Review

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Management of Antibiotic-Resistant Acute Pyelonephritis

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Acute pyelonephritis (APN) is a common urinary tract infection that affects a large proportion of women. Although antimicrobial therapy is a successful treatment in most cases, empirically, antibiotic resistance has emerged as a serious issue, including high resistance rate of fluoroquinolone and the advent of extended-spectrum β-lactamase (ESBL)-producing organisms. Several agents can be considered for the management of antibiotic resistant APN. Fosfomycin trometamol is effective in treating ESBL-producing bacterial infection. Oral trimethoprim/sulfamethoxazole, β-lactam agents, such as cephalosporin, and fluoroquinolone can be regarded as appropriate agents if pathogen is susceptible. Carbapenem, such as imipenem, meropenem, and doripenem, is one of the best and widely used agents for treating antibiotic resistant APN. However, there have recently been concerns regarding the increased rates of resistance to carbapenems. Daptomycin, linezolid, and tigecycline can be considered as solutions to antibiotic resistant organisms. Antibiotic resistant APN should be treated as other systemic infections to prevent antibiotic overuse with proper treatment duration considering carbapenem-saving strategy.

Keywords: Pyelonephritis; Drug resistance, microbial; Urinary tract infections

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INTRODUCTION

Acute pyelonephritis (APN) is a common infection that affects a large population of women. The determinants of infection have been adequately described, and the current strategies for preventing recurrence are highly effective. Although antimicrobial therapy is successful in most cases, the rapid evolution of antimicrobial susceptibility and resistance in common etiologic organisms, particularly *Escherichia coli* and *Enterobacter* species, has become a therapeutic dilemma for many urologists, requiring continuous re-evaluation of appropriate empiric therapy.

In Korea, Shin et al. [1] evaluated 719 uncomplicated APN cases, and found that *E. coli* was the most common pathogen (661/719, 91.9%). Susceptibility of *E. coli* to several antibiotics was reported to be as follows: ciprofloxacin, 84.1%; trimethoprim-sulfamethoxazole (TMP-SMX), 67.2%; and extended-spectrum β-lactamase (ESBL)-negative, 92.4%. Fluoroquinolone was the most frequently prescribed antibiotic for uncomplicated APN (45.3% intravenously and 53.9% orally) [2].

Some urinary tract infection (UTI)-causing micro-organisms have been well-established and known to possess resistance to antibiotics, posing great challenges to urologists. Examples of these include vancomycin-resistant *Enterococci* (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA),

ESBL-producing gram-negative bacteria, *Klebsiella pneumoniae*, carbapenemase-producing gram-negative bacteria, and multidrug-resistant gram-negative rod bacteria, including *Enterobacter* species, *E. coli*, *K. pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and etc.

According to reports from the World Health Organization and European Commission, ESBL-producing *E. coli* bacteria are emerging worldwide. Therefore, further studies and strategies for controlling the growth of antibiotic resistance in these are necessary [3-8]. ESBL-producing organisms require special attention because they are resistant to almost all broad-spectrum antibiotics that are commonly used in clinical practice, such as penicillins, all generations of cephalosporins, including third and fourth generations, and aztreonam [9]. Moreover, ESBL-producing organisms can easily become cross-resistant to TMP-SMX and quinolones. Drug resistance can have a significant impact on the clinical course of treatment, in both uncomplicated and complicated upper UTIs.

This paper reviews the management of antibiotic-resistant APN, emergence of newer drugs controlling resistance, and proper treatment strategies.

MANAGEMENT OF ACUTE PYELONEPHRITIS

In uncomplicated UTIs, *E. coli* is the most common etiologic pathogen. Meanwhile, 34-46% of all UTIs in a hospital are caused by VRE [10]. The standard treatment for uncomplicated APNs includes starting empiric antibiotic treatment until a susceptibility test of urine culture reveals specific antibiotics. Treatment for a 5-14-day period causes the urine to become free of pathogens. For uncomplicated APN, oral administration for 10-14 days is usually sufficient [11]. If a patient has any kind of urinary catheters such as ureteric stents or nephrostomy tubes, they should be removed whenever possible. In case of relapse or recurrence of APN, despite proper antibiotic management, structural urinary anomaly should be considered.

In regions with a resistance rate of less than 10% for *E. coli*, fluoroquinolone can be recommended as the first line therapy for 7-10 days [11]. If the dose of fluoroquinolone is increased, the treatment duration can be reduced to 5 days. However, there appears to be an increasing number of fluoroquinolone-resistant *E. coli* in many countries, particularly in the Asia-pacific region. Therefore, the empirical use of fluoroquinolones should be restricted. Fluoroquinolone is also contraindicated during pregnancy.

MECHANISMS OF ANTIBIOTIC RESISTANCE

Resistance can be classified into two categories: i) inherent, primary resistance, constitutively against an antibacterial substance; and ii) acquired, secondary resistance, which emerges in intrinsically susceptible bacteria. The following mechanisms are ways in which organisms develop antibiotic resistance.

1. Permeability and Efflux Mechanism Modifications

A gram-negative microorganism has an impermeable outer membrane that confers resistance against macrolide antibiotics. Its permeability can be altered by an outer membrane modification, leading to decreased susceptibility to fluoroquinolones or β-lactam antibiotics.

The efflux mechanism, by which antibiotic substances are pumped out of the cell, is another way to achieve resistance against antibiotics, such as quinolones. The efflux mechanism is important for clinical resistance to β-lactams or quinolones in *Pseudomonas* species, *S. aureus*, coagulase-negative *Staphylococci*, and *Citrobacter freundii* [12-15].

2. Target Structure Modifications

Mutations, inactivation of antibiotics through enzymatic modifications, and acquisition of genetic materials may affect target structures, leading to alterations in their microstructures. For example, fluoroquinolone resistance in *E. coli* is known to be mediated by modifications of the target DNA gyrase [12].

Meanwhile, resistance to TMP-SMX is acquired by enzyme alterations, as a result of the production of plasmid-encoded TMP-resistant forms of dihydrofolate reductase, which contributes to significant clinical resistance. Enzyme overproduction, cellular impermeability, inhibitor modification, or loss of binding capacity also contribute to rendering organisms resistant to TMP-SMX [16-18].

MRSA achieves resistance with additional proteins, resulting in lower affinity to β-lactam antibiotics [16].

3. Inactivation of Antibiotics

Bacteria producing β-lactamases inactivate β-lactam antibiotics by breaking the β-lactam ring. Penicillinase, which is produced in more than 90% of *S. aureus* strains, hydrolyzes the β-lactam ring of penicillin, conferring resistance to penicillin. Penicillinase-stable penicillin, such as oxacillin, may prevent such development of resistance [19]. Another resistance mechanism in *E. coli* and *Proteus* species involves the production of TEM-1, a plasmid-mediated β-lactamase [20]. In this mechanism, resistance can be conferred in strains that acquired resistance plasmids, for example, to ampicillin and ampicillin/sulbactam.

Enterobacter species, such as *C. freundii* and *Serratia*, have a chromosomally encoded β-lactamase that can be induced for hyperproduction due to mutation or depression [21]. Hyperproduction of β-lactamase also results in a resistance phenotype comparable to that in ESBL producers.

High-level aminoglycoside resistance is induced in *Staphylococcus* and *Enterococcus* species by the expression of a bifunctional aminoglycoside inactivating enzyme, 60-N-aminoglycoside acetyltransferase-20-O-aminoglycoside phosphotransferase [22]. Although *Enterococci* exhibit intrinsically low resistance levels, an aminoglycoside combination therapy may be ineffective in cases of a high-level antibiotic-resistant enterococcal infection. Gentamycin-modifying enzymes are common in *Pseudomonas* species and *Enterobacteriaceae* [23].

As bacteria exhibit various unspecific (reduced permeability or efflux) and specific (inactivating antibiotics) mechanisms for achieving resistance, they should all be considered to sustain the susceptibility to antibiotics (Table 1).

SPECIFIC AGENTS FOR APN TREATMENT

1. Nitrofurantoin

Nitrofurantoin has a weak antibacterial activity, interfering with carbohydrate metabolism. A certain urinary concentration is usually sufficient (urinary excretion; 40%) to control *E. coli*, *Klebsiella* species, and *Enterobacter* species in the case of uncomplicated cystitis [24]. However, it is less effective against non-*E. coli* gram-negative pathogens; it is also inactive against *Proteus* species or *P. aeruginosa*.

It does not share cross-resistance with the commonly used antibiotics and its use for the empiric treatment of lower UTIs, such as cystitis, prevents resistance. However, because of its extremely poor tissue penetration and low blood levels, nitrofurantoin is not recommended for the treatment of APN [25].

2. Fosfomycin

Fosfomycin, *cis*-(1R,2S)-epoxypropylphosphonic acid, is an oxirane antibiotic unrelated to other substances. It is produced as a secondary metabolite by *Streptomyces* and *Pseudomonas* species [26]. *E. coli* exhibits a low resistance rate of <3% [27].

Fosfomycin trometamol is effective against quinolone-resistant *E. coli* [24]. It is active against gram-positive and gram-negative bacteria, but its activity decreases in against *Proteus vulgaris*, *P. aeruginosa*, and *E. faecium*. It is also active against VRE, MRSA, and ESBL-producing gram-negative pathogens. In uncomplicated UTIs, a single dose of 3 g of fosfomycin trometamol is effective. However, in complicated UTIs, administration of 3 g every 3 days, for up to 21 days, is recommended. In ESBL-producing bacterial

Table 1. Mechanisms for achieving antibiotic resistance

Mechanism	Antibiotics	Representative pathogens
Permeability and efflux mechanism modifications	β-Lactams	*Pseudomonas* species
	Fluoroquinolone	*Staphylococcus aureus*
		Coagulase-negative *Staphylococci*
		Citrobacter freundii
Target structure modifications	Fluoroquinolone	*Escherichia coli*
	TMP-SMX	MRSA
Inactivation of antibiotics	β-Lactam	*S. aureus*
		Proteus species
		Enterobacter species such as *C. freundii* and *Serratia* species
	Aminoglycoside	*Staphylococcus*
		Enterococcus species
		Pseudomonas species

TMP-SMX: trimethoprim-sulfamethoxazole, MRSA: methicillin-resistant *Staphylococcus aureus*.

infection, fosfomycin was non-inferior to ertapenem for the treatment of outpatient ESBL UTIs [28].

In a controlled open study of 38 patients with APN, fosfomycin 8 g bid (twice a day). was compared with ampicillin 2 g tid (three times a day) for one week [29]. The success rate was 44% in the fosfomycin-treated group and 28% in the ampicillin-treated group ($p>0.20$). According to a previous study, the peak concentrations of fosfomycin in the serum were much lower (395 mg/L) than those in urine (6,990-24,320 mg/L). Fosfomycin trometamol exhibits 40% of oral bioavailability and 40% of urine recovery [30].

3. TMP-SMX

Oral TMP-SMX (160/800 mg [1 double-strength tablet] twice-daily for 14 days) is an appropriate therapy if the uropathogen is known to be susceptible [25]. If TMP-SMX is used when the susceptibility is uncertain, an initial intravenous dose of a long-acting parenteral antimicrobial, such as 1 g of ceftriaxone, or a consolidated 24-hour dose of an aminoglycoside is recommended [25]. The reported resistance rate of *E. coli* strains to cotrimoxazole in Korea is 35.9% [2].

4. Beta-Lactam Based Regimen

1) Ampicillin

Despite the high urine concentrations of amoxicillin or ampicillin, these should not be used as an empiric treatment due to their relatively poor efficacy [31] and high prevalence of antimicrobial resistance to these agents worldwide [25]. *Enterococcus faecalis* achieves resistance by enzyme modification.

However, in some studies, synergic effects could be observed by combining aminoglycosides. These effects would be much stronger when ampicillin is combined with streptomycin or gentamycin than with tobramycin or amikacin [2,25].

2) Cephalosporin

Oral β-lactam agents are less effective than other available agents for the treatment of APN [25]. If an oral β-lactam agent is used, an initial intravenous dose of a long-acting parenteral antimicrobial, such as 1 g of ceftriaxone, or a consolidated 24-hour dose of an aminoglycoside (e.g., one 5-7 mg/kg dose of gentamicin) is recommended [25]. β-lactam agents can be continued only if the pathogen is susceptible. The usual duration of treatment is 10-14 days.

Sanchez et al. [32] reported similar outcomes using one dose of ceftriaxone versus a 3-day course of ceftriaxone followed by oral β-lactam therapy in women with uncomplicated pyelonephritis.

In areas where prevalence of quinolone resistance is >10%, including parts of the United States, Korea, and some European countries, a long-acting parenteral antimicrobial is recommended at therapy initiation [25].

5. Fluoroquinolone

In regions with low levels of fluoroquinolone resistance, fluoroquinolones are the preferred antimicrobial agents for oral therapy [33].

The administration of oral ciprofloxacin (500 mg twice a day) for 7 days is an appropriate choice for outpatients with APN, where the resistance rate to fluoroquinolone is lower than 10%. However, in regions where fluoroquinolone resistance exceeds 10%, an initial intravenous long-acting antimicrobial (e.g., 1 g of ceftriaxone) or a

Table 2. Initial empiric therapy oral antibiotics for acute uncomplicated pyelonephritis

Antibiotics	Dose	Duration (d)
Ciprofloxacin	500-750 mg bid	7-10
Levofloxacin	500 mg qd	7-10 (or 750 mg qd for 5 d)
Alternatives (clinical but not microbiological equivalent efficacy compared with fluoroquinolones)		
Cefodoximeproxetil	200 mg bid	10
Ceftibuten	400 mg qd	10
Only if pathogen is susceptible		
Co-amoxiclav	0.5/0.125 g tid	14

Bid: twice a day, qd: once a day, tid: three times a day.

consolidated 24-hour dose of a combination of aminoglycosides is recommended [25].

In Korea, the resistance rates of *E. coli* to levofloxacin and ciprofloxacin are 21.3% and 24.8%, respectively [2,34]. Although a well-controlled ciprofloxacin treatment for APN is successful, even with quinolone resistance [2], caution is warranted prior to starting empiric treatment with fluoroquinolone; the susceptibility test must be used for confirmation (Table 2).

6. Carbapenem

Recently, carbapenem has been widely used and considered as the most effective treatment for antibiotic-resistant UTIs, including APN.

Carbapenems are active against most of the β-lactamase producing gram-positive, gram-negative, or anaerobic organisms. They exhibit broad-spectrum activity against gram-negative pathogens and slightly narrower-spectrum activity against gram-positive pathogens. For empiric therapy, they are often combined with a second drug having a broader spectrum of gram-positive activity.

The trans-1-hydroxyethyl substituent and its unique juxtaposition with the β-lactam carbonyl group makes carbapenem maintain its activity against specific pathogens [35]. Several types of carbapenems are clinically available only in parenteral forms, owing to their instability in gastrointestinal fluid. Carbapenems are predominantly excreted by renal excretion, and nephrotoxicity, neurotoxicity, and immunomodulation have been reported with the use of carbapenems [36]. Therefore, administering carbapenems requires a consideration of risk factors, particularly in compromised patients.

Imipenem is one of the first carbapenems developed to treat complex microbial infections. It is susceptible to deactivation by dehydropeptidase I, found in the human renal brush border. Therefore, co-administration with the inhibitor, cilastatin, is necessary [35].

Ertapenem is effective against gram-negative organisms, but ineffective against *P. aeruginosa*, MRSA, and *Enterococci*. Ertapenem has a long serum half-life and a urinary excretion rate of 80% [35].

Imipenem and meropenem are effective against gram-positive and gram-negative uropathogens, excluding MRSA, *E. faecium*, and VRE. If imipenem is combined with cilastatin, the urinary excretion of its active form is approximately 70%. Meropenem (70% of its active form), which is more active against *P. aeruginosa* than imipenem, is also excreted through urine [24].

Doripenem (urinary excretion rate 75%) is a newer carbapenem, which has an activity against gram-positive pathogens and *P. aeruginosa*, excluding MRSA, VRE, and *E. faecium*.

Continuous ongoing research has made carbapenem active against resistant pathogens, such as MRSA, VRE, *E. faecium*, or *Haemophilus influenza*, via either oral or parenteral administration. However, its clinical applications are not available yet due to the high prevalence of adverse reactions [37].

Recently, there has been increasing concerns regarding the increasing rates of resistance to carbapenems, as there are only a few therapeutic options for treating infections caused by carbapenem-resistant bacteria, such as carbapenem-resistant *Enterobacteriaceae* [36,37].

7. Datpomycin

Daptomycin exhibits a rapid concentration-dependent bactericidal activity against gram-positive bacteria [38]. It has a half-life of approximately 8.5 hours and a urinary excretion rate of 80%. In an animal study, the reversible skeletal muscle toxicity was most common with dose dependency. However, phase II randomized clinical trials showed that a dose of either 2 mg/kg every 24 hours for up to 25 days or 3 mg/kg every 12 hours for up to 34 days, was tolerable in patients [38,39]. It showed in vitro synergy with gentamycin, rifampin, or fosfomycin. It is successfully used as a treatment for VRE APN.

8. Linezolid

Linezolid is the first oxazolidinone bacteriostatic antibiotic, and it inhibits protein synthesis in gram-positive bacteroids, such as *Staphylococcus* species, *Streptococcus* species, *Enterococcus*, *Diphtheroids*, *Bacteroides fragilis*, anaerobes, and mycobacteria [40]. It binds to the 50S ribosome and inhibits protein synthesis. Therefore, cross-resistance with macrolides or lincosamides is rarely observed [39-41]. Linezolid exhibits approximately 100% absolute bioavailability; its concentration in serum is maximal within 1-2 hours of oral administration. It is not necessary to reduce the linezolid dosage in patients with renal insufficiency [42].

9. Tigecycline

Tigecycline was developed as a tetracycline-derived antibiotic. It is effective against many antibiotic-resistant organisms, such as *E. coli*, MRSA, *Stenotrophomonas maltophilia*, *H. influenzae*, *Neisseria gonorrhoeae*, and multi-drug-resistant strains of *A. baumannii*. However, it is not effective against infections caused by *Pseudomonas* or *Proteus* species [43]. Tigecycline is administered by slow intravenous infusion (for 30 to 60 minutes) every 12 hours. It is primarily eliminated as an unchanged form in the feces and secondarily eliminated by the kidneys [43,44]. Although dose reduction is required in severe hepatic impairment, no adjustment is necessary for patients with renal insufficiency or for those undergoing hemodialysis.

CONCLUSIONS

Antibiotic resistance has become an inevitable problem in the treatment of urogenital infections. While starting an empiric therapy in a patient with APN, it is necessary to consider the possible evolution of antibiotic resistance and susceptibility along with antibiotic resistance rates in the local region or country.

In Korea, the resistance rate of microorganisms to fluoroquinolone is relatively high; it is greater than 20%. The increased clinical use of carbapenem against multidrug-resistant strains has been accompanied by a decrease in the effectiveness in some complicated cases. The risk of carbapenems resistance has grown with an increase in its significance in the initial empiric therapy of the high-risk group.

Therefore, antibiotic resistant APN should be treated as other systemic infections, preventing antibiotic overuse with proper treatment duration considering the carbapenem saving strategy.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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