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SYSTEMATIC REVIEWS

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 recent years have supported 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 UTI and acute pyelonephritis.

METHOD

A search of PubMed, EMBASE, and Google Scholar was 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 lists of selected papers. Eligibility criteria for this systematic review were diagnosis of either complicated UTI or acute pyelonephritis and use of antibiotics in management. Clinical trials and observational studies were included, 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.

RESULT

A total of 183 studies were screened, and 8 matched all the eligibility criteria and were included in this review. The antibiotics used included ceftazidime-avibactam, doripenem, levofloxacin, meropenem-vaborbactam, piperacillin-tazobactam, plazomicin, tazobactam-ceftolozane, and gentamicin. Two clinical trials reported that shorter-duration levofloxacin or non-fluoroquinolone antibiotic 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

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tazobactam-ceftolozane can be used as alternatives to carbapenem in treating extended-spectrum -lactamase-producing *Escherichia coli*. The cure rates of complicated UTI and pyelonephritis by meropenem-vaborbactam, piperacillin-tazobactam and tazobactam-ceftolozane was comparable (95.6%-98.4%). Furthermore, levofloxacin had a relatively high rate of adverse events (33.1% and 47.7% in two clinical trials respectively), while tazobactam-ceftolozane had a relatively low rate of adverse events (17.5%). All studies have limitations and a potential for bias.

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

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.

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INTRODUCTION

A complicated urinary tract infection (UTI) is associated with structural or functional abnormalities 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 UTI 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 in the United States are about 15 to 17 cases per 10000 females and 3 to 4 cases per 10000 males annually[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 following three intravenous therapies is recommended by the Infectious Diseases Society of America for patients 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 was to investigate the clinical efficacy and safety of antibiotics for the treatment of complicated UTI and acute pyelonephritis based on the 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". The search was conducted using the three major literature databases of 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.

Eligibility criteria

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

Selection of studies and analyses

The titles and abstracts of all studies were screened for their eligibility for inclusion. The full-text manuscript was used to assess eligibility when a decision could not 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. Outcome of the patients was defined as one of the following: Clinical failure rate; microbiological eradication; cure rate; duration of treatment; or length of hospital stay. Due to variation among the interventions and study designs, a descriptive approach was used to report the data (instead of a meta-analysis). The methodological quality of the studies was assessed using Cochrane risk of bias assessment for randomized control trials (RCTs)[4], The Newcastle-Ottawa scale for non-randomized control trial[5] and Downs and Black Checklist for Study Quality for observational studies[6] (author LTO) were used. PRISMA guidelines were used as a basis for reporting the results of this systematic review.

RESULTS

A total of 331 articles were retrieved by the search strategy, of which 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]. Among them, 5 studies were RCTs, 2 studies were observational studies, and 1 study was a non-randomized trial (Figure 1). A total of 2531 participants were 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 the cases of complicated UTI 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 studies. Park *et al*[7] compared the efficacy of carbapenem and non-carbapenem antibiotics in treating patients with acute pyelonephritis due to extended-spectrum -lactamase (ESBL)-producing *E. coli*[7]. The non-carbapenem antibiotics used in the treatment were aminoglycosides, -lactam/-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 for the two groups. The aim of the study was to determine if the initial dosing of gentamicin 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, in general, showed an association with better outcomes.

Based on the RCTs and a non-randomized trial, 1 study used oral antibiotic

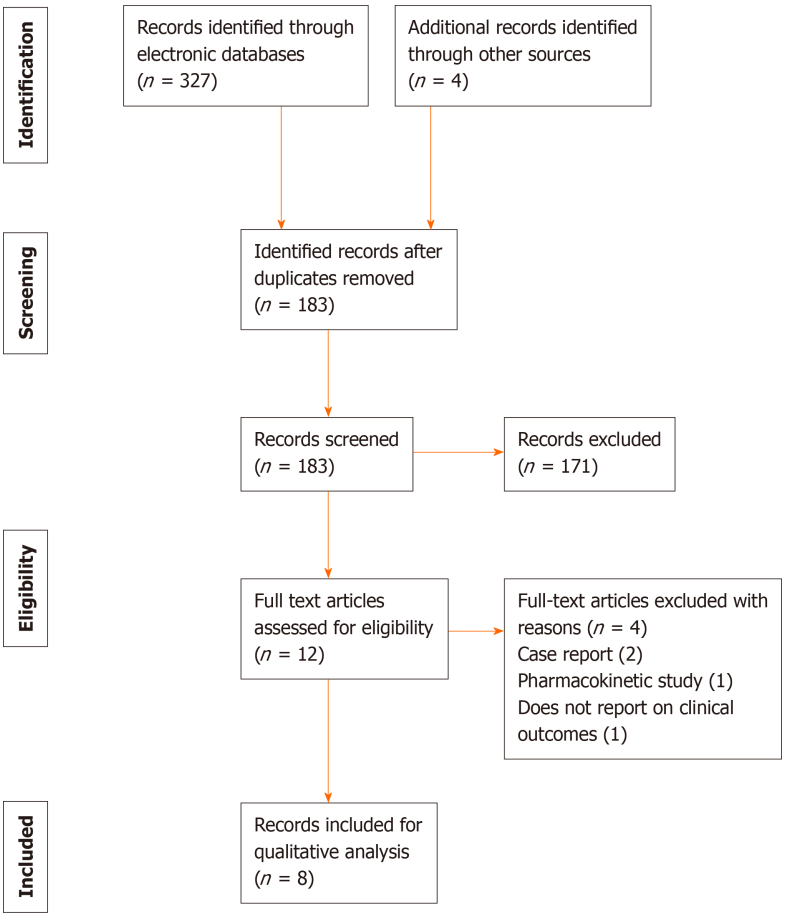

Figure 1 Flow diagram of the study selection process.

therapy[8], 6 studies used IV antibiotic therapy[8-13], and 2 studies used a combination of oral and IV antibiotic therapy[9,10]. Two RCTs involved studying the efficacy of antibiotics used in different doses and duration, while three RCTs involved studying the efficacy of different antibiotic therapies. The outcome was most commonly assessed at 5-9 d post-treatment and 1-2 mo post-treatment[8-13]. Most of the patients showed improvement in clinical symptoms, such as fever, dysuria, urinary frequency, and suprapubic pain, after 5-9 d of initiation of antibiotic therapy[8-13]. All of the antibiotic therapy used in the studies had cure rates greater than 60%[8-13]. All the studies described the microbiological etiology in their cases. The infections were caused primarily by *E. coli*, and *Klebsiella pneumoniae* was the second most common bacteria identified[8-13]. All of the clinical findings of the studies are shown in Table 1.

Adverse events

The rates of adverse events associated with the antibiotic therapy in the trials were mostly around 30% to 50%[8-11]. Levofloxacin, in the Connolly *et al*[11] trial, had a relatively 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 that trial. The most common adverse effects reported in the trials was headache, which was reported in the use of ceftazidime-avibactam, doripenem, levofloxacin, meropenem-vaborbactam. piperacillin-tazobactam, and plazomicin[8-11]. Both levofloxacin and tazobactam-ceftolozane were frequently associated with gastrointestinal illness and abnormal laboratory findings, which were reduced leukocyte count and increased aminotransferase respectively[11,13]. 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.

Quality assessment

The clinical studies included in this review varied in study design, eligibility, time to follow-up, and outcomes. The most common diagnostic criteria used in the studies were pyuria, presence of 1-2 uropathogens, or presence of clinical symptoms, such as

Table 1 Key studies of antibiotic therapy for complicated urinary tract infections and pyelonephritis

Ref.	Study design	Population	Therapy	Findings
Park *et al*[7], 2014	Observational study	152 patients with pyelonephritis caused by ESBL-producing *Escherichia coli*	Carbapenems for median 12 d *vs* non-carbapenems for median 8 d	Clinical failure was similar between the two groups (weighted HR: 1.05)
Wagenlehner *et al*[8], 2016	RCT	1033 with suspected or confirmed cUTI/APN, randomized 1:1 to each arm	Ceftazidime-avibactam *vs* doripenem up to 10 d or 14 d for patients with bacteremia	Microbiological eradication rate: 77.4% ceftazidime-avibactam; 71.0% doripenem
Ren *et al*[9], 2017	TCT	330 patients diagnosed with cUTI or APN, randomized 1:1 to each arm	IV levofloxacin 750 mg for 5 d *vs* IV levofloxacin 500 mg and shift to oral levofloxacin 500 mg for 7-14 d	Clinical success rate: 89.87% in IV levofloxacin 750 mg *vs* 89.31% in IV/oral levofloxacin 50 *vs* 0 mg
Kaye *et al*[10], 2018	RCT	550 patients with cUTI or APN, randomized 1:1 to each arm	Meropenem-vaborbactam *vs* piperacillin-tazobactam for 10 d	Clinical success rate: 98.4% in the meropenem-vaborbactam group *vs* 95.6% in the piperacillin-tazobactam group
Connolly *et al*[11], 2018	RCT	145 patients diagnosed with cUTI and APN, randomized at 22, 76 and 47 in each arm	Plazomicin at 10 mg/kg *vs* plazomicin at 15 mg/kg *vs* levofloxacin 750 mg for 5 d	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)
Rudrabhatla *et al*[12], 2018	RCT	54 patients diagnosed with APN, randomized 1:1 to each arm	Non-fluoroquinolone antibiotics for 7 d *vs* 14 d	Patients who received antibiotics for 7 d had shorter hospital stay (8 d *vs* 14 d) and less antibiotic consumption (8.4 DDs *vs* 17.4 DDs) No patients required retreatment
Arakawa *et al*[13], 2018	Non-randomized, trial	115 patients diagnosed with pyelonephritis or complicated cystitis	IV tazobactam-ceftolozane every 8 h for 7 d	Clinical response rate was 96.6%
Ryanto *et al*[14], 2019	Observational study	152 patients diagnosed with severe pyelonephritis/urosepsis	Gentamicin was prescribed for 43.4% patients; 32% of patients were given initial dosing of gentamicin	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

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

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. One RCT had good quality and four RCTs had fair quality, based on the thresholds for converting the Cochrane risk of bias tool to agency for healthcare research and quality standards[4]. The total score for methodological quality for the two observational studies based on the Downs and Black Checklist for Study Quality[6] was 12 and 15.

DISCUSSION

Antibiotic resistance is one of the major reasons for exploration of other antibiotics to manage complicated UTI and acute pyelonephritis[3]. Rates of quinolone resistance among *Enterobacteriaceae* were 1% in the mid-to-late 1900s and 1% to 3% as late as 2008 but the quinolone resistance rates have increased to 10%-30% in recent years[15]. Besides that, some of the antibiotics recommended by the current clinical guidelines may cause serious adverse drug reactions. For example, cephalosporin may result in rashes, diarrhea, anaphylaxis and haemolytic anaemia, and has shown a frequent association with morbidity from *Clostridium difficile* infection[16]. 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 ototoxicity[17,18].

ESBL-producing *E. coli* is one of the causative bacteria for acute pyelonephritis and carbapenems are considered first-choice treatment for ESBL producers[19]. 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 against ESBL-producing *E. coli* as carbapenems;

Table 2 Adverse events associated with antibiotic therapy reported in the studies

Antibiotics	Ref.	Adverse events reported	Most common adverse effects	Frequency, *n* /total (%)
Ceftazidime-avibactam	Wagenlehner *et al*[8]	Headache, nausea, diarrhea, constipation	Headache	185/511 (36.2)
Doripenem	Wagenlehner *et al*[8]	Headache, nausea, diarrhea, constipation	Headache	158/509 (31.0)
Levofloxacin	Ren *et al*[9]	Reduction in leukocyte count, reduction in neutrophil count, increased ALT, increased AST, increased platelet count, increased blood pressure, gastrointestinal, reaction at injection site, cutaneous/subcutaneous, nervous system/mental, immune, infection, hepatobiliary, metabolic/nutritional, musculoskeletal/connective tissue	Reduction in leukocyte count and gastrointestinal	109/329 (33.1)
	Connolly *et al*[11]	Headache, diarrhea, vomiting, nausea, dizziness	Headache	21/44 (47.7)
Meropenem-vaborbactam	Kaye *et al*[10]	Headache, diarrhea, nausea, asymptomatic bacteriuria, catheter site phlebitis, infusion site phlebitis, urinary tract infection, hypokalemia, vaginal infection, ALT increased, anemia, AST increased, pyrexia	Headache	106/272 (39.0)
Piperacillin-tazobactam	Kaye *et al*[10]	Headache, diarrhea, nausea, asymptomatic bacteriuria, catheter site phlebitis, infusion site phlebitis, urinary tract infection, hypokalemia, vaginal infection, ALT increased, anemia, AST increased, pyrexia, dyspnea	Headache	97/273 (35.5)
Plazomicin	Connolly *et al*[11]	Headache, diarrhea, vomiting, nausea, dizziness	Headache	33/96 (34.4)
Tazobactam-ceftolozane	Arakawa *et al*[13]	Diarrhea, ALT increased, constipation, AST increased, insomnia, headache, pyelonephritis, pyelonephritis acute, contusion, viral upper respiratory tract infection	Diarrhea and ALT increased	20/114 (17.5)

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

however, insufficient research data and conflicting study results have discouraged the use of non-carbapenem antibiotics[7]. Besides that, amikacin was suggested as an alternative due to low resistance rate but there are insufficient data about the therapeutic efficacy and association of amikacin with nephrotoxicity[7,20].

An RCT showed that ceftazidime-avibactam and doripenem have the same efficacy in treating hospitalized patients with complicated UTI and acute pyelonephritis[8]. Moreover, the clinical cure rate of ceftazidime-avibactam was found to be similar for patients with ceftazidime-nonsusceptible and ceftazidime-susceptible pathogens[8]. 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. An RCT showed that levofloxacin at 750 mg/d for 5 d is as effective as 500 mg/d plus oral regimen of levofloxacin for 7-14 d in treating complicated UTI and acute pyelonephritis in terms of clinical efficacy, microbiological efficacy, and tolerance[9]. High-dose levofloxacin can have prolonged bactericidal activity against *E. coli* with minimum inhibitory concentration up to 32 mg/mL, due to increased concentration of the antibiotic in the urine[21]. Therefore, levofloxacin at 750 mg/d is preferred because the duration of treatment is shorter and the total drug dose was 23% less[9]. Another RCT involved patients stopping non-fluoroquinolone antibiotics at day 7 or continuing 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 and treatment-related adverse events, and generally yield the same outcome as seen in the patients who continued the antibiotic treatment until day 14[12]. Studies have shown that shorter durations of antibiotic therapy are effective for common infections, such as bacteremia and community-acquired pneumonia and can prevent the rise of antimicrobial resistance[22].

Both meropenem-vaborbactam and piperacillin-tazobactam are effective in treating complicated UTI and acute pyelonephritis, with the overall success rates of 98.4% and 95.6% respectively[10]. Piperacillin-tazobactam has been shown to be effective in patients from whom *Enterobacteriaceae* was isolated, including ESBL-producers[10]. Plazomicin is a aminoglycoside that is effective in treating adult patients with complicated UTI including acute pyelonephritis, with microbiological eradication over 85%[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[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[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[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 encompass the *Enterobacteriaceae* spp., including ESBL-producing strains and multidrug-resistant *Pseudomonas aeruginosa*[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 *P. aeruginosa*[14]. However, only 54% of *E. coli* strains found in urine have been reported as sensitive to gentamicin[24]. Duration and dose of gentamicin need to be monitored closely, due to increased risk of adverse effects, such as nephrotoxicity[14].

This systematic review has limitations. It is possible that evidence and clinical studies were missed by the search strategy employed. A comparison of efficacy between different antibiotic therapies 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 therapies 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 of 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 offer 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

This systematic review is intended to provide comprehensive information to help clinicians 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 UTI and pyelonephritis.

Research methods

A search of three medical literature databases (PubMed, EMBASE and Google Scholar) was 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 UTI or acute pyelonephritis and use of antibiotics in management. Clinical trials and observational studies were included in this review, while case reports and reviews were excluded.

Research results

Eight studies matched all the eligibility criteria and were included in this review. The antibiotics included in those 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 is effective for treatment and can reduce the development of multiple drug resistance bacteria. Ceftazidime-avibactam, piperacillin-tazobactam and tazobactam-ceftolozane can be used as alternatives 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 regimens are effective in managing complicated UTI and acute pyelonephritis when resistance to recommended antibiotics occurs.

Research perspectives

Further research is needed to compare the efficacy of different antibiotic therapies and identify the spectrum of patients in whom different antibiotics offer better clinical outcomes and prognosis.

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CASE REPORT

Abdominal aortic thrombosis as initial presentation of COVID-19 infection: A case report

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Abstract

BACKGROUND

The hypercoagulable state associated with coronavirus disease 2019 (COVID-19) has been shown to complicate the course of this viral illness with both venous and arterial clots. Often presenting after hospitalization and known COVID-19 diagnosis, the etiology of thrombosis has been attributed to the hyperinflammatory state and endothelial dysfunction associated with COVID-19. This report portrays a patient who experienced an aortic thrombosis resulting in back and leg pain with subsequent loss of motor function of his legs as his initial presentation of COVID-19.

CASE SUMMARY

Patient is a 60-year-old Caucasian male with no medical history who presented with sudden onset pain in his lower back and lower extremities. He went on to experience complete motor loss of the lower extremities two hours after admission. Chest pain and shortness of breath developed one day later but were not present at time of presentation. Computed tomography angiography of the chest, abdomen, and pelvis revealed occlusion by thrombosis of the abdominal aorta in addition to multifocal pulmonary ground-glass opacities prompting COVID-19 PCR, which was positive. He was taken to surgery for attempted thrombectomy and the thrombus was retrieved starting from the right common femoral artery, but a second thrombus had immediately reformed in place of the prior thrombectomy site resulting in conclusion of the procedure. He was continued on unfractionated heparin and received a dose of tocilizumab 400 mg, but rapidly developed hemodynamic compromise and expired from cardiac arrest.

CONCLUSION

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This presentation emphasizes the importance of evaluating patients for COVID-19 who experience unusual thromboses without superior explanation.

Key Words: COVID-19; Aortic thrombosis; Arterial thrombosis; Atypical COVID-19 presentation; COVID-19 complication; Case report

Core Tip: Aortic thrombosis preceding respiratory symptoms should raise suspicion for testing for coronavirus disease 2019 in patients with unusual thrombosis presentation.

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INTRODUCTION

The known hypercoagulable state associated with coronavirus disease 2019 (COVID-19) infection has been implicated as a common cause of morbidity and mortality. The presentation can range from microthrombi to large thromboses in both intra- and extrapulmonary vessels. In addition, the diagnosis of thrombosis often occurs days to weeks after the initial onset of respiratory symptoms, resulting in worsening of overall clinical status and prognosis. One study in France showed that pulmonary embolism (PE) was diagnosed with a mean of 12 days since initial onset of symptoms in COVID positive patients[1]. The converse, of having an obvious thrombotic event preceding onset of respiratory symptoms, may lead providers away from testing a patient for COVID-19. There have been two reports of aortic thromboses in patients with COVID-19 pneumonia, but thrombosis occurred after the patient was already known to be positive for COVID-19. The hypercoagulable state associated with this infection should be considered in patients with no obvious risk factors for thrombosis or evidence of thrombosis in an unusual location, as endothelial dysfunction coupled with hyperinflammation are thought to be mediators of this hypercoagulable state. In this case report, we describe a patient who presented with back and leg pain, and further work up revealed extensive thrombosis in the aorta, iliac, and superior mesenteric arteries (SMA). His abnormal chest imaging prompted PCR testing for COVID-19, which was positive. Our case displays the importance of appreciating the hypercoagulability associated with COVID-19 and raises awareness to a variety of possible presentations.

CASE PRESENTATION

Chief complaints

Patient is a 60-year-old incarcerated Caucasian male with no past medical history who presented to the hospital with complaints of sudden onset pain in his lower back and lower extremities.

History of present illness

He went on to experience complete motor loss of the lower extremities two hours after admission. Chest pain and shortness of breath developed one day later but were not present at time of presentation. He did not have any other symptoms indicative of infection including fever, chills, or cough. He was not taking any medications.

History of past illness

Patient has no past medical history.

Physical examination

Vitals at presentation were blood pressure 99/47, pulse 126 beats per minute, temperature 36.8 °C, respirations 15 per minute, and oxygenation 99% on room air. Neurologic exam of the lower extremities initially revealed 3/5 motor strength, but sensation was intact. Repeat exam in 2 hours revealed complete motor loss of the lower extremities. Dorsalis pedis and posterior tibial pulses were not palpable and femoral pulses were weak at 1+. Pulmonary exam revealed diffuse rhonchi in all lung fields. Cardiac exam revealed tachycardia, but no murmurs were noted, and the rhythm was regular. He was alert and oriented to person, place, and time.

Laboratory examinations

Patient had a positive COVID-19 PCR blood test. His laboratory values were remarkable for leukocytosis of 22.3 cells/L (4.5-11.0) with an absolute lymphocyte count of 0.58 K/uL (1.32-3.57), PT 16.4 seconds (12-14.5), INR 1.3 U (< 1.0), PTT 28.9 seconds (23.9-36.6), and d-dimer > 20 μg/mL (< 0.5). Ferritin was significantly elevated at > 40000 μg/L (22-275), C reactive protein was 210 mg/L (0-5), and creatine phosphokinase was 46800 U/L (0-200).

Imaging examinations

Patient underwent computed tomography (CT) angiography of the chest, abdomen, and pelvis which revealed occlusion by thrombosis of the abdominal aorta, depicted in Figures 1 and 2, in the infrarenal segment with extension to his iliac arteries with reconstitution of flow in the bilateral common femoral arteries. Additional nonocclusive thrombosis in the SMA was noted. In addition to these thromboses, multifocal ground-glass opacities were visualized in the bilateral lung fields which prompted COVID-19 PCR testing.

FINAL DIAGNOSIS

This patient suffered from an occlusive abdominal aortic thrombosis secondary to COVID-19 infection.

TREATMENT

Patient was emergently taken to surgery for attempted thrombectomy and a heavy burden of thrombus was retrieved starting initially from the right common femoral artery. After several minutes of closing of vasculature, it was noted that the femoral artery pulsation had weakened and disappeared and it was noted that a second thrombus had formed again in place of the prior thrombectomy site after reevaluation despite running of heparin. At this point, the procedure was concluded as it was clear that the patient was hypercoagulable due to his COVID-19 infection.

Patient remained intubated following the operation due to respiratory compromise in the setting of his known COVID-19 pneumonia. He was continued solely on unfractionated heparin infusion at 18 U/kg/h. He also received a dose of Tocilizumab 400 mg, but continued to worsen from a hemodynamic standpoint, requiring the initiation of vasopressors. No additional anti-viral agents or COVID-19 targeted therapies were employed.

OUTCOME AND FOLLOW-UP

Despite ventilatory support and triple vasopressors with norepinephrine, phenylephrine, and epinephrine, patient continued to deteriorate and soon expired from cardiac arrest in the setting of his occlusive abdominal thrombosis.

DISCUSSION

As a respiratory virus, COVID-19 typically presents with signs of lung infection including shortness of breath, cough, and fever which can progress to acute respiratory distress syndrome. Patients requiring admission to an intensive care unit

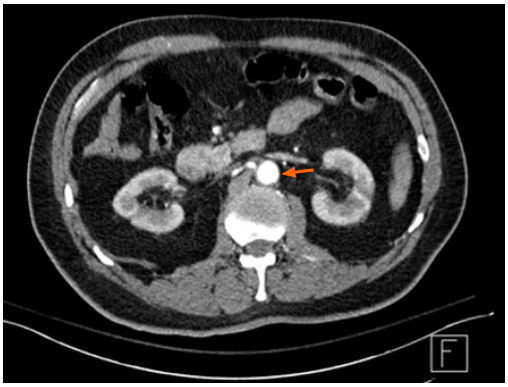

Figure 1 Computed tomography angiogram of the abdomen- portrays a patent aorta with contrast visualized just prior to the complete thrombotic occlusion.

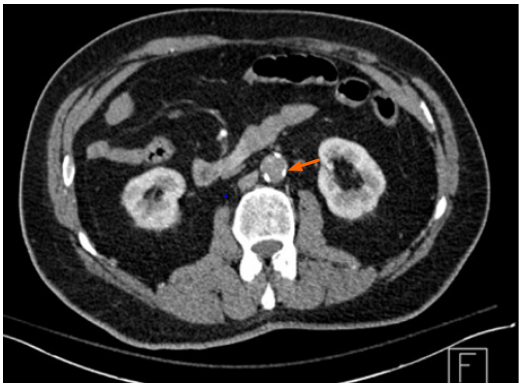

Figure 2 Computed tomography angiogram of the abdomen- shows the abrupt loss of contrast in the aortic lumen indicating the occlusive thrombus that resulted in the patient's symptoms of back pain and loss of lower extremity motor function due to vascular insufficiency. This imaging modality was chosen to visualize the vasculature to evaluate for aortic dissection, aneurysm, or thrombosis given patient's symptoms of crushing back pain with lower extremity motor loss. Aortic calcification incidentally visualized.

(ICU) have been found to have acute thromboses, most commonly being PE in the setting of the severe inflammatory response, endothelial dysfunction, and multi-organ system failure elicited by the virus. Overt thrombosis has been reported to be as high as 25%-50% in this population[2]. Unlike traditional thrombotic events in ICU patients, COVID-19-associated thrombosis has a higher incidence of arterial clot and a greater mortality[3,4]. In a study of three Dutch hospitals, there was a 31% incidence of thrombosis in ICU patients, with 3.7% being arterial[5]. Markers such as D-dimer, lactate dehydrogenase, ferritin, and CRP have been used to stratify patients for risk of thrombosis and potential benefit with prophylactic anticoagulation, but degree of elevation associated with arterial clot has yet to be appreciated.

A report by Berre *et al*[6] presented a patient who was found to have acute aortic thrombosis and concomitant pulmonary embolism after being diagnosed with COVID-19 pneumonia. This patient was found to have a D-dimer of 17.28 μg/mL with normal platelets and prothrombin time. An additional report by Katchanov *et al*[7] described a patient with extensive aortic thrombosis and a D-dimer level of 15.28 μg/mL. Consistent with this trend of severely elevated inflammatory markers, particularly D-dimer, our patient's D-dimer was severely elevated at > 20 μg/mL and ferritin > 40000 μg/L. These findings suggest that extensive thrombosis involving the arterial circulation may be more likely at the far end of the spectrum of extreme inflammation and endothelial dysfunction. Interestingly, both our patient and the above case presented by Katchanov *et al*[7] showed involvement of the abdominal aorta and iliac arteries in addition to occlusion of the SMA. Given these two reports of SMA occlusion and the possibility of intestinal ischemia, providers should consider this in patients to receive the anti-IL-6 agent tocilizumab for severe inflammatory dysregulation, as intestinal perforation is a known side effect despite its single-dose indication[8]. Alternative COVID-19 directed therapies include the anti-viral remdesivir and convalescent plasma, as these agents may have been additional options for this

patient in absence of his rapid clinical decline. Due to the fact that his decline was thought to be more related to his aortic thrombosis and not to COVID-19 induced lung dysfunction, the mainstay of therapy was unfractionated heparin, which was chosen due to rapid reversibility compared to newer direct oral anticoagulants such as apixaban or rivaroxaban.

As arterial thrombi may not always be visualized with routine CT angiography PE protocols, it is important to consider additional scanning for patients with severely elevated inflammatory markers in which suspicion is high for arterial clot. A contrast CT of the abdomen or aortic CT angiography may be necessary to diagnose these aortic thromboses, and our patient was diagnosed with CT angiography of the chest, abdomen, and pelvis given his overt lower back and lower extremity pain as his presenting symptoms. The most impressive finding in our patient was the evidence of a rapidly forming thrombi after successfully removing the initial thrombi and reperfusion of the lower extremities. This echoes the profound hypercoagulable state as a result of COVID-19.

CONCLUSION

Acute thrombosis in the setting of COVID-19 can be a devastating complication with a drastic increase in morbidity and mortality. Our case highlights the profound hypercoagulable state of severe inflammatory response due to COVID-19, with the rapid formation of a thrombi immediately following thrombectomy, compromising perfusion and hastening refractory shock and death. We hope to raise awareness in the importance of recognizing arterial thrombi as a result of COVID-19 in patients with no other obvious explanation, as a prompt diagnosis may influence potential treatment options and lead to better outcomes.

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