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Review

Imipenem/Cilastatin/Relebactam for MDR *Pseudomonas aeruginosa*: Real-World Clinical Effectiveness and Contexts of Use

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Abstract

Background: Multidrug-resistant (MDR) *Pseudomonas aeruginosa* infections are associated with substantial morbidity, mortality and therapeutic uncertainty, particularly in critically ill and immunocompromised patients. Imipenem/cilastatin/relebactam (IMI/REL) combines the established carbapenem imipenem with cilastatin, a dehydropeptidase-I inhibitor, and relebactam, a diazabicyclooctane beta-lactamase inhibitor that restores imipenem activity against selected class A and class C beta-lactamase-mediated resistance mechanisms. Methods: A targeted narrative review was undertaken to identify and provide an overview of published observational studies and conference abstracts reporting clinical outcomes with IMI/REL in patients with confirmed or suspected MDR *P. aeruginosa* infection. Evidence was summarized descriptively, because the available studies were heterogeneous in design, infection site, patient severity, pathogen mix, susceptibility testing and outcome definitions. Results: Real-world IMI/REL data remain limited but are increasingly informative. IMI/REL was commonly used in high-risk patients, including those with pneumonia, bacteremia, intensive care admission, prior antimicrobial exposure, polymicrobial infection or limited alternative treatment options. Reported clinical success or clinical cure was observed in approximately 56–70.2% of patients, although interpretation is limited by non-comparative designs, small patient populations and mixed-pathogen populations. Thirty-day all-cause mortality varied widely, broadly reflecting baseline severity, infection site and salvage-therapy use. Emergence of IMI/REL non-susceptibility was variably reported, but some recent studies report high rates of treatment-emergent resistance; this requires caution and remains an important area for surveillance. Conclusions: IMI/REL appears to be a clinically useful option for susceptible MDR *P. aeruginosa* infections, particularly in patients with limited alternatives. Available real-world evidence should be interpreted cautiously, because most data derive from retrospective uncontrolled cohorts.

Keywords: imipenem/cilastatin/relebactam; *Pseudomonas aeruginosa*; multidrug resistance; difficult-to-treat resistance; carbapenem resistance; real-world evidence; antimicrobial stewardship

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1. Introduction

Pseudomonas aeruginosa is a ubiquitous Gram-negative pathogen associated with substantial clinical burden, particularly for hospitalized, critically ill and immunocompromised patients [1–4]. The clinical importance of *P. aeruginosa* reflects both its intrinsic virulence and its ability to acquire or upregulate resistance mechanisms during antimicrobial exposure. Resistance may arise through reduced outer-membrane permeability, loss or alteration of the OprD porin, upregulation of multidrug efflux pumps, target-site changes, AmpC beta-lactamase overexpression and acquisition of additional beta-lactamases, including carbapenemases [2–4].

P. aeruginosa is a leading cause of healthcare-associated infections and is strongly associated with pneumonia, including hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP), as well as bloodstream, urinary tract, intra-abdominal, skin and soft tissue, and device-associated infections [1,2,5]. *P. aeruginosa* survives in a wide range of healthcare environments and forms biofilms on medical devices and hospital equipment (such as implantable devices, ventilator tubes, catheters and sinks), increasing the difficulty of eradication and the risk of recurrent or persistent infection [2,4].

The emergence of multidrug resistant (MDR) and difficult-to-treat resistant (DTR) *P. aeruginosa* has narrowed treatment options and increased reliance on agents with less favorable tolerability profiles, including polymyxins and aminoglycosides [6–8]. In the World Health Organization (WHO) Bacterial Priority Pathogens List 2024, carbapenem-resistant *P. aeruginosa* was reclassified as a high priority pathogen from critical priority in 2017 [6]. Therefore, *P. aeruginosa* infections remain a universal burden to healthcare systems; there is a global need for effective, safe and stewardship-compatible treatment strategies.

1.1. Treatment Evolution and Rationale for IMI/REL

Historically, the treatment of severe *P. aeruginosa* infections relied on conventional antipseudomonal beta-lactams, carbapenems, aminoglycosides and polymyxins. Although these agents remain important in selected settings, their use may be limited by resistance, toxicity, pharmacokinetic challenges or inadequate activity at key infection sites [7–9]. In response, newer beta-lactam/beta-lactamase inhibitor (BL/BLI) combinations and cefiderocol have expanded the therapeutic armamentarium for resistant Gram-negative infections [7–9].

IMI/REL is a novel antibiotic combination that comprises imipenem, cilastatin and relebactam. Imipenem is a carbapenem whose activity may be limited by degradation by dehydropeptidase-I in the kidneys and hydrolysis by beta-lactamases. Cilastatin inhibits renal dehydropeptidase-I, reducing the renal degradation of imipenem. Relebactam, a non-beta-lactam diazabicyclooctane beta-lactamase inhibitor structurally related to avibactam, inhibits Ambler class A and class C beta-lactamases, including KPC enzymes and chromosomal or plasmid-mediated AmpC beta-lactamases. However, relebactam does not inhibit metallo-beta-lactamases (MBL) such as NDM, VIM or IMP, nor most class D oxacillinases [10,11].

The rationale for IMI/REL is particularly relevant in *P. aeruginosa*, where carbapenem resistance commonly reflects combinations of AmpC overexpression, OprD loss and efflux pump upregulation rather than carbapenemase production alone [2,7,8,12]. Relebactam cannot reverse the resistance caused solely by porin loss or efflux, but inhibition of AmpC can restore imipenem activity in isolates where beta-lactamase production is an important contributor to resistance. Furthermore, it is particularly noteworthy that relebactam not only restores imipenem susceptibility among non-susceptible isolates of *P. aeruginosa* but also enhances imipenem susceptibility against susceptible isolates that can produce chromosomal AmpC [13]. It has been postulated that the addition of relebactam to imipenem leads to a “pharmacodynamic boost”, where the percentage of time for the free drug con-

centration exceeds the Minimum Inhibitory Concentration (%fT > MIC) for the imipenem component, resulting in a higher probability of target attainment at the site of infection, further underpinning the role of IMI/REL in selected MDR *P. aeruginosa* infections, provided susceptibility is confirmed.

1.2. Clinical Development Context

A pivotal clinical development program established that IMI/REL maintained the efficacy of imipenem/cilastatin in conventional infection settings and provided clinical evidence in more resistant infections (Table 1). Early Phase 2 trials in complicated urinary tract infection (cUTI) and complicated intra-abdominal infection (cIAI) demonstrated non-inferior efficacy and comparable safety for IMI/REL relative to imipenem/cilastatin alone [14,15]. Subsequent Phase 3 trials, RESTORE-IMI 1 and RESTORE-IMI 2, supported its role in imipenem-non-susceptible Gram-negative infections and HAP/VAP, respectively [16,17].

Table 1. Key clinical development studies providing context for IMI/REL use.

Study	Geography	Population	Primary Endpoint	Key Result	Interpretation
Sims et al., 2017; Phase 2 cUTI [14]	International, including sites in North America and Europe	cUTI or acute pyelonephritis; n = 298 treated	Favorable microbiological response at discontinuation of IV therapy in microbiologically evaluable population	95.5% with IMI/REL 250 mg vs. 98.7% with imipenem/cilastatin alone; clinical response 97.1% vs. 98.8%	Non-inferior efficacy; no major additional safety signal
Lucasti et al., 2016; Phase 2 cIAI [15]	Multinational (North America, Europe, Latin America)	cIAI; n = 347 treated	Favorable clinical response at discontinuation of IV therapy in microbiologically evaluable population	96.3% with IMI/REL 250 mg vs. 95.2% with imipenem/cilastatin alone	Non-inferior efficacy; safety broadly comparable
RESTORE-IMI 1; Motsch et al., 2020; Phase 3 [16]	Multinational; conducted across Europe, Asia–Pacific, Latin America and North America	Imipenem-non-susceptible Gram-negative infections; mMITT n = 31	Favorable overall response	71.4% with IMI/REL vs. 70.0% with colistin plus imipenem; treatment difference reported with 90% CI −27.5 to 21.4	Comparable efficacy with markedly less nephrotoxicity
RESTORE-IMI 1; Brown et al. 2020; Phase 3; renal safety [18]		Same program	Safety/secondary endpoint: treatment-emergent nephrotoxicity	10.3% with IMI/REL vs. 56.3% with colistin plus imipenem; $p = 0.002$	Important toxicity advantage over polymyxin-based salvage therapy
RESTORE-IMI 2; Titov et al., 2021; Phase 3 [17]	Global multicenter study across 27 countries	HABP/VABP; n = 537	Day-28 all-cause mortality	15.9% with IMI/REL vs. 21.3% with piperacillin/tazobactam; adjusted difference −5.3% (95% CI −11.9 to 1.2)	Met prespecified non-inferiority margin
		HABP/VABP; n = 537	Favorable clinical response at early follow-up	61.0% with IMI/REL vs. 55.8% with piperacillin/tazobactam; adjusted difference 5.0% (95% CI −3.2 to 13.2)	Comparable clinical efficacy in nosocomial pneumonia

Abbreviations: cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; HABP, hospital-acquired bacterial pneumonia; IMI/REL, imipenem/cilastatin/relebactam; mMITT, modified microbiological intent-to-treat; VABP, ventilator-associated bacterial pneumonia.

The clinical trial program provides the foundation for IMI/REL use; however, randomized trials included relatively small numbers of patients with MDR and DTR *P. aeruginosa* and may not fully reflect contemporary salvage use, polymicrobial infection, prior exposure to other novel beta-lactams, or the severity of patients encountered in real-world practice. Further, a realistic overview of patients with MDR *P. aeruginosa* was not captured effectively in the RESTORE-IMI-2 Phase 3 study, as isolates had to be susceptible to both treatments, yet many MDR *P. aeruginosa* isolates are resistant to piperacillin/tazobactam.

Health Technology Assessment (HTA) authorities such as the National Institute of Health and Care Excellence (NICE) encourage real world evidence to address evidence gaps and resolve uncertainties [19]. A review of observational studies on the use and outcomes of IMI/REL in MDR *P. aeruginosa* will provide complementary evidence and help address evidence gaps.

1.3. Aim

This targeted narrative review provides an overview of the currently available real-world evidence for IMI/REL in MDR *P. aeruginosa* infection, with emphasis on clinical outcomes, patient context, resistance considerations and limitations of the evidence base. The review also considers how available data from a real-world setting may inform antimicrobial stewardship and future research priorities, as a supplement to clinical trial evidence.

2. Results

This review identified published observational studies, case series and relevant conference abstracts reporting clinical outcomes with IMI/REL in patients with confirmed or suspected MDR *P. aeruginosa* infection. Mixed-pathogen cohorts were included when they reported a substantial number of patients with *P. aeruginosa* or *P. aeruginosa*-specific information, but outcomes from such studies were interpreted cautiously when pathogen-specific outcomes were not available.

2.1. Identified Real-World Evidence

Seven real-world or clinically relevant observational reports were identified for inclusion in the descriptive synthesis (Table 2). Five reports were multicenter studies, and two were single-center or small case-series reports. Most evidence originated from the United States, with additional data from Spain and Italy. The cohort size ranged from 10 patients in a small case series to 160 patients in a multicenter observational cohort study. Importantly, not all cohorts were restricted to MDR *P. aeruginosa*; several included broader MDR Gram-negative or polymicrobial infections. Where studies included mixed populations, outcomes are reported for the overall cohort unless *P. aeruginosa*-specific outcomes were available.

Table 2. Identified real-world evidence for IMI/REL in MDR *P. aeruginosa* or relevant mixed Gram-negative cohorts.

Study	Design/Location	Cohort Size	Pathogen Population	Clinical Context	Interpretive Caveat
Rebold et al., 2021 [20]	Multicenter retrospective cohort; USA; eight centers	21	MDR Gram-negative infections; *P. aeruginosa* in 76%	Early post-approval use across high-risk infections; pulmonary infections common	Mixed-pathogen cohort; useful early signal but limited pathogen-specific inference

Table 2. *Cont.*

Study	Design/Location	Cohort Size	Pathogen Population	Clinical Context	Interpretive Caveat
Shields et al., 2022 [21]	Single-center resistance case series; USA	19, of which 5 patients were identified with emergent non-susceptibility	MDR *P. aeruginosa* pneumonia in all patients	Focused on evolution of IMI/REL non-susceptibility after treatment	Mechanistic/resistance report rather than effectiveness cohort
Shields et al., 2024 [22]	Retrospective, multicenter observational study; USA	160	*P. aeruginosa*, *K. pneumoniae*, Enterobacter cloacae and *Escherichia coli*	Overall largest real-world cohort. Hospitalized patients with HABP, VABP and cUTIs	Microbiology data were available for 37 unique patients; the most common pathogen identified was *P. aeruginosa* (89.2%); and 75.7% of patients were positive for MDR *P. aeruginosa* (28/37).
Caniff et al., 2025 [23]	Multicenter retrospective observational cohort; USA; 24 centers	151	MDR Gram-negative infections; *P. aeruginosa* targeted in 72.2%; MDR *P. aeruginosa* 45.0%; DTR *P. aeruginosa* 14.6%	Largest real-world cohort with focus on *P. aeruginosa*; lower respiratory tract infection common; polymicrobial index cultures frequent	Overall outcomes should not be interpreted as purely *P. aeruginosa*-specific
Leanza et al., 2024 [24]	Single-center case series; Italy	10	DTR *P. aeruginosa*, KPC-producing Klebsiella pneumoniae or mixed infection	Complex infections including HAP/VAP, bloodstream infection, cUTI, skin/soft tissue infection and osteomyelitis	Small, mixed-pathogen case series with high reported cure
Machuca et al., 2025; IMRECOR [25]	Multicenter retrospective case series; Spain; nine hospitals	14	DTR *P. aeruginosa* only	Compassionate-use salvage therapy after failure or intolerance of a primary active regimen	Highly relevant pathogen-specific salvage cohort, but very small
Wangchinda et al., 2025; MIRAGE [26]	Multicenter retrospective observational study; USA; nine centers	63	MDR *P. aeruginosa* pneumonia or bloodstream infection	Strict inclusion criteria; critically ill population; 79% ICU, 76% mechanically ventilated	Most directly relevant full publication for MDR *P. aeruginosa* pneumonia/bacteremia

Abbreviations: cUTI, complicated urinary tract infection; DTR, difficult-to-treat resistant; HAP, hospital-acquired pneumonia; ICU, intensive care unit; IMI/REL, imipenem/cilastatin/relebactam; KPC, Klebsiella pneumoniae carbapenemase; MDR, multidrug-resistant; VAP, ventilator-associated pneumonia.

2.2. Patient Severity and Treatment Context

The largest observational cohort was by Shields et al. who reported on hospitalized patients who received IMI/REL for ≥2 days, of whom 45% were in the intensive care unit; when considering all patients, 89.2% had *P. aeruginosa*, and 75.7% had MDR *P. aeruginosa* [22]. Caniff et al. was the largest observational cohort study with a focus on *P. aeruginosa;* this study reported that patients had a median age of 60 years, frequent antimicrobial exposure in the preceding 90 days and a high proportion of lower respiratory tract infections. The study reported on a broad MDR Gram-negative cohort rather than a *P. aeruginosa*-only study; *P. aeruginosa* was targeted in 72.2% of patients, while 47.7% of index cultures were polymicrobial [23]. In contrast, the MIRAGE study used stringent criteria to evaluate IMI/REL

for MDR *P. aeruginosa* pneumonia or bloodstream infection and included a particularly high-risk population, with 79% admitted to ICU, 76% receiving mechanical ventilation and 48% requiring vasopressors [26].

Across studies, IMI/REL was typically used in medically complex patients with limited treatment options; within Shields et al., patients had received up to nine different antibacterial treatment courses during their hospital stay and often initiated other β-lactams prior to IMI/REL [22]. Common features across patients included experiencing critical illness, ICU admission, hospitalization, mechanical ventilation, pneumonia or bloodstream infection, prior antimicrobial exposure, polymicrobial infection and prior or suspected resistance to other novel beta-lactams. This real-world evidence indicates that IMI/REL was often used as salvage or directed therapy in patients who already had limited alternative options and poor prognostic features, making crude outcome rates difficult to compare with those from controlled trials or earlier-line treatment settings. In many studies, IMI/REL was also often used in combination with another agent.

2.3. Endpoints and Outcome Definitions

Outcome definitions differed across the identified studies. Clinical success or clinical cure was the most common primary endpoint, but the definitions varied with respect to the timing, requirement for survival, microbiological clearance, completion of planned therapy and absence of recurrence. Mortality was usually reported at 30 days, although some studies also reported 90-day mortality. Resistance outcomes were reported inconsistently and were influenced by whether repeat cultures and susceptibility testing were performed (Table 3).

Table 3. Endpoint definitions across real-world IMI/REL studies.

Study	Primary Endpoint	Secondary/Additional Endpoints
Rebold et al., 2021 [20]	30-day all-cause mortality from index culture	Clinical cure within 30 days after end of antibiotic therapy; microbiological recurrence; adverse effects; emergence of non-susceptibility
Shields et al., 2022 [21]	Detection of IMI/REL non-susceptible *P. aeruginosa* after treatment during/after 10–28 days of IMI/REL treatment	Whole-genome sequencing; assessment of efflux mechanisms; susceptibility testing with and without PAβN
Shields et al., 2024 [22]	Duration of hospitalization during which IMI/REL was prescribed	Hospital and ICU length of stay, in-hospital and 30-day mortality, and readmission to any hospital within 30 days of discharge
Caniff et al., 2025 [23]	Clinical success at 30 days	30-day all-cause mortality, microbiologic failure, infection recurrence, readmission, length of stay and adverse effects
Leanza et al., 2024 [24]	Clinical cure at end of treatment	Mortality and adverse effects attributable to IMI/REL
Machuca et al., 2025; IMRECOR [25]	30-day all-cause mortality	Clinical efficacy and microbiological success at day 30
Wangchinda et al., 2025; MIRAGE [26]	Clinical success at day 30	30- and 90-day mortality, recurrence and development of non-susceptibility

Endpoint heterogeneity is a major reason descriptive synthesis was used rather than pooled analysis.

2.4. Clinical and Microbiological Outcomes

Across observational cohorts, the reported clinical success or cure was generally encouraging but heterogeneous. In studies or analyses reporting clinical success as a primary endpoint, values ranged from 56% in the highly selected MIRAGE pneumonia/bacteremia cohort to approximately 70% in broader cohorts [23,26]. In smaller studies, clinical cure ranged from 62% in a multicenter study to 100% in a case series of 10 patients with DTR

P. aeruginosa/KPC-producing *K. pneumoniae* [20,24]. These values should not be treated as pooled estimates because they reflect markedly different inclusion criteria, infection sites, pathogen mixes and definitions of success (Table 4).

Table 4. Key outcomes reported in real-world IMI/REL studies.

Study	Mortality	Clinical Outcome	Microbiology/Recurrence/Resistance	Safety/Context
Rebold et al., 2021 [20]	30-day mortality 33% (7/21)	Clinical cure: 62% (13/21)	Microbiological recurrence: 24% (5/21); IMI/REL non-susceptibility: 5% overall (1/21) or 11% among isolates with repeat MIC testing	Two adverse events; neither led to discontinuation
Shields et al., 2022 [21]	Not an effectiveness cohort	Five patients developed IMI/REL non-susceptible *P. aeruginosa* after 10–28 days of therapy	Resistance associated with treatment-emergent mutations in efflux operons; PAβN restored susceptibility in testing	Highlights need for repeat susceptibility testing in persistent/recurrent infection
Shields et al., 2024 [22] *	30-day mortality 21.3%; all-cause in-hospital mortality 24.4%	Not reported	Not reported	Not reported
Caniff et al., 2025 [23]	30-day mortality 18.5%	Clinical success: 70.2%	Microbiological failure: 14.6%; infection recurrence: 11.9%	ADRs: 6.0%; discontinuation in three cases
Leanza et al., 2024 [24]	No deaths reported	Clinical cure: 100% (10/10)	Microbiological outcomes favorable in reported cases	No treatment-related adverse events reported
Machuca et al., 2025; IMRECOR [25]	30-day mortality 42.9% (6/14)	Clinical and microbiological success: 64.3% (9/14)	Clinical and microbiological success: 64.3% (9/14); mortality among patients with bacteremia: 50% (2/4)	Small compassionate-use salvage cohort; high baseline severity
Wangchinda et al., 2025; MIRAGE [26]	30-day mortality 18%; 90-day mortality 29%	Clinical success at day 30: 56%	Recurrent infection: 37% within 90 days; resistance: 39% (16/41) of evaluable patients	One case of interstitial nephritis considered related to IMI/REL; no other adverse events reported

*Mixed-pathogen cohorts are included for context; pathogen-specific interpretation should be restricted to studies reporting MDR/DTR P. aeruginosa-specific populations or outcomes. * Microbiology data were available for 37 unique patients, where 33 patients had P. aeruginosa.*

The mortality also varied substantially, with 30-day all-cause mortality reported at 18–42.9% across included studies. The highest mortality was observed in the small IMRECOR compassionate-use cohort, which enrolled patients with DTR *P. aeruginosa* infection and limited treatment options, most of whom were critically ill and many of whom had septic shock [25]. In MIRAGE, the 30- and 90-day all-cause mortality were 18% and 29%, respectively, despite high baseline severity [26].

Recurrence and resistance are important interpretive issues. Rebold et al. reported microbiological recurrence in 24% of patients and emergence of non-susceptibility in 5% overall, although repeat susceptibility testing was performed only in a subset [20]. MIRAGE reported recurrent infection in 37% of patients within 90 days and emergent resistance in 39% of evaluable patients, although the authors highlighted important caveats including the variability in susceptibility testing methods and the proximity of baseline MICs to clinical breakpoints [26]. Therefore, treatment-emergent IMI/REL non-susceptibility should be viewed as variably reported and incompletely characterized, not simply rare.

3. Discussion

The available real-world evidence suggests that IMI/REL is used primarily as salvage therapy in high-risk patients with resistant Gram-negative infections, particularly MDR or DTR *P. aeruginosa*, who had previously received antibiotic therapy, and where limited alternative treatment options are available. Across heterogeneous cohorts, IMI/REL was associated with clinical success in approximately 56–70.2% of patients, despite frequent critical illness, prior antimicrobial exposure and complex infection contexts [23,26]. Limited alternative effective therapies are available for these patients, and thus, the potential of IMI/REL is encouraging. These findings are consistent with, but not equivalent to, the efficacy signals observed in the clinical development program [14–17].

Resistance emergence is one of the most important unresolved issues in the effective treatment of Gram-negative infections. Earlier experience suggested the infrequent emergence of IMI/REL non-susceptibility, but more recent and more tightly defined MDR *P. aeruginosa* data have identified higher rates among evaluable patients [21,26]. This does not necessarily mean that resistance is common in all clinical settings, because estimates depend heavily on repeat culture practices, testing methodology, baseline MIC distribution and patient selection. Mixed pathogen populations including MBL-producers that relebactam is not active against may suggest IMI/REL resistance, and therefore, appropriate laboratory diagnostics are essential to ensure IMI/REL is used in susceptible isolates. Nevertheless, persistent or recurrent infection should prompt repeat culture and susceptibility testing, and resistance monitoring should be considered a key component of IMI/REL stewardship.

The safety findings remain reassuring overall. IMI/REL avoids the well-recognized nephrotoxicity associated with colistin-based salvage therapy, as demonstrated in RESTORE-IMI 1 [16]. In identified real-world studies, adverse events were relatively infrequent, although individual adverse reactions, including neutropenia, rash and interstitial nephritis, were reported [23,26]. These observations support ongoing pharmacovigilance but do not suggest a major unexpected safety signal.

A key strength of the current evidence base is that it reflects patients who are often excluded from or under-represented in randomized trials, including those with polymicrobial infections (~20–40% of *P. aeruginosa* infections), prior exposure to other novel beta-lactams, ICU admission and recurrent infection. This makes the data clinically valuable; however, the same features may also introduce substantial confounding in interpretation of results. Most studies were retrospective, non-comparative and uncontrolled, and IMI/REL was frequently used after previous antimicrobial exposure or treatment failure. Consequently, favorable outcomes should be interpreted with caution. The role of combination therapy remains uncertain but could inflate positive outcomes. Several real-world patients received IMI/REL with adjunctive agents, reflecting clinician caution with novel antibiotics, illness severity or the need to cover multiple co-infecting pathogens. However, this may introduce considerable confounding, limiting the interpretation of the results. However, combination therapy complicates attribution of benefit and may not be required when susceptibility to an active novel beta-lactam is confirmed. Future studies should clarify whether combination therapy improves outcomes in specific high-risk subgroups or merely reflects confounding by severity.

The evidence also supports a careful distinction between efficacy and effectiveness. Clinical trials demonstrated non-inferiority and favorable safety relative to comparators in selected populations, whereas real-world cohorts describe outcomes in more heterogeneous and often sicker patients. The observed mortality range is therefore not unexpected and likely reflects the baseline severity, infection site, source control, timing of active therapy, pathogen susceptibility and concomitant therapy as much as drug activity itself.

Guideline positioning also matters. Contemporary Infectious Diseases Society of America (IDSA) guidance lists newer beta-lactam agents, including IMI/REL, among the preferred options for DTR *P. aeruginosa* infections when susceptibility is demonstrated, while emphasizing that treatment decisions should be guided by organism identification, susceptibility results, infection site and patient-level factors [20]. This aligns with the real-world evidence, as IMI/REL appears to be a rational therapeutic option when the isolate is susceptible and resistance mechanisms are compatible with relebactam activity, particularly where other options are unavailable, unsuitable or resistant. Real-world evidence signifies that IMI/REL was frequently used as salvage last-line therapy in patients with prior antibiotic exposure and limited options remaining. This is consistent with IMI/REL being a viable option for last-resort use, particularly as a substantial proportion of C/T or CZA-resistant isolates that remained susceptible to IMI/REL. Antimicrobial stewardship principles suggest that earlier intervention with IMI/REL against DTR *P. aeruginosa* infections known to be susceptible to IMI/REL may further improve patient outcomes, although clinical studies are necessary to confirm this. This could reduce the reliance on conventional therapies with toxic safety profiles.

3.1. Limitations

This review has several limitations. First, it is a targeted narrative synthesis rather than a systematic review and therefore may not capture all unpublished or non-indexed real-world experience. Secondly, only seven publications were identified, some of which included small patient numbers for MDR or DTR *P. aeruginosa*. Thirdly, the included studies had small sample sizes limiting any subgroup analyses; the studies were also heterogeneous in design, population, infection site, pathogen mix, susceptibility testing and outcome definitions, precluding meta-analysis. Fourth, several cohorts included mixed Gram-negative or polymicrobial infections, meaning that overall outcomes cannot always be attributed specifically to MDR or DTR *P. aeruginosa*. Fifth, most studies were retrospective and non-comparative, creating the risk of confounding by indication and survivorship bias.

In addition, IMI/REL was frequently used as salvage therapy in patients with high baseline severity and prior antibiotic exposure. Poor outcomes in such cohorts may reflect delayed active therapy, inadequate source control, advanced comorbidity or infection severity rather than lack of drug activity. Conversely, favorable outcomes cannot establish comparative superiority over other novel beta-lactams or earlier treatment strategies. Finally, resistance estimates are limited by inconsistent repeat-culture and susceptibility-testing practices.

3.2. Conclusions

IMI/REL is an important option for susceptible MDR and DTR *P. aeruginosa* infections, particularly in high-risk patients with limited alternatives and resistance mechanisms compatible with relebactam activity. Real-world data are encouraging but should be interpreted cautiously, because the evidence derives largely from retrospective, uncontrolled, non-comparative and heterogeneous cohorts. IMI/REL appears clinically effective and generally well tolerated in difficult real-world settings, while further comparative, pathogen-specific and stewardship-focused studies are needed to define its optimal sequencing, timing and role relative to other novel beta-lactam agents. Further, IMI/REL may help reduce the reliance on more toxic legacy therapies, which further highlights the need for continued evidence generation. However, treatment-emergence resistance to IMI/REL is possible, and therefore, susceptibility testing and resistance monitoring should be considered a key component of IMI/REL stewardship.

Until more robust comparative data are available, IMI/REL use should be guided by the infection site, patient severity, source control, prior antimicrobial exposure and local resistance epidemiology. Repeat susceptibility testing should be considered in persistent or recurrent infection to support the timely detection of emerging non-susceptibility.

4. Methods

A targeted narrative literature search was conducted to identify published observational studies, case series and relevant conference abstracts reporting clinical outcomes with IMI/REL (manufactured by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA) in patients with confirmed or suspected MDR *P. aeruginosa* infection. Searches were performed across PubMed/MEDLINE and Google Scholar, with a supplementary review of conferences (IDWeek, European Society of Clinical Microbiology and Infectious Diseases [ESCMID], and British Society for Antimicrobial Chemotherapy [BSAC]), reference lists from relevant articles, prescribing information and guideline documents. Search terms included combinations of "imipenem relebactam", "imipenem cilastatin relebactam", "*Pseudomonas aeruginosa*", "multidrug resistant", "real-world", "observational", "clinical success", "mortality", "resistance" and "non-susceptibility".

Eligible evidence included observational studies, retrospective or prospective cohorts, case series and conference abstracts published or available from 2019 to 2026 that reported clinical, microbiological, mortality, safety or resistance outcomes for adult patients after IMI/REL treatment. Mixed-pathogen cohorts were included when they reported a substantial number of *P. aeruginosa* patients or *P. aeruginosa*-specific information, but outcomes from such studies were interpreted cautiously when pathogen-specific outcomes were not available. Studies evaluating only in vitro susceptibility, pharmacokinetic outcomes or pediatric populations were excluded from the primary synthesis, although mechanistic and pharmacological studies were used to provide context.

Data were extracted descriptively, including the study design, location, number of centers, cohort size, pathogen mix, infection sites, illness severity, prior antimicrobial exposure, IMI/REL regimen, combination therapy, primary and secondary endpoints, clinical success or cure, mortality, recurrence, microbiological outcomes, adverse events and emergence of non-susceptibility. Because the available evidence was heterogeneous in design, infection site, pathogen composition, susceptibility testing and endpoint definitions, no meta-analysis was performed, and no pooled estimates were generated. Outcome ranges are therefore presented as descriptive summaries rather than comparative effectiveness estimates.

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