Abstract # 2185

In vitro activity of aztreonam-avibactam, cefiderocol, and cefepime-taniborbactam against multi-species, NDM-producing Enterobacterales causing a local outbreak

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INTRODUCTION

- New Delhi metallo-β-lactamase (NDM)-producing *Enterobacterales* are increasing in the United States
- Recommended treatment options include ceftazidime-avibactam (CZA) plus aztreonam (ATM) or cefiderocol (FDC)
- We aimed to assess the *in vitro* activity of treatment options in the setting of a multi-species NDM outbreak at our center

METHODS

- Patient isolates were identified through active surveillance and characterized by whole-genome sequencing
- Minimum inhibitory concentrations (MICs) for aztreonam +/- avibactam (AVI), ceftazidime +/- AVI, FDC +/- AVI, cefiderocol +/- AVI, and cefepime +/- taniborbactam (TAN) were determined in triplicate; AVI and TAN were tested at 4 mg/L
- Index isolates were defined as the first NDM (+) isolate per species per patient
- CLSI Breakpoints were applied. ATM+/-AVI, CAZ, and FDC+/-AVI: Susceptible ≤4 mg/L, Intermediate 8 mg/L, Resistant ≥16 mg/L. CZA Susceptible ≤8 mg/L, Resistant ≥16 mg/L. FEP+/-TAN: Susceptible ≤2 mg/L, Susceptible Dose Dependent 4-8 mg/L, Resistant ≥16 mg/L

RESULTS

- 52 isolates from 2018-2023 were included; 83% were collected in 2022-2023
- Isolates were 31 index and 21 follow-up isolates from 26 unique patients
- 15% of patients were infected with more than one NDM-producing organism
- Susceptibility rates ranged from 44% to 92% among recommended treatment options

Table 1. Summary of susceptibility testing results.

		ATM	ATM + AVI	CAZ	CAZ + AVI	FDC	FDC + AVI	FEP	FEP + TAN
All (n = 52)	MIC_{50}	4	0.06	>256	>256	8	4	>64	1
	P value	<0.0001		>0.9999		0.0485		<0.0001	
	Fold Change	-64		0		-2		-128	
	% S	52%	92%	0%	0%	44%	69%	2%	83%
	% I/SDD	0%	0%	0%	--	44%	19%	2%	4%
	% R	48%	8%	100%	100%	12%	12%	96%	13%
Index (n = 31)	MIC_{50}	0.5	0.06	>256	>256	4	2	64	0.5
	P value	<0.0001		>0.9999		0.1934		<0.0001	
	Fold Change	-8		0		-2		-128	
	% S	61%	94%	0%	0%	65%	81%	3%	87%
	% I/SDD	0%	0%	0%	0%	29%	10%	3%	3%
	% R	39%	6%	100%	100%	6%	10%	94%	10%
Serial (n = 21)	MIC_{50}	128	0.06	>256	>256	8	4	128	1
	P value	0.0015		>0.9999		0.0266		<0.0001	
	Fold Change	-2048		0		-2		-128	
	% S	38%	90%	0%	0%	14%	52%	0%	76%
	% I/SDD	0%	0%	0%	0%	67%	33%	0%	5%
	% R	62%	10%	100%	100%	19%	14%	100%	19%

MIC_{50} compared by Mann Whitney U test. Abbreviations: ATM, aztreonam. AVI, avibactam. CAZ, ceftazidime. CZA, ceftazidime-avibactam. FDC, cefiderocol. FEP, cefepime. I, intermediate. MIC, minimum inhibitory concentration. R, resistant. S, susceptible. SDD, susceptible dose dependent. TAN, taniborbactam.

RESULTS

Index Isolates.

- Among 31 index isolates, 9 spp. were identified
- *Enterobacter cloacae complex* (n=16) was most common (including subspecies *E. cloacae* [n=2], *E. hormaechei* [n=12], and *E. roggenkampii* [n=2]) followed by *E. coli, K. aerogenes,* and *K. pneumoniae* (n=3 each)
- Isolates harbored NDM-5 (74%) or NDM-1 (26%)
- Other β-lactamases included ACT (17), SHV (8), TEM (8), and CTX-M (7) variants
- 94%, 87%, and 65% of index isolates were susceptible to ATM-AVI, FEP-TAN, and FDC, respectively; corresponding MIC_{50} values were 0.06, 0.5, and 4 mg/L, respectively (Table)
- FDC susceptibility improved to 81% with addition of AVI (Table 1, Figure 1).

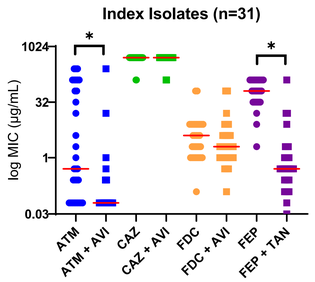

Figure 1. Index Isolates MIC_{50} compared by Mann Whitney U test. ATM, aztreonam. AVI, avibactam. CAZ, ceftazidime. CZA, ceftazidime-avibactam. FDC, cefiderocol. FEP, cefepime. MIC, minimum inhibitory concentration. TAN, taniborbactam.

Serial Isolates.

- Among 21 serial isolates, rates of susceptibility were 90%, 76%, and 14% for ATM-AVI, FEP-TAN, and FDC, respectively (Table)
- Two patients were treated with CZA-ATM; in 1 case, ATM-AVI MICs increased *against E. coli* from 16 to >128 mg/L post-CZA-AVI therapy, attributed to an insertion (YRIN) and substitution (A417V) in *ftsI* (PBP3)
- The addition of AVI to ATM and FDC caused a significant drop in MIC (Table 1, Figure 2)

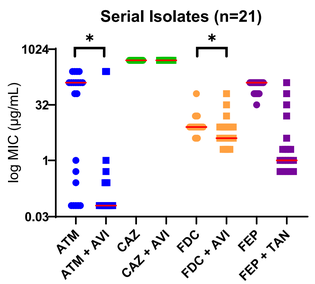

Figure 2. Serial Isolates MIC_{50} compared by Mann Whitney U test. ATM, aztreonam. AVI, avibactam. CAZ, ceftazidime. CZA, ceftazidime-avibactam. FDC, cefiderocol. FEP, cefepime. MIC, minimum inhibitory concentration. TAN, taniborbactam.

Table 3. Characterization of all 52 NDM-producing isolates included in the study stratified by unique patient

Patient	Isolate Code	Species	Days Since Index	ST	NDM Plasmid Family	β-lactamases	ATM	ATM + AVI	CAZ	CAZ + AVI	FDC	FDC + AVI	FEP	FEP + TAN
1	ENTC0920	*E. hormaechei*		600	None/chromosome	blaACT-16, blaNDM-1, blaOXA-16	0.5	0.25	>256	>256	1	1	32	0.5
2	ECOL0644	*E. coli*		361	IncFIA, IncFII	blaCMY-145, blaNDM-5	128	16	>256	>256	8	4	>64	16
2	SURV0315	*E. coli*	21	361	IncFIA, IncFII	blaCMY-145, blaNDM-5	>128	>128	>256	>256	16	8	>64	32
3	SURV0324	*E. coli*		361	Pending	blaCMY-145, blaNDM-5	>128	>128	>256	>256	8	8	>64	>64
3	SURV0325	*E. coli*	25	ND	ND	ND	>128	>128	>256	>256	16	32	>64	>64
4	ENTC0964	*E. cloacae*		Unk	IncX3	blaACT-15, blaNDM-5	0.5	0.25	>256	>256	4	4	64	1
5	KLPN2485	*K. pneumoniae*		147	IncC, IncFIB	blaCTX-M-15, blaNDM-5, blaOXA-1, blaSHV-11, blaTEM-1B	128	≤0.12	>256	>256	4	2	64	0.25
6	SURV0356	*C. freundii*		Unk	IncC	blaCMY-79, blaCTX-M-14, blaNDM-1	4	≤0.12	>256	>256	2	1	64	0.06
7	KLOX2582	*R. planticola*		-	IncU	blaIMP-4, blaNDM-1, blaPLA-5A, blaSHV-12	64	≤0.12	>256	>256	2	1	64	0.5
8	PRMI0653	*P. mirabilis*		-	IncX3	blaNDM-5	≤0.12	≤0.12	128	128	0.12	0.12	8	0.12
8	MGMG0651	*M. morganii*		-	IncX3	blaDHA-13, blaNDM-5	≤0.12	≤0.12	128	128	1	0.5	2	≤0.06
8	SURV0398	*E. coli*		131	IncX3	blaNDM-5	≤0.12	≤0.12	>256	>256	8	8	>64	2
8	ECOL0757	*E. coli*	13	ND	ND	ND	≤0.12	≤0.12	>512	>256	8	8	>64	2
8	ECOL0759	*E. coli*	19	ND	ND	ND	≤0.12	≤0.12	>256	>256	8	8	>64	4
8	ECOL0766	*E. coli*	70	ND	ND	ND	≤0.12	≤0.12	>256	>256	8	8	>64	2
8	SURV0440	*E. coli*	99	ND	ND	ND	≤0.12	≤0.12	>256	>256	8	4	>64	2
8	ECOL0784	*E. coli*	129	ND	ND	ND	≤0.12	≤0.12	>256	>256	8	8	>64	2
9	KAER1083	*K. aerogenes*		Unk	IncX3	blaNDM-5	0.25	≤0.12	>256	>256	1	0.5	>64	1
10	ENTC1089	*E. hormaechei*		45	IncX3	blaACT-15, blaNDM-5, blaTEM-1B	1	≤0.12	>256	>256	1	1	16	0.25
11	ENTC1086	*E. hormaechei*		45	IncX3	blaACT-15, blaNDM-5, blaTEM-1B	0.5	≤0.12	>256	>256	1	2	32	0.25
12	KLPN2612	*K. pneumoniae*		20	Pending	blaCTX-M-15, blaNDM-1, blaOXA-16, blaSHV-187, blaTEM-1B	128	≤0.12	>256	>256	4	2	64	0.5
12	SURV0436	*E. hormaechei*		62	IncHI2, IncHI2A	blaACT-7, blaCTX-M-15, blaNDM-1, blaOXA-1, blaOXA-16, blaTEM-1B	64	≤0.12	>256	>256	2	1	>64	0.5
12	SURV0437	*K. pneumoniae*	11	ND	ND	ND	128	≤0.12	>256	>256	4	2	64	1
13	ENTC1121	*E. hormaechei*		45	IncX3	blaACT-15, blaNDM-5	≤0.12	≤0.12	>256	>256	2	1	32	0.25
14	SURV0442	*E. hormaechei*		45	IncX3	blaACT-15, blaNDM-5	≤0.12	≤0.12	>256	>256	1	0.5	32	0.5
15	SURV0447	*K. aerogenes*		239	IncX3	blaNDM-5	0.25	≤0.12	>256	>256	4	2	>64	0.5
15	ENTC1133	*E. hormaechei*		45	IncX3	blaACT-15, blaNDM-5, blaTEM-1B	2	≤0.12	>256	>256	2	2	>64	0.5
15	SURV0448	*K. aerogenes*	7	ND	ND	ND	1	0.25	>256	>256	4	2	64	1
16	SURV0450	*K. aerogenes*		137 SLV	IncX3	blaNDM-5	≤0.12	≤0.12	>256	>256	4	2	64	0.5
16	KAER1127	*K. aerogenes*	13	137 SLV	IncX3	blaNDM-5	0.5	0.25	>256	>256	4	2	>64	1
17	ENTC1134	*E. hormaechei*		78	IncC	blaACT-5, blaCTX-M-14, blaNDM-1, blaSHV-12	128	≤0.12	>256	>256	8	4	64	0.5
17	ENTC1135	*E. hormaechei*	5	78	IncC	blaACT-5, blaCTX-M-14, blaNDM-1, blaSHV-12	128	≤0.12	>256	>256	8	4	64	1
17	ENTC1138	*E. hormaechei*	13	ND	ND	ND	128	≤0.12	>256	>256	8	4	64	0.5
17	ENTC1154	*E. hormaechei*	13	ND	ND	ND	128	≤0.12	>256	>256	8	8	64	0.5
17	ENTC1140	*E. hormaechei*	13	ND	ND	ND	64	≤0.12	>256	>256	8	4	>64	0.5
17	ENTC1155	*E. hormaechei*	13	ND	ND	ND	>128	≤0.12	>256	>256	8	4	64	0.5
17	SURV0467	*E. hormaechei*	30	ND	ND	ND	128	≤0.12	>256	>256	8	4	>64	0.5
18	SURV0459	*E. hormaechei*		45	IncX3	blaACT-15, blaNDM-5	0.25	≤0.12	>256	>256	1	1	>64	2
19	ENTC1145	*E. hormaechei*		145	IncX3	blaACT-14, blaLAP-1, blaNDM-5, blaSHV-12, blaTEM-1B	>128	0.25	>256	>256	8	8	64	2
19	KLPN2676	*R. ornithinolytica*		Unk	IncX3	blaNDM-5, blaPLA1a	≤0.12	≤0.12	>256	>256	1	1	32	0.12
19	SURV0473	*E. hormaechei*	19	ND	ND	ND	128	≤0.12	>256	>256	8	8	32	0.5
20	SURV0466	*E. hormaechei*		78	IncC	blaACT-5, blaCTX-M-14, blaNDM-1, blaSHV-12	128	≤0.12	>256	>256	8	4	>64	0.5
20	SURV0468	*E. hormaechei*	7	78	IncC	blaACT-5, blaCTX-M-14, blaNDM-1, blaSHV-12	128	0.25	>256	>256	8	2	>64	1
21	ENTC1162	*E. roggenkampii*		997	IncX3	blaMIR-6, blaNDM-5	≤0.12	≤0.12	>256	>256	8	16	32	0.12
22	ENTC1167	*E. cloacae*		997	IncX3	blaMIR-6, blaNDM-5	0.25	≤0.12	>256	>256	8	4	>64	1
22	ENTC1165	*E. cloacae*	1	ND	ND	ND	0.25	≤0.12	>256	>256	8	4	>64	1
23	SURV0485	*E. roggenkampii*		997	IncX3	blaMIR-6, blaNDM-5	≤0.12	≤0.12	>256	>256	8	2	32	0.12
26	CITF0257	*C. freundii*		ND	IncC	blaCMY-110, blaNDM-1, blaSHV-189	16	≤0.12	>256	>256	2	2	64	1
27	KLEB2751	*K. pneumoniae*		147 SLV	IncHI1B	blaCTX-M-15, blaNDM-5, blaOXA-9, blaSHV-11, blaTEM-1A	>128	0.5	>512	>256	>32	>32	>64	16
27	SURV0518	*K. pneumoniae*	12	ND	ND	ND	>128	0.5	>512	>256	16	16	>64	16
28	SURV0520	*E. hormaechei*		170	IncX3	blaACT-7, blaNDM-5	32	1	>512	>256	>32	>32	>64	8
28	SURV0528	*E. hormaechei*	27	ND	ND	ND	64	1	>512	>256	>32	>32	>64	64

ATM, aztreonam. AVI, avibactam. CAZ, ceftazidime. CZA, ceftazidime-avibactam. FDC, cefiderocol. FEP, cefepime. ST, sequence type. TAN, taniborbactam.

- Few isolates were non-susceptible to potential treatment options
- Four *E. coli* from 2 patients were non-susceptible to each ATM-AVI, FEP-TAN, and FDC (Table 3)
  - All were related by WGS and harbored CMY-145, NDM-5, and a YRIN duplication in PBP3
- Two patients were colonized with isolates demonstrating increased FDC and FDC-AVI MICs
  - Isolates harbored NDM-5, as well as truncated *cirA*, that has previously been implicated in FDC resistance

CONCLUSIONS

- ATM-AVI and FEP-TAN demonstrated potent *in vitro* activity against diverse NDM-producing clinical isolates
  - Susceptibility rates were 92% (ATM-AVI) and 87% (FEP-TAN)
- Susceptibility rates for FDC were lower than either β-lactam/β-lactamase inhibitor
  - FDC MICs were categorized as non-susceptible against 56% of isolates overall
  - The addition of AVI to FDC restored activity against some, but not all isolates (31% non-susceptible)
- Mutations in PBP3 was selected after treatment in a single patient whose isolates were non-susceptible to all agents tested; PBP3 mutations are a concerning threat to novel β-lactam/β-lactamase inhibitor active against NDM-producing *Enterobacterales*