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ABOUT COVER

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Antibiotics for complicated urinary tract infection and acute pyelonephritis: A systematic review

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Abstract

BACKGROUND
The increasing rates of antibiotic-resistance in the recent years has caused the emergence of multiple drug-resistant bacteria. Therefore, antibiotics that are recommended by the current clinical guidelines may not be effective for the treatment of complicated urinary tract infection (UTI) and acute pyelonephritis.

AIM
To determine the clinical efficacy and safety of antibiotics for the treatment of complicated urinary tract infection and acute pyelonephritis.

METHODS
A search of three medical databases (PubMed, EMBASE and Google Scholar) were conducted for eligible articles describing the use of antibiotics in managing complicated UTI and acute pyelonephritis. The following keywords were used to perform the literature search: "urinary tract infection", "complicated UTI", "pyelonephritis", "treatment" and "antibiotics". Additional articles of interest were retrieved from the reference list of selected papers. Eligibility criteria for this systematic review were diagnosis of either complicated urinary tract infection or acute pyelonephritis and the use of antibiotics in management. Clinical trials and observational studies were included in this review while case reports and reviews were excluded. The methodological quality of clinical trials and observational studies was assessed. A descriptive approach was adopted to analyze the data due to the variation of methodology and interventions.

RESULTS
A total of 183 studies were screened; eight studies that matched all the eligibility criteria were included in this review. The antibiotics included in this systematic review were ceftazidime-avibactam, doripenem, levofloxacin, meropenem-vaborbactam, piperacillin-tazobactam, plazomicin, tazobactam-ceftolozane and gentamicin. Two clinical trials reported that shorter duration of levofloxacin or non-fluoroquinolone antibiotics treatment was as effective as the duration of antibiotic therapy recommended by the current guidelines in treating complicated UTI and pyelonephritis. Besides that, ceftazidime-avibactam, piperacillin-
tazobactam and tazobactam-ceftolozane can be used as an alternative to carbapenem in treating extended-spectrum β-lactamase -producing *Escherichia coli*. In the included studies, the cure rates of the complicated UTI and pyelonephritis by meropenem-vaborbactam, piperacillin-tazobactam and tazobactam-ceftolozane was comparable at between 95.6% and 98.4%. Furthermore, the clinical trials showed that levofloxacin had a relatively high rate of adverse events (33.1% and 47.7% in two clinical trials) while tazobactam-ceftolozane had a relatively low rate of adverse events (17.5%). All studies have limitations and a potential for bias.

**CONCLUSION**

The use of novel antibiotics and combination antibiotic therapy can be considered in treating complicated UTI and acute pyelonephritis when resistance to recommended antibiotics occurs.

**Key Words:** Antibiotics; Urinary tract infections; Pyelonephritis; Therapeutics; Drug resistance

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**Core Tip:** There is an increasing resistance rate to the antibiotics recommended by current guidelines for the treatment of complicated urinary tract infection (UTI) and acute pyelonephritis. Therefore, alternative antibiotics need to be explored to increase the cure rate and improve the outcomes of patients. The aim of this systematic review is to investigate the efficacy and safety of different antibiotic therapy in treating complicated UTI and acute pyelonephritis. The use of novel antibiotics and combination antibiotic therapy can be considered in treating complicated UTI and acute pyelonephritis when resistance to recommended antibiotics occurs.

**INTRODUCTION**

A complicated urinary tract infection is a urinary tract infection (UTI) associated with structural or functional abnormality of the genitourinary tract or presence of any underlying disease[1]. Patients who have complicated UTI may experience relapse with an organism similar to the pretherapy isolate or reinfection with a new organism[1]. Complicated urinary tract infection may be associated with severe morbidity such as septic shock, renal failure or even death[1]. Acute pyelonephritis is a bacterial infection causing inflammation of the kidney and renal pelvis which occurs due to the spread of bacteria from the bladder to the kidneys in ascending UTI[2]. The rates of acute pyelonephritis are about 15 to 17 cases per 10000 females and 3 to 4 cases per 10000 males annually in United States[2].

Current guidelines (Infectious Diseases Society of America and European Society of Clinical Microbiology and Infectious Diseases) recommend the use of oral fluoroquinolones for treatment of acute pyelonephritis and complicated UTI as an outpatient because fluoroquinolones are absorbed well from the gastrointestinal tract and can penetrate the kidney[3]. Oral amoxicillin-clavulanate potassium, a cephalosporin and trimethoprim-sulfamethoxazole can be used as alternatives[3]. One of the three intravenous therapies is recommended by Infectious Diseases Society of America for patient hospitalized for acute pyelonephritis: (1) A fluoroquinolone, (2) An aminoglycoside (with or without ampicillin), or (3) An extended spectrum cephalosporin (with or without an aminoglycoside)[3].

However, there are limitations of the antibiotics currently recommended such as adverse events associated with the antibiotics, presence of antibiotic-resistant bacteria or compliance of medication. Therefore, alternative antibiotics must be considered to improve the prognosis and outcome of the patients. Alternative antibiotics such as...
novel antibiotics or combination therapy may be more effective than the antibiotics suggested by the guidelines in treating complicated UTI or acute pyelonephritis. The aim of this review is to investigate the clinical efficacy and safety of antibiotics for the treatment of complicated UTI and acute pyelonephritis based on current literature.

**MATERIALS AND METHODS**

**Search strategy**
A systematic search was conducted to identify studies involving the treatment of complicated UTI or pyelonephritis with antibiotics. Search terms included the following keywords and word combinations: “urinary tract infection”, “complicated UTI”, “pyelonephritis”, “treatment” and “antibiotics”. Search was conducted using the three major databases which were PubMed, EMBASE and Google Scholar. Relevant articles published in English from 2010 to 2019 were identified. Additional articles of interest were retrieved from the reference list of selected papers.

**Eligible criteria**
Only adults diagnosed with complicated UTI or acute pyelonephritis were included in this review. The eligibility criteria include diagnosis of the complicated UTI or acute pyelonephritis based on clinical or microbiological evaluation and the use of antibiotics in management. Both oral antibiotics therapy and intravenous antibiotics therapy were included in this review. Case reports, articles without original data and review articles are excluded in this study.

**Selection of studies and analyses**
The titles and abstracts of all studies were screened for their eligibility for inclusion. Full text manuscript was used to assess eligibility when the decision cannot be made based on title and abstract solely. Data on population, study design, intervention, clinical outcomes and adverse events were collected using a standardized electronic database within Microsoft word. The outcome of the patients is defined as one of the following: Clinical failure rate, microbiological eradication, cure rate, duration of treatment or length of hospital stay. Due to the variation in interventions and study design, a descriptive approach was used to report the data instead of metanalysis. The methodological quality of the studies was assessed using Cochrane risk of bias assessment for randomized control trials (RCT)\[^4\], Newcastle-Ottawa scale for non-randomized control trial\[^5\] and Downs and Black Checklist for Study Quality for observational studies\[^6\] (author LTO). PRISMA guidelines was used as a basis for reporting the results of this systematic review.

**RESULTS**
A total of 331 articles were retrieved by the search strategy, 183 studies were screened and 12 studies were assessed for eligibility based on the full manuscript. After exclusion, 8 studies matched the eligibility criteria and were included in the review for analyses\[^7\]-\[^14\]. 5 studies were RCTs, 2 studies were observational studies and 1 study was a non-randomized trial (Figure 1). A total of 2531 participants enrolled in all the studies identified. The antibiotics included in the studies were ceftazidime-avibactam, doripenem, levofloxacin, meropenem-vaborbactam, piperacillin-tazobactam, plazomicin, tazobactam-ceftolozane and gentamicin. *Escherichia coli* (*E. coli*) was the most common causative pathogen of patients with complicated UTIs and pyelonephritis but other Gram-negative and Gram-positive species had been isolated from patients.

**Therapy and outcomes**
Two observational studies included in this review were retrospective cohort study. Park *et al*\[^7\] compared the efficacy of carbapenem and non-carbapenem antibiotics in treating patient with acute pyelonephritis due to extended-spectrum β-lactamase (ESBL)-producing *E. coli*\[^7\]. The non-carbapenem antibiotics used in the treatment were aminoglycosides, β-lactam/β-lactamase inhibitors, fluoroquinolones and trimethoprim/sulfamethoxazole. The risk of microbiological failure (weighted hazard ratio 0.99) and clinical failure rate (weighted hazard ratio 1.05) were similar in the two groups. The aim of the study was to determine if the initial dosing of gentamicin...
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Figure 1  Flow diagram of the study selection process.

improved patient’s outcomes in pyelonephritis\(^8\). Initial dosing of gentamicin decreased the intravenous (IV) antibiotic treatment length and length of hospital stay. Patients who were given gentamicin generally associated with better outcomes.

Based on the RCTs and a non-randomized trial, one study used oral antibiotic therapy\(^8\), six studies used IV antibiotic therapy\(^8-13\) and two studies used a combination of oral and intravenous antibiotic therapy\(^8-13\). Two randomized control trials involved studying the efficacy of antibiotics used in different doses and duration while three randomized control trials involved studying the efficacy of different antibiotic therapy. The outcome was most commonly assessed at 5 to 9 d post-treatment and 1 to 2 mo post-treatment\(^8-13\). Most of the patients showed improvement in clinical symptoms such as fever, dysuria, urinary frequency, suprapubic pain after 5 to 9 d of initiation of antibiotics therapy\(^8-13\). All of the antibiotics therapy used in the studies had cure rates greater than 60\%\(^8-13\). All the studies described the microbiological etiology in their cases. The infection caused primarily by *E. coli* and *Klebsiella pneumoniae* was the second common bacteria identified\(^8-13\). All the clinical findings of the studies are shown in Table 1.

**Adverse events**

The rates of adverse events associated with the antibiotics therapy in the trials were mostly around 30% to 50%\(^8-13\). Levofloxacin in Connolly *et al*\(^11\) trial had a relative high rate of adverse events (47.7\%)\(^11\). However, this could be due to the small population of patients \(n = 7\) taking levofloxacin therapy in the trial. The most common adverse effects reported in the trials was headache which were reported in the use of ceftazidime-avibactam, doripenem, levofloxacin, meropenem-vaborbactam. Piperacillin-tazobactam and plazomicin\(^8-12\). Both levofloxacin and tazobactam-ceftolozane were frequently associated with gastrointestinal illness and abnormal laboratory findings which were reduced in leukocytes count and increased aminotransferase respectively\(^8-13\). Tazobactam-ceftolozane had a low rate at 17.5% of adverse events reported\(^13\). All the adverse events associated with antibiotic therapy are shown in Table 2.
Table 1 Key studies of antibiotic therapy for complicated urinary tract infections and pyelonephritis

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Study design</th>
<th>Population</th>
<th>Therapy</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Park et al.</td>
<td>Observational study</td>
<td>152 patients with pyelonephritis caused by ESBL</td>
<td>Carbapenems for median 12 d vs non-carbapenems for median 8 d</td>
<td>Clinical failure was similar between two groups (weighted HR 1.05)</td>
</tr>
<tr>
<td>Wagenlehner et al.</td>
<td>Randomized control trial</td>
<td>1033 with suspected or confirmed cUTI/APN, randomized 1:1 to each arm</td>
<td>Ceftriaxone-avibactam vs doripenem up to 10 d or 14 d for patients with bacteremia</td>
<td>Microbiological eradication rate: 77.4% ceftriaxone-avibactam 71.0% doripenem</td>
</tr>
<tr>
<td>Ren et al.</td>
<td>Randomized control trial</td>
<td>330 patients diagnosed with cUTI or APN randomized 1:1 to each arm</td>
<td>IV levofloxacin 750 mg for 5 d vs IV levofloxacin 500 mg and shift to oral levofloxacin 500 mg for 7-14 d</td>
<td>Clinical success rate: 89.87% in IV levofloxacin 750 mg &amp; 89.31% in IV/oral levofloxacin 50 mg vs 0 mg</td>
</tr>
<tr>
<td>Kaye et al.</td>
<td>Randomized control trial</td>
<td>550 patients with cUTI or APN, randomized 1:1 to each arm</td>
<td>Meropenem-vaborbactam vs piperacillin-tazobactam for 10 d</td>
<td>Clinical success rate: 98.4% in the meropenem-vaborbactam group vs 95.6% in the piperacillin-tazobactam group</td>
</tr>
<tr>
<td>Connolly et al.</td>
<td>Randomized control trial</td>
<td>145 patients diagnosed with cUTI and APN, randomized at 22, 76 and 47 in each arm</td>
<td>Plazomicin at 10 mg/kg vs plazomicin at 15 mg/kg vs levofloxacin 750 mg for 5 d</td>
<td>Microbiological eradication rate in MITT and MIE population: 50.0% and 85.7% (plazomicin at 10 mg/kg) vs 60.8% and 88.6% (plazomicin at 15 mg/kg) vs 58.6% and 81.0% (levofloxacin)</td>
</tr>
<tr>
<td>Rudrabhatla et al.</td>
<td>Randomized control trial</td>
<td>54 patients diagnosed with APN randomized 1:1 to each arm</td>
<td>Non-fluoroquinolone antibiotics for 7 d vs 14 d</td>
<td>Patients received antibiotics for 7 d has shorter hospital stay (8 d vs 14 d) and less antibiotic consumption (8.4 DDs vs 17.4 DDs). No patients required retreatment</td>
</tr>
<tr>
<td>Arakawa et al.</td>
<td>Non-randomized, trial</td>
<td>115 patients diagnosed with pyelonephritis or complicated cystitis</td>
<td>IV tazobactam-ceftolozane every 8 h for 7 d</td>
<td>Clinical response rate was 96.6%</td>
</tr>
<tr>
<td>Ryanto et al.</td>
<td>Observational study</td>
<td>152 patients diagnosed with severe pyelonephritis/urosepsis</td>
<td>Gentamicin was prescribed for 43.4% patients. 32% patients were given initial dosing of gentamicin</td>
<td>Duration of IV, time of resolution and length of stay is short in patients given gentamicin. Initial dose of IV gentamicin improved the outcome of patients</td>
</tr>
</tbody>
</table>

ESBL: Extended-spectrum β-lactamase; cUTI: Complicated urinary tract infection; APN: Acute pyelonephritis; IV: Intravenous; HR: Hazard ratio; MITT: Modified intent-to-treat; ME: Microbiologically evaluable; DD: Daily dose.

Quality assessment

The clinical studies included in this review are varied in study design, eligibility, time to follow-up and outcomes. Most of the diagnostic criteria used in the studies were pyuria, presence of 1-2 uropathogens or presence of clinical symptoms such as dysuria, urinary frequency, flank tenderness or fever. Biases were identified in the RCTs including selection bias, performance bias and response bias. Overall, the methodological quality of the studies was moderate. 1 RCTs had good quality and 4 RCTs had fair quality based on the thresholds for converting the Cochrane risk of bias tool to agency for healthcare research and quality standards. The total score for methodological quality for the two observational studies based on Downs and Black Checklist for Study Quality was 12 and 15.

DISCUSSION

Antibiotic resistance is one of the major reason for exploration of other antibiotics to manage complicated UTI and acute pyelonephritis. Rates of quinolone resistance among Enterobacteriaceae were < 1% in mid-to-late 1900s and 1% to 3% as late as 2008 but the quinolone resistance rates have increased until > 10%-30% in recent years. Besides that, some of the antibiotics recommended by the current clinical guidelines may cause serious adverse drug reactions. For examples, cephalosporin may result in rashes, diarrhea, anaphylaxis, haemolytic anaemia and frequent morbidity from Clostridium difficile infection. Besides that, trimethoprim-sulfamethoxazole therapy has been associated with neurological defect, reduced oxygen-carrying capacity, gastrointestinal illness and drug hypersensitivity while aminoglycosides have been associated with nephrotoxicity such as acute tubular necrosis and otoxicity. ESBL-producing E. coli is one of the causative bacteria for acute pyelonephritis and carbapenems are considered first choice treatment for ESBL producers. However
due to the increasing carbapenem resistance rate in *Enterobacteriaceae*, carbapenems should be used judiciously\(^7\). The study by Park *et al*\(^7\) suggested non-carbapenem antibiotics had the same efficacy as carbapenems against ESBL-producing *E. coli*, however insufficient research data and conflicting study results have discouraged the use of non-carbapenem antibiotics\(^8\). Besides that, amikacin was suggested as alternative due to low resistance rate but there are insufficient data about the therapeutic efficacy and association of amikacin with nephrotoxicity\(^9\,10\).

Besides that, RCT has shown that ceftazidime-avibactam and doripenem have the same efficacy in treating hospitalized patients with complicated UTI and acute pyelonephritis\(^10\). Moreover, the clinical cure rate of ceftazidime-avibactam is similar for patients with ceftazidime-non-susceptible and ceftazidime-susceptible pathogens\(^10\). Therefore, ceftazidime-avibactam can be used as an alternative to carbapenem to reduce the spread of carbapenem-resistant bacteria.

Dosing of antibiotics is also an important factor in reducing antibiotic resistance, therefore it is essential to optimize the current regimens. RCT has shown that levofloxacin 750 mg/d for 5 d is as effective as 500 mg/d plus oral regimen of levofloxacin for 7 to 14 d in treating complicated UTI and acute pyelonephritis in terms of clinical efficacy, microbiological efficacy and tolerance\(^11\). High-dose levofloxacin can have prolonged bactericidal activity against *E. coli* with minimum inhibitory concentration up to 32 microg/mL due to increased concentration of the antibiotic in the urine\(^12\). Therefore, levofloxacin 750 mg/d is preferred because the duration of treatment is shorter and the total drug dose was 23% lesser\(^12\). Another RCT involved patients stopping non-fluoroquinolone antibiotics at day 7 or continued treatment until day 14\(^12\). Truncating non-fluoroquinolone antibiotics at day 7 is advised as this strategy can reduce antibiotic consumption, length of hospital stay, treatment-related adverse events and generally yield the same outcome as the patients continuing the antibiotic treatment until day 14\(^12\). Studies have shown that shorter durations of antibiotic therapy is effective for common infections such as bacteremia and community-acquired pneumonia and can prevent the rise of antimicrobial resistance\(^12\).

Both meropenem-vaborbactam and piperacillin-tazobactam are effective in treating complicated UTI and acute pyelonephritis with the overall success rate of 98.4% and 95.6% respectively\(^13\). Piperacillin-tazobactam has shown to be effective in patients where *Enterobacteriaceae* was isolated, including ESBL-producers\(^13\). Plazomicin is a aminoglycoside which is effective in treating for adult patients with complicated UTI.
including acute pyelonephritis with microbiological eradication over 85%\cite{11}. Plazomicin is derived from sisomicin with structural modifications that can prevent degradation from aminoglycoside-modifying enzymes, which is a common mechanism of aminoglycosides resistance\cite{23}. Therefore, plazomicin has the potential to treat complicated UTI and acute pyelonephritis caused by multidrug-resistant Enterobacteriaceae however further studies involving larger sample size should be conducted\cite{11}.

Tazobactam-ceftolozane is a novel antibiotic therapy that is effective in the treatment of complicated UTI and pyelonephritis with microbiological response rate and clinical repose rate of 80.7% and 96.6% respectively\cite{13}. Tazobactam-ceftolozane has a favourable safety profile with a low rate of adverse events (17.5%) and has excellent antibacterial activity against gram-negative bacteria which include Enterobacteriaceae, including ESBL-producing strains and multidrug-resistant Pseudomonas aeruginosa\cite{13}. Finally, an initial dose of IV gentamicin has been associated with positive patient outcomes due to its effectiveness in severe cases of suspected gram-negative sepsis especially against Pseudomonas aeruginosa\cite{14}. However, based on a study, only 54% of E.coli strains found in urine was sensitive to gentamicin\cite{24}. Duration and dose of gentamicin need to be monitored closely due to increased risk of adverse effects such as nephrotoxicity\cite{14}.

This systematic review has limitations. It is possible that evidence and clinical studies had been missed during the search strategy. A comparison of efficacy between different antibiotic therapy is difficult due to the significant variation in study designs, interventions and outcome measures. Besides that, some novel antibiotic therapies have limited and incomplete clinical data for comparison.

In conclusion, several novel antibiotics and combination therapy have proven to be effective in treating complicated UTI and pyelonephritis. The clinical data have shown that shorter duration of treatment with lower consumption of antibiotics are effective for treatment and can reduce the development of multiple drug resistance bacteria. Ceftazidime-avibactam, piperacillin-tazobactam and tazobactam-ceftolozane can be used as an alternative to carbapenem to treat ESBL-producing E.coli. Finally, meropenem-vaborbactam, piperacillin-tazobactam and tazobactam-ceftolozane have high cure rates in treating complicated UTI and pyelonephritis. Therefore, the use novel antibiotics and combination antibiotic therapy can be considered for treating complicated UTI and acute pyelonephritis when resistance to recommended antibiotics occurs. In future trials, standardized diagnostic criteria and outcome measures should be adopted for direct comparison. Moreover, further research is needed to identify the spectrum of patients in whom different antibiotics offers a better clinical outcomes and prognosis.

### ARTICLE HIGHLIGHTS

**Research background**

Antibiotics that are recommended by the current clinical guidelines may not be effective for treatment of complicated urinary tract infection (UTI) and acute pyelonephritis due to the increasing resistance rates to the antibiotics.

**Research motivation**

The key significance of this systematic review is to help clinician in determining suitable antibiotics for the management of complicated UTI and acute pyelonephritis.

**Research objectives**

The aim of this study was to determine the clinical efficacy and safety of antibiotics for the treatment of complicated urinary tract infection and pyelonephritis.

**Research methods**

A search of three medical databases (PubMed, EMBASE and Google Scholar) were conducted for eligible articles describing the use of antibiotics in managing complicated UTI and acute pyelonephritis. The following keywords were used to perform the literature search: “urinary tract infection”, “complicated UTI”, “pyelonephritis”, “treatment” and “antibiotics”. Eligibility criteria included diagnosis of either complicated urinary tract infection or acute pyelonephritis and use of antibiotics in management. Clinical trials and observational studies were included in this review, case reports and reviews were excluded.
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Research results
Eight studies which matched all the eligibility criteria were included in this review. The antibiotics included in the studies were ceftazidime-avibactam, doripenem, levofloxacin, meropenem-vaborbactam, piperacillin-tazobactam, plazomicin, tazobactam-ceftolozane and gentamicin. The clinical data have shown that shorter duration of treatment with lower consumption of antibiotics are effective for treatment and can reduce the development of multiple drug resistance bacteria. Ceftazidime-avibactam, piperacillin-tazobactam and tazobactam-ceftolozane can be used as an alternative to carbapenem to treat ESBL-producing Escherichia coli. Besides that, meropenem-vaborbactam, piperacillin-tazobactam and tazobactam-ceftolozane have high cure rates in treating complicated UTI and pyelonephritis.

Research conclusions
Novel antibiotics and combination antibiotic therapy are effective in managing complicated UTI and acute pyelonephritis when resistance to recommended carbapenem antibiotics occurs.

Research perspectives
Further research is needed to compare the efficacy of different antibiotic therapy and identify the spectrum of patients in whom different antibiotics offers a better clinical outcomes and prognosis.

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