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Potent Activity of Sulbactam-Durlobactam Against Pan-Drug Resistant *Acinetobacter baumannii calcoaceticus* Complex (ABC) Isolates from a Recent 5-Year Surveillance Study (2016-2020)

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Abstract

Background: Sulbactam-durlobactam (SUL-DUR) is a β-lactam–β-lactamase inhibitor combination is being developed for treatment of infections due to *Acinetobacter baumannii-calcoaceticus* complex (ABC), including multidrug-resistant (MDR) and carbapenem-resistant strains. ABC is a highly resistant group of organisms that causes severe and difficult to treat infections in both hospital and outpatient settings. The *in vitro* activity of SUL-DUR was recently tested against 4,252 geographically diverse, clinical isolates of ABC from 2016 to 2020. SUL-DUR $MIC_{50/90}$ values were 1/2 µg/mL and 98.2% of isolates were inhibited at ≤ 4 µg/mL. SUL-DUR maintained activity across time, species, regions and source of infection. 11% of isolates were XDR and 2.2% (N = 95) were pan-drug resistant (PDR). Here we report the activity of SUL-DUR against these PDR ABC isolates.

Methods: Susceptibility testing was performed according to CLSI guidelines. PDR was defined as non-susceptibility to all antibiotics tested (amikacin, cefepime, ciprofloxacin, colistin, imipenem, meropenem, minocycline and sulbactam) based on CLSI 2021 breakpoints. Tigecycline (TGC) was excluded due to lack of approved breakpoints for ABC, although many isolates had high TGC MICs. SUL-DUR MICs were interpreted using a preliminary susceptible breakpoint of ≤4 µg/mL. Although strains collected from the same site could have been clonal, each was from a single patient and was therefore considered unique.

Results: 93 out of 95 PDR ABC were *A. baumannii*; 2 were *A. nosocomialis*. 88 were from Europe: Greece (N = 56), Turkey (N = 12), Lithuania (N = 11), Italy (N = 4), Spain (N = 1) and the Czech Republic (N = 1). PDR ABC was also isolated in Argentina (N = 1), Thailand (N = 5) and the USA (N = 1). In this study, the number of PDR ABC isolated increased over time and spread across the world, from N = 11 over 5 sites in 2016 to 28 at 8 sites in 2020. SUL-DUR $MIC_{50/90}$ values against this collection were 2/4 µg/mL, with 100% of PDR isolates inhibited at ≤4 µg/mL.

Conclusions: The likelihood that PDR ABC infections will lead to poor clinical outcomes is extremely high due to the lack of available treatment options. Notably, all 95 PDR isolates were susceptible to SUL-DUR. In a recent Phase 3 clinical trial, SUL-DUR demonstrated a statistically significant difference in clinical cure compared to colistin for the treatment of drug resistant ABC infections. Taken together, these results suggest that SUL-DUR, if approved, may be an important new treatment option for PDR ABC infections, which is a growing threat to public health..

Introduction

The Gram-negative organisms collectively named the *Acinetobacter baumannii-calcoaceticus* complex (ABC) are serious pathogens commonly isolated from the hospital environment and hospitalized patients that can cause severe, difficult-to-treat infections[1]. Globally, the susceptibility of ABC to all antimicrobial agents has declined over the last 20 years[2].

Sulbactam-durlobactam (SUL-DUR) is a β-lactam-β-lactamase inhibitor combination antibiotic that recently completed a Phase 3 clinical trial for the treatment of ABC infections, including those caused by carbapenem-resistant or MDR strains. In a recent 5-year surveillance study, the in vitro activity of SUL-DUR was tested against 4,252 geographically diverse, clinical isolates of ABC from 2016 to 2020[3]. The SUL-DUR $MIC_{50/90}$ values were 1/2 µg/mL and 98.2% of isolates were inhibited at ≤ 4 µg/mL. Almost half (48.5%) of these strains were MDR, 11% were XDR and 2.2% (N = 95) were pan-drug resistant (PDR). The goal of this study was to further characterize these PDR isolates by comparing their demographics and SUL-DUR susceptibility to those of the entire surveillance set.

Methods

Broth microdilution susceptibility testing was conducted at IHMA according to CLSI guidelines[4]. SUL-DUR was tested by two-fold serial dilutions of SUL in the presence of a fixed concentration of 4 µg/mL DUR. MDR and XDR were defined according to Magiorakis *et al.*[5] Pan-drug resistance was defined as non-susceptibility to all antibiotics tested (amikacin, cefepime, ciprofloxacin, colistin, imipenem, meropenem, minocycline and sulbactam) based on CLSI 2020 breakpoints. Tigecycline was not included due to lack of approved breakpoints for ABC.

Table 1. Distribution of 95 PDR ABC isolates by infection source, species, region and year of collection compared to the total surveillance study set

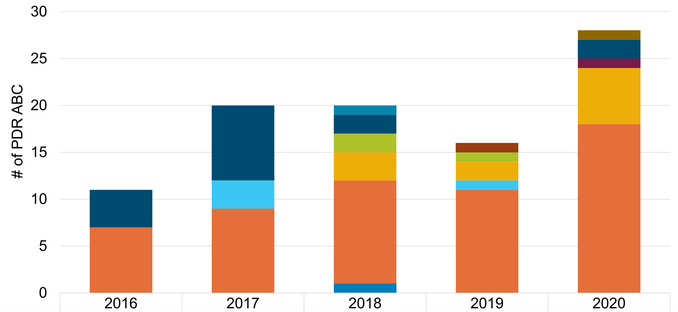
Infection Source	% total (N = 4,252)	% PDR (N = 95)
Bloodstream	21.0	28.4
Intra-abdominal	4.5	5.3
Respiratory tract	54.8	56.8
Skin/soft tissue	2.1	1.1
Urinary tract	17.5	8.4

Acinetobacter species	% total (N = 4,252)	% PDR (N = 95)
A. baumannii	80	97.9
A. pittii	13	0
A. nosocomialis	5.8	2.1
A. calcoaceticus	1.1	0
other	0.1	0

Geographic Region	% total (N = 4,252)	% PDR (N = 95)
North America	29.9	1.0
Europe	41.8	92.6
Latin America	12.5	1.0
Asia	10.7	5.2
South Pacific	3	0.0
Middle East	2.1	0.0

Year of collection	% total (N = 4,252)	% PDR (N = 95)
2016	19.8	11.6
2017	19.4	21.1
2018	21.8	21.1
2019	20.2	16.8
2020	18.7	29.5

Figure 1. Number and country of origin of PDR ABC from SUL-DUR 5-year surveillance program



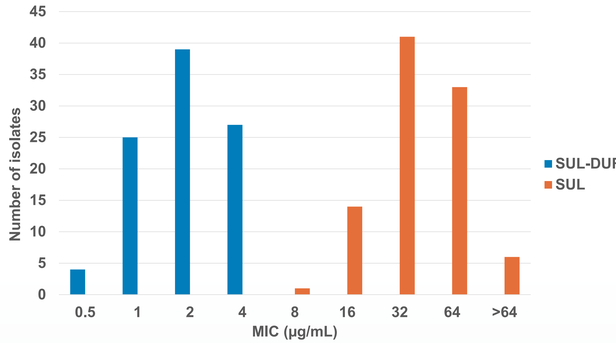
	2016	2017	2018	2019	2020
USA					1
Argentina			1		
Thailand				1	
Turkey	4	8	2		2
Spain					1
Poland			2	1	
Lithuania			3	2	6
Italy		3		1	
Greece	7	9	11	11	18
Czech Republic			1		

Table 2. Activity of sulbactam-durlobactam and comparators against 95 PDR ABC isolates compared to the total surveillance set (N = 4,252)

Compound	All isolates tested (N = 4,252)				PDR ABC isolates (N = 95)			
	MIC_{50}	MIC_{90}	Range	%S CLSI*	MIC_{50}	MIC_{90}	Range	%S CLSI*
SUL-DUR	1	2	≤0.03 - >64	98.2**	2	4	0.5 - 4	100**
Sulbactam	8	64	0.25 - >64	na	32	64	8 - >64	0
Amikacin	4	>64	≤0.5 - >64	58.6	>64	>64	32 - >64	0
Cefepime	16	>16	≤0.12 - >16	44.3	>16	>16	16 - >16	0
Ciprofloxacin	>4	>4	≤0.12 - >4	44.0	>4	>4	>4	0
Colistin	0.5	1	≤0.25 - >8	0	>8	>8	4 - >8	0
Imipenem	8	64	0.06 - >64	48.7	64	>64	16- >64	0
Meropenem	16	>64	0.06 - >64	47.6	64	>64	16- >64	0
Minocycline	0.5	16	≤0.12 - >16	79.1	16	16	8->16	0

$MIC_{50/90}$ and range are measured in µg/L; *%S, percent susceptible according to 2020 CLSI susceptibility breakpoints[6]; na, no breakpoint available
**Sulbactam-durlobactam MICs were interpreted using a preliminary breakpoint of ≤4 mg/L (susceptible)

Figure 2. MIC distribution of SUL-DUR vs. sulbactam alone against 95 PDR ABC from 2016-2020



Results

- The majority of PDR ABC from a recent five-year surveillance study were *A. baumannii* from patients with respiratory tract infections in Europe (primarily from Greece).
- The number of PDR ABC isolates increased over time and spread across the world, from N = 11 over 5 sites in 2016 to 28 at 8 sites in 2020.
- SUL-DUR $MIC_{50/90}$ values against this collection were 2/4 µg/mL, with 100% of PDR isolates inhibited at ≤4 µg/mL.

Conclusions

- In this study, all 95 PDR ABC isolates were susceptible to SUL-DUR.
- In a recent Phase 3 clinical trial, SUL-DUR was generally well-tolerated and met the primary efficacy endpoint for 28-day all-cause mortality.
- Taken together, these results suggest that SUL-DUR, if approved, may be an important new treatment option for PDR ABC infections, which is a growing threat to public health.

References

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