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The β-lactamase inhibitor ETX1317 restores the activity of cefpodoxime against recent (2017-2019), geographically diverse drug-resistant *Enterobacterales* isolates

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Background

The treatment of infections caused by Gram-negative pathogens has been exacerbated by the emergence of multi-drug resistant, β-lactamase (BLA)-expressing organisms. ETX0282 is an oral prodrug that is hydrolyzed *in vivo* to release ETX1317, a diazabicyclooctane (DBO) β-lactamase inhibitor active against serine BLAs. ETX0282 is currently in clinical development with cefpodoxime proxetil (CPDP), a clinically approved oral antibiotic which is hydrolyzed *in vivo* to release cefpodoxime (CPD).

We sought to determine the *in vitro* antibacterial activity of CPD-ETX1317 against recent Enterobacterales clinical isolates encoding extended-spectrum β-lactamases (ESBLs) and KPC carbapenemases.

Methods/Study Design

The bacterial isolates (n=609) were collected as part of the SENTRY Antimicrobial Surveillance Program between 2017-2019 and were comprised of 303 ESBL-encoding and 306 KPC-encoding *Enterobacterales*. There were 358 *Klebsiella* spp., 152 *Escherichia coli*, 58 *Enterobacter* spp., 20 *Citrobacter* spp., 13 *Proteus mirabilis* and 8 *Serratia marcescens* isolates. Isolates originated from 33 countries across the USA, Europe, Latin America, and the Asia-Pacific region. Susceptibility testing was performed at JMI Laboratories using broth microdilution following Clinical and Laboratory Standards Institute guidelines. The CPD-ETX1317 combination was tested at a 1:2 ratio. Molecular confirmation of ESBL- and KPC-*Enterobacterales* isolates was determined through next-generation sequencing.

CPD-ETX1317 retains activity across bacterial species

All isolates (N = 609)	%S*	Antibacterial Activity (mg/L)		
		MIC_{50}	MIC_{90}	Range
Cefpodoxime	<1	>32	>32	1 - >32
ETX1317	NA	0.5	16	≤0.06 - 32
CPD-ETX1317 (1:2)	NA	0.13	1	0.03 - 4
Ertapenem	46	0.5	1	≤0.03 - 2
Tebipenem	NA	4	> 8	≤0.008 - >8
Ceftazidime	12	> 32	> 32	0.13 - >32
Levofloxacin	22	16	> 16	0.02 - >16
Tetracycline	32	2	4	0.5 - >16
Piperacillin-tazobactam	40	128	>128	0.25 - >128
Trimethoprim-sulfamethoxazole	26	>8	>16	≤0.25 - >16

*according to CLSI interpretive criteria; CPD = cefpodoxime

E. coli (N = 152)	%S*	Antibacterial Activity (mg/L)		
		MIC_{50}	MIC_{90}	Range
Cefpodoxime	1	>32	>32	1->32
ETX1317	NA	0.25	0.25	0.13-4
CPD-ETX1317 (1:2)	NA	0.13	0.13	0.06-0.5
Tebipenem	NA	0.03	0.13	≤0.008->8
Levofloxacin	30	16	>16	0.02->16
Tetracycline	28	>16	>16	1->16
Trim-Sulfa	39	>8	>8	≤0.125->16

*according to CLSI interpretive criteria; CPD = cefpodoxime

K. pneumoniae (N = 358)	%S*	Antibacterial Activity (mg/L)		
		MIC_{50}	MIC_{90}	Range
Cefpodoxime	1	>32	>32	1->32
ETX1317	NA	0.25	0.25	0.13-4
CPD-ETX1317 (1:2)	NA	0.13	0.13	0.06-0.5
Tebipenem	NA	0.03	0.13	≤0.008->8
Levofloxacin	19	16	>16	0.02->16
Tetracycline	37	>16	>16	1->16
Trim-Sulfa	13	>8	>8	≤0.125->16

*according to CLSI interpretive criteria; CPD = cefpodoxime

Other** (N = 99)	%S*	Antibacterial Activity (mg/L)		
		MIC_{50}	MIC_{90}	Range
Cefpodoxime	0	>32	>32	>32
ETX1317	NA	0.5	>32	<0.06->32
CPD-ETX1317 (1:2)	NA	0.12	1	0.02-4
Tebipenem	NA	8	>8	0.02->8
Levofloxacin	23	9	>16	0.02->16
Tetracycline	37	8	>16	1->16
Trim-Sulfa	24	8	>16	≤0.125->16

*according to CLSI interpretive criteria; **_Citrobacter, Enterobacter, Proteus, Serretia_ spp. CPD = cefpodoxime

CPD-ETX1317 retains activity against ESBL+, KPC+ and antibiotic-resistant subsets

ESBL+ (N = 303)	%S*	Antibacterial Activity (mg/L)		
		MIC_{50}	MIC_{90}	Range
CPD-ETX1317 (1:2)	NA	0.25	2	0.06-4
Tebipenem	NA	0.03	0.13	≤0.008 - 4
Levofloxacin	33	4	>16	0.02->16
Tetracycline	24	8	>16	0.5 - >16
Trim-Sulfa	29	>8	>8	≤0.125->16

*according to CLSI interpretive criteria; CPD = cefpodoxime

KPC+ (N = 306)	%S*	Antibacterial Activity (mg/L)		
		MIC_{50}	MIC_{90}	Range
CPD-ETX1317 (1:2)	NA	0.25	2	0.06-4
Tebipenem	NA	>8	>8	2 - >8
Levofloxacin	11	>16	>16	0.02->16
Tetracycline	35	8	>16	1 - >16
Trim-Sulfa	23	>8	>8	≤0.125->16

*according to CLSI interpretive criteria; CPD = cefpodoxime

Carbapenem-Resistant (N = 388)	%S*	Antibacterial Activity (mg/L)	
		MIC_{50}	MIC_{90}
CPD-ETX1317 (1:2)	NA	0.12	1
Tebipenem	NA	>8	>8
Levofloxacin	33	16	>16
Tetracycline	24	8	>16
Trim-Sulfa	29	>8	>8

*according to CLSI interpretive criteria; CPD = cefpodoxime

Fluoroquinolone-Resistant (N = 525)	%S*	Antibacterial Activity (mg/L)	
		MIC_{50}	MIC_{90}
CPD-ETX1317 (1:2)	NA	0.12	1
Tebipenem	NA	>8	>8
Levofloxacin	0	>16	>16
Tetracycline	29	8	>16
Trim-Sulfa	16	>8	>8

*according to CLSI interpretive criteria; CPD = cefpodoxime

Tetracycline-Resistant (N = 315)	%S*	Antibacterial Activity (mg/L)	
		MIC_{50}	MIC_{90}
CPD-ETX1317 (1:2)	NA	0.12	1
Tebipenem	NA	0.12	>8
Levofloxacin	19	>16	>16
Tetracycline	0	8	>16
Trim-Sulfa	12	>8	>8

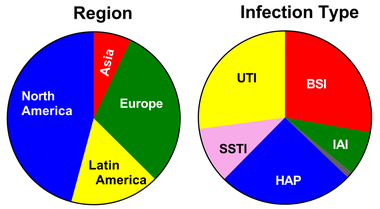
*according to CLSI interpretive criteria; CPD = cefpodoxime

Trim-Sulfa-Resistant (N = 451)	%S*	Antibacterial Activity (mg/L)	
		MIC_{50}	MIC_{90}
CPD-ETX1317 (1:2)	NA	0.12	1
Tebipenem	NA	8	>8
Levofloxacin	19	16	>16
Tetracycline	0	1	>16
Trim-Sulfa	12	>8	>8

*according to CLSI interpretive criteria; CPD = cefpodoxime

Breakdown by Geography and Infection Source

609 *Enterobacterales* isolates
(Collected between 2017-2019 in the SENTRY global surveillance program)



UTI = urinary tract;
BSI= bloodstream;
SSTI = skin/soft tissue;
HAP = hospital acquired pneumonia;
IAI = intra-abdominal

Results

The susceptibility of this set of 609 isolates to both IV and oral approved antibiotics, was very low (percent susceptibilities: fluoroquinolones, 13-22%; trimethoprim-sulfamethoxazole, 26%; carbapenems, 51%; piperacillin-tazobactam, 40%; aminoglycosides, 55-85%; ceftazidime 12%). In contrast, addition of ETX1317 to CPD reduced the MIC_{90} over 32-fold from >32 mg/L to 1 mg/L. This level of potency for the CPD-ETX1317 combination was stable across all species of *Enterobacterales* tested and infection sources (MIC_{90} values range 0.12 – 1 mg/L). For the 303 ESBL-encoding isolates, the MIC_{90} of CPD-ETX1317 was 0.25 mg/L while for the 306 KPC-encoding isolates, the CPD-ETX1317 MIC_{90} was 2 mg/L.

Conclusions

- The combination of CPD and ETX1317 demonstrated potent antibacterial activity against a diverse set of *Enterobacterales* isolates expressing either ESBL or KPC BLAs.
- These data support the continued development of the oral combination of ETX0282 and CPDP for the treatment of antibiotic resistant *Enterobacterales* infections.

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