Ceftolozane + tazobactam

Section: 6. Anti-infective medicines > 6.2. Antibacterials > 6.2.3. Reserve group antibiotics

EMLc | ATC codes: J01DI54

Indication	Carbapenem-resistant Pseudomonas aeruginosa ICD11 code: MG50.80
INN	Ceftolozane + tazobactam
Medicine type	Chemical agent
Antibiotic groups	R RESERVE
List type	Complementary
Formulations	**Parenteral > General injections > IV:** 1 g + 0.5 g powder for injection
EML status history	Application rejected in 2019 (TRS 1021) Added in 2023 (TRS 1049)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Main patent is active in several jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Read more about patents.
Wikipedia	Ceftolozane + tazobactam
DrugBank	Ceftolozane, Tazobactam

Expert Committee recommendation

The Expert Committee recognized the global health importance of effective new treatments for infections caused by multidrug-resistant pathogens, especially those designated as critical priority on the WHO priority pathogens list, for which few effective treatment options exist or are in development. The Committee noted that clinical trial evidence for efficacy of ceftolozane + tazobactam against carbapenem-resistant P. aeruginosa and Enterobacterales specifically was positive, albeit limited, and that the medicine had shown good activity against carbapenem-resistant P. aeruginosa in in vitro studies. The Committee considered that data presented from observational studies also supported the efficacy of ceftolozane + tazobactam in the treatment of infections caused by drug-resistant P. aeruginosa. The Committee noted no serious safety or tolerability concerns associated with ceftolozane + tazobactam, in both adult and paediatric patients. Overall, the Committee considered that the availability of carbapenem-sparing alternatives for treatment of drug-resistant P. aeruginosa was important as part of the strategy to limit and prevent further emergence and spread of carbapenem-resistant organisms. The Committee noted the higher price of ceftolozane + tazobactam compared with other antibiotics, but also that it had generally been found to be acceptably cost-effective in high-income settings. Given the seriousness of infections due to carbapenem-resistant P. aeruginosa, particularly hospital-acquired and ventilator-associated pneumonia, and the limited number of effective treatment options available, the Committee considered that inclusion of ceftolozane + tazobactam on the Model Lists was sufficiently justified. The Expert Committee therefore recommended the addition of ceftolozane + tazobactam as a reserve group antibiotic on the

complementary list of the EML and EMLc for the treatment of infections caused or suspected to be caused by carbapenem-resistant P. aeruginosa. The Committee also emphasized the importance of associated stewardship activities to ensure its appropriate use.

Background

Ceftolozane + tazobactam was previously considered for inclusion on the EML for treatment of infections due to carbapenem-resistant Pseudomonas aeruginosa. Inclusion was not recommended at the time, with the Expert Committee noting that although ceftolozane + tazobactam was active against some strains of carbapenem-resistant P. aeruginosa, it lacked activity against carbapenemase-producing Enterobacteriaceae, which is more prevalent in the community and represents a greater public health threat (1).

Public health relevance

According to data from the United States Centers for Disease Control and Prevention, from 2015 to 2017, Escherichia coli, Klebsiella pneumoniae and P. aeruginosa represented over 30% of all pathogens associated with health care-associated infections in US hospitals (2). A recent study estimated that drug-resistant E. coli, K. pneumoniae, and P. aeruginosa were directly responsible for almost 500 000 deaths globally in 2019 (3). Rates of resistance of these pathogens to carbapenems and third-generation cephalosporins show wide global variability. For example, resistance of P. aeruginosa to carbapenems is reported to range from 8% in Australia and the United Kingdom, to 30% in India and South Africa, to 87% in Belarus (4). In 2017, WHO designated carbapenem-resistant P. aeruginosa and carbapenem-resistant and third-generation cephalosporin-resistant Enterobacterales critical priority pathogens in need of new therapeutic options (5).

Benefits

The applicants conducted a comprehensive review of the available evidence for ceftolozane + tazobactam. A summary of the included evidence published since the 2019 EML application is reported below. A summary of the evidence considered in the 2019 application is reported in the technical report of the 2019 Expert Committee meeting (1). Randomized clinical trials ASPECT-NP was a randomized, double-blind, non-inferiority, phase III trial assessing the efficacy and safety of ceftolozane + tazobactam (3 g every 8 hours) compared with meropenem (1 g every 8 hours) for the treatment of adults with Gram-negative nosocomial pneumonia – ventilated hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) (6). Antibiotic treatment was given for 8–14 days. The primary efficacy endpoint was all-cause mortality at day 28 in the intention-to-treat population. Mortality at 28 days was 24.0% in the ceftolozane + tazobactam group and 25.3% in the meropenem group with a weighted treatment difference of 1.1% (95% confidence interval (CI) –5.1% to 7.4%). Ceftolozane + tazobactam met the criteria for non-inferiority to meropenem with a prespecified 10% margin. In the VAP subgroup, 28-day mortality was 24% in the ceftolozane + tazobactam group and 20.3% in the meropenem group with a weighted treatment difference of –3.6% (95% CI –10.7% to 3.5%). Of note, the lower limit of the 95% CI included the 10% non-inferiority margin (i.e. results inconclusive), but the authors stated that this analysis was not powered for non-inferiority testing. The key secondary endpoint was clinical response 7–14 days after the end of therapy. Clinical cure was achieved in 54% of patients in the ceftolozane + tazobactam group and 53% in the meropenem group with a weighted treatment difference of 1.1% (95% CI –6.2% to 8.3%) demonstrating non-inferiority of ceftolozane + tazobactam with a prespecified 12.5% margin. A substudy of the ASPECT-NP trial investigated the emergence of non-susceptibility and found that all 59 isolates that were susceptible to ceftolozane + tazobactam at baseline remained susceptible, while 22.4% (13/58) of those initially susceptible to meropenem became resistant during treatment (7). A randomized, single-centre, open-label trial compared the efficacy and safety of ceftolozane + tazobactam (1.5 g every 8 hours plus vancomycin, daptomycin or linezolid) with standard of care (cefepime, piperacillin + tazobactam or meropenem plus vancomycin, daptomycin or linezolid) for the empiric treatment of febrile neutropenia in 100 adults with haematological malignancies (8). The duration of treatment was between 3 and 14 days. The primary efficacy endpoint was favourable clinical response at the end of intravenous treatment in the modified intention-to-treat population. The non-inferiority margin for the primary outcome was 10%. At the end of intravenous treatment, the proportion of patients with a favourable clinical response was higher in the

ceftolozane + tazobactam group than the standard of care group (87% versus 72%, P = 0.1). From the 1-sided non-inferiority analysis, non-inferiority of ceftolozane + tazobactam was concluded because the lower limit of the 95% CI for favourable clinical response was –1.4% (i.e. it did not cross the prespecified –10% non-inferiority margin). All-cause 30-day mortality was 4% in both treatment groups with no deaths attributed to the infection. Observational studies A retrospective study using data collected from 20 hospitals in the United States investigated outcomes in 205 patients who received ceftolozane + tazobactam for the treatment of multidrug-resistant P. aeruginosa infections from any source (pneumonia in 59% of cases) (9). The primary outcome was 30-day and inpatient mortality. Secondary outcomes were clinical success and microbiological cure. Death occurred in 39 patients (19.0%), clinical success in 151 (73.7%) and microbiological cure in 145 (70.7%). Of note the median time from culture collection to treatment initiation was 9 days. Commencement of treatment with ceftolozane + tazobactam more than 4 days after culture collection was associated with worse outcomes in the multivariable analysis (odds ratio (OR) 5.5, 95% CI 2.1 to 14.4) although a causative association cannot be assumed. High doses of ceftolozane + tazobactam (3 g every 8 hours) were used in 47.3% of patients. Another retrospective study reported outcomes in 101 adult patients with severe P. aeruginosa infections from any source (pneumonia in 31.7% of cases) treated with ceftolozane + tazobactam in 22 hospitals across Italy (10). Just over half (52.5%) of the patients were infected with an extensively drug-resistant or pandrug-resistant isolate, 17.8% with a multidrug-resistant isolate and 29.7% were classified as non-multidrug-resistant. The primary outcome was clinical success at the end of treatment which occurred in 83.2% of cases – 77.7% of cases with multidrug-resistant infections, 81.1% with extensively drug-resistant or pandrug-resistant infections, and 90% with non-multidrug-resistant infections. Predictive factors for clinical failure included sepsis (OR 3.02, P = 0.05) and continuous renal replacement therapy (OR 4.50, P = 0.02). High doses of ceftolozane + tazobactam (3 g every 8 hours) were used in 65.6% of patients. A case–control study in Spain compared patients with haematological malignancy and P. aeruginosa infection treated with ceftolozane + tazobactam (19 cases) or other antibiotics (38 controls) (11). A higher proportion of cases than controls had neutropenia (63.2% versus 52.6%) and were infected with extensively drug-resistant pathogens (47.4% versus 21.1%). Patients treated with ceftolozane + tazobactam had higher clinical success rates than controls (89.5% versus 71.1%) and lower mortality (5.3% versus 28.9%). Another retrospective, multicentre observational cohort study compared ceftolozane + tazobactam with treatment with either polymyxins or aminoglycosides-based regimens for infections due to drug-resistant P. aeruginosa (12). Baseline characteristics were similar between the two groups and the outcomes assessed were clinical cure, acute kidney injury and in-hospital mortality. Clinical cure was 81% in the ceftolozane + tazobactam group and 61% in the comparator group. In-hospital mortality was 20% with ceftolozane + tazobactam and 25% in the comparator group. The development of acute kidney injury occurred in 6% of patients treated with ceftolozane + tazobactam and 34% of patients in the comparator group. After adjusting for differences between groups, treatment with ceftolozane + tazobactam was independently associated with clinical cure (adjusted OR 2.63, 95% CI 1.31 to 5.30) and protection against acute kidney injury (adjusted OR 0.08, 95% CI 0.03 to 0.22). No difference between the groups was seen for in-hospital mortality. The ZENITH study was a matched case–control study that compared ceftolozane + tazobactam with other antibiotics with anti-pseudomonas activity for the treatment of bloodstream infections due to P. aeruginosa in neutropenic haematological patients (13). Matching was done on the multidrug-resistance profile of the P. aeruginosa isolate, closest date of bloodstream infection, underlying disease and polymicrobial infection. A total of 44 cases (treated with ceftolozane + tazobactam as empiric and/or targeted therapy) and 88 controls (treated with other antibiotic regimens) were analysed. Among the cases, 91% of infections were caused by multidrug-resistant P. aeruginosa. The primary endpoints were 7- and 30-day case fatality rates. At both time points, the case fatality rate was lower in the ceftolozane + tazobactam group (day 7: 6.8% versus 34.1%; day 30: 22.7 % versus 48.9%). After adjusting for potential confounders, the odds of dying from the Pseudomonas infection were lower in the ceftolozane + tazobactam group compared with the control group both at day 7 (adjusted OR 0.16, 95% CI 0.04 to 0.58) and day 30 (adjusted OR 0.19, 95% CI 0.07 to 0.55).

Harms

The application reported that among patients in the randomized trials, ceftolozane + tazobactam was generally

well tolerated and the overall safety profile and tolerability were similar to the comparator in the ASPECT-cUTI (14), ASPECT-cIAI (15) and ASPECT-NP (6) trials. The safety results of the ASPECT-NP trial are reported below. Safety results from ASPECT-cUTI and ASPECT-cIAI trials considered by the Expert Committee were previously reported in 2019 (1). In ASPECT-NP, the incidence of treatment-emergent and severe adverse events, discontinuation due to adverse events, and death were comparable between treatment groups (6). Overall, 11% of patients in the ceftolozane + tazobactam group experienced at least one treatment-related adverse event compared with 8% in the meropenem group. The most frequently reported treatment-related adverse events in the ceftolozane + tazobactam group were liver function test abnormalities, Clostridioides difficile colitis and diarrhoea. The most common treatment-emergent adverse events were anaemia, urinary tract infections, diarrhoea and decubitus ulcers (16). The proportion of severe treatment-related events was the same in both groups (1%) as was the proportion of treatment-related adverse events leading to drug discontinuation (1% in both groups). No treatment-related adverse event resulted in death (6). The application presented safety data for ceftolozane + tazobactam in the paediatric population. Two randomized, double-blind, phase II trials compared ceftolozane + tazobactam and meropenem in treatment of paediatric patients with complicated urinary tract infections (17) and intra-abdominal infections (18). In the trial including patients with complicated urinary tract infections, 133 children were included and the proportion of patients with treatment-related adverse events was similar in the two groups (14.0% with ceftolozane + tazobactam versus 15.2% with meropenem) with no serious treatment-related adverse events. In the trial including patients with complicated intra-abdominal infections, 91 patients were included and the proportion of treatment-related adverse events was higher with ceftolozane + tazobactam (plus metronidazole) than with meropenem (18.6% versus 14.3%). Overall adverse events were also higher in the ceftolozane + tazobactam group (80.0% versus 61.9%).

Additional evidence

The ASPIRE-ICU team recently published a study where resistance to ceftolozane + tazobactam in P. aeruginosa isolates from mechanically ventilated patients in the intensive care unit was 23.4% (19). In the study, 723 isolates obtained from respiratory samples or perirectal swabs from 402 patients in 11 European countries were analysed.

Cost / cost effectiveness

A cost–effectiveness analysis was performed comparing ceftolozane + tazobactam to meropenem to treat hospital-acquired pneumonia and ventilator-associated pneumonia in Italy (22). Cost–effectiveness of both empiric and targeted use were analysed. The study concluded that ceftolozane + tazobactam was cost-effective compared with meropenem with an incremental cost–effectiveness ratio (ICER) of €1913 to €2203 (for empiric treatment) and €6163 to €6597 (for targeted treatment) per quality-adjusted life year (QALY) gained. The same comparison was done from the perspective of the US health care sector (23) and showed that in the confirmed treatment setting, the ICER for ceftolozane + tazobactam compared with meropenem for the treatment of ventilated hospital-acquired pneumonia or ventilator-associated pneumonia was US$ 12 126 per QALY. The ICER decreased to US$ 4775 per QALY when used early (before susceptibility results). A cost–effectiveness analysis compared ceftolozane + tazobactam with piperacillin + tazobactam for the empiric treatment of complicated urinary tract infection in Taiwan, China (24). Empiric use of ceftolozane + tazobactam resulted in higher total costs per patient compared with piperacillin + tazobactam (US$ 4199 versus US$ 3594) but a higher gain in QALYs (4.80 versus 4.78 QALYs). The additional cost per discounted QALY gained associated with the empiric use of ceftolozane + tazobactam was US$ 32 521. The same comparison was done from the perspective of the United States health care sector (25), and showed that treatment with ceftolozane + tazobactam had higher costs than piperacillin + tazobactam (US$ 36 413 versus US$ 36 028), a higher QALY gained (9.19 versus 9.13 QALY) and an ICER of US$ 6128/QALY. The authors concluded that ceftolozane + tazobactam remained cost-effective at a willingness to pay of US$ 100 000 per QALY compared with piperacillin + tazobactam. Another cost–effectiveness analysis compared ceftolozane + tazobactam (plus metronidazole) with piperacillin + tazobactam for the empiric treatment of patients with nosocomial complicated intra-abdominal infections at risk of infection with resistant pathogens (26). The authors concluded that based on national antimicrobial resistance surveillance data in the United States, ceftolozane + tazobactam with metronidazole was associated with lower costs per patient compared to

piperacillin + tazobactam (US$ 44 226 versus US$ 44 811) and a higher QALY gain (12.85 versus 12.70 QALYs). They concluded that ceftolozane + tazobactam was more likely to be an appropriate empiric therapy for complicated intra-abdominal infections in the US. The same comparison was done in the United Kingdom, which showed that ceftolozane + tazobactam (plus metronidazole) was cost-effective compared with piperacillin + tazobactam with an ICER of £4350 per QALY and 0.36 hospitalization days saved per patient (27). Treatment with ceftolozane + tazobactam was associated with higher costs per patient compared with piperacillin + tazobactam (£2576 versus £2168) and a higher QALY gain (14.31 versus 14.21).

WHO guidelines

Ceftolozane + tazobactam is not currently included in existing WHO guidelines. The Infectious Diseases Society of America guidelines (20) and the European Society of Clinical Microbiology and Infectious Diseases guidelines (21) include ceftolozane + tazobactam as a preferred treatment option for drug resistant P. aeruginosa infections. In particular, the US guidelines recommend it for difficult-to-treat Pseudomonas infections and as a reasonable alternative for moderate-to-severe infections caused by carbapenem-resistant Pseudomonas susceptible to traditional β-lactams (20). The European Society of Clinical Microbiology and Infectious Diseases guidelines recommend ceftolozane + tazobactam for difficult-to-treat carbapenem-resistant P. aeruginosa, if active in vitro (21).

Availability

Ceftolozane + tazobactam is manufactured by Merck, Sharp & Dohme and has regulatory approval from the United States Food and Drug Administration and the European Medicines Agency. It is currently available in 27 European countries, 17 Asian countries and nine countries in the Americas. In Africa, it is only available in Egypt and South Africa. It is also available in Australia and New Zealand.

Other considerations

The Global Coordination and Partnership department within the Antimicrobial Resistance division reviewed the application and advised that it supported the inclusion of ceftolozane + tazobactam on the Model Lists as a reserve group antibiotic. The technical department stressed that the use of ceftolozane + tazobactam must always be informed by evidence-based guidance and strong stewardship activities, and that access and affordability of the medicine must be considered, particularly for patients in low- and middle-income countries. The EML Antimicrobial Working Group reviewed the application and advised that it supported the inclusion of ceftolozane + tazobactam on the EML and EMLc as reserve antibiotic for the treatment of infections caused or suspected to be caused by carbapenem-resistant P. aeruginosa, but emphasized the importance of associated stewardship interventions to ensure its appropriate use. The Working Group highlighted that ceftolozane + tazobactam has particularly high activity against carbapenem-resistant P. aeruginosa, a critical priority pathogen on the WHO priority pathogens list, which in some settings is a common cause of severe pneumonia in ventilated patients in intensive care, including patients with coronavirus disease 2019 (COVID-19). The Working Group noted that clinical trial and observational data suggest that ceftolozane + tazobactam is as effective in patients with nosocomial pneumonia as other commonly used older antibiotics. However, high levels of resistance to the most widely used antibiotics in high-risk settings are increasingly common and alternative antibiotics are needed to provide wider treatment options. The Working Group also noted that ceftolozane + tazobactam was generally well tolerated, with no specific safety concerns. Published phase I pharmacokinetic and phase II safety studies also support the safety of ceftolozane + tazobactam in paediatric patients (28,29). The Working Group commented that ceftolozane + tazobactam was notably more expensive than other antibiotics for which generics are available. The primary patent is due to expire in 2023, but secondary patents will be active until 2035. The Working Group also noted that limited cost–effectiveness data were available from low- and middle-income settings.

1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2019 (including the 21st WHO Model List of Essential Medicines and the 7th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2019 (WHO Technical Report Series, No. 1021; https://apps.who.int/iris/handle/10665/330668,

accessed 6 October 2023).
2. Weiner-Lastinger LM, Abner S, Edwards JR, Kallen AJ, Karlsson M, Magill SS, et al. Antimicrobial-resistant pathogens associated with adult healthcare-associated infections: summary of data reported to the National Healthcare Safety Network, 2015-2017. Infect Control Hosp Epidemiol. 2020;41(1):1–18.
3. Murray CJL, Ikuta KS, Sharara F, Swetschinski L, Aguilar GR, Gray A, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet. 2022;399(10325):629–55.
4. Onehealthtrust. Resistancemap: Antibiotic resistance. Washington, DC: Center for Disease Dynamics, Economics & Policy; 2023 (https://resistancemap.onehealthtrust.org/antibioticresistance.php, accessed 6 October 2023).
5. Prioritization of pathogens to guide discovery, research and development of new antibiotics for drug-resistant bacterial infections, including tuberculosis. Geneva: World Health Organization; 2017 (https://apps.who.int/iris/handle/10665/311820, accessed 6 October 2023).
6. Kollef MH, Nováček M, Kivistik Ü, Réa-Neto Á, Shime N, Martin-Loeches I, et al. Ceftolozane-tazobactam versus meropenem for treatment of nosocomial pneumonia (ASPECT-NP): a randomised, controlled, double-blind, phase 3, non-inferiority trial. Lancet Infect Dis. 2019;19(12):1299–311.
7. Johnson MG, Bruno C, Castanheira M, Yu B, Huntington JA, Carmelitano P, et al. Evaluating the emergence of nonsusceptibility among Pseudomonas aeruginosa respiratory isolates from a phase-3 clinical trial for treatment of nosocomial pneumonia (ASPECT-NP). Int J Antimicrob Agents. 2021;57(3):106278.
8. Chaftari AM, Hachem R, Malek AE, Mulanovich VE, Szvalb AD, Jiang Y, et al. A Prospective randomized study comparing ceftolozane/tazobactam to standard of care in the management of neutropenia and fever in patients with hematological malignancies. Open Forum Infect Dis. 2022;9(6):ofac079.
9. Gallagher JC, Satlin MJ, Elabor A, Saraiya N, mccreary EK, Molnar E, et al. Ceftolozane-tazobactam for the treatment of multidrug-resistant Pseudomonas aeruginosa infections: a multicenter study. Open Forum Infect Dis. 2018;5(11):ofy280.
10. Bassetti M, Castaldo N, Cattelan A, Mussini C, Righi E, Tascini C, et al. Ceftolozane/tazobactam for the treatment of serious P. Aeruginosa infections: a multicenter nationwide clinical experience. Int J Antimicrob Agents. 2019;53(4):408–15.
11. Fernández-Cruz A, Alba N, Semiglia-Chong MA, Padilla B, Rodríguez-Macías G, Kwon M, et al. A case-control study of real-life experience with ceftolozane-tazobactam in patients with hematologic malignancy and Pseudomonas aeruginosa infection. Antimicrob Agents Chemother. 2019;63(2):e02340-18.
12. Pogue JM, Kaye KS, Veve MP, Patel TS, Gerlach AT, Davis SL, et al. Ceftolozane/tazobactam vs polymyxin or aminoglycoside-based regimens for the treatment of drug-resistant Pseudomonas aeruginosa. Clin Infect Dis. 2020;71(2):304–10.
13. Bergas A, Albasanz-Puig A, Fernández-Cruz A, Machado M, Novo A, van Duin D, et al. Real-life use of ceftolozane/tazobactam for the treatment of bloodstream infection due to Pseudomonas aeruginosa in neutropenic hematologic patients: a matched control study (ZENITH Study). Microbiol Spectr. 2022;10(3):e0229221.
14. Wagenlehner FM, Umeh O, Steenbergen J, Yuan G, Darouiche RO. Ceftolozane-tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infections, including pyelonephritis: a randomised, double-blind, phase 3 trial (ASPECT-cuti). Lancet. 2015;385(9981):1949–56.
15. Solomkin J, Hershberger E, Miller B, Popejoy M, Friedland I, Steenbergen J, et al. Ceftolozane/tazobactam plus metronidazole for complicated intra-abdominal infections in an era of multidrug resistance: results from a randomized, double-blind, phase 3 trial (ASPECT-ciai). Clin Infect Dis. 2015;60(10):1462–71.
16. Data on file: ASPECT-NP clinical study report. New York, NY: Merck & Co; 2018.
17. MK-7625A versus meropenem in pediatric participants with complicated urinary tract infection (cuti) (MK-7625A-034). Bethesda, MD: US National Library of Medicine; 2023 (clinicaltrials.gov identifier: NCT03230838; https://www.clinicaltrials.gov/study/NCT03230838, accessed 6 October 2023).
18. MK-7625A plus metronidazole versus meropenem in pediatric participants with complicated intra-abdominal infection (ciai) (MK-7625A-035). Bethesda, MD: US National Library of Medicine; 2023 (clinicaltrials.gov Identifier: NCT03217136; https://www.clinicaltrials.gov/study/NCT03217136, accessed 6 October 2023).
19. Torrens G, van der Schalk TE, Cortes-Lara S, Timbermont L, Del Barrio-Tofiño E, Xavier BB, et al. Susceptibility profiles and resistance genomics of Pseudomonas aeruginosa isolates from European icus participating in the ASPIRE-ICU trial. J Antimicrob Chemother. 2022;77(7):1862–72.
20. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America 2022 guidance on the treatment of extended-spectrum β-lactamase producing enterobacterales (ESBL-E), carbapenem-resistant enterobacterales (CRE), and Pseudomonas aeruginosa with difficult-to-treat resistance (DTR-P. Aeruginosa). Clin Infect Dis. 2022;75(2):187–212.
21. Paul M, Carrara E, Retamar P, Tängdén T, Bitterman R, Bonomo RA, et al. European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European Society of Intensive Care Medicine). Clin Microbiol Infect. 2022;28(4):521–47.
22. Mennini FS, Paoletti M, Bini C, Marcellusi A, Falcone M, Andreoni M. Cost-utility analysis of ceftolozane/tazobactam vs meropenem in patients with hospital-acquired pneumonia (HABP) or ventilator-associated pneumonia (VABP). Glob Regl Health Technol Assess. 2022;9(1):45–57.
23. Naik J, Puzniak L, Critchlow S, Elsea D, Dillon RJ, Yang J. Cost effectiveness of ceftolozane/tazobactam compared with meropenem for the treatment of patients with ventilated hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia.
Infect Dis Ther. 2021;10(2):939–54.
24. Chen GJ, Pan SC, Foo J, Morel C, Chen WT, Wang JT. Comparing ceftolozane/tazobactam versus piperacillin/tazobactam as empiric therapy for complicated urinary tract infection in Taiwan: a cost-utility model focusing on gram-negative bacteria. J Microbiol Immunol Infect. 2019;52(5):807–15.
25. Kauf TL, Prabhu VS, Medic G, Borse RH, Miller B, Gaultney J, et al. Cost-effectiveness of ceftolozane/tazobactam compared with piperacillin/tazobactam as empiric therapy based on the in-vitro surveillance of bacterial isolates in the United States for the treatment of complicated urinary tract infections. BMC Infect Dis. 2017;17(1):314.
26. Prabhu VS, Solomkin JS, Medic G, Foo J, Borse RH, Kauf T, et al. Cost-effectiveness of ceftolozane/tazobactam pl

us metronidazole versus piperacillin/tazobactam as initial empiric therapy for the treatment of complicated intra-abdominal infections based on pathogen distributions drawn from national surveillance data in the United States. Antimicrob Resist Infect Control. 2017;6:107.
27. Prabhu V, Foo J, Ahir H, Sarpong E, Merchant S. Cost-effectiveness of ceftolozane/tazobactam plus metronidazole compared with piperacillin/tazobactam as empiric therapy for the treatment of complicated intra-abdominal infections based on the in-vitro surveillance of bacterial isolates in the UK. J Med Econ. 2017;20(8):840–9.
28. Bradley JS, Ang JY, Arrieta AC, Larson KB, Rizk ML, Caro L, et al. Pharmacokinetics and safety of single intravenous doses of ceftolozane/tazobactam in children with proven or suspected gram-negative infection. Pediatr Infect Dis J. 2018;37(11):1130–6.
29. Roilides E, Ashouri N, Bradley JS, Johnson MG, Lonchar J, Su FH, et al. Safety and efficacy of ceftolozane/tazobactam versus meropenem in neonates and children with complicated urinary tract infection, including pyelonephritis: a phase 2, randomized clinical trial. Pediatr Infect Dis J. 2023;42(4):292–8.

