

# A Systematic Review and Meta-analysis of Efficacy of Carbapenems Versus Other Best Available Antibiotics in the Management of Patients with Urinary Tract Infections

## Abstract

### Introduction

Carbapenems are found in high concentrations in urine and are mainly eliminated by the kidney. Hence, they are the preferred treatment for pyelonephritis and complicated urinary tract infections (cUTIs) caused by extended-spectrum  $\beta$ -lactamase (ESBL) producing bacteria. The recent emergence of bacterial resistance to carbapenems has resulted in the need to search for alternative treatments for complicated UTIs. This review aims to evaluate the efficacy of carbapenems versus piperacillin/tacobactam (or the best available antibiotic therapy) in the management of pyelonephritis in patients with upper UTIs.

### Methods

A systematic review was carried out to compile all relevant studies on the use of carbapenems versus tazocin in the treatment of upper urinary tract infections, namely pyelonephritis. A meta-analysis was carried out of the selected studies, including clinical trials composed of adult patients aged between 18 and 80 years old diagnosed with pyelonephritis. Primary screening of eligible studies was followed by the removal of duplicates and exclusion of non-eligible and unavailable full-text trials.

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### Results

This review included four studies on the treatment of complicated pyelonephritis. The number of patients included per study varied and ranged from 62 to 421 cases. Different types and regimes of carbapenems were used, including intravenous meropenem-vaborbactam, meropenem, biapenem, doripenem, or ertapenem. The included studies

compared carbapenems to piperacillin/tazobactam or other best available therapies, such as third-generation cephalosporin. For microbial failure, the overall risk ratio was 0.95 with a confidence interval range between 0.62 and 1.45, and for clinical failure, the overall risk ratio was 0.86 with a confidence interval range between 0.51 and 1.45.

**Comment [ah2]:** Clarify the number for each case and its impact

### **Conclusions**

According to the meta-analysis, the included studies showed that carbapenems are not inferior to the comparators for the management of complicated urinary tract infections.

### **Keywords**

Carbapenems, pyelonephritis, complicated, urinary tract, antibiotic resistance, tasocin, piperacillin/tazobactam

## Introduction

A urinary tract infection (UTI) is an infection that involves many parts of the urinary tract, including the urethritis, cystitis, prostatitis, and pyelonephritis [4]. UTIs are considered one of the most common infections in community and healthcare-associated settings with an estimate of 250,000 cases of acute pyelonephritis each year in the United States. Incidences occur much more frequently in women than in men for several reasons, such as sexual activity, shorter urethra, and menopause [3]. The majority of UTIs are caused by a single bacterium such as *Escherichia coli* which accounts for 65% to 75% of the cases. Other causative organisms are *Klebsiella* species, especially *klebsiella pneumoniae* (23%), *proteus mirabilis* (7%), *Enterobacteriaceae*, *Enterococcus* species, *Pseudomonas aeruginosa*, and *Staphylococcus saprophyticus* (1% to 4%) [1, 2].

Urinary tract infections (UTIs) are categorised based on the nature of occurrence and by primary and recurrent infections. According to the severity, UTIs are classified into two types, uncomplicated and complicated infections. Uncomplicated UTIs are traditionally associated with a good prognosis, while complicated UTIs affect deeper layers of the tissue and invade the parenchyma pyelonephritis or prostatitis, mainly due to urinary stone obstruction, instrumentation or other comorbid diseases [4]. Uncomplicated UTIs are mostly caused by *Escherichia coli*. A complicated UTI is any infection that occurs in males, pregnant women, immunocompromised or comorbid patient, extends beyond the bladder, or results from a congenital abnormality or obstruction in the urinary tract [2]. Complicated UTIs often have a poor prognosis, as they can cause sepsis, renal abscess, or acute renal failure, especially during the first three years of life and in the worst-case scenario, they can lead to renal damage and lead to end-stage renal disease. Early diagnosis and intervention with effective antibiotic treatment is highly recommended for mitigating morbidity and mortality [5-7].

Whilst UTIs can be asymptomatic, they can also present symptoms, and the main clinical symptoms of UTIs include increased urgency of urination, painful urination, bloody or cloudy urine, and strong odor [8]. Complicated UTIs can lead to fever, flank pain, and urine retention, and in severe cases, pus may accumulate around the kidneys,

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which is known as “pyonephrosis”, and urgent drainage is required [9]. The main diagnostic test for a UTI is urinalysis; in some cases, such as with complicated UTIs, recurrent UTIs, treatment failures, and for inpatients who develop UTIs, urine culture can also be used to detect the infection [10].

### **Pharmacological Treatments**

Initial therapy with intravenous antibiotics is recommended for hospitalized patients [11], including aminoglycoside, fluoroquinolone or extended-spectrum cephalosporin [12]. Switching to oral medication reduces hospitalization and results in cost reduction [11]. Recommended oral antibiotics include ciprofloxacin, levofloxacin, or trimethoprim-sulfamethoxazole for outpatient therapy [13].

A piperacillin/tazobactam combination is used to treat a wide range of bacterial infections such as skin infections, respiratory tract infections and urinary tract infections (UTIs) [14]. Piperacillin belongs to the beta-lactams group and works by attaching to proteins on the surface of the bacteria and eventually killing them whilst preventing the bacteria from building cell walls. Tazobactam blocks the beta-lactamases enzyme that is produced by the bacteria [15]. Lactamases render the bacteria resistant to beta-lactam antibiotics such as piperacillin, as the lactamases break down the beta-lactam group. Tazobactam inhibits bacteria resistance to piperacillin, making piperacillin more effective [15]. Side effects of piperacillin/tazobactam include diarrhea, trouble sleeping, nausea, constipation, and headaches [16].

Carbapenems are parenteral broad-spectrum  $\beta$ -lactam antimicrobial agents with a similar structure to penicillin and cephalosporins [17]. They provide wide activity against gram-positive, gram-negative, and anaerobic microorganisms. Carbapenems act as a cell wall synthesis inhibitor by binding to Penicillin Binding Proteins (PBP), through which they inhibit bacterial peptidoglycan formation [18]. Drugs that belong to carbapenems are ertapenem, meropenem, imipenem-cilastatin, biapenem, and doripenem [19]. All carbapenems demonstrate similar adverse effects that include diarrhea, skin rashes, confusion, and seizures, especially with high doses [20].

Doripenem exhibits high activity against *pseudomonas aeruginosa* compared to the other drugs of the same class [21]. Ertapenem shares a similar safety profile as meropenem and imipenem/cilastatin. However, ertapenem has a long plasma half-life and limited activity against *Acinetobacter baumannii*, *Enterococcus spp*, and *Pseudomonas aeruginosa* [21]. All carbapenems have renal elimination and achieve high concentration in urine. For this reason, carbapenems are the preferred treatment for pyelonephritis and complicated urinary tract infections (cUTIs) caused by extended-spectrum  $\beta$ -lactamase (ESBL) producing bacteria [22].

### **Aims and Objectives**

The aim of this review is to screen and evaluate the efficacy of carbapenems versus piperacillin/tacobactam (or the best available antibiotic therapy) in the management of pyelonephritis in patients with upper UTIs.

### **Study objective:**

1. To review the microbiological success/failure of carbapenems versus piperacillin/tacobactam (or the best available antibiotic therapy) in the management of pyelonephritis in patients with upper UTIs.
2. To review the clinical success/failure of carbapenems versus piperacillin/tacobactam (or the best available antibiotic therapy) in the management of pyelonephritis in patients with upper UTIs.

## **Methods**

### **Search Strategy**

This systematic review employs a meta-analysis to compile all relevant studies on the use of tazocin and carbapenem in the treatment of upper urinary tract infections and pyelonephritis. The quality and relevancy of the titles and abstracts generated by the search techniques were assessed, and papers were modified and selected for inclusion in the meta-analysis based on the results of this review. Keywords searched include, Pyelonephritis – Tasocin– Carbapenem – Piperacillin / Tazobactam – Upper urinary tract infection.

### **Eligibility and Exclusion**

Selected studies in this paper are clinical trials composed of adult patients aged between 18 and 80 years old diagnosed with pyelonephritis. The intervention of choice was carbapenem, and the comparators are a combination of Piperacillin/Tazobactam or the best available treatment. Patients should have no other infections at the time of assessment and should not be undergoing any other antibiotic treatments. All published articles written in English were considered for this study, and publications written in other languages were excluded. If the study did not meet the eligibility criteria, it was excluded from the analysis.

### **Selection of Studies**

All articles related to the utilization of antibiotics in the treatment of upper urinary tract infections and pyelonephritis, mainly carbapenem and tazocin, to compare the effect of tazocin and carbapenem in the treatment of upper urinary tract infections and pyelonephritis were identified through database searching. Duplicates and non-eligible and unavailable full-text trials were excluded from the selection.

## Quality Evaluation of the Included Studies

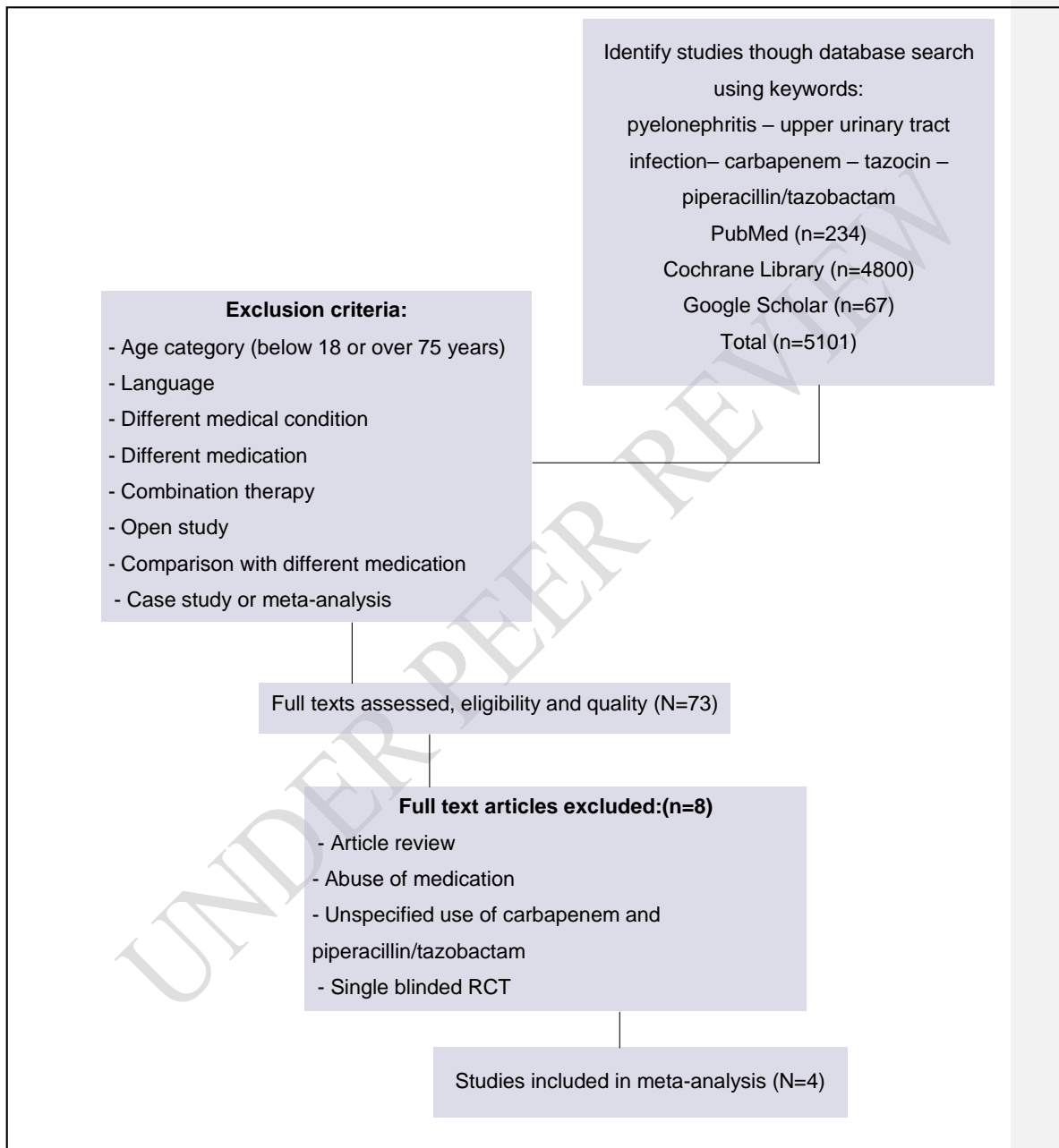
All the included studies comprised of clinical trials; hence the Cochrane checklist for the assessment of the risk of bias in the clinical trials was employed. The Cochrane checklist was implemented electronically in RevMan software (Version 5.4), and the figure of risk of bias was associated with forest plot output. The quality of the included studies was evaluated using the grading system in the Cochrane checklist, which rated the quality of evidence as follows:

1. High quality: further research is very unlikely to change our confidence in the estimate of effect.
2. Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
3. Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
4. Very low quality: we are very uncertain about the estimate.

## Data Extraction and Analysis

A meta-analysis method was used to pool the results of these independent studies, followed by a statistical analysis to pool outcome data for trials that compare the same intervention with a suitable comparator before inputting them into RevMan5. RevMan5 is a software application used to facilitate the review professionally, run statistical analysis, show the risks of bias, and manage references and is available on the university's website in the Student Centre and with a video tutorial, and it can be downloaded straightforwardly. The isolated information was that of sample size, length of treatment, intervention, and outcome measure [23].

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**Figure 1: PRISMA flow diagram demonstrating search strategy, n=number**

## Results

### Description of the Included Studies

This review included four studies that focused on the treatment of complicated pyelonephritis. The included studies compared carbapenems to piperacillin/tazobactam [24-26] or other best available therapies, such as third-generation cephalosporin [25, 27].

### Characteristics of the Included Studies

The number of included patients varied across the studies and ranged from 62 in a study conducted by Dizbay et al. to 421 in a study by Lai et al. The baseline characteristics of the patients included in the intervention and comparison groups were compared only in three studies [24-26], while Takahashi et al. presented a table without statistical comparisons [27]. Lai et al. compared the baseline characteristics between groups using statistical significance tests and they found no significant differences between intervention and comparison groups [25]. However, Dizbay et al. found significant differences between groups regarding the frequency of cancer, history of recurrent UTIs, and previous antibiotic therapy within the last three months. Moreover, Sharara et al. created a pseudo-population using propensity score analysis to balance the baseline characteristics between intervention and comparison groups.

Regarding intervention therapy, different types and regimes of carbapenems were used including intravenous meropenem-vaborbactam every 8 hours for 10 days [25], 500 mg of meropenem twice/day [27], 300 mg biapenem twice/day [27], or 0.250 mg doripenem (DRPM) twice/day [27], and ertapenem [24]. After the cases were stabilized, oral antibiotics were prescribed.

## Main Outcomes

The main outcome in the included studies showed mainly microbial success through the elimination of pathogenic bacteria, which was assessed in intervention and comparison groups; however, there was some variability in the time of assessment of microbial clearance among the included studies. Moreover, clinical success, which means the disappearance of the symptoms, was used to assess the efficacy of treatment in both groups. Lai et al. considered two time points to assess both the clinical and microbiological success of treatment, which were at the end of treatment and  $7\pm 2$  days after treatment [25]. Sharara et al. assessed clinical success by day 7, while they assessed microbial success within 30 days of the infection [26]. On the other hand, Takahashi et al. defined clinical success as patients becoming afebrile within 2 to 4 weeks, while bacterial success was assessed 7 days after antibiotic therapy [27]. Only microbial success was assessed by Dizbay et al. after 48 hours of the treatment and once more after 48 hours [24].

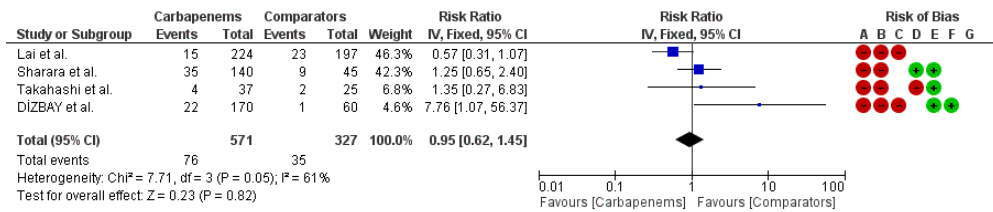
All included studies found carbapenem non-inferior to comparison medications, including piperacillin-tazobactam [24-26] or other best available therapies such as third-generation cephalosporin [25, 27]. There are no significant differences in the efficacy between intervention and comparison medications. Only the incidence of superinfections was found to be significantly different between the ertapenem group and the piperacillin-tazobactam group (29.4% versus 8.3%) in a retrospective analysis conducted by Dizbay et al. [24].

**Table 1: Main Outcomes**

Studies	Carbapenems Group		Comparators Group		Total	Risk Ratio
	Event	Total Participants	Event	Total Participants	The Trial Population at the Endpoint	Effect Size
Lai et al. 2019	15	224	23	197	421	0.57
Sharara et al. 2020	35	140	9	45	185	1.25
Takahashi et al. 2009	4	37	2	25	62	1.35
Dizbay et al. 2016	22	170	1	60	230	7.76

**Findings of the Meta-Analysis**

A meta-analysis was conducted for clinical failure as well as for microbial failure, which may be associated with the development of antimicrobial resistance by the targeted bacteria. For microbial failure, all included studies were introduced into the analysis and risk ratios for the occurrence of microbial failure were calculated using a fixed-effect model. A fixed effect model performs well in this meta-analysis which is clear from visual inspection as confidence intervals of the studies overlapped, despite the presence of moderate heterogeneity between studies ( $I^2=61\%$ ). Moreover, when a random effect model was employed, the results of the meta-analysis were similar. In this meta-analysis, the risk ratio was used as an effect-size measure as the outcome (occurrence of microbial failure) is dichotomous. The overall risk ratio was 0.95, with a confidence interval range between 0.62 and 1.45 (Figure 2).

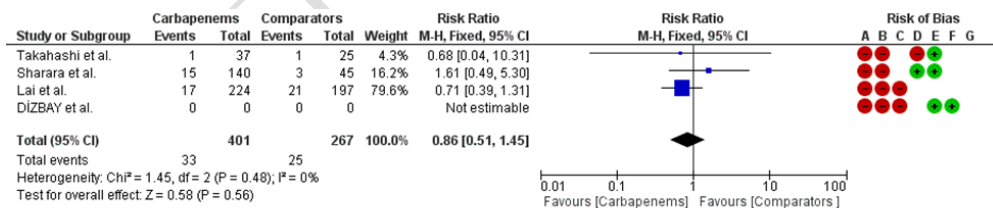


Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

**Figure 2: Occurrence of microbial failure in the intervention and comparison groups among the included studies**

For clinical failure, only three studies were included, as Dizbay et al. did not assess the clinical outcome in their retrospective analysis. A fixed effect model performs well in this meta-analysis due to the absence of heterogeneity between studies ( $I^2=0\%$ ) which was insignificant ( $p=0.48$ ). Moreover, when we used a random effect model, the results of the meta-analysis were similar, and the risk ratio was used as an effect-size measure as the outcome (occurrence of clinical failure) was dichotomous. The overall risk ratio was 0.86, with a confidence interval range between 0.51 and 1.45 (Figure 3).



Risk of bias legend

- (A) Random sequence generation (selection bias)
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- (F) Selective reporting (reporting bias)
- (G) Other bias

**Figure 3: Occurrence of clinical failure in the intervention and comparison groups among the included studies**

### **Quality Assessment**

The included studies are not high-quality clinical trials, and we recommend the conduction of randomized, double-blind clinical trials to increase the strength of the evidence. Based on the Cochrane grade system, the quality of the included studies was generally low, which means that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

UNDER PEER REVIEW

## Discussion

Recently, bacterial resistance to carbapenems has emerged and searching for alternative treatments for complicated UTIs is recommended [28]. Piperacillin/tazobactam and third-generation cephalosporins were indicated to treat complicated UTIs and reduce the risk of emerging carbapenem resistance [29]. However, a limited number of clinical trials have addressed the use of carbapenems as an alternative to treat UTIs, and a few of these studies were prospective clinical trials.

Complicated urinary tract infections are associated with a high risk of hospital admission and are usually associated with nosocomial transmission of antibiotic-resistant bacteria [30]. Due to high morbidity and mortality, it is highly recommended to administer a combination of antibiotic therapy for patients with complicated UTIs as soon as possible [31, 32]. There are many recommendations for the treatment of complicated UTIs, such as European recommendations, which indicate the use of carbapenem and cephalosporin combinations in severe cases or cases with initial failure [33]. Carbapenems and 3<sup>rd</sup> generation cephalosporins are highly effective in the management of complicated febrile UTIs [27]. However, randomized clinical trials investigating the efficacy of these medications are limited. The clinical evidence related to the efficacy of carbapenems in the management of UTIs was evaluated in this study.

As demonstrated in Figures 1 and 2, the risk of bias was high among the majority of items related to the assessment of the quality of the study. For example, all studies missed the randomization element of the clinical trials, and there was no random allocation of the participants. It was also unclear if there was blinding for the outcome assessors or the patients. The follow-up of the patients and prevention of attrition seems to be good since there was no report of patient selective attrition.

The baseline characteristics of the study groups differed significantly in some included studies, which increases the risk of selection bias due to incomparable groups. Moreover, the use of the propensity score analysis to make groups comparable is not the best practice, as using randomization is the best technique to ensure the groups' comparability and prevent bias and confounding effects. The variability in the time of

outcome assessment could generate a significant heterogeneity between studies and could mitigate the effect of therapy as some studies assessed the outcome after weeks of antibiotic therapy.

### **Limitations of the Review**

Although the most common comparison group was piperacillin/tacobactam, an important limitation of the review is the use of different comparators, which may alter the effect size, as the clinical and microbiological success differed based on the type and regime of antibiotic therapy. Another limitation is related to the use of data from the patient records, which could be associated with confounders, particularly when the baseline characteristics of the groups were not balanced. Moreover, in a study conducted by Takashi et al., the assignment of the intervention medication was not randomized and was mainly based on clinical indications. Hence, there is a high risk of confounding by indication in this study. The use of data from patient records in clinical trials, which is known as Real World Trials, has increased in the last few decades; however, many quality issues should be obtained to ensure the validity of the conclusions. One of these issues is the inclusion of a large sample size involving thousands of patients from different hospitals to improve the generalizability of the findings. However, the included studies had relatively small sample sizes ranging from 62 to 421 patients.

### **Study Recommendations**

Due to quality issues in the included studies, further research could change our confidence and is very likely to have an important impact on our confidence in the estimate of medication effect. This review encouraged the conduction of randomized clinical trials with double blinding and allocation concealment. It can also be recommended to conduct a Real World Trial, which depends on patient records with the proper management of confounding and issues of bias [34].

## **Conclusion and Implications for Practice**

Based on the included studies, carbapenems were not inferior to the comparators for the management of complicated urinary tract infections. Moreover, the use of alternatives for carbapenems, such as tazobactam and third-generation cephalosporins, in the management of complicated UTI cases shows similar efficacy and can reduce the risk of the emergence of carbapenem-resistant bacteria.

UNDER PEER REVIEW

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## Appendix

**Table 2: Characteristics for Each Individual Study**

Author	Study	Study sitting	Design	Population	Number of participants	Intervention	Duration	Outcome measure
<b>Lai, et al. 2019</b>	Two phase III randomized, multicenter, multinational studies	Taiwan	Parallel	Aged ≥ 65 years (Mean 55.2)	A total of 421 patients. meropenem-vaborbactam: 224 comparator: 197	meropenem-vaborbactam (2 g/2 g)	TANGO I for 10 days TANGO II for 7–14 days	Efficacy endpoint: clinical cure rate and microbiological eradication rate. Safety endpoint: risk of adverse events.
<b>Sharara, et al. 2020</b>	Multicenter observational study	USA	Parallel	Aged 48-74 years (Mean 63)	A total of 186 patients TZP: 45 Carbapenem: 141	Carbapenem or TZP	30 days	Recurrent cystitis or pyelonephritis with the same ESBL-producing organism, resolution of symptoms by day 7, 30-day mortality, or identification of an incident carbapenem resistant organism.

<b>Takahashi, et al. 2009</b>	Non-randomized clinical trial depending on historical controls.	Japan	Parallel	Aged 23-92 years (mean 90)	A total of 62 patients. Carbapenem: 37 third-generation cephalosporin: 25	In 2006, patients received 0.5 g meropenem twice/day (IV), 0.3 g biapenem twice/day, or 0.25 g doripenem twice/day. In 2007, patients received 1.0 g cefozopran or cefepime twice a day (IV).	April 2012 to January 2008	Primary endpoint: clinical success; patient return to afebrile, 37°C or less, within 2 to 4 weeks post treatment Secondary endpoint: bacterial elimination.
<b>Dizbay, et al. 2016</b>	Randomized clinical trial.	Turkey	Parallel	Aged 18-59 years (Mean 61)	A total of 230 patients. Ertapenem: 170 TZP: 60	Ertapenem or TZP	Carbapenem was done in 2006 while third generation cephalosporin in 2007	The microbiological response of each patient was evaluated after 48 h of treatment, and then followed up once again.