


Imipenem + cilastatin + relebactam

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

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

ATC codes: J01DH56

Indication	Carbapenem-resistant <i>Pseudomonas aeruginosa</i>	ICD11 code: MG50.80
INN	Imipenem + cilastatin + relebactam	
Medicine type	Chemical agent	
Antibiotic groups	 RESERVE	
List type	Complementary	
Formulations	Parenteral > General injections > IV: 500 mg (as monohydrate) + 500 mg (as sodium) + 250 mg (as monohydrate) powder for injection	
EML status history	Application rejected in 2023 (TRS 1049) Application rejected in 2025 (TRS 1064)	
Sex	All	
Age	Adolescents and adults	
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	Imipenem + cilastatin + relebactam	
DrugBank	Imipenem , Cilastatin , Relebactam	

Expert Committee recommendation

The Expert Committee acknowledged that antimicrobial resistance remains a critical global health threat, disproportionately affecting low- and middle-income countries. The Committee recognized the increasing mortality associated with carbapenem-resistant gram-negative bacterial infections. The Committee noted that imipenem + cilastatin + relebactam has in vitro activity against most carbapenemase-producing Enterobacterales, excluding metallo-beta-lactamase producers and OXA-48-like enzymes. The Committee also noted that imipenem + cilastatin + relebactam has in vitro activity against *P. aeruginosa*, including some isolates resistant to other beta-lactam/beta-lactamase inhibitor combinations. The Committee recalled the decision of the 2023 Expert Committee not to recommend the inclusion of imipenem + cilastatin + relebactam on the EML due to its lack of in vitro activity against metallo-beta-lactamase-producing carbapenemase-producing Enterobacterales, the inclusion of other Reserve antibiotics with a similar mechanism of action and spectrum of activity on the EML, limited clinical evidence and high price. In consideration of the clinical evidence presented in the current application, the Committee noted that no new randomized trials to those presented in the previous application were available. The Committee noted new evidence from observational studies and acknowledged the potential role of imipenem + cilastatin + relebactam in treating multidrug-resistant and extensively drug-resistant *P. aeruginosa* infections. However, the Committee noted that these studies were small, all conducted in the United States and most were published only as conference abstracts. Therefore, the Committee concluded that high-quality clinical data for imipenem + cilastatin + relebactam remained limited. The Committee appreciated and considered the reviews of the application by

the TAG-AWwRe and the WHO technical unit, noting the different conclusions. Overall, the Committee concluded that there was insufficient new high-quality evidence to justify revising the 2023 Expert Committee's conclusions. Therefore, the Expert Committee did not recommended the inclusion of imipenem + cilastatin + relebactam for the treatment of infections caused by multidrug-resistant organisms for the same reasons as given by the previous Expert Committee: imipenem + cilastatin + relebactam lacks in vitro activity against the carbapenemase genotypes most commonly associated with carbapenem resistance in Enterobacterales globally, other Reserve antibiotics with a similar spectrum of activity are already included on the Model Lists. The Committee advised that future evaluation of an application for inclusion of imipenem + cilastatin + relebactam on the Model List could be considered following any changes to the definition of the AWwRe Reserve category arising from the planned revision of AWwRe definitions.

Background

An application for the inclusion of imipenem + cilastatin + relebactam on the EML was evaluated by the Expert Committee in 2023. The 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 imipenem + cilastatin + relebactam has broad in vitro activity against multidrug-resistant gram-negative pathogen but lacked in vitro activity against the carbapenemase genotypes most commonly associated with carbapenem resistance in Enterobacterales globally. The Committee also noted that other Reserve antibiotic options which have a similar spectrum of activity were already included on the EML for treatment of other types of carbapenem resistance in Enterobacterales (e.g. cefiderocol, ceftazidime + avibactam and meropenem + vaborbactam). The Committee considered that the available clinical trial evidence for efficacy was generally positive, although limited, and noted that no serious safety or tolerability concerns were identified. The Committee also noted the high price of the medicine compared with older antibiotics, but also that it had been found to be acceptably cost-effective at willingness-to-pay thresholds in high-income settings. Based on these considerations, the Expert Committee did not recommend listing at that time (1).

Public health relevance

Antimicrobial resistance is identified by WHO as one of the foremost global public health and developmental threats. Efforts to combat antimicrobial resistance, such as guaranteeing universal access to appropriate treatment options, are widely acknowledged as a critical public health priority (2). A 2019 analysis estimated that 4.95 million people died with drug-resistant bacterial infections in 2019. Of these deaths, 1.27 million were directly attributable to resistant infections, most of which occurred in low- and middle-income countries. Drug resistant *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Escherichia coli* were responsible for 84 600, 193 000 and 219 000 deaths, respectively, of which 45.0%, 28.9% and 13.5%, respectively were carbapenem-resistant (3). Based on historical resistance trends, projections indicate that by 2050, annual deaths attributable to antimicrobial resistance and deaths associated with antimicrobial resistance will increase to 1.91 million and 8.22 million, respectively, highly concentrated in low- and middle-income countries (4). There is an unmet need for treatment options for priority pathogens that have antimicrobial resistance, especially for multidrug- and extensively drug-resistant gram-negative pathogens (5).

Benefits

The application presented data on the benefits of imipenem + cilastatin + relebactam from randomized trials and real-world evidence from observational data. Randomized trials RESTORE-IMI 1 was a randomized, double-blind, multicentre, phase III trial that investigated the activity of imipenem + cilastatin + relebactam (500 mg + 500 mg + 250 mg every 6 hours) compared with colistin (300 mg loading dose, then 150 mg every 12 hours) plus imipenem + cilastatin (500 mg + 500 mg every 6 hours) for the treatment of complicated intra-abdominal and urinary tract infections and hospital-acquired pneumonia, including ventilator-associated pneumonia (6). The primary efficacy endpoint was favourable overall response, calculated on the microbiological modified intention-to-treat population (i.e. patients with a positive culture for an imipenem-resistant gram-negative pathogen who had received at least one dose of the study medicine) which included 21 and 10 patients in the intervention and comparator groups, respectively. The study was not powered to infer statistically significant differences in efficacy between treatment arms. A favourable overall response was reported in 15/21 (71.4%) and 7/10 (70.0%) patients in the intervention and comparator groups, respectively (adjusted difference -7.3%, 90% confidence interval (CI) -27.7% to 21.4%). Definitions of overall response differed by

type of infection: for hospital-acquired pneumonia/ventilator-associated pneumonia, it was survival at day 28; for complicated intra-abdominal infections, it was clinical response at day 28; and for complicated urinary tract infections, it was clinical plus microbiological response 5–9 days after the end of therapy. A favourable clinical response at day 28 was reported in 15/21 (71.4%) and 4/10 (40.0%) patients in the intervention and comparator groups, respectively (adjusted difference 26.3%, 90% CI 1.3% to 51.5%). Among secondary endpoints, all-cause mortality at day 28 was lower in the intervention group (9.5% versus 30.0%; adjusted difference –17.3%, 90% CI –46.4% to 6.4%). Results by type of infection showed that for hospital-acquired pneumonia/ventilator-associated pneumonia 28-day survival was higher with imipenem + cilastatin + relebactam (87.5% versus 66.7%). None of the four patients with a complicated intra-abdominal infection had a favourable response at day 28. For complicated urinary tract infections, results for the primary efficacy endpoint favoured the comparator group (adjusted difference –27.3%, 90% CI –52.8% to 12.8%). The primary efficacy endpoint was met, indicating that imipenem + cilastatin + relebactam was at least as efficacious as colistin plus imipenem + cilastatin for the treatment of infections caused by imipenem-non-susceptible, colistin-susceptible gram-negative pathogens. A secondary analysis of RESTORE-IMI1 data compared outcomes between the microbiological modified intent-to-treat (mMITT) and supplemental mMITT (SmMITT) populations, in which eligibility was based on local site testing (n = 41). Outcomes in the SmMITT population were consistent with those in the mMITT population (7). RESTORE-IMI 2 was a randomized controlled, double-blind, multicentre, non-inferiority, phase III trial comparing imipenem + cilastatin + relebactam (500 mg + 500 mg + 250 mg every 6 hours) with piperacillin + tazobactam (4 g + 500 mg every 6 hours) for the treatment of hospital-acquired pneumonia/ventilator-associated pneumonia in adults (8). Participants were randomized 1:1 to receive imipenem + cilastatin + relebactam (n = 268) or piperacillin + tazobactam (n = 269) for 7–14 days. The primary efficacy endpoint was all-cause mortality through day 28, while the key secondary endpoint was favourable clinical response at early follow-up (7–14 days after the end of treatment). Primary and secondary endpoints were evaluated in the modified intention-to-treat population, which excluded patients where only gram-positive cocci were isolated at baseline. Results for the primary endpoint of 28-day all-cause mortality showed lower mortality in the intervention group (15.9% versus 21.3%; adjusted difference –5.3%, 95% CI –11.9% to 1.2%). For favourable clinical response at early follow-up, results favoured the intervention group (61.0% versus 55.8%; adjusted difference 5.0%, 95% CI –3.2% to 13.2%). At day 28, a favourable clinical response was reported in 51.9% versus 50.6% of patients in the intervention and comparator groups, respectively (adjusted difference 1.1%, 95% CI –7.2% to 9.4%). The primary and secondary efficacy endpoints were met, indicating that imipenem + cilastatin + relebactam was at least as efficacious as piperacillin + tazobactam for the treatment of adults with hospital-acquired pneumonia/ventilator-associated pneumonia. A randomized, double-blind, multicentre, non-inferiority, dose-ranging, phase II study compared the efficacy of relebactam 250 mg, relebactam 125 mg or placebo each given with imipenem 500 mg + cilastatin 500 mg for the treatment of 351 adult patients with complicated intra-abdominal infections irrespective of the type or susceptibility profile of the causative pathogen (9). The primary efficacy endpoint was favourable clinical response at discontinuation of therapy (5–9 days after end of treatment) and at late follow-up (28–42 days after end of treatment). With a prespecified non-inferiority margin of 15%, both doses of relebactam with imipenem + cilastatin were non-inferior to imipenem + cilastatin monotherapy for the primary efficacy endpoint. A similar study was conducted in adult patients with complicated urinary tract infections irrespective of the type or susceptibility profile of the causative pathogen (10). Again, with a prespecified non-inferiority margin of 15%, both doses of relebactam with imipenem + cilastatin were non-inferior to imipenem + cilastatin monotherapy for the primary efficacy endpoint of the proportion of patients who achieved a favourable microbiological response. A randomized non-inferiority study compared imipenem + cilastatin + relebactam with standard of care gram-negative coverage (cefepime, piperacillin + tazobactam or meropenem) in 100 cancer patients with febrile neutropenia (11). Patients receiving imipenem + cilastatin + relebactam had a higher favourable clinical response at the end of intravenous therapy compared with those receiving standard of care (90% versus 74%; P = 0.042). Responses between treatment groups were similar for test of cure at days 21–28, and late follow-up at days 35–74. Microbiological eradication responses were similar at all timepoints. Observational studies A 2024 retrospective, multicentre observational study described clinical characteristics and outcomes in 160 patients who received imipenem + cilastatin + relebactam for at least 2 days using data from a centralized database in the United States (12). Indications for antibacterial treatment during hospitalization included hospital-acquired or ventilator-associated bacterial pneumonia (53.8%) and complicated urinary tract infection (16.9%). Microbiology data were available for 37 patients, with the most commonly identified pathogens being *P. aeruginosa*, *Enterobacter cloacae* and *E. coli*. Multidrug-resistant *P. aeruginosa* was reported in 28/37 (75.7%) patients. Imipenem + cilastatin + relebactam was started a median of 8 days after hospital admission, and the median duration of treatment was 7 days. The all-cause in-hospital mortality rate overall was 24.4% and the 30-day mortality rate was 21.3%. In-hospital mortality was 57.6% and 15.7% among patients with and without coronavirus disease 2019 (COVID-19), respectively. Among

patients with hospital-acquired or ventilator-associated bacterial pneumonia, the all-cause in-hospital mortality rate was 39.5%, which was higher than rates reported in the RESTORE-IMI 1 and RESTORE-IMI 2 trials and likely due to the inclusion of patients with COVID-19. MIRAGE was a retrospective, multicentre, observational study describing the real-world effectiveness of imipenem + cilastatin + relebactam against multidrug-resistant *P. aeruginosa* pneumonia and bloodstream infections. Preliminary results have been published in abstract form (13). The study included patients who received imipenem + cilastatin + relebactam for more than 48 hours which was started within 7 days of first positive culture. Of 32 critically ill patients in the preliminary analysis, 72% and 53% achieved clinical success at day 7 and day 30, respectively. This was defined as survival, resolution of signs and symptoms of infection, and the absence of a recurrent infection due to multidrug-resistant *P. aeruginosa*. Rates of all-cause mortality at day 30 and day 90 were 22% and 31%, respectively. A retrospective review of electronic health records reported treatment patterns of hospitalized patients with gram-negative infections treated with imipenem + cilastatin + relebactam in the United States. Results have been published in abstract form (14). Of 58 patient charts reviewed, the all-cause in-hospital mortality rate was 13.8%. Among the 25.9% of patients who experienced a 30-day hospital readmission after receiving imipenem + cilastatin + relebactam, two thirds had a single hospital readmission. In another retrospective observational study published in abstract form, patient characteristics, and the effectiveness and safety of imipenem + cilastatin + relebactam were evaluated in 104 adult patients with infections due to *P. aeruginosa* (15). In more than 50% of patients, treatment was for lower respiratory-tract infections. Multidrug-resistant *P. aeruginosa* was isolated in 84.6% of patients. Clinical success was reported for 73.1% of patients, while the 30-day all-cause mortality was 16.3%. Thirty-day microbiologic recurrence occurred in 14.4% of patients. A retrospective case series described the outcomes in 21 adult patients with mixed infection sources (52% were pulmonary infections) who were treated with imipenem + cilastatin + relebactam (16). Most infections were caused by *P. aeruginosa* (76%), of which all except one were multidrug-resistant. The 30-day all-cause mortality rate was 33%, and clinical cure rate was 62%. Results from an extension of this study were presented as a conference poster in 2023; the study reported a 30-day all-cause mortality rate of 15.4% (17). In vitro studies Data from an in vitro study which assessed the antimicrobial activity of imipenem + cilastatin + relebactam and aztreonam alone and in combination against 10 well characterized *P. aeruginosa* isolates (three parent and seven metallo- β -lactamase producers) demonstrated synergy in five of the strains and restoration of aztreonam activity in the remaining five when combination treatment was used (18). Among multidrug-resistant *P. aeruginosa* isolates collected before and after treatment-emergent resistance to ceftolozane + tazobactam, whole genome sequencing identified treatment-emergent mutations in *ampC* in 79% (11/14) of paired isolates. *AmpC* mutations were associated with cross-resistance to ceftazidime + avibactam but increased or maintained susceptibility to imipenem + cilastatin + relebactam. A high percentage (81%) of isolates resistant to ceftolozane + tazobactam were susceptible to imipenem + relebactam (19). A second assessment found that imipenem + cilastatin + relebactam retained activity against 70–75% of cephalosporin-resistant *P. aeruginosa* isolates resistant to ceftolozane + tazobactam, ceftazidime + avibactam and meropenem + vaborbactam (20).

Harms

In RESTORE-IMI 1, the incidence of ≥ 1 adverse events, serious adverse events, serious drug-related adverse events and treatment discontinuations due to adverse events was lower in patients who received imipenem + cilastatin + relebactam than in patients who received colistin plus imipenem + cilastatin, although the trial was not powered to detect statistical significance in these outcomes. A statistically significant lower incidence of treatment-emergent nephrotoxicity was found in patients who received imipenem + cilastatin + relebactam than in patients who received colistin plus imipenem + cilastatin (10.3% versus 56.3%; $P = 0.002$) (6). In an additional analysis of RESTORE-IMI, nephrotoxicity was retrospectively evaluated using two acute kidney injury assessment criteria (kidney disease improving global outcomes (KDIGO) and risk, injury, failure, loss and end-stage kidney disease (RIFLE)). The analysis found that, based on KDIGO and RIFLE criteria, imipenem + cilastatin + relebactam had a more favourable renal safety profile than colistin-based therapy in patients with serious gram-negative bacterial infections not susceptible to imipenem (21). In RESTORE-IMI 2, the incidence of ≥ 1 adverse events, deaths, serious adverse events, drug-related adverse events and treatment discontinuations due to adverse events were comparable between treatment groups (8). A secondary analysis of RESTORE-IMI 2 observed that emergence of non-susceptibility to imipenem + cilastatin + relebactam occurred rarely. Emergence of non-susceptibility to imipenem + cilastatin + relebactam was identified by isolates that were susceptible at baseline but subsequently were identified during treatment and tested non-susceptible. Of all randomized participants who received imipenem + cilastatin + relebactam, 5/268 (1.9%) and 2/268 (0.7%) had non-susceptible post-baseline isolates by Clinical and Laboratory Standards Institute criteria and European Committee on Antimicrobial Susceptibility Testing criteria, respectively (22). In the dose-ranging phase II studies in patients with complicated intra-abdominal infections (9) and

complicated urinary tract infections (10), imipenem + cilastatin + relebactam had a comparable safety profile to imipenem + cilastatin monotherapy, with similar rates of adverse events, serious adverse events and drug-related adverse events between each group and between different doses of relebactam.

Cost / cost effectiveness

The application presented global cost-effectiveness and budgetary impact analyses from the United States payer perspective. Cost-effectiveness of imipenem + cilastatin + relebactam versus colistin plus imipenem for the treatment of infection(s) caused by confirmed carbapenem-non-susceptible pathogens was examined (23). The analysis comprised a decision-tree depicting initial hospitalization and a Markov model projecting long-term health and economic impacts following discharge. The decision tree, informed by clinical data from RESTORE-IMI 1 trial, modelled clinical outcomes (mortality, cure rate and adverse events including nephrotoxicity) in the two comparison scenarios of imipenem + cilastatin + relebactam versus colistin plus imipenem for patients with carbapenem-non-susceptible gram-negative infection. Subsequently, a Markov model translated these hospitalization stage outcomes (i.e. death or uncured infection) to long-term consequences such as quality-adjusted life years (QALYs). Sensitivity analyses were conducted to test the model's robustness. Imipenem + cilastatin + relebactam compared to colistin plus imipenem demonstrated a higher cure rate (79.0% versus 52.0%), lower mortality (15.2% versus 39.0%) and reduced nephrotoxicity (14.6% versus 56.4%). On average, a patient treated with imipenem + cilastatin + relebactam gained an additional 3.7 QALYs over a lifetime. Higher drug acquisition costs for imipenem + cilastatin + relebactam were offset by shorter length of hospital stay and lower costs related to adverse events, which resulted in net savings of 11 015 United States dollars (US\$) per patient. Sensitivity analyses suggested that imipenem + cilastatin + relebactam had a high likelihood of being cost-effective at a United States willingness-to-pay threshold of US\$ 100 000 to US\$ 150 000 per QALY. The cost-effectiveness of imipenem + cilastatin + relebactam versus piperacillin + tazobactam for the treatment of health-care-acquired and ventilator-associated bacterial pneumonia was examined (24). An economic model comprising of a decision-tree depicting initial hospitalization and a Markov model projecting long-term health and economic impacts following discharge was developed. Efficacy data to determine clinical outcomes in the short-term decision tree were taken from the modified intent-to-treat population of RESTORE-IMI 2. Hospitalization costs were modelled using the average observed length of stay as reported in RESTORE-IMI 2, and unit costs for intensive care units and general wards (US\$ 5743 and US\$ 2694 per day, respectively) were sourced from the literature. Total costs in both arms were primarily driven by hospitalization costs in the short term. Costs of resources use, adverse event and monitoring were comparable across treatment arms, with incremental costs for imipenem + cilastatin + relebactam primarily being driven by increased treatment acquisition costs. The resulting incremental cost-effectiveness ratio was US\$ 14 053 per QALY gained, well below the typical United States willingness-to-pay threshold of US\$ 100 000 per QALY gained.

WHO guidelines

WHO guidelines for the use of imipenem + cilastatin + relebactam are not currently available.

Availability

As of October 2024, imipenem + cilastatin + relebactam has regulatory approval in 51 countries and market availability in 33 countries. It is not currently included on national essential medicines lists.

Other considerations

The WHO Control and Response Strategies Unit within the Division of Antimicrobial Resistance reviewed the application and advised that it did not support the inclusion of imipenem + cilastatin + relebactam on the EML. The technical unit highlighted that the circumstances that underpinned the 2023 Expert Committee's decision not to recommend inclusion had not changed. The WHO Technical Advisory Group on AWaRe (TAG-AWaRe) reviewed the application and advised that it supported the inclusion of imipenem + cilastatin + relebactam on the EML. Comments from the TAG-AWaRe highlighted: • infections due to multidrug-resistant organisms, particularly high-priority carbapenem-resistant Enterobacterales, *Pseudomonas* and *Acinetobacter* species continue to be associated with considerable morbidity and mortality globally; • access to essential Reserve antibiotics is still limited in many settings; • limited clinical trial data suggest imipenem + cilastatin + relebactam has similar clinical efficacy and a more favourable safety profile than the combination of imipenem and colistin for treatment of complicated intra-abdominal infections, complicated urinary tract infections and hospital-acquired bacterial pneumonia/ventilator-associated bacterial

pneumonia; • small observational studies conducted in the United States, in which most patients had infections caused by difficult-to-treat resistant *Pseudomonas* species and a minority had infections caused by *K. pneumoniae* carbapenemase--producing carbapenem-resistant Enterobacterales, demonstrated a clinical success rate of about 70%, but with documented recurrent infections and development of resistance; • imipenem + cilastatin + relebactam may play a role as an additional therapeutic option in countries where *K. pneumoniae* carbapenemase-producing carbapenem-resistant Enterobacterales and difficult-to-treat resistant *Pseudomonas* species are prevalent. However, other carbapenemases against which imipenem + cilastatin + relebactam is not active are more prevalent than KPC in many countries. • concern for price, access and potential inappropriate use due to limited capacity for microbiological diagnosis and surveillance (including genotyping) and limited implementation of antimicrobial stewardship policies and interventions, particularly in low- and middle-income countries.

1. The selection and use of essential medicines. Report of the WHO Expert Committee on Selection and Use of Essential Medicines, 2023 (including the 23rd WHO Model List of Essential Medicines and the 9th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2024 (WHO Technical Report Series, No. 1049; <https://iris.who.int/handle/10665/376570>). Licence: CC BY-NC-SA 3.0 IGO.
2. Antimicrobial resistance – fact sheet [internet]. Geneva: World Health Organization; 2023 (<https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance>).
3. Murray CJL, Ikuta KS, Sharara F, Swetschinski L, Robles Aguilar G, Gray A et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet*. 2022;399(10325):629–55 ([https://doi.org/10.1016/S0140-6736\(21\)02724-0](https://doi.org/10.1016/S0140-6736(21)02724-0)).
4. Naghavi M, Vollset SE, Ikuta KS, Swetschinski LR, Gray AP, Wool EE et al. Global burden of bacterial antimicrobial resistance 1990–2021: a systematic analysis with forecasts to 2050. *Lancet*. 2024;404(10459):1199–226 ([https://doi.org/10.1016/S0140-6736\(24\)01867-1](https://doi.org/10.1016/S0140-6736(24)01867-1)).
5. Antibacterial agents in clinical development: an analysis of the antibacterial clinical development pipeline, including tuberculosis. Geneva: World Health Organization; 2017 (WHO/EMP/IAU/2017.11; <https://apps.who.int/iris/handle/10665/258965>). Licence: CC BY-NC-SA 3.0 IGO.
6. Motsch J, Murta de Oliveira C, Stus V, Köksal I, Lyulko O, Boucher HW et al. RESTORE-IMI 1: A multicenter, randomized, double-blind trial comparing efficacy and safety of imipenem/relebactam vs colistin plus imipenem in patients with imipenem-nonsusceptible bacterial infections. *Clin Infect Dis*. 2020;70(9):1799–808 (<https://doi.org/10.1093/cid/ciz530>).
7. Kaye KS, Boucher HW, Brown ML, Aggrey A, Khan I, Joeng HK et al. Comparison of treatment outcomes between analysis populations in the RESTORE-IMI 1 phase 3 trial of imipenem-cilastatin-relebactam versus colistin plus imipenem-cilastatin in patients with imipenem-nonsusceptible bacterial infections. *Antimicrob Agents Chemother*. 2020;64(5):e02203–19. (<https://doi.org/10.1128/aac.02203-19>).
8. Titov I, Wunderink RG, Roquilly A, Rodríguez Gonzalez D, David-Wang A, Boucher HW et al. A randomized, double-blind, multicenter trial comparing efficacy and safety of imipenem/cilastatin/relebactam versus piperacillin/tazobactam in adults with hospital-acquired or ventilator-associated bacterial pneumonia (RESTORE-IMI 2 Study). *Clin Infect Dis*. 2021;73(11):e4539–e48 (<https://doi.org/10.1093/cid/ciaa803>).
9. Lucasti C, Vasile L, Sandesc D, Venskutonis D, McLeroth P, Lala M et al. Phase 2, dose-ranging study of relebactam with imipenem-cilastatin in subjects with complicated intra-abdominal infection. *Antimicrob Agents Chemother*. 2016;60(10):6234–43 (<https://doi.org/10.1128/aac.00633-16>).
10. Sims M, Mariyanovski V, McLeroth P, Akers W, Lee YC, Brown ML et al. Prospective, randomized, double-blind, phase 2 dose-ranging study comparing efficacy and safety of imipenem/cilastatin plus relebactam with imipenem/cilastatin alone in patients with complicated urinary tract infections. *J Antimicrob Chemother*. 2017;72(9):2616–26 (<https://doi.org/10.1093/jac/dkx139>).
11. Chaftari A-M, Dagher H, Hachem R, Jiang Y, Lamie P, Wilson D R et al. A randomized non-inferiority study comparing imipenem/cilastatin/relebactam with standard-of-care Gram-negative coverage in cancer patients with febrile neutropenia. *J Antimicrob Chemother*. 2024;79(10):2543–53 (<https://doi.org/10.1093/jac/dkae254>).
12. Shields RK, Yücel E, Turzhitsky V, Merchant S, Min JS, Watanabe AH. Real-world evaluation of imipenem/cilastatin/relebactam across US medical centres. *J Glob Antimicrob Resist*. 2024;37:190–4 (<https://doi.org/https://doi.org/10.1016/j.jgar.2024.03.002>).
13. Wangchinda W, Pogue JM, Abbo LM, Klatt M, Kline EG, Kubat RC et al. P-1105. Effectiveness of imipenem-relebactam for multidrug-resistant *Pseudomonas aeruginosa* in pneumonia and bloodstream infections in the United States (MIRAGE). *Open Forum Infect Dis*. 2025;12(Suppl 1):ofae631.1293 (<https://doi.org/10.1093/ofid/ofae631.1293>).
14. Yucel E, Lee L, Modi K, Zhou Y, Shields RK. P-1075. Treatment patterns among hospitalized patients with gram-negative infection treated with imipenem/cilastatin/relebactam (i/r): retrospective US-based EHR medical chart review. *Open Forum Infect Dis*. 2025;12(Suppl 1):ofae631.1263 (<https://doi.org/10.1093/ofid/ofae631.1263>).
15. Caniff KE, Xhemali X, Tran N, Eubank TA, Garey KW, Guo Y et al. P-1500. Evaluation of imipenem-cilastatin-relebactam for the treatment of infections caused by *Pseudomonas aeruginosa*. *Open Forum Infect Dis*. 2025;12(Suppl 1):ofae631.1669 (<https://doi.org/10.1093/ofid/ofae631.1669>).
16. Rebold N, Morrisette T, Lagnf AM, Alosaimy S, Holger D, Barber K et al. Early multicenter experience with imipenem-cilastatin-relebactam for multidrug-resistant gram-negative infections. *Open Forum Infect Dis*. 2021;8(12):ofab554 (<https://doi.org/10.1093/ofid/ofab554>).
17. Caniff KE, Rebold N, Lucas K, Guo Y, Chang M, Tran N et al. P2259. Real-world, multicenter experience with imipenem-cilastatin-relebactam for infections due to *Pseudomonas aeruginosa*. In: 33rd European Congress of Clinical Microbiology and Infectious Disease, Copenhagen, Denmark, 15–18 April 2023.
18. O'Donnell JN, Putra V, Belfiore GM, Maring BL, Young K, Lodise TP. In vitro activity of imipenem/relebactam plus aztreonam against metallo- β -lactamase-producing, OprD-deficient *Pseudomonas aeruginosa* with varying levels of *Pseudomonas*-derived cephalosporinase production. *Int J Antimicrob Agents*. 2022;59(6):106595 (<https://doi.org/https://doi.org/10.1016/j.ijantimicag.2022.106595>).
19. Rubio AM, Kline EG, Jones CE, Chen L, Kreiswirth BN, Nguyen MH et al. In vitro susceptibility of multidrug-resistant *Pseudomonas aeruginosa* following treatment-emergent resistance to ceftolozane-tazobactam. *Antimicrob Agents Chemother*. 2021;65(6):e00084-21 (<https://doi.org/10.1128/aac.00084-21>).
20. Arca-Suárez J, Lasarte-Monterrubio C, Rodiño-Janeiro B-K, Cabot G, Vázquez-Ucha JC, Rodríguez-Iglesias M et al. Molecular mechanisms driving the in vivo development of OXA-10-mediated resistance to ceftolozane/tazobactam and ceftazidime/avibactam during treatment of XDR *Pseudomonas aeruginosa* infections. *J Antimicrob Chemother*. 2020;76(1):91–100 (<https://doi.org/10.1093/jac/dkaa396>).
21. Brown ML, Motsch J, Kaye KS, File TM, Boucher HW, Vendetti N et al. Evaluation of renal safety between imipenem/relebactam and colistin plus imipenem in patients with imipenem-nonsusceptible bacterial infections in the randomized, phase 3 RESTORE-IMI 1 study. *Open Forum Infect Dis*. 2020;7(3):ofaa054 (<https://doi.org/10.1093/ofid/ofaa054>).
22. Young K. Characterization of molecular enzymes RESTORE-IMI-2 trial isolates vs SMART surveillance isolates. ASM Microbe online, July 2020.
23. Yang J, Naik J, Massello M, Ralph L, Dillon RJ. Cost-effectiveness of imipenem/cilastatin/relebactam compared with colistin in treatment of gram-negative infections caused by Carbapenem-non-susceptible organisms. *Infect Dis Ther*. 2022;11(4):1443–57 (<http>

[s://doi.org/10.1007/s40121-022-00607-x](https://doi.org/10.1007/s40121-022-00607-x)).

24. Naik J, Dillon R, Massello M, Ralph L, Yang Z. Cost-effectiveness of imipenem/cilastatin/relebactam for hospital-acquired and ventilator-associated bacterial pneumonia. *J Comp Eff Res*. 2023;12(3):e220113 (<https://doi.org/10.2217/ce-2022-0113>).

