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Antibiotic Resistance Patterns of *Enterobacteriaceae* Isolated from Patients with Healthcare-Associated Infections

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ABSTRACT

Background: There have been recent proposals to categorize healthcare-associated infections (HCAIs) separately from community-acquired infections (CAIs). The aim of this study was to compare the antibiotic resistance of pathogens causing CAIs, HCAIs, and hospital-acquired infections (HAIs) in Korea, and to investigate the need for different empirical antibiotics therapy for CAIs and HCAIs.

Materials and Methods: This prospective study was conducted in a university hospital between March and December 2019. Inpatients who underwent a bacterial culture within 2 days of hospitalization, with a *Enterobacteriaceae* strain identified at the infection site and available antibiotic susceptibility results, were included in the analysis. Infections were classified as CAIs, HCAIs or HAIs, depending on the source.

Results: Of the 146 patients included in the analysis, the prevalence of fluoroquinolone-resistant *Enterobacteriaceae* was 18.8%, 38.5%, and 55.0%; the prevalence of pathogens showing third-generation cephalosporins resistance was 8.3%, 50.0%, and 60.0%; and the prevalence of pathogens showing piperacillin-tazobactam resistance was 8.3%, 7.7%, 15.0% in the CAIs, HCAIs, and HAIs groups, respectively. The prevalence of extended-spectrum beta-lactamase-positive pathogens was 6.3%, 47.3%, and 55.0% in the CAIs, HCAIs, and HAIs group, respectively, with no significant difference between the HCAIs and HAIs groups. Resistance patterns of the HCAIs group more closely resembled those of the HAIs group than those of the CAIs group.

Conclusion: The pathogens isolated from patients with HCAIs showed resistance patterns that were more similar to those of patients with HAIs than those with CAIs. Thus, CAIs and HCAIs should be distinguished from each other when selecting antibiotic agents.

Keywords: Community-acquired infection; Healthcare-associated infection; Hospital-acquired infection; *Enterobacteriaceae*

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INTRODUCTION

In 2018, the Korean Global Antimicrobial Resistance Surveillance System (Kor-GLASS) research team reported the emergence of antibiotic-resistant hospital-acquired and community-acquired pathogens in Korea [1]. In particular, the prevalence of hospital-acquired and community-acquired urinary tract infection (UTI)-causing *Escherichia coli* resistant to ciprofloxacin was 59.5% and 42.8%, respectively, and the prevalence of *E. coli* resistant to cefotaxime was 46.1% and 30.0%, respectively. Similarly, Fasguba et al. [2] reported a higher rate of antibiotic resistance among hospital-acquired pathogens than community-acquired pathogens. However, these results are questionable because the prevalence of antibiotic resistance among community-acquired pathogens was higher than that observed in actual clinical settings. Furthermore, Kor-GLASS reported the prevalence of hospital-acquired and community-acquired *Streptococcus pneumoniae* isolates resistant to sulfamethoxazole-trimethoprim to be 20.0% and 30.4%, respectively, and the prevalence of *S. pneumoniae* resistant to erythromycin to be 60.0% and 78.3%, respectively. In this case, the higher prevalence of antibiotic resistance among community-acquired pathogens compared to that among hospital-acquired pathogens indicates that hospital-acquired infections (HAIs) and community-acquired infections (CAIs) have not been appropriately differentiated.

Infections can be divided into either CAIs or HAIs depending on the route of infection acquisition. Kor-GLASS defines HAIs as infections caused by hospital-acquired pathogens two or more calendar days after hospitalization, including a previous hospital stay at a different hospital in the case of hospital transfer. However, trends in medical service usage are changing. For instance, the numbers of long-term care facilities and procedures or operations performed at outpatient clinics without hospitalization have been increasing. In response to these changes, antibiotic susceptibility patterns of pathogens have also changed. Accordingly, several researchers have highlighted the need to create a new category specific to "healthcare-associated infections" (HCAIs)" distinguishable from CAIs [3, 4]. Toward this end, the aim of the present study was to differentiate HCAIs from CAIs, and to compare the prevalence and patterns of antibiotic resistance of pathogens causing HCAIs with those of hospital-acquired and community-acquired pathogens. The findings of this study can provide further insight into whether the inclusion of HCAIs in CAIs is appropriate from a practical perspective, such as for the selection of empirical antibiotics.

MATERIALS AND METHODS

1. Study design

This prospective study was conducted at a single institution in Korea with 655 wards from March to December 2019. The subjects of this study were patients who underwent a bacterial culture test within 2 days of hospitalization among all other patients admitted to the hospital due to fever. A list of newly admitted patients was obtained from all wards during the study period and the admission records of patients who were prescribed a bacterial culture test within 2 days after admission were reviewed. A single researcher directly examined the patients for any infection and obtained their consent forms. Infections were diagnosed according to the criteria developed by the Centers for Disease Control and Prevention/ National Healthcare Safety Network Surveillance Definitions for Specific Types of Infections (2019) [5].

2. Sample collection and bacterial culture test

A medical team in one of the general wards, including the intensive care unit (ICU) and emergency department, collected blood samples from patients who were prescribed to obtain a bacterial culture from the clinical department. The bacterial culture tests were performed at the Department of Laboratory Medicine of the same institution and data were collected digitally. In cases where multiple bacterial cultures were performed for the same patient, only the results of the first sample were used in the analysis. In cases where two or more bacterial strains were identified in a sample obtained from an infection site, the bacterial strain identified from the blood sample was considered the causative agent of the infection.

Blood cultures were performed with at least two types of aerobes and anaerobes. Blood samples were incubated at 36.5 - 37°C for 7 days. For urine culture tests, a mid-stream urine sample was collected and incubated until there were at least 10^5 colony-forming unit per milliliter of bacteria. For the sputum culture test, expectorated sputum, bronchoalveolar lavage, or tracheal aspirates were collected from the lower respiratory tract. Bacteria identified in the lower respiratory tract samples, with >25 leukocytes and <10 epithelial cells visualized by Gram staining and observed under a microscope at low magnification, were included in the analysis. For bile and ascitic fluid culture tests, bile and ascitic fluids were collected in blood culture bottles and subjected to the same incubation process described above for the blood culture test. For the wound culture test, exudates from the wound site were collected using a sterilized cotton swab, inoculated on a blood agar plate with fluid thioglycolate medium, and incubated at 37°C for 72 h.

Bacteria were identified using the Vitek-2 system (BioMérieux Vitek, Hazelwood, MO, USA). *Enterobacteriaceae* were tested for extended-spectrum beta-lactamase (ESBL) production using Vitek-2 cards according to the manufacturer's instructions.

3. Patient classification

Patients with identified bacterial strains were classified into the CAI, HCAI, and HAI groups. The HAI group included patients who had been at the hospital for at least 48 h prior to the infection [6]. The HCAI group included a set of patients who did not meet the criterion for inclusion in the HAI group and satisfied the following conditions: (1) received intravenous treatment in the last 30 days [7-9]; (2) received wound treatment in the last 30 days [7, 8, 10, 11]; (3) hospitalization within 30 days [12, 13]; (4) hospital treatment (outpatient) within the last 30 days [14]; (5) underwent dialysis in the last 30 days [8, 10, 12, 15, 16]; (6) stayed in a hospital for at least 2 days within the last 90 days [7, 8, 10, 12, 16, 17]; (7) transferred from a care home or long-term care facility [7, 8, 11, 13, 16, 17]; (8) immunosuppressed, including human immunodeficiency virus (HIV)-positive patients [10, 15, 18, 19], patients with active or metastatic cancer [10, 15, 16, 19] patients who received radiotherapy or chemotherapy within 6 months after hospitalization for treatment of malignant tumors [10, 15, 19], patients with a history of solid organ or bone marrow transplantation [15, 19], and patients on immunosuppressants (prednisolone at 10 mg/day or other substitutes for over 30 days) [10, 15, 18, 19]; (9) underwent an invasive procedure or operation in the last 6 months [11, 12]; (10) family members with multidrug-resistant bacterial infection [7, 8]; and (11) underwent antibiotic therapy in the last month [8, 10]. Patients who did not meet the aforementioned conditions for classification in either the HAI or HCAI group were included in the CAI group.

4. Bacterial strain classification

Enterobacteriaceae identified in the isolates from the patients were included for antibacterial susceptibility and ESBL production analysis. A bacterial strain was deemed to be susceptible to fluoroquinolones or carbapenems if it was susceptible to all antibiotics belonging to these classes. Similarly, a bacterial strain was deemed to be resistant to an entire class of antibiotics if it was resistant to at least one antibiotic of that class. Intermediate antibiotic resistance was considered an indicator of resistance.

5. Data collection

Basic demographic and clinical information of the patients, including gender, hospital record number, age, diagnosis, Charlson comorbidity index, history of ICU admission, length of hospital stay, culture test type, antibiotic susceptibility of the identified bacteria, and antibiotic use, were collected by reviewing medical charts and case report forms.

6. Statistical analysis

The Kruskal-Wallis and Mann-Whitney *U* tests were used to compare clinical and demographic data of patients among the three groups. The Chi-square test and Fisher's exact test were used to assess differences in antibiotic susceptibility. The level of statistical significance was set at $P < 0.05$. All statistical analyses were performed using IBM SPSS version 20 (IBM SPSS Inc., Armonk, NY, USA).

7. Ethics statement

This study was approved by the Institutional Review Board of Hallym University Kangnam Sacred Heart Hospital and all researchers complied with research ethics (IRB no. 2019-01-029-002).

RESULTS

1. Basic patient characteristics according to infection classification

Of the 691 patients who underwent a bacterial culture test within 2 days of admission, 567 were included in this study, after excluding 124 patients who refused to participate. *Enterobacteriaceae* were identified at the infection site in 146 out of the 567 patients, showing a positivity rate of 25.7%. These 146 isolates were included in the final analysis. Of these 146 patients, 48 (32.9%), 78 (53.4%), and 20 (13.7%) had CAIs, HCAIs, and HAIs, respectively.

Table 1 lists the baseline characteristics of the patients; no significant difference was found in the sex ratio ($P = 0.89$), age ($P = 0.40$), or rates of ICU admission ($P = 0.87$) among the three groups. Patients in the HAIs group had a significantly higher Charlson comorbidity index than those of the other two groups, which had similar Charlson comorbidity indices. Patients in the HAIs group had the longest hospital duration ($P = 0.004$), whereas the average hospital

Table 1. Clinical characteristics of patients whose causative pathogens were isolated

Characteristic	Community-acquired infections (n = 48)	Healthcare-associated infections (n = 78)	Hospital-acquired infections (n = 20)	*P*-value
Male, n (%)	22 (45.8)	33 (42.3)	8 (40.0)	0.890
Age, mean ± SD	69.1 ± 14.5	68.6 ± 13.8	73.0 ± 10.7	0.400
Charlson comorbidity index, mean ± SD	3.4 ± 2.0	3.9 ± 2.6	5.3 ± 2.0	0.007
Intensive care unit admission, n (%)	12 (25.0)	23 (29.4)	6 (30.0)	0.870
Duration of hospital stay (days), mean ± SD	12.6 ± 11.0	16.4 ± 18.2	28.4 ± 37.7	0.004

SD, standard deviation.

durations in the CAIs and HCAIs groups were not significantly different (*P* = 0.28). Therefore, the HCAIs and CAIs groups had similar baseline characteristics, which differed from those of the HAIs group.

Of the patients admitted for an HCAI caused by *Enterobacteriaceae*, 53.8% were treated at the hospital (outpatient) within 30 days, 44.9% underwent antibiotic therapy within 30 days, 37.2% stayed at a hospital for at least 2 days within 90 days, 32.1% were hospitalized within 30 days, 32.1% received intravenous treatment within 30 days, 17.9% underwent an invasive procedure or operation within 6 months, 10.3% were transferred from a care home or long-term care facility, 6.4% had received chemotherapy or radiation therapy due to a malignant tumor within 6 months, 5.1% had active or metastatic cancer, 1.3% used immunosuppressants, 0% had a history of solid organ or bone marrow transplantation, 0% were HIV-positive, 2.5% were on dialysis within 30 days, 1.3% received wound treatment at home within 30 days and 0% had a family member with multi-drug resistant bacterial infection (**Table 2**).

The disease categories caused by identified *Enterobacteriaceae* were UTIs in 99 cases (67.8%), intraabdominal infections in 21 cases (14.4%), pneumonia in 18 cases (12.3%), and skin and soft tissue infections in 8 cases (5.5%).

2. Causative bacteria and antibiotic susceptibility

The *Enterobacteriaceae* identified through culturing included *E. coli* (100 strains, 68.5%), *Klebsiella* spp. (28 strains, 19.2%), *Proteus mirabilis* (8 strains, 5.5%), *Citrobacter* spp. (5 strains, 3.4%), *Enterobacter cloacae* (2 strains, 1.4%), *Serratia marcescens* (2 strains, 1.4%), and *Haemophilus influenzae* (1 strain, 0.7%).

Among the *Enterobacteriaceae* identified as the causal pathogen, the antibiotic resistance rates against fluoroquinolones were 18.8%, 38.5%, and 55.0% in the CAIs, HCAIs, and HAIs groups, respectively. The difference between the HCAIs and HAIs groups was not significant (*P* = 0.18), whereas a significantly higher fluoroquinolones resistance rate was observed in the HCAIs group than in the CAIs group (*P* = 0.02). The antibiotic resistance rates of these strains against third-generation cephalosporins were 8.3%, 50.0%, and 60.0% in the CAIs,

Table 2. Distribution of factors defining HCAIs in 78 patients with *Enterobacteriaceae* infection (duplicates allowed)

HCAIs defining factors	n (%)
Hospital treatment (outpatient) within 30 days	42 (53.8)
Antibiotic therapy within 30 days	35 (44.9)
Stayed at a hospital for at least 2 days (at least 3 hospital days) within 90 days	29 (37.2)
Hospitalization within 30 days	25 (32.1)
Received an intravenous treatment within 30 days	25 (32.1)
Underwent an invasive procedure or surgery within 6 months	14 (17.9)
Transfer from a care home or long-term care facility	8 (10.3)
Immunocompromised status	
Chemotherapy or radiation therapy for a malignant tumor within 6 months after hospitalization	5 (6.4)
Active or metastatic cancer	4 (5.1)
Immunosuppressant	1 (1.3)
History of solid organ or bone marrow transplantation	0 (0.0)
HIV-positive patient	0 (0.0)
Dialysis within 30 days	2 (2.5)
Received a wound treatment within 30 days	1 (1.3)
A family member has multidrug-resistant bacterial infection	0 (0.0)

HCAIs, healthcare-associated infections; HIV, human immunodeficiency virus.

Table 3. Antibiotic resistance rates of *Enterobacteriaceae* based on different routes of infection acquisition

Antibiotic	Resistance, n (%)			P-values among the three groups			
	CAIs (n = 48)	HCAIs (n = 78)	HAIs (n = 20)	CAIs vs. HCAIs vs. HAIs	CAIs vs. HCAIs	CAIs vs. HAIs	HCAIs vs. HAIs
Fluoroquinolone	9 (18.8)	30 (38.5)	11 (55.0)	0.008	0.020	0.003	0.180
Third-generation cephalosporin	4 (8.3)	39 (50.0)	12 (60.0)	<0.001	<0.001	<0.001	0.290
Piperacillin-tazobactam	4 (8.3)	6 (7.7)	3 (15.0)	0.550	0.570	0.330	0.260
Carbapenem	0 (0.0)	0 (0.0)	0 (0.0)	-	-	-	-

The statistical significance of the comparison of antibiotic resistance between CAIs, HCAIs, and HAIs was tested by chi-square test. Fisher's exact test was used when the number of samples in either group was less than 5.
CAIs, community-acquired infections; HCAIs, healthcare-associated infections; HAIs, hospital-acquired infections.

HCAIs, and HAIs groups, respectively; again, the HCAIs and HAIs groups did not differ significantly (P = 0.29), whereas the difference between the HCAIs and CAIs groups was significant (P <0.001) (**Fig. 1A** and **Table 3**).

Of the 51 patients harboring ESBL-positive bacterial strains, 3 (6.3%), 37 (47.3%), and 11 (55.0%) had CAIs, HCAIs, and HAIs, respectively. A significantly higher proportion of ESBL-positive bacterial strains was observed in the HCAIs group than in the CAIs group (P <0.001; **Fig. 1B**). None of these ESBL-positive bacterial strains showed resistance to carbapenem. Among the ESBL-positive pathogens, the prevalence of antibiotic resistance to ciprofloxacin, gentamicin, ampicillin-sulbactam, sulfamethoxazole-trimethoprim, and piperacillin-tazobactam (TZP) was 72.5%, 60.8%, 58.8%, 51.0%, and 17.7%, respectively.

Among the defining factors of HCAIs, the response rate of hospital treatment within 30 days (outpatient) was the highest. Of the 78 patients classified as having HCAIs, 20 (25.6%) were included in the HCAIs group based on this factor alone. The third-generation cephalosporins resistance rate of these 20 causal pathogens was 55% (11 cases), which was much higher than the 8.3% of the CAIs group (P <0.001), and the ESBL-positive rate was also 55% (11 cases), which was also significantly higher than the 7.7% rate of the CAIs group (P <0.001). The resistance rate to fluoroquinolone was 35% (7 cases), which was not significantly different
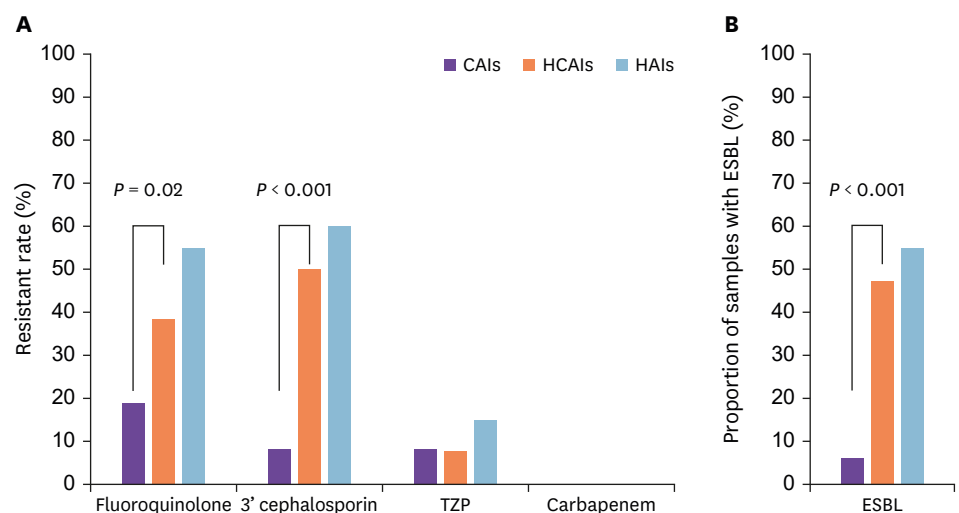

Figure 1. Antibiotic resistance (A) and ESBL production (B) of *Enterobacteriaceae* based on different routes of infection acquisition.
ESBL, extended-spectrum beta-lactamases; CAIs, community-acquired infections; HCAIs, healthcare-associated infections; HAIs, hospital-acquired infections; 3' cephalosporin, third-generation cephalosporin; TZP, piperacillin-tazobactam.

from the rate of 18.8% of the CAIs group (P = 0.13), and the resistance rate to TZP was 5% (1 case), which was not significantly different from the rate of 8.3% of the CAIs group (P = 0.54). None of these strains showed resistance to carbapenem.

DISCUSSION

In this study, we found a significant difference in antibiotic resistance against fluoroquinolones and third-generation cephalosporin in *Enterobacteriaceae* from the HCAIs and CAIs groups. This finding highlights the need to review existing guidelines regarding UTIs, which accounted for the majority of infections caused by *Enterobacteriaceae* in this study. The 2018 clinical practice guidelines for the antibiotic treatment of community-acquired urinary tract infections [20] excludes patients with diabetes, those who are immunosuppressed, or patients with chronic comorbidities from their definition of patients with community-acquired UTIs. However, in addition to the aforementioned patients, other patients in the HCAIs group harbored pathogens with a distinct antibiotic susceptibility profile from that exhibited in the CAIs group. As HCAIs are included in CAIs, the current guidelines, which recommend fluoroquinolones or third-generation cephalosporins as empirical antibiotics for the treatment of patients with community-acquired UTIs, should consider distinguishing between CAIs and HCAIs in future revisions. In addition, it is necessary to identify and analyze each agent causing endemic HCAIs. The antibiotic resistance rate of community-acquired UTI pathogens against fluoroquinolones has been reported to be 30 - 40% [20], which is higher than that observed in this study (19.2%). Thus, the antibiotic resistance rate of community-acquired pathogens against fluoroquinolones could be lower if HCAIs are categorized separately from CAIs.

In the present analysis of 78 patients with healthcare-associated *Enterobacteriaceae* infections, 33.3% harbored strains that were resistant to fluoroquinolones and third-generation cephalosporins. Of the 30 patients with pathogens resistant to fluoroquinolones, 26 (86.7%) were also resistant to third-generation cephalosporins. Of the 39 patients with pathogens resistant to third-generation cephalosporins, 26 (66.7%) were also resistant to fluoroquinolones. Thus, third-generation cephalosporins and fluoroquinolones cannot substitute one another for treating patients with healthcare-associated infections and should not be used concomitantly.

Less than 10% of the pathogens isolated from patients with *Enterobacteriaceae* in the CAIs group were ESBL-positive, whereas nearly 50% of those isolated from patients in the HCAIs and HAIs groups were ESBL-positive. Approximately 94.9% and 86.7% of the *Enterobacteriaceae* strains of healthcare-associated infections resistant to third-generation cephalosporins and fluoroquinolones, respectively, were ESBL-positive. Dalhoff et al. [21] reported that ESBL-positive strains have high resistance to fluoroquinolones, suggesting the inappropriate classification of HCAIs and CAIs as a single category. In the present study, none of the ESBL-positive bacteria showed resistance to carbapenem. Considering that carbapenem can be used as a first-line antibiotic for ESBL-positive bacterial infections with TZP as a substitute [22], and taking into account the antibiotic resistance of these strains, it may be more appropriate to empirically use TZP and carbapenems for patients with healthcare-associated infections instead of third-generation cephalosporin or fluoroquinolones.

This study has a few limitations. First, previous studies have reported that antibiotic exposure is associated with antibiotic resistance [23, 24]. Indeed, a high proportion of patients in the

HCAIs group had a history of medication, including antibiotics. This suggests that the HCAIs group harbored antibiotic-resistant pathogens more frequently than the CAIs group due to previous exposure to antibiotics. However, we did not assess the differences according to antibiotic types, frequency, period of use, or number of hospital stays. Whether these factors could be used to classify HCAIs remains to be determined.

Second, among the definition factors of HCAIs, the response rate of "hospital treatment within 30 days (outpatient)" was the highest. As this single factor of 24 patients included in the HCAIs group, third-generation cephalosporins and ESBL-positive expression were different from those of the CAIs group, but there was no significant difference in the resistance rate of the other antibiotic groups. Therefore, subgroup analysis of the definition factors of HCAIs will be needed in the future.

Third, a detailed analysis was planned for evaluating differences between each infection group for each HCAIs definition factor, but this analysis was not ultimately possible because of the small number of cases. If more cases can be collected in the future, it is likely that the antibiotic resistance rate of *Enterobacteriaceae* can be investigated according to acquisition type in various disease groups.

In summary, the *Enterobacteriaceae* pathogens isolated from patients with HCAIs showed resistance patterns that were more similar to those of patients with HAIs than those with CAIs. Thus, CAIs and HCAIs should be distinguished from each other when selecting antibiotic agents.

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