Activity of β–lactam/taniborbactam (VNRX-5133) combinations against carbapenem-resistant Gram-negative bacteria

Shazad MUSHTAQ[1], Anna VICKERS[1], Michel DOUMITH,[1,a] Matthew J ELLINGTON[1], Neil WOODFORD[1] and David M LIVERMORE[1,2*]

[1]*Antimicrobial Resistance and Healthcare Associated Infections (AMRHAI) Reference Unit, National Infection Service, Public Health England, London NW9 5EQ; United Kingdom*

[2]*Norwich Medical School, University of East Anglia, Norwich NR4 7TJ, United Kingdom*

Running head: Taniborbactam as a β-lactamase inhibitor

Current address:

[a] King Abdullah International Medical Research Center, Infectious Diseases Research Department, Riyadh, Saudi Arabia and King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia

*__Corresponding author:__ David M Livermore, Norwich Medical School, University of East Anglia, Norwich, NR4 7TJ; tel. +44-(0)1603-597-568; d.livermore@uea.ac.uk

Background. Boronates are of growing interest as β–lactamase inhibitors. The only marketed analogue, vaborbactam, targets KPC carbapenemases, but taniborbactam (VNRX-5133, Venatorx) has a broader spectrum. **Materials and methods.** MICs of cefepime and meropenem were determined combined with taniborbactam or avibactam for carbapenem-resistant UK isolates. β–Lactamase genes and porin alterations were sought by PCR or sequencing. **Results.** Taniborbactam potentiated partner β–lactams against (i) Enterobacterales with KPC, other Class A, OXA-48-like, VIM and NDM (not IMP) carbapenemases and against (ii) Enterobacterales inferred to have combinations of ESBL or AmpC activity and impermeability. Potentiation of cefepime (the partner for clinical development) by taniborbactam was slightly weaker than by avibactam for Enterobacterales with KPC or OXA-48-like carbapenemases, but MICs of cefepime/taniborbactam were similar to those of ceftazidime/avibactam and the spectrum was wider. MICs of cefepime/taniborbactam nonetheless remained >8+4 mg/L for 22-32% of NDM-producing Enterobacterales. Correlates of raised cefepime/taniborbactam MICs among these NDM Enterobacterales were: a cefepime MIC >128 mg/L, particular sequence types, also, for *Escherichia coli* only: (i) the bla_{NDM} variant (even though published data suggest all are inhibited similarly), (ii) inserts in PBP3, and (iii) raised aztreonam/avibactam MICs. Little or no potentiation of cefepime or meropenem was seen for *Pseudomonas aeruginosa* and *Acinetobacter baumannii* with MBLs, probably reflecting less uptake or more efflux. Potentiation of cefepime was seen for *Stenotrophomonas maltophilia* and *Elizabethkingia meningoseptica*, which have both chromosomal ESBLs and MBLs. **Conclusion**. Taniborbactam broadly reversed cefepime or meropenem non-susceptibility in Enterobacterales, less reliably for non-fermenters.

Introduction

Boronates have long been known to inhibit some β–lactamases, with this property used to identify AmpC enzymes,[1] and to purify them by affinity chromatography.[2] Recent interest has moved to using boronates as clinical β–lactamase inhibitors. One analogue, vaborbactam, has been licensed in combination with meropenem. Vaborbactam inhibits KPC and other Class A carbapenemases (IMI/NMC and SME), but not Class D (OXA) or metallo (Class B, IMP, NDM, VIM) types.[3] Consequently meropenem/ vaborbactam is most likely to find a niche in countries where KPC enzymes are the predominant carbapenemases – as in the Americas, Italy, Portugal, Greece and China.[4] Utility is less in the Middle East and in much of the rest of Europe, where OXA-48-like enzymes predominate in Enterobacterales, or in south Asia, where NDM-1 is the prevalent carbapenemase.[5-7] These limitations have stimulated a search for broader-spectrum boronates, leading, *inter alia*, to taniborbactam (formerly VNRX-5133, Venatorx, figure 1), which acts as an irreversible, covalent inhibitor of serine β–lactamases and as a competitive inhibitor of MBLs.[8,9] We investigated the activity of taniborbactam combined with cefepime and meropenem against Gram-negative bacteria with a range of β–lactamase types; cefepime is now favoured as a partner for clinical development.

Materials and methods

Two organism panels were used. The first comprised clinical Enterobacterales and non-fermenters selected to represent a diversity of carbapenemases and other modes of carbapenem resistance. The organisms were chosen from among these received by the PHE Antimicrobial Resistance and Healthcare Associated Infections (AMRHAI) Reference Unit, mostly from UK hospitals, between 2013 and 2016. Bacterial identification was by MALDI-ToF; carbapenemase genes were characterised by PCR[10] or sequencing. Combinations of ESBL or AmpC and impermeability were inferred on the bases of isolates: (i) being resistant to ertapenem on EUCAST criteria and with an meropenem MIC >0.12 mg/L,[11] (ii) showing synergy between oxyimino-cephalosporins and clavulanate 4 mg/L (ESBL

69 producers) or between cefotaxime and cloxacillin 100 mg/L (AmpC hyperproducers), and (iii) lacking
70 detectable carbapenemase genes.
71 The second panel comprised 124 consecutively-referred *bla*$_{NDM}$–positive Enterobacterales (29
72 *Escherichia coli*, 82 *Klebsiella pneumoniae* and 13 *Enterobacter cloacae*) received in 2014 to 2015 – a
73 period when AMRHAI routinely sequenced each new patient's first carbapenemase-producing isolate.
74
75 *Susceptibility testing*
76 MIC determinations were performed and interpreted according to CLSI agar dilution criteria.[12,13]
77 Taniborbactam, vaborbactam and avibactam were provided by Venatorx; cefepime and meropenem
78 were provided by Venatorx for initial studies, but subsequently purchased from Alfa Aesar (Heysham,
79 UK) and Sequoia Research Products (Pangbourne, UK) respectively; ceftazidime was purchased from
80 Sigma (Poole, UK) and aztreonam from Alfa Aesar. Control organisms included throughout comprised
81 *Escherichia coli* ATC 25922, *Pseudomonas aeruginosa* ATCC27853 and *Klebsiella pneumoniae* ATCC
82 BAA-1705 (KPC). For the second panel we additionally included *K. pneumoniae* ATCC70060 (ESBL), also
83 *E. coli* 113, *E. coli* RIC and *K. pneumoniae* BS047 – all with NDM carbapenemases, these were supplied
84 by Venatorx and sourced by them from Dr Docquier and Nordmann. Synergy was taken as a $\geq$8-fold
85 reduction in MIC of the partner β–lactam in the presence of a β–lactamase inhibitor. Unless stated
86 otherwise, taniborbactam and avibactam were used at a fixed 4 mg/L and vaborbactam at 8 mg/L.
87
88 *Analysis of genomic sequences*
89 WGS was undertaken on an Illumina HiSeq instrument. Reads from each genome were assembled *de*
90 *novo* and screened for antimicrobial resistance genes using Blast software and PHE's in-house
91 Genefinder bioinformatics pipeline.[14] Porin alterations and the presence of resistance determinants
92 were confirmed using a mapping-based approach. Specifically, genes encoding the major porins
93 OmpF and OmpC of *E. coli* and *Enterobacter* spp. and their homologues OmpK35 and OmpK36 in
94 *Klebsiella* spp. were extracted and checked for alterations that introduced translational frameshifts or

premature stop codons. Similarly, the PBP3-encoding gene *ftsI* was extracted and examined for insertion sequences. Copy numbers of bla_{NDM} were estimated by comparing sequencing read depths to those for the single-copy chromosomal genes, *gyrA* and *parC*.

Results

MICs for isolates with diverse modes of carbapenem resistance

MIC distributions of the taniborbactam combinations and their comparators for the first collection– i.e. Enterobacterales with various modes of carbapenem resistance – are shown in Table 1, with results for non-fermenters in Table 2. Taniborbactam itself lacked antibacterial activity against any species at 32 mg/L and achieved no potentiation or antagonism with cefepime or meropenem against control strains lacking resistance to these β–lactams (Tables 1 and 2).

Carbapenem-resistant Enterobacterales

At 4 mg/L, taniborbactam reduced the MICs of cefepime for isolates (n=41) with KPC carbapenemases from 4 - >128 mg/L to 0.03 – 2 mg/L and those of meropenem from 1->128 mg/L to ≤0.015-8 mg/L. MICs of cefepime/taniborbactam and meropenem/taniborbactam remained 2- to 4- fold above those of cefepime/avibactam and meropenem/avibactam, but were similar to those of ceftazidime/avibactam. Only four isolates with non-KPC Class A carbapenemases (IMI/NMC or SME types) were tested. These were susceptible to unprotected cefepime, with MICs of 0.06-0.5 mg/L. These values only reduced 2- to 4-fold by taniborbactam or avibactam 4 mg/L. MICs of meropenem were elevated to 8-64 mg/L and were reduced to 0.06-0.25 mg/L by either taniborbactam or avibactam at 4 mg/L, indicating that both β-lactamase inhibitors protected meropenem, but not cefepime, from these enzymes. Avibactam also potentiated ceftazidime against one isolate, which was inferred additional to have high-level AmpC enzyme activity, as it remained cefepime-susceptible.

Cefepime MICs for Enterobacterales with OXA-48-like enzymes (n=40) ranged from 0.25->128 mg/L, with the wide range likely reflecting co-presence or not of ESBLs. This range fell and narrowed to 0.03-2 mg/L with taniborbactam 4 mg/L added and to 0.03-0.5 mg/L if avibactam 4 mg/L was added. MIC reductions were often ≥64-fold for highly cefepime-resistant isolates but only 2- or 4-fold for isolates with cefepime MICs ≤2 mg/L, consistent with the view that the former group have (taniborbactam-inhibited) ESBLs and that the latter group lack these enzymes and that OXA-48 itself lacks appreciable activity against cefepime. Taniborbactam and avibactam also potentiated meropenem, typically by around 16-fold and 64-fold, respectively; nevertheless; 13/40 meropenem/taniborbactam MICs remained >1 mg/L and 5/40 were >4 mg/L; corresponding proportions for meropenem/avibactam were 2/40 and 1/40, respectively.

Taniborbactam potentiated cefepime and meropenem against Enterobacterales with VIM and NDM MBLs, though not those with IMP enzymes. MICs of unprotected cefepime were 2->128 mg/L for Enterobacterales with VIM MBLs (excepting one anomalously low value of 0.5 mg/L). This range was reduced to 0.06-8 mg/L by taniborbactam 4 mg/L, with 37/40 values ≤2+4 mg/L. For unprotected meropenem the MIC range was 2-128 mg/L, reducing to ≤0.015-4 mg/L in the presence of taniborbactam 4 mg/L, with 37/40 of values ≤1 mg/L and with MIC reductions mostly >32-fold. Isolates with NDM carbapenemases were more resistant to unprotected β–lactams than those with VIM MBLs: MIC ranges were 32->128 and 8->128 mg/L for cefepime and meropenem, respectively. These MICs were reduced by taniborbactam: thus, 25/40 of the NDM-positive Enterobacterales were inhibited by cefepime/taniborbactam at 2+4 mg/L and 32/40 were inhibited at 8+4 mg/L. Proportions inhibited by meropenem/taniborbactam were 27/40 at 1+4 mg/L, rising to 35/40 at 4+4 mg/L. Avibactam often achieved some potentiation of cefepime, but not meropenem, against MBL producers; this is consistent with it inhibiting coproduced ESBLs but not the MBLs themselves.

Almost all isolates with inferred combinations of ESBL and impermeability were highly resistant to cefepime, with 17/20 MICs ≥128 mg/L; these values were reduced by taniborbactam, with

13/20 brought at least 64-fold lower to ≤2+4 mg/L and 18/20 to ≤8+4 mg/L. Potentiation was stronger with avibactam, which reduced all cefepime MICs to ≤2+4 mg/L. Meropenem MICs ranged from 0.12-16 mg/L, with 14/20 values >1 mg/L; in all cases except one these values were reduced to ≤1 mg/L by either taniborbactam or avibactam at 4 mg/L.

MICs of cefepime ranged from 0.25-16 mg/L for the 20 isolates with inferred combinations of AmpC activity and impermeability; 9 values exceeded 2 mg/L, and 3 exceeded 8 mg/L. These MICs were reduced by the inhibitors, with 19/20 isolates inhibited by cefepime/taniborbactam at 2+4 mg/L and all 20 by cefepime/avibactam at 2+4 mg/L. MICs of meropenem ranged from 1-8 mg/L and, for 19/20 isolates were reduced to ≤1 mg/L by either taniborbactam or avibactam.

Non-fermenters

Cefepime MICs for *P. aeruginosa* isolates with VIM MBLs were 16->128 mg/L and were reduced to ≤8 mg/L by taniborbactam in 7/20 cases. For meropenem, 19/20 MICs were ≥32 mg/L and 6/20 were reduced to ≤4 mg/L by taniborbactam (Table 2). Cefepime/taniborbactam MICs against *P. aeruginosa* isolates with NDM or SPM carbapenemases remained >128 mg/L irrespective of addition of taniborbactam. In the case of *A. baumannii* with NDM carbapenemases, meropenem was potentiated 2- to 4-fold by taniborbactam but with no MICs reduced below 32+4 mg/L; cefepime was not usefully potentiated by avibactam against these NDM-positive isolates of *A. baumannii*. Avibactam did not potentiate partner β–lactams against *P. aeruginosa* or *A. baumannii* with any of these MBLs.

Taniborbactam commonly reduced the MICs of cefepime, though not meropenem, by one doubling dilution for *A. baumannii* isolates with OXA carbapenemase; nonetheless MICs of both combinations typically remained >8+4 mg/L. avibactam reduced the modal MIC of meropenem by two doubling dilutions, but only to 16 mg/L.

More substantial interactions were seen for non-fermenters with chromosomal carbapenemases. Thus, MICs for unprotected cefepime for *Elizabethkingia meningoseptica* were 16-32 mg/L and were reduced to 2-8 mg/L by either taniborbactam or avibactam at 4 mg/L; MICs of unprotected meropenem for *E. meningoseptica* were 16-128 mg/L and were reduced to 4-16 mg/L by taniborbactam at 4 mg/L, but were little affected by avibactam. Cefepime MICs for *S. maltophilia* were reduced from 8-128 mg/L to 2-16 mg/L by either taniborbactam or avibactam at 4 mg/L but MICs of meropenem were unaffected by either inhibitor.

MIC ranges for Enterobacterales with NDM carbapenemases

In the second part of this study we tested 124 genomically-sequenced Enterobacterales with NDM carbapenemases, as consecutively received by the reference service. The organisms were clonally diverse. They comprised 82 *Klebsiella* spp., 29 *E. coli* and 13 *Enterobacter* spp. MIC distributions for cefepime and cefepime/taniborbactam resembled the earlier results: thus 89/124 (71.8%) isolates were inhibited by cefepime/taniborbactam at 8+4 mg/L (Table 3) as compared with 32/40 (80%) of the NDM-positive Enterobacterales in the first series (Table 1). The proportion susceptible to cefepime 8 mg/L rose to 79.8% if the taniborbactam concentration was raised from 4 to 8 mg/L. More isolates (87.9% versus 71.8%) were inhibited by aztreonam/avibactam at 8+4 mg/L than cby efepime/taniborbactam, whereas resistances to meropenem/vaborbactam 8+8 mg/L and ceftazidime/ avibactam 8+4 mg/L were near universal. Notably, the isolates with cefepime/taniborbactam MICs >8+4 mg/L were predominantly were *E. coli* (15/29) rather than *Klebsiella* spp. (19/82) and *Enterobacter* spp. (1/13).

Regardless of species, the clearest correlate ($p < 0.001$) of a cefepime/taniborbactam MIC >8+4 mg/L was a cefepime MIC >128 mg/L (Table 4). On the other hand, there was no general association to lesions in porin genes nor to bla_{NDM} gene copy number. For *E. coli* only, there were associations between a cefepime/taniborbactam MIC >8+4 mg/L and an aztreonam/avibactam MIC >8+4 mg/L (p

<0.001) also with (i) carriage of *bla*$_{NDM-5}$ or *bla*$_{NDM-7}$ rather than *bla*$_{NDM-1}$ and (ii) with the presence (always in isolates that had NDM-5 or -7 rather than NDM-1) of Tyr-Arg-Ile-Asn/Pro insertions at amino-acid 334 of penicillin-binding protein (PBP)3. Both these traits were only seen among the isolates with cefepime/taniborbactam MICs >8+4 mg/L but were not universal among them: in particular only 4/15 NDM isolates with cefepime/taniborbactam MICs >8+4 mg/L had PBP3 insertions and, complicating analysis, all these also had NDM-5 or -7 MBLs. Nine sequence types (STs) were represented among the 15 *E. coli* isolates with cefepime/taniborbactam MICs >8+4 mg/L, with ST167, 410 and 648 each having three or four representatives; ST167 – always with NDM-5 or -7 but without the PBP3 insert – had no representatives with cefepime/taniborbactam ≤8+4 mg/L.

Only NDM-1 carbapenemase was seen in the 82 *K. pneumoniae* isolates and, unlike for *E. coli*, there was no association between cefepime/taniborbactam MICs >8+4 mg/L, seen for 19 isolates, and aztreonam/avibactam MICs >8+4 mg/L, which were seen for only two isolates. PBP3 remained unaltered and there was no clear association between resistance and porin changes. There was a weak statistical association ($p < 0.05$) between co-carriage of *bla*$_{CTX-M}$ and cefepime/taniborbactam MIC >8+4 mg/L, nevertheless *bla*$_{CTX-M}$ was also present in more than half the *Klebsiella* isolates with cefepime/taniborbactam MICs ≤8+4 mg/L. Eight STs were represented among the 19 *Klebsiella* isolates with cefepime/taniborbactam MICs >8+4 mg/L, with 10, from seven centres, belonging to ST14, which only had one representative with cefepime/taniborbactam MICs ≤8+4 mg/L. Among the 13 *E. cloacae* isolates there was only one with a cefepime/taniborbactam MIC >8+4 mg/L. Perhaps of note, this isolate was the only one among the 13 with an aztreonam/avibactam MIC >8+4 mg/L, and it had insertion of an additional Glu residue at position 258 of PBP3.

Discussion

Taniborbactam irreversibly inhibits serine β–lactamases and competitively inhibits MBLs.[8] We showed that this behaviour is reflected in antibacterial activity. At 4 mg/L, it lowered the MICs of cefepime and

meropenem for Enterobacterales with all carbapenemases except IMP types and for those with carbapenem resistance inferred due to combinations of impermeability with AmpC or ESBL activity. Cefepime/taniborbactam - the combination now in clinical development - had lower MICs than meropenem/taniborbactam for Enterobacterales with OXA-48-like carbapenemases, probably because cefepime is stable to OXA-48-like enzymes, meaning that the critical requirement is to inhibit co-produced ESBLs, not OXA-48 itself, as for meropenem/taniborbactam. Although avibactam achieved 2- to 4-fold greater potentiation of cefepime than taniborbactam for Enterobacterales with several enzyme types (e.g. KPC and OXA-48), MICs of cefepime/ taniborbactam for these groups were as low as for ceftazidime/avibactam, reflecting the greater potency of cefepime than ceftazidime.

Spectrum gaps nonetheless remain. Lack of coverage of IMP MBLs has been remarked already. This is a limitation but IMP MBLs are rarer than VIM and NDM types.[4-7] Secondly, potentiation was weak or absent for *P. aeruginosa* with MBLs and for *A. baumannii* with NDM or OXA enzymes - a less encouraging result than on recent (2018-2019) global surveillance by broth microdilution, which found that cefepime/taniborbactam 8+4 mg/L inhibited 63.5% (33/52) of MBL *P. aeruginosa*.[15] Thirdly, 20-30% of Enterobacterales with NDM carbapenemases evaded cefepime/taniborbactam at 8+4 mg/L, a higher proportion than the 6/38 (14%) found for globally-collected NDM-positive Enterobacterales.[16]

Greater potentiation against Enterobacterales than *P. aeruginosa* and *A. baumannii* with MBLs probably likely reflects the non-fermenters' greater impermeability and, at least for *P. aeruginosa*, greater efflux.[17,18] In the same context, although no useful potentiation of partners was seen here *for P. aeruginosa* with SPM-1 enzyme, resistance mediated by this MBLs was reversed when it was cloned into *E. coli*.[9] Lack of potentiation against *A. baumannii* with OXA carbapenemases may reflect limited uptake or failure to inhibit these enzymes.

The behaviour of the non-fermenter species with chromosomal carbapenemases reflected their known β–lactamase profiles: *E. meningoseptica*. have multiple chromosomal β–lactamases including BlaB, a strain-variable MBL, and a chromosomal ESBL.[19,20] Taniborbactam potentiated both

meropenem and cefepime, whereas avibactam potentiated only cefepime, results compatible with both the ESBL and BlaB being inhibited by taniborbactam whereas avibactam inhibits only the ESBL. For *S. maltophilia*, resistance to β–lactams involves the L-1 MBL and L-2, a class A cephalosporinase.[21] MICs of cefepime were generally reduced 4-8-fold by both taniborbactam and avibactam whereas MICs of meropenem were little affected by either inhibitor; we infer that both taniborbactam and avibactam inhibit the cefepime-hydrolysing L-2 enzyme, but not the L-1 MBL.

Higher MICs of taniborbactam combinations for Enterobacterales with NDM rather than VIM MBLs may reflect NDM enzymes (i) being inhibited less well;[8] (ii) being expressed more strongly and/or (iii) having greater substrate affinity, protecting against inhibition. These possibilities deserve future investigation. More immediately, we explored reasons for MIC variation in a collection of 124 consecutively-referred and genomically-sequenced Enterobacterales with NDM MBLs. Cefepime/taniborbactam MICs for 35 of these (15/29 *E. coli*, 19/82 *K. pneumoniae* and 1/13 *E. cloacae*) exceeded 8+4 mg/L. We failed to find a single universal correlate of raised cefepime/taniborbactam MICs but, for *E. coli*, did associate these with raised MICs also for aztreonam/avibactam, with carriage of NDM-5 or -7, with isolates belonging to ST167, and with the presence of a Tyr-Arg-Ilu-Pro/Asn insert in PBP3.[22,23] The last trait, though seen for only 4/15 representatives provides the clearest explanation of reduced activity, being known to be reduce affinity for β–lactams, including cefepime, that target this PBP; it was also recorded for *E. coli* isolates with elevated cefepime/taniborbactam MICs from China.[24] The apparent association with NDM-5 and -7 enzymes is more doubtful. Four isolates with these enzymes and raised cefepime/taniborbactam MICs also had the PBP3 insert providing an alternative explanation for their behaviour. Moreover, aztreonam/avibactam MICs were also raised, yet aztreonam evades NDM-5 and -7 enzymes.[25,26] Lastly, taniborbactam is able to protect cefepime for *E. coli* with cloned, and identically expressed, NDM-1, -5 and -7 enzymes,[9] implying that these enzymes are similarly inhibited by the boronate. It remains possible that NDM-5 or -7 enzymes tend to be more strongly expressed.

A combination of OmpF mutations and a single amino-acid insertion in PBP3 may explain raised cefepime/taniborbactam and aztreonam/avibactam MICs for the sole *E. cloacae* with these traits, but confirmation with more isolates evidently is needed. For *K. pneumoniae*, we found no convincing correlates of reduced susceptibility: all 19 isolates with cefepime/taniborbactam MIC >8+4 mg/L had NDM-1 enzymes, wild-type PBP3 and, with a solitary exception, were inhibited by aztreonam/avibactam ≤8+4 mg/L. Ten, from seven hospitals, belonged to ST14 versus only 1/63 that were inhibited by cefepime/taniborbactam at 8+4 mg/L. Whilst this association is statistically significant ($p < 0.001$, Chi Square test) we caution that ST14 is a frequent *K. pneumoniae* type known to acquire MBLs repeatedly and independently.[27] We cannot exclude novel mechanisms, not represented in the Genefinder bioinformatic database.

These uncertainties may be elucidated by future mutant, transconjugant and laboratory mutant studies. What is nonetheless clear is that taniborbactam has a broader spectrum of direct inhibition than any other β–lactamase inhibitor presently in use or in Phase III. Except for isolates with IMP MBLs, cefepime/taniborbactam has similarly extensive coverage against carbapenem-resistant Enterobacterales as (i) combinations employing triple-action diazabicyclooctanes,[28-30] (ii) aztreonam/avibactam,[31] or (iii) carbapenemase-relatively-stable molecules such as cefiderocol[32] and BOS-228 (LYS-228)[33]. Coverage was more limited against non-fermenters. Only clinical experience will reveal which approach provides the best spectrum answer to the carbapenemase challenge; what is encouraging is that multiple different potential remedies are now in development.

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Transparency declaration

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405 **Table 1.** MICs of taniborbactam and avibactam combinations for Enterobacterales, according to β–lactamase type

	Categorisation based on partner β–lactam[a]			No. isolates with indicated MIC (mg/L)														
	S	I/SDD	R	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128
Controls (n=30: 10 *E. coli,* 10 *Enterobacter spp*., 10 *K. pneumoniae*)																		
Cefepime	100	0	0	3	11	13	3											
+ Tani 4 mg/L	100	0	0	2	12	14	2											
+ Avi 4 mg/L	100	0	0	7	12	8	2	1										
Meropenem	100	0	0	8	16	3		3										
+ Tani 4 mg/L	100	0	0	13	14	2		1										
+ Avi 4 mg/L	100	0	0	25	5													
Ceftazidime	100	0	0			1	2	12	13	2								
+ Avi 4 mg/L	100	0	0		3	1	7	14	5									
KPC carbapenemases (n=41: 10 *E. coli,* 10 *Enterobacter spp*., 21 *K. pneumoniae*)																		
Cefepime	0	41.5	58.5									6	11	4	3	5	8	4
+ Tani 4 mg/L	100	0	0		8	12	5	4	8	3	1							
+ Avi 4 mg/L	100	0	0	9	11	7	2	10	2									
Meropenem	2.4	7.3	90.2							1	3	10	10	3	3	2	5	4
+ Tani 4 mg/L	92.7	2.4	4.9	2	21	4	3		4	4	1	1	1					
+ Avi 4 mg/L	100	0	0	22	7		5	2		5								
Ceftazidime	0	7.3	92.7										3	8	10	4	2	14
+ Avi 4 mg/L	95.1	4.9	0					6	14	11	4	4	2					

IMI/NMC/SME carbapenemase (n=4: 3 *Enterobacter* spp. with IMI enzymes; 1 *Serratia marcescens* with SME-1)																		
Cefepime	100	0	0			1	1		2									
+ Tani 4 mg/L	100	0	0		1	1	1	1										
+ Avi 4 mg/L	100	0	0		1		3											
Meropenem	0	0	100										1		2	1		
+ Tani 4 mg/L	100	0	0			1	2	1										
+ Avi 4 mg/L	100	0	0			2	2											
Ceftazidime	75.0	0	25.0						2		1				1			
+ Avi 4 mg/L	100	0	0						2	1	1							
OXA-48 carbapenemases (n=40: 10 *E. coli,* 10 *Enterobacter spp*., 20 *K. pneumoniae*)																		
Cefepime	50	12.5	37.5					7	2	7	4	2	3	1	5	2	4	3
+ Tani 4 mg/L	100	0	0		2	9	6	9	6	5	3							
+ Avi 4 mg/L	100	0	0		7	13	8	5	7									
Meropenem	17.5	32.5	50				1			6	13	5	1	5	4	2	3	
+ Tani 4 mg/L	67.5	12.5	20			6	13	1	5	2	5	3	4	1				
+ Avi 4 mg/L	95.0	2.5	2.5	3	14	8	5	1	2	5	1	1						
Ceftazidime	60	5.0	35.0					2	7	3	7	5	2		1	3	6	4
+ Avi 4 mg/L	100	0	0				3	11	15	11								
NDM carbapenemases (n=40: 10 *E. coli,* 10 *Enterobacter spp*., 20 *K. pneumoniae*)																		
Cefepime	0	0	100												2	11	8	19
+ Tani 4 mg/L	62.5	17.5	20					1	12	2	10	6	1	1	2	4		1
+ Avi 4 mg/L	2.5	2.5	95.0							1			1	3	6	10	7	12

Meropenem	2.5	0	97.5			1							1	6	6	16	8	2
+ Tani 4 mg/L	67.5	17.5	15.0		1			15	4	7	7	1	3					2
+ Avi 4 mg/L	2.5	0	97.5	1								1	3	9	8	13	3	2
Ceftazidime	0	0	100															40
+ Avi 4 mg/L	2.5	0	97.5									1						39
VIM carbapenemases (n=40: 10 *E. coli,* 10 *Enterobacter spp*., 20 *K. pneumoniae*)																		
Cefepime	15.0	27.5	57.5						1		5	7	4	6	5	6	2	4
+ Tani 4 mg/L	92.5	7.5	0			8	10	8	5	6		1	2					
+ Avi 4 mg/L	60	20	20						2	8	14	5	3	3		1		4
Meropenem	0	10	90								4	11	14	7	2	1	1	
+ Tani 4 mg/L	97.5	0	2.5	1	19	8	8		1	2		1						
+ Avi 4 mg/L	12.5	15.0	72.5						3	2	6	11	10	6	1		1	
Ceftazidime	0	0	100												4	4	9	23
+ Avi 4 mg/L	2.5	0	97.5							1				8	12	6	9	4
IMP carbapenemases (n=13: 5 *E. coli,* 3 *Enterobacter spp*., 5 *K. pneumoniae*)																		
Cefepime	0	30.8	69.2									2	2	1	4	3		1
+ Tani 4 mg/L	0	30.8	69.2									3	1	5	2	2		
+ Avi 4 mg/L	7.7	23.1	69.2								1	2	1	1	4	2	2	
Meropenem	23.1	7.7	69.2						1	2	1	3	1	3	2			
+ Tani 4 mg/L	23.1	15.4	61.5						1	2	2	2		4	2			
+ Avi 4 mg/L	23.1	23.1	53.8				1		1	1	3	1	2	3	1			

Ceftazidime	0	0	100														13
+ Avi 4 mg/L	0	0	100													1	2	10
ESBL + impermeability (n=20, all *K. pneumoniae*)																		
Cefepime	0	5.0	95.0									1			2		1	16
+ Tani 4 mg/L	65.0	25.0	10				1	1	4	4	3	4	1	1		1		
+ Avi 4 mg/L	100	0	0				3	11	2	4								
Meropenem	30	10	60				1	2	3		2	4	5	3				
+ Tani 4 mg/L	80	5.0	15.0		1	1	3	2	9		1	3						
+ Avi 4 mg/L	90	5.0	5.0	1	1	3	5	5	3		1	1						
Ceftazidime	0	0	100												1	4	4	11
+ Avi 4 mg/L	100	0	0					3	3	8	6							
AmpC + impermeability (n=20, all *Enterobacter* spp.)																		
Cefepime	55.0	30	15.0					1	1	3	6	4	2	3				
+ Tani 4 mg/L	95.0	5.0	0				3	4	12			1						
+ Avi 4 mg/L	100	0	0				1	12	6		1							
Meropenem	30	20	50							6	4	7	3					
+ Tani 4 mg/L	95.0	0	5.0			1	4	7	6	1		1						
+ Avi 4 mg/L	95.0	5.0	0			3	11	5			1							
Ceftazidime	0	0	100											1	1	4	9	5
+ Avi 4 mg/L	95.0	0	5.0						2	13	3	1			1			

406 [a]Based on current CLSI breakpoints for cefepime (S ≤2, R >8 mg/L) and meropenem (S ≤1, R >4 mg/L) and for ceftazidime/avibactam, (R ≤8, R >8 mg/L);

407 Abbreviations: S, susceptible; I, intermediate; SDD, Susceptible-dose dependent; R, resistant; Avi, avibactam; Tani, taniborbactam

408 **Table 2** MICs of taniborbactam and avibactam combinations for non-fermenters, according to β–lactamase type

	Categorisation based on partner β–lactam			No. isolates with indicated MIC (mg/L)														
	S	I	R	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128
***P. aeruginosa* controls (=9)**																		
Cefepime	77.8	22.2	0							2	1	3	1	2				
+ Tani 4 mg/L	77.8	22.2	0							2	1	4		2				
+ Avi 4 mg/L	100	0	0						1	1	2	3	2					
Meropenem	100	0	0			1	2	2	2	2								
+ Tani 4 mg/L	100	0	0		1		1	4	1	2								
+ Avi 4 mg/L	100	0	0	1			2	4		2								
Ceftazidime	88.9	0	11.1								5	3			1			
+ Avi 4 mg/L	100	0	0							1	4	3	1					
***P. aeruginosa* VIM carbapenemases (n=20)**																		
Cefepime	0	10	90											2	5	1	5	7
+ Tani 4 mg/L	35.0	15.0	50							1		1	5	3		1	7	2
+ Avi 4 mg/L	0	20	80											4	6	5	2	3
Meropenem	0	5.0	95.0									1			4	4	5	6
+ Tani 4 mg/L	15.0	15.0	70					1			2	3	4	2	3	2		3
+ Avi 4 mg/L	0	5.0	95.0									1			4	5	4	6
Ceftazidime	0	0	100												3	5	5	7
+ Avi 4 mg/L	0	0	100												3	5	6	6

***P. aeruginosa* NDM/SPM carbapenemases (n=4: 3 with NDM and 1 with SPM enzymes)**																		
Cefepime	0	0	100															4
+ Tani 4 mg/L	0	0	100															4
+ Avi 4 mg/L	0	0	100															4
Meropenem	0	0	100															4
+ Tani 4 mg/L	0	0	100															4
+ Avi 4 mg/L	0	0	100															4
Ceftazidime	0	0	100															4
+ Avi 4 mg/L	0	0	100															4
***Acinetobacter* controls (n=10)**																		
Cefepime	90	0	10							2	5	2			1			
+ Tani 4 mg/L	90	0	10							1	6	2			1			
+ Tani 8 mg/L	90	0	10							1	6	2			1			
+ Avi 4 mg/L	90	0	10							1	4	1	3		1			
Meropenem	100	0	0				1	6	2	1								
+ Tani 4 mg/L	100	0	0				1	6	2	1								
+ Tani 8 mg/L	100	0	0				1	6	2	1								
+ Avi 4 mg/L	100	0	0				1	5	3	1								
Ceftazidime	100	0	0								2	5	3					
+ Avi 4 mg/L	80	20	0								1	4	3	2				
***A. baumannii* OXA carbapenemases (n=40)**																		
Cefepime	2.5	5.0	92.5									1		2	23	12	1	1

+ Tani 4 mg/L	5.0	25.0	70									2		10	19	8		1
+ Avi 4 mg/L	12.5	20	67.5								1	2	2	8	14	11	2	
Meropenem	0	2.5	97.5										1	3	12	14	7	3
+ Tani 4 mg/L	0	2.5	97.5										1	4	13	12	7	3
+ Avi 4 mg/L	10	7.5	82.5								2	2	3	12	11	6	3	1
Ceftazidime	2.5	2.5	95.0										1	1	2	2	16	18
+ Avi 4 mg/L	0	12.5	87.5											5	7	13	3	12
***A. baumannii* NDM carbapenemases (n=10)**																		
Cefepime	0	0	100															10
+ Tani 4 mg/L	0	0	100														4	6
+ Avi 4 mg/L	0	0	100															10
Meropenem	0	0	100														8	2
+ Tani 4 mg/L	0	0	100												4	6		
+ Avi 4 mg/L	0	0	100													1	7	2
Ceftazidime	0	0	100															10
+ Avi 4 mg/L	0	0	100															10
***E. meningoseptica* (n=10)**																		
Cefepime	0	60	40											6	4			
+ Tani 4 mg/L	100	0	0								1	8	1					
+ Avi 4 mg/L	100	0	0								5	5						
Meropenem	0	0	100											1	3	3	3	
+ Tani 4 mg/L	10	60	30									1	6	3				

+ Avi 4 mg/L	0	0	100												3	5	2	
Ceftazidime	0	0	100														2	8
+ Avi 4 mg/L	0	10	90											1	1	7	1	
***S. maltophilia* (n=10)**																		
Cefepime	20	20	60							1			1	2	2	3	1	
+ Tani 4 mg/L	80	20	0						1		1	3	3	2				
+ Avi 4 mg/L	80	20	0						1		1	3	3	2				
Meropenem	0	0	100													3	3	4
+ Tani 4 mg/L	0	0	100											1		4	1	4
+ Avi 4 mg/L	0	0	100													3	3	4
Ceftazidime	40	10	50						1			2	1	1	1	1	2	1
+ Avi 4 mg/L	40	10	50						1		1	1	1	1	1	2	1	1

[a]Based on current CLSI breakpoints for cefepime (S ≤8, R >16 mg/L) and meropenem (S ≤2, R >4 mg/L) and for ceftazidime/avibactam, (R ≤8, R >8 mg/L);

Abbreviations: S, susceptible; I, intermediate; R, resistant; Avi, avibactam; Tani, taniborbactam

412 **Table 3.** MICs of cefepime/taniborbactam and comparators for consecutive Enterobacterales with
413 NDM carbapenemases (n=124)

	No. isolates with indicated MIC (mg/L)												
***E. coli* (n=29)**	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128
Cefepime											5	4	20
Cefepime/Tani 4 mg/L					5	5	1	3	6	6	3		
Cefepime/Tani 8 mg/L			1	7	2	1	2	7	5	4			
Aztreonam		1	1	1	1				1	1	13	3	7
Aztreonam/Avi 4 mg/L		4	1	3	3	2		3	3	6	3	1	
Ceftazidime/Avi 4 mg/L													29
Meropenem/Vab 8 mg/L									2	11	9	7	
***E. cloacae*. (n=13)**													
Cefepime										3	1	2	7
Cefepime/Tani 4 mg/L	1	2	1			4	1	3			1		
Cefepime/Tani 8 mg/L			1	2	2	3	4				1		
Aztreonam		1		1					1	2	4	1	3
Aztreonam/Avi 4 mg/L	1	2	1			4	1	3			1		
Ceftazidime/Avi 4 mg/L													13
Meropenem/Vab 8 mg/L									2	4	6	1	
***K. pneumoniae* (n=82)**													
Cefepime										3	19	24	36
Cefepime/Tani 4 mg/L				2	15	20	16	10	3	5	6	5	
Cefepime/Tani 8 mg/L			1	13	23	17	8	5	5	8	2		
Aztreonam		4	1	5	1				1	4	36	26	4
Aztreonam/Avi 4 mg/L		8	4	38	19	11		1	1				
Ceftazidime/Avi 4 mg/L													82
Meropenem/Vab 8 mg/L							1	4	3	27	22	16	9
All (n=124)													
Cefepime										6	25	30	63
Cefepime/Tani 4 mg/L				3	20	28	21	17	9	11	9	6	
Cefepime/Tani 8 mg/L			3	22	27	21	14	12	10	12	3		

Aztreonam		6	2	7	2				3	7	53	30	14
Aztreonam/Avi 4 mg/L	1	14	6	41	22	17	1	7	4	6	4	1	
Ceftazidime/Avi 4 mg/L													124
Meropenem/Vab 8 mg/L							1	4	7	42	37	24	9

414 Abbreviations, Avi, avibactam; Tani, taniborbactam and Vab, vaborbactam.

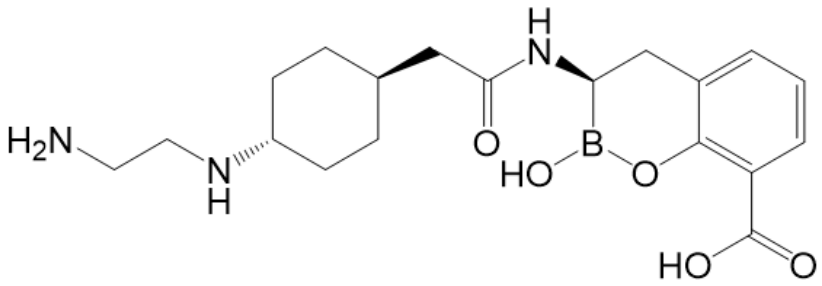
Table 4: Comparison of NDM Enterobacterales in relation to MICs of cefepime/taniborbactam

	Number of isolates with stated character among those with :	
Cefepime/taniborbactam MIC	**Cefepime/taniborbactam MIC ≤8+4 mg/L**	**Cefepime/taniborbactam MIC >8+4 mg/L**
E. coli (n=29)	**14**	**15**
Cefepime MIC >128	5	15***
No with NDM-1	8	3*
No with NDM-5 or -7	6	12
No with >2 bla_{NDM} copies	0	0
No also with bla_{CTX-M}	7	7
No also with bla_{CMY}	7	12
No with lesions in OmpC	2	0
No with lesions in OmpF	2	1
No with Tyr-Arg-Ile-Asn/Pro insert in PBP3	0	4
No AZT MIC ≤2 mg/L	3	0
No with aztreonam/avibactam MIC >2 mg/L	1	15***
No with aztreonam/avibactam MIC >8 mg/L	0	13***
No belonging to ST167	0	4
No belonging to ST410	2	2
No belonging to ST648	1	2
***E. cloacae*. (n=13)**	**12**	**1**
Cefepime MIC >128	6	1
No with NDM-1	12	1
No with NDM-5 or -7	0	0
No with >2 bla_{NDM} copies	0	0
No also with bla_{CTX-M}	7	1
No with lesions in OmpC	1	0
No with lesions in OmpF	4	1
No with Glu 258 insert in PBP3	0	1
No aztreonam MIC ≤2 mg/L	2	0
No with aztreonam/avibactam MIC >2 mg/L	4	1
No with aztreonam/avibactam MIC >8 mg/L	0	1
***K. pneumoniae* (n=82)**	**63**	**19**
Cefepime MIC >128	17	19***
No with NDM-1	63	19
No with NDM-5 or -7	0	0
No with >2 bla_{NDM} copies	2	1
No also with bla_{CTX-M}	45	18*
No also with bla_{CMY}	7	2
No also with bla_{OXA-1}	30	14
No with lesions in OmpC/OmpK36	3	3
No with lesions in OmpF/OmpK35	31	7
No AZT MIC ≤2 mg/L	9	2
No with aztreonam/avibactam MIC >2 mg/L	0	2
No with aztreonam/avibactam MIC >8 mg/L	0	1
No isolates belonging to ST14	1	10***

[a]Includes three pairs that may represent local cross infections.

*p <0.05; **p <0.01; *** p <0.001, all by Chi-square tests

418 **Figure 1.** Structure of taniborbactam



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