Sulbactam Activity Against US ABC Isolates from 2016-2020

Distribution by state

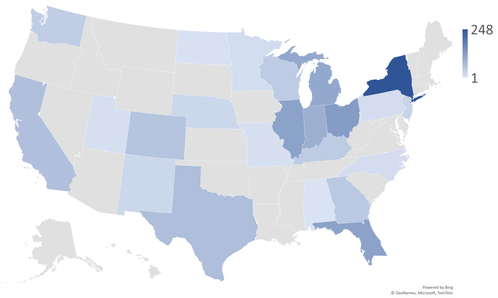


Figure 1. MIC distribution for SUL vs SUL-DUR against 1,271 US ABC isolates

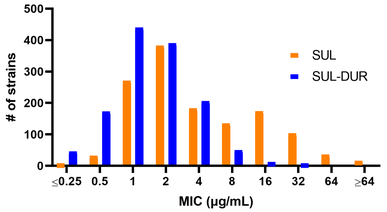
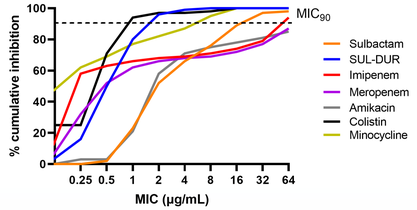


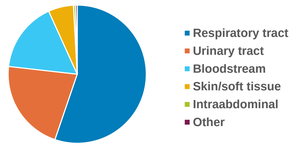
Figure 2. Cumulative % inhibition of SUL-DUR vs. comparators against 1,271 US ABC isolates



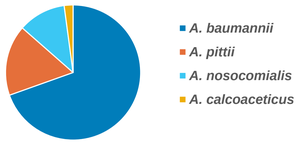
Antibiotic	MIC (μg/mL)			%S*
	Range	MIC_{50}	MIC_{90}	
SUL-DUR	<0.03 - >64	0.5	2	99**
SUL	0.25 - >64	2	32	66**
Amikacin	<0.5 - >64	2	>64	78
Cefepime	0.25 - >16	4	>16	60
Ciprofloxacin	<0.125 - >4	0.5	>4	61
Colistin	<0.25 - >8	0.5	1	NA
Imipenem	0.06 - >64	0.25	64	68
Meropenem	0.06 - >64	0.5	>64	66
Minocycline	<0.125 - >16	0.25	8	87
Tigecycline	0.03 - 32	0.25	2	NA

*percent susceptible according to 2020 CLSI breakpoint criteria. NA, not applicable (CLSI does not recognize susceptibility breakpoints for colistin against any organism. Tigecycline is not approved for use against *Acinetobacter* spp.)
** based on preliminary breakpoint of 4 μg/mL.

Distribution by infection type



Distribution by ABC species



Activity by infection type	N	SUL-DUR MIC (μg/mL)		
		Range	MIC_{50}	MIC_{90}
Respiratory tract	702	≤0.03 to >64	1	2
Urinary tract	271	0.06 to >64	0.5	2
Bloodstream	209	0.06 to >64	0.5	2
Skin/soft tissue	75	0.25 to 4	0.5	2
Activity by ABC species	**N**	**SUL-DUR MIC (μg/mL)**		
		Range	**MIC_{50}**	**MIC_{90}**
All ABC	1271	≤0.03 to >64	0.5	2
A. baumannii	884	≤0.03 to >64	1	2
A. pittii	215	0.12 to 2	0.5	1
A. nosocomialis	145	0.12 to 2	0.5	1
A. calcoaceticus	27	0.12 to 1	0.5	1

Activity by Resistance Phenotype	Definition	N	SUL-DUR (μg/mL)		
			MIC_{50}	MIC_{90}	Range
Carbapenem-NS	MIC > 2 μg/mL	403	1	4	0.12 to >64
Colistin-resistant	MIC > 2 μg/mL	37	1	2	0.25 to 4
MDR	NS to ≥1 agent in ≥3 antimicrobial categories[7]	450	1	4	0.12 to >64
XDR	NS to ≥1 agent in all but ≤2 categories[7]	297	2	4	1 to >64
PDR	NS to all approved agents in this study	2	NA	NA	0.25 to 2

Methods

Broth microdilution susceptibility testing was conducted at IHMA according to CLSI guidelines[5]. SUL-DUR was tested by two-fold serial dilutions of SUL in the presence of a fixed concentration of 4 μg/mL DUR. Genomic DNA was extracted from select isolates was used to prepare Nexterra libraries, which were subjected to whole genome sequencing with an Illumina MiSeq V2 instrument and analyzed using CLCBio Genomics Workbench v6.5 at Entasis Therapeutics.

Characterization of ABC isolates with SUL-DUR MIC > 4 μg/mL

Year	Location	Type of infection	SUL-DUR MIC (μg/mL)	Whole genome sequencing results (β-lactamases, PBP mutations, efflux pump-related)	MLST (Oxford/ Institut Pasteur)
2016	New Jersey	Respiratory	8	ADC-30; OXA-23; OXA-66; PBP3 [T526S]	ST_{OX}1806, 208 / ST_{IP}2
2016	Michigan	Blood	8	ADC-73; OXA-23; OXA-66; PBP3 [A515V]	ST_{OX}1806, 208 / ST_{IP}2
2017	Illinois	Respiratory	8	ADC-25; OXA-23; OXA-66; PBP3 [F548I]	ST_{OX}1701 / ST_{IP}2
2019*	New Jersey	Urine	>64	ADC-30 [R172L]; OXA-23; OXA-66; **NDM-1**	ST_{OX}1839, 281 / ST_{IP}2
2019*	Ohio	Respiratory	>64	ADC-30 [R172L]; OXA-23; OXA-66; **NDM-1**	ST_{OX}1839, 281 / ST_{IP}2
2020	New York	Respiratory	8	ADC-73; OXA-23; OXA-66; PBP3 [N392T A515V]; AdeR [Δ L127-D151]	ST_{OX}1806, 208 / ST_{IP}2
2020	New York	Blood	>64	ADC-30-like [R172L]; OXA-23; OXA-66; **NDM-1**	ST_{OX}1839, 281 / ST_{IP}2
2020	Illinois	Respiratory	16	ADC-30; OXA-24; OXA-66	ST-2057, 473 / ST_{IP}2

*same clone
MLST, multilocus sequence type

Conclusions

- **DUR restored SUL antibacterial activity against 1,271 ABC clinical isolates collected between 2016 and 2020 from across the US, with an MIC_{90} of 2 μg/mL.**
- **99.3% of ABC isolates from the US were inhibited by ≤ 4 μg/mL SUL-DUR.**
- **SUL-DUR activity was consistent across ABC species, sources of infection and subsets of resistance phenotypes.**
- **7 of the 8 SUL-DUR-non-susceptible isolates encoded either the metallo-β-lactamase NDM-1, which is not inhibited by DUR, or a mutation in PBP3, the target of sulbactam.**
- **These data support development of SUL-DUR for the potential treatment of multidrug-resistant *A. baumannii-calcoaceticus* complex infections.**

References

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