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Original Article

Trends in Pathogen Occurrence and Antimicrobial Resistance of Urinary Isolates in a Tertiary Medical Center over Ten Years: 2004~2013

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To provide guidelines for the empirical treatment of urinary tract infections, we observed annual changes in the occurrence frequency and antimicrobial susceptibility of urinary isolates in a university hospital in the Chungbuk province, South Korea, over a period of 10 years (2004~2013). *Escherichia coli* (38.2%), *Enterococcus faecalis* (11.7%), *Klebsiella pneumoniae* (7.3%), *Pseudomonas aeruginosa* (4.3%), *E. faecium* (4.3%), and *Staphylococcus aureus* (4.1%) were commonly isolated urinary pathogens. The prevalence of *E. coli*, *E. faecium* and *Streptococcus agalactiae* were significantly higher in females ($P < 0.001$), whereas *E. faecalis*, *P. aeruginosa* and *S. aureus* were significantly more common in male patients ($P < 0.001$). *E. coli* mostly frequently showed resistance to ampicillin (67.94%), followed by trimethoprim/sulfamethoxazole (36.06%) and ciprofloxacin (26.84%). Over the studied time period, resistance rates of *E. coli* to ciprofloxacin significantly increased (20.44% to 33.55%). Moreover, extended-spectrum β-lactamase (ESBL) producing isolates also significantly increased in *E. coli* (4.2% to 18.3%) and *K. pneumoniae* (9.6% to 26.9%). In addition, the proportion of vancomycin-resistant *Enterococcus facium* (VRE) also increased (15.7% to 25.0%). In conclusion, over the last 10 years, the proportions of ciprofloxacin resistant *E. coli* and multidrug-resistant bacteria, such as ESBL and VRE have significantly increased. This trend must be strictly controlled and demonstrates the need for more updated guidelines for the treatment of urinary tract infections.

Key Words: Urinary tract infection, Occurrence, Antimicrobial susceptibility, Trend

INTRODUCTION

Urinary tract infections (UTIs) are the most common community- and hospital-acquired infections. Uncomplicated UTIs typically affect young women who are immunocompetent and have anatomically normal physiology (Warren 2001). Complicated UTIs often affect patients with underlying functional and metabolic or anatomical defects of the urinary tract. In addition, most nosocomial UTIs are related to catheterization (Ronald 2003). The etiologic bacteria of UTIs are predictable, with *Escherichia coli* being the principle pathogen (Hooton et al., 1999; Warren et al., 1999). *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Enterococcus* spp. are also commonly isolated (Warren et al., 1999; Turnidge et al., 2002; Shin et al., 2005).

E. coli and other uropathogens are becoming increasingly resistant to commonly used antimicrobial agents, reducing the effectiveness of some standard regimens (Thomson et al., 1994; Friedrich et al., 1999; Gupta et al., 1999; Hooton

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et al., 1999; Jones et al., 1999; Warren et al., 1999). Meanwhile, epidemiologic and resistance patterns of the pathogens in UTIs show inter-regional variability, and the susceptibility patterns are continually changing depending on different regional antibiotic treatment regimens (Karlowsky et al., 2002; den Heijer et al., 2010). In most cases of UTI, empirical antibiotic therapy is initiated before the laboratory results of urine cultures are received. Such therapy should be tailored to the surveillance data on the epidemiology and resistance patterns of common uropathogens to reduce treatment failures and the emergence of bacterial resistant strains (Gupta 2002). In the present study, we examined changes in the pattern of the causative organisms of UTIs isolated from patients in a university hospital.

MATERIALS AND METHODS

Retrospective clinical study

This was a retrospective study based on laboratory records over 10 years from 2004 to 2013 at the Chungbuk National University Hospital, Cheongju, Republic of Korea, which is a tertiary teaching hospital with 600 beds and has 173,000 admissions a year. Only an isolate of pathogens that were repeatedly isolated from patients were included. All patients with a suspected UTI were examined. Significant bacteriuria was defined as a urine specimen containing more than 10^5 CFU/mL.

Urine culture

The identification of organisms was performed using the VITEK II automatic analyzer (bioMérieux Inc., Hazelwood, MO, USA) and routine biochemical tests.

Antimicrobial susceptibility testing

Antimicrobial susceptibility testing (AST) was done with the VITEK II system or the Kirby Bauer disc diffusion method using Muller Hinton agar. Quality-control tests of AST ware performed using standard strains of *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27953, *Staphylococcus aureus* ATCC 25923 and *Enterococcus faecalis* ATCC 29212 as per the recommendations of the Clinical Laboratory Standard Institute (CLSI, 2012). The antimicrobial susceptibility against each antimicrobial agent was interpreted as CLSI guideline. When vancomycin resistance in Gram-positive cocci or imipenem resistance in Gram-negative bacilli was observed in the VITEK II system or the disc diffusion method, the results were further confirmed using the E-test (bioMérieux, Inc., Durham, NC, USA).

Statistical analysis

The data were collected from the laboratory information system of the hospital and were analyzed using Microsoft Excel 7.0 software. Differences in proportions of UTI isolates by gender and trend in change of antimicrobial susceptibilities were compared using a chi-square test with SPSS 19.0. Statistical significance was reached at $P < 0.05$.

RESULTS

Distribution of urine culture positive isolates

Of 106,269 cultured urine specimens, 19,075 (17.9%) were positive. Among the positive isolates, 93.4% were bacteria, and 6.6% were fungi. The overall female to male ratio was 1.19:1. A significant gender-dependent difference, with a two-fold male dominance was observed for *E. faecalis*, *P. aeruginosa* and *S. aureus*, and a two-fold female dominance was noted for *E. coli* (Table 1).

Among the pathogens, the most common 10 isolates were: *E. coli* (7,283 cases, 38.2%), *E. faecalis* (2,231 cases, 11.7%), *Klebsiella pneumoniae* (1,398 cases, 7.3%), *P. aeruginosa* (828 cases, 4.3%), *E. faecium* (814 cases, 4.3%), *S. aureus* (778 cases, 4.1%), *Candid*a species not *albicans* (650 cases, 3.4%), *Candida albicans* (615 cases, 3.2%), *Morganella morganii* (487 cases, 2.6%), and *Enterobacter aerogenes* (358 cases, 1.9%) (Table 1).

Antimicrobial resistance patterns of positive isolates

Antimicrobial resistance trends are presented in Table 2. *E. coli* was frequently resistant to ampicillin (67.94%). The resistance rate against ciprofloxacin and trimethoprim/sulfamethoxazole (SXT) increased to more than 30% (33.55%, 38.9%, respectively). In addition, the resistance rate of *E. coli* to cefazolin and cefotaxime was increased from 11.5%

and 3.72% in 2004~5 to 25.63% and 21.32%, respectively in 2012~3 (Table 2, Fig. 1). The resistance rate of *K. pneumoniae* for cefotaxime increased from 11.34% in 2004~5 to 29.05% in 2012~3 (Table 2). A constant annual increase in ESBL producing *E. coli* and *K. pneumoniae* was observed over the 10-year time period (Fig. 2). *P. aeruginosa* was frequently resistant to ciprofloxacin (37.32%), imipenem (24.64.9%), and ceftazidime (22.71%). The resistance rate of imipenem was rather decreased from 33.33% in 2004~2005 to 24.38% in 2012~3 (Table 2).

Table 1. Frequency and distribution of isolates causing urinary tract infection over a period of 10 years (2004~2013)

Microorganism	Isolates, N(%)			*P*-value
	Male (45.61%)	Female (54.39%)	Total	
E. coli	2,160 (24.83)	5,123 (49.38)	7,283 (38.18)	<0.001
E. faecalis	1,338 (15.38)	893 (8.61)	2,231 (11.70)	<0.001
K. pneumoniae	645 (7.41)	753 (7.26)	1,398 (7.33)	NS
P. aeruginosa	533 (6.13)	295 (2.84)	828 (4.34)	<0.001
E. faecium	270 (3.10)	544 (5.24)	814 (4.27)	<0.001
S. aureus	494 (5.68)	284 (2.74)	778 (4.08)	<0.001
C. spp. NA	312 (3.59)	338 (3.26)	650 (3.41)	NS
C. albicans	313 (3.60)	302 (2.91)	615 (3.22)	0.007
M. morganii	361 (4.15)	126 (1.21)	487 (2.55)	<0.001
E. aerogenes	199 (2.29)	159 (1.53)	358 (1.88)	<0.001
S. agalactiae	107 (1.23)	230 (2.22)	337 (1.77)	<0.001
A. baumanii	232 (2.67)	96 (0.93)	328 (1.72)	<0.001
P. mirabilis	180 (2.08)	145 (1.40)	326 (1.71)	<0.001
C. freundii	189 (2.17)	131 (1.26)	320 (1.68)	<0.001
E. cloacae	173 (1.99)	135 (1.30)	308 (1.61)	<0.001
K. oxytoca	204 (2.34)	84 (0.81)	288 (1.51)	<0.001
S. marcescens	137 (1.57)	34 (0.33)	171 (0.90)	<0.001
Others	852 (9.79)	703 (6.78)	1,555 (8.15)	<0.001
Total	8,700 (100)	10,375 (100)	19,075 (100)	

Abbreviations: N, number; NS, not significant: NA, not *albican*s

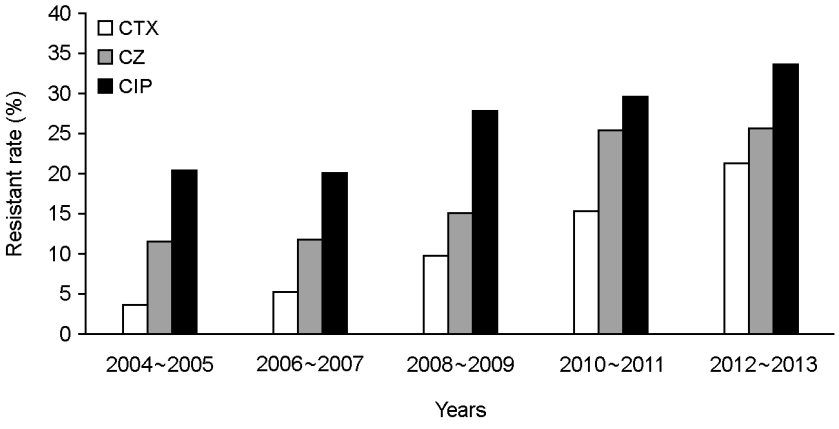

Fig. 1. Trends of resistance rate (%) against cefotaxime (CTX), cefazolin (CZ) and ciprofloxacin (CIP) in *E. coli* isolated from urine culture with significant bacteriuria during 2004~2013 years.

Table 2. Trends of antimicrobial resistance of common isolates causing urinary tract infection over 10 years

Microorganisms	Antimicrobial resistance rate (%)						
	2004~5	2006~7	2008~9	2010~11	2012~13	Mean of 10 years	*P*-value
SAU							
CIP	48.41	43.55	45.99	48.99	46.43	46.40	0.881
OXA	68.25	73.12	74.33	80.58	69.29	73.26	0.156
PEN	98.41	96.77	98.93	99.28	94.29	97.56	0.035
TET	51.59	48.92	54.01	59.71	53.57	57.34	0.417
VAN	0	0	0	0	0	0	-
EFA							
AMP	1.34	1.59	4.71	NA	0.33	2.31	<0.001
VAN	2.23	1.99	0.41	0.47	0.67	1.39	0.031
EFM							
AMP	95.10	88.24	96.34	98.56	97.16	95.58	<0.001
VAN	15.69	18.38	18.32	20.57	25.00	20.03	0.339
ECO							
AMP	69.56	64.22	66.96	69.99	69.07	67.94	0.004
AMK	1.42	0.95	0.62	1.39	1.05	1.07	0.222
CIP	20.44	20.07	27.87	29.61	33.55	26.84	<0.001
CTX	3.72	5.31	9.84	15.33	21.32	11.82	<0.001
CZ	11.56	11.90	15.21	25.45	25.63	18.56	<0.001
SXT	37.08	29.66	34.55	39.72	38.90	36.06	<0.001
KPN							
AMK	12.55	7.37	5.95	10.31	4.39	8.01	0.003
CIP	16.60	13.14	15.87	14.78	22.97	16.67	0.016
CTX	11.34	9.29	19.44	26.80	29.05	19.31	
PAE							
CAZ	21.79	20.45	21.51	24.39	25.63	22.71	0.779
CIP	44.87	38.07	34.88	35.37	33.75	37.32	0.247
IMP	33.33	22.16	22.67	21.34	24.38	24.64	0.083

Abbreviations: SAU, *Staphylococcus aureus*; CIP, ciprofloxacin; OXA, oxacillin; PEN, penicillin; TET, tetracycline; VAN, vancomycin; EFA, *Enterococcus faecalis*; AMP, ampicillin; EFM, *Entercoccus faecium*; ECO, *Escherichia coli*; AMK, amikacin; CTX, cefotaxime; CZ, cefazolin; KPN, *Klebsiella pneumoniae*; PAE, *Pseudomonas aeruginosa*; CAZ, ceftazidime; IMP, imipenem; ABA, *Acinetobacter baumannii*; NA, not available.

Vancomycin resistant *S. aureus* (VRSA) were not observed, although the average rate of MRSA over the 10 years did not significantly change (Table 2). The average resistance rates to ampicillin in *E. faecalis* and *E. faecium* were 2.31% and 95.58%, respectively. The average vancomycin resistance rate of *E. faecalis* was 1.39%, but that of *E. faecium* was 20.03%. Among Gram positive cocci, a major change in the resistant rate was showed in VRE (from 15.69% to 25.0%) over the 10-year study period (Table 2). In other microorganisms, only minor changes in resistant rates were noted.

DISCUSSION

Antibiotic resistance is now a major factor contributing to therapeutic failure in not only nosocomial complicated

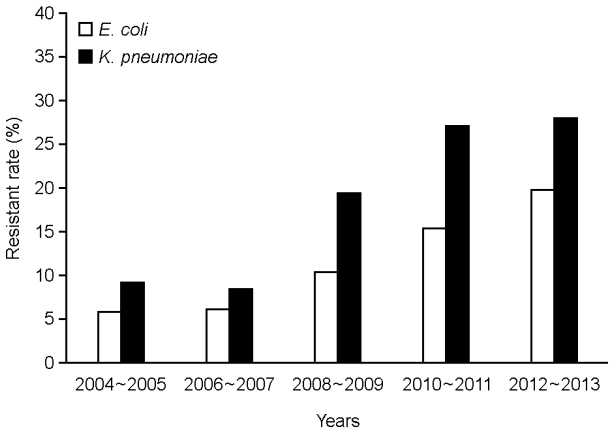

Fig. 2. Prevalence (%) of ESBL producing *E. coli* and *K. pneumoniae* isolated from urine culture with significant bacteriuria during 2004~2013 years.

UTIs, but also uncomplicated community-acquired UTIs (Gupta 2002). Geographic variation in individual patient risk factors and an understanding of the resistance trends need to be incorporated into the management strategies for UTI.

The present study illustrates the UTI bacterial spectrum and antimicrobial susceptibility patterns in a university hospital over a period of 10 years. The average rate of positive urine culture was determined to be 17.9%, and *E. coli*, *E. faecalis*, *K. pneumoniae*, *P. aeruginosa*, *E. faecium*, *S. aureus* were the most frequent causative pathogens. *E. coli* is the most common one associated with UTI, with a reported frequency of 38% to 85% depending on the study (Gupta et al., 1999; Farrel et al., 2003; Kahlmeter et al., 2003; Ti et al., 2003; Chazan et al., 2004; Shin et al., 2005). In addition, studies that have been limited to uncomplicated CA-UTIs or to female subjects only have reported a prevalence of *E. coli* of more than 50% (Gupta et al., 1999; Farrel et al., 2003; Kahlmeter et al., 2003; Ti et al., 2003; Chazan et al., 2004). In the present study, *E. coli* was the main uropathogen in 38% of samples and it was also more prevalent in females (49%) (Table 1). The anatomical differences in the female urinary system, including a short urethra and the proximity to the vulvar and perianal areas, result in a higher prevalence of UTI in females (Sobel and Kaye 2010). The guidelines of the Infectious Diseases Society of America (IDSA) for the treatment of UTI recommend avoiding empirical treatment with a specific antibiotic when the local level of resistance among *E. coli* strains exceeds 20% (Warren et al., 1999). In previous, the first empirical antibiotic for UTI treatment was SXT. However, resistance rate to SXT in *E. coli* was reached at 50% in several Korean studies (Ko et al., 2003; Shin et al., 2005) and was 36.06% in this study. And these finding demonstrated that SXT was no longer reasonable choice in empirical treatment of UTI. In addition, the most alarming finding in our study was the exceedingly high resistance rate of *E. coli* to ciprofloxacin (33.55% in 2012~3) (Fig. 1). This rate is lower than that reported in Shin et al. (2005) but higher than that of Cullen et al. (2013). These results imply that quinolones, which are commonly used in the management of UTI, might gradually lose their utility in the empiric treatment of UTI. In addition, the resistance rates for first-generation and third-generation cephalosporins in *E. coli* increased over time (Fig. 1). ESBL-producing *E. coli* is an emerging cause of nosocomial healthcare-associated, and community-acquired infection worldwide (Jacobby and Medeiros, 1991; Bush, 2001). Inadequate empirical antibiotic therapy for infections caused by this microorganism is associated with poor outcomes and the use of carbapenem or cefepime is only effective for patients infected by ESBL (Ramphal and Ambrose, 2006). In addition, although imipenem-resistant isolates were not observed in this study, isolates producing carbapenemase, such as NDM, and KPC (Nordmann et al., 2011; Kim et al., 2013), have recently been reported worldwide. Therefore more constricted surveillance is required in the clinical laboratory.

The incidence of vancomycin-intermediate *S. aureus* (VISA) and VRSAs is in an increasing trend globally, including in Korea. In a nationwide surveillance study of VISA in Korean hospital from 2001 to 2006 (Chung et al., 2010), the prevalence of VISA was 0.09% (33/37,856 MRSA). In Asia, VISA prevalence is in Thailand (0.3~2.3%) and Japan (0.24%). In this study, MRSA is 570 isolates (73% of 784 *S. aureus*) for 10 yrs. Therefore, estimated prevalence of VISA may be 0.5 isolate (0.09% of 570 isolates) and both VRSA and VISA were not observed in

this study. However, because the E-test or broth dilution methods are required to confirm VISA, the routine antibiotic susceptibility testing (disk diffusion or Vitek) had a possibility of non-detecting VISA.

For the treatment of enterococcal infection, ampicillin and aminoglycosides are the drugs of choice. Diseases caused by strains resistant to ampicillin and aminoglycosides can be treated with vancomycin. In the present study, vancomycin resistance in *E. faecium* was 20.03% over a period of 10 years and vancomycin resistance in *E. faecium* increased from 15.69% in 2004~5 to 25.00% in 2012~3. The occurrence of VRE represents a serious problem because the treatment of infections provoked by VRE may be highly problematic because the choice of suitable medicaments is mainly limited to linezolid and quinupristin/dalfopristin, or due to the transmission of vancomycin resistant genes, such as *vanA* or *vanB*. A significant correlation between vancomycin use and VRE occurrence has been demonstrated (Quale et al., 1996; Empey and Rapp, 2002; Kolar et al., 2002) and the use of infection control measures including frequent hand washing, has been successful for containing small monoclonal outbreaks (Boyce et al., 1994). Therefore, the VRE problem requires not only improved hygiene in clinical department but also the responsible use of antibiotics.

The *P. aeruginosa* was highly resistant to most antibiotics and recently, an increase in imipenem-resistant *P. aeruginosa* (IRPA) has become a serious problem. In the present study, the prevalence IRPA was 33.33% during 2004~5 and after that time, was decreased to 21~24%. IRPA usually causes various nosocomial infections in long term hospitalized patients. However, Shin et al. (2005) reported that IRPA in even CA-UTI was 47% in 2001~3. Moreover, metallo-β-lactamase (MBL; class B β-lactamase defined by Ambler), the most important resistance mechanism to imipenem in *P. aeruginosa*, was easily transmitted to other isolates using various genetic element, such as integrin (Poirel et al., 2000; Lee et al., 2002, Shin et al., 2008). Therefore, rapid detection or strict control of the transmission of the MBL producer is also required.

This study had several limitations due to the fact that it was a retrospective study. First, the results of the antimicrobial susceptibility testing obtained from conventional disk diffusion or the Vitek II system were confirmed by the E-test only in isolates exhibiting resistance to vancomycin or imipenem. Second, we did not interpret the positive cultures in terms of contamination or clinically relevant infection. Third, we included bacteria isolated from both CA-UTIs and hospital associated UTI due to difficulties associated with the classification of clinical infection, which demonstrated different distributions of pathogens and antimicrobial susceptibility patterns.

In conclusion, over the last 10 years, the proportions of ciprofloxacin resistant *E. coli* and multidrug-resistant bacteria, including ESBL and VRE, have significantly increased. These findings demonstrate the need for strict control over the use of antibiotics and indicate the need for updated guidelines for the treatment of UTIs.

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Conflict of interest

The authors have no conflicts of interest to disclose.

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