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ORIGINAL ARTICLE

Chronological change of antibiotic use and antibiotic resistance in *Escherichia coli* causing urinary tract infections

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Abstract Overuse of antibiotics can cause the emergence of resistant bacterial strains. This study retrospectively investigated recent trends in *Escherichia coli* causing urinary tract infections (UTIs), focusing on antibiotic use and antibiotic susceptibilities. Patients diagnosed with UTIs caused by *E. coli* in Akashi Municipal Hospital between April 2004 and March 2010 were enrolled in the study. A total of 858 UTI cases were examined. Antibiotics used in our hospital during that period and the antibiotic susceptibilities of *E. coli* in UTI cases were assessed. We analyzed the data on a yearly basis, with the year being defined as the period from April to the following March (e.g., in this study the period from April 2004 to March 2005 represents 2004). The first 3 years (2004–2006) were compared to the last 3 years (2007–2009). The use of piperacillin, cephazolin, amikacin, oral cefotiam, and levofloxacin decreased significantly and the use of imipenem, gentamicin (GM), cefcapene, and oral minocycline (MINO) increased significantly in the last 3 years compared to the previous 3 years. The susceptibilities of MINO in complicated cystitis significantly increased and those of GM in uncomplicated pyelonephritis significantly decreased in these 3 years (2007–2009) compared to the previous 3 years (2004–2006) ($P < 0.05$). Additionally, extended-spectrum β-lactamase (ESBL)-producing *E. coli* tended to be isolated more often; this was statistically significant in the last 3 years (2007–2009) compared to the previous 3 years (2004–2006) ($P < 0.05$). In conclusion, we found changes in our pattern of antibiotic use associated with changes in antibiotic susceptibilities and an increase in ESBL-producing *E. coli* isolated from our UTI cases. Monitoring of antibiotic use and emergence of resistant strains should be continued.

Keywords *Escherichia coli* · Urinary tract infection · Drug resistance · Antibiotic use · Chronological change

Introduction

Escherichia coli (*E. coli*) is one of the most important causative bacteria in urinary tract infections (UTIs) [1], especially uncomplicated UTIs in which the patients have no underlying diseases of the urinary tract. Thus, *E. coli* has long been the most commonly isolated bacteria especially in this UTI category [2]. The isolation rate of *E. coli* in complicated or hospitalized UTIs has tended to be lower than in uncomplicated UTIs, partly because of the isolation of other bacteria such as *Klebsiella* spp., *Pseudomonas aeruginosa*, and *Proteus mirabilis* [2, 3]. UTIs caused by *E. coli* have been considered easier to handle because this bacterium showed good susceptibility to many kinds of antibiotics. More recently, however, extended-spectrum beta-lactamase (ESBL)-producing *E. coli* and fluoroquinolone-resistant *E. coli* (FQRE) have been reported [4, 5].

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Bacterial exposure to antibiotics is one of the reasons for the acquisition of bacterial resistance [6, 7]. The long-standing exposure of *E. coli* to a wide variety of antibiotics may have resulted in the emergence of resistant strains, with risks ranging from the diffusion of resistant strains to the cost of administering useless drugs. In particular, guidelines for antibiotic therapy using a single kind of drug may have tended to lead to the emergence and spread of resistant strains [7].

In this study, we investigated the use and susceptibility profiles of several representative oral and i.v. antimicrobial agents used frequently for UTIs. The results shed light on how UTIs can be treated without increasing the number of resistant strains.

Materials and methods

Bacterial isolates

A total of 858 *E. coli* cases were identified from UTI patients in Akashi Municipal Hospital between April 2004 and March 2010. The year was defined as from April to the following March (e.g., in this study April 2004 to March 2005 represents 2004). We defined UTIs as symptomatic bacteriuria with 10^5 or more (in outpatients) or 10^4 or more (in inpatients) colony-forming units/ml urine. The UTIs in this study included cystitis, pyelonephritis, prostatitis, epididymitis, and urethritis with bacteriuria. Species identification was confirmed with the Micro Scan Walk/Away 40 system (Siemens, Munich, Germany). Antimicrobial agent use and the following data on antibiotic susceptibilities were derived from outpatients and inpatients in this hospital.

Susceptibility testing

Results of the antimicrobial susceptibility tests were interpreted using the reference broth microdilution method as described by the Clinical and Laboratory Standards Institute (CLSI) M7-A5 (2003 CLSI document M100-S13). Minimal inhibitory concentration (MIC) was defined as the lowest antimicrobial concentration that totally inhibited bacterial growth. Susceptibilities were evaluated by CLSI category and categorization of the presence of underlying urinary tract diseases (uncomplicated or complicated) and of disease (cystitis, pyelonephritis, prostatitis, epididymitis, or urethritis). Antimicrobial agents with no criteria in that category are referred to by a generic term, such as third-generation cephalosporins. We tested bacterial strains against the following antimicrobial agents: piperacillin (PIPC), cefazolin (CEZ), cefotiam (CTM), cefcapene (CFPN), imipenem (IPM), gentamicin (GM), amikacin (AMK), minocycline (MINO), and levofloxacin (LVFX). *E. coli* ATCC 25922 was used for quality control.

Antibiotic usage

Use of these representative antimicrobial agents in outpatients and inpatients in our hospital was investigated from April 2004 to March 2010. Oral antibiotics were totaled by tablet and i.v. antibiotics were counted by vial.

Statistical analysis

Statistical analyses were performed using chi square or Wilcoxon rank-sum (Mann–Whitney) tests. Data on the susceptibility rates of each antimicrobial agent and rates of their use were divided into two groups: (1) April 2004 to March 2007 and (2) April 2007 to March 2010. The first 3 years (2004–2006) were compared to the next 3 years (2007–2009). We analyzed the susceptibility rates of each antimicrobial agent and the total quantity of representative antimicrobial agents used in this period. All tests used STATA (Stata, College Station, TX, USA). Statistical significance was set at 0.05.

Results

Patients' backgrounds

Patient background data are shown in Table 1. Of a total of 858 UTI cases included in this study, 423 were uncomplicated UTIs (49.3%) and 435 were complicated UTIs (50.7%). Details of the underlying disease in complicated infections are also shown in Table 1.

Antibiotic usage

Table 2 shows the amount and type of antimicrobial agents used, comparing 2004–2006 with 2007–2009. Use of PIPC, CEZ, AMK, and oral CTM decreased significantly and use of IPM, GM, CFPN, oral MINO, and LVFX increased

Table 1 Patients' backgrounds

N	858
Male	176
Female	682
Complicated urinary tract infection (UTI)	435
Uncomplicated UTI	423
Cystitis	616
Pyelitis	221
Prostatitis	15
Epididymitis	5
Urethritis	1

Table 2 Chronological changes of antibiotic usage (2004–2006 vs. 2007–2009)

Antibiotic usage	Used quantity		Odds ratio (OR) (95% confidence interval, CI)	*P* value
	2004–2006	2007–2009		
i.v. antibiotics: vial				
PIPC	2,356	1,406	0.9306 (0.8702–0.9952)	0.034
CEZ	21,150	10,015	0.7180 (0.6978–0.7389)	0.0000
IPM	9,456	8,461	1.664 (1.610–1.719)	0.0000
GM	262	383	2.477 (2.109–2.909)	0.0000
AMK	5,982	3,081	0.8545 (0.8162–0.8946)	0.0000
CTM (vial)	17,565	10,547	1.015 (0.9865–1.045)	0.2984
MINO	3,134	1,799	0.9645 (0.9084–1.024)	0.2345
Total	59,905	35,692		
Oral antibiotics: tablet				
CTM	7,343	2,711	0.4128 (0.3948–0.4316)	0.0000
MINO	25,046	28,455	1.314 (1.291–1.337)	0.0000
CFPN	111,242	102,501	1.063 (1.052–1.074)	0.0000
LVFX	215,867	183,998	0.9159 (0.9071–0.9248)	0.0000
Total	359,498	317,665		

PIPC piperacillin, *CEZ* cefazolin, *IPM* imipenem, *GM* gentamicin, *AMK* amikacin, *CTM* cefotiam, *MINO* minocycline, *CFPN* cefcapene, *LVFX* levofloxacin

significantly when these two 3-year periods are compared ($P < 0.05$) (Table 2).

Susceptibilities to antimicrobial agents

The antibiotic susceptibilities of *E. coli* are shown in Table 3, comparing the 2004–2006 period to 2007–2009. Susceptibilities to MINO in cystitis of complicated UTI significantly increased ($P = 0.0474$) but those to GM in pyelonephritis of uncomplicated UTI significantly decreased ($P = 0.0222$) (Table 3). Other UTI diseases such as prostatitis, epididymitis, and urethritis had fewer cases (15, 5, and 1 cases, respectively) (see Table 3).

ESBL-producing *E. coli*

Extended-spectrum beta-lactamase (ESBL)-producing *E. coli* tended to be isolated more often, which was statistically significant when comparing 2007–2009 to 2004–2006 ($P < 0.005$) (Table 4). Table 4 also shows the underlying diseases of the patients with ESBL-producing *E. coli*. Seven of 25 cases were uncomplicated UTI and 18 were complicated UTI. Neurogenic bladder, benign prostatic hyperplasia, and renal stones were often detected (see Table 4).

Discussion

E. coli is the common causative bacteria in UTIs, especially in uncomplicated infections where it tends to be the most common bacterium isolated in many studies. The trend is similar in complicated cases, but the isolation ratio of *E. coli* is lower than in uncomplicated cases. Some studies have reported that rates of causative *E. coli* have recently decreased [8] in both uncomplicated and complicated cases.

E. coli has been generally sensitive to antimicrobial agents [4] and is thus simple to treat. However, more recently several resistant strains have emerged, such as FQRE and ESBL-producing *E. coli*. The emergence of resistant strains may be partly caused by overuse of the same kind of antimicrobial agents, including prophylactic use to prevent surgical site infections or other urological interventions such as retrograde pyelography or prostate biopsy. In Japan, fluoroquinolones such as LVFX have been used very frequently, which might be based on reliance on unrevised drug use guidelines. In this respect, our use of LVFX decreased in 2007–2009, and we did not see a trend toward LVFX-resistant *E. coli* in contrast to the increase in LVFX-resistant *E. coli* commonly reported in the recent literature, as mentioned earlier. This finding suggests our reduction in LVFX use might have helped restrict the spread of resistant strains. The susceptibility of *E. coli* to LVFX should be monitored over the coming years to determine the future trend. Additionally, our susceptibilities results showed significantly more sensitivity to MINO in cystitis with complicated UTI but less sensitivity to GM in pyelonephritis with uncomplicated UTI in the latter 3 years, which may help guide antibiotic use, especially for cases in which we do not use LVFX or CFPN for reasons such as history of use of those antimicrobial agents.

Table 3 Chronological changes of susceptibilities to antibiotics (2004–2006 vs. 2007–2009)

	Cystitis				Pyelonephritis				Others[a]			
	Uncomplicated		Complicated		Uncomplicated		Complicated		Uncomplicated		Complicated	
Antibiotic	2004–2006 Sensitivity (%)	2007–2009 *S*[b]	2004–2006 Sensitivity (%)	2007–2009 *S*	2004–2006 Sensitivity (%)	2007–2009 *S*	2004–2006 Sensitivity (%)	2007–2009 *S*	2004–2006 Sensitivity (%)	2007–2009 *S*	2004–2006 Sensitivity (%)	2007–2009 *S*
CTM	100	99.3	96.2	98.4	95.8	100	100	94.1	100	80	100	100
MINO	92	86.6	**79.2**	**89.4**[c, e]	92.9	91.3	89.8	86.8	50	100	100	100
PIPC	78.5	72.4	52.8	64.9	74.6	73.9	69.5	64.7	50	60	100	58.3
CEZ	92	93.3	87.7	90.9	93	95.7	89.8	79.9	50	60	100	83.3
IPM	100	100	100	100	100	100	100	100	100	100	100	100
GM	93.1	94.8	89.6	89.4	**90.1**	**78.3**[d, e]	88.1	89.7	100	80	100	75
AMK	100	100	100	100	100	100	100	100	100	100	100	100
CFPN	71.6	79.9	68.2	75.5	83.3	73.9	68.4	61.8	0	60	NA	75
LVFX	84	85.8	72.6	75.5	85.9	82.6	72.9	75	100	80	100	66.7
N	188	134	106	188	71	23	59	68	2	5	2	12

NA, not applicable

[a] Others include prostatitis, epididymitis, and urethritis (no statistical data)

[b] *S*, sensitive in Clinical and Laboratory Standards Institute (CLSI) criteria

[c] Susceptibility to MINO significantly increased ($P = 0.0474$)

[d] Susceptibility to GM significantly decreased ($P = 0.0222$)

[e] Statistical significance was set at 0.05

Table 4 Isolated ratio, patient background, and antibiotic susceptibilities (%) of extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli*

Isolated ratio			
Year	ESBL *E. coli*	All *E. coli*	Rate (%)
2004	0	132	0
2005	1	135	0.74
2006	5	160	3.1
2007	6	169	3.6
2008	4	131	3.3
2009	9	131	6.9

Patient background	
n	25
Age (years)	37–85 (median, 79)
Cystitis	16
Pyelonephritis	9
Uncomplicated urinary tract infection (UTI)	7
Complicated UTI	18
Underlying diseases	
Neurogenic bladder	6
Benign prostatic hyperplasia	4
Renal stone	4
Overactive bladder	2
Bladder stone	1
Urinary tract tuberculosis	1

Antibiotic susceptibilities (%)												
PIPC	CEZ	CTM	CFPN	CMZ	FMOX	IMP	GM	AMK	MINO	LVFX	ST	FOM
0	0	0	0	100	97	100	92	100	88	21	56	94

Exposure to fluoroquinolones in the previous 6 months to 1 year has been reported as an important risk factor in the emergence and spread of FQRE [6, 9–11]. However, our data showed decreased use and no increase in overall *E. coli* resistance. Penicillins were long used to treat *E. coli* and showed good activity [1]. However, the third-generation cephalosporins or fluoroquinolones have recently been replaced from the penicillins, as our results showed. ESBL-producing *E. coli* is well known to be resistant to beta-lactams [5] and currently poses a therapeutic challenge. However, recently beta-lactamase inhibitor-combined penicillins have showed good treatment efficacy for use in urogenital infections.

In uncomplicated UTIs such as acute bacterial cystitis caused by *E. coli*, Japanese guidelines generally recommend treating with oral fluoroquinolones or the third-generation cephalosporins such as CFPN [8]. Our data showed that biased use of these two antimicrobial agents (LVFX and CFPN) as dominant drugs may result in higher ratios of resistant strains [11, 12], suggesting their rate of use may be due for reconsideration. Regarding fluoroquinolones, Yamaguchi et al. [13] reported in a study of 18,639 clinical isolates that FQRE rates were rapidly increasing. Arslan et al. [6] found a 17% resistance rate against ciprofloxacin and ofloxacin in the *E. coli* strains from 288 uncomplicated UTI cases in Turkey. Johnson et al. [11] reported that resistance to LVFX increased from 1% to 9% ($P < 0.01$) in a U.S. outpatient study from 1998 to 2005, partly because LVFX use increased from 3.1 to 12.7 prescriptions per 1,000 visits ($P < 0.01$). We should continue our study for several years to monitor how *E. coli* susceptibilities to LVFX are affected by patterns of antibiotic use.

CFPN use increased in our institution, and our data did not show the spread of resistant strains so far. However, our annual use of this antibiotic agent tended to increase yearly partly because of the decrease in LVFX use, especially in uncomplicated UTIs, which could lead to future *E. coli*

resistance. Even though our study did not show a significant trend in susceptibility to this drug, it may be appropriate to switch to other drugs.

Our data showed a significant increase of ESBL-producing *E. coli*, and their trend of resistance to antibiotics is problematic. Azap and colleagues demonstrated that ESBL-producing *E. coli* in UTI were seen in complicated UTI more often than uncomplicated UTI, and prostatic disease is one risk factor for their isolation. In addition, simultaneous resistance to trimethoprim-sulphamethoxazole, ciprofloxacin, and GM was found in the ESBL-positive group more often than in the ESBL-negative group [14]. Our cases showed simultaneous resistance to trimethoprim-sulphamethoxazole, LVFX, PIPC, and cephalosporins, suggesting geographical differences that may result partly from the methodology of antibiotic use. Esther and colleagues showed that previous bacterial infection, intravenous antimicrobial treatment, and previous exposure to the second-generation cephalosporins were significant risk factors for *E. coli* harboring ESBL in their UTI cases [15]. This fact may support our results showing an increase in ESBL-producing *E. coli* and our frequent use of intravenous second-generation cephalosporins.

In conclusion, we found changes in the pattern of antibiotic use in our institution, some changes in the pattern of *E. coli* antibiotic resistance in UTIs, and an increase of ESBL-producing *E. coli* isolated from our UTI cases. Taken together, our findings suggest that patterns of antibiotic use might cause or help restrict the spread of resistant strains. We should continue this survey to acquire more data on the relationship between antibiotic use and the emergence of antibiotic-resistant bacterial strains in UTIs.

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