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Activity of Sulbactam-Durlobactam, Antibacterial Combinations, and Comparators Against a Challenge Set of 66 *Acinetobacter baumannii-calcoaceticus* Species Complex Isolates

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Introduction

- Sulbactam-durlobactam (SUL-DUR) was recently approved by the US FDA (May 2023) for the treatment of hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) caused by susceptible strains of *Acinetobacter baumannii-calcoaceticus* species complex (*A. baumannii*) in adults.
- Sulbactam-durlobactam is a co-packaged product of sulbactam, a β-lactam with intrinsic antibacterial activity against *A. baumannii*, and durlobactam, a β-lactamase inhibitor with activity against Class A, C, and D β-lactamases.
- In this study, we evaluated the *in vitro* activity of sulbactam-durlobactam, as well as double and triple combinations of sulbactam, durlobactam, and cefiderocol (FDC) or imipenem (IPM), against a challenge set of 66 highly resistant *A. baumannii* isolates containing 87.9% carbapenem-resistant (imipenem MIC, ≥8 mg/L) and 60.6% cefiderocol-resistant (cefiderocol MIC, ≥16 mg/L) isolates.

Materials and Methods

- Bacterial isolates consisted of 41 carbapenem- and/or cefiderocol-resistant *A. baumannii* isolates from the Centers for Disease Control and Prevention Antimicrobial Resistance Bank and 25 carbapenem- and/or cefiderocol-resistant *A. baumannii* clinical isolates from other sources.
- *A. baumannii* identifications were confirmed by MALDI-TOF MS.
- Broth microdilution susceptibility testing of sulbactam-durlobactam (fixed 4 mg/L) and comparator agents and combinations was conducted according to CLSI M07 (2018) and M100 (2023) guidelines.
- Durlobactam was supplied by Entasis Therapeutics Inc., an affiliate of Innoviva Specialty Therapeutics, Inc. (Waltham, MA), cefiderocol was obtained from MedChemExpress (Monmouth Junction, NJ), and imipenem and sulbactam were obtained from USP (Rockville, MD).
- Susceptibility testing of cefiderocol and cefiderocol combinations was conducted in iron-depleted Mueller-Hinton broth.
- Cefiderocol and imipenem MIC results were interpreted using CLSI breakpoint criteria.
- FDA breakpoint interpretative criteria were applied for sulbactam-durlobactam.

Results

- Sulbactam-durlobactam ($MIC_{50/90}$, 2/4 mg/L), cefiderocol-sulbactam-durlobactam ($MIC_{50/90}$, 0.5/1 mg/L), and imipenem-sulbactam-durlobactam ($MIC_{50/90}$, 1/2 mg/L) were the most active combinations tested against this highly resistant challenge set of 66 carbapenem- and/or cefiderocol-resistant *A. baumannii* isolates with 98.5% susceptible to sulbactam-durlobactam (Table 1 and Figure 1).
- The addition of cefiderocol or imipenem to sulbactam-durlobactam (98.5% susceptible) did not improve the overall susceptibility of the carbapenem- and/or cefiderocol-resistant *A. baumannii* isolates beyond 98.5%; however, MIC_{90} values for the triple combinations with cefiderocol or imipenem decreased by up to 4-fold compared to sulbactam-durlobactam (Table 1 and Figure 1).
- Sulbactam-durlobactam ($MIC_{50/90}$, 2/4 mg/L), cefiderocol-sulbactam-durlobactam ($MIC_{50/90}$, 0.5/1 mg/L), and imipenem-sulbactam-durlobactam ($MIC_{50/90}$, 1/2 mg/L) were the most active combinations tested against a sub-set of 58 carbapenem-resistant *A. baumannii* isolates with 98.3% susceptible to sulbactam-durlobactam (Table 2 and Figure 2).
- The addition of cefiderocol or imipenem to sulbactam-durlobactam did not improve the overall susceptibility against this challenge set of 58 carbapenem-resistant *A. baumannii* beyond 98.3%; however, MIC_{90} values for the triple antimicrobial combinations with cefiderocol or imipenem decreased by up to 4-fold compared to sulbactam-durlobactam (Table 2 and Figure 2).
- Sulbactam-durlobactam ($MIC_{50/90}$, 2/4 mg/L), cefiderocol-sulbactam-durlobactam ($MIC_{50/90}$, 0.5/1 mg/L), and imipenem-sulbactam-durlobactam ($MIC_{50/90}$, 1/1 mg/L) were the most active combinations tested against a highly resistant collection of 40 cefiderocol-resistant *A. baumannii* isolates with 97.5% susceptible to sulbactam-durlobactam (Table 3 and Figure 3).
- The addition of cefiderocol or imipenem to sulbactam-durlobactam did not improve the overall susceptibility of cefiderocol-resistant *A. baumannii* beyond 97.5%; however, MIC_{90} values for the triple combinations with cefiderocol or imipenem decreased by 4-fold compared to sulbactam-durlobactam (Table 3 and Figure 3).

Conclusions

- Sulbactam-durlobactam ($MIC_{50/90}$, 2/4 mg/L), cefiderocol-sulbactam-durlobactam ($MIC_{50/90}$, 0.5/1 mg/L), and imipenem-sulbactam-durlobactam ($MIC_{50/90}$, 1/2 mg/L) were active with 98.5% susceptible to sulbactam-durlobactam against this highly resistant challenge set of 66 carbapenem- and/or cefiderocol-resistant *A. baumannii* isolates.
- The addition of cefiderocol or imipenem to sulbactam-durlobactam decreased MIC_{90} values by up to 4-fold for these triple combinations compared to sulbactam-durlobactam tested alone.
- The potent activity of sulbactam-durlobactam against this collection of highly resistant *A. baumannii* isolates, including cefiderocol-resistant and imipenem-resistant strains, supports the continued development and use of this antibacterial combination.

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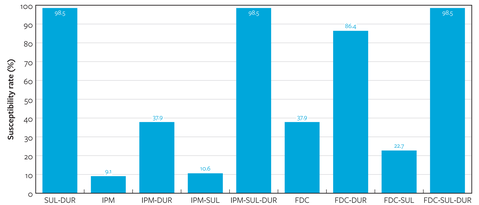
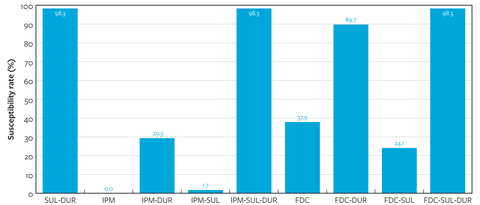
Figure 1. Susceptibility of sulbactam-durlobactam (fixed 4 mg/L), antibacterial combinations, and comparator agents against a highly resistant challenge set of 66 carbapenem- and/or cefiderocol-resistant *Acinetobacter baumannii-calcoaceticus* species complex isolates



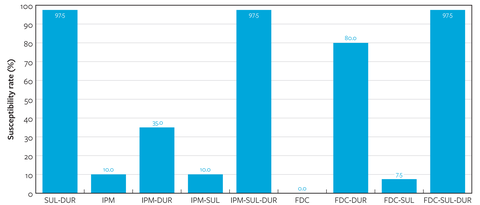
Abbreviations: DUR, durlobactam; FDC, cefiderocol; IPM, imipenem; SUL, sulbactam.
CLSI breakpoint interpretive criteria for cefiderocol and imipenem were applied to cefiderocol and imipenem combinations for comparison purposes.
FDA breakpoint interpretive criteria were applied to sulbactam-durlobactam.

Figure 2. Susceptibility of sulbactam-durlobactam (fixed 4 mg/L), antibacterial combinations, and comparator agents against a highly resistant challenge set of 58 carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* species complex isolates



Abbreviations: DUR, durlobactam; FDC, cefiderocol; IPM, imipenem; SUL, sulbactam.
CLSI breakpoint interpretive criteria for cefiderocol and imipenem were applied to cefiderocol and imipenem combinations for comparison purposes.
FDA breakpoint interpretive criteria were applied to sulbactam-durlobactam.

Figure 3. Susceptibility of sulbactam-durlobactam (fixed 4 mg/L), antibacterial combinations, and comparator agents against a highly resistant challenge set of 40 cefiderocol-resistant *Acinetobacter baumannii-calcoaceticus* species complex isolates



Abbreviations: DUR, durlobactam; FDC, cefiderocol; IPM, imipenem; SUL, sulbactam.
CLSI breakpoint interpretive criteria for cefiderocol and imipenem were applied to cefiderocol and imipenem combinations for comparison purposes.
FDA breakpoint interpretive criteria were applied to sulbactam-durlobactam.

Table 1. *In vitro* activity of sulbactam-durlobactam (fixed 4 mg/L), antibacterial combinations, and comparator agents against a highly resistant challenge set of 66 carbapenem- and/or cefiderocol-resistant *Acinetobacter baumannii-calcoaceticus* species complex isolates

A. baumannii-calcoaceticus species complex	No. and cumulative % of isolates inhibited at MIC (mg/L) of: ≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	> [a]	MIC_{50}	MIC_{90}
Sulbactam-durlobactam (fixed 4 mg/L)			0 0.0	1 1.5	3 6.1	24 42.4	28 84.8	**9** **98.5**	0 98.5	1 100.0			2	4
Imipenem [b]					2 3.0	4 9.1	0 9.1	2 12.1	8 15.2	14 27.3	**34** **48.5**	**100.0**	>32	>32
Imipenem-durlobactam (fixed 4 mg/L) [c]	0 0.0	1 1.5	0 1.5	5 9.1	7 19.7	5 27.3	7 37.9	24 74.2	**11** **90.9**	5 98.5	0 98.5	1 100.0	4	8
Imipenem-sulbactam (1:1) [c]	0 0.0	1 1.5	0 1.5	1 3.0	3 7.6	1 9.1	1 10.6	8 22.7	17 48.5	19 77.3	**14** **98.5**	1 100.0	16	32
Imipenem-sulbactam-durlobactam (1:1/fixed 4 mg/L) [c]	0 0.0	1 1.5	2 4.5	9 18.2	16 42.4	29 86.4	**8** **98.5**	0 98.5	0 98.5	1 100.0			1	2
Cefiderocol [b]	0 0.0	1 1.5	5 9.1	5 16.7	7 27.3	2 30.3	1 31.8	4 37.9	1 39.4	4 45.5	5 53.0	**31** **100.0**	32	>32
Cefiderocol-durlobactam (fixed 4 mg/L) [d]	1 1.5	1 3.0	5 10.6	10 25.8	17 51.5	17 77.3	4 83.3	2 86.4	1 87.9	**4** **93.9**	4 100.0		0.5	16
Cefiderocol-sulbactam (1:1) [d]		0 0.0	3 4.5	2 7.6	3 12.1	2 15.2	0 15.2	5 22.7	3 27.3	10 42.4	19 71.2	**19** **100.0**	32	>32
Cefiderocol-sulbactam-durlobactam (1:1/fixed 4 mg/L) [d]	1 1.5	1 3.0	10 18.2	13 37.9	26 77.3	**11** **93.9**	3 98.5	0 98.5	1 100.0				0.5	1

MIC_{50} values listed in **bold**.
[a] Greater than the highest concentration tested.
[b] 2023 CLSI or FDA breakpoint interpretive criteria applied, green = susceptible, yellow = intermediate, red = resistant.
[c] CLSI breakpoint interpretive criteria for imipenem were applied to imipenem combinations for comparison purposes.
[d] CLSI breakpoint interpretive criteria for cefiderocol were applied to cefiderocol combinations for comparison purposes.

Table 2. *In vitro* activity of sulbactam-durlobactam (fixed 4 mg/L), antibacterial combinations, and comparator agents against a highly resistant challenge set of 58 carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* species complex isolates

A. baumannii-calcoaceticus species complex	No. and cumulative % of isolates inhibited at MIC (mg/L) of: ≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	> [a]	MIC_{50}	MIC_{90}
Sulbactam-durlobactam (fixed 4 mg/L)			0 0.0	1 1.7	2 5.2	20 39.7	26 84.5	**8** **98.3**	0 98.3	1 100.0			2	4
Imipenem [b]								0 0.0	2 3.4	8 17.2	14 41.4	**34** **100.0**	>32	>32
Imipenem-durlobactam (fixed 4 mg/L) [c]					0 0.0	5 8.6	5 17.2	7 29.3	24 70.7	11 89.7	**5** **98.3**	0 98.3	1 100.0	4	16
Imipenem-sulbactam (1:1) [c]							0 0.0	1 1.7	6 12.1	17 41.4	19 74.1	**14** **98.3**	1 100.0	16	32
Imipenem-sulbactam-durlobactam (1:1/fixed 4 mg/L) [c]		0 0.0	1 1.7	3 6.9	16 34.5	29 84.5	**8** **98.3**	0 98.3	0 98.3	1 100.0			1	2
Cefiderocol [b]	0 0.0	1 1.7	3 6.9	4 13.8	7 25.9	2 29.3	1 31.0	4 37.9	1 39.7	3 44.8	5 53.4	**27** **100.0**	32	>32
Cefiderocol-durlobactam (fixed 4 mg/L) [d]	1 1.7	1 3.4	4 10.3	9 25.9	16 53.4	16 81.0	4 87.9	1 89.7	**1** **91.4**	3 96.6	2 100.0		0.5	8
Cefiderocol-sulbactam (1:1) [d]		0 0.0	3 5.2	1 6.9	3 12.1	2 15.5	0 15.5	5 24.1	3 29.3	8 43.1	16 70.7	**17** **100.0**	32	>32
Cefiderocol-sulbactam-durlobactam (1:1/fixed 4 mg/L) [d]	1 1.7	1 3.4	10 20.7	10 37.9	24 79.3	**9** **94.8**	2 98.3	0 98.3	1 100.0				0.5	1

MIC_{50} values listed in **bold**.
[a] Greater than the highest concentration tested.
[b] 2023 CLSI or FDA breakpoint interpretive criteria applied, green = susceptible, yellow = intermediate, red = resistant.
[c] CLSI breakpoint interpretive criteria for imipenem were applied to imipenem combinations for comparison purposes.
[d] CLSI breakpoint interpretive criteria for cefiderocol were applied to cefiderocol combinations for comparison purposes.

Table 3. *In vitro* activity of sulbactam-durlobactam (fixed 4 mg/L), antibacterial combinations, and comparator agents against a highly resistant challenge set of 40 cefiderocol-resistant *Acinetobacter baumannii-calcoaceticus* species complex isolates

A. baumannii-calcoaceticus species complex	No. and cumulative % of isolates inhibited at MIC (mg/L) of: ≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	> [a]	MIC_{50}	MIC_{90}
Sulbactam-durlobactam (fixed 4 mg/L)			0 0.0	1 2.5	1 5.0	16 45.0	16 85.0	**5** **97.5**	0 97.5	1 100.0			2	4
Imipenem [b]					2 5.0	2 10.0	0 10.0	1 12.5	0 12.5	7 30.0	10 55.0	**18** **100.0**	32	>32
Imipenem-durlobactam (fixed 4 mg/L) [c]	0 0.0	1 2.5	0 2.5	2 7.5	5 20.0	2 25.0	4 35.0	16 75.0	**7** **92.5**	2 97.5	0 97.5	1 100.0	4	8
Imipenem-sulbactam (1:1) [c]	0 0.0	1 2.5	0 2.5	1 5.0	2 10.0	0 10.0	0 10.0	4 20.0	11 47.5	13 80.0	**7** **97.5**	1 100.0	16	32
Imipenem-sulbactam-durlobactam (1:1/fixed 4 mg/L) [c]	0 0.0	1 2.5	2 7.5	4 17.5	10 42.5	**19** **90.0**	3 97.5	0 97.5	0 97.5	1 100.0			1	1
Cefiderocol [b]									0 0.0	4 10.0	5 22.5	**31** **100.0**	>32	>32
Cefiderocol-durlobactam (fixed 4 mg/L) [d]		0 0.0	1 2.5	6 17.5	9 40.0	11 67.5	3 75.0	2 80.0	1 82.5	**3** **90.0**	4 100.0		1	16
Cefiderocol-sulbactam (1:1) [d]							0 0.0	3 7.5	2 12.5	6 27.5	15 65.0	**14** **100.0**	32	>32
Cefiderocol-sulbactam-durlobactam (1:1/fixed 4 mg/L) [d]	0 0.0	1 2.5	4 12.5	5 25.0	19 72.5	**7** **90.0**	3 97.5	0 97.5	1 100.0				0.5	1

MIC_{50} values listed in **bold**.
[a] Greater than the highest concentration tested.
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