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Risk factors of community-onset extended-spectrum β-lactamase-producing *Klebsiella pneumoniae* bacteraemia in South Korea using national health insurance claims data

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ABSTRACT

Background: Although it is essential to know the particular causes of antibiotic-resistant infections in the community, there is lack of evidence regarding risk factors for community-onset extended-spectrum β-lactamase-producing *Klebsiella pneumoniae* (ESBL-KP) bacteraemia in South Korea. As such, this study aimed to identify risk factors for community-onset ESBL-KP bacteraemia.

Methods: From May 2016 to April 2017, patients with community-onset KP bloodstream infection (BSI) ($n = 408$) from six sentinel hospitals participating in the Global Antimicrobial Surveillance System in South Korea were included in this study. Risk factors of ESBL-KP BSI were assessed. Polymerase chain reaction and sequencing to identify genes encoding ESBLs and multi-locus sequence typing were performed.

Results: Of the 408 patients with community-onset KP BSI, 70 (17%) had ESBL-KP BSI. Admission to a long-term-care hospital within the previous 3 months [odds ratio (OR) 5.7, 95% confidence interval (CI) 2.1–15.6; $P = 0.001$], previous use of trimethoprim/sulfamethoxazole (TMP/SMT; OR 11.5, 95% CI 2.7–48.6; $P = 0.001$) or extended-spectrum cephalosporin (OR 2.2, 95% CI 1.2–3.9; $P = 0.01$), and previous use of a urinary catheter (OR 2.3, 95% CI 1.1–4.5; $P = 0.02$) were independent risk factors for community-onset ESBL-KP BSI. ESBL-KP isolates most frequently carried the CTX-M-1 group ESBL (74%, $n = 52$). The most prevalent sequence type (ST) among the ESBL-KP isolates was ST48 (14%, $n = 10$). Among non-ESBL-KP isolates, ST23 was most prevalent (21%, $n = 70$).

Conclusion: Previous admission to a long-term-care hospital, use of a urinary catheter and use of TMP/SMT or extended-spectrum cephalosporin within the previous 3 months were identified as risk factors for community-onset ESBL-KP BSI. Strict antibiotic stewardship and infection control measures are needed for long-term-care hospitals.

1. Introduction

Antibiotic resistance is a significant threat to public health, not only in healthcare settings but also in communities, because antimicrobial-resistant infections can be transmitted within communities. Although extended-spectrum β-lactamase-producing *Klebsiella pneumoniae* (ESBL-KP) infections are prevalent in healthcare settings, there is growing evidence that ESBL-KP in-

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fections are also increasing in the community [1,2], with increasing reports of community-based CTX-M type ESBL-KP [3].

Although it is essential to know the particular causes of antibiotic-resistant infections in the community for proper management, there is insufficient evidence regarding risk factors for community-onset ESBL-KP bloodstream infection (BSI). As such, this multi-centre study aimed to determine the independent risk factors for community-onset ESBL-KP bacteraemia in South Korea. Genotypes of community-onset ESBL-KP were also investigated.

2. Materials and methods

2.1. Study design

From May 2016 to April 2017, patients with community-onset KP BSI from six sentinel hospitals participating in the Global Antimicrobial Surveillance System (GLASS) in South Korea were included in this study [4]. GLASS is an antimicrobial surveillance system that was established by the World Health Organization (WHO) in 2015, and was introduced to Korea in July 2016 [2]. Participating hospitals are located in different districts throughout South Korea, and have a total of 5194 beds, ranging from 715 to 1050 beds per hospital. During the study period, 67,803 patients were subjected to blood culture, and 585 patients were diagnosed with KP BSI. Of these, 408 patients had community-onset KP BSI.

Clinical information on age, sex, comorbidities and laboratory findings for each BSI episode were gathered from electronic medical records of the sentinel hospitals. Upon BSI diagnosis, the Charlson comorbidity index [5] and SOFA score [6] were calculated to assess underlying conditions and disease severity. Data regarding previous use of antibiotics and medical devices before bacteraemia were acquired from the national health insurance claims database (HIRA claims data).

Only the first bacterial isolate from each patient was collected for microbiological studies, and sequential isolates were discarded. All isolates collected at the sentinel hospitals were transferred to an analysis centre for microbiological assessment. Requirement for informed consent was waived by all local institutional review boards of the sentinel hospitals.

2.2. Definitions

Community-onset infection was defined when bacteraemia was confirmed within 2 days of admission. If a patient was transferred from another hospital, the date was counted from the admission date to the previous hospital. Previous admission was noted when the patient was admitted to any hospital, excluding a nursing home, in the 3 months preceding bacteraemia. Previous history of antibiotic use was defined as the use of any antibiotic in the 3 months preceding bacteraemia. ESBL-KP was confirmed by ESBL genotype rather than by antibiotic resistance phenotype. Any detection of the CTX-M group gene was regarded as ESBL-producing. Detection of the TEM- and SHV group genes, excluding TEM-1, TEM-2 and SHV-1, was also regarded as ESBL-producing.

2.3. Microbiological analysis

All bacterial isolates were identified using MALDI Biotyper (Bruker Daltonik GmbH, Bremen, Germany) and 16S rRNA sequencing. Antimicrobial susceptibilities were tested by disk diffusion methods on cation-adjusted Mueller-Hinton agar (Difco Laboratories, Detroit, MI, USA) according to the guidelines of the Clinical and Laboratory Standards Institute [23]. Genes encoding ESBLs (groups 1 and 9 CTX-M, SHV and TEM) were analysed by polymerase chain reaction and sequencing using primer sets previously described for potential β-lactamase producers exhibiting corresponding resistance phenotypes [7].

Multi-locus sequence typing (MLST) was performed by comparing partial sequences of the seven housekeeping genes (gapA, infB, mdh, pgi, phoE, rpoB and tonB) to determine the allelic types and STs of KP isolates. STs were interpreted with reference to the KP MLST database (http://bigsdb.pasteur.fr/klebsiella/klebsiella.html).

2.4. Statistical analysis

All categorical variables were compared using Pearson's Chi-squared test. As they were not normally distributed, the Mann–Whitney *U*-test was used to compare age, Charlson comorbidity index and SOFA score. Variables that yielded a *P*-value <0.05 on univariate analysis were included in the multi-variate logistic regression model using the backward stepwise (Wald) method. As history of long-term-care hospital admission is a subset of admission history, a second model that looked at long-term care alone was examined. A *P*-value <0.05 was considered to indicate statistical significance. SPSS Version 23.0 (IBM Corp., Armonk, NY, USA) was used for statistical analyses.

3. Results

During the research period, 408 cases of community-onset KP BSI occurred. Of these, 338 (83%) were non-ESBL-KP BSI and 70 (17%) were ESBL-KP BSI (Table 1). The median age of patients with non-ESBL-KP BSI was 71.0 years [interquartile range (IQR) 61–79.0] and the median age of patients with ESBL-KP BSI was 75.0 years (IQR 64.0–81.0). Among patients with ESBL-KP BSI, 71.4% had a history of admission during the previous 3 months, while only 45% of patients with non-ESBL-KP BSI had a recent admission history. Similarly, recent history of long-term-care admission was more common among patients with ESBL-KP BSI (12.9%, 9/70) compared with patients with non-ESBL-KP BSI (2.7%, 9/338). The most prevalent underlying disease in both groups was malignancy: 27.2% (92/338) of patients with non-ESBL-KP BSI and 28.6% (20/70) of patients with ESBL-KP BSI. Diabetes mellitus was the second most prevalent underlying disease: 22.8% (77/338) of patients with non-ESBL-KP BSI and 18.6% (13/70) of patients with ESBL-KP BSI. There was no significant difference in comorbidities between the two groups, including Charlson comorbidity index.

The most frequently used antibiotic during the 3 months preceding bacteraemia among patients with non-ESBL-KP BSI was extended-spectrum cephalosporin (29%, 98/338), followed by ß-lactam and ß-lactamase inhibitors (25.7%, 87/338) and fluoroquinolone (20.1%, 68/338). Among patients with ESBL-KP BSI, extended-spectrum cephalosporin was the most frequently used antibiotic (51.4%, 36/70), followed by fluoroquinolone (40.0%, 28/70) and ß-lactam and ß-lactamase inhibitors (30.0%, 21/70). Antibiotics were more frequently used among patients with ESBL-KP BSI than patients with non-ESBL BSI, especially fluoroquinolone (20.1% vs 40.0%, $P<0.001$), carbapenem (8.9% vs 22.9%, $P=0.001$), extended-spectrum cephalosporin (29.0% vs 51.4%, $P<0.001$), glycopeptide (4.1% vs 12.9%, $P=0.004$) and TMP/SMT (0.9% vs 10.0%, $P<0.000$). Of the patients with ESBL-KP BSI, 22 had received urinary catheterization in the previous 3 months and nine had a history of nasogastric tube insertion. Meanwhile, among the patients with non-ESBL-KP BSI, 37 had a history of urinary catheterization and 19 had experienced nasogastric tube insertion.

Univariate analysis of risk factors for community-onset ESBL-KP BSI showed associations with intensive care unit admission, recent admission history, recent history of long-term hospital admission, previous antibiotic use (fluoroquinolone, carbapenem, extended-spectrum cephalosporins, glycopeptide or TMP/SMT),

Table 1
Risk factors for community-onset extended-spectrum β-lactamase-producing *Klebsiella pneumoniae* bloodstream infection (ESBL-KP BSI) using univariate analysis.

Variable	Non-ESBL-KP BSI ($n=338$)	ESBL-KP BSI ($n=70$)	*P*-value
Age	71.0 [61–79.0]	75.0 [64.0–81.0]	0.083
Male	201 (59.5%)	48 (68.6%)	0.155
ICU admission	16 (4.7%)	10 (14.3%)	0.003
Previous history of admission	152 (45%)	50 (71.4%)	0.000
Previous history of long-term-care hospital admission	9 (2.7%)	9 (12.9%)	0.000
Underlying disease			
End-stage renal disease	38 (11.2%)	10 (14.3%)	0.472
Cerebrovascular disease	17 (5.0%)	6 (8.6%)	0.242
Liver cirrhosis	9 (2.7%)	1 (1.4%)	0.543
Chronic pulmonary disease	15 (4.4%)	2 (2.9%)	0.547
Diabetes mellitus	77 (22.8%)	13 (18.6%)	0.439
Cardiovascular disease	25 (7.4%)	5 (7.1%)	0.941
Malignancy	92 (27.2%)	20 (28.6%)	0.817
Charlson comorbidity index	1.0 [0.0–2.0]	1.0 [0.0–2.0]	0.630
SOFA score	4.0 [2.0–7.0]	5.0 [2.75–7.0]	0.349
Previous usage of antibiotics			
Penicillin	17 (5.0%)	2 (2.9%)	0.432
ß-lactam and ß-lactamase inhibitor	87 (25.7%)	21 (30.0%)	0.462
Fluoroquinolone	68 (20.1%)	28 (40.0%)	0.000
Colistin	2 (0.6%)	0 (0%)	0.519
Macrolide	26 (7.7%)	2 (2.9%)	0.145
Aminoglycoside	22 (5.4%)	6 (8.6%)	0.534
Carbapenem	30 (8.9%)	16 (22.9%)	0.001
First-generation cephalosporin	28 (8.3%)	8 (11.4%)	0.399
Second-generation cephalosporin	33 (9.8%)	11 (15.7%)	0.144
Extended-spectrum cephalosporin	98 (29%)	36 (51.4%)	0.000
Glycopeptide	14 (4.1%)	9 (12.9%)	0.004
TMP/SMT	3 (0.9%)	7 (10.0%)	0.000
Previous history of intervention			
Urinary catheterization	37 (10.9%)	22 (31.4%)	0.000
Central catheter	21 (6.2%)	6 (8.6%)	0.470
Intubation	5 (1.5%)	1 (1.4%)	0.974
Nasogastric tube	19 (5.6%)	9 (12.9%)	0.029
Major surgery	5 (1.5%)	4 (5.7%)	0.028

ESBL, extended-spectrum β-lactamase-producing; KP, *Klebsiella pneumonia*; BSI, bloodstream infection; ICU, intensive care unit; SOFA, sequential organ failure assessment; TMT/SMT, trimethoprim/sulfamethoxazole.
Values are median [interquartile range] or *n* (%).

Table 2
Multi-variate analysis of risk factors for community-onset extended-spectrum β-lactamase-producing *Klebsiella pneumoniae* bloodstream infection using previous history of admission.

	OR (95% CI)	*P*-value
Previous history of admission	2.226 (1.195–4.145)	0.012
TMP/SMT	8.662 (2.047–36.647)	0.003
Urinary catheterization	2.207 (1.109–4.391)	0.024

TMT/SMT, trimethoprim/sulfamethoxazole; OR, odds ratio; CI, confidence interval.

major surgery and previous intervention history (urinary catheterization or nasogastric tube insertion). As history of long-term hospital admission is a part of admission history, two multi-variate models that included each variable separately were examined. A multi-variate model identified the following as independent risk factors for community-onset ESBL-KP BSI: recent admission history, previous admission history (OR 2.2, 95% CI 1.2–4.1; $P=0.012$), previous TMP/SMT use (OR 8.7, 95% CI 2.0–36.6; $P=0.003$) and urinary catheterization history (OR 2.2, 95% CI 1.1–4.4; $P=0.024$; Table 2). Meanwhile, fitting the multi-variate model with previous history of long-term-care hospital admission rather than previous admission history yielded the following estimates: previous admission to long-term-care hospital within the previous 3 months (OR 5.7, 95% CI 2.1–15.6; $P=0.001$), previous TMP/SMT use (OR 11.5, 95% CI 2.7–48.6; $P=0.001$), extended-spectrum cephalosporin use (OR 2.2, 95% CI 1.2–3.9; $P=0.01$) and previous urinary catheter use (OR 2.3, 95% CI 1.1–4.5; $P=0.02$; Table 3).

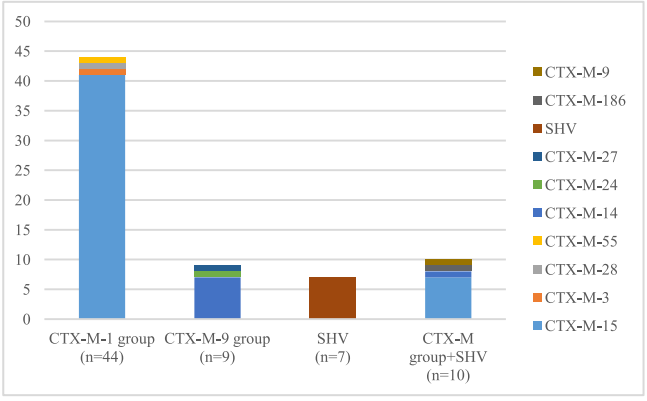

Fig. 1. Distribution of extended-spectrum β-lactamase genotype.

3.1. Molecular analysis

All ESBL-KP isolates were examined to identify ESBL genotypes. The most frequently carried ESBL gene was CTX-M-1 group ESBL (74%, $n=52$), followed by CTX-M-9 group ESBL (16%, $n=11$). Ten isolates carried both the CTX-M group and SHV ESBLs (Fig. 1).

MLST analyses showed that all isolates were classified into 101 different STs, suggesting substantial genetic diversity (Fig. 2). The most prevalent ST among KP isolates was ST23 (17.4%, $n=71$), followed by ST86 (6.6%, $n=27$). ST23 was also the most preva-

Table 3
Multi-variate analysis of risk factors for community-onset extended-spectrum β-lactamase-producing *Klebsiella pneumoniae* bloodstream infection using previous history of long-term-care hospital admission instead of previous history of admission.

	OR (95% CI)	*P*-value
Previous history of long-term-care hospital admission	5.648 (2.073–15.589)	0.001
Extended-spectrum cephalosporins	2.170 (1.207–3.900)	0.010
TMP/SMT	11.546 (2.746–48.551)	0.001
Urinary catheterization	2.258 (1.136–4.489)	0.020

TMT/SMT, trimethoprim/sulfamethoxazole; OR, odds ratio; CI, confidence interval.

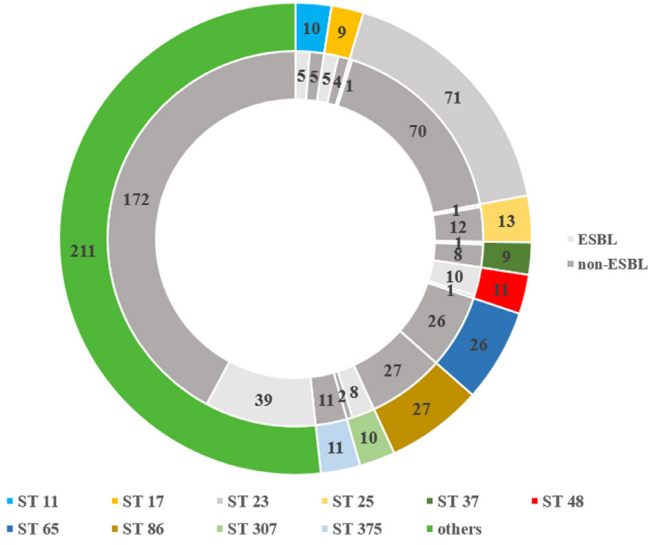

Fig. 2. Sequence type of community-onset *Klebsiella pneumoniae* bloodstream infection.

lent among non-ESBL-KP isolates (21%, $n = 70$). However, the most prevalent ST among ESBL-KP isolates was ST48 (14%, $n = 10$).

4. Discussion

This multi-centre study showed that ESBL-KP caused a significant proportion of community-onset KP BSI in South Korea. Urinary catheterization, previous admission to a long-term-care hospital and previous antibiotic use (e.g. TMP/SMP and extended-spectrum cephalosporin) were documented as risk factors for ESBL-KP BSI. According to the MLST results, there was clonal diversity among KP isolates, which suggests that ESBL-producing strains are nationally endemic throughout South Korea.

ESBL *Escherichia coli* (ESBL-EC) has emerged in recent years as a worldwide cause of community-onset infections. Several studies have attempted to identify risk factors for community-onset ESBL-EC bacteraemia [2]. An association with healthcare facilities, urinary catheter use, previous antimicrobial use, underlying liver diseases and unknown primary infection site were found to be independently associated with ESBL-EC bacteraemia [8]. However, there is insufficient evidence regarding risk factors for community-onset ESBL-KP infections. A study from Spain reported that nursing home residence and previous cephalosporin or fluoroquinolone use are risk factors for community-onset urinary tract infection by ESBL-KP [1]. A prospective case–control study from China found that heart failure was a risk factor for community-onset ESBL-KP BSI [9]. As previous studies showed significant discrepancies between the risk factors for community-onset ESBL-KP infections, it is important to identify risk factors for community-onset ESBL-KP infections that are specific to South Korea. This study provides a comprehensive analysis of community-onset ESBL-KP BSI in South Korea. Admission to a long-term-care hospital, urinary catheter use and previous antibiotic use were identified as risk factors for community-onset ESBL-KP BSI.

The strengths of the present study are that it was a multi-centre prospective study, and the HIRA claims database, which is representative of the entire South Korean population, was used. Almost all antibiotics and medical procedures are listed as reimbursable drugs/procedures under national health insurance. As it was possible to evaluate previous antibiotic use and medical procedures accurately from this database, the possibility of recall bias was eliminated, making this study more reliable. A previous study from a tertiary hospital in South Korea reported that corticosteroid use, percutaneous tube use and prior antibiotic use were independent risk factors of community-onset ESBL-KP BSI, but this study was conducted at a large referral centre and the results do not represent other medical contexts, especially community hospitals [2]. The present study was conducted at six sentinel hospitals in different districts in South Korea. All cultured organisms were sent to the central laboratory and analysed using identical standards.

The significance of long-term-care hospitals as important sources of multi-drug-resistant organisms should be noted, because long-term-care hospitals were identified as one of the risk factors for ESBL-KP BSI in this study. A high prevalence of antimicrobial-resistant organisms has been reported from long-term-care facilities [10]. Not only meticillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci, but also ESBL Enterobacteriaceae [7,11,12], *Klebsiella pneumoniae* carbapenemase producers [13] and *Acinetobacter* spp. [14] have been reported repeatedly in long-term-care hospitals. According to data from the Korean Antimicrobial Resistance Monitoring System, the cefotaxime resistance rate for KP was higher in geriatric care hospitals than in general hospitals (67.2% vs 44.5%, respectively) [15]. Several studies claimed that antibiotic misuse, including overuse, is a serious problem in long-term-care hospitals [16]. These results emphasize the need for infection control measures and antibiotic stewardship in long-term-care hospitals [17].

Co-production of DHA-1 (AmpC β-lactamase) and CTX-M-15 (ESBL) has emerged and disseminated in South Korean hospitals in blood isolates from patients with bacteraemia [18]. Consistent with a previous study, CTX-M-1 group ESBLs, including CTX-M-15, were common (74%, $n = 52$) in this study (Fig. 1). The CTX-M-9 group ESBLs, including CTX-M-14, were also frequently detected (16%, $n = 11$). SHV-12 has also been found to be disseminated in clinical isolates of KP in South Korea [19]. Isolates carrying both the CTX-M group and SHV-12 show high resistance to both ceftazidime and cefotaxime [19].

KP ST11 was the most frequently identified clone in South Korea in a nationwide study of urinary isolates (57.4%, 27/47) and blood isolates (70%, 21/30) collected from 2006 to 2007 [20]. Another study also found high prevalence of KP ST11 in blood isolates collected from 2010 to 2014 at a single tertiary hospital [18]. Recently, the ESBL-producing serotype K1 KP ST23 strain was reported in

Singapore and Indonesia [21]. This is a well-known invasive community strain, but its ESBL production is rare. The present study detected many ST23 in the total sample of KP isolates but mostly in non-ESBL isolates (21%, $n = 70$); however, one ESBL-producing ST23 strain was detected. The most prevalent ST among ESBL-KP isolates was ST48 (14%, $n = 10$). This study found that KP ST11 was no longer the predominant clone, and that various clones circulate in Korean communities.

In this study, the proportion of ESBL-KP BSI among community-onset KP BSI cases was 17% (70/408). Several previous studies have reported proportions of community-onset ESBL-KP infections that ranged from 2.6% to 34.9% according to country and time period [1,2,9,22]. A study from Italy reported that 2.6% of *K. pneumoniae* isolates from outpatients were ESBL-positive, and a study from Spain reported that 34.9% of community-onset *K. pneumoniae* isolates from patients with urinary tract infections were ESBL-producing organisms. This result suggests that community-onset ESBL-KP infections currently have a significant impact on community health in South Korea, and ESBL-producing organisms should be considered when managing patients with risk factors.

A limitation of this study is that it was not possible to investigate nursing home admission history. As nursing homes are not regarded as medical facilities, they are not included in national health insurance claim data. Further study is needed to investigate the influence of nursing homes on antibiotic resistance.

5. Conclusions

In conclusion, previous admission to a long-term-care hospital, urinary catheter use and antibiotic use (e.g. TMP/SMT, extended-spectrum cephalosporin) within the previous 3 months were identified as risk factors for community-onset ESBL-KP BSI. Strict antibiotic stewardship and infection control measures are needed in long-term-care hospitals.

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Ethical approval: This study was approved by the local ethics committees of all local institutional review boards of the sentinel hospitals.

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