Determining the in vitro susceptibility of tebipenem, an oral carbapenem, against third-generation cephalosporin-resistant Escherichia coli and Klebsiella pneumoniae isolated from bloodstream infections

Ama Ranasinghe¹, Andrew Henderson¹,², Kyra Cottrell¹, Cindy S. E. Tan¹, Delaney Burnard¹, Hideo Kato¹, David L. Paterson ¹,³ and Patrick N. A. Harris ¹,⁴*

¹Centre for Clinical Research, Faculty of Medicine, The University of Queensland, Royal Brisbane and Women’s Hospital Campus, Brisbane, Australia; ²Infection Management Services, Princess Alexandra Hospital, Brisbane, Australia; ³Department of Infectious Diseases, Royal Brisbane and Women’s Hospital, Brisbane, Australia; ⁴Central Microbiology, Pathology Queensland, Royal Brisbane and Women’s Hospital, Brisbane, Australia

*Corresponding author. E-mail: p.harris@uq.edu.au
@padstamundo, @davidantibiotic

Received 19 April 2022; accepted 8 September 2022

Background: Antimicrobials for bloodstream infections due to ESBL- and AmpC-producing Escherichia coli and Klebsiella pneumoniae are significantly limited due to widespread antimicrobial resistance. Tebipenem, an oral carbapenem, exhibits stability against these resistance mechanisms and may prove an attractive alternative.

Methods: The in vitro susceptibility of tebipenem was assessed against previously whole-genome sequenced ESBL- and AmpC-producing E. coli (274 isolates) and K. pneumoniae (42 isolates) derived from bloodstream infections using broth microdilution testing. Resulting tebipenem MICs were compared with those of other carbapenems previously tested against the isolate collection. Tebipenem activity was also compared against those isolates expressing co-resistance to the common oral antibiotics ciprofloxacin and trimethoprim/sulfamethoxazole.

Results: The tebipenem MIC₉₀ value was found to be 0.03 mg/L for E. coli and 0.125 mg/L for K. pneumoniae. For E. coli, the tebipenem MIC₉₀ value was equivalent to that of meropenem, 2-fold lower than that of doripenem, and 8-fold and 4-fold lower than that of imipenem and ertapenem, respectively. For K. pneumoniae, the tebipenem MIC₉₀ value was 2-fold higher than that of meropenem, equivalent to that of doripenem, and 4-fold and 2-fold lower than that of imipenem and ertapenem, respectively. Tebipenem MICs were also unaffected by the expression of co-resistance to ciprofloxacin and trimethoprim/sulfamethoxazole.

Conclusions: The in vitro activity of tebipenem was unaffected by the production of ESBL and AmpC enzymes. Tebipenem also retained its activity against those isolates expressing co-resistance to ciprofloxacin and trimethoprim/sulfamethoxazole. These findings therefore highlight tebipenem as a potential option for the treatment of invasive MDR infections.

Introduction

Bloodstream infections (BSIs) are a significant source of morbidity and mortality worldwide.¹ Of those that originate from urinary tract infections (UTIs), the most common causative agents of BSIs are the members of the Enterobacterales order, Escherichia coli and Klebsiella pneumoniae.²⁻⁴ The third-generation cephalosporin (3GC) subclass of the β-lactam antimicrobial family has often been preferred for the treatment of infections caused by these organisms but overuse and subsequent selection pressure has led to widespread antimicrobial resistance (AMR) amongst these species towards this versatile class of antibiotics.⁵,⁶

Resistance to 3GCs is primarily conferred via the production of ESBL enzymes, especially the clinically significant CTX-M-type, which is regarded as the most widely disseminated ESBL and whose spread has been broadly attributed to the E. coli lineage.
AmpC-type β-lactamasess also contribute towards 3GC resistance with enzyme production being either plasmid-mediated (pAmpC) or due to the overexpression of the ampC gene. Furthermore, 3GC-resistant E. coli and K. pneumoniae often possess additional genes encoding resistance to multiple other antimicrobials such as fluoroquinolones, aminoglycosides and trimethoprim/sulfamethoxazole, thus resulting in MDR bacteria.

A global increase in the prevalence of 3GC-resistant E. coli and K. pneumoniae has been observed within both nosocomial and community settings over the last two decades and this invites significant concern as it severely limits the availability of treatment options for MDR BSIs. Carbapenems are first-line treatment for infections caused by these organisms as they exhibit the greatest stability towards ESBL- and AmpC-mediated resistance and have been associated with excellent clinical outcomes. Therefore, further additions to this antimicrobial subclass would prove invaluable for the treatment of MDR BSIs.

Tebipenem/pivoxil hydrobromide is an orally bioavailable novel carbapenem prodrug that was approved in Japan in 2009 for paediatric respiratory infections. It was in development by Spero Therapeutics for the treatment of complicated UTIs, including acute pyelonephritis, but a recent re-analysis of the original randomized controlled trial by the US FDA has interrupted its pathway to registration until completion of further clinical studies. Tebipenem—the active conformation of the prodrug tebipenem/pivoxil—possesses potent in vitro activity against 3GC-resistant E. coli and K. pneumoniae but is less active against Pseudomonas aeruginosa. These promising results, together with its convenient oral formulation, therefore highlight the potential for tebipenem as an option for the treatment of uncomplicated episodes of BSIs due to 3GC-resistant E. coli and K. pneumoniae within a community setting. Consequently, tebipenem may also provide an attractive alternative to traditional non-β-lactam oral step-down options such as ciprofloxacin and trimethoprim/sulfamethoxazole, since 3GC-resistant E. coli and K. pneumoniae often exhibit high rates of resistance towards these long-preferred step-down antimicrobials.

However, there is currently a lack of data to support the use of tebipenem for the treatment of BSIs caused by these MDR organisms. Therefore, the primary aim of this study was to assess the in vitro susceptibility to tebipenem of carbapenem-susceptible E. coli and K. pneumoniae derived from BSIs, expressing 3GC resistance conferred by ESBLs, AmpC overexpression or pAmpCs as assessed via molecular characterization. The activity of tebipenem was also compared with those of other commercially available carbapenems. Additionally, the activity of tebipenem against selected strains within the tested collection expressing co-resistance to ciprofloxacin and trimethoprim/sulfamethoxazole was also assessed in order to ascertain the suitability of tebipenem as a potential alternative to these traditional oral options. Although there has been renewed interest in the use of fosfomycin for the treatment of bacteremia due to MDR E. coli, several studies have reported an increased likelihood of treatment failure with regard to K. pneumoniae and, consequently, caution in the use of fosfomycin for such infections.

Materials and methods

Bacterial isolates

Three hundred and sixteen clinical BSIs consisting of E. coli (274 isolates) and K. pneumoniae (42 isolates) expressing phenotypic 3GC resistance and carbapenem (meropenem) susceptibility, acquired between 2014 and 2016 from the MERINO trial, were tested (UTI source = 64%, community-onset infections = 78%). The isolates were sourced from Australia (n = 74), Canada (n = 2), Italy (n = 6), Lebanon (n = 12), New Zealand (n = 19), Saudi Arabia (n = 21), Singapore (n = 116), South Africa (n = 8) and Turkey (n = 38). All isolates were stored in 30% (vol/vol) glycerol stock at −80°C at the University of Queensland Centre for Clinical Research. The identification of bacterial species, 3GC resistance and carbapenem susceptibility had been conducted during the MERINO trial microbiological studies as previously described. Furthermore, isolates had also undergone WGS and in silico analysis as previously described for the characterization of β-lactamase composition (ESBL, overexpressed AmpC, pAmpC). Isolate specific β-lactamase characterization can be found in Table S1, available as Supplementary data at JAC Online.

Antimicrobial susceptibility testing

The in vitro susceptibility of isolates to tebipenem was assessed through MICs obtained via broth microdilution (BMD) testing performed as per the International Organization for Standardization standard 20776-1:2019. Tebipenem (Spero Therapeutics) dry powder was dissolved in deionized water to prepare a 1000 mg/L stock solution, which was further diluted in BBL™ CAMHB (Becton, Dickinson and Company) to achieve eleven doubling dilutions of final concentrations ranging between 0.004 and 4 mg/L (after addition of bacterial inoculum). Concentrations within the selected range were consistent with tebipenem MICs reached by 3GC-resistant E. coli and K. pneumoniae in previous BMD studies.

The dilutions were dispensed into 96-well plates (Thermo Fisher Scientific) using the Hamilton Microlab STAR Liquid Handling system (Hamilton Company). All plates contained both negative and positive control wells. Prepared plates were stored at −80°C and thawed for 2 h prior to use. All isolates were cultured on 5% horse blood agar (Edwards Group) and incubated at 37°C for 18–24 h, prior to the preparation of a 0.5 McFarland solution in 0.9% sterile saline using the direct colony suspension method. The resulting inoculum was further diluted in CAMHB and added to the plates to give a final cell concentration of 5 × 10^5 cfu/mL. All isolates were tested in triplicate.

Quality assurance was performed concurrently for every tested plate in accordance with CLSI M100 guidelines, using the quality control strains E. coli (ATCC 25922), Staphylococcus aureus (ATCC 29213) and P. aeruginosa (ATCC 27853). A purity check and colony count were also performed for both test isolates and quality strains. Inoculated plates were incubated at 35°C for 18–20 h and MIC endpoints were determined visually using the Sensititre™ Manual Viewbox (Thermo Fisher Scientific).

Data analysis

The median from the triplicate set of values for each isolate was selected as the tebipenem MIC.

The MIC_S50 and MIC_S90, which are the MICs at which 50% and 90% of the isolates are inhibited, respectively, were calculated for E. coli and K. pneumoniae isolates separately.

Comparison of tebipenem MICs with those of other carbapenems

Tebipenem MIC_S90 values were compared against the MIC_S90 values of other carbapenems—meropenem, imipenem, doripenem and doripenem carbapenem.
Characterization of tebipenem MICs for isolates expressing co-resistance to ciprofloxacin and trimethoprim/sulfamethoxazole

Tebipenem MICs were categorized according to the expression of co-resistance to the common oral antimicrobials ciprofloxacin and trimethoprim/sulfamethoxazole (Figure 1). A majority of isolates were inhibited at an MIC of 0.03 mg/L and many of them carried co-resistance to both ciprofloxacin and trimethoprim/sulfamethoxazole, followed by ciprofloxacin alone, together with a smaller proportion carrying resistance to trimethoprim/sulfamethoxazole only. Similar grouping patterns were observed at MICs of 0.015, 0.06 and 0.125 mg/L. A number of isolates inhibited at a tebipenem MIC of 0.25 mg/L were resistant to trimethoprim/sulfamethoxazole alone while several expressed co-resistance to both trimethoprim/sulfamethoxazole and ciprofloxacin. Several isolates were susceptible to both antimicrobials.

Discussion

BSIs due to 3GC-resistant E. coli and K. pneumoniae are associated with a high health and economic cost due to the widespread prevalence of AMR towards most agents that are available to combat them. Tebipenem/pivoxil hydrobromide may therefore prove an invaluable addition to the armamentarium as it combines the potent activity of a carbapenem together with a convenient oral formulation. However, there is a noticeable lack of literature regarding the effectiveness of tebipenem against 3GC-resistant E. coli and K. pneumoniae isolated from BSIs, which this study aimed to address.

As expected, tebipenem exhibited excellent activity against all isolates in this study, with MIC90 values of ≤0.125 mg/L for both species tested, thereby confirming the in vitro susceptibility of tebipenem against 3GC-resistant E. coli and K. pneumoniae. Furthermore, as per the tebipenem provisional susceptibility breakpoint of ≤0.125 mg/L generally utilized for Gram-negative organisms, a majority of the isolates in the current study can be regarded as provisionally susceptible, thus demonstrating the stability of tebipenem against hydrolysis by ESBL and AmpC enzymes. A number of isolates (n=3) also exhibited an MIC of 0.25 mg/L (Table S1) but without the availability of established susceptibility breakpoints, it is impossible to make any further interpretations about the clinical significance of these findings.

When the MIC90 values of tebipenem were compared with those of other commercially available carbapenems (Table 1), tebipenem demonstrated equivalent activity to meropenem and 2-fold greater activity than doripenem against E. coli and equivalent activity to doripenem against K. pneumoniae. Tebipenem was also found to exhibit 2-fold lower activity than meropenem against K. pneumoniae but this is most likely due to the availability of a smaller number of K. pneumoniae isolates within the collection for testing, thus resulting in a limited distribution of MICs and, therefore, a higher MIC90 value. The activity of tebipenem was also found to be 4- to 8-fold greater than the activity of ertapenem and imipenem, respectively, against E. coli. Against K. pneumoniae isolates, tebipenem activity was found to be 2- to 4-fold greater than that of ertapenem and imipenem, respectively. A similar trend in activity between the

### Table 1. MICs of tebipenem and comparator carbapenems against 3GC-resistant E. coli and K. pneumoniae

| Antimicrobial | E. coli (mg/L) | K. pneumoniae (mg/L) |
|--------------|---------------|---------------------|
|              | MIC50 | MIC90 | MIC50 | MIC90 | MIC50 | MIC90 |
| Tebipenem    | 0.03  | 0.03  | 0.03  | 0.125 | 0.03  | 0.125 |
| Meropenem    | 0.03  | 0.03  | 0.03  | 0.06  | 0.25  | 0.5   |
| Imipenem     | 0.25  | 0.25  | 0.25  | 0.5   | 0.06  | 0.12  |
| Doripenem    | 0.03  | 0.06  | 0.06  | 0.12  | 0.06  | 0.25  |
| Ertapenem    | 0.03  | 0.12  | 0.06  | 0.25  | 0.06  | 0.25  |
The effectiveness of tebipenem against such resistance mechanisms therefore support its use as a successful form of oral step-down therapy and also as a potential treatment option for non-severe episodes of BSIs due to 3GC-resistant *E. coli* and *K. pneumoniae* within a community setting. BSIs due to such MDR Enterobacterales are known to frequently originate from UTIs, mostly carry the CTX-M-type ESBL and are predominantly caused by ST131 *E. coli*; these distributions were also observed among the MERINO trial isolates, which were primarily derived from community-onset BSIs. In this study, tebipenem exhibited potent activity against these commonly isolated strains and resistance mechanisms, which together with its oral formulation may prove extremely beneficial for community-based treatment. Additionally, the narrower spectrum of activity possessed by tebipenem can be well utilized to treat BSIs acquired in the community where Enterobacterales predominate and infections due to *P. aeruginosa* are rare.

The current study serves to contribute to the growing literature assessing the in vitro activity of tebipenem against 3GC-resistant *E. coli* and *K. pneumoniae* derived from BSIs. It had several strengths—the first of which was the assessment of isolates from nine different countries. Resistance patterns are known to vary between locations, and the inclusion of a sizeable multinational isolate collection enabled the assessment of the effectiveness of tebipenem against a considerable internationally representative sample. Secondly, antimicrobial activity was assessed against numerous AMR genes and the integration of genotypic and phenotypic data enabled the development of a comprehensive picture of the in vitro activity of tebipenem against MDR *E. coli* and *K. pneumoniae*.

However, the study also had several limitations. The number of *K. pneumoniae* isolates was significantly less than that of *E. coli*, and this may have led to a less accurate representation of tebipenem activity against the species. Furthermore, the MICs of the comparator carbapenems were acquired via custom-made Sensititre™ plates, unlike the tebipenem MICs, which were obtained through plates prepared via an in-house liquid-handling system. There was also no determination of the impact of the inoculum effect on the in vitro activity of tebipenem as it was understood as a phenomenon that was less likely to be observed with carbapenems. However, a study reported a decrease in the antibacterial activity of tebipenem against reference *E. coli* and *K. pneumoniae* strains with increasing inoculum size, thus highlighting the need for further study concerning the inoculum effect on tebipenem with regard to clinical isolates.

Nevertheless, the results generated from this study have significant implications for the treatment of BSIs caused by 3GC-resistant Enterobacterales. We managed to confirm the in vitro susceptibility of tebipenem against 3GC-resistant *E. coli* and *K. pneumoniae* thereby providing supporting data towards the introduction of a novel treatment form for MDR BSIs in the form of an oral carbapenem. Such an option can prove to be extremely convenient and cost-effective as the management of such infections outside of a hospital setting can lead to reduced healthcare-associated costs. Furthermore, the introduction of tebipenem/pivoxil hydrobromide into clinical practice can significantly limit the unnecessary prolonged use of IV carbapenems, which may carry risks of thrombophlebitis and vascular access-related infections.

As tebipenem/pivoxil hydrobromide appears to confer a wide range of benefits, the need for future study regarding its effectiveness in humans in addition to further in vitro research is most certainly warranted to support its use within a clinical context.

**Funding**

Tebipenem was kindly provided by Spero Therapeutics, although the company had no role in the study design, data generation or reporting. Otherwise the study was supported by internal funding.
Determining the in vitro susceptibility of tebipenem

Transparency declarations

D.L.P. has received funding from AstraZeneca, Pfizer, Shionogi, Spero Therapeutics, Leo Pharmaceuticals, Bayer, GlaxoSmithKline (GSK), Cubist, Entasis, Sumitomo, Qpx, Venatorx, bioMérieux and Accelerate; reports board membership from Entasis, Qpx, Merck, Shionogi, Achaogen, AstraZeneca, Leo Pharmaceuticals, Bayer, GSK, Cubist, Venatorx, and Accelerate; reports grants/grants pending from Shionogi and Merck; and has received payment for lectures including service on speaker’s bureaus from Pfizer and Merck, outside the submitted work. P.N.A.H. has received research grants from Merck, Sandoz and Shionogi, as well as speaker’s fees from Pfizer and Sandoz and has served on advisory boards for Merck and Sandoz, outside the submitted work. All other authors have no conflicts of interest to declare.

Supplementary data

Table S1 is available as Supplementary data at JAC Online.

References

1 Goto M, Al-Hasan MN. Overall burden of bloodstream infection and nosocomial bloodstream infection in North America and Europe. Clin Microbiol Infect 2013; 19: 501–9. https://doi.org/10.1111/j.1469-0691.2012.12195
2 Diekema DJ, Hsueh P-R, Mendes RE et al. The microbiology of bloodstream infection: 20-year trends from the SENTRY antimicrobial surveillance program. Antimicrob Agents Chemother 2019; 63: e00355-19. https://doi.org/10.1128/AAC.00355-19
3 Søgaard M, Nørgaard M, Dethlefsen C et al. Temporal changes in the incidence and 30-day mortality associated with bacteremia in hospitalized patients from 1992 through 2006: a population-based cohort study. Clin Infect Dis 2011; 52: 61–9. https://doi.org/10.1093/cid/ciq069
4 Wilson J, Elgohari S, Livermore DM et al. Trends among pathogens reported as causing bacteremia in England, 2004–2008. Clin Microbiol Infect 2011; 17: 451–8. https://doi.org/10.1111/j.1469-0691.2010.03262.x
5 Byrne MK, Miellet S, McGlinn A et al. The drivers of antibiotic use and misuse: the development and investigation of a theory driven community measure. BMC Public Health 2019; 19: 1425. https://doi.org/10.1186/s12889-019-7796-8
6 Eyler RF, Shvets K. Clinical pharmacology of antibiotics. Clin J Am Soc Nephrol 2019; 14: 1080–90. https://doi.org/10.2215/CJN.08140718
7 D’Andrea MM, Arena F, Pallecchi L et al. CTX-M-type β-lactamasem: a successful story of antibiotic resistance. Int J Med Microbiol 2013; 303: 305–17. https://doi.org/10.1016/j.ijmm.2013.02.008
8 Dao Y, Iovleva A, Bonomo RA. The ecology of extended-spectrum β-lactamases (ESBLs) in the developed world. J Travel Med 2017; 24: S44–51. https://doi.org/10.1093/jtm/taw102
9 Jacoby GA, Munoz-Price LS. Mechanisms of disease: the new β-lactamases. N Engl J Med 2005; 352: 380–430. https://doi.org/10.1056/NEJMra041359
10 Paterson DL, Bonomo RA. Extended-spectrum β-lactamases: a clinical update. Clin Microbiol Rev 2005; 18: 657–86. https://doi.org/10.1128/CMR.18.4.657-686.2005
11 Bajaj P, Singh NS, Virdi JS. Escherichia coli β-lactamases: what really matters. Front Microbiol 2016; 7: 417. https://doi.org/10.3389/fmicb.2016.00417
12 Harris PNA. Clinical management of infections caused by Enterobacteriaceae that express extended-spectrum β-lactamase and AmpC enzymes. Semin Respir Crit Care Med 2015; 36: 056–73. https://doi.org/10.1055/s-0034-1398387
13 Rawat D, Nair D. Extended-spectrum β-lactamases in gram negative bacteria. J Glob Infect Dis 2010; 2: 263–74. https://doi.org/10.4103/0974-777X.68531
14 Rodríguez-Baño J, Gutiérrez-Gutiérrez B, Machuca I et al. Treatment of infections caused by extended-spectrum-beta-lactamase-, AmpC-, and carbapenemase-producing Enterobacteriaceae. Clin Microbiol Rev 2018; 31: e00079-17. https://doi.org/10.1128/CVR.00079-17
15 Jain A, Utey L, Parr TR et al. Tebipenem, the first oral carbapenem antibiotic. Expert Rev Anti Infect Ther 2018; 16: 513–22. https://doi.org/10.1080/14787210.2018.1496821
16 Eckburg PB, Muir L, Critchley IA et al. Oral tebipenem pivoxil hydrobromide in complicated urinary tract infection. N Engl J Med 2022; 386: 1327–38. https://doi.org/10.1056/NEJMoa2105462
17 Spero Therapeutics. https://www.sperotherapeutics.com/patients/tebipenem-hbr.
18 McEntee L, Johnson A, Farrington N et al. Pharmacodynamics of tebipenem: new options for oral treatment of multidrug-resistant gram-negative infections. Antimicrob Agents Chemother 2019; 63: e00603-19. https://doi.org/10.1128/AAC.00603-19
19 Arends SJR, Rhomberg PR, Cotoroneo N et al. Antimicrobial activity evaluation of tebipenem (SPR859), an orally available carbapenem, against a global set of Enterobacteriaceae isolates, including a challenge set of organisms. Antimicrob Agents Chemother 2019; 63: e02618-18. https://doi.org/10.1128/AAC.02618-18
20 Meje Y, Pigrau C, Fernández-Hidalgo N et al. Non-intravenous carbapenem-sparing antibiotics for definitive treatment of bacteremia due to Enterobacteriaceae producing extended-spectrum β-lactamase (ESBL) or AmpC β-lactamase: a propensity score study. Int J Antimicrob Agents 2019; 54: 189–96. https://doi.org/10.1016/j.ijantimicag.2019.05.004
21 Gutiérrez-Gutiérrez B, Rodríguez-Baño J. Current options for the treatment of infections due to extended-spectrum beta-lactamase-producing Enterobacteriaceae in different groups of patients. Clin Microbiol Infect 2019; 25: 932–42. https://doi.org/10.1016/j.cmi.2019.03.030
22 Ibrahim ME, Abbas M, Al-Shahrai AM et al. Phenotypic characterization and antibiotic resistance patterns of extended-spectrum β-lactamase- and Ampc β-lactamase-producing Gram-negative bacteria in a referral hospital, Saudi Arabia. Can J Infect Dis Med Microbiol 2019; 2019: 6056494–9. https://doi.org/10.1155/2019/6056494
23 Sojo-Dorado J, López-Hernández I, Rosso-Fernández C et al. Effectiveness of fosfomycin for the treatment of multidrug-resistant Escherichia coli bacteremic urinary tract infections: a randomized clinical trial. JAMA Netw Open 2022; 5: e2137277. https://doi.org/10.1001/jamanetworkopen.2021.37277
24 Zhanel GG, Zhanel MA, Karlowsky JA. Oral and intravenous fosfomycin for the treatment of complicated urinary tract infections. Can J Infect Dis Med Microbiol 2020; 2020: 8513405. https://doi.org/10.1155/2020/8513405
25 Abbott LJ, van Gorp E, Wyres KL et al. Fosfomycin activity against Klebsiella pneumoniae in a dynamic bladder infection model. J Antimicrob Chemother 2022; 77: 1324–33. https://doi.org/10.1093/jac/dkac045
26 Harris PNA, Tambyah PA, Lye DC et al. Effect of piperacillin-tazobactam vs meropenem on 30-day mortality for patients with E coli or Klebsiella pneumoniae bloodstream infection and ceftiraxone resistance: a randomized clinical trial. JAMA 2018; 320: 984–94. https://doi.org/10.1001/jama.2018.12163
27 International Organization for Standardization. Susceptibility testing of infectious agents and evaluation of performance of antimicrobial susceptibility test devices—Part 1: Broth micro-dilution reference method for testing the in vitro activity of antimicrobial agents against.
rapidly growing aerobic bacteria involved in infectious diseases: ISO 20776-1. 2019.

28 Cotroneo N, Rubio A, Critchley IA et al. In vitro and in vivo characterization of tebipenem, an oral carbapenem. Antimicrob Agents Chemother 2020; 64: e02240-19. https://doi.org/10.1128/AAC.02240-19

29 CLSI. Performance Standards for Antimicrobial Susceptibility Testing—Thirtieth Edition: M100. 2020.

30 R Development Core Team. R Foundation for Statistical Computing. https://www.r-project.org/.

31 Wickham H. ggplot2: Elegant Graphics for Data Analysis. https://ggplot2.tidyverse.org.

32 Critchley IA, Cotroneo NS, Pucci MJ et al. 1695. Tebipenem: an oral carbapenem with activity against multi-drug resistant urinary tract infection isolates of Escherichia coli collected from US medical centers during 2019. Open Forum Infect Dis 2020; 7: S831. https://doi.org/10.1093/ofid/ofaa439.1873

33 Gerges B, Rosenblatt J, Hachem RY et al. 1069. In vitro activity of tebipenem against clinically significant gram-negative bacteria isolated from patients with cancer. Open Forum Infect Dis 2021; 8: S627. https://doi.org/10.1093/ofid/ofab466.1263

34 Livermore DM, Sefton AM, Scott GM. Properties and potential of ertapenem. J Antimicrob Chemother 2003; 52: 331–44. https://doi.org/10.1093/jac/dkg375

35 Livermore DM, Pearson A. Antibiotic resistance: location, location, location. Clin Microbiol Infect 2007; 13: 7–16. https://doi.org/10.1111/j.1469-0691.2007.01724.x

36 Lenhard JR, Balman ZP. Inoculum effect of β-lactam antibiotics. J Antimicrob Chemother 2019; 74: 2825–43. https://doi.org/10.1093/jac/dkz226