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KJIM

Third-generation cephalosporin resistance of community-onset *Escherichia coli* and *Klebsiella pneumoniae* bacteremia in a secondary hospital

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Background/Aims: To enable appropriate antimicrobial treatment for community-onset infections in emergency departments (EDs), data are needed on the resistance profiles of *Escherichia coli* and *Klebsiella pneumoniae*, which are the main pathogens of community-onset bacteremia.

Methods: Records were reviewed of 734 patients with *E. coli* and *K. pneumoniae* bacteremia who visited the Daegu Fatima Hospital ED, Daegu, Korea between 2003 and 2009. We investigated the demographic data, clinical findings, and antimicrobial susceptibility patterns of the organisms.

Results: Of 1,208 cases of community-onset bacteremia, 62.8% were caused by *E. coli* or *K. pneumoniae* in an ED of a secondary care hospital. Five hundred and forty-eight cases of *E. coli* (75%) and 183 cases of *K. pneumoniae* (25%) were analyzed. Urinary tract infection (43.1%) was most common, followed by intra-abdominal infection (39%) and pneumonia (7.2%). Trimethoprim/sulfamethoxazole, fluoroquinolone, third-generation cephalosporin (3GC) and amikacin resistance rates among *E. coli* and *K. pneumoniae* were 22.8%, 19.6%, 6.2%, and 1.3%, respectively. In 2009, the rate of 3GC resistance (10.6%) was significantly higher, compared to the annual averages of 2003 to 2008 (6.1%; $p = 0.03$). Previous exposure to antibiotics was an independent risk factor for 3GC resistance in multivariate logistic regression analysis.

Conclusions: The rate of 3GC resistance increased in community-onset infections, and previous exposure to antibiotics was an independent risk factor. Despite the increased 3GC resistance in community-onset infections, an amikacin combination therapy could provide an option for treatment of bacteremic patients with previous antibiotic exposure in an ED.

Keywords: *Escherichia coli*; *Klebsiella pneumonia*; Bacteremia; Emergency department; Secondary hospital

INTRODUCTION

Escherichia coli and *Klebsiella pneumoniae* are the major pathogens of community-onset infections, such as urinary tract and intra-abdominal infections [1]. Guidelines recommend the use of fluoroquinolones, cephalosporins, and β lactam/β lactamase inhibitor combinations as treatment options [2,3]. Third-generation cephalosporins (3GCs) are now used widely, due to the global prevalence of fluoroquinolone resistance

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[4-6]. Recently, 3GC resistant *E. coli* and *K. pneumoniae* producing extended-spectrum β-lactamases (ESBL), or imported AmpC β-lactamases have been emerging in community-onset infections [7-9].

A nationwide survey reported that community-onset infection caused by ESBL-producers is increasing in South Korea [10]. However, the data on 3GC-resistant *E. coli* and *K. pneumoniae* in community-onset infections at secondary and primary care hospitals are limited, as previous studies have focused on tertiary care hospitals. To this end, we performed a risk factor analysis for 3GC resistance in *E. coli* and *K. pneumoniae* bacteremia in the emergency department (ED) of a secondary care hospital.

METHODS

Study population and design

This study was performed at Daegu Fatima Hospital, a 750-bed secondary care hospital. Databases from the clinical microbiology laboratory were reviewed and patients had blood cultures taken in the ED. Organisms detected in the blood cultures were considered to be pathogens except for known contaminants, such as *Corynebacterium* spp., *Bacillus* spp., *Micrococcus* spp., *Propionibacterium* spp., and coagulase-negative staphylococci. A specialist in infectious diseases confirmed whether an organism was a pathogen or not, in cases where two sets of blood cultures yielded common contaminants.

Patient discharge summaries were used for analysis of the site of infection from the total organisms found in the ED between January 2003 and December 2009. Patients with positive blood cultures for *E. coli* or *K. pneumoniae* were included in further analysis. Only the first bacteremic episode for each patient was included in the analysis.

Medical records were reviewed for collection of clinical data, including age, sex, underlying disease, site of infection, previous antibiotics use (within 3 months), antibiotics prescribed for bacteremia treatment, and outcomes. The sites of infection were defined following the criteria of the Centers for Disease Control and Prevention, with slight modifications. To classify the severity of any underlying disease, the Charlson comorbidity index (CCI) was used [11], and the severity of illness at presentation was classified according to the Pitt bacteremic score [12]. Appropriate administration of antibiotics was used within 48 hours after the onset of bacteremia. Treatment outcomes were analyzed after exclusion of follow-up loss cases. Cases were defined as follow-up loss if patients were not seen 30 days after the bacteremic event, and the termination of follow-up was not decided by physicians. Treatment success was defined as the absence of signs or symptoms of infection within 2 weeks after completion of antibiotics. Strains resistant to ceftriaxone and/or cefotaxime were considered 3GC resistant. Fluoroquinolone resistance was defined as decreased susceptibility to ciprofloxacin and/or levofloxacin. This study was approved by the Institutional Review Board at the Daegu Fatima Hospital.

Microbiological study

We used a Bactec 9240 system (Becton, Dickinson and Company, Franklin Lakes, NJ, USA). Species identification and antibiotic susceptibility tests were performed on the VITEK I automated system from January 2003 to May 2008, and on the VITEK II system (bioMérieux, Durham, NC, USA) from May 2008 to December 2009.

Statistical analysis

The results were analyzed using the SPSS version 15.0 for Windows software (SPSS Inc., Chicago, IL, USA). The categorical variables were compared by Fisher exact tests or Pearson chi-square tests, as appropriate, and the continuous variables were compared using Student *t* test or the Mann-Whitney *U* test. All tests of significance were two-tailed; $p \leq 0.05$ was considered to indicate significance. Logistic regression analysis was performed to identify risk factors for 3GC resistance in community-onset *E. coli* and *K. pneumoniae* bacteremia.

RESULTS

One thousand two hundred and eight episodes of community-onset bacteremia were identified, of which 551 (45.6%) and 206 (17.1%) were caused by *E. coli* and *K.*

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pneumoniae, respectively, at the Daegu Fatima Hospital ED during the study period. *E. coli* and *K. pneumoniae* were present in 85% (318/373), 71% (304/429), and 35% (53/153) of urinary tract infections, intra-abdominal infections, and pneumonia, respectively (Fig. 1). Five hundred and forty-eight patients with *E. coli* bacteremia, and 183 patients with *K. pneumoniae* bacteremia, whose clinical data were available, were included in the analysis. The mean age was 65.93 ± 13.8 years and 62.4% (458/734) were female. The most common infections were urinary tract (43.1%) infections, followed by intra-abdominal (39.0%), lower respiratory tract (7.2%), and primary bacteremia (6.7%) infections.

Among 731 clinical isolates of *E. coli* and *K. pneumoniae*, 93.8% were susceptible and 6.2% were resistant to 3GC. Resistance rates of ampicillin/sulbactam, trimethoprim/sulfamethoxazole, fluoroquinolone, tobramycin, cefazolin, 3GC, and amikacin were 45.8% (245/535), 22.8% (165/725), 19.6% (143/731), 11.4% (83/728), 9.8% (68/695), 6.2% (45/731), and 1.3% (9/715), respectively. Rate of resistance rates to the antibiotics, with the exception of imipenem, were significantly higher in the 3GC-resistant group ($p < 0.01$ for all tested antibiotics except imipenem). Rate of resistance rates to the antibiotics according to organism and infection site are shown in Table 1. Thirty-two (4.4%) were resistant to a 3GC and fluoroquinolone combination, and six (0.8%) were resistant to a 3GC and amikacin combination (Table 1).

The rate of 3GC resistance increased significantly in 2009 (10.6%), compared to the previous annual average rate from 2003 to 2008 (6.1%; $p = 0.03$) (Fig. 2). Of 45 3GC-resistant isolates, resistance rates to fluoroquinolone, trimethoprim/sulfamethoxazole, piperacillin/tazobactam, amikacin, and imipenem were 71.1%, 55.6%, 20.0%, 13.3%, and 2.2%, respectively and 41 (91.1%) were ESBL-producers. From 2003 to 2008, 53.1% (17/32) of 3GC-resistant isolates were susceptible to cefepime, but in 2009, 84.6% (11/13) were susceptible to cefepime ($p = 0.03$) (Fig. 2).

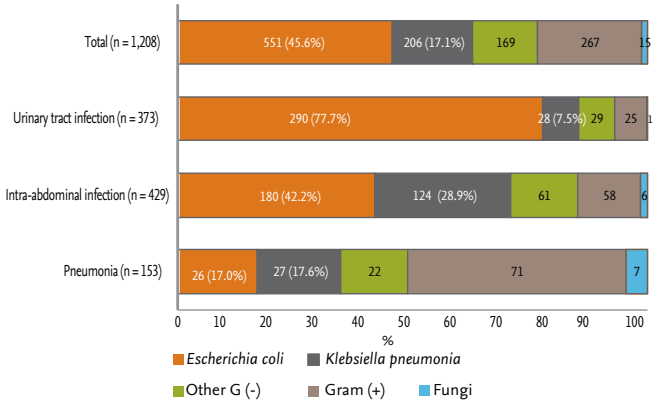

Figure 1. Proportion of causative organisms among 1,208 episodes of community-onset bacteremia in the emergency department of a secondary care hospital from 2003 to 2009.

Comparisons of clinical characteristics between the 3GC-susceptible and resistant groups are shown in Table 2. There were no significant differences in the median Pitt bacteremia score and the CCI between the two groups (Table 2).

Bivariate analyses showed that prior admission to hospital ($p < 0.01$), prior antibiotic use ($p < 0.01$), metastatic cancer ($p < 0.01$), and neutropenia ($p = 0.04$) were significantly associated with 3GC resistance in *E. coli* and *K. pneumoniae* bacteremia (Table 3). In a multivariate logistic regression analysis, previous exposure to antibiotics was an independent risk factor for 3GC resistance (odds ratio, 5.02; 95% confidence interval, 1.54 to 16.39; $p = 0.01$) (Table 3).

Among 73 isolates from patients with known prior antibiotics use, 13 (17.8%) were resistant to 3GC, 10 (13.7%) were resistant to a 3GC-fluoroquinolone combination and two (2.7%) were resistant to a 3GC-amikacin combination. Excluding the 104 follow-up loss cases, 627 cases were included in the final analysis. There was no significant difference between the 3GC-susceptible and -resistant groups in treatment success rates ($p = 0.1$) or 30-day mortality ($p = 0.9$). Further analysis according to species and sites of infection showed similar results (Table 4).

DISCUSSION

3GC is frequently used as an initial empirical antibiotic in primary and secondary hospitals. However, recent studies have warned of an increasing prevalence of infections in community-onset infections due to 3GC-resistant organisms, which produce ESBL or AmpC β-lactamase [9,13,14]. A recent nationwide multicenter study of bacteremia reported that 9.5% of

Table 1. Resistance rates of isolates from community-onset *Escherichia coli* or *Klebsiella pneumoanie* bacteremia to various antibiotics

Antibiotic	Total	3GC resistant	*K. pneumoniae*	*E. coli*	UTI	IAI	Pneumonia
Amikacin	9/715 (1.3)	6/45 (13.3)	4/178 (2.2)	5/537 (0.9)	5/311 (1.6)	3/277 (1.1)	2/53 (3.8)
Tobramycin	83,728 (11.4)	21/45 (46.7)	8/183 (4.4)	75/545 (13.8)	44/316 (13.9)	23/280 (8.2)	5/53 (9.4)
Ampicillin	502/729 (68.9)	45/45 (100)	183/183 (100)	319/546 (58.4)	208/316 (65.8)	191/281 (68)	42/53 (79.2)
Ampicillin/ Sulbactam	245/535 (45.8)	29/29 (100)	17/133 (12.8)	228/402 (56.7)	142/238 (59.7)	57/188 (30.3)	13/38 (34.2)
Piperacillin/ Tazobactam	15/729 (2.1)	9/45 (20)	8/183 (4.4)	7/546 (1.3)	7/316 (2.2)	6/281 (2.1)	1/53 (1.9)
Aztreonam	30/730 (4.1)	24/45 (53.3)	13/183 (7.1)	17/547 (3.1)	10/316 (3.2)	12/282 (4.3)	5/53 (9.4)
Cefazolin	67/695 (9.6)	41/43 (95.3)	14/175 (8.0)	53/520 (10.2)	29/299 (9.7)	23/265 (8.7)	5/50 (10)
3GC	45/731 (6.2)	-	9/183 (4.9)	36/548 (6.6)	17/316 (5.4)	17/283 (6)	4/53 (7.5)
Cefepime	18/730 (2.5)	18/45 (40)	4/183 (2.2)	14/547 (2.6)	8/316 (2.5)	4/282 (1.4)	3/53 (5.7)
Fluoroquinolone	143/731 (19.6)	32/45 (71.1)	9/183 (4.9)	134/548 (24.5)	76/316 (24.1)	40/283 (14.1)	13/53 (24.5)
TMP-SMX	165/725 (22.8)	25/45 (55.6)	6/180 (3.3)	159/545 (29.2)	89/313 (28.4)	44/280 (15.7)	9/53 (17)
Imipenem	1/731 (0.1)	1/45 (2.2)	1/183 (0.5)	0/548 (0)	0/316 (0)	0/283 (0)	1/53 (1.9)
3GC + amikacin	6/731 (0.8)	6/45 (13.3)	3/183 (1.6)	3/548 (0.5)	3/316 (0.9)	2/283 (0.7)	1/53 (1.9)
3GC + fluoroquinolone	32/731 (4.4)	32/45 (71.1)	5/183 (2.7)	27/548 (4.9)	14/316 (4.4)	10/283 (3.5)	3/53 (5.7)
3GC + TMP-SMX	25/731 (3.4)	25/45 (55.6)	5/183 (2.7)	20/548 (3.6)	9/316 (2.8)	6/283 (2.1)	3/53 (5.7)
ESBL	41/728 (5.6)	41/45 (91.1)	6/183 (3.3)	35/545 (6.4)	16/315 (5.1)	15/281 (5.3)	3/53 (5.7)

Values are presented as numbers resistant/the number of total strains and proportions (%).
3GC, third-generation cephalosporin; UTI, urinary tract infection; IAI, intra-abdominal infection; TMB-SMX, trimethoprim/sulfamethoxazole; ESBL, extended-spectrum β-lactamases.

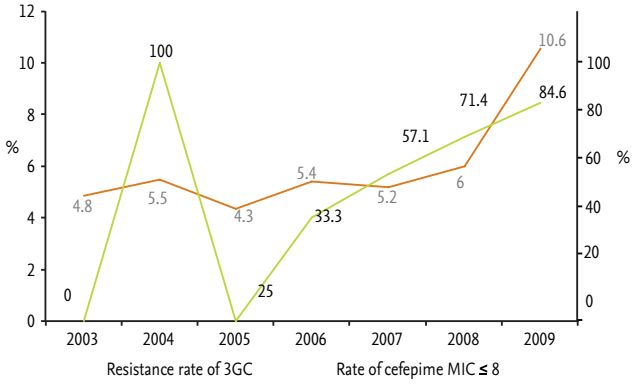

Figure 2. Trend of third-generation cephalosporin (3GC)-resistance of *Escherichia coli* and *Klebsiella pneumoniae* bacteremia (orange line, left axis) and proportions of cefepime-susceptible organisms among 3GC-resistant organisms (gray line, right axis) in the emergency department of a secondary care hospital from 2003 to 2009.
MIC, minimum inhibitory concentration.

community-onset *E. coli* bacteremia was caused by ESBL-producers [10]. However, there is no certainty that the findings from the previous studies are applicable to secondary and primary hospitals, because the majority of the data came from tertiary care hospitals. The Daegu Fatima Hospital, however, is a secondary care hospital which is more community-oriented, and most of the ED patients present without a referral letter. Therefore, the results of this study may better reflect the conditions in primary and secondary hospitals.

We found that the proportion of cefepime-susceptible organisms among the 3GC-resistant organisms increased in accordance with an increasing prevalence of 3GC resistance. ESBL-producing strains of Enterobacteriaceae showed different resistance patterns to various cephalosporins, which may reflect the different

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Table 2. Clinical characteristics of patients with *Escherichia coli* or *Klebsiella pneumoniae* bacteremia

Variable	3GC-resistant (n = 45)	3GC-susceptible (n = 686)	*p* value
Age, yr	67.6 ± 12.2	65.76 ± 13.9	0.39
Female sex	28 (62.2)	429 (62.5)	0.97
Prior history of admission	15 (35.7)	98 (14.8)	< 0.01
Prior use of antibioticsa	13 (54.2)	60 (16.8)	< 0.01
Neutropenia	2 (4.8)	16 (2.4)	0.29
Underlying disease			
Cardiovascular diseases	3 (7.1)	26 (3.9)	0.25
Cerebrovascular diseases	9 (21.4)	85 (12.8)	0.11
Diabetes mellitus	10 (23.8)	186 (28.1)	0.55
Tumors	7 (16.7)	58 (8.8)	0.10
Metastatic tumor	5 (11.9)	17 (2.6)	0.01
Liver disease	7 (16.7)	79 (11.9)	0.36
Site of infection			
Urinary tract infection	17 (40.5)	299 (45.2)	0.55
Lower respiratory tract	4 (9.5)	49 (7.4)	0.55
Intra-abdominal	17 (40.5)	266 (40.2)	0.97
Pitt bacteremia score	0.5 (0–2.25)	0 (0–2)	0.25
Charlson score	1.5 (0–3.25)	1 (0–2)	0.07

Values are presented as mean ± SD, number (%) or median (interquartile range).
3GC, third-generation cephalosporin.
[a]Three hundred eighty-one patients with data of previous antibiotics use were included in this analysis.

Table 3. Bivariable and multivariable analysis for clinical variables associated with third-generation cephalosporin-resistance of *Escherichia coli* or *Klebsiella pneumoniae* incommunity-onset bacteremia

Variable	Bivariable analysis		Multivariable analysis	
	OR (95% CI)	*p* value	aOR (95% CI)	*p* value
Prior use of antibiotics	3.20 (1.64–6.23)	< 0.01	5.02 (1.54–16.39)	0.01
Prior history of admission	5.85 (2.50–13.68)	< 0.01	0.96 (0.28–3.30)	0.95
Metastatic tumor	5.13 (1.79–14.66)	0.01	6.50 (0.90–46.97)	0.06
High Charlson score	1.96 (1.03–3.75)	0.04	1.26 (0.25–6.25)	0.78

OR, odds ratio; aOR, adjusted odds ratio.

abilities of ESBL types [15]. A nationwide study reported that 3CG-resistant organisms, such as ESBL-producers, are disseminated throughout the South Korean community, which may be associated with nationwide dissemination of the CTX-M ESBLs [16]. The increased proportions of cefepime-susceptible organisms among 3GC-resistant organisms might reflect the increase in a particular type of CTX-M ESBL.

Secondly, 3GC resistance had less impact on treatment outcomes (except for pneumonia patients) even though 83% of patients with a 3GC-resistant infection received inappropriate antibiotics. There is an ongoing debate about the association between ESBL-producing organism and clinical outcomes [17-21]. We suggest the main reason for the reduced impact of 3GC-resistance in our hospital was due to the lower severity of the condition of our patients: 86% of patients had a Pitt bacteremia score ≤ 3. These findings

Table 4. Outcomes of third-generation cephalosporin-resistant and -susceptible community-onset *Escherichia coli* and *Klebsiella pneumoniae* bacteremia

	3GC-resistant	3GC-susceptible	*p* value
Total (n = 627, 34 vs. 593)			
30-Day mortality	6 (17.6)	93 (15.7)	0.76
Bacteremia-related mortality	6 (17.6)	60 (10.1)	0.16
Treatment success	21 (61.8)	415 (70.0)	0.31
Urinary tract infection (n = 278, 13 vs. 265)			
30-Day mortality	2 (15.4)	18 (6.8)	0.24
Bacteremia-related mortality	1 (7.1)	13 (4.9)	0.50
Treatment success	10 (76.9)	209 (78.9)	> 0.99
Intra-abdominal infection (n = 261, 16 vs. 245)			
30-Day mortality	2 (12.5)	42 (17.1)	> 0.99
Bacteremia-related mortality	2 (12.5)	29 (11.8)	> 0.99
Treatment success	10 (62.5)	171 (69.8)	0.58
Pneumonia (n = 46, 4 vs. 42)			
30-Day mortality	2 (50.0)	23 (54.8)	> 0.99
Bacteremia-related mortality	4 (100)	16 (38.1)	0.03
Treatment success	0 (0)	15 (35.7)	0.29
E. coli (n = 465, 25 vs. 440)			
30-Day mortality	3 (12.0)	56 (12.7)	> 0.99
Bacteremia-related mortality	3 (12.0)	35 (8.0)	0.45
Treatment success	18 (72.0)	322 (73.2)	0.90
K. pneumoniae (n = 162, 9 vs. 153)			
30-Day mortality	3 (33.3)	37 (24.2)	0.69
Bacteremia-related mortality	3 (33.3)	25 (16.3)	0.19
Treatment success	3 (33.3)	93 (60.8)	0.16

Values are presented as number (%).
3GC, third-generation cephalosporin.

are likely similar to those in other primary or secondary care hospitals in Korea.

We found that only 0.8% of community-onset *E. coli* and *K. pneumoniae* bacteremia was simultaneously resistant to 3GC and amikacin. ESBL-producers are frequently resistant to fluoroquinolone, trimethoprim-sulfamethoxazole, and aminoglycoside [12,22]. Rodriguez-Bano et al. [9] reported that 64%, 63%, and 15% of ESBL-producers in community-onset *E. coli* bacteremia were resistant to ciprofloxacin, trimethoprim-sulfamethoxazole and amikacin, respectively. In this study, 71.1% and 13.3% of 3GC-resistant *E. coli* and *K. pneumoniae* were also resistant to fluoroquinolone and amikacin, respectively. However, among 731 isolates from community-onset *E. coli* and *K. pneumoniae* bacteremia, less than 1% were simultaneously resistant to 3GC and amikacin. Therefore, instead of carbapenem, a 3GC-amikacin combination could be an option for treating patients with community-onset gram-negative bacteremia with a high risk of resistance, unless those patients have an impaired renal function. The piperacillin/tazobactam resistance rate was low (2.1%) in this study. Recent retrospective studies demonstrated that piperacillin/tazobactam had comparable outcomes to carbapenem [23,24]. Therefore, piperacillin/tazobactam could also be an option for treating patients with a high risk of resistance in primary and secondary care hospitals.

Because the resistance rate to ampicillin/sulbactam

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was ~45%, its empirical use for treating infections caused by gram-negative organisms could be inappropriate.

This study had some limitations. Firstly, it was conducted at a single center, and therefore our data should be interpreted and applied with caution. Secondly, we were unable to collect detailed demographic information on the patients as the study was performed retrospectively. This prevented calculation of risk factors for 3GC-resistance other than previous antibiotics use. Thirdly, our data on ESBL production were generated from an automated data collection system; thus there are likely some discrepancies between the susceptibility data in this study and standard methods. We did not perform ESBL-confirmation tests or genotype analysis. We identified an increasing trend in 3GC resistance but could not define the association between the increasing 3GC resistance and the dissemination of CTX-M ESBLs in the community.

To conclude, the rate of 3GC resistance in community-onset infections in primary and secondary care hospitals in Korea is increasing, and prior antibiotic use is an independent risk factor. Carbapenem should be considered an empirical antibiotic for patients with community-onset bacteremia and a high risk of resistance. However, in spite of the increasing rate of 3GC resistance in community-onset bacteremia, simultaneous resistance to 3GC and amikacin is rare, and most patients had a less severe infection. We suggest a combination of 3GC and aminoglycoside as an empirical antimicrobial option for treating patients with community-onset infections with a high risk of resistance in primary or secondary care hospitals in Korea.

KEY MESSAGE

1. Resistant rate of third generation cephalosporin (3GC) is increasing but, resistance to aminoglycoside is rare in primary and secondary care hospital in Korea.
2. Combination of 3GC and aminoglycoside could be an empirical option for community-onset infections with a high risk of resistance in primary or secondary care hospitals.

Conflict of interest
No potential conflict of interest relevant to this article is reported.

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