Activity of ceftolozane/tazobactam against surveillance and ‘problem’ Enterobacteriaceae, Pseudomonas aeruginosa and non-fermenters from the British Isles

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Background: We assessed the activity of ceftolozane/tazobactam against consecutive isolates collected in the BSAC Bacteraemia Surveillance from 2011 to 2015 and against ‘problem’ isolates sent to the UK national reference laboratory from July 2015, when routine testing began.

Methods: Susceptibility testing was by BSAC agar dilution with resistance mechanisms identified by PCR and interpretative reading.

Results: Data were reviewed for 6080 BSAC surveillance isolates and 5473 referred organisms. Ceftolozane/tazobactam had good activity against unselected ESBL producers in the BSAC series, but activity was reduced against ertapenem-resistant ESBL producers, which were numerous among reference submissions. AmpC-derepressed Enterobacter spp. were widely resistant, but Escherichia coli with raised chromosomal AmpC frequently remained susceptible, as did Klebsiella pneumoniae with acquired DHA-1-type AmpC. Carbapenemase-producing Enterobacteriaceae were mostly resistant, except for ceftazidime-susceptible isolates with OXA-48-like enzymes. Ceftolozane/tazobactam was active against 99.8% of the BSAC Pseudomonas aeruginosa isolates; against referred P. aeruginosa it was active against 99.7% with moderately raised efflux, 94.7% with strongly raised efflux and 96.6% with derepressed AmpC. Resistance in P. aeruginosa was largely confined to isolates with metallo-β-lactamases (MBLs) or ESBLs. MICs for referred Burkholderia spp. and Stenotrophomonas maltophilia were 2–4-fold lower than those of ceftazidime.

Conclusions: Ceftolozane/tazobactam is active against ESBL-producing Enterobacteriaceae; gains against other problem Enterobacteriaceae groups were limited. Against P. aeruginosa it overcame the two most prevalent mechanisms (up-regulated efflux and derepressed AmpC) and was active against 51.9% of isolates non-susceptible to all other β-lactams, rising to 80.9% if ESBL and MBL producers were excluded.

Introduction

Ceftolozane/tazobactam is a cephalosporin/β-lactamase inhibitor combination, recently approved for complicated intra-abdominal and urinary tract infections.¹ EUCAST breakpoints, with a fixed 4 mg/L concentration of tazobactam, are susceptible ≤1 mg/L resistant >1 mg/L for Enterobacteriaceae and ≤4/>4 mg/L for Pseudomonas aeruginosa. Tazobactam protects ceftolozane against ESBLs, with the combination’s efficacy against producers confirmed in the Phase III trials.² Ceftolozane is also notably active against P. aeruginosa, with MICs lower than ceftazidime—hitherto the most active anti-pseudomonal β-lactam.² This activity is retained for many strains with derepressed AmpC or up-regulated efflux,² which are the major routes to resistance to established penicillins and cephalosporins in the species.³

Here, we review the activity of ceftolozane/tazobactam against two large, contrasting series of Gram-negative isolates. First, we considered consecutive bloodstream isolates collected by the
BSAC Bacteraemia Surveillance during 2011–15. Secondly, we reviewed isolates referred to PHE’s Antimicrobial Resistance and Healthcare Associated Infections (AMRHAL) Reference Unit in the first year that ceftolozane/tazobactam was tested; thereby providing a large snapshot of UK ‘problem’ organisms.

Materials and methods

BSAC surveillance

The BSAC Bacteraemia Surveillance has been described previously.\(^4\) Results were reviewed from 2011, when testing of ceftolozane/tazobactam began, to 2015; 38–40 UK and Irish laboratories contributed annually, submitting up to seven consecutive bloodstream isolates each of Klebsiella, Enterobacter and Pseudomonas spp. and up to 14 Escherichia coli. Identifications were confirmed at AMRHAL by MALDI-TOF or API20E or API20NE strips (bioMérieux, Marcy-l’Étoile, France). Among Pseudomonas spp., only confirmed P. aeruginosa were considered; these comprised 95.1% of all Pseudomonas spp. collected. Susceptibility testing was by BSAC agar dilution.\(^5\) Enterobacteriaceae with ceftaxime or ceftazidime MICs ≥ 1 mg/L were further characterized by: (i) comparing cefepime, ceftaxime and ceftazidime MICs with and without 4 mg/L clavulanate to identify ESBL producers (with ≥8-fold potentiation of ≥1 cephalexin); (ii) comparing ceftaxime MICs with and without 100 mg/L clavulanate to identify AmpC producers (with ≥4-fold potentiation, no ceftaxime/clavulanate potentiation, and ≥8-fold higher MICs of ceftaxime and ceftazidime than cefepime); and (iii) by PCR for bla\(_{CTX-M}\) and plasmid AmpC enzymes. Enterobacteriaceae with reduced carbapenem susceptibility were screened for carbapenemase genes by PCR, as were P. aeruginosa that were both (i) broadly resistant to β-lactams and (ii) positive for imipenem/EDTA synergy.

Reference submissions

MICs, determined by BSAC agar dilution,\(^5\) were reviewed for all non-fastidious Gram-negative bacteria referred to PHE’s AMRHAL Reference Unit over 1 year from July 2015, when routine testing of ceftolozane/tazobactam began. Around 90% of submission are from diagnostic laboratories in England, 9% from elsewhere in the UK and 1% from overseas, principally Ireland. We excluded isolates tested for internal and external quality assurance and repeat/multiple tests on the same isolate from the same submission. Testing employed a wide panel of antibiotics. To predict β-lactamase types, MICs of cefotaxime/clavulanate 2 mg/L, ceftaxime/cladoxacin 100 mg/L, cefazidime/clavulanate 2 mg/L, ceftazidime/avibactam 2 mg/L, cefepime/clavulanate 2 mg/L and imipenem/EDTA 320 mg/L were compared with those of the same β-lactams alone.

Genes for KPC, VIM, NDM and OXA-48-like carbapenemases were sought by multiplex PCR. Enterobacteriaceae resistant to meropenem and imipenem but lacking genes for these common carbapenemases were subjected to further multiplex PCRs, seeking (i) blα\(_{OXA}\), blα\(_{VIM}\), blα\(_{GIM}\), blα\(_{IMP}\) and blα\(_{IMI}\) and (ii) blβ\(_{IMP}\), blβ\(_{GES}\), blβ\(_{OXA}\) and blβ\(_{OCH}\). Metallo-carbapenemase genes were sought in P. aeruginosa isolates showing ≥8-fold or greater imipenem/EDTA synergy together with broad resistance to penicillins and cephalosporins. blα\(_{LOB}\) and blβ\(_{PER}\) genes were sought by PCR in most P. aeruginosa isolates with ceftazidime MICs >256 mg/L and cefazidime/clavulanate MICs ≤32 mg/L. Referred Acinetobacter spp. isolates were screened for blα\(_{OXA}\) S-1-like to identify A. baumanii where this gene is universal and chromosomal.

Categorization of isolates

Detection of a β-lactamase gene was considered ‘definitive’ identification of a mechanism. Carbapenemase-negative isolates were categorized by in-house mathematical algorithms employing the principles of interpretive reading of phenotypes.\(^6\) Two levels of match were allowed: ‘hard’, where the phenotype was a perfect match; and ‘soft’, where the phenotype was less perfectly matched, but the mechanism remained the most likely. For example, to meet hard-match criteria for highly raised (putatively MexAB-OprM-mediated) efflux, a P. aeruginosa isolate required a carbencillin MIC >512 mg/L with carbencillin/cefotaxime:piperacillin:ceftazidime MIC ratios in the ranges 1.025–1.03: 0.120.015–0.06 (note these are ratios, not actual MICs, and are predicated on the fact that up-regulated MexAB-OprM raises MICs of these agents in rough proportion);\(^7\) to meet soft-match criteria the strain needed a carbencillin MIC >512 mg/L and carbencillin/cefotaxime:piperacillin:ceftazidime MIC ratios in the ranges 1.012–2.015–0.250.008–0.12. Some isolates did not match any of the phenotypes considered and were left as ‘unassigned’, then categorized according to their level of resistance to reference agents, principally ceftazidime.

Results

BSAC Bacteraemia Surveillance isolates

The BSAC collection provided a random and geographically diverse sample of bloodstream isolates. Because no temporal trend was seen for ceftolozane/tazobactam (not shown), data for 2011 to 2015 were pooled (Table 1). Using EUCAST’s 1+4 mg/L Enterobacteriaceae breakpoint, susceptibility rates to ceftolozane/tazobactam were 91.5% for Enterobacter spp., 97.6% for Klebsiella spp. and 99.7% for E. coli, exceeding those for all other β-lactams tested except carbapenems. In the case of P. aeruginosa, 99.8% of isolates (1097/1099) were susceptible at EUCAST’s 4+4 mg/L breakpoint, versus 97.9% for gentamicin, 97.6% for ceftazidime, 95.5% for piperacillin/tazobactam, 91.7% for meropenem (not tested in 2012 and 2013), 92.5% for imipenem (not tested in 2014) and 90.4% for ciprofloxacin.

Almost all ESBL- and AmpC-producing E. coli (97.9% and 96.6%, respectively) were susceptible to ceftolozane/tazobactam 1+4 mg/L, as were 93.7% of Klebsiella oxytoca hyperproducing K1 β-lactamase. Susceptibility rates for ESBL-producing Klebsiella and Enterobacter were lower, at 84%–85%. Around half the ceftolozane/tazobactam resistance among ESBL-producing Klebsiella was low level, with MICs of 2+4 mg/L; but other isolates were substantially resistant, with MICs up to ≥256 mg/L. High MICs were not associated with particular ESBL types: 9/13 (69.2%) ESBL-producing isolates with MICs =8 mg/L had CTX-M group 1 enzymes, as did 85/140 (60.7%) with MICs ≤1 mg/L. It is possible that the more resistant isolates had larger amounts of ESBL, a different CTX-M variant, or multiple β-lactamases. Half of the AmpC hyperproducing Enterobacter spp. were resistant; significantly, these ceftolozane/tazobactam-resistant organisms also were much more resistant to ceftaxime and ceftazidime (geometric mean MICs 76.8 and 69.8 mg/L respectively) than were ceftolozane/tazobactam-susceptible AmpC enterobacters (geometric mean ceftaxime and ceftazidime MICs 6.5 and 5.0 mg/L respectively). It is likely that this variation reflected the amount of AmpC enzyme.

Just 11/4981 (0.2%) BSAC E. coli, Klebsiella and Enterobacter spp. isolates had carbapenemases, 2 with KPC, 3 with VIM and 6 with OXA-48-like enzymes. Three of the six with OXA-48-like enzymes were susceptible to ceftazidime at breakpoint (<1 mg/L); these also were susceptible to ceftolozane/tazobactam 1+4 mg/L. The remaining three OXA-48-like isolates, which were resistant to ceftazidime (MICs 16–128 mg/L), also were resistant to ceftolozane/tazobactam, as were all the isolates with KPC and VIM enzymes.
One of the two ceftolozane/tazobactam-resistant P. aeruginosa, with an MIC of 32–4 mg/L, had a VIM carbapenemase; mechanisms remain uncertain in the other, with an MIC of 8–4 mg/L.

Isolates referred to PHE

The isolates examined in ceftolozane/tazobactam’s first year of testing comprised 3249 Enterobacteriaceae, 1414 P. aeruginosa and 810 other non-fermenters, including 419 Acinetobacter spp. They lack a denominator and are referred for numerous reasons. There is a considerable bias towards submitting isolates suspected of carbapenem resistance, but some have suspected colistin, aminoglycoside or tigecycline resistance; a few are referred owing to anomalous susceptibility, e.g. to ampicillin in P. aeruginosa. The overall performance data shown in Table 2 should be considered with these biases in mind. Nevertheless two points are striking: first, that ceftolozane/tazobactam was more widely active against these ‘problem’ P. aeruginosa than any other β-lactam, whereas, secondly, gains against problem Enterobacteriaceae were modest, with carbapenem resistance remaining more active.

Enterobacteriaceae by inferred or proven mechanism

Table 3 shows the MIC distributions of ceftolozane/tazobactam for referred Enterobacteriaceae by species and resistance type. Because there was little difference in their distributions, MICs are pooled for the hard- and soft-matched groups.

At its 1–4 mg/L breakpoint, ceftolozane/tazobactam was active against 41.7% of the ESBL producers, rising to 53.0% for E. coli and falling to 26.3% for Klebsiella pneumoniae. It was active also against 26.2% of AmpC hyperproducers, rising to 50.8% for E. coli and 88.9% for Morganella morganii, but falling to 18.4% for Enterobacter spp. The high susceptibility rate for AmpC-derepressed M. morganii reflects the vulnerability of Morganella AmpC to tazobactam, whilst frequent susceptibility in E. coli was associated with cefotaxime and ceftazidime MICs of 2–4 mg/L, a phenotype usually reflecting small elevations of chromosomal AmpC via promoter mutations. Frequent resistance among the AmpC Enterobacter spp. is in keeping with the fact that 554/649 (85.4%) of these referrals had high-level cefotaxime resistance (MIC > 32 mg/L), as typically associated with total derepression of chromosomal enzyme. Klebsiella spp. have no chromosomal ampC, meaning AmpC phenotypes in this genus reflect acquired.

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**Table 1.** MIC distributions of ceftolozane/tazobactam for E. coli, Klebsiella spp., Enterobacter spp. and P. aeruginosa in the BSAC Bacteraemia Surveillance Programme, 2011–15 inclusive

| Organism                  | ≤0.03 | 0.06 | 0.12 | 0.25 | 0.5  | 1   | 2   | 4   | 8   | 16  | 32  | 64  | 128 | 256 | >256 | Total | %Sa  |
|---------------------------|-------|------|------|------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|-------|------|
| All                       | 2     | 67   | 1710 | 775  | 94   | 20  | 5   | 3   | 2676| 99.7|     |     |     |     |      |       |      |
| E. coli                   | 2     | 18   | 160  | 568  | 114  | 61  | 27  | 22  | 1009| 91.5|     |     |     |     |      |       |      |
| Enterobacter spp.         | 12    | 338  | 662  | 192  | 61   | 14  | 2   | 2   | 1296| 97.6|     |     |     |     |      |       |      |
| P. aeruginosa             | 7     | 242  | 756  | 82   | 6    | 4   | 1   | 1   | 1099| 99.8|     |     |     |     |      |       |      |
| ESBL (all)                | 1     | 42   | 151  | 66   | 15   | 4   | 2   | 281 | 97.9|     |     |     |     |     |      |       |      |
| E. coli                   | 3     | 17   | 14   | 6    | 4    | 1   | 1   | 47  | 85.1|     |     |     |     |     |      |       |      |
| Enterobacter spp.         | 4     | 11   | 57   | 28   | 9    | 1   | 1   | 119 | 84.0|     |     |     |     |     |      |       |      |
| Klebsiella spp.           | 29    | 133  | 54   | 12   | 3    | 2   |     | 233 | 97.9|     |     |     |     |     |      |       |      |
| CTX-M group 1 ESBLs       | 3     | 7    | 4    | 2    |     |     |     | 16  | 87.5|     |     |     |     |     |      |       |      |
| E. coli                   | 3     | 7    | 47   | 14   | 2    | 1   | 1   | 3   | 82  | 86.6|     |     |     |     |      |       |      |
| Enterobacter spp.         | 6     | 16   | 5    | 1    | 1    |     |     |     | 29  | 96.6|     |     |     |     |      |       |      |
| Klebsiella spp.           | 3     | 14   | 20   | 35   | 20   | 24  | 20  | 6   | 1   | 114 | 50.0|     |     |     |      |       |      |
| AmpC                      | 1     | 1    |     |     |     |     |     |     | 20  | 75  |     |     |     |     |      |       |      |
| Enterobacter spp.         | 7     | 4    | 4    | 2    | 1    | 1   | 1   | 1   | 20  |     |     |     |     |     |      |       |      |
| Klebsiella spp.           | 1     | 1    |     |     |     |     |     |     | 1   |     |     |     |     |     |      |       |      |
| K1 K. oxytoca             | 1     | 8    | 9    | 9    | 2    |     |     |     | 29  | 93.7|     |     |     |     |      |       |      |
| KPC Klebsiella            | 1     | 1    |     |     |     |     |     | 2   | 0/2 |     |     |     |     |     |      |       |      |
| VIM Klebsiella            | 1     | 1    | 1    | 1    | 3    | 0/3 |     |     |     |     |     |     |     |     |      |       |      |
| OXA-48 Enterobacteriaceae | 3     | 1    | 2    |     |     |     |     |     | 6   | 3/6 |     |     |     |     |      |       |      |

aS, susceptible. Based on a breakpoint of 1–4 mg/L for Enterobacteriaceae and 4–4 mg/L for P. aeruginosa; percentage susceptibility is cited if > 10 isolates, otherwise the proportion of isolates found susceptible is shown.

bExcluding isolates also found to have carbapenemase and/or AmpC activity.
Activity of ceftolozane/tazobactam

Table 2. Overall susceptibilities of Enterobacteriaceae and P. aeruginosa referred to AMRHAI

| Enterobacteriaceae (n = 3249) | P. aeruginosa (n = 1414) |
|------------------------------|--------------------------|
| BP (mg/L) | no. S | %S | BP (mg/L) | no. S | %S |
| Colistin | S ≤ 2 | 2951 | 90.8 | S ≤ 2 | 1351 | 95.5 |
| Amikacin | S ≤ 8 | 2729 | 84.0 | S ≤ 4 | 1369 | 96.8 |
| Tigecycline | S ≤ 1 | 2649 | 75.4 | S ≤ 8 | 1033 | 73.1 |
| Imipenem | S ≤ 2 | 2365 | 72.8 | — | — | — |
| Gentamicin | S ≤ 2 | 2062 | 62.5 | S ≤ 4 | 235 | 16.6 |
| Meropenem | S ≤ 2 | 2300 | 70.8 | S ≤ 4 | 991 | 70.1 |
| Tobramycin | S ≤ 2 | 1748 | 53.8 | S ≤ 4 | 149 | 10.5 |
| Ciprofloxacin | S ≤ 0.5 | 1465 | 45.1 | S ≤ 8 | 245 | 17.3 |
| Ceftolozane/tazobactam | S ≤ 4/4 | 1048 | 32.3 | S ≤ 4/4 | 1193 | 84.4 |
| Cefepime | S ≤ 1 | 947 | 29.1 | S ≤ 8 | 744 | 52.6 |
| Temocillin | S ≤ 8 | 880 | 27.1 | — | — | — |
| Ertapenem | S ≤ 0.5 | 731 | 22.5 | — | — | — |
| Aztreonam | S ≤ 1 | 678 | 20.9 | — | — | — |
| Piperacillin/tazobactam | S ≤ 8/4 | 531 | 16.3 | S ≤ 16/4 | 661 | 46.7 |
| Ceftazidime | S ≤ 1 | 505 | 15.5 | S ≤ 8 | 802 | 56.7 |
| Cefotaxime | S ≤ 1 | 432 | 13.3 | — | — | — |
| Amoxicillin/clavulanate | S ≤ 8 | 118 | 3.6 | — | — | — |
| Ampicillin | S ≤ 8 | 18 | 0.6 | — | — | — |
| Carbenicillin | — | — | — | S ≤ 128 | 555 | 39.3 |

BP, breakpoint; no. S, number susceptible; %S, percentage susceptible.

plasmid-mediated enzymes: a 51.0% susceptibility rate accords with the observation that many examined by PCR (24/26) had blaoXA-23, a chromosomal ‘escape’ from M. morganii encoding a tazobactam-inhibited variant.9 Close relationships existed between ceftazidime-susceptible/intermediate (MIC criteria) or ceftazidime-resistant (MIC >2 mg/L) isolates, with the percentage of isolates susceptible to ceftolozane/tazobactam falling as ceftazidime MIC increased (Figure 1). Previous experience indicates that raised ertapenem to ceftolozane/tazobactam falling as ertapenem MIC increased and AmpC producers, with the percentage of isolates susceptible to these enzymes poor cephalosporinases. OXA-48-like carbapencemases are poor cephalosporinases too, especially against cef-

P. aeruginosa

The two largest groups of referred P. aeruginosa were those inferred to have increased efflux or derepressed AmpC. The increased efflux group was subcategorized into those with carbencillin MICs of 256–512 mg/L and those with carbencillin MICs >512 mg/L (Table 4). MICs of ceftolozane/tazobactam increased in tandem with those of carbenicillin, piperacillin and ceftazidime for these isolates (Table 4); nevertheless, even among efflux-type isolates with carbencillin MICs >512 mg/L, 94.7% remained susceptible to ceftolozane/tazobactam 4+4 mg/L, versus 27.6% for ceftazidime and 5.9% for piperacillin/tazobactam. Among efflux-type isolates with carbenicillin MICs 256–512 mg/L, but one
| Matching to mechanism | No. of isolates with indicated MIC (mg/L) | %S at 1+4 mg/L BP |
|-----------------------|------------------------------------------|-------------------|
|                       | molecular | hard | soft | total | ≤0.25 | 0.5 | 1 | 2 | 4 | 8 | 16 | >16 | void |
| ESBL producers        |           |      |      |       |       |     |   |   |   |   |    |     |      |
| Citrobacter spp.      |           |      |      |       |       | 1   | 1 | 1 | 1 | 1 | 1   | 1    | 50.0 |
| E. coli               |           | 337  | 25  | 362   |       | 100 | 57 | 35 | 38 | 21 | 17  | 32   | 61   | 1    | 53.0 |
| Enterobacter spp.     |           | 45   | 49  |       |       | 6   | 4  | 10 | 7  | 4  | 6   | 6    | 6    | 40.8 |
| K. oxytoca            |           | 3    | 3   |       |       | 1   | 1  | 1 | 1  |    |     |     |      |      | 33.3 |
| K. pneumoniae         |           | 229  | 26  | 255   |       | 17  | 27 | 23 | 39 | 23 | 24  | 28   | 74   | 26.3 |
| rare fermenters       |           | 2    | 2   |       |       | 2   |    |   |    |    |     |     |      |      | 0.0  |
| Serratia spp.         |           | 1    | 1   |       |       | 1   |    |   |    |    |     |     |      |      | 0.0  |
| all                   |           | 616  | 58  | 674   |       | 123 | 89 | 69 | 87 | 49 | 48  | 66   | 142  | 1    | 41.7 |
| AmpC hyperproducers   |           |      |      |       |       |     |   |   |   |   |    |     |      |      |      |
| Citrobacter spp.      |           | 39   | 7   | 46    |       | 3   | 3  | 4 | 6  | 8  | 8   | 7    | 7    | 21.7 |
| E. coli               |           | 101  | 19  | 120   |       | 35  | 15 | 11 | 11 | 8  | 11  | 7    | 22   | 50.8 |
| Enterobacter spp.     |           | 625  | 24  | 649   |       | 13  | 53 | 53 | 95 | 131| 115 | 125  | 63   | 1    | 18.4 |
| Hafnia alvei          |           | 11   | 1   | 12    |       | 1   |    | 1 |    | 2  | 8   |     |      |      | 8.3  |
| K. pneumoniae         |           | 39   | 10  | 49    |       | 9   | 6  | 10 | 3  | 6  | 3   | 12   |      |      | 51.0 |
| M. morganii           |           | 7    | 2   | 9     |       | 3   | 3  | 2 | 1  |    |     |     |      |      | 88.9 |
| Providencia spp.      |           | 1    | 1   |       |       | 1   |    |   |    |    |     |     |      |      | 1.0  |
| rare fermenters       |           | 1    | 1   |       |       | 1   |    |   |    |    |     |     |      |      | 0.0  |
| Serratia spp.         |           | 30   | 4   | 34    |       | 1   | 16 | 10 | 4  | 1  | 1   | 1    |      | 50.0 |
| all                   |           | 854  | 67  | 921   |       | 63  | 81 | 97 | 123| 156| 141 | 145  | 114  | 1    | 26.2 |
| Isolates with both ESBL + AmpC activity |           |      |      |       |       |     |   |   |   |   |    |     |      |      |      |
| Citrobacter spp.      |           | 1    | 1   |       |       | 1   |    |   |    |    |     |     |      |      | 0.0  |
| E. coli               |           | 28   | 14  | 42    |       | 2   | 1  | 1 | 4  | 5  | 29  | 42   |      |      | 7.1  |
| Enterobacter spp.     |           | 18   | 2   | 20    |       | 1   | 1  | 4 | 3  | 9  | 2   | 20   |      |      | 10.0 |
| K. pneumoniae         |           | 6    | 2   | 8     |       | 1   | 1  | 1 | 1  | 5  | 8   |      |      |      | 12.5 |
| all                   |           | 53   | 18  | 71    |       |     |   |   |   |    |    |      |      |      | 8.5  |
| K1 hyperproducers    |           |      |      |       |       |     |   |   |   |   |    |     |      |      |      |
| K. oxytoca            |           | 8    | 8   |       |       | 3   | 3 | 1 | 1 |    |    |      |      | 75.0 |
| KPC producers         |           |      |      |       |       |     |   |   |   |   |    |     |      |      |      |
| Citrobacter spp.      |           | 4    | 4   |       |       | 2   | 2 | 2 |    |    |    |      |      |      | 0.0  |
| E. coli               |           | 36   | 36  |       |       | 1   | 2 | 9 | 14 | 7  | 2   | 1    |      |      | 8.3  |
| Enterobacter spp.     |           | 28   | 28  |       |       | 1   | 3 | 5 | 7  | 8  | 4   |      |      |      | 3.6  |
| K. oxytoca            |           | 4    | 4   |       |       | 1   | 1 | 2 |    |    |    |      |      |      | 25   |
| K. pneumoniae         |           | 138  | 138 |       |       | 1   | 1 | 4 | 44 | 29 | 33  | 26   |      |      | 1.4  |
| rare fermenters       |           | 2    | 2   |       |       | 2   |    |   |    |    |     |      |      |      | 0.0  |
| Serratia spp.         |           | 4    | 4   |       |       | 3   | 1 |   |    |    |     |      |      |      | 0.0  |
| all                   |           | 216  | 216 |       |       | 2   | 1 | 4 | 17 | 63 | 47  | 50   | 32   |      | 4.3  |
| GES carbapenemases    |           |      |      |       |       |     |   |   |   |   |    |     |      |      |      |
| E. coli               |           | 4    | 4   |       |       | 1   | 3 |    |    |    |    |      |      |      | 0.0  |
| Enterobacter spp.     |           | 1    | 1   |       |       | 1   |    |   |    |    |     |      |      |      | 0.0  |
| K. oxytoca            |           | 15   | 15  |       |       | 1   | 11 | 4 |    |    |    |      |      |      | 0.0  |
| K. pneumoniae         |           | 3    | 3   |       |       | 1   | 1  | 1 |    |    |    |      |      |      | 0.0  |
| rare fermenters       |           | 3    | 3   |       |       | 1   |    |   |    |    |     |      |      |      | 0.0  |
| Serratia spp.         |           | 1    | 1   |       |       | 1   |    |   |    |    |     |      |      |      | 0.0  |
| all                   |           | 25   | 25  |       |       | 2   | 2 | 12| 9  |    |    |      |      |      | 0.0  |
| Other class A carbapenemases |           |      |      |       |       |     |   |   |   |   |    |     |      |      |      |
| Enterobacter spp.     |           | 8    | 8   |       |       | 3   | 3 | 1 | 1 |    |    |      |      | 1    | 87.5 |
| Serratia spp.         |           | 4    | 4   |       |       | 1   | 1 | 2 |    |    |    |      |      |      | 50.0 |
| all                   |           | 12   | 12  |       |       | 3   | 4 | 2 | 2 |    | 1   |      |      | 75.0 |

Continued
### Table 3. Continued

| Matching to mechanism | No. of isolates with indicated MIC (mg/L) | %S at 1+4 mg/L BP |
|-----------------------|------------------------------------------|------------------|
|                       | molecular | hard | soft | total | <0.25 | 0.5 | 1 | 2 | 4 | 8 | 16 | >16 | void |            |
| MBL producers         |           |      |      |       |       |     |   |   |   |    |    |     |      |       |            |
| Citrobacter spp.      | 13        | 13   |      |       | 1     | 12  | 0.0 |
| E. coli               | 95        | 95   |      |       | 95    | 0.0 |
| Enterobacter spp.     | 29        | 29   |      |       | 29    | 0.0 |
| K. oxytoca            | 3         | 3    |      |       | 3     | 0.0 |
| K. pneumoniae         | 169       | 169  |      |       | 169   | 0.0 |
| M. morganii           | 2         | 2    |      |       | 2     | 0.0 |
| Providencia spp.      | 4         | 4    |      |       | 4     | 0.0 |
| Serratia spp.         | 1         | 1    |      |       | 1     | 0.0 |
| all                   | 316       | 316  |      | 1     | 315   | 0.0 |
| Isolates with both NDM + OXA-48 carbapenemases |           |      |      |       |       |     |   |   |   |    |    |     |      |       |            |
| E. coli               | 4         |      | 4    |       | 4     | 0.0 |
| K. pneumoniae         | 28        | 28   |      |       | 28    | 0.0 |
| all                   | 32        | 32   |      |       | 32    | 0.0 |
| OXA-48 producers ceftazidime ≤4 mg/L |           |      |      |       |       |     |   |   |   |    |    |     |      |       |            |
| Citrobacter spp.      | 3         | 3    | 1    | 2    |       | 100 |
| E. coli               | 74        | 74   | 24   | 33   | 8    | 7   | 1  | 1 | 1  |     |     |     | 87.8 |
| Enterobacter spp.     | 22        | 22   | 1    | 6    | 8    | 7   | 0.0 |
| K. oxytoca            | 3         | 3    | 1    | 2    |       | 100 |
| K. pneumoniae         | 50        | 50   | 2    | 16   | 20   | 9   | 3  |    |     |     |     | 76  |
| rare fermenters       | 1         | 1    |      |       | 1     | 100 |
| Serratia spp.         | 2         | 2    |      |       | 2     | 100 |
| all                   | 155       | 155  | 28   | 57   | 42   | 23  | 4  | 1 |    |     |     | 81.9 |
| OXA-48 producers ceftazidime >4 mg/L |           |      |      |       |       |     |   |   |   |    |    |     |      |       |            |
| Citrobacter spp.      | 10        | 10   | 4    | 6    |       | 100 |
| E. coli               | 59        | 59   | 4    | 6    | 3    | 9   | 13 | 5  | 19 |     |     | 17.0 |
| Enterobacter spp.     | 23        | 23   | 4    | 3    | 4    | 3   | 5  | 4  |    |     |     | 17.4 |
| K. oxytoca            | 4         | 4    |      |       | 1     | 2   | 1  |    |    |     |     | 0.0  |
| K. pneumoniae         | 100       | 100  | 1    | 1    | 3    | 5   | 10 | 8  | 72 |     |     | 2.0  |
| Serratia spp.         | 2         | 2    |      |       | 2     | 100 |
| all                   | 198       | 198  | 1    | 5    | 10   | 9   | 18 | 27 | 24 | 104 |     | 8.1  |
| Impermeability        |           |      |      |       |       |     |   |   |   |    |    |     |      |       |            |
| E. coli               | 36        | 36   | 6    | 14   | 8    | 4   | 3  | 1 | 6  |    |     | 77.8 |
| K. oxytoca            | 1         | 1    |      |       | 1     | 100 |
| K. pneumoniae         | 51        | 51   | 2    | 11   | 28   | 8   | 2  |    |    |     |     | 80.4 |
| all                   | 88        | 88   | 8    | 25   | 36   | 13  | 5  | 1 |    |     |     | 78.4 |
| WT, cephalosporin susceptible |           |      |      |       |       |     |   |   |   |    |    |     |      |       |            |
| Citrobacter spp.      | 2         | 2    | 1    | 1    |       | 100 |
| E. coli               | 35        | 35   | 34   | 1    |       | 100 |
| Enterobacter spp.     | 47        | 47   | 30   | 14   | 2    | 1   |    |    |    |     | 97.9 |
| K. oxytoca            | 2         | 2    | 1    | 1    |       | 100 |
| K. pneumoniae         | 18        | 18   | 17   | 1    |       | 100 |
| M. morganii           | 14        | 14   | 12   | 1    |       | 100 |
| Providencia spp.      | 2         | 2    | 1    | 1    |       | 100 |
| rare fermenters       | 6         | 6    | 4    | 2    |       | 100 |
| Serratia spp.         | 19        | 19   | 4    | 7    | 6    | 1   | 1  |    |    |     |     | 89.5 |
| all                   | 145       | 145  | 104  | 26   | 11   | 3  | 1  |    |    |     |     | 97.2 |
| Unassigned, ceftazidime MIC ≤4 mg/L |           |      |      |       |       |     |   |   |   |    |    |     |      |       |            |
| Citrobacter spp.      | 2         | 1    |      | 1    |       | 50  |
| E. coli               | 75        | 48   | 13   | 14   |       | 100 |
| Enterobacter spp.     | 12        | 1    | 1    | 8    | 2    |     |    |    |    |     | 83.3 |
| K. oxytoca            | 9         |      | 1    | 2    | 5    | 1   |     |    |    |    |     | 11.1 |

Continued
(99.7%) were susceptible to ceftolozane/tazobactam versus
65.3% for ceftazidime and 39.4% for piperacillin/tazobactam.
Ceftolozane/tazobactam retained activity against 96.6% of
*P. aeruginosa* inferred to have derepressed AmpC, whereas
ceftazidime was active against only 20.8%, rising to 94.5% for cef-
tazidime/avibactam. Carbenicillin, which has good stability to
pseudomonal AmpC,13 remained active against 84.6% of AmpC-
derepressed isolates at its 128 mg/L breakpoint. Isolates with ‘WT’

Table 3. Continued

| Matching to mechanism | No. of isolates with indicated MIC (mg/L) |
|-----------------------|------------------------------------------|
|                       | ≤0.25 | 0.5 | 1  | 2  | 4  | 8  | 16 | >16 | void | %S at 1+4 mg/L BP |
| K. pneumoniae         | 61    | 17  | 17 | 17 | 8  | 1  | 1  |     |     | 83.6             |
| Providencia spp.      | 2     | 2   |    |    |    |    |    |     |     | 100              |
| rare fermenters       | 1     | 1   |    |    |    |    |    |     |     | 100              |
| Serratia spp.         | 7     | 4   | 2  | 1  |    |    |    |     |     | 57.1             |
| all                   | 167   | 67  | 34 | 44 | 15 | 7  | 2  |     |     | 86.8             |

Unassigned, ceftazidime MIC 8-32 mg/L

| Citrobacter spp.      | 1     | 1   |    |    |    |    |    |     |     | 0.0              |
| E. coli               | 10    | 1   | 1  | 1  | 2  | 4  |    |     |     | 20               |
| Enterobacter spp.     | 5     | 1   | 1  | 1  | 2  |    |    |     |     | 20               |
| K. oxytoca            | 3     | 1   | 1  |    | 2  |    |    |     |     | 0.0              |
| K. pneumoniae         | 49    | 13  | 1  | 24 | 8  | 3  |    |     |     | 2.0              |
| rare fermenters       | 1     | 1   |    |    |    |    |    |     |     | 0.0              |
| all                   | 69    | 12  | 2  | 15 | 27 | 9  | 8  | 6   |     | 5.8              |

Unassigned, ceftazidime MIC ≥64 mg/L

| Citrobacter spp.      | 2     |    |    |    | 1  |    |    |     |     | 0.0              |
| E. coli               | 80    | 1   | 1  | 24 | 36 | 40 |    |     |     | 0.0              |
| Enterobacter spp.     | 16    |    |    |    | 7  | 8  |    |     |     | 0.0              |
| K. oxytoca            | 2     |    |    |    | 1  | 1  |    |     |     | 0.0              |
| K. pneumoniae         | 204   | 9   | 7  | 86 | 102| 0.0|     |     |     | 0.0              |
| all                   | 304   | 12  | 8  | 131| 152| 0.0|     |     |     | 0.0              |

BP, breakpoint; %S, percentage susceptible.

aHard-matched, isolate’s antibiogram conforms precisely to expected phenotype for the mechanism; soft-matched, isolate’s antibiogram best matches the phenotype expected for the mechanism, but with minor discrepancies.

Figure 1. Susceptibility to ceftolozane/tazobactam among Enterobacteriaceae with ESBLs (grey bars, n = 674) or raised AmpC (white bars, n = 920) in relation to ertapenem MICs. Hard- and soft-matched isolates are included. None of the isolates included had a carbapenemase. Numbers on the bars indicate the numbers of isolates in the groups.
### Table 4. MIC distributions of ceftolozane/tazobactam for all referred *P. aeruginosa* by assigned group and for other non-fermenters

| Category                                      | Match level | No. of isolates with indicated ceftolozane/tazobactam MIC, mg/L | %S at 4+4 mg/L |
|-----------------------------------------------|-------------|------------------------------------------------------------------|----------------|
|                                               | Molecular   | hard<sup>a</sup> | soft<sup>a</sup> | total | ≤0.25 | 0.5 | 1 | 2 | 4 | 8 | 16 | >16 | void |
| *P. aeruginosa*                                |             |                  |                  |       |       |     |   |   |   |    |    |     |      |      |
| AmpC hyperproducers                           | 143         | 6                | 149              | 3     | 42    | 51  | 39 | 9  | 4  | 1  | 96.6 |       |      |
| carbenicillin hypersusceptible (MIC ≤16 mg/L) | 12          | 63               | 75               | 23    | 28    | 17  | 4  | 3  | 1  | 100.0 |       |      |
| normal efflux, carbenicillin MIC 32–128 mg/L; | 68          | 1                | 69               | 20    | 44    | 4   | 1  |    |    | 100.0 |       |      |
| imipenem MIC ≤4 mg/L                          |             |                  |                  |       |       |     |   |   |   |    |     |      |      |
| normal efflux, carbenicillin MIC 32–128 mg/L; | 161         | 73               | 234              | 40    | 159   | 33  | 2  |    |    | 100.0 |       |      |
| imipenem MIC >4 mg/L                          |             |                  |                  |       |       |     |   |   |   |    |     |      |      |
| raised efflux, carbenicillin MIC 256–512 mg/L | 262         | 136              | 398              | 7     | 182   | 158 | 41 | 9  | 1  | 99.7  |       |      |
| high efflux, carbenicillin MIC >512 mg/L      | 126         | 26               | 152              | 21    | 66    | 37  | 20 | 7  | 1  | 94.7  |       |      |
| ESBL producers                                 | 10<sup>b</sup> | 21              | 31               | 1     | 2     | 28  |    |    |    | 3.2   |       |      |
| GES carbapenemase producers                    | 19          | 1                | 19               | 16    | 2     | 1   |    |    |    | 84.2  |       |      |
| MBL producers                                  | 125         |                  | 125              | 1     | 124   |    |    |    |    | 0.0   |       |      |
| unassigned, ceftazidime MIC ≤8 mg/L           | 79          | 9                | 37               | 25    | 6     | 2   |    |    |    | 100.0 |       |      |
| unassigned, ceftazidime MIC 16–128 mg/L       | 40          | 2                | 4                | 6     | 15    | 5   | 4  | 4  |    | 67.5  |       |      |
| unassigned, ceftazidime MIC ≥256 mg/L         | 43          |                  | 16               | 8     | 11    | 17  |    |    |    | 16.3  |       |      |
| Other non-fermenters                           |             |                  |                  |       |       |     |   |   |   |    |      |      |
| *A. baumannii*                                 | 335         | 12               | 9                | 2     | 13    | 37  | 42 | 68 | 152| no BP |       |      |
| Acinetobacter non-*baumannii*                  | 84          | 44               | 10               | 7     | 6     | 5   | 1  | 1  | 10 | no BP |       |      |
| Achromobacter spp.                             | 61          |                  | 2                | 3     | 3     | 11  | 42 |    |    | no BP |       |      |
| *Burkholderia* spp.                           | 76          | 14               | 14               | 16    | 8     | 9   | 5  | 2  | 8  | no BP |       |      |
| *Chryseobacterium* spp.                       | 9           | 2                | 1                | 2     | 3     | 1   |    |    |    | no BP |       |      |
| *Elizabethkingia* spp.                        | 26          |                  | 1                | 5     | 6     | 10  | 4  |    |    | no BP |       |      |
| *Pandoraea* spp.                               | 24          |                  | 1                | 1     | 22    |    |    |    |    | no BP |       |      |
| Pseudomonas non-*aeruginosa*                   | 86          | 24               | 23               | 14    | 5     | 3   | 2  | 7  | 1  | no BP |       |      |
| *S. maltophilia*                               | 78          | 9                | 16               | 19    | 10    | 3   | 5  | 2  | 14 | no BP |       |      |
| others                                        | 31          | 7                | 1                | 2     | 2     | 1   | 3  | 2  | 13 | no BP |       |      |

BP, breakpoint; %S, percentage susceptible.

<sup>a</sup>Hard-matched, isolate’s antibiogram conforms precisely to expected phenotype for the mechanism; soft-matched, isolate’s antibiogram best matches the phenotype expected for the mechanism, but with minor discrepancies.

<sup>b</sup>*bla*<sub>VEB</sub> confirmed by PCR; other ESBL producers were identified by phenotype.
were non-susceptible to all established β-lactams. Secondly, (Table 5) among 422 referred P. aeruginosa isolates, compared with 74% for ceftazidime 8 mg/L, however, 14 of these were from a single outbreak, and the results may not be generalizable. Aside from MBL and ESBL producers, the only P. aeruginosa groups where ceftolozane/tazobactam resistance was frequent were the unassigned categories with ceftazidime MICs of 16–128 mg/L and imipenem MICs >4 mg/L, thus slightly lower than for MBL and ESBL producers.

Two wider associations were seen. First, across all 1414 P. aeruginosa, there was broad correlation between the MICs of ceftolozane/tazobactam and ceftazidime, with ceftolozane/tazobactam MICs 2–8-fold lower except for isolates with MBLs or ESBLs. Secondly, (Table 5) among 422 referred P. aeruginosa that were non-susceptible to all established β-lactams (i.e. carbenicillin MIC >128 mg/L, piperacillin/tazobactam >16+4 mg/L, ceftazidime >8 mg/L, imipenem >4 mg/L and meropenem >4 mg/L), 51.9% were susceptible to ceftolozane/tazobactam 4+4 mg/L, rising to 80.9% among the 267 lacking ESBLs, MBLs or GES enzymes.

### Other non-fermenters

MIC distributions of ceftolozane/tazobactam for other non-fermenters besides P. aeruginosa are shown in Table 4. The A. baumannii submissions had a major bias towards carbapenem-resistant isolates, with 303/355 non-susceptible to imipenem at its 2 mg/L breakpoint, mostly (>95%) owing to OXA carbapenemases (not shown). Other species tend to be submitted owing to multiresistance, with many of the isolates from cystic fibrosis patients.

There are no ceftolozane/tazobactam breakpoints for non-fermenters besides P. aeruginosa but a few general points can be made. First, MICs for A. baumannii, Elizabethkingia spp. and Pandorea spp. were mostly above the P. aeruginosa breakpoint of 4+4 mg/L, whereas MICs for non-baumannii Acinetobacter, Burkholderia spp., Chryseobacterium spp., non-aeruginosa Pseudomonas and Stenotrophomonas maltophilia were mostly at or below this breakpoint. Secondly, 29/32 imipenem-susceptible A. baumannii were susceptible to ceftolozane/tazobactam 4+4 mg/L versus only 44/303 imipenem-non-susceptible isolates. Thirdly, the MICs of ceftolozane/tazobactam for S. maltophilia and Burkholderia spp. correlated with those of ceftazidime, but were 2–4-fold lower (Figure 2).

### Discussion

Ceftolozane/tazobactam combines a new oxymino-cephalosporin with an established β-lactamase inhibitor. It is licensed for complicated intra-abdominal and urinary tract infections, with efficacy including ESBL-producing Enterobacteriaceae up to the 1+4 mg/L breakpoint. Activity against P. aeruginosa is striking, but this species was poorly represented in the licensing trials. We reviewed the combination’s activity against: (i) consecutive bloodstream isolates including ESBL-producing Enterobacteriaceae up to the 1+4 mg/L breakpoint; (ii) consecutive bloodstream isolates including ESBL-producing Enterobacteriaceae up to the 1+4 mg/L breakpoint; (iii) consecutive bloodstream isolates including ESBL-producing Enterobacteriaceae up to the 1+4 mg/L breakpoint.

The BSAC Bacteraemia Surveillance showed ceftolozane/tazobactam to be active against 91.5%–99.7% of the major Enterobacteriaceae species. Activity included 97.9% of ESBL E. coli, but only 84%–85% of ESBL-producing Klebsiella and Enterobacter spp. and 50% of AmpC-derepressed Enterobacter. The latter result is in keeping with tazobactam being a poor inhibitor of Enterobacter AmpC and ceftolozane being a substrate; high resistance rates were likewise seen for referred AmpC-derepressed Enterobacter (Table 3), and have been observed previously. The 15%–16% resistance rates for ESBL-producing Enterobacter and Klebsiella in the BSAC Bacteraemia Surveillance are more surprising, since ESBLs are inhibited by tazobactam. About half this resistance was borderline, with MICs of 2 mg/L, but MICs for the remainder ranged up to 256 mg/L, with resistance not obviously associated with ESBL type. Plausible explanations are that some ESBL-producing Klebsiella and Enterobacter had secondary β-lactamases or permeability lesions. Farrell et al. previously reported 12.1% ceftolozane/tazobactam resistance in ‘ESBL phenotype’
**Figure 2.** MICs of ceftolozane/tazobactam in relation to those of ceftazidime for *S. maltophilia* and *Burkholderia* spp., pooled. Grey squares indicate the line of equivalence, numbers below this line indicate that ceftolozane/tazobactam is more active than ceftazidime.

| Ceftazidime MIC (mg/L) | ≤0.25 | 0.5 | 1 | 2 | 4 | 8 | 16 | >16 |
|------------------------|-------|-----|---|---|---|----|----|-----|
| 0.25                   |       |     |   |   |   |    |    |     |
| 0.5                    |       | 2   |   |   |   |    |    |     |
| 1                      | 15    | 16  | 4 |   |   |    |    |     |
| 2                      | 2     | 12  | 24| 6 | 3 |    |    |     |
| 4                      |       | 2   | 4 | 5 | 3 | 1  | 1  |     |
| 8                      |       | 3   | 7 | 3 | 1 |    |    |     |
| 16                     | 3     | 8   | 1 | 1 |   |    |    |     |
| 32                     |       |     |   |   |   | 3  | 3  |     |
| 64                     | 6     |     |   |   |   |    |    |     |
| 128                    | 4     |     |   |   |   |    |    |     |
| 256                    | 5     |     |   |   |   |    |    |     |
| >256                   | 2     |     |   |   |   |    |    |     |

**Total: S. maltophilia** (*n* = 78) 9 16 19 10 3 5 2 14
**Total: Burkholderia spp.** (*n* = 76) 14 14 16 8 9 5 2 8

E. coli and 69.6% resistance in ‘ESBL phenotype’ *K. pneumoniae* from 41 medical centres in Europe, Turkey and Israel; these high resistance rates seem unrepresentative of the generality of UK and Irish ESBL producers and closer to results for referred problem isolates (Table 3). They may reflect (i) larger proportions of ESBL producers with secondary mechanisms in the countries surveyed, or (ii) inclusion of strains with KPC enzymes, which can give a false ‘ESBL phenotype’ in terms of cephalosporin/clavulanate synergy. Frequent resistance to ertapenem among referred ESBL and AmpC producers is probably due to impermeability, and, among these isolates, ceftolozane/tazobactam resistance was common (Figure 1).

Unlike the BSAC collections, the AMRHAI referrals provided numerous carbapenemase-producing Enterobacteriaceae, most of which proved resistant to ceftolozane/tazobactam. This is unsurprising for MBL and KPC producers as (i) MBLs are not inhibited by tazobactam and (ii) KPC enzymes hydrolyse penicillanic acid sulphones, mitigating inhibition. Better activity might be expected against isolates with OXA-48-like enzymes, which are poorly active against oxyimino-cephalosporins, with any cephalosporin resistance arising from secondary mechanisms, principally ESBLs, which should be inhibited by tazobactam. Yet, in reality, ceftolozane/tazobactam susceptibility was largely restricted to those OXA-48-like isolates that were susceptible or intermediate to unprotected ceftazidime (MIC ≤4 mg/L) and therefore are inferred to lack secondary β-lactamases. Similar behaviour (not shown) was seen for ceftazidime/clavulanate. Plausible explanations, deserving investigation, are: (i) many resistant isolates additionally had permeability lesions or multiple β-lactamases, thus overwhelming the tazobactam; or (ii) OXA-48-like enzymes inactivate tazobactam and clavulanate.

In contrast to this mixed performance against Enterobacteriaceae, ceftolozane/tazobactam was the most active β-lactam against both series of *P. aeruginosa* isolates. For the BSAC isolates its modal MIC was 4-fold lower than for ceftazidime and the proportion non-susceptible was only 0.2%. More strikingly, ceftolozane/tazobactam was active, at breakpoint, against 99.7% and 94.7% of referred isolates with moderately and strongly increased efflux and against 96.6% with derepressed AmpC. These are the most common resistance mechanisms in *P. aeruginosa* in the UK, and Western Europe, though MBLs and ESBLs, which ceftolozane/tazobactam did not overcome, are more prevalent in Russia, Eastern Europe and the Middle East. Ceftolozane does not entirely escape efflux and AmpC, and its MICs are slightly raised, nevertheless it is less compromised than other cephalosporins and penicillins, and seems less prone to select for these traits.

High-level ceftolozane/tazobactam resistance (MIC >16 mg/L) in *P. aeruginosa* was largely confined to isolates with MBLs or ESBLs, and these associations were so strong that AMRHAI now uses a ceftolozane/tazobactam MIC >16 mg/L as a predictor of these enzymes for the species. The lack of activity against ESBL-producing *P. aeruginosa* may seem surprising, since ESBL-producing Enterobacteriaceae were widely susceptible, but we note: (i) the predominant VEB ESBLs may be less susceptible to tazobactam than the CTX-M, TEM and SHV enzymes of Enterobacteriaceae; and (ii) tazobactam may be a poor permeant, or good efflux substrate, for *P. aeruginosa*. Piperacillin/tazobactam by analogy is poorly active against *P. aeruginosa* with acquired penicillins.

Ceftolozane/tazobactam offered no gain compared with earlier cephalosporins against Acinetobacter spp. or *Elizabethkingia* spp., but was more active than ceftazidime against *Burkholderia* spp. and *S. maltophilia*. β-Lactams remain controversial in infections due to these species, with medium-dependent MICs and no EUCAST breakpoints. Nevertheless they are often the next-most-active option after co-trimoxazole in vitro, and may be considered in sulphonamide-intolerant patients or those with co-trimoxazole-resistant strains. Ceftazidime, meropenem and temocillin have the
lowest MICs among β-lactams for *Burkholderia* spp. with ticarcillin/clavulanate and ceftazidime the most active against *S. maltophilia*. It now seems appropriate to add ceftolozane/tazobactam to this list. Activity against *S. maltophilia* may reflect tazobactam inhibiting the L-2 cephalosporinase, and this possibility deserves exploration.

In countries with conservative antimicrobial usage, such as the UK, new agents enter use as microbiologically directed treatments of problem infections, not as the empirical therapy modelled by Phase III trials. *P. aeruginosa* is the likely major target for ceftolozane/tazobactam, since β-lactams are core to anti-pseudomonal regimens and the combination inhibited many isolates resistant to all other β-lactams (Table 5). Results of a high-dosage ventilator-associated pneumonia trial, where *P. aeruginosa* is likely to be a frequent pathogen, are awaited with interest. In the meantime there is a growing catalogue of case reports of success in chronic and acute *P. aeruginosa* infections. These data are encouraging, although reports of resistance associated with AmpC sequence variants are a concern.

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D. M. L. has participated in Advisory Boards or ad hoc consultancy for Accelerate, Achaogen, Adenium, Allecra, AstraZeneca, Auspherix, Baselga, BioVersys, Centauri, Discuva, Meiji, Pfizer, Roche, Shionogi, Tetraphase, The Medicines Company, VenatoRx, Wockhardt, Zambon and Zealand, and has given paid lectures for Astellas, AstraZeneca, Beckman Coulter, Cardiome, Cepheid, Merck and Nordic. He has relevant shareholdings in: Dechra, GlaxoSmithKline, Merck, PerkinElmer and Pfizer amounting to <10% of portfolio value. The remaining authors have no personal interests to declare. However, PHE’s AMR/HAI Reference Unit has received financial support for conference attendance, lectures, research projects or contracted evaluations from numerous sources, including: Accelerate Diagnostics, Achaogen Inc., Allecra Therapeutics, Amplex, AstraZeneca UK Ltd, Baselga Pharmaceutica, Becton Dickinson Diagnostics, bioMérieux, Bio-Rad Laboratories, BSAC, Cepheid, Check-Points BV, Cubist Pharmaceuticals, Department of Health, Enigma Diagnostics, Food Standards Agency, GlaxoSmithKline Services Ltd, Henry Stewart Talks, JHMA Ltd, Kaldex Pharmaceuticals, Melinta Therapeutics, Merck Sharpe & Dohme Corp., Meiji Seika Pharma Co., Ltd, Mobidiag, Momentum Biosciences Ltd, Nordic Pharma Ltd, Norgine Pharmaceuticals, Rempex Pharmaceuticals Ltd, Roche, Rokitan Ltd, Smith & Nephew UK Ltd, Trius Therapeutics, VenatoRx Pharmaceuticals and Wockhardt Ltd.

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