



Original Article



Clinical and Microbiologic Efficacy and Safety of Imipenem/Cilastatin/Relebactam in Complicated Infections: A Meta-analysis

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Ethics Approval and Consent to

Participate

The data extracted and the manuscript was reviewed with Research Department

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ABSTRACT

Background: Antimicrobial resistance is on the rise. The use of redundant and inappropriate antibiotics is contributing to recurrent infections and resistance. Newer antibiotics with more robust coverage for Gram-negative bacteria are in great demand for complicated urinary tract infections (cUTIs), complicated intra-abdominal infections (cIAIs), hospital-acquired bacterial pneumonia (HABP), and ventilator-associated bacterial pneumonia (VABP).

Materials and Methods: We performed this meta-analysis to evaluate the efficacy and safety profile of a new antibiotic, Imipenem/cilastatin/relebactam, compared to other broad-spectrum antibiotics for complicated infections. We conducted a systemic review search on PubMed, Embase, and Central Cochrane Registry. We included randomized clinical trials-with the standard of care as comparator arm with Imipenem/cilastatin/relebactam as intervention arm. For continuous variables, the mean difference was used. For discrete variables, we used the odds ratio. For effect sizes, we used a confidence interval of 95%. A *P*-value of less than 0.05 was used for statistical significance. Analysis was done using a random-effects model irrespective of heterogeneity. Heterogeneity was evaluated using the I^2 statistic.

Results: The authors observed similar efficacy at clinical and microbiologic response levels on early follow-up and late follow-up compared to the established standard of care. The incidence of drug-related adverse events, serious adverse events, and drug discontinuation due to adverse events were comparable across both groups.

Conclusion: Imipenem/cilastatin/relebactam has a non-inferior safety and efficacy profile compared to peer antibiotics to treat severe bacterial infections (cUTIs, cIAIs, HABP, VABP).

Keywords: Bacterial pneumonia; Complicated intra-abdominal infections; Complicated urinary tract infection; Imipenem; Imipenem/cilastatin/relebactam

INTRODUCTION

Inadequately treated bacterial infections in medical and surgical settings equate to high in-patient morbidity and mortality [1, 2]. Selecting appropriate antibiotics for serious infections makes a life and death difference. Proper initiation of empiric antibiotics, which cover a broad array of pathogens without the cost of universal resistance, is a riddle today [3]. The bacterial genome sequencing in 1955 opened many vistas and introduced newer molecular



and Ethics Committee. No experimental intervention was performed. It did not require any specification of guidelines, legislations, or permissions.

Conflict of Interest

No conflicts of interest

Author Contributions

Conceptualization: AJ (1), SS. Data curation: AJ (1), SS. Formal analysis: AJ (1), AJ (2), SS. Investigation: AJ (1), RH, SS. Methodology: AJ (1), SS. Project administration: SS. Resources: AJ (1), SS. Software: AJ (1), SS. Supervision: AG, AJ (1), SS. Validation: AJ (1), SS. Visualization: AJ (1), SS. Writing - original draft: AJ (1), AJ (2), RH, SS. Writing - review & editing: AJ (1), AJ (2), RH, AG, SS.

targets for customizing purpose-built antibiotics [4]. But the repeated use of the same antibiotics has led to resistance [5]. Emerging antimicrobial resistance has been a challenge for the already overburdened health care system [6, 7]. It is damaging not only in terms of increased morbidity and length of stay in hospital but also to the emergence of resistant bacterial strains, especially multi-drug resistant gram-negative bacteria [8, 9]. ESKAPE pathogens, including *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species, have caused havoc for the health care systems [10, 11].

Increasing carbapenem use in emergency and critical care settings to cover pathogens proved efficient initially, but then it gave rise to a global outbreak of carbapenem-resistant strains [12]. The resistance results were noticeable even at institutional levels where the use of one carbapenem (*e.g.*, meropenem) was predominant over the other [13-15].

The World Health Organization (WHO) has issued multiple warnings throughout the years to publicize the dire need for newer, more potent antibiotics for combating the advanced resistance mechanisms [16]. We have plenty of antibiotics for Gram-positive bacteria, such as methicillin-resistant *S. aureus* (MRSA), but there is a global deficit for adequate coverage against Gram-negative bacterial infections [17].

Enterobacteriaceae with *K. pneumoniae* carbapenemase (KPC) are particularly resistant and threaten hospital infection control [18]. KPCs are only moderately inhibited by beta-lactamase inhibitors, including clavulanic acid, tazobactam, and boronic acid [19]. Cephalosporin and beta-lactamase inhibitor combinations are introduced to overcome the beta-lactamases, especially for severe and complicated bacterial infections [20]. Carbapenemase-producing Enterobacteriaceae (CPE) is better handled with a combination antibiotic compared to monotherapy [21].

Imipenem/cilastatin/relebactam, a relatively newer antibiotic, combines imipenem, cilastatin, and relebactam. Imipenem is a bactericidal carbapenem known for binding and inhibiting penicillin-binding proteins (PBP 1 B and PBP 2) in *Enterobacteriaceae* and *P. aeruginosa* inhibits bacterial cell wall synthesis [22, 23]. Cilastatin is a renal dehydropeptidase inhibitor. Cilastatin lacks any antibacterial activity and maintains the serum concentrations of imipenem by inhibiting its renal metabolism; it is also said to have a nephroprotective effect by inhibiting drug-induced kidney injury [24, 25]. Relebactam is a beta-lactamase inhibitor that potentiates the action of imipenem. It is known to antagonize certain serine beta-lactamases, including KPC, *Enterobacter cloacae* P99; *Pseudomonas* derived cephalosporins (PDC), *Temoneira* (TEM), Sulhydryl variable (SVH), and *Cefotaximase-Munich* (CTX-M) [26, 27]. Recently, imipenem/cilastatin/relebactam was approved by the Food and Drug Administration (FDA) for use in ventilator-associated bacterial pneumonias (VAPBs) and hospital-acquired bacterial pneumonias (HABPs) in June 2020, along with the already established use for complicated urinary tract infection (cUTI) [28, 29].

We performed this meta-analysis to explore the efficacy and safety of imipenem/cilastatin/relebactam compared to other antibiotics for serious bacterial infections, including cUTIs, complicated intraabdominal infections (cIAIs), HABP, and VABP. Comparable or improved performance can give clinicians confidence in prescribing it without the fear of inducing resistance and recurrent infections.

MATERIALS AND METHODS

The databases accessed were Cochrane Central Registry of Clinical Trials, Embase, and PubMed. Search terms used were imipenem/cilastatin/relebactam, Relebactam, and imipenem. The deadline for publication was set as December 20, 2020.

1. Inclusion and Exclusion Criteria

Those studies were included, which:

- 1) were randomized control trials comparing imipenem/cilastatin/relebactam against standard of care in patients with cIAI, UTI and hospital-acquired pneumonia
- 2) enrolled patients with age greater than 18 years
- 3) were available in the English language without any restrictions of date or status of publications.

Those papers which did not meet the above criteria were excluded.

2. Trial Selection and Evaluation

Three authors independently reviewed all articles and abstracts and excluded irrelevant. The risk of bias for selected papers was assessed using Cochrane collaborative tool and classified into high, uncertain, and low.

3. Data Extraction

Information was extracted using a pre-specified extraction table. Data was extracted from trials reading through text and tables by A.J.-and a second author reviewed the data collected to ensure the accuracy of the information. The extracted data included clinical response at early follow-up (EFU: 5 - 9 days) and late follow-up (LFU: 28 - 42 days), the microbiologic response at early follow-up (EFU), and adverse effects of imipenem/cilastatin/relebactam.

4. Statistical Analysis

The meta-analysis was executed employing the Comprehensive Meta-analysis software version 3 (Biostat Inc., Englewood, NJ, USA). We calculated the odds ratio (OR) for discrete variables. Standard errors were calculated using a 95% confidence interval, and for determining statistical significance, a *P*-value of 0.05 was used. For consistency in analysis, it was performed using a random-effects model irrespective of heterogeneity. Heterogeneity was evaluated using I^2 statistic; heterogeneity less than 40 was considered low, 40 - 60 moderate, and above 60 as high.

RESULTS

1. Literature Search

A total of 177 articles were identified in the initial search. After the removal of duplicates and the first screening, we excluded 162 articles. We analyzed the full texts of 15 articles. Two papers were excluded due to being review articles; three studies were single-arm, three were abstracts, and three were microbiological studies. Four randomized controlled trials (RCTs) were selected for review and analysis. PRISMA flowsheet for selection of studies and search string is added to supplementary files. The main characteristics are given in **Table 1**.

Table 1. Main characteristics of the studies

| Study | Study Type | Number of participants | Infection Type | Inclusion Criteria | Exclusion Criteria | Intervention Arm | Comparator Arm |
|---------------------|------------|------------------------|--|---|---|--|--|
| Lucasti (2016) [28] | RCT | 351 | cIAI | Age >18, Clinically suspected or bacteriologically documented cIAI | APACHE score >30, CrCl <50 mL/min, ALT/AST >3 x UNL, Effective antibiotic therapy against pathogen before study drug | REL 250 + Imipenem (n = 118) REL 125 + Imipenem (n = 116) | Placebo + Imipenem (n = 117) |
| Sims (2017) [29] | RCT | 298 | cUTI | Age >18 years, clinically presumed and/or registered cUTI or acute pyelonephritis, needing intravenous antimicrobial treatment, confirmatory urine culture results within 48h | Uncomplicated UTI, CrCl <5 mL/min, ALT/AST >3 x UNL, complete urinary obstruction, effective antibiotic therapy before study drug initiation | REL 250 + Imipenem (n = 99) REL 125 + Imipenem (n = 99) | Placebo + Imipenem (n = 100) |
| Motsch (2020) [40] | RCT | 57 | Imipenem resistant bacteria: cIAI, cUTI, HABP/VABP | Age ≥18 years, diagnosis of HABP/VABP, cUTI, cIAIs secondary to imipenem nonsusceptible, I/R susceptible, and colistin-susceptible bacteria | APACHE >30, CrCl <15 mL/min, cUTI with urinary obstruction, HABP/VABP with complete obstruction | REL 250 + Imipenem (n = 31) | Colistin + Imipenem (n = 16) |
| Titov (2020) [38] | RCT | 531 | HABP/VABP | Age >18, LRT Specimen collected within 48h of screening, meet diagnostic criteria for HABP/VABP | >24h of effective antibacterial therapy within 72h of randomization, LRT showing only Gram-positive cocci, CrCl <15, pneumonia by an obstructive process like lung cancer | REL 250/500 + Imipenem (n = 264) | Piperacillin/Tazobactam 4 g/500 mg (n = 267) |

RCT, randomized controlled trials; APACHE: acute physiology and chronic health evaluation score; cIAI: complicated intra-abdominal infection; CrCl, creatinine clearance; ALT, alanine transaminase; AST, aspartame transaminase; UNL, upper limit of normal; REL, relebactam; cUTI, complicated urinary tract infection; LRT, lower respiratory tract; HABP, hospital-acquired bacterial pneumonia; VABP, ventilator-associated bacterial pneumonia.

2. Risk of Bias

The results of the risk of bias are depicted in **Figure 1** and **Figure 2**.

3. Results of quantitative analysis

1) Overall clinical response at EFU

Four studies with a total of six intervention arms reported clinical response at EFU, and there was no statistically significant difference between the groups, OR 1.126 (0.717 - 1.569) $P=0.605$, $I^2 = 48.22$ (**Fig. 2**).

2) Overall clinical response at LFU

Four studies with a total of six intervention arms reported clinical response at LFU, and there was no statistically significant difference between the groups, OR 1.264 (0.858 - 1.861) $P=0.236$, $I^2 = 31.149$ (**Fig. 3**).

3) Overall microbiologic response at EFU

Three studies with a total of five intervention arms reported microbiologic response at EFU, and there was no statistically significant difference between the groups, OR 1.246 (0.831 - 1.868) $P=0.287$, $I^2 = 27.627$ (**Fig. 4**).

4. Subgroup Analysis of 150 mg vs 250 mg dose subgroups

1) Clinical response

Two studies reported clinical response at early and late follow-up in 150 mg doses, and there was no statistically significant difference between the two groups. For EFU, OR was 0.932 (0.501 - 1.736) $P=0.824$, $I^2 = 0$. For LFU, OR was 0.952 (0.454 - 1.993) $P=0.895$, $I^2 = 34.572$.

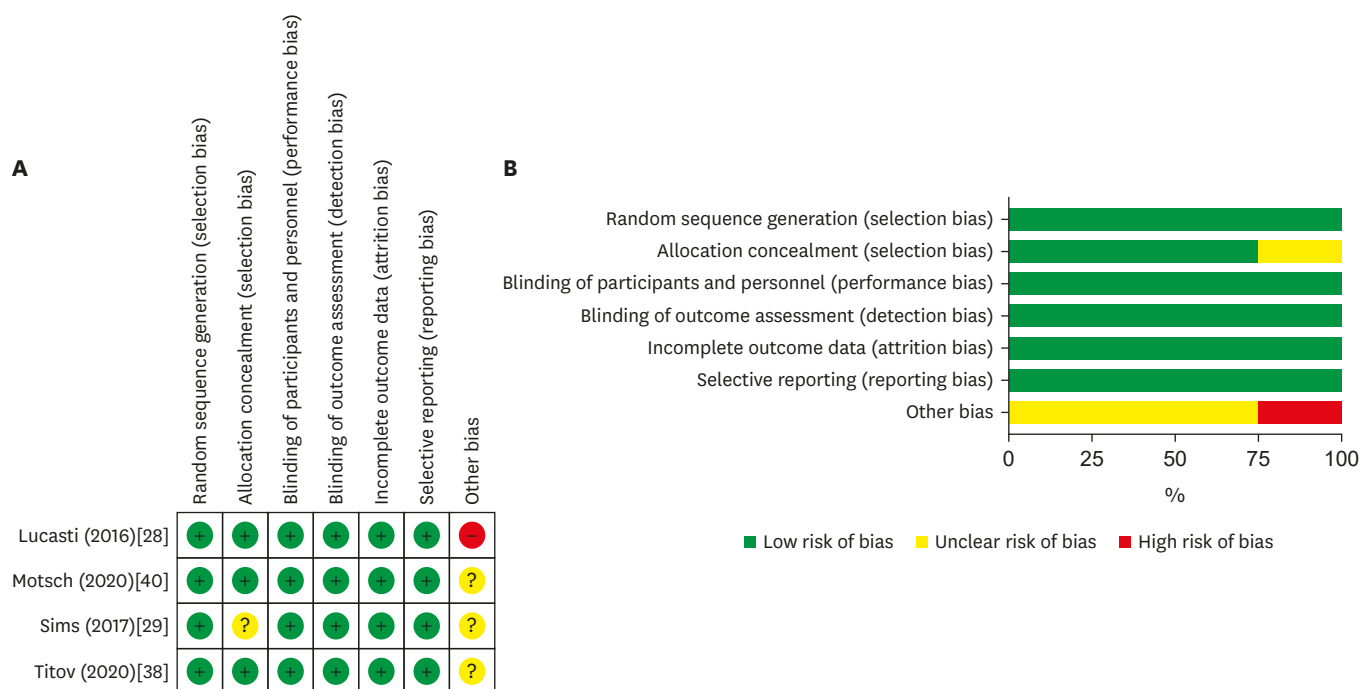


Figure 1. Risk of Bias in studies included (classified into high, low, and uncertain).

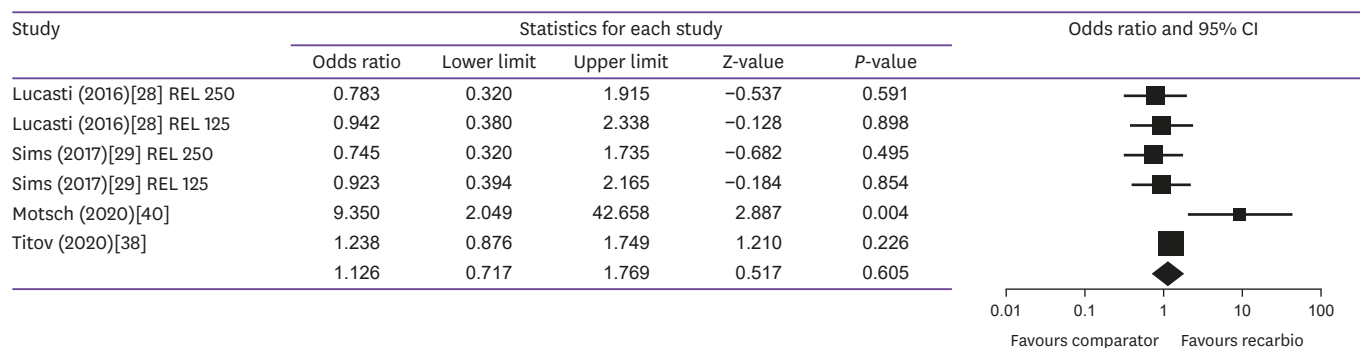


Figure 2. Overall clinical response at early follow up. CI, confidence interval.

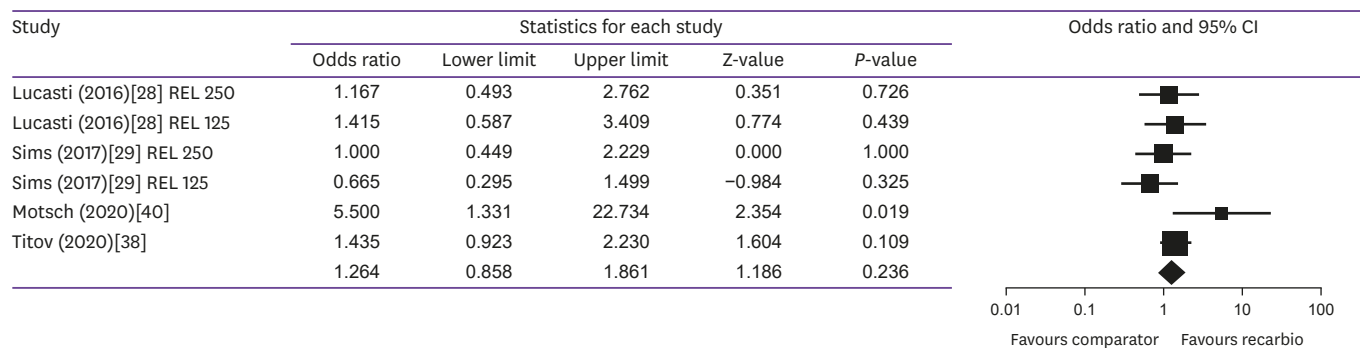


Figure 3. Overall clinical response at late follow up. CI, confidence interval.

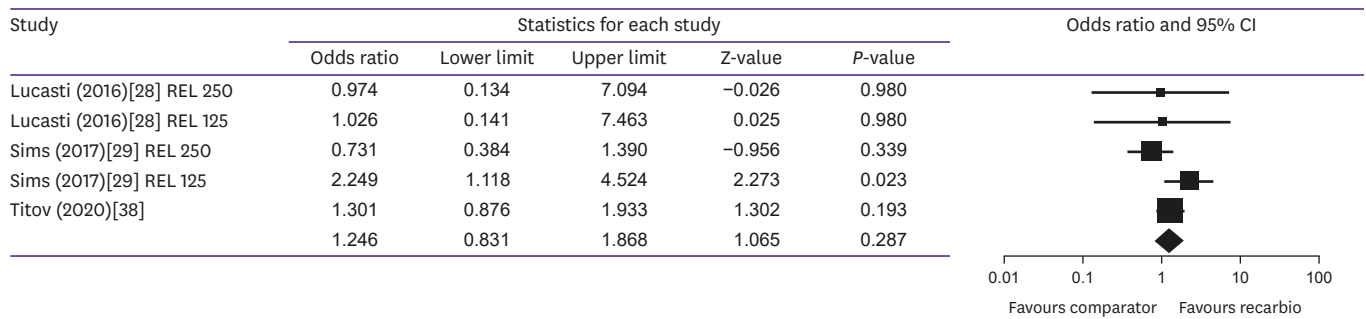


Figure 4. Overall microbiologic response at early follow up. CI, confidence interval.

Four studies reported clinical response in early and late follow-up in 250 mg dose, and there was no statistically significant difference between the two groups. For EFU, OR was 1.291 (0.640 - 2.603) $P = 0.475$, $I^2 = 67.231$. For LFU, OR was 1.434 (0.896 to 2.293) $P = 0.133$, $I^2 = 32.297$.

2) Microbiologic response

Two studies reported microbiologic response early to follow up for 125 mg dose, and the imipenem/cilastatin/relebactam showed statistically better response with an OR of 2.062 (1.067 - 3.987) $P = 0.031$, $I^2 = 0$.

Three studies reported microbiologic response at early follow up for 250mg dose, and there was no statistically significant difference between the groups with an OR of 1.079 (0.736 - 1.582) $P = 0.696$, $I^2 = 11.357$.

3) Clinical response based on the type of infection

One study with two-dose arms reported clinical response in early follow-up in intraabdominal infections with no statistically significant difference between the groups; for EFU, the OR was 0.858 (0.453 - 1.622) $P = 0.637$. For LFU, two studies with three intervention arms reported clinical response in early follow-up with no statistically significant difference; the OR was 1.238 (0.693 - 2.373), $P = 0.428$.

One study with two-dose arms reported clinical response in early and late-term follow-up in urinary tract infections with no statistically significant difference between the groups. For EFU, OR was 0.829 (0.455 - 1.510) $P = 0.539$. For LFU, OR was 0.818 (0.462 - 1.447) $P = 0.490$.

One study reported clinical response in early and late-term follow-up in HABP/VABP with no statistically significant difference between the groups. For EFU, OR was 1.238 (0.876 - 1.749) $P = 0.226$. For LFU, OR was 1.435 (0.923 - 2.230) $P = 0.109$.

4) Microbiologic response

One study with two-dose arms reported microbiologic response in early follow-up in cIAIs with no statistically significant difference between the groups, OR 1.000 (0.246 - 4.068) $P = 1.000$.

One study with two-dose arms reported microbiologic response in early follow-up in cUTIs with no statistically significant difference between the groups, OR 1.271 (0.422 - 3.824) $P = 0.670$.

One study with reported microbiologic response in early follow-up in HABP/VABP with no statistically significant difference between the group, OR 1.301 (0.876 - 1.933) $P = 0.193$.

5. Side effects

1) Drug-related adverse effects

There was no statistical difference between imipenem/cilastatin/relebactam and standard of care regarding drug-related adverse events, OR 1.251 (0.896 - 1.746) $P = 0.189$, $I^2 = 0$ (Fig. 5).

2) Serious adverse events

There was no statistical difference between imipenem/cilastatin/relebactam and standard of care regarding serious adverse events, OR 0.779 (0.565 - 1.073) $P = 0.127$, $I^2 = 0$ (Fig. 6).

3) Drug discontinued due to adverse events

There was no statistical difference between imipenem/cilastatin/relebactam and standard of care regarding drug discontinuation secondary to adverse events, OR 0.771 (0.447 - 1.328) $P = 0.349$, $I^2 = 0.344$ (Fig. 7).

6. Summary of results

Imipenem/cilastatin/relebactam had similar efficacy at clinical and microbiologic response levels at early follow-up and late follow-up compared to an established standard of care. The incidence of drug-related adverse events, serious adverse events, and drug discontinuation due to adverse events were similar across both groups.

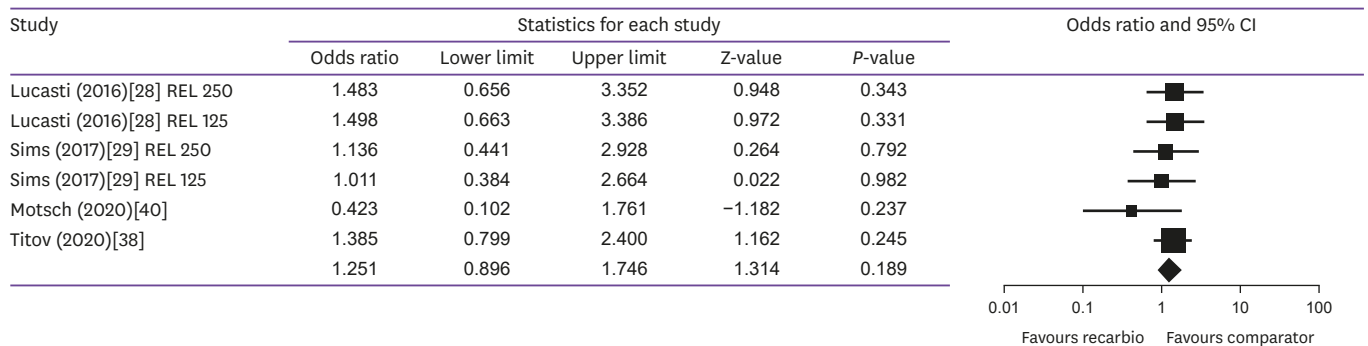


Figure 5. Drug-related adverse effects. CI, confidence interval.

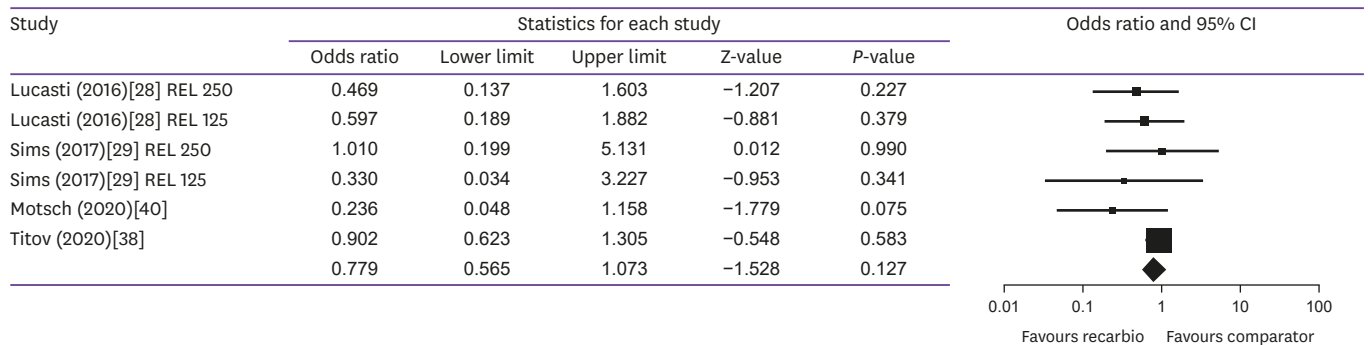


Figure 6. Serious adverse events. CI, confidence interval.



Imipenem/Cilastatin/Relebactam in complicated infections

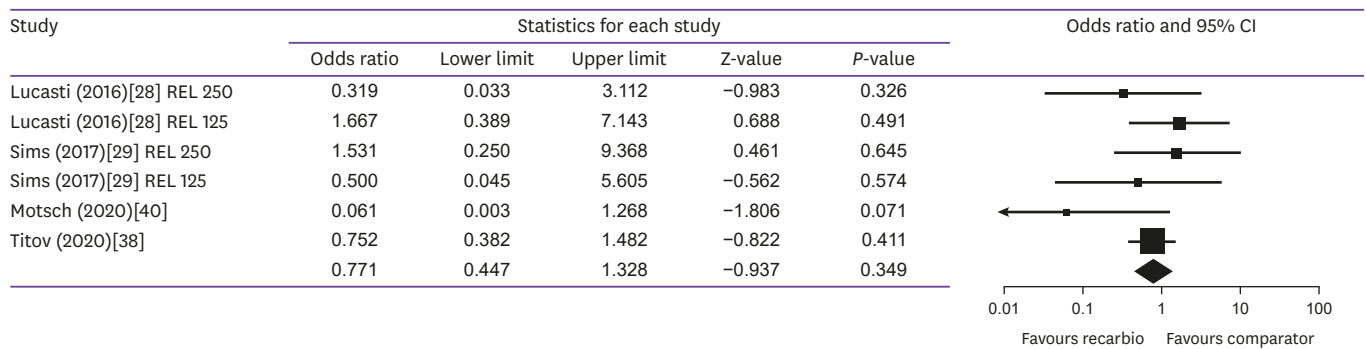


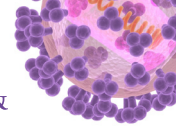
Figure 7. Drug discontinued due to adverse events. CI, confidence interval.

DISCUSSION

In this meta-analysis, we reached several key findings after systematically reviewing and evaluating four RCTs and observational studies for the efficacy and safety of imipenem/cilastatin/relebactam. We compared it with alternative antibiotics to treat bacterial infections, including cUTIs, cIABIs, HABP, and VABP. All eligible studies were included regardless of the risk of bias assessment and sample size. Prior systematic reviews and meta-analyses have not investigated imipenem/cilastatin/relebactam for the treatment for all the infections mentioned above, and subgroup analysis for the dosage and type of infections has not been done. The non-inferiority of imipenem/cilastatin/relebactam compared to imipenem, piperacillin/tazobactam, imipenem + colistin for the treatment of carbapenem-resistant gram-negative presents an alternative treatment of progressively carbapenem-resistant serious bacterial infections.

Carbapenems rose to fame since their debut for their distinctive structural benefit of having a beta-lactam ring, providing a broad spectrum of coverage and supposed some level of immunity against metallo-beta-lactamase and other broad-spectrum beta-lactamases [30]. Carbapenem resistance is secondary to carbapenemases encoding, New Delhi Metallo-β-lactamase-1, and OXA-48 (oxacillinase-48). Other resistance mechanisms include reduction in antibiotic entry by decreasing cell membrane permeability (loss of OprD porin), enhanced expression of efflux pumps, rRNA methylases, and aminoglycoside-modifying enzymes in addition to intrinsic resistance to carbapenems like displayed by *Stenotrophomonas maltophilia* from mutations and novel atypical mechanisms [31, 32].

Carbapenem resistance represents a serious phenomenon as they are considered the main stay treatment for resistant Gram-negative bacteria such as *K. pneumoniae*, *P. aeruginosa*, and *A. baumannii*. The emergence of carbapenem resistance has led to the use of alternatives such as colistin and amikacin, but their use is limited due to their relative toxicities [33]. The novel idea of antimicrobial stewardship has been implemented in hospitals since the beginning of this century to overcome this pandemic of antimicrobial resistance [34]. The solution to this giant of resistance should have been newer potent antibiotics whose efficacy and safety profile were well determined through randomized clinical trials. Unfortunately, we saw no meaningful and targeted antibiotic production in the last decade. The cost-benefit analysis of investment in researching newer drugs with better outcomes in a burdened health care system should be addressed by pharmaceutical companies and health care stakeholders, including government and private groups [35].



Newer antibiotics containing avibactam as the beta-lactamase inhibitor, *e.g.*, ceftazidime + avibactam, has convincing coverage for class A and C Beta lactamases, extended-spectrum beta-lactamases, ampC (cephalosporins), and KPC enzymes implicated in cUTI, cIAI and pneumonia [36].

Considering these facts, clinicians highly anticipated the advent of imipenem/cilastatin/relebactam (a beta-lactam and beta-lactamase inhibitor combination). Gram-negative pathogens, including *Enterobacterias*, *P. aeruginosa*, the anaerobic *Bacteroides* spp, multidrug-resistance pathogens including KPC-producing bacteria and extended-spectrum β -lactamases (ESBL) producing pathogens are sensitive to it owing to an inhibition of expressed class A/C β -lactamases. It also displayed *in vitro* activity versus many KPC- and ESBL-producing Enterobacters and multidrug-resistant *P. aeruginosa*. The addition of relebactam to imipenem can also reduce the minimum inhibitory concentration of the latter in susceptible organisms. *In vitro* studies also showed that most *P. aeruginosa* isolate strains of intensive care unit (ICU) patients in the USA were susceptible to imipenem/relebactam [37].

The RESTORE-IMI 1 trial compared imipenem/cilastatin/relebactam to imipenem-cilastatin plus colistin when treating carbapenem-nonsusceptible cIAIs, cUTIs, HABP and VABP. The patient cohort of 47 adults comprised mainly sick and ICU care patients. The scientists saw a statistically insignificant 20% lower mortality rate in the imipenem/relebactam group. Serious adverse events, including nephrotoxicity, occurred more frequently in the imipenem + colistin group than in the imipenem/relebactam group. RESTORE-IMI 2 trial was a phase 3 study where Imipenem/cilastatin/relebactam was appraised for the treatment of HABP and VABP compared with piperacillin-tazobactam (TZP) in ICU settings [38].

Imipenem/relebactam was proven to be relatively more tolerated than the comparator in prior. Adverse events in RESTORE-IMI 1 trial included were diminished creatinine clearance, fever, hyperglycemia, and injection site reaction [28]. Diarrhea and elevated liver enzymes were seen most frequently in RESTORE-IMI 2 trial [38]. Imipenem (in addition to other carbapenems) is known to decrease the seizure threshold. It also causes myoclonus and altered mental status. Its usage with other epileptogenic drugs should proceed with great caution [39]. The specific adverse effects of relebactam are not significant.

Hence, this medication has a safety profile that is tolerable and comparable to the comparator group.

This meta-analysis has its set of limitations. One of the main limitations of this study is the small number of participants overall in the studies, with 1,237 patients. The small sample size is due to the limited clinical trials so far and difficulty in recruiting patients with confirmed carbapenem resistance who were ill enough to require treatment, stable enough to participate in the study, and receiving treatment at qualified clinical trial sites. It becomes particularly cumbersome when recruitment is done for non-FDA-approved indications. The representation of the patient cohort with carbapenem-resistant *Enterobacteriaceae* (CRE) was limited. The difference in laboratory susceptibility interpretation can also be a limiting factor. Half of the patients with cIAI had adverse outcomes, which can be explained by increased medical complexity, extensive antibiotic exposure in the recent past, and higher APACHE II scores.

Additionally, most included patients were adults, so clinicians should use caution in applying these results to the pediatric population. Most of the study populations consisted mainly of elderly patients at increased risk of abysmal prognosis. Previous data reported adverse fetal outcomes in mammals treated with imipenem/cilastatin and relebactam. The data to support the use of imipenem/cilastatin/relebactam combination, imipenem, cilastatin, and relebactam in pregnant or lactating mothers are lacking. Imipenem/cilastatin/relebactam dose reduction is recommended with creatinine clearance of less than 90 mL/min due to fewer data in patients with chronic kidney disease or similar components. Our subgroup analysis showed no statistically significant difference in clinical response when using 125 mg *vs.* 250 mg dose of imipenem/cilastatin/relebactam. The improved microbiologic response was seen in the 125 mg subgroup in two studies at early follow-up. More RCTs are needed to reach a consensus on dosage recommendations in appropriate clinical settings.

Potentially the most limiting factor in the future widespread use of Imipenem/cilastatin/relebactam would be its high cost compared to already available treatment, with the price for imipenem/cilastatin/relebactam intravenous powder for injection 1.25 g reaching around 7,201 USD for a supply of 25 powder for injection. In contrast, the cost for piperacillin/tazobactam intravenous powder for injection (2 g - 0.25 g) is around 87.5 USD for a supply of 25 powder for injection.

An overstated clinical response is expected from a meta-analysis of the limited number of studies. Current unpublished articles and missing data can contribute to bias. The studies included in this meta-analysis did not comment on global health with the emergence of Carbapenem-resistant organisms. Therefore, antimicrobial selection should be based on local epidemiology and susceptibility patterns. Future randomized controlled trials with larger sample size and inclusion of pediatric and obstetric populations can support our study findings.

Our study suggests that imipenem/cilastatin/relebactam is a compelling new treatment option for HABP/VABP, cUTIs, cIAIs, including critically ill, high-risk patients. In conclusion, while balancing the overall benefit with the efficacy and safety proven for imipenem/cilastatin/relebactam in short and late follow-up, we can state that Imipenem/cilastatin/relebactam is an emerging treatment for the various carbapenem-resistant infections with proven safety and efficacy. Given the overall safety and efficacy profile, there seems to be a non-inferiority profile demonstrated by this study which should be utilized in appropriate clinical and research settings.

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