Session - 036
FRIDAY - 82

The Antibacterial Activity of Sulbactam and the Novel β-lactamase Inhibitor ETX2514 Combined with Imipenem or Meropenem Against Recent Clinical Isolates of *Acinetobacter baumannii* and *Pseudomonas aeruginosa*

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Abstract

Background
ETX2514 is a novel, diazabicyclooctenone inhibitor of serine β-lactamases that restores β-lactam activity against multidrug-resistant Gram negative bacteria. ETX2514 is more potent and has a broader spectrum of inhibition than the recently approved related β-lactamase inhibitor, avibactam. ETX2514 combined with sulbactam is currently in clinical development for the treatment of *Acinetobacter baumannii* infections. We sought to determine the relative potency of imipenem or meropenem with and without sulbactam-ETX2514 against recent, geographically diverse *Pseudomonas aeruginosa* and *A. baumannii* isolates.

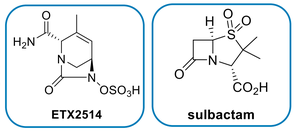
Methods
Approximately 600 *P. aeruginosa* and 600 *A. baumannii* isolates collected during 2013, 2014 and 2015 from geographically diverse medical centers in the United States, Europe, Latin America and the Asia-Pacific region were chosen for testing. Susceptibility testing was performed according to CLSI guidelines, and data analysis was performed using CLSI breakpoint criteria.

Results
Sulbactam plus ETX2514 (fixed at 4 mg/L) was highly active against the *A. baumannii* isolates, with MIC50/90 values of 1/2 mg/L, corresponding to 93.3% of strains inhibited at ≤2 mg/L. A total of 28.9% and 26.8% of isolates were susceptible to imipenem and meropenem, respectively, which improved to 46.5% and 42.8% in the presence of ETX2514 and to 98.7%. and 99.0% when sulbactam and ETX2514 (each fixed at 4 mg/L) were added to the carbapenem. A total of 73.6% and 75.4% of the *P. aeruginosa* isolates tested were susceptible to imipenem and meropenem, respectively, which improved to 94.7% and 82.6% in the presence of ETX2514. Adding sulbactam (fixed at 4 mg/L) to these combinations did not improve the potency of the carbapenem-ETX2514 combinations against *P. aeruginosa*.

Conclusions
A triple combination of imipenem or meropenem plus sulbactam and ETX2514 demonstrated potent antibacterial activity against recent, geographically diverse clinical isolates of *A. baumannii* and *P. aeruginosa*. These data support the continued development of ETX2514 in combination with sulbactam and/or a carbapenem against *A. baumannii* and *P. aeruginosa*.

Introduction

Sulbactam-ETX2514 is a β-lactam/β-lactamase inhibitor combination currently in clinical development for the treatment of resistant *A. baumannii* infections (Durand-Réville *et al.* (2017) *Nature Microbiol.* in press)



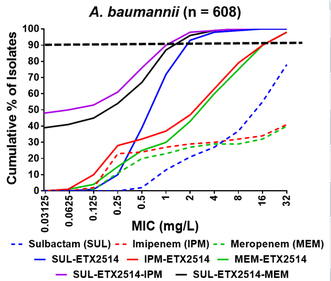
ETX2514 is a novel BLI from a series of diazabicyclooctenones with best-in-class broad spectrum activity against Class A, C and D β-lactamases.
Here we measure the antibacterial potency of a triple combination of sulbactam, ETX2514, and imipenem or meropenem against recent and geographically diverse *P. aeruginosa* and *A. baumannii* isolates.

Study Design

Methods:
Broth microdilution susceptibility testing was conducted at JMI Laboratories according to CLSI guidelines using cation-adjusted Mueller-Hinton broth.

Organisms:
All isolates were collected from geographically diverse medical centers located in United States, Europe, Latin American and the Asia-Pacific region as part of the SENTRY surveillance program during 2013, 2014 and 2015.

MIC Distributions of ETX2514 Combinations against 608 Geographically Diverse *A. baumannii*



Drug	Number (cumulative %) of isolates inhibited at MIC (mg/L)											
	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	> 32
IPM		0 0.0%	13 2.1%	126 22.9%	6 23.8%	19 27.0%	12 28.9%	8 30.3%	11 32.1%	9 33.6%	44 40.8%	**360 100.0%**
IPM-ETX2514	1 0.2%	3 0.7%	58 10.2%	109 28.1%	23 31.9%	32 37.2%	57 46.5%	97 62.5%	100 78.9%	**70 90.5%**	47 98.2%	11 100.0%
MEM		0 0.0%	4 0.7%	62 10.9%	53 19.6%	23 23.4%	21 26.8%	13 28.9%	3 29.4%	18 32.4%	47 40.1%	**364 100.0%**
MEM-ETX2514	0 0.0%	4 0.7%	21 4.1%	69 15.5%	55 24.5%	33 29.9%	78 42.8%	107 60.4%	87 74.7%	93 89.9%	**47 97.7%**	14 100.0%
SUL				0 0.0%	11 1.8%	67 12.8%	49 20.9%	37 27.0%	58 36.5%	115 55.4%	138 78.1%	**133 100.0%**
SUL-ETX2514	0 0.0%	1 0.2%	4 0.8%	55 9.9%	178 39.1%	200 72.0%	**129 93.3%**	31 98.4%	4 99.0%	4 99.7%	1 99.8%	1 100.0%
SUL-ETX2514-IPM	291 47.9%	10 49.5%	19 52.6%	50 60.9%	91 75.8%	85 89.8%	**49 97.9%**	6 98.8%	4 99.5%	2 99.8%	0 99.8%	1 100.0%
SUL-ETX2514-MEM	237 39.0%	14 41.3%	20 44.6%	60 54.4%	79 67.4%	120 87.2%	**55 96.2%**	14 98.5%	6 99.5%	2 99.8%	0 99.8%	1 100.0%

MIC_{90} value is highlighted with a red box and MIC_{50} value is highlighted with a blue box. ETX2514 was tested at a fixed concentration of 4 mg/L. IPM and MEM were added to SUL-ETX2514 at a fixed concentration of 2 mg/L

-Sulbactam-ETX2514 was highly active against *A. baumannii*
-98.4% of isolates were inhibited by 4 mg/L sulbactam-ETX2514
-Only 27% of isolates were inhibited by 4 mg/L sulbactam alone

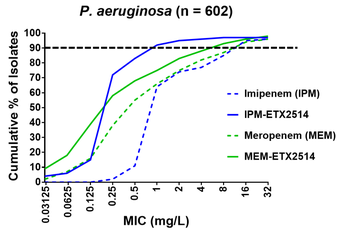
-Carbapenem-ETX2514 combinations were less active against *A. baumannii*
-Addition of either carbapenem (fixed at 2 mg/L) did not improve the MIC_{90} of sulbactam-ETX2514 (red squares) but significantly improved the MIC_{50} (blue squares)

The activity of sulbactam-ETX2514 is stable over time, across regions and sources of infection

		SUL			SUL-ETX2514			SUL-ETX2514-IPM			SUL-ETX2514-MEM		
Year	n	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}
2013	201	0.5->32	16	>32	0.06-16	1	4	≤0.03-16	0.25	2	≤0.03-16	0.25	2
2014	205	0.5->32	16	>32	0.12->32	1	2	≤0.03->32	0.12	1	≤0.03->32	0.25	2
2015	202	0.5->32	16	>32	0.12-16	1	2	≤0.03-8	≤0.03	1	≤0.03-16	0.12	1
Region													
Asia-Pacific	107	0.5->32	32	>32	0.06-16	1	2	≤0.03-16	0.5	2	≤0.03-8	0.5	2
Europe	196	0.5->32	32	>32	0.12->32	1	2	≤0.03->32	0.25	2	≤0.03->32	0.25	2
North America	194	0.5->32	4	>32	0.12-16	1	2	≤0.03-8	≤0.03	1	≤0.03-16	0.25	1
Latin America	111	0.5->32	16	>32	0.12-4	1	2	≤0.03-4	≤0.03	1	≤0.03-4	0.5	1
Source of Infection													
Blood	106	0.5->32	16	>32	0.25-4	1	2	≤0.03-4	0.25	2	≤0.03-8	0.25	2
Respiratory	301	0.5->32	16	>32	0.12-16	1	2	≤0.03-16	0.25	1	≤0.03-16	0.25	2
Skin/Soft Tissue	122	0.5->32	16	>32	0.06->32	1	2	≤0.03->32	≤0.03	1	≤0.03->32	0.25	2
Urinary Tract	33	1->32	8	>32	0.25-2	0.5	2	≤0.03-1	≤0.03	1	≤0.03-4	≤0.03	1
Other	46	1->32	16	>32	0.12-8	1	2	≤0.03-2	≤0.03	2	≤0.03-4	0.06	2
Total	608	0.5->32	16	>32	0.06->32	1	2	≤0.03->32	0.12	2	≤0.03->32	0.25	2

ETX2514 was tested at a fixed concentration of 4 mg/L. IPM and MEM were added to SUL-ETX2514 at a fixed concentration of 2 mg/L.

MIC Distributions of ETX2514 Combinations against 602 Geographically Diverse *P. aeruginosa*



Drug	Number (cumulative %) of isolates inhibited at MIC (mg/L)											
	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	> 32
IPM		0 0.0%	3 0.5%	8 1.8%	54 10.8%	321 64.1%	57 73.6%	21 77.1%	47 84.9%	**59 94.7%**	10 96.3%	22 100.0%
IPM-ETX2514	25 4.2%	10 5.8%	56 15.1%	342 71.9%	68 83.2%	**54 92.2%**	15 94.7%	9 96.2%	4 96.8%	1 97.0%	1 97.2%	17 100.0%
IPM-ETX2514-SUL	28 4.7%	6 5.6%	59 15.4%	343 72.4%	67 83.6%	**52 92.2%**	15 94.7%	9 96.2%	4 96.8%	1 97.0%	1 97.2%	17 100.0%
MEM	11 1.8%	29 6.6%	55 15.8%	132 37.7%	104 55.0%	69 66.4%	54 75.4%	42 82.4%	27 86.9%	**42 93.9%**	15 96.3%	22 100.0%
MEM-ETX2514	57 9.5%	52 18.1%	128 39.4%	113 58.1%	61 68.3%	38 74.6%	48 82.6%	30 87.5%	**30 92.5%**	19 95.7%	11 97.5%	15 100.0%
MEM-ETX2514-SUL	59 9.8%	52 18.4%	121 38.5%	131 60.3%	48 68.3%	38 74.6%	51 83.1%	29 87.9%	**28 92.5%**	20 95.8%	10 97.5%	15 100.0%

MIC_{90} value is highlighted. ETX2514 was tested at a fixed concentration of 4 mg/L. Sulbactam was added at a fixed concentration of 4 mg/L.

-Imipenem-ETX2514 was highly active against *P. aeruginosa*
-92% of isolates were inhibited by 1 mg/L imipenem-ETX2514
-Only 64% of isolates were inhibited by 1 mg/L of imipenem alone

-Meropenem-ETX2514 combinations were less active against *P. aeruginosa*
-Addition of sulbactam (fixed at 4 mg/L) did not improve the MIC_{90} of either carbapenem in the presence of ETX2514 (fixed at 4 mg/L) (red squares)

The activity of imipenem-ETX2514 is stable over time, across regions and sources of infection

		Imipenem			Imipenem-ETX2514			Meropenem			Meropenem-ETX2514		
Year	n	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}
2013	202	0.12->32	1	16	≤0.03->32	0.25	1	≤0.03->32	0.5	16	≤0.03->32	0.25	8
2014	196	0.12->32	1	16	≤0.03->32	0.25	1	≤0.03->32	0.5	16	≤0.03->32	0.25	8
2015	204	0.12->32	1	16	≤0.03->32	0.25	1	≤0.03->32	0.5	16	≤0.03->32	0.25	8
Region													
Asia-Pacific	103	0.25->32	1	16	≤0.03->32	0.25	1	≤0.03->32	0.5	16	≤0.03->32	0.25	16
Europe	200	0.25->32	1	16	≤0.03->32	0.25	1	≤0.03->32	1	16	≤0.03->32	0.5	8
Latin America	106	0.5->32	1	16	≤0.03->32	0.25	2	≤0.03->32	1	32	≤0.03->32	0.5	16
North America	193	0.12->32	1	8	≤0.03-8	0.25	0.5	≤0.03->32	0.5	8	≤0.03->32	0.25	2
Source of Infection													
Blood	72	0.5->32	1	8	≤0.03->32	0.25	1	0.06->32	0.5	4	≤0.03->32	0.25	4
Respiratory	301	0.12->32	1	16	≤0.03->32	0.25	1	≤0.03->32	0.5	16	≤0.03->32	0.25	8
Skin/Soft Tissue	143	0.12->32	1	16	≤0.03->32	0.25	1	≤0.03->32	0.5	16	≤0.03->32	0.25	8
Urinary Tract	34	0.5->32	1	8	0.06->32	0.25	1	0.06->32	0.5	16	≤0.03->32	0.25	4
Other	52	0.5->32	1	16	0.12->32	0.25	1	0.06->32	1	8	≤0.03->32	0.5	4
Total	602	0.12->32	1	16	≤0.03->32	0.25	1	≤0.03->32	0.5	16	≤0.03->32	0.25	8

ETX2514 was tested at a fixed concentration of 4 mg/L.

Conclusions

- **ETX2514 restores sulbactam antibacterial activity against a global collection of 608 *A. baumannii* clinical isolates with an MIC_{90} of 2 mg/L**
- **Addition of 2 mg/L imipenem or meropenem does not change the MIC_{90} of sulbactam-ETX2514 versus *A. baumannii***
- **ETX2514 restores imipenem antibacterial activity against a global collection of 602 contemporary *P. aeruginosa* clinical with an MIC_{90} of 1 mg/L**
- **These data support development of ETX2514 in combination with sulbactam for the treatment of *A. baumannii* and ETX2514 in combination with imipenem against *P. aeruginosa*.**

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