Potential of high-dose cefepime/tazobactam against multi-resistant Gram-negative pathogens

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Background: Early β-Lactamase inhibitors were combined with established penicillins, but different combinations may be more appropriate to current β-lactamase threats, with development facilitated by the US GAIN (Generating Antibiotic Incentives Now) Act. Cefepime/tazobactam is especially attractive, combining an AmpC-stable cephalosporin with a clinically established inhibitor, active against ESBLs and suitable for high-dose administration.

Materials/methods: Organisms (n=563) were clinical isolates submitted to the UK national reference laboratory. MICs were determined by CLSI agar dilution with tazobactam at 4 mg/L and, for a subset, at 8 mg/L.

Results: Cefepime/tazobactam 8+4 mg/L achieved coverage of 96-100% of Enterobacteriaceae with penicillinases, AmpC, ESBL, K1 or OXA-48 β-lactamases. Even at 1+4 mg/L, the combination inhibited >94% of isolates with penicillinases, AmpC enzymes or ESBLs. Most Enterobacteriaceae with KPC and NDM carbapenemase were resistant at current cefepime breakpoints but 80% of those with VIM types were susceptible at 8+4 mg/L. Tazobactam did little to potentiate cefepime against non-fermenter groups, though gains were seen against AmpC-producing *Acinetobacter* spp. and *Stenotrophomonas maltophilia*. Increasing the tazobactam concentration to 8 mg/L gave further small increases in activity against Enterobacteriaceae groups.

Conclusions: High-dose cefepime/tazobactam, justifying an 8+4 or 8+8 mg/L, breakpoint, would achieve a carbapenem-like spectrum, with some additional coverage of OXA-48 (and maybe VIM) Enterobacteriaceae. Clinical evaluation is warranted.

Introduction

The 1970s and early 80s saw two strategies to overcome acquired penicillinases, then already prevalent in Gram-negative bacteria. Many companies developed 'β-lactamase-stable' oxyimino-cephalosporins whilst a few developed β-lactamase inhibitors to protect existing penicillins. Both approaches achieved some success, though resistance accumulated over time. By the late 1980s, ESBLs were already eroding oxyimino cephalosporin utility, and have since proliferated greatly.[1] Meanwhile, the penicillins used in inhibitor combinations – particularly amoxicillin and ticarcillin – proved challenging to protect owing to their extreme lability, and resistance is frequent in bacteria that have multiple or copious β-lactamases.[2] It was quickly recognised that clavulanate and tazobactam could protect oxyimino cephalosporins against ESBLs, with MICs often reduced far below those of the penicillins used in clinical combinations. This behaviour is exploited in ESBL detection tests[1] but not in clinical combinations. With (i) oxyimino-cephalosporin and inhibitor patents owned by different companies and eroding in parallel and (ii) the general challenges of antibacterial development and commercialization,[3] there was little scope or business incentive for development of combinations of soon-to-be-generic agents. Moreover, most prospective cephalosporin-inhibitor combinations failed to cover bacteria with hyperproduced AmpC enzymes, making them less attractive than carbapenems, which evade both AmpC and ESBL enzymes. Cefepime-inhibitor combinations were the obvious exception, given cefepime's stability to AmpC,[4] but cefepime's sponsors took the view that their molecule was adequately active against many ESBL strains at CLSI's then breakpoints (S $\leq$8, R >16 mg/L) and did not need protection with an inhibitor. The fact that this breakpoint was too high for the commonly-used 1g twice daily regimen only gradually achieved acceptance, as clinical failures were reported against ESBL strains with MICs of 2-4 mg/L.[5] EUCAST[6] adopted S $\leq$1, R >4mg/L breakpoints, and CLSI later lowered their susceptible breakpoint to $\leq$2, with MICs of 4-8 mg/L considered susceptible to higher and/or more frequent doses.[7] Another shift was that the TEM and SHV ESBLs, often conferring only modest rises in cefepime MICs, were supplanted by CTX-M-15, typically conferring substantive resistance.[8,9]

We previously showed that cefepime-clavulanate was widely active *in vitro* against Enterobacteriaceae with ESBLs and AmpC enzymes.[4] Subsequent interest has concentrated on cefepime/tazobactam, based on tazobactam being more chemically stable than clavulanate, easier to manufacture, less likely to induce AmpC,[2] and better-tolerated at high dosage (up to 2g thrice daily, by 90 min infusion, for 7 days, in combination with equal amounts of cefepime).[10]

Several cefepime/tazobactam combinations are marketed in India,[11] with positive case series described.[12] A trial in urinary tract infection, with or without concurrent genitourinary tract pathology, reported 93.3% clinical cure.[13] However all these combinations retain an 8:1 cefepime:tazobactam ratio, as for piperacillin/tazobactam, meaning that even the maximal 2 + 0.25g thrice daily regimen delivers only 0.75g tazobactam per day. This is low compared with 1.5g exposure used in recently-licensed ceftolozane/tazobactam, which uses a strongly antipseudomonal cephalosporin that lacks cefepime's stability to enterobacterial AmpC.[14]

Legislation to encourage the repurposing and reformulating of old antibiotics, notably the US Generating Antimicrobial Incentives Now (GAIN) Act, may give commercial viability to the development of cefepime with high-dose tazobactam, and we explored this potential of this combination using panels of characterised organisms.

Methods and materials

Bacteria

Organisms (n=593) were recent clinical submissions to the UK national reference laboratory (Antimicrobial Resistance and Healthcare Associated Infections Reference Unit, AMRHAI, at PHE Colindale, London). Bacterial identification was by MALDI-ToF (Bruker Daltonics, Bremen, Germany), and carbapenemase genes (*bla*$_{IMP}$, *bla*$_{KPC}$, *bla*$_{IMP}$, *bla*$_{NDM}$, *bla*$_{OXA-48-like}$, *bla*$_{VIM}$) were detected by PCR;[15] other mechanisms were inferred by interpretive reading of phenotypes.[16] The species distribution of Enterobacteriaceae isolates representing different resistance mechanisms is shown in Table 1. None of these species is inherently resistant to cefepime or any comparator tested.

Susceptibility testing

MICs of cefepime were determined by CLSI agar dilution[17] with tazobactam at 0 and 4 mg/L; comparators were piperacillin with tazobactam 4 mg/L and ceftazidime (all Sigma, Poole, UK) and meropenem (Sequoia, Pangbourne, UK). MICs of cefepime with 8 mg/L tazobactam were determined for a sub-set of the isolates.

Given the differences in EUCAST and CLSI breakpoints for cefepime, and the lack of current guidance for cefepime/tazobactam we reviewed data against a 'most conservative' breakpoint of cefepime/tazobactam 1+4 mg/L, predicated upon EUCAST's current 1 mg/L susceptibility breakpoint for unprotected cefepime and a 'most liberal' value of 8+4 mg/L based upon the upper bound of CLSI's 'Dose Dependent Susceptibility' category.[17] The ultimate breakpoint for any commercial cefepime/tazobactam formulation will depend on the dosage and pharmacodynamic analysis.

Results

Enterobacteriaceae

Irrespective of the presence of tazobactam, cefepime was universally active against control and penicillinase-producing Enterobacteriaceae at 1 mg/L; it was also active against 81.3% of the AmpC producers at 1 mg/L, rising to 100% at 8 mg/L (Table 2). Tazobactam, at 4 mg/L, expanded the proportion of AmpC hyperproducers susceptible at 1 mg/L to 96.7%, but did not cause major MIC reductions. By contrast tazobactam greatly potentiated cefepime against ESBL producers: whereas only 20.5% of producers were susceptible to unprotected cefepime at 1 mg/L, 94.9% were susceptible to cefepime/tazobactam 1+4 mg/L; similarly, 54.5% of ESBL producers were inhibited by cefepime at 8 mg/L and 99.4% by cefepime/tazobactam 8+4 mg/L. MICs for *K. oxytoca* hyperproducing K1 enzyme were reduced one or two doubling dilutions by tazobactam, but largely remained in the 2-8 mg/L range.

All Enterobacteriaceae with NDM carbapenemases were resistant to cefepime/tazobactam 8+4 mg/L, as were 63% of those with KPC carbapenemases. The behaviours of isolates with VIM and OXA-48-like carbapenemases were more complex. Sixty-five per cent (13/20) of isolates with VIM metallo-carbapenemases were resistant to cefepime at 8 mg/L, but this proportion fell to 20% (4/20) in the presence of 4 mg/L tazobactam, with 75% of MICs falling into the 2+4 to 8+4 mg/L range. All of the cefepime-resistant VIM-positive isolates that gained 'susceptibility' to cefepime/tazobactam were aztreonam resistant, based on previous testing, supporting the view that they co-produced further β-lactamases, probably ESBLs. For isolates with OXA-48-like enzymes the MIC distribution of unprotected cefepime was bimodal, with values clustered between 0.25 to 2 mg/L or above 32 mg/L, corresponding to the fact that OXA-48 itself does not attack these oxyimino-cephalosporins[18] and that

any resistance depends on co-produced enzymes, principally ESBLs (AmpC enzymes would have little effect on cefepime). With tazobactam added, cefepime MICs for the cefepime-resistant OXA-48 producers were reduced into the 1-8 mg/L range, with only 1/25 values remaining >8 mg/L.

The expansion of anti-Enterobacteriaceae activity was impressive compared to both piperacillin/tazobactam and ceftazidime, particularly against isolates that did not have carbapenemases, where the overall spectrum of cefepime/tazobactam more closely resembled that of meropenem. Based on the CLSI criterion of >16+4 mg/L, non-susceptibility to piperacillin/ tazobactam was seen for 9/22 penicillinase-producers and 66/176 ESBL producers along with 71/91 AmpC producers and all the *K. oxytoca* hyperproducing K1 enzymes, whereas all these isolates, except for one ESBL producer, were susceptible to cefepime/tazobactam 8+4 mg/L. Ceftazidime non-susceptibility, based on CLSI's >2 mg/L criterion, was seen in more than 90% of isolates in most groups except (i) controls and penicillinase producers, (ii) *K. oxytoca* hyperproducing K1 β-lactamase. Meropenem was active at the CLSI susceptible breakpoints (S ≤1 mg/L) against all the ESBL producers, K1 isolates and AmpC producers as well as control strains and penicillinase producers. Comparator activity, like that of cefepime/tazobactam, was limited against carbapenemase producers. All were non-susceptible to piperacillin/tazobactam, with ceftazidime susceptibility seen only for cefepime-susceptible isolates with OXA-48-like enzymes. In the case of meropenem, isolates with NDM enzymes consistently were resistant whereas MICs for those with other enzyme type straddled breakpoints, with many OXA-48 isolates appearing meropenem susceptible at CLSI's S ≤1 mg/L criterion and with MICs of 2-8 mg/L for many with VIM metallo-enzymes.

Non-fermenters

Addition of tazobactam caused little or no shift in the MIC distribution of cefepime for (i) *P. aeruginosa* with normal or up-regulated efflux, (ii) *P. aeruginosa* with MBLs, which were universally resistant, or (iii) *Acinetobacter* spp. with OXA carbapenemases. Tazobactam did cause downward shifts in the MIC distributions of cefepime for *P. aeruginosa* with VEB and PER ESBLs, *S. maltophilia* and, more surprisingly, for *Acinetobacter* spp. with AmpC activity; only in the last of these cases, however, were

cefepime MICs commonly shifted below 8 mg/L. Most cefepime-susceptible *Acinetobacter* spp. were directly inhibited by tazobactam at 4 mg/L.

In vitro dose-response effects

The effect of raising the tazobactam to 8 mg/L rather than 4 mg/L, as routinely used, is illustrated for sub-sets of the Enterobacteriaceae isolates in Table 3. Small additional downward shifts in MIC distributions, of around one doubling dilution, were seen were seen for many β-lactamase-producing groups, including those with AmpC, ESBL KPC, and K1 enzymes, though not for MBL-producing Enterobacteriaceae. MIC shifts for non-fermenter groups were minimal (not shown).

Discussion

Even at the most conservative likely breakpoint (1+4 mg/L), cefepime/tazobactam achieved good activity against Enterobacteriaceae with ESBLs and AmpC enzymes as well as those with acquired penicillinases. At 8+4 mg/L or 8+8 mg/L, corresponding to the upper edge of CLSI's 'dose-dependent susceptibility category'[7] –susceptibility was seen also for most cefepime-resistant isolates with K1, OXA-48 and VIM enzymes. Against non-fermenters, cefepime/tazobactam essentially retained cefepime's activity with only small further gains, notably against AmpC-producing *Acinetobacter* spp. This spectrum is impressive and exceeded that of unprotected cefepime, ceftazidime or piperacillin/tazobactam, more closely resembling meropenem.

Ceftolozane/tazobactam was not included here, but is an obvious comparator. The major difference between ceftolozane and cefepime, in relation to Enterobacteriaceae, is that ceftolozane is less stable to AmpC enzymes, which are poorly inhibited by tazobactam. Consequently, ceftolozane/tazobactam MICs for AmpC-derepressed *Enterobacter* spp. are mostly 4-8 mg/L, compared with 0.12 to 1 mg/L found for cefepime/tazobactam (Table 2).[16,19] ESBL producers too were more often susceptible to cefepime/tazobactam, though less strikingly so. Thus, among isolates collected in the BSAC Bacteraemia Surveillance from 2011-2015 (inclusive) 97.9% of ESBL *E. coli* and 86.5% of ESBL *K. pneumoniae* were susceptible to ceftolozane/tazobactam at 1+4 mg/L (the FDA and

EUCAST Breakpoint)[16] compared, here, with 98.3% (59/60) ESBL *E. coli* and 92.4% (73/79) ESBL *K. pneumoniae* susceptible to cefepime/tazobactam 1+4 mg/L and all except one *K. pneumoniae* susceptible at 8+4 mg/L. The more consistent activity of cefepime/tazobactam against ESBL producers may relate to a shorter time above a concentration threshold being needed for tazobactam to protect cefepime than ceftolozane, at least for strains with CTX-M-15, which is the commonest ESBL.[20,21] Easier protection of cefepime, in turn, may depend on the molecule's rapid permeation of Gram-negative bacteria and its low affinity for some enzyme types[22] and/or its greater affinity for PBP2, which may enhance cidality.[23] However, there is insufficient information on these aspects for ceftolozane to allow definitive conclusions and it is it unclear if the shorter time needed above threshold for tazobactam to protect cefepime is specific to CTX-M-15 or is generalizable to other ESBLs. Moreover, experience with piperacillin/tazobactam shows significant unexplained variation in susceptibility among ESBL producers, even when these have the same β-lactamase(s) and belong to the same strain.[24]

The frequent activity of cefepime/tazobactam against Enterobacteriaceae with VIM MBLs is surprising but mirrors behaviour AMRHAI see with cefepime-clavulanate in reference testing (the combination is tested to detect ESBLs in AmpC-inducible species but also gets to be tested, gratuitously, against all Gram-negative submissions). Since neither tazobactam nor clavulanate significantly inhibits metallo β-lactamases,[25] the likeliest explanation is that VIM enzymes themselves are only weakly active against cefepime and that resistance caused by co-produced ESBLs is substantially reversed by tazobactam or clavulanate. In the case of strains with OXA-48-like enzymes, MICs of cefepime/tazobactam for most cefepime-resistant isolates were reduced into the 2+4 to 8+4 mg/L range. This incomplete potentiation may seem surprising, given that cefepime, like ceftazidime, evades OXA-48 like enzymes,[18,26] with any resistance arising from co-produced ESBLs, which should be inhibited by tazobactam. The behaviour may reflect isolates having multiple enzymes, permeability lesions or, speculatively, to OXA-48-like enzymes being able to inactivate tazobactam, as can KPC enzymes.[27] Ceftolozane/tazobactam MICs for ceftazidime-resistant OXA-48 producers referred to AMRHAI are mostly higher than found here for cefepime/tazobactam, exceeding 16+4 mg/L in just over 50% of cases.[16] These data again support the view that cefepime is an easier molecule to protect.

In summary, these data, along with a 7891-isolate survey of consecutive Gram-negative bacilli from international sources,[28] support the development of cefepime/tazobactam as a potential

'workhorse' combination, potentially supplanting piperacillin/tazobactam – the present workhorse – and achieving similar coverage to a carbapenem against ESBL and AmpC-producing Enterobacteriaceae. There was also some activity –at least at cefepime's 'dose-dependent' breakpoints- also against many strains with VIM and OXA-48-like carbapenemases. Whilst unlikely to be preferred definitive therapy where strains with these enzymes are implicated, the combination may have sufficient activity not to be a major selector of these carbapenemases.

Given the propensity of bacteria to acquire complex batteries of β-lactamases, often copiously expressed, it seems prudent to use the highest levels of tazobactam that can be safely dosed – and certainly more than in the 8:1 cefepime/tazobactam preparations currently marketed in India. A 1:1 combination (WCK 4282) has been proposed by Wockhardt and, in a Phase I trial, was well tolerated at up to 2+2g iv when given thrice daily, by 90 min infusion, for up to 7 days.[10] Comparison to published data suggests that cefepime/tazobactam should achieve a wider spectrum than ceftolozane/tazobactam against problem Enterobacteriaceae, whereas the advantage against *P. aeruginosa* lies with ceftolozane/tazobactam, based on ceftolozane being inherently more active than cefepime (or ceftazidime) against this species.[16]

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Transparency declaration

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Cardiome, Cepheid, Merck, Nordic and Pfizer. Relevant shareholdings– Dechra, GSK, Merck, Perkin Elmer and Pfizer collectively amounting to <10% of portfolio value. **S**T ad hoc consultancy for Wockhardt **All others:** No personal interests to declare. However, PHE's AMRHAI Reference Unit has received financial support for conference attendance, lectures, research projects or contracted evaluations from numerous sources, including: Accelerate, Achaogen, Allecra, Amplex, AstraZeneca, Basilea, Becton Dickinson Diagnostics, bioMérieux, Bio-Rad Laboratories, The BSAC, Cepheid, Check-Points, Cubist Pharmaceuticals, Department of Health, Enigma Diagnostics, Food Standards Agency, GlaxoSmithKline, Henry Stewart Talks, IHMA, Kalidex, Melinta, Merck Sharpe & Dohme , Meiji, Mobidiag, Momentum Biosciences, Nordic, Norgine, Rempex, Roche, Rokitan, Smith & Nephew, Trius , VenatoRx and Wockhardt.

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Table 1. Genus distribution among Enterobacteriaceae panels

	Citrobacter	*Enterobacter*	*Escherichia*	*Klebsiella*	*Morganella*	*Proteus*	*Providencia*	*Serratia*	*Total*
Susceptible controls	16	20	10	10	10	10		10	86
Penicillinase			10	12					22
ESBL	4	20	60	79	2	11			176
K. oxytoca hyperproducing K1				20					20
AmpC	15	20	18	18	10			10	91
KPC		10	10	21					41
OXA-48			5	20					25
NDM	1	4	5	10	1		4		25
VIM		5	5	10					20
Total	**36**	**79**	**123**	**200**	**23**	**21**	**4**	**20**	**506**

339 **Table 2.** Comparative activity of cefepime/tazobactam 4 mg/L against isolate panels

	No. isolates with indicated MIC (mg/L)														% susceptible to cefepime and cefepime/tazobactam at	
Enterobacteriaceae	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128	1+4	8+4
Susceptible controls (86)																
Cefepime	42	31	8	5											100	100
Cefepime/tazobactam 4 mg/L	44	28	9	5											100	100
Ceftazidime		11	12	25	32	6									-	-
Piperacillin/tazobactam 4 mg/L			11*	4	6	1	41	19	3	1					-	-
Meropenem	55	22	4	5											-	-
Penicillinase producers (22)																
Cefepime	2	9	5	4	1	1									100	100
Cefepime/tazobactam 4 mg/L	9	5	6	1	1										100	100
Ceftazidime			2	12	8										-	-
Piperacillin/tazobactam 4 mg/L						4	5	1	3		1	2		6	-	-
Meropenem	21	1													-	-

AmpC hyperproducers (91)																
Cefepime	4	4	12	10	24	20	14	3							81.3	100
Cefepime/tazobactam 4 mg/L	7	9	23	21	18	10	3								96.7	100
Ceftazidime						5	1	3	3	13	15	29	18	4	-	-
Piperacillin/tazobactam 4 mg/L				2	4		2	3	9	16	25	17	8	5	-	-
Meropenem	30	39	13	9											-	-
ESBL producers (176)																
Cefepime		2	2	2	9	21	31	19	10	21	12	13	11	23	20.5	54.5
Cefepime/tazobactam 4 mg/L	19	55	37	34	18	4	1	5	2			1			94.9	99.4
Ceftazidime				2	3	12	14	15	3	7	27	31	34	28	-	-
Piperacillin/tazobactam 4 mg/L			4		5	6	31	40	24	28	14	5	3	16	-	-
Meropenem	124	42	6	2		2									-	-
K1 hyperproducing *K. oxytoca* (20)																
Cefepime					1	3	1	8	6		1				20	95
Cefepime/tazobactam 4 mg/L				1	2	1	11	4	1						20	100
Ceftazidime					4	4	10	2							-	-
Piperacillin/tazobactam 4 mg/L														20	-	-
Meropenem	5	12	3												-	-
KPC producers (41)																

Cefepime						1	1	3	5	2	3	7	19	0	12.2
Cefepime/tazobactam 4 mg/L					2	4	5	4	7	6	5	5	3	4.9	36.3
Ceftazidime							1	7	3	7	7	4	12	-	-
Piperacillin/tazobactam 4 mg/L											1	2	38	-	-
Meropenem					1	2	5	6	4	10	1	5	7	-	-
OXA-48 β-lactamase producers (25)															
Cefepime			7	2	3	1		1		1	5	3	2	48.0	56.0
Cefepime/tazobactam 4 mg/L		4	4	2	2	7	4	1	1					48.0	96.0
Ceftazidime		1	6	4	2	1	3				4	3	1	-	-
Piperacillin/tazobactam 4 mg/L												3	22	-	-
Meropenem	1			5	11	3	1		1	3				-	-
NDM β-lactamase producers (25)															
Cefepime									1	3	5	1	15	0	0
Cefepime/tazobactam 4 mg/L								1	2	7	6	3	6	0	0
Ceftazidime													25	-	-
Piperacillin/tazobactam 4 mg/L											1	1	23	-	-
Meropenem							1	2	2	11	6	1	2**	-	-
VIM β-lactamase producers (20)															
Cefepime			1			3	1	2	5	1	4	3		5	35

Cefepime/tazobactam 4 mg/L				1		2	7	2	4			2	2		15	80
Ceftazidime									1	1		3	4	11	-	-
Piperacillin/tazobactam 4 mg/L											1			19	-	-
Meropenem						2	4	8	4	2					-	-
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128	1+4	8+4
P. aeruginosa																
Normal /upregulated efflux (30)																
Cefepime		1				1	9	5	8	5	1				-	80
Cefepime/tazobactam 4 mg/L		1				4	6	5	8	5	1				-	80
Ceftazidime	1					3	12	4	5	5					-	-
Piperacillin/tazobactam 4 mg/L			1*		2		1	6	7	1	11	1			-	-
Meropenem		2	3	1	8	4	4	2	2	3	1				-	-
ESBL producers (7 PER, 3 VEB)																
Cefepime											1	4	2	3	-	0
Cefepime/tazobactam 4 mg/L							1			2	3	4			-	10
Ceftazidime														10	-	-
Piperacillin/tazobactam 4 mg/L					1			1	2		2	2	2		-	-
Meropenem				1	3		1	3	1		1				-	-

MBL producers (5 IMP, 5 VIM)																		
Cefepime												1	2	1	6	-	0
Cefepime/tazobactam 4 mg/L										1		1	1	2	4	-	0
Ceftazidime												1	1	3	5	-	-
Piperacillin/tazobactam 4 mg/L										2		1	2	2	3	-	-
Meropenem								1				1	2	2	4	-	-
Acinetobacter baumannii																		
Control strains (7)																		
Cefepime						2	5									-	100
Cefepime/tazobactam 4 mg/L	7															-	100
Ceftazidime							6	1								-	-
Piperacillin/tazobactam 4 mg/L			6		1											-	-
Meropenem		1		5	1											-	-
AmpC producers (10)																		
Cefepime								1		4	4				1	-	10
Cefepime/tazobactam 4 mg/L						2		2	2	3			1			-	60
Ceftazidime								1		1	1	1	5	1		-	-

Piperacillin/tazobactam 4 mg/L				1	1			1	2	4	1	-	-
Meropenem	1		5	2	2							-	-
OXA carbapenemase producers (10)													
Cefepime								4	4	1	1	-	0
Cefepime/tazobactam 4 mg/L						1	2	4	2		1	-	10
Ceftazidime						1	2		1	2	4	-	-
Piperacillin/tazobactam 4 mg/L							2	1			7	-	-
Meropenem					1		3	4	2			-	-
S. maltophilia													
Cefepime						1	2	2	4		1	-	10
Cefepime/tazobactam 4 mg/L					1	3		5		1		-	40
Ceftazidime					1	1	2		3	1	2	-	-
Piperacillin/tazobactam 4 mg/L								2			8	-	-
Meropenem								1	3	4	2	-	

342 **Table 3.** Dose response effect of tazobactam at 4 or 8 mg/L in potentiating cefepime

Group and tazobactam	No isolates with indicated MIC (mg/L)														
concentration, mg/L	≤0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	>256
Susceptible controls (25)															
0	12	7	4	2											
4	14	4	5	2											
8	12	7	4	2											
AmpC (34)															
0	2	2	5	4	7	6	5	3							
4	4	2	11	4	4	6	3								
8	5	8	8	2	7	4									
ESBL (35)															
0					2	4	9	3	1	4	1	3		1	7
4	4	12	4	7	2	3		2				1			
8	5	14	7	4	2	2	1								
K. oxytoca K1 (5)															
0					1	3		1							
4				1	2		2								
8			1		3	1									

KPC (30)															
0						1	1	3	5	2	3	7	2	6	
4					2	4	5	4	6	5	2	2			
8				1	2	4	4	6	6	3	2	2			
OXA-48 (15)															
0			3	1	3					1	5	1		1	
4		2	2	1	2	4	2	1	1						
8			4		6	4		1							
NDM (20)															
0									1	3	3		5	8	
4								1	1	6	4	2	6		
8								1	1	6	4	2	6		
VIM (15)															
0			1				1	2	3	1	4	3			
4			1			4	2	4			2	2			
8			1			4	3	3				4			