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Activity of NXL104 combinations with ceftazidime and aztreonam against carbapenemase-producing *Enterobacteriaceae*

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Running head: NXL104 with ceftazidime or aztreonam

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NXL104 combinations with ceftazidime and aztreonam were tested against carbapenem-resistant *Enterobacteriaceae*. Ceftazidime+NXL104 was active against strains with OXA-48 enzyme or with combinations of impermeability and an ESBL or AmpC enzyme, also against most *Klebsiella* spp. with KPC enzyme, but metallo-β-lactamase producers were resistant. Aztreonam+ NXL104 was active against all strains at 4+4 μg/ml, including those with metallo-β-lactamases.

Carbapenems are the preferred treatment for severe infections due to multiresistant *Enterobacteriaceae*, including those with extended-spectrum β–lactamases (ESBLs) or copious AmpC. Carbapenemase-producing *Enterobacteriaceae* remained extremely rare for around 20 years after imipenem's launch in 1985,[11] though there was concern that resistance, particularly to ertapenem, could arise via porin loss in strains with extended-spectrum or AmpC β-lactamases.[19]

More recently carbapenemases have begun to accumulate in *Enterobacteriaceae*. In particular, clonal *Klebsiella pneumoniae* with KPC (class A) carbapenemases have spread widely in the USA, Israel and, latterly, Greece.[8,16] Meanwhile, plasmids coding VIM metallo-carbapenemases have disseminated among *K. pneumoniae* strains in Greece[18] and, to a lesser degree, elsewhere in southern Europe, and those coding NDM metallo-enzyme have become distributed among enterobacterial species in the Indian subcontinent.[9] OXA (class D) carbapenemases are most important in *Acinetobacter* spp. but OXA-48 is widespread in *K. pneumoniae* in Turkey, and is an emerging problem elsewhere. [2] International travel and migration are facilitating the dissemination of these enzymes. The UK, for example, sees repeated import of strains with VIM and KPC enzymes via patients previously hospitalised in Greece, Cyprus and Israel and of NDM enzymes via those who have a history of travel and hospitalisation in the Indian subcontinent.[,9]

This diversity presents a considerable challenge, which might best be overcome with β–lactamase inhibitor combinations.[5] We examined the ability of NXL104,[1,22] a novel-structure inhibitor, to protect against carbapenemases when tested with ceftazidime (this combination is currently is in phase II trials), and aztreonam, which has the advantage of stability to metallo-β–lactamases. A smaller study on ceftaroline+NXL104 -also under clinical development- was published previously.[15]

Clinical isolates with carbapenemases were recent submissions to the Health Protection Agency's Antibiotic Resistance Monitoring and Reference Laboratory, mostly from UK hospitals. The Reference Laboratory encourages UK diagnostic microbiology laboratories to submit all *Enterobacteriaceae* that appears resistant to carbapenems for further investigation and the basic characterisation of many of the isolates included here has been described. [4,6,9,22] There is some overlap of the collections with those of a previously published study,[10] however the numbers of isolates and enzymes studied here was substantially greater and the investigation included aztreonam+NXL104, which was not studied previously. Carbapenemases were identified by PCR [22] and, in some cases, sequencing. Isolates with bla_{NDM} were examined for bla_{AmpC} and bla_{CTX-M} genes, again by PCR.[20,21] Porin lesions were characterised as described previously.[4] Identification was by API20E.

NXL104 was from Novexel, Romainville, France; meropenem from AstraZeneca, Macclesfield UK; clavulanate from GlaxoSmithKline, Wembley UK and both piperacillin and tazobactam from Wyeth, Taplow UK. Other antibiotics, including ceftazidime and aztreonam were purchased from Sigma, Poole, UK. MICs were determined by the CLSI agar dilution method,[3] with NXL104, tazobactam and clavulanate all used at a fixed concentration of 4 μg/ml. Transconjugants and transformants of *E. coli* with carbapenemase-encoding plasmids were prepared as described previously.[14] The *E. coli* DH5α transformant with bla_{NDM-1} cloned in pUC19 was obtained from screening a genomic library generated by cloning genomic DNA fragments from of a *K. pneumoniae* isolate that produced the carbapenemase. The DNA was partially digested with *Alu*I and cloned into the *Sma*I site of the vector.

Carbapenem MICs for the 65 organisms with carbapenemases (i.e. excluding those with combinations of impermeability and an ESBL or AmpC enzyme) ranged upwards from 0.06 μg/ml, with wide scatters of values for producers of single enzyme types. Nevertheless these MICs were >4 μg/ml in 54 cases with imipenem, 51 cases

with meropenem and 59 with ertapenem (Table 1). Many of the lowest MICs were for isolates with OXA-48 carbapenemase, though other producers of this enzyme were highly resistant to all three analogues. Isolates with combinations of porin loss and AmpC or ESBL enzymes consistently were more resistant to ertapenem than other carbapenems, with MICs >4 μg/ml in 14/15 cases, whereas imipenem and meropenem MICs mostly were 1-8 μg/ml, thus straddling the CLSI[3] and EUCAST (http://www.eucast.org) breakpoints.

Eleven of 19 *K. pneumoniae* isolates with OXA-48 enzyme were susceptible to ceftazidime at ≤1 μg/ml, as was the sole strain with SME-1 enzyme; the ceftazidime MICs for all other organisms were ≥16 μg/ml. Aztreonam MICs ≤2 μg/ml were recorded for the same 11/19 OXA-48$^+$ *K. pneumoniae* that were susceptible to ceftazidime and for 8/13, 2/5 and 3/17 with IMP, VIM and NDM metallo-carbapenemases respectively; otherwise all aztreonam MICs were ≥8 μg/ml and mostly >64 μg/ml.

NXL104 reduced the MICs of ceftazidime to ≤2 μg/ml for: (i) the eight ceftazidime-resistant isolates with OXA-48 enzymes, (ii) all 15 isolates with combinations of impermeability and ESBLs or AmpC and (iii) for 7/10 of those with KPC carbapenemases. The remaining 3/10 isolates with KPC enzymes, all of them *Enterobacter* spp., were more resistant, with ceftazidime + NXL104 MICs of 8-32 μg/ml. Isoelectric focusing showed that these isolates also copious production of cloxacillin-inhibited pI >8.5 enzymes, which were inferred to be AmpC types. It is likely that these AmpC types, combined with the KPC enzymes simply overwhelmed the inhibitor. With one exception, the isolates with metallo (IMP, NDM or VIM) enzymes remained equally resistant (± 1 doubling dilution) to ceftazidime + NXL104 as to ceftazidime alone. The exception was an *E. coli* isolate with IMP-1 enzyme, where the ceftazidime MIC fell from 256 μg/ml to 0.03 μg/ml, apparently owing to susceptibility to NXL104 itself at ≤8 μg/ml. In our experience, MICs of NXL104 for *E.*

coli are commonly c. 16 mg/L whereas those for other *Enterobacteriaceae* are higher (unpublished).

MICs for aztreonam + NXL104 were ≤4 μg/ml for all the 83 clinical isolates with carbapenemases or combinations of impermeability and AmpC or ESBL, and were ≤1 μg/ml for all except five *E. coli* with NDM-1 carbapenemase, two *Enterobacter* spp. with KPC enzymes and one *E. cloacae* with a combination of porin loss and AmpC.

MICs for *E. coli* J62, DH5α and JM83/109 transformants and transconjugants with representative class A, B and D carbapenemases were determined (Table 2). These organisms were less resistant to the carbapenems than the clinical isolates, probably reflecting greater permeability, particularly among the DH5α derivatives. Thus, carbapenem MICs for *E. coli* DH5α and JM109 transformants with IMP-1, NMC-A and OXA-48 enzymes all remained ≤2 μg/ml.

KPC-3, IMP-1 and NDM enzymes conferred resistance to ceftazidime in the transconjugants and transformants whereas NMC-A and OXA-48 enzymes had little or no effect. Ceftazidime resistance mediated by KPC-3 enzyme was reversed by NXL104, with the MIC reduced from 64 to 0.25 μg/ml, whereas that mediated by IMP and NDM enzymes was little affected. KPC-3 and NMC-A enzymes conferred resistance to aztreonam that was reversed by NXL104, with MICs reduced from >128 to 0.06 μg/ml and 16 to 0.03 μg/ml, respectively. OXA-48, IMP-1 and NDM-1 (as expressed by the cloned gene in pUC19) enzymes had minimal effect on the MICs of aztreonam. Resistance to aztreonam was however seen in the transformant with a native plasmid that determined both NDM carbapenemase and a CIT-type AmpC enzyme, and was reversed by the presence of NXL104.

Carbapenemase-producing *Enterobacteriaceae* present a challenge to the pharmaceutical chemist and the clinician. Producers are increasing in prevalence

and are commonly resistant to multiple antibiotic classes; in addition their enzymes are diverse, including representatives of β–lactamase classes A, B and D.[13] From a US perspective it is easy to perceive KPC carbapenemases as the main emerging problem, but the VIM and NDM metallo-carbapenemases are most frequent among *Enterobacteriaceae* in southern Europe [12,18] and India,[9] respectively, whereas OXA-48 is widespread in Turkey.[2] All of these enzymes are being disseminated internationally by human travel and migration and it would be a brave man who wagered which will be dominant in another 3-4 years, when cephalosporin+NXL104 combinations potentially may reach the market.

We showed previously that NXL104 at 1-4 μg/ml could overcome ceftaroline resistance mediated by OXA-48 and KPC carbapenemases, though not that mediated by metallo-enzymes.[10,15] The present data show that NXL104 can restore the activity of ceftazidime against *K. pneumoniae* with KPC carbapenemase, though resistance remained in some *Enterobacter* spp. isolates with this enzyme, probably because these organisms were also impermeable and had copious AmpC, overwhelming the inhibitor. This limitation is of limited likely impact because KPC enzymes are far more prevalent in *K. pneumoniae* than *Enterobacter* spp.[16] OXA-48 enzyme did not confer resistance to ceftazidime, so no synergy arose unless other NXL104-inhibited ceftazidime-hydrolysing enzymes were present; this is in contrast to the behaviour seen with ceftaroline, where OXA-48 did confer resistance, overcome by NXL104.

If KPC or OXA-48 are the predominant carbapenemases of the future, then either ceftazidime+NXL104 or ceftaroline+NXL104 should prove an effective answer. These combinations should also be effective against isolates with carbapenem resistance contingent on combinations of AmpC or ESBL and impermeability, though these have shown little ability to spread in clinical settings and are a lesser concern. The problem arises if metallo-carbapenemases become dominant, since NXL104

cannot inhibit these enzymes, and nor can any other inhibitor in advanced development. One answer is to use a monobactam as the partner drug, as these are stable to metallo-carbapenemases,[17] and to protect it against co-produced ESBLs or AmpC enzymes using NXL104 or another inhibitor. The present study has illustrated the potential of this approach, with MICs of aztreonam+NXL104 found to be ≤4 μg/ml against all carbapenemase producers, including those with metallo-enzymes, and ≤1 μg/ml for the huge majority, the exceptions mostly being *E. coli* isolates with NDM-1 enzyme. The activity of aztreonam+NXL104 against *K. pneumoniae* with KPC carbapenemases was noted also by Endimiani *et al.* [7] who, as in the present study, found MICs consistently lower than those of ceftazidime+NXL104.

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266 **Table 1.** MIC distributions for carbapenemase-producing isolates and those with combination of AmpC or ESBL and impermeability
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	MIC (μg/ml)														
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512
KPC (n=10: 7 *K. pneumoniae* + 3 *Enterobacter* spp.)															
Ceftazidime															10*
Ceftazidime + NXL104			1		3	3			1		2				
Ceftazidime + clav											2	8*			
Aztreonam													10*		
Aztreonam + NXL104		2	3	2	1		1	1							
Piperacillin														10*	
Piperacillin + tazobactam												1		9*	
Imipenem									1	1	3	2	2	1*	
Meropenem										1	3	1	3	2*	
Ertapenem												3	2	5*	
SME-1 (n=1: *S. marcescens*)															
Ceftazidime				1											
Ceftazidime + NXL104				1											
Ceftazidime + clav				1											
Aztreonam										1					
Aztreonam + NXL104				1											
Piperacillin												1			
Piperacillin + tazobactam								1							
Imipenem														1*	
Meropenem									1						
Ertapenem									1						
OXA-48 (n=19: all *K. pneumoniae*)															
Ceftazidime			1**		8	2					1		2		5
Ceftazidime + NXL104		1**	1	8	6	3									
Ceftazidime + clav					1	3	2	6	2	2		3*			
Aztreonam		1	2	7	1								2	6*	
Aztreonam + NXL104	1**	4	10	2	2										
Piperacillin														19*	

Piperacillin + tazobactam													1		18*	
Imipenem				1		1	2	4	2		2	3	2	2*		
Meropenem		1			1	2	2	3			5	1	4			
Ertapenem				1			1	1	5	1		3	3	4*		
IMP (n=13: 7 *K. pneumoniae*, 5 *Enterobacter* spp. and 1 *E. coli*)																
Ceftazidime															1	12
Ceftazidime + NXL104	1**															12
Ceftazidime + clav												13*				
Aztreonam			2	5	1				1					4*		
Aztreonam + NXL104		2	3	2	3		1	1								
Piperacillin											1		1	11*		
Piperacillin + tazobactam										1		1		11*		
Imipenem							1	1	2	7	1			1*		
Meropenem								2		2	8	1				
Ertapenem									2	2	8			1*		
VIM (n=5: 4 *K. pneumoniae* and 1 *Enterobacter* spp.)																
Ceftazidime												1				4
Ceftazidime + NXL104												1		1		3
Ceftazidime + clav												5*				
Aztreonam				1		1							1	2*		
Aztreonam + NXL104			2	2	1											
Piperacillin														5*		
Piperacillin + tazobactam														5*		
Imipenem								1		2		2				
Meropenem						1		1			1		1	1*		
Ertapenem								2			2			1		
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	
NDM-1 (n=17: 6 *K. pneumoniae*, 6 *E. coli*, 2 *Enterobacter* spp., 2 *Citrobacter freundii* and 1 *Morganella morganii*																
Ceftazidime																17
Ceftazidime + NXL104																17

Ceftazidime + clav											17*			
Aztreonam		1	1	1					1			2	11*	
Aztreonam + NXL104	2**	2	1	4	1	2	3	2						
Piperacillin													17*	
Piperacillin + tazobactam												1	16*	
Imipenem									1	1	8	3	2	2*
Meropenem								1			7	3	3	3*
Ertapenem								1			3	3	5	5*
Porin loss & AmpC (5: all *Enterobacter* spp.)														
Ceftazidime												1		4
Ceftazidime + NXL104				1	1	3								
Ceftazidime + clav												5*		
Aztreonam												3	1	1*
Aztreonam + NXL104				1	1	3								
Piperacillin												1	1	3*
Piperacillin + tazobactam										1		2		2*
Imipenem							1	1	3					
Meropenem							2	2	1					
Ertapenem									1	1	2	1		
Porin loss & ESBL (n=10: all *K. pneumoniae*)														
Ceftazidime										1			4	5
Ceftazidime + NXL104					2	7	1							
Ceftazidime + clav						1			2	1	1	4*		
Aztreonam												2	8*	
Aztreonam + NXL104		1		7	1	1								
Piperacillin													10*	
Piperacillin + tazobactam													10*	
Imipenem					1	2	5	2						
Meropenem				1				2	4		3			
Ertapenem						1			1		3	5		

Abbreviations: clav, clavulanate; * MIC ≥ indicated value; ** MIC ≤ indicated value

Table 2. MICs (μg/ml) for *E. coli* transconjugants and transformants with carbapenemases

	Ceftaz-idime	Ceftaz-idime+ NXL104	Ceftaz-idime+ clavulanate	Aztreo-nam	Aztreo-nam +NXL104	Cefot-axime	Pipera-cillin	Pipera-cillin+ Tazo-bactam	Imi-penem	Mero-penem	Erta-penem
Class A											
J62 KPC-3	64	0.25	32	>128	0.06	128	>128	>128	8	8	8
JM109 NMCA	0.25	≤0.060	0.125	16	≤0.030	≤0.125	32	2	2	1	2
Class B											
DH5α IMP-1	16	4	16	≤0.030	≤0.030	4	2	1	0.5	0.125	0.125
DH5α NDM[a]	>256	>256	>32	8	0.125	128	128	128	8	4	8
DH5α NDM (cloned pUC19)	>256	>256	>32	0.06	≤0.030	256	>128	>128	32	16	16
Class D											
DH5α OXA-48	≤0.125	≤0.060	0.125	≤0.030	≤0.030	0.25	128	32	2	0.125	0.5
Recipients											
DH5α	≤0.125	≤0.060	≤0.060	≤0.030	≤0.030	≤0.125	1	1	0.125	≤0.030	≤0.030
J62	≤0.125	≤0.060	0.125	≤0.030	≤0.030	≤0.125	2	2	0.125	≤0.030	≤0.030
JM83	≤0.125	0.125	0.125	0.06	0.06	≤0.125	2	2	0.25	≤0.030	≤0.030

[a] Also produced CIT-type AmpC β–lactamase