Original article

Risk factor analysis of urinary tract infection by cefotaxime-resistant *Escherichia coli* and *Klebsiella pneumoniae*: a simple and effective analysis using the National Health Insurance Data Sharing Service

Jae Kwang Lee[1], Yoonseon Park[2], Young Ah Kim[3]

[1]Department of Research and Analysis, National Health Insurance Service Ilsan Hospital, Goyang, [2]Division of Infectious Diseases Department of Internal Medicine Gil Medical Center, Gachon University College of Medicine, Incheon, [3]Department of Laboratory Medicine, National Health Insurance Service Ilsan Hospital, Goyang, Korea

Abstract

Background: This study aims to analyze the risk factors for urinary tract infection (UTI) by cefotaxime-resistant *Escherichia coli* or *Klebsiella pneumoniae*, using data from the National Health Insurance Data Sharing Service.

Methods: A retrospective case-control study was conducted to analyze the risk factors during 11 years (2010–2020). Study groups were selected based on the laboratory data of the hospital, which comprised 3,638 and 877 cases of cefotaxime-resistant *E. coli* and *K. pneumoniae*, respectively. Controls comprised 8,994 and 1,573 cases of cefotaxime-non-resistant (intermediate or susceptible) *E. coli* and *K. pneumoniae*, respectively. Clinical and socioeconomical features were obtained from the National Health Insurance service data.

Results: In a multivariate analysis of risk factors for UTI by cefotaxime-resistant *E. coli*, the odds ratio (OR) of the male sex was 1.335 (95% confidence interval, 1.204–1.480), age 0–9 years was 1.794 (1.468–2.191), chronic renal disease was 1.227 (1.062–1.417), and hemodialysis was 1.685 (1.255–2.262). Moreover, the ORs of L-tube, central venous pressure catheter, and Foley catheter use were 1.204 (1.047–1.385), 1.332 (1.156–1.534), and 1.473 (1.316–1.649), respectively; the OR of previous antimicrobial use was 1.103 (1.009–1.206) and that of healthcare facility use was 1.782 (1.576–2.014). In a multivariate analysis of risk factors for UTI by cefotaxime-resistant *K. pneumoniae*, OR of the male sex was 1.460 (1.199–1.778), liver disease was 1.295 (1.037–1.617), and hemodialysis was 2.046 (1.263–3.315). The ORs of L-tube and Foley catheter use were 2.329 (1.861–2.915) and 1.793 (1.431–2.246), respectively, and the OR of the healthcare facility use was 1.545 (1.161–2.056).

Conclusion: In this study, the risk factors for UTI caused by cefotaxime-resistant *E. coli* or *K. pneumoniae* were analyzed based on the data of a specific healthcare facility linked to the National Health Insurance system. We suggest that it is a simple and effective way to elucidate risk factors of infections caused by major antimicrobial-resistant pathogens.

Keywords: Risk factor, Urinary tract infection, Cefotaxime resistance, *Escherichia coli*, *Klebsiella pneumoniae*

pISSN : 2288-0585
eISSN : 2288-6850

Ann Clin Microbiol 2023 September, 26(3): 59-66
https://doi.org/10.5145/ACM.2023.26.3.3

Corresponding author
Young Ah Kim
E-mail: yakim@nhimc.or.kr
Yoonseon Park
E-mail: yoonseony@gilhospital.com

Received: April 24, 2023
Revised: August 17, 2023
Accepted: August 30, 2023

Introduction

Urinary tract infection (UTI) refers to bacterial infection in a part of the urinary system consisting of the kidneys, ureter, bladder, and urethra [1]. UTI is a very common type of bacterial infection, and many women experience recurrent UTIs [2]. Well-known etiologic agents of UTI are *Escherichia coli* (most common), and other enteric gram-negative bacteria (*Klebsiella*, *Pseudomonas*, *Proteus*, *Enterobacter*, and *Citrobacter* spp.) [3,4]. Extended-spectrum ß-lactamase (ESBL)-producing *E. coli* or *K. pneumoniae* (most of them show the resistance to third generation cephalosporin, such as cefotaxime) are common in Korea, and resistance rates to cefotaxime were 37.1% and 24.9% for *E. coli* and *K. pneumoniae*, respectively, in 2019 [5].

The purpose of this study is to analyze the risk factors for UTI by cefotaxime-resistant *E. coli* or *K. pneumoniae*, using data from the National Health Insurance Data Sharing Service. The data of a specific healthcare facility can be linked to the national health insurance data with this service, which can be a simple and effective way, including not only the use of medical, but also service socio-demographic characteristics. With this methodology, entire antibacterial prescriptions can be obtained with this service, including antimicrobial use in the community.

Materials and methods

A total of 599,883 cases of urine culture over 11 years (2010-2020) were linked to the national health insurance service data in one general hospital (818 beds). Excluding repeated cases and missing data, 12,632 cases of *E. coli* and 2,450 cases of *K. pneumoniae* were included for a retrospective case-control study. Based on laboratory data of the hospital, study groups were selected. Cases comprised 3,638 cases of cefotaxime-resistant *E. coli* and 877 cases of cefotaxime-resistant *K. pneumoniae*, which were isolated from urine cultures (UTI patients caused by ESBL-producers). Controls comprised 8,994 cases of cefotaxime-non-resistant (intermediate or susceptible) *E. coli* and 1,573 cases of cefotaxime-non-resistant *K. pneumoniae*, which were isolated from urine cultures (UTI patients caused by non-ESBL-producers).

Clinical and socioeconomical features were obtained from the national health insurance service data. The variables were defined as follows: underlying diseases were obtained in the inpatients during the admission period or outpatients within one month, using the major diagnostic code or four minor codes (total five codes), corresponding to malignancy (C00-D48), diabetes (E10-E14), ischemic heart disease (I20-I25), cardiovascular disease (I60-I69), chronic lower respiratory disease (J40-J47), liver disease (K70-K77), and chronic renal disease (N18).

Using health insurance claim codes, major surgery history (general anesthesia prescription), hemodialysis, anticancer treatment, and total parenteral nutrition history were confirmed. The use of a device, such as an L-tube, central venous pressure (CVP) catheter, and Foley catheter was evaluated within 90 days of pathogen isolation. Previous antimicrobial use was verified within 30 days of pathogen isolation, using J01 Anatomical Therapeutic Chemical codes, excluding local application or external preparation. The healthcare facility use comprised any healthcare facilities, including clinics before 30 days of pathogen isolation. The Charlson

comorbidity index (CCI) was calculated according to the previous report [6].

Statistical analysis was performed with the Chi-square test and logistic regression. SAS program version 9.4 (SAS Institute, Cary, NC, USA) was used.

Results

Risk factors for cefotaxime-resistant *E. coli*-mediated UTI

In a univariate analysis, male sex, childhood or older age, underlying disease (malignancy, diabetes, ischemic heart disease, cardiovascular disease, chronic lower respiratory disease, liver disease, and chronic renal disease), hemodialysis, anticancer treatment, device use (L-tube, CVP catheter, and Foley catheter), previous antimicrobial use, frequent healthcare facility use, and high CCI (more than 3) were statistically significant for cefotaxime-resistant *E. coli* UTI (Table 1).

In a multivariate analysis, the odds ratio (OR) of male sex was 1.335 (95% confidential interval, 1.204-1.480); OR of age 0-9 years was 1.794 (1.468-2.191); OR of chronic renal disease was 1.227 (1.062-1.417); OR of hemodialysis was 1.685 (1.255-2.262); ORs of L-tube, CVP catheter, and Foley catheter use were 1.204 (1.047-1.385), 1.332 (1.156-1.534), and 1.473 (1.316-1.649), respectively; OR of previous antimicrobial use was 1.103 (1.009-1.206); OR of healthcare facility use was 1.782 (1.576-2.014) (Table 2).

Risk factors for cefotaxime-resistant *K. pneumoniae*-mediated UTI

In a univariate analysis, male sex, older age, underlying disease (malignancy, diabetes, ischemic heart disease, cardiovascular disease, chronic lower respiratory disease, liver disease, and chronic renal disease), hemodialysis, device use (L-tube, CVP catheter, and Foley catheter), and previous antimicrobial use, and frequent healthcare facility use were statistically significant for cefotaxime-resistant *E. coli* UTI (Table 3).

In a multivariate analysis, OR of male sex was 1.460 (1.199-1.778); OR of liver disease was 1.295 (1.037-1.617); OR of hemodialysis was 2.046 (1.263-3.315); OR of L-tube and Foley catheter use were 2.329 (1.861-2.915) and 1.793 (1.431-2.246), respectively; and OR of healthcare facility use was 1.545 (1.161-2.056) (Table 2).

Table 1. Risk factors for cefotaxime-resistant *Escherichia coli* urinary tract infections: A univariate analysis.

Variable		CTX-NR % (N)	CTX-R % (N)	*P*-value
All		71.2 (8,994)	28.8 (3,638)	
Sex	Female	58.2 (7,355)	21.7 (2,742)	**< 0.0001**
	Male	13.0 (1,639)	7.1 (896)	
Age (yr)	0-9	8.6 (1,086)	3.3 (416)	**< 0.0001**
	10-19	0.8 (98)	0.2 (20)	
	20-29	2.7 (346)	0.6 (77)	
	30-39	3.4 (425)	0.8 (106)	
	40-49	6.2 (789)	1.6 (208)	
	50-59	9.7 (1,221)	2.8 (357)	
	60-69	9.4 (1,187)	3.5 (442)	
	70-79	15.7 (1,980)	7.7 (971)	
	≥ 80	14.7 (1,862)	8.2 (1,041)	
Underlying disease				
Malignancy	Yes	35.1 (4,433)	15.4 (1,946)	**< 0.0001**
Diabetes	Yes	36.2 (4,576)	18.0 (2,279)	**< 0.0001**
Ischemic heart disease	Yes	25.5 (3,216)	13.4 (1,699)	**< 0.0001**
Cardiovascular disease	Yes	24.7 (3,120)	13.9 (1,760)	**< 0.0001**
Chronic LRT disease	Yes	53.0 (6,698)	23.3 (2,942)	**< 0.0001**
Liver disease	Yes	42.0 (5,303)	18.9 (2,392)	**< 0.0001**
Chronic renal disease	Yes	4.9 (625)	3.8 (477)	**< 0.0001**
Major surgery	Yes	0.1 (7)	0.0 (5)	0.3247
Hemodialysis	Yes	0.8 (100)	0.9 (120)	**< 0.0001**
Anticancer treatment	Yes	0.7 (87)	0.5 (60)	**0.0012**
TPN use	Yes	0.0 (3)	0.0 (3)	0.2514
Device				
L-tube	Yes	5.6 (704)	4.5 (564)	**< 0.0001**
CVP catheter	Yes	5.8 (735)	5.0 (629)	**< 0.0001**
Foley catheter	Yes	14.9 (1,885)	10.6 (1,345)	**< 0.0001**
Previous antimicrobial use	Yes	41.5 (5,240)	19.7 (2,483)	**< 0.0001**
Healthcare facility use	Yes	25.5 (3,220)	6.3 (790)	**< 0.0001**
CCI	0	43.3 (5,465)	19.8 (2,500)	**< 0.0001**
	1	8.7 (1,094)	2.1 (267)	
	2	5.8 (738)	1.7 (212)	
	≥ 3	13.4 (1,697)	5.2 (659)	

Bold fonts are statistically significant.
Abbreviations: CTX-NR, cefotaxime-intermediate or susceptible; CTX-R, cefotaxime-resistant; N, number; LRT, lower respiratory tract; TPN, total parenteral nutrition; CVP, central venous pressure; CCI, Charlson comorbidity index

Table 2. Risk factors of cefotaxime-resistant *Escherichia coli* or *Klebsiella pneumoniae* urinary tract infections: A multivariate analysis.

Variable		cefotaxime-resistant *E. coli*		cefotaxime-resistant *K. pneumoniae*	
		OR	95% CI	OR	95% CI
Sex	Female	1	-	1	-
	Male	**1.335**	**1.204-1.480**	**1.460**	**1.199-1.778**
Age (yr)	**0-9**	**1.794**	**1.468-2.191**	0.722	0.448-1.162
	10-19	0.873	0.526-1.449	1.966	0.585-6.612
	20-29	1.014	0.762-1.349	0.938	0.372-2.364
	30-39	1.033	0.804-1.327	0.909	0.402-2.055
	40-49	0.997	0.820-1.212	1.518	0.961-2.398
	50-59	0.984	0.838-1.155	0.899	0.620-1.304
	60-69	1.018	0.881-1.177	0.908	0.651-1.267
	70-79	1.086	0.969-1.217	0.983	0.782-1.236
	≥ 80	1	-	1	-
Underlying disease					
Malignancy	No	1	-	1	-
	Yes	0.979	0.895-1.070	0.913	0.748-1.115
Diabetes	No	1	-	1	-
	Yes	0.862	0.774-0.960	0.823	0.643-1.054
Ischemic heart disease	No	1	-	1	-
	Yes	0.906	0.822-0.999	0.966	0.784-1.189
Cardiovascular disease	No	1	-	1	-
	Yes	0.784	0.711-0.865	0.785	0.637-0.968
Chronic LRT disease	No	1	-	1	-
	Yes	0.743	0.667-0.828	0.729	0.575-0.925
Liver disease	No	1	-	1	-
	Yes	0.944	0.855-1.043	**1.295**	**1.037-1.617**
Chronic renal disease	No	1	-	1	-
	Yes	**1.227**	**1.062-1.417**	1.127	0.681-1.476
Major surgery	No	1	-	-	-
	Yes	1.602	0.476-5.395	-	-
Hemodialysis	No	1	-	1	-
	Yes	**1.685**	**1.255-2.262**	**2.046**	1.263-3.315
Anticancer treatment	No	1	-	1	-
	Yes	1.322	0.936-1.866	1.286	0.691-2.393
TPN use	No	1	-	-	-
	Yes	1.274	0.229-7.084	-	-
Devices					
L-tube	No	1	-	1	-
	Yes	**1.204**	**1.047-1.385**	**2.329**	**1.851-2.915**
CVP catheter	No	1	-	1	-
	Yes	**1.332**	**1.156-1.534**	1.261	0.999-1.592
Foley Catheter	No	1	-	1	-
	Yes	**1.473**	**1.316-1.649**	**1.793**	**1.431-2.246**
Previous antimicrobial use	No	1	-	1	-
	Yes	**1.103**	**1.009-1.206**	0.979	0.793-1.209
Healthcare facility use	No	1	-	1	-
	Yes	**1.782**	**1.576-2.014**	**1.545**	**1.161-2.056**
CCI	0	1	-	1	-
	1	0.834	0.712-0.976	0.991	0.660-1.487
	2	0.945	0.792-1.126	0.891	0.584-1.359
	3	1.063	0.926-1.220	0.925	0.691-1.238

Bold fonts are statistically significant.

Abbreviations: OR, odds ratio; CI, confidential interval; LRT, lower respiratory tract; TPN, total parenteral nutrition; CVP, central venous pressure; CCI, Charlson comorbidity index

Table 3. Risk factors for cefotaxime-resistant *Klebsiella pneumoniae* urinary tract infections: A univariate analysis.

Variable		CTX-NR % (N)	CTX-R % (N)	*P*-value
All		64.2 (1,573)	35.8 (877)	
Sex	Female	44.1 (1,081)	22.7 (557)	**< 0.0001**
	Male	20.1 (492)	13.1 (320)	
Age (yr)	0-9	11.9 (292)	2.2 (53)	**< 0.0001**
	10-19	0.3 (8)	0.2 (5)	
	20-29	0.9 (22)	0.3 (7)	
	30-39	1.1 (28)	0.4 (9)	
	40-49	2.9 (72)	1.8 (43)	
	50-59	6.0 (148)	2.6 (64)	
	60-69	6.8 (166)	3.5 (86)	
	70-79	17.3 (423)	11.7 (286)	
	≥ 80	16.9 (414)	13.2 (324)	
Underlying disease				
Malignancy	Yes	30.4 (745)	20.6 (505)	**< 0.0001**
Diabetes	Yes	37.2 (912)	26.4 (648)	**< 0.0001**
Ischemic heart disease	Yes	25.8 (631)	19.1 (469)	**< 0.0001**
Cardiovascular disease	Yes	27.5 (673)	21.8 (534)	**< 0.0001**
Chronic LRT disease	Yes	44.0 (1,078)	28.7 (703)	**< 0.0001**
Liver disease	Yes	38.2 (935)	24.4 (597)	**< 0.0001**
Chronic renal disease	Yes	7.8 (192)	79.9 (1,957)	**< 0.0001**
Hemodialysis	Yes	1.5 (36)	2.7 (67)	**< 0.0001**
Anticancer treatment	Yes	1.1 (26)	0.9 (22)	0.1429
Device				
L-tube	Yes	10.4 (256)	15.2 (373)	**< 0.0001**
CVP catheter	Yes	10.6 (260)	12.9 (317)	**< 0.0001**
Foley catheter	Yes	24.9 (609)	24.3 (596)	**< 0.0001**
Previous antimicrobial use	Yes	42.0 (1,029)	26.8 (656)	**< 0.0001**
Healthcare facility use	Yes	22.1 (541)	7.6 (187)	**< 0.0001**
CCI	0	39.6 (969)	23.6 (579)	**0.0232**
	1	5.3 (130)	1.9 (46)	
	2	3.8 (92)	1.8 (45)	
	≥ 3	15.6 (382)	8.4 (207)	

Bold fonts are statistically significant.
Abbreviations: CTX-NR, cefotaxime-intermediate or susceptible; CTX-R, cefotaxime-resistant; N, number; LRT, lower respiratory tract; CVP, central venous pressure; CCI, Charlson comorbidity index

Discussion

Antimicrobial resistance and emerging ESBL infections are rising concerns in public health [7]. The production of β-lactamase enzymes is the primary mechanism by which Gram-negative bacteria resist the action of all β-lactam antibiotics, except carbapenems and cephamycins [8]. Additionally, ESBL-producing isolates have demonstrated rising rates of resistance to other classes of antibiotics, such as sulfonamides, aminoglycosides, and fluoroquinolones [8]. These multidrug-resistant organisms significantly limit the treatment options, and initial empirical therapy is often ineffective and associated with poor outcomes [9].

Defining risk factors for UTI by ESBL-producing *E. coli* or *K. pneumoniae* is very important to manage antimicrobial resistance in Korea because UTIs by these organisms are very common even in the community and they frequently progress to bloodstream infections, showing a serious prognosis [10]. The well-known risk factors for community-acquired UTI by ESBL-producing *E. coli* were prior use of antibiotics (OR from 2.2 to 21.4), previous hospitalization (OR from 1.7 to 3.9), and UTI history (OR from 1.3 to 3.8) after reviewing 16 previous observational studies [11]. In a multicenter study, a total of 983 patient-specific isolates were reviewed (890 were *E. coli*, 68 were *Klebsiella* species, and 25 were *Proteus mirabilis*) and significant risk factors for ESBL-producing Enterobacteriaceae-mediated infections were recent antibiotic use, residence in a long-term care facility, recent hospitalization, age 65 years, and male sex [12]. In this study, we found similar risk factors for UTI by cefotaxime-resistant *E. coli* or *K. pneumoniae* (ESBL-producers), such as male sex, underlying disease, hemodialysis, use of a device, previous antimicrobial use, and healthcare facility.

The National Health Insurance Data Sharing Service was used in this study, which can link the data of a specific healthcare facility to the national health insurance data. The strength of this study was that whole antibacterial prescriptions can be obtained with this service, including antimicrobial use in the community and healthcare facility use can also be identified. The risk factors for UTI caused by cefotaxime-resistant *E. coli* or K. pneumoniae were analyzed after the data of a specific healthcare facility were linked to the national health insurance data. Therefore, we suggest that it is a simple and effective way to elucidate risk factors of infections by major antimicrobial-resistant pathogens.

Ethics statement

The Institutional Review Board of the National Health Insurance Service Ilsan Hospital approved this study (NHIMC 2022-05-019) and waiver of informed consent was obtained.

Conflicts of interest

No potential conflicts of interest relevant to this article were reported.

Acknowledgements

This study used the National Health Insurance Data Sharing Service with permission (NHIS-2022-1-394).

Funding

This study was funded by a grant from the National Health Insurance Service Ilsan Hospital (2021-20-001).

References

1. Gupta K, Grigoryan L, Trautner B. Urinary tract infection. Ann Intern Med 2017;167:ITC49-64.
2. Jung C, Brubaker L. The etiology and management of recurrent urinary tract infections in postmenopausal women. Climacteric 2019;22:242-9.
3. Millner R, Becknell B. Urinary tract infections. Pediatr Clin North Am 2019;66:1-13.
4. Lee H, Yoon EJ, Kim D, Jeong SH, Won EJ, Shin JH, et al. Antimicrobial resistance of major clinical pathogens in South Korea, May 2016 to April 2017: first one-year report from Kor-GLASS. Euro Surveill 2018;23:1800047.
5. Kim D, Yoon EJ, Hong JS, Choi MH, Kim HS, Kim YR, et al. Major bloodstream infection-causing bacterial pathogens and their antimicrobial resistance in South Korea, 2017-2019: Phase I report from Kor-GLASS. Front Microbiol 2022;12:799084.
6. Kim KH. Comparative study on three algorithms of the ICD-10 Charlson comorbidity index with myocardial infarction patients. J Prev Med Public Health 2010;43:42-9.
7. van Driel AA, Notermans DW, Meima A, Mulder M, Donker GA, Stobberingh EE, at al. Antibiotic resistance of *Escherichia coli* isolated from uncomplicated UTI in general practice patients over a 10-year period. Eur J Clin Microbiol Infect Dis 2019;38:2151–8.
8. Rawat D, Nair D. Extended-spectrum β-lactamases in gram negative bacteria. J Glob Infect Dis 2010;2:263–74.
9. Al-Tamimi M, Abu-Raideh J, Albalawi H, Shalabi M, Saleh S. Effective oral combination treatment for extended-spectrum beta-lactamase-producing *Escherichia coli*. Microb Drug Resist 2019;25:1132–41.
10. Holmes CL, Anderson MT, Mobley HLT, Bachman MA. Pathogenesis of Gram-negative bacteremia. Clin Microbiol Rev 2021;34:e00234-20.
11. Larramendy S, Deglaire V, Dusollier P, Fournier JP, Caillon J, Beaudeau F, et al. Risk factors of extended-spectrum beta-lactamases-producing *Escherichia coli* community acquired urinary tract infections: a systematic review. Infect Drug Resist 2020;13:3945-55.
12. Ben-Ami R, Rodríguez-Baño J, Arslan H, Pitout JD, Quentin C, Calbo ES, et al. A multinational survey of risk factors for infection with extended-spectrum ß-lactamase-producing Enterobacteriaceae in nonhospitalized patients. Clin Infect Dis 2009;49:682-90.