Compassionate use of meropenem/vaborbactam for infections caused by KPC-producing Klebsiella pneumoniae: a multicentre study

Mario Tumbarello 1,2*, Francesca Raffaelli 3, Antonio Cascio 6, Marco Falcone 5, Liana Signorini 6, Cristina Mussini 7, Francesco Giuseppe De Rosi 8, Angela Raffaella Losito 3, Gennaro De Pascale 9,10, Renato Pascale 11, Daniele Roberto Giacobbe 12,13, Alessandra Oliva 14, Alberto Farese 15, Paola Morelli 16,17, Giusy Tiseo 5, Marianna Meschiari 7, Paola Del Giacomo 3, Francesca Montagnani 1,2, Massimiliano Fabbiani 2, Joel Vargas 10, Teresa Spanu 7,10, Matteo Bassetti 12,13, Mario Venditti 16 and Pierluigi Viale 11

1 Dipartimento di Biotecnologie Mediche, Università degli Studi di Siena, Siena, Italy; 2 UOC Malattie Infettive e Tropicaali, Azienda Ospedaliero-Università Senese, Siena, Italy; 3 Dipartimento di Scienze di Laboratorio e Infettivologiche, Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italy; 4 Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties, University of Palermo, 90127, Palermo, Italy; 5 Infectious Diseases Unit, Azienda Ospedaliera Universitaria Pisana, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy; 6 UOC Malattie Infettive, Spedali Civili di Brescia, Brescia, Italy; 7 Clinica delle Malattie Infettive, Università di Modena e Reggio Emilia, Modena, Italy; 8 Department of Medical Sciences, University of Turin, Torino, Italy; 9 Dipartimento di Scienze Biotecnologiche di Base, Cliniche Intensivologiche e Perioperatorie, Università Cattolica del Sacro Cuore, Roma, Italy; 10 Dipartimento di Scienze dell’emergenze, anestesiologiche e della rianimazione, Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Roma, Italy; 11 Dipartimento scienze mediche e chirurgiche, Università di Bologna/IRCCS Policlinico Sant’Orsola, Bologna, Italy; 12 Clinica Malattie Infettive, IRCCS Ospedale Policlinico San Martino, Genova, Italy; 13 Dipartimento di Scienze della Salute (DISSAL), Università di Genova, Genova, Italy; 14 Dipartimento di Sanità Pubblica e Malattie Infettive, Università Sapienza, Roma, Italy; 15 Infectious and Tropical Diseases Unit, Careggi University Hospital, Florence, Italy; 16 Infectious Diseases Unit, Hospital Health Direction, Humanitas Clinical and Research Center – IRCCS, Rozzano, Milan, Italy; 17 Humanitas University, Department of Biomedical Sciences, Pieve Emanuele, Milan, Italy

*Corresponding author. E-mail: mario.tumbarello@unisi.it; mariotumb@gmail.com

Received 25 November 2021; accepted 15 February 2022

Objectives: To explore the real-life performance of meropenem/vaborbactam for treating serious KPC-producing Klebsiella pneumoniae infections, including those resistant to cepazidime/avibactam.

Methods: A retrospective observational cohort study was conducted in 12 Italian hospitals. Enrolled patients had K. pneumoniae carbapenemase (KPC)-producing K. pneumoniae (KPC-Kp) infections (59.5% of which were ceftazidime/avibactam resistant). Patients who received ≥72 h of meropenem/vaborbactam therapy (with or without other antimicrobials) in a compassionate-use setting were included.

Results: The 37 infections (all hospital-acquired) were mainly bacteraemic (BSIs, n = 23) or lower respiratory tract infections (LRTIs, n = 10). Clinical cure was achieved in 28 (75.6%) cases and microbiologically confirmed in all 25 with follow-up cultures. Three (10.7%) of the 28 clinical cures (all BSIs, 2/3 microbiologically confirmed) were followed by in-hospital recurrences after meropenem/vaborbactam was discontinued (median interval: 18 days). All three recurrences were susceptible to meropenem/vaborbactam and successfully managed with meropenem/vaborbactam combined with colistin or fosfomycin. Nine patients (24.3%) (all with BSIs or LRTIs) died in hospital with persistent signs of infection. Most were aged over 60 years, with high comorbidity burdens and INCREMENT scores ≥8. Only one had received meropenem/vaborbactam monotherapy. Six began meropenem/vaborbactam therapy ≥48 h after infection onset. Outcomes were unrelated to the isolate’s ceptazidime/avibactam susceptibility status. The single adverse event observed consisted of severe leukopenia with thrombocytopenia.

Conclusions: With the well-known limitations of real-life retrospective studies, our results support previous findings indicating that meropenem/vaborbactam therapy will be a safe, effective tool for managing serious KPC-Kp infections, including the increasing proportion displaying resistance to ceftazidime/avibactam.

© The Author(s) 2022. Published by Oxford University Press on behalf of British Society for Antimicrobial Chemotherapy. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (https://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com
Introduction

The fixed-dose antimicrobial agent meropenem/vaborbactam combines the broad-spectrum antimicrobial meropenem with a novel cyclic boronic acid β-lactamase inhibitor, vaborbactam, which restores meropenem’s activity against bacteria producing Klebsiella pneumoniae carbapenemase (KPC) and several other serine β-lactamases. Meropenem/vaborbactam is inactive against bacteria that produce MBLs or oxacillinases with carbapenemase activity.1 The drug was approved in 2017 by the FDA for treating complicated urinary tract infections (cUTIs) and in 2018 by the EMA for treating cUTIs, complicated intra-abdominal infections, hospital-acquired pneumonia and aerobic Gram-negative infections in adults with limited treatment options.1

The approvals were based on data from two randomized Phase 3 clinical trials: TANGO 1, which documented meropenem/vaborbactam’s non-inferiority to piperacillin/tazobactam for treating cUTIs,2 and TANGO II, which showed the new drug to be safer and more effective than best available therapies for managing infections caused by carbapenem-resistant Enterobacterales (CRE).3 Evidence on the real-life use of meropenem/vaborbactam is limited and based exclusively on observational studies, which confirm its efficacy and safety in the treatment of CRE infections2–6 and suggest that they are similar to those of ceftazidime/avibactam.7 The latter is now widely used as first-line treatment of CRE infections8–11 despite increasing reports of the emergence during treatment of in vitro and in vivo resistance.12–15

To expand the real-life treatment evidence base for use of meropenem/vaborbactam in treating CRE infections, we conducted a retrospective observational study of patients with KPC-producing K. pneumoniae (KPC-Kp) infections treated with meropenem/vaborbactam, including a large number caused by isolates that were resistant to ceftazidime/avibactam.

Results

During the study period, 37 adults hospitalized in the participating centres received meropenem/vaborbactam for a KPC-Kp infection (Table 1). All infections were hospital-acquired, almost 90% were bloodstream or lower respiratory tract infections (BSI and LRTI, respectively), and 70% were diagnosed in an ICU. All 37 isolates were resistant to penicillins, extended-spectrum cephalosporins, ciprofloxacin and meropenem, and 22 were resistant to ceftazidime/avibactam. All displayed in vitro susceptibility to meropenem/vaborbactam. Some were also susceptible to fosfomycin, colistin, gentamicin, tigecycline or amikacin.

The median interval from infection onset to the initiation of meropenem/vaborbactam therapy was 5 days. The median duration of treatment was 13.5 days (Table 1). In over 60% of the cases, the meropenem/vaborbactam regimen included at least 48 h of treatment with one or more other active antibacterial agents. The 14 patients who received meropenem/vaborbactam alone had BSIs (n = 10), cUTIs (n = 2), LRTI (n = 1) or acute bacterial skin and skin structure infection (n = 1).

Clinical cure was observed in 28 of the 37 cases, and 25 of those cures were microbiologically confirmed (Table 1). (Follow-up cultures were not done in the remaining 12 cases of the cohort.) Three of the 28 infections (all BSIs) classified as clinically cured (including 2 with negative follow-up cultures), all initially treated with combination regimens, recurred after meropenem/vaborbactam treatment was discontinued (median interval: 18 days). In all three cases, the KPC-Kp isolates remained susceptible to meropenem/vaborbactam, and microbiological and/or clinical cures were achieved after re-treatment with meropenem/vaborbactam plus colistin (two cases) or meropenem/vaborbactam plus fosfomycin (one case). The in-hospital mortality rate was 24.3%. In Figure 1 within patients with BSIs or LRTIs, mortality data are shown for patients who received meropenem/vaborbactam alone versus with other active antimicrobials and with subgroups defined by the ceftazidime/avibactam susceptibility status of the KPC-Kp isolate.

All nine patients who died (Table 2) had BSIs or LRTIs, and none had achieved clinical cure. Most were over 60 years of age, had Charlson Comorbidity Indexes (CCIs) ≥4, and/or INCREMENT scores ≥8, and all but one received meropenem/vaborbactam with another active antimicrobial. Six had been started on meropenem/vaborbactam >48 h after infection onset (although, during that interval, four of the six had received another active antibacterial).

As shown in Table 1, the 15 patients with ceftazidime/avibactam-susceptible KPC-Kp infections were generally older...
Table 1. Baseline characteristics, treatment features and outcomes of the KPC-Kp infections treated with meropenem/vaborbactam, stratified according to the isolate’s ceftazidime/avibactam susceptibility status

| Variables                                      | All infections (n = 37) | CZARES (n = 22) | CZASUSC (n = 15) | P value CZARES vs CZASUSC |
|------------------------------------------------|-------------------------|-----------------|------------------|--------------------------|
| **Patient variables**                          |                         |                 |                  |                          |
| Males                                          | 22 (59.5)               | 13 (59.1)       | 9 (60.0)         | 0.95                     |
| Age, years, median (IQR)                       | 65 (31–71)              | 61 (43–66)      | 69 (53–74)       | 0.07                     |
| CCI ≥ 4                                        | 19 (51.3)               | 8 (36.4)        | 11 (73.3)        | 0.02                     |
| **Pre-infection healthcare interventions**      |                         |                 |                  |                          |
| Previous hospitalizationb                      | 19 (51.3)               | 12 (54.5)       | 7 (46.7)         | 0.64                     |
| Previous antibiotic therapyc                   | 34 (91.9)               | 21 (95.4)       | 13 (86.7)        | 0.33                     |
| Previous CZA therapyc                          | 13 (35.1)               | 12 (54.5)       | 1 (6.7)          | 0.0002                   |
| **Infection characteristics**                  |                         |                 |                  |                          |
| Hospital acquiredd                             |                         |                 |                  |                          |
| BSI                                            | 23 (62.2)               | 15 (68.2)       | 8 (53.3)         | 0.36                     |
| LRTI                                           | 10 (27.0)               | 5 (22.7)        | 5 (33.3)         | 0.47                     |
| IAI                                            | 1 (2.7)                 | 1 (4.5)         | 0                | 0.40                     |
| cUTI                                           | 2 (5.4)                 | 1 (4.5)         | 1 (6.7)          | 0.78                     |
| ABSII                                          | 1 (2.7)                 | 0               | 1 (6.7)          | 0.22                     |
| **Severity of illness at onset**               |                         |                 |                  |                          |
| INCREMENT score ≥ 8                            | 19 (51.3)               | 8 (36.4)        | 11 (73.3)        | 0.03                     |
| Septic shock                                   | 7 (18.9)                | 1 (4.5)         | 6 (40.0)         | 0.007                    |
| **Ward submitting index culture**              |                         |                 |                  |                          |
| Medical                                        | 7 (18.9)                | 4 (18.2)        | 3 (20.0)         | 0.89                     |
| Surgical                                       | 4 (10.8)                | 3 (13.6)        | 1 (6.7)          | 0.51                     |
| ICU                                            | 26 (70.3)               | 15 (68.2)       | 11 (73.3)        | 0.73                     |
| **MEM/VAB treatment variables**                |                         |                 |                  |                          |
| Days before MEM/VAB treatment, median (IQR)^e  | 5 (2–8)                 | 4 (1–8)         | 5 (2–9)          | 0.91                     |
| Monotherapy regimens                           | 14 (37.8)               | 10 (45.5)       | 4 (26.7)         | 0.24                     |
| Combination regimensf                          | 23 (62.2)               | 12 (54.5)       | 11 (73.3)        | 0.24                     |
| MEM/VAB + 1 other active antimicrobial:        | 17 (45.9)               | 9 (40.9)        | 8 (53.3)         | 0.46                     |
| Fosfomycin                                     | 6 (16.2)                | 2 (9.1)         | 4 (26.7)         | 0.15                     |
| Tigecycline                                    | 3 (8.1)                 | 3 (13.6)        | 0                | 0.14                     |
| Gentamicin                                      | 1 (2.7)                 | 1 (4.5)         | 0                | 0.40                     |
| Colistin                                       | 6 (16.2)                | 3 (13.6)        | 3 (20.0)         | 0.61                     |
| Amikacin                                       | 1 (2.7)                 | 0               | 1 (6.7)          | 0.22                     |
| MEM/VAB + ≥ 2 active antimicrobials             | 6 (16.2)                | 3 (13.6)        | 3 (20.0)         | 0.61                     |
| Days of treatment, median (IQR)^d              | 13.5 (8.5–15.5)         | 14 (12–16)      | 12.5 (7–15)      | 0.41                     |
| Dose adjusted for renal function               | 14 (37.8)               | 10 (45.5)       | 4 (26.7)         | 0.25                     |
| **Outcomes**                                   |                         |                 |                  |                          |
| Clinical cure^g                                 | 28 (75.6)               | 18 (81.8)       | 10 (66.6)        | 0.29                     |
| Microbiological eradication^h                   | 25 (68.9)               | 16 (88.9)       | 9 (90.0)         | 0.93                     |
| Microbiological data N/A^h                      | 3 (10.7)                | 2 (11.1)        | 1 (10.0)         | 0.93                     |
| In-hospital infection recurrence^i,j           | 3 (10.7)                | 1 (5.5)         | 2 (20.0)         | 0.24                     |
| Adverse reactions                               | 1 (2.7)                 | 0               | 1 (6.7)          | 0.22                     |
| In-hospital mortality                           | 9 (24.3)                | 4 (18.2)        | 5 (33.3)         | 0.29                     |

Unless otherwise stated, data are expressed as n (%).

ABSSI, acute bacterial skin and skin structure infection; CZARES, ceftazidime/avibactam resistant; CZASUSC, ceftazidime/avibactam susceptible; IAI, intra-abdominal infection; MEM/VAB, meropenem/vaborbactam N/A, not available.

^Ceftazidime/avibactam MIC ≥ 16 mg/L.
^During the 12 months preceding infection onset.
^During the 6 months preceding infection onset.
^Index culture collected ≥ 48 h after hospital admission.
^From collection of index culture to first dose of meropenem/vaborbactam.
^Regimens that included ≥ 48 h of treatment with one or more other drugs with in vitro activity against the KPC-Kp isolate.
^Resolution of all signs and symptoms of infection followed by discontinuation of meropenem/vaborbactam therapy.
^Percentages of microbiological eradication and microbiological data. N/A outcomes have been computed within cases that achieved clinical cures (28).
^Diagnosed microbiologically during the index hospitalization after the original infection had been classified as microbiologically and/or clinically cured.
^Severe leukopenia with thrombocytopenia, which developed after 10 days of meropenem/vaborbactam therapy.
and more likely to have a CCI > 4, an INCREMENT score > 7 and/or septic shock. Their clinical cure and in-hospital survival rates were somewhat lower than those of their counterparts with ceftazidime/avibactam-resistant isolates, but neither difference was statistically significant.

Discussion

The last decade has seen striking worldwide increases in the incidence of CRE infections, particularly those caused by KPC-Kp. These infections are associated with high mortality rates and a dearth of treatment options.\textsuperscript{16-19} Meropenem/vaborbactam is a potentially powerful addition to clinicians' armamentarium for treating these infections.\textsuperscript{20} Since the TANGO I and TANGO II trial results were reported,\textsuperscript{2,3} meropenem/vaborbactam's efficacy and safety for treating serious Gram-negative bacterial infections have been assessed mainly in small retrospective observational studies.\textsuperscript{4,5,7} Promising findings have also emerged, however, from a larger multicentre study of 126 severe Gram-negative bacterial infections, 99 (78.6%) of which were caused by CRE.

Figure 1. In-hospital mortality. All deaths occurred in patients with BSIs or LRTIs. Within each group, data are shown for patients who received meropenem/vaborbactam alone versus with other active antimicrobials and with subgroups defined by the ceftazidime/avibactam susceptibility status of the KPC-Kp isolate. CZA res, ceftazidime/avibactam resistant; CZA susc, ceftazidime/avibactam susceptible.

Table 2. Features of cases characterized by all-cause in-hospital mortality

| Patient | Age/Sex | CCI | Infection type | INCR score | MIC (mg/L) | MEM/VAB treatment start (days)\textsuperscript{a} | Active concomitant antimicrobials | Dose adjustment for renal function | MEM/VAB treatment duration (days) | Clinical cure\textsuperscript{b} | Time of death (days)\textsuperscript{a} |
|---------|---------|-----|----------------|------------|------------|-----------------------------------------------|---------------------------------|--------------------------------|-------------------------------|----------------|-------------------------------|
| 1       | 31/M    | 3   | BSI            | 6          | 0.5        | ≥16                                            | 5 Tigecycline                   | Yes                                          | 5                            | No              | 10                            |
| 2       | 66/M    | 5   | BSI            | 8          | 1          | ≥16                                            | 4 Colistin                      | No                                           | 8                            | No              | 12                            |
| 3       | 75/M    | 6   | BSI            | 15         | 0.5        | 4                                              | 6 Colistin                      | No                                           | 4                            | No              | 10                            |
| 4       | 61/F    | 4   | LRTI           | 10         | 0.5        | 2                                              | 9 Colistin                      | Yes                                          | 6                            | No              | 15                            |
| 5       | 69/F    | 2   | BSI            | 13         | 1          | 1                                              | 1 Colistin                      | No                                           | 9                            | No              | 10                            |
| 6       | 73/F    | 5   | BSI            | 10         | 1          | 2                                              | 8 Fosfomycin                    | No                                           | 11                           | No              | 19                            |
| 7       | 52/M    | 10  | BSI            | 12         | 1          | 8                                              | 1 Fosfomycin                    | Yes                                          | 7                            | No              | 8                             |
| 8       | 61/F    | 3   | LRTI           | 10         | 1          | ≥16                                            | 1 Colistin                      | No                                           | 15                           | No              | 16                            |
| 9       | 64/F    | 4   | LRTI           | 13         | 0.25       | ≥16                                            | 3 Colistin                      | No                                           | 18                           | No              | 21                            |

CZA, ceftazidime/avibactam; INCR, INCREMENT; MEM/VAB, meropenem/vaborbactam.
\textsuperscript{a}Calculated from date of index culture.
\textsuperscript{b}Resolution of all signs and symptoms of infection while on meropenem/vaborbactam.
most represented by \textit{K. pneumoniae} (n = 53).\textsuperscript{6} Real-world studies conducted after the initial approval of a new drug are provide invaluable information on the drug’s performance in the treatment of specific conditions and/or patient populations. Unlike conventional randomized controlled trials, real-world studies tend to include patients who are older, more critically ill, more severely immunocompromised and/or more likely to have chronic end-organ damage (e.g. renal insufficiency).\textsuperscript{6}

Consistent with the findings cited above,\textsuperscript{4,5,7} our multicentre cohort study found meropenem/vaborbactam to be an effective, well-tolerated option for treating BSIs, LRTIs and other serious infections caused by \textit{K. pneumoniae} producing only KPC \textbeta-lactamases. Clinical cure was recorded in over three-quarters of the cases (28/37), and all but three of those were microbiologically confirmed. Equally important, 3 of the 28 clinical cures were followed by in-hospital recurrences, but all three recurrences remained susceptible to meropenem/vaborbactam and were successfully eradicated with a second course of meropenem/vaborbactam plus another active drug.

The fact that our patients received meropenem/vaborbactam in a compassionate-use programme largely explains the fairly long period between infection onset and the initiation of meropenem/vaborbactam therapy (median: 5 days—appreciably longer than the intervals reported in a post-marketing setting).\textsuperscript{5} Although our cohort is too small to allow reliable conclusions on predictors of negative responses to meropenem/vaborbactam, six of the nine patients who died in hospital had initiated meropenem/vaborbactam ≥48 h after the index culture, a finding consistent with those of Alosaimy \textit{et al.}\textsuperscript{8} and with the growing body of evidence highlighting the importance of prompt initiation of effective antimicrobial therapy in multiresistant Gram-negative infections.

Importantly, almost 60\% of the KPC-Kp infections in our cohort were caused by ceftazidime/avibactam-resistant isolates, and in most of these cases, meropenem/vaborbactam treatment—alone or with other active drugs—produced favourable responses in terms of both clinical cure and in-hospital survival rates. The fact that clinical cure and in-hospital survival were appreciably (but not significantly) less common among the 15 patients with ceftazidime/avibactam-susceptible isolates is almost certainly related to the severity of their infections (see Table 1) and their baseline comorbidity burdens. Almost none of these 15 infections was treated with ceftazidime/avibactam prior to the administration of meropenem/vaborbactam. Consequently, it is impossible to tell whether outcomes in this subgroup would have been more favourable if they had received ceftazidime/avibactam instead of meropenem/vaborbactam.

Meropenem/vaborbactam’s performance against ceftazidime/avibactam-resistant KPC-Kp isolates is encouraging given the reports of resistance to the latter drug during treatment.\textsuperscript{12,14} Meropenem/vaborbactam retains activity against strains producing KPC variants that confer resistance to ceftazidime/avibactam. Moreover pharmacodynamic aspects of vaborbactam are more effective than avibactam, which often needs to be maintained at a high concentration to be effective against KPC.\textsuperscript{1} Meropenem/vaborbactam resistance was not observed in any of our patients (including those with in-hospital recurrence, all of which were still susceptible to meropenem/vaborbactam). This finding is fully consistent with previous reports.\textsuperscript{6} However, follow-up cultures were not collected in most of the cases we analysed, and larger studies are undoubtedly necessary to reliably estimate the actual frequency of resistance.

Despite these limitations, however, our findings expand the growing body of real-life data pointing to meropenem/vaborbactam as a valuable option for treating serious infections in hospitals where KPC-Kp are endemic. Further study, particularly clinical trials, should be performed to devise strategies for the optimal use of this important new drug in the treatment of KPC-Kp infections and provide strong evidence for the real-life practice.

**Funding**

This work was partially supported by grants from the Università Cattolica del Sacro Cuore, Roma, Italy (Fondi Ateneo Linea D-1 2020).

**Transparency declarations**

None to declare.

**References**

1. Novelli A, Del Giacomo P, Rossolini GM \textit{et al.} Meropenem/vaborbactam: a next generation \textbeta-lactam/\textbeta-lactamase inhibitor combination. \textit{Expert Rev Anti Infect Ther} 2020; 18: 643–55.
2. Kaye KS, Bhowmick T, Metallidis S \textit{et al.} Effect of meropenem-vaborbactam vs piperacillin-tazobactam on clinical cure or improvement and microbial eradication in complicated urinary tract infection: the TANGO I randomized clinical trial. \textit{JAMA} 2016; 315: 788–99.
3. Wunderink RG, Giannarelos-Bourboulis EJ, Rahov G \textit{et al.} Effect and safety of meropenem-vaborbactam versus best-available therapy in patients with carbapenem-resistant Enterobacteriaceae infections: the TANGO II randomized clinical trial. \textit{Infect Dis Ther} 2018; 7: 439–55.
4. Shields RK, McCready EK, Marini RV \textit{et al.} Early experience with meropenem-vaborbactam for treatment of carbapenem-resistant Enterobacteriaceae infections. \textit{Clin Infect Dis} 2020; 71: 667–71.
5. Alosaimy S, Jorgensen SCJ, Logn AM \textit{et al.} Real-world multicenter analysis of clinical outcomes and safety of meropenem-vaborbactam in patients treated for serious Gram-negative bacterial infections. \textit{Open Forum Infect Dis} 2020; 7: ofaa051.
6. Alosaimy S, Logn AM, Morrisette T \textit{et al.} Real-world, multicenter experience with meropenem-vaborbactam for Gram-negative bacterial infections including carbapenem-resistant Enterobacteriaceae and Pseudomonas aeruginosa. \textit{Open Forum Infect Dis} 2021; 8: ofab371.
7. Ackley R, Roshdy D, Meredith J \textit{et al.} Meropenem-vaborbactam versus ceftazidime-avibactam for treatment of carbapenem-resistant Enterobacteriaceae infections. \textit{Antimicrob Agents Chemother} 2020; 64: e02313-19.
8. van Duin D, Lok JJ, Earley M \textit{et al.} Colistin versus ceftazidime-avibactam in the treatment of infections due to carbapenem-resistant Enterobacteriaceae. \textit{Clin Infect Dis} 2018; 66: 163–71.
9. Tumbarello M, Raffaelli F, Giannella M \textit{et al.} Ceftazidime-avibactam use for Klebsiella pneumoniae carbapenemase-producing \textit{K. pneumoniae} infections: a retrospective observational multicenter study. \textit{Clin Infect Dis} 2021; 73: 1664–76.
10. Karaiskos I, Daikos GL, Gkoufa A \textit{et al.} Ceftazidime-avibactam in the era of carbapenemase-producing Klebsiella pneumoniae: experience from a national registry study. \textit{J Antimicrob Chemother} 2021; 76: 775–83.
11. Tamma PD, Atiken SL, Bonomo RA \textit{et al.} Infectious Diseases Society of America guidance on the treatment of extended-spectrum \textbeta-lactamase producing Enterobacteriales (ESBL-E), carbapenem-resistant Enterobacteriales
(CRE), and Pseudomonas aeruginosa with difficult-to-treat resistance (DTR-P. aeruginosa). Clin Infect Dis 2021; 72: e169–83.

12 Tumbarello M, Trecarichi EM, Corona A et al. Efficacy of ceftazidime-avibactam salvage therapy in patients with infections caused by Klebsiella pneumoniae carbapenemase-producing K. pneumoniae. Clin Infect Dis 2019; 68: 355–64.

13 Livermore DM, Warner M, Jamrozy D et al. In vitro selection of ceftazidime-avibactam resistance in Enterobacteriaceae with KPC-3 carbapenemase. Antimicrob Agents Chemother 2015; 59: 5324–30.

14 Shields RK, Potoski BA, Haidar G et al. Clinical outcomes, drug toxicity, and emergence of ceftazidime-avibactam resistance among patients treated for carbapenem-resistant Enterobacteriaceae infections. Clin Infect Dis 2016; 63: 1615–8.

15 Haidar G, Clancy CJ, Shields RK et al. Mutations in blaKPC-3 that confer ceftazidime-avibactam resistance encode novel KPC-3 variants that function as extended-spectrum β-lactamases. Antimicrob Agents Chemother 2017; 61: e02534–16.

16 Rodríguez-Baño J, Gutiérrez-Gutiérrez B, Machuca I et al. Treatment of infections caused by extended-spectrum-β-lactamase-, AmpC-, and carbapenemase-producing Enterobacteriaceae. Clin Microbiol Rev 2018; 31: e00079-17.

17 Tumbarello M, Viale P, Bossetti M et al. Infections caused by KPC-producing Klebsiella pneumoniae: differences in therapy and mortality in a multicentre study—authors’ response. J Antimicrob Chemother 2015; 70: 2922.

18 Doi Y, Bonomo RA, Hooper DC et al. Gram-negative bacterial infections: research priorities, accomplishments, and future directions of the Antibacterial Resistance Leadership Group. Clin Infect Dis 2017; 64 Suppl 1: S30–5.

19 Bossetti M, Giacobbe DR, Giamarelou H et al. Management of KPC-producing Klebsiella pneumoniae infections. Clin Microbiol Infect 2018; 24: 133–44.

20 Tompkins K, van Duin D. Treatment for carbapenem-resistant Enterobacteriales infections: recent advances and future directions. Eur J Clin Microbiol Infect Dis 2021; 40: 2053–68.