Review

ISSN 2465-8243(Print) / ISSN 2465-8510(Online)
http://dx.doi.org/10.14777/uti.2015.10.2.67
Urogenit Tract Infect 2015;10(2):67-73

Uropathogens Based on Antibiotic Susceptibility

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Urinary tract infections are one of the most commonly encountered infections in clinical practice. Due to the emergence of and increase in urinary tract bacteria that are resistant to trimethoprim-sulfamethoxazole, penicillin, cephalosporins, and fluoroquinolones, selection of appropriate antibiotics in treatment of these infections is important. In addition, the emergence of extended-spectrum beta-lactamase-producing organisms makes antibiotic selection difficult. This article provides a review of disease-specific uropathogens and their susceptibilities to antimicrobial agents.

Keyword: Anti-infective agents

Received: 30 June, 2015
Revised: 29 July, 2015
Accepted: 14 August, 2015

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INTRODUCTION

Urinary tract infections are among the most common bacterial infections in clinical practice and a prevalent cause of hospital-acquired infections. Urinary tract infections have been reported to affect more than 250 million people per year worldwide [1]. In the past, treatment of urinary tract infections was relatively easy because uropathogens, the bacteria that cause such infections, responded well to treatment with antibiotics, making inpatient hospital care less necessary. However, selection of antibiotics for treatment of urinary tract infections has become increasingly difficult because of changes in the antibiotic susceptibility of uropathogens, including the development of new antibiotics, overuse of antibiotics by medical professionals, and the resulting emergence of an increase in bacteria with resistance to certain antibiotics. Due to the increased antibiotic resistance of uropathogens, it has become necessary to reassess the antibiotics used in the past for empirical therapy, including trimethoprim-sulfamethoxazole, amoxicillin, and ciprofloxacin. To this end, many studies have been and are being conducted at home and abroad, through which the importance of appropriate treatment for resistant organisms has become apparent. Analyses of bacteria for specific diseases encountered in clinics, understanding the rate of resistance to antibiotics, and awareness of the treatment of new resistant organisms are particularly important.

ACUTE UNCOMPLICATED CYSTITIS

Acute, or uncomplicated, lower urinary tract infections occur most commonly in healthy women with no anatomical abnormalities, except for pregnant women. One-third of all women experience cystitis more than once during their lifetime [2]. The presenting symptoms include pelvic discomfort, dysuria, frequent urination, urgency to urinate, nocturnal urination, and hematuria. *Escherichia coli* is the most common causative organism, accounting for ~70-95% of cases of acute cystitis, followed by *Staphylococcus saprophyticus* at 5-10% [3]. In addition, *Enterococcus faecalis*, *Klebsiella pneumonia*, and *Proteus mirabilis* are sometimes

cultured as causative organisms. *Citrobacter*, *Enterobacter*, and *Pseudomonas aeruginosa* are less common causative agents of uncomplicated lower urinary tract infections. A multicenter study of patients with acute uncomplicated cystitis in Korea found that *E. coli* was the most common cause at 71.1%; enterococci and coagulase-negative staphylococci were also isolated as causative bacteria (Table 1) [4].

In the past, three days of treatment with trimethoprim-sulfamethoxazole was the standard approach for acute uncomplicated cystitis; however, it is now rarely used due to the increased resistance rate. Instead, fluoroquinolones are often selected as first-line agents. According to the results of analyses conducted in several countries around the world, use of fluoroquinolones as the first empirical selection is still appropriate. In Korea, however, the resistance of *E. coli* isolated from patients with acute uncomplicated cystitis to fluoroquinolones increased from 15.2% in 2002 to 23.4% in 2006 (Table 2), suggesting that the guidelines for empirical antibiotic therapy should be reassessed [4]. According to the 2010 Guidelines of the Infectious Disease Society of America, use of empirical antibiotic therapy is not recommended when the local prevalence of antibiotic resistance for an *E. coli* strain exceeds 20%. Thus, fluoroquinolones should be used with caution in Korea, considering the approximately 20% resistance level. In conclusion, when a fluoroquinolone, as an empirical therapy for acute uncomplicated cystitis, does not produce any response to treatment, amikacin, an aminoglycoside antibiotic with high susceptibility, can be used. Currently, carbapenem is used for extended-spectrum beta-lactamase (ESBL)-positive strains, but it is not recommended by the Guidelines.

Table 1. Distribution of urinary isolates from acute uncomplicated cystitis patients (n=301)

Species	Isolates, n (%)
Enterobateriaceae	246 (81.7)
Escherichia coli	214 (71.1)
Klebsiella spp.	11 (3.7)
Enterobacter spp.	9 (3.0)
Citrobacter spp.	9 (3.0)
Proteus spp.	3 (1.0)
Non-enterobateriaceae	55 (18.3)
Enterococci	39 (13.0)
CoNS	16 (5.3)

Adapted from the article of Kim et al. Int J Antimicrob Agents 2008;31 Suppl 1:S15-8 [4] with permission.
spp.: species, CoNS: coagulation-negative staphylococci.

ACUTE PYELONEPHRITIS

Acute pyelonephritis is a representative urinary tract infection that requires inpatient care. The condition requires attention because it may be accompanied by sepsis, respiratory failure, kidney scars, or renal dysfunction, although it may be treated with a short stay in hospital. It can be accompanied by flank pain and high fever, along with the preceding voiding symptoms, and it can be easy to diagnose with imaging. However, when accompanied by continued high fever or complications despite hospitalization, empirical antibiotic therapy should be discontinued and the use of other antibiotics should be considered in many cases, depending on the results of urine cultures and antibiotic susceptibility testing.

In a study conducted in 2013 to analyze the results of urine cultures from 230 acute pyelonephritis patients and 30,687 acute uncomplicated cystitis patients, the most

Table 2. Susceptability of urinary Enterobacteriaceae isolates from female outpatients with acute uncomplicated cystitis to various antimicrobial agents

	Susceptable strains in 2006/2002 (%)		
	Escherichia coli (n=214/191)	Other Enterobacteriaceae (n=32/20)	Total (n=246/211)
Ampicillin	35.2/37.2	6.3/15.0	31.4/35.5
Ampicillin/sulbactam	52.4/44.5	51.6/50.0	52.3/45.0
Piperacillin/tazobactam	98.6/97.4	90.6/95.0	97.6/97.2
Ciprofloxacin	76.6/84.8	93.8/95.0	78.9/85.7
Gatifloxacin	78.2/NA	93.8/NA	80.3/NA
Cefazolin	92.4/92.2	50.0/60.0	86.8/89.1
Amikacin	99.5/99.0	100/100	99.6/99.1
Gentamicin	77.6/81.7	100/80.0	80.5/81.5
Tobramycin	78.2/85.9	100/80.0	81.1/85.3
TMP/SMX	70.6/61.3	96.8/70.0	73.9/62.1

Adapted from the article of Kim et al. Int J Antimicrob Agents 2008;31 Suppl 1:S15-8 [4] with permission.
NA: not available, TMP/SMX: trimethoprim/sulfamethoxazole.

common causative agent of acute pyelonephritis was *E. coli*, as with other urinary tract infections. However, the ratio of *E. coli* to all uropathogens was 92.4%, higher than the ratio of 66% for all urinary tract infections (Table 3) [5]. Several studies conducted in Korea also reported that the most common causative agent of acute pyelonephritis was *E. coli*, at approximately 90% [6,7]. A study on the antibiotic susceptibility of *E. coli* found that the resistance rates to ampicillin and trimethoprim- sulfamethoxazole worldwide were too high to support their use as primary drugs. It was also found in most studies from Korea that the resistance rate was even worse, reaching 40-50%.

In the 2000s, fluoroquinolones, which were used most commonly to replace the above mentioned antibiotics, were reported to be ineffective in approximately ~20% of cases. Thus it is anticipated that new empirical therapy guidelines will be needed soon. Fortunately, because susceptibility to third-generation cephalosporins and amikacin has been found to exceed 90% (Table 4) [5], it is considered that the primary empirical antibiotics for acute pyelonephritis should be selected from among fluoroquinolones, third-generation cephalosporins, and aminoglycosides. However, because the resistance rates to these drugs are also expected to increase, monitoring for resistance is needed, along with regular analyses of antibiotic susceptibility.

ACUTE BACTERIAL PROSTATITIS

Acute bacterial prostatitis, an inflammation of the prostate caused by a lower urinary infection in males, is accompanied by a high fever, chills, and myalgia, as well as voiding symptoms. Infection routes include direct transmission from the rectum, blood-borne transmission, transmission from lymphatic vessels, transmission via sexual intercourse, and transmission via urinary catheters. The most common route is an ascending infection from the urinary tract. Cultured urine samples can be screened for identification of uropathogens. The most common pathogen to date is the eosinophilic Gram-negative bacterium *E. coli* (80%), followed by *P. aeruginosa*, *Serratia*, *Klebsiella*, *Proteus* spp. (10-15%), and enterococci (5-10%). A multicenter study of acute bacterial prostatitis in Korea conducted in 2008 found that the most common pathogen among cultured bacteria was *E. coli*, followed by *P. aeruginosa* and *Klebsiella* spp.

The study divided patients with acute bacterial prostatitis according to those who had previously received urinary treatments (e.g., a prostate biopsy, urological surgery, and catheter insertion), and those who had not, and assessed the difference between the groups. *Pseudomonas* strains were isolated from the group with previous treatments at a much higher rate than the group without treatments [8]. Tables 5 and 6 show the antibiotic susceptibilities of the isolated bacteria [8]. The prevalence of antibiotic susceptibility to ampicillin, ampicillin-sulbactam, first-generation cephalosporins, and trimethoprim-sulfamethoxazole was very low, while susceptibility to second-, third-, and fourth-generation cephalosporins and aminoglycosides was relatively high. Among the aminoglycosides, amikacin had the highest susceptibility rate (94.3%), followed by tobramycin (85.1%) and gentamicin (82.3%). Ciprofloxacin and tobramycin were found to have a significant difference in susceptibility between the groups.

Table 3. Microbial prevalence in pyelonephritis requiring hospital admission and ED related UTI

	Pyelonephritis		ED related UTI	
	Case	Total (%)	Case	Total (%)
Escherichia coli	230	92.4	30,687	66
Klebsiella spp.	8	3.2	3,108	6.6
E. faecalis	-	-	3,153	6.7
Proteus spp.	6	2.5	2,497	5.3
Pseudomonas spp.	2	0.8	1,939	4.1
Enterobacter spp.	3	0.8	-	-
Citrobacter spp.	-	-	340	0.72
Group B *Streptococcus*	-	-	4,726	10.1
Staphylococcus saprophyticus	-	-	210	0.45

Adapted from the article of Prabhu et al. Nephrology (Carlton) 2013;18:463-7 [5] with permission.
ED: emergency department, UTI: urinary tract infection, spp.: species.

Table 4. Resistance of *Escherichia coli* for all UTI presenting to the ED and pyelonephritis patients

	Pyelonephritis		ED related UTI	
	Case	Total (%)	Case	Total (%)
Ampicillin	120	52.1	14,120	46
Trimethoprim	81	32.5	6,214	10.4
Gentamicin	9	3.9	1,169	3.8
Cephalexin	4	1.7	1,079	3.5
Ceftriaxone	3	1.3	875	2.8
Norfloxacin	2	0.8	1,360	4.4

Adapted from the article of Prabhu et al. Nephrology (Carlton) 2013;18:463-7 [5] with permission.
UTI: urinary tract infection, ED: emergency department.

Table 5. Microbial spectrum of patients with acute bacterial prostatitis

	Total (n=115)	With prior manipulation (n=39)	Without prior manipulation (n=76)	p-value
Escherichia coli	60 (52.2)	18 (46.2)	42 (55.3)	0.3546
Pseudomonas spp.	18 (15.7)	12 (30.8)	6 (7.9)	0.0014
Klebsiella spp.	11 (9.6)	4 (10.3)	7 (9.2)	0.8567
Enterobacter spp.	4 (3.5)	1 (2.6)	3 (3.9)	-
Streptococcus agalactiae	4 (3.5)	1 (2.6)	3 (3.9)	-
Serratia marcescens	2 (1.7)	1 (2.6)	1 (1.3)	-
CoNS	3 (2.6)	1 (2.6)	2 (2.6)	-
Enterococci	3 (2.6)	0 (0)	3 (3.9)	-
Mixed infection	5 (4.3)	3 (7.7)	2 (2.6)	0.2077
Others[a)]	5 (4.3)	1 (2.6)	4 (5.3)	-

Values are presented as number (%). Adapted from the article of Ha et al. Int J Antimicrob Agents 2008;31 Suppl 1:S96-101 [8] with permission.
spp.: species, CoNS: coagulase-negative staphylococci.
[a)]*Neisseria gonorrhoeae*, *Salmonella* and *Candida*.

Table 6. Antibiotic susceptibility (%) of pathogens isolated in patients with acute bacterial prostatitis, according to prior manipulation

	Total (n=115)	With prior manipulation (n=39)	Without prior manipulation (n=76)	p-value
Ampicillin	29.8	21.4	32.6	0.4292
Ampicillin/sulbactam	38.9	45.5	36.0	0.5919
Piperacillin/tazobactam	88.9	84.6	90.2	0.5737
First-generation cephalosporins	60.0	53.8	61.9	0.8965
Second-generation cephalosporins	82.0	75.0	84.2	0.4691
Third-generation cephalosporins	82.5	78.6	83.7	0.6599
Fourth-generation cephalosporins	84.2	80.0	85.7	0.6706
Ciprofloxacin	73.8	53.3	80.4	0.0383
Ofloxacin	88.5	91.5	85.7	0.3689
Amikacin	94.3	92.3	95.0	0.7152
Gentamicin	82.3	66.7	87.2	0.0695
Tobramycin	85.1	66.8	91.4	0.0376
Imipenem	99.4	99.3	99.5	0.8985
Trimethoprim/sulfamethoxazole	67.4	54.6	71.9	0.2900

Adapted from the article of Ha et al. Int J Antimicrob Agents 2008;31 Suppl 1:S96-101 [8] with permission.

PROSTATE BIOPSY

Prostate cancer is the most common tumor among American males. According to statistics from the US, 240,890 cases of prostate cancer were detected in 2011 by transrectal ultrasound prostate biopsy [9]. In addition, more than 1 million cases of prostate biopsy are performed every year [10]. Urinary tract infections are the second most common complication following bleeding after a prostate biopsy. Uncomplicated infection has been reported at a rate of 1.2-11.3%, and febrile infection at 1.4-4.5% [11,12]. Sepsis, the most serious complication, was reported at a rate of 0.1-2.2% [13]. There is no standardized protocol to prevent infection associated with prostate biopsy; however one study suggested that the best practice was to perform a bowel preparation and to administer fluoroquinolones as prophylactic antibiotics. *E. coli*, the most common organism causing an infection after biopsy [14], has a wide susceptibility range to fluoroquinolones. Fluoroquinolones are effective because they maintain high and sustained concentrations in urine and prostate tissue. However, an organism with resistance has emerged due to the overuse of fluoroquinolones [15,16].

A study by Nam et al. [17] (2010) of more than 75,000 men in Canada reported that the need for in-hospital care due to prostate infection after a prostate biopsy increased from 1% in 1996 to 4.1% in 2005, suggesting that the antibiotic resistance of prostatitis pathogens associated with prostate biopsy had increased significantly. Ozden et al. [18] reported that of 1,339 patients who underwent a prostate biopsy, there were 28 cases (2.1%) of acute bacterial prostatitis, of which 14 cases were cultured with *E. coli* and 6 cases (42.9%) were ultimately identified as ESBL-producing *E. coli*. All six cases of ESBL-positive *E.*

coli were susceptible to imipenem, and were therefore treated with imipenem. Liss et al. [19] (2015), who examined 764 patients who had undergone a prostate biopsy, found that 121 (15.8%) cases were cultured for fluoroquinolone-resistant strains; the results of antibiotic susceptibility testing are shown in Table 7.

In Korea, a high resistance rate for fluoroquinolones has been reported, and the effectiveness of this class of drugs has decreased to a level too low to follow the preventative antibiotic guidelines used in the US and Europe. As a result, the use of amikacin or third-generation cephalosporins along with fluoroquinolones is on the rise. This, however, also promotes the emergence of ESBL-producing bacteria.

Table 7. Co-resistence profiles of 121 ciprofloxacin-resistent *Escherichia coli* rectal and clinical isolates from men undergoing transrectal prostate biopsy

Drug	Prevalance of resistence, n (%)
Ampicillin	120 (99)
Trimethoprim-sulfamethoxazole	41 (34)
Gentamicin	31 (26)
Tobramycin	22 (18)
Cefazolin	20 (17)
Nitrofurantoin	18 (15)
Ceftriaxone	8 (7)
Aztreonam	6 (5)
Imipenem	2 (2)
Piperacillin-tazobactam	1 (1)
Ertapenem	1 (1)
Tigecycline	1 (1)
Meropenem	0 (0)
Amikacin	0 (0)

Adapted from the article of Liss et al. Clin Infect Dis 2015;60:979-87 [19] with permission.

According to a report from Korea, ESBL-producing bacteria were isolated from 20% of patients with infectious complications [20]. Most ESBL-producing bacteria are susceptible to carbapenems, but are not recommended for preventative purposes due to the possibility of causing new resistance to the drugs. When an infection with a fluoroquinolone-resistant strain is identified, if a preliminary rectal culture screen was performed, appropriate antibiotics can be administered depending on the susceptibility results; however, if there was no rectal culture screen, treatment can be administered using amikacin or a third-generation cephalosporin. In cases where ESBL-producing bacteria were cultured or no effect was found with a cephalosporin, treatment should be administered immediately using carbapenem antibiotics such as imipenem or meropenem.

ESBL-PRODUCING UROPATHOGENS

ESBL is an enzyme that hydrolyzes and inactivates beta-lactam antibiotics such as penicillin and cephalosporin. ESBLs are largely divided into three groups, TEM, SHV, and CTX-M, which are further divided into sub-groups. Until the late 1990s, a *Klebsiella pneumoniae* strain that produced SHV- and TEM-type ESBLs was the primary pathogen in hospital-acquired infections, but *E. coli* producing a CTX-M type beta-lactamase has become the most important focus in community acquired infections, including urinary tract infections, worldwide. According to a report from Korea, the susceptibility of ESBL-producing *E. coli* to all antibiotics (except imipenem and cefotetan) among

Table 8. Comparison of antimicrobial susceptibilities between O-UTI and I-UTI

	Antimicrobial susceptibility of *Escherichia coli*			
	O-UTI (n, %)	I-UTI (n, %)	OR	95% CI[a]
Ampicillin/clavulanate	667 (66.0)	151 (54.5)	1.63	1.24-2.13
Cefazolin	769 (76.1)	192 (69.3)	1.41	1.05-1.89
Cefotaxime	885 (87.6)	216 (78.0)	1.99	1.42-2.81
Cefotetan	994 (98.4)	258 (93.1)	4.57	2.32-9.02
Ceftazidime	943 (93.4)	234 (84.5)	2.59	1.71-3.89
Ceftriaxone	887 (87.8)	213 (76.9)	2.05	1.49-2.89
Cefuroxime	848 (84.0)	192 (69.3)	2.32	1.71-3.15
Ciprofloxacin	688 (68.1)	160 (57.8)	1.56	1.19-2.05
Imipenem	1,003 (99.3)	271 (97.8)	3.17	1.05-9.51
Trimethoprim/sulfamethoxazole	619 (61.3)	141 (50.9)	1.53	1.17-1.99
ESBL	122 (12.1)	64 (23.1)	2.19	1.56-3.07

Adapted from the article of Lee et al. Korean J Urol 2010;51:492-7 [21].
O-UTI: outpatient urinary tract infection, I-UTI: inpatient urinary tract infection, OR: odds ratio, CI: confidence interval, ESBL: extended spectrum beta-lactamase.
[a]$p < 0.01$ except for imipenem ($p = 0.047$).

Table 9. Antibiotic susceptibility patterns of extended spectrum beta-lactamase-producing *Escherichia coli*

Antibiotic susceptibility	Value (%)
Ampicillin/clavulanate	3.8
Cefazolin	1.3
Cefotetan	95.9
Cefotaxim	3.8
Ceftazidime	42.3
Ceftriaxone	3.8
Ciprofloxacin	28.2
Imipenem	98.7
Trimethoprim/sulfamethoxazole	42.3

Adapted from the article of Lee et al. Korean J Urol 2010;51:492-7 [21].

outpatients, including emergency room patients, with a community-acquired infection was 12.1%, while that in patients with a hospital-acquired infection was 23.1% (Table 8) [21].

The most significant problem with treating an infectious disease caused by ESBL-producing bacteria is that the bacteria have simultaneous resistance to other antibiotics. The most effective antibiotics for treatment of ESBL-producing *E. coli* include imipenem (99.9%), amikacin (95.8%), piperacillin-tazobactam (83.6%), gentamicin (76.5%), and tobramycin (66.1%). However, when a severe infection with ESBL-producing *E. coli* occurs, other carbapenem antibiotics are recommended because resistance to imipenem has been identified [22-24]. There is also the possibility of resistant organisms due to the widespread use of carbapenems. Amikacin can be used for ESBL-producing *E. coli*, but little clinical evidence has been documented [25,26]. In a study from Korea, the prevalence of susceptibility to imipenem was 98.7%, indicating that it may be an appropriate choice for treatment of ESBL-producing *E. coli* (Table 9) [21].

CONCLUSIONS

Urinary tract infections are among the most common infections encountered in clinical practice. However, the prevalence of antibiotic-resistant bacteria is increasing rapidly in Korea because such infections are widely treated with antibiotics by non-specialist departments, not by urologists or infection specialists, without culture screening. Among the uropathogens known to cause urinary tract infections the most common species is *E. coli*, which is also a major cause of other diseases that cause urinary tract infections. Due to the emergence of an increase in urinary tract bacteria that are resistant to trimethoprim-sulfamethoxazole, penicillin, cephalosporins, and fluoroquinolones, selection of appropriate antibiotics is important in treating these diseases. In addition, the emergence of ESBL-producing organisms causes difficulty in selection of antibiotics. Thus, regular monitoring activities and guidelines for antibiotic resistance should be provided at the academic society and national levels. Only the selection and use of antibiotics according to scientific principles can prevent the increase in resistant bacteria and the emergence of multidrug-resistant organisms.

CONFLICT OF INTEREST

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

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