

Differences in antibiotic usage patterns for acute pyelonephritis according to hospital type and region in the Republic of Korea

A population-based study

Rangmi Myung, MSc^a, Jun Hee Han, PhD^b, Bongyoung Kim, MD, PhD^{c,*}

Abstract

This study aimed to determine the differences in antibiotic usage patterns in the treatment of acute pyelonephritis according to hospital type and region in Korea.

The claims database of the Health Insurance Review and Assessment Service in Korea was used to select patients with the *International Classification of Diseases*, Tenth Revision code N10 (acute tubulo-interstitial nephritis) or N12 (tubulo-interstitial nephritis, neither acute nor chronic) as the primary discharge diagnosis in 2010-2014. Usage of each class of antibiotics was expressed as the defined daily dose (DDD)/event.

The average antibiotic usage per inpatient event was 11.3 DDD. The average antibiotic usage was the highest among patients admitted to tertiary hospitals (13.8 DDD), followed by those admitted to secondary hospitals (11.5 DDD), clinics (10.0 DDD), and primary hospitals (9.8 DDD). According to the geographic analyses, third-generation cephalosporins were highly prescribed in some southern regions; fluoroquinolones and aminoglycosides were highly prescribed in some centrally located regions of the Korean peninsula. The hotspots for carbapenem usage included Seoul and Gyeonggi province cluster and Busan cluster: these regions include the capital city and the second biggest city in Korea, respectively.

In conclusion, the antibiotic usage patterns for acute pyelonephritis in Korea differ according to the hospital type and region.

Abbreviations: 1G = first-generation, 3G = third-generation, AG = aminoglycoside, ASP = antimicrobial stewardship program, APN = acute pyelonephritis, DDD = defined daily dose, FQ = fluoroquinolones, HIRA = Health Insurance Review and Assessment Service.

Keywords: pyelonephritis, anti-bacterial agents, health insurance, Korea

1. Introduction

Antimicrobial resistance is a current worldwide problem and 1 of the biggest threats to public health.^[1] The increasing resistance of microorganisms reduces the efficacy of antibiotics, leading to increased mortality, morbidity, and medical costs.^[2] According

to a report sponsored by the UK government, infectious diseases caused by antimicrobial-resistant pathogens are predicted to result in more than 10 million deaths each year by 2050 if the world fails to act in terms of controlling resistance,^[3] and this will become the leading cause of death globally.

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^a Department of Economics, College of Political Science and Economics, Korea University, Seoul, ^b Department of Statistics, Hallym University, Chuncheon,

^c Department of Internal Medicine, College of Medicine, Hanyang University, Seoul, Korea.

* Correspondence: Bongyoung Kim, Department of Internal Medicine, College of Medicine, Hanyang University 222-1 Wangsimni-ro, Seongdong-gu, Seoul, Korea 04763 (e-mail: sobakas@hanyang.ac.kr).

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Since the main cause for the emergence of antimicrobial-resistant organisms is excessive and inappropriate antibiotic usage,^[4] antimicrobial stewardship programs (ASPs) are considered a key strategy to tackle this issue.^[5] Accordingly, the 2016 Korean National Action Plan on antimicrobial resistance included ASPs as the main component.^[6]

The first step in implementing ASPs was to identify the current status of antibiotic usage, especially the amount of antibiotic usage. Acute pyelonephritis (APN) is an appropriate index disease for the evaluation of antibiotic prescribing patterns for the following reasons:

- (1) APN is one of the most common community-acquired bacterial infections along with pneumonia and skin and soft tissue infections;
- (2) there is homogeneity in the pathogens causing APN as *Escherichia coli* is overwhelmingly the most common pathogen and comprises approximately 90% of the causative pathogens;
- (3) the diagnostic criteria for APN are simple; generally, the diagnosis of APN does not require imaging evaluation and is only based on clinical symptoms and urine test results; and
- (4) the guidelines for APN treatment are clear.^[7–10]

Our previous study using National Health Insurance claims data in Korea showed that the number of prescriptions of broad-spectrum antibiotics for APN treatment increased annually between 2010 and 2014.^[11] However, we were not able to obtain enough evidence to determine the main reason for such phenomenon.

We aimed to determine the antibiotic prescribing practices for the treatment of APN according to hospital type and region. To achieve this goal, we reanalyzed our previous data, which focused on the annual change in antibiotic usage patterns for the treatment of APN,^[11] from a different viewpoint.

2. Material and methods

2.1. Data source

In the Republic of Korea (hereafter referred to as “Korea”), approximately 98% of the entire population, including low-income families receiving medical aid, is covered by the National Health Insurance System.^[12] The Healthcare Big Data Hub provides an online health insurance data service as part of the Health Insurance Review and Assessment Service (HIRA). We obtained insurance claims data from this service.

2.2. Definitions

We included hospitalized patients with a primary discharge diagnosis of APN from 2010 to 2014. Outpatients were excluded. Patients with the *International Classification of Diseases*, Tenth Revision code N10 (acute tubulo-interstitial nephritis) or N12 (tubulo-interstitial nephritis, not specified as acute or chronic) were selected because these codes are used as diagnostic codes for APN in Korea.^[13] Two or more claims within a 14-day period were regarded as a single event. Following were the exclusion criteria:

- (1) age less than 15 years;
- (2) events with zero admission/visit days, zero medical cost, or no antibiotic prescriptions; and

- (3) Veteran Health Insurance claims (beneficiaries of the Veteran Health Insurance could have made duplicate claims for a single event).

Antibiotics were defined as medications belonging to class J01 in the anatomical therapeutic chemical classification system, which does not include antifungal agents or anti-tuberculosis agents. Oral antibiotics and parenteral antibiotics were included, while topical agents were excluded. The usage of each class of antibiotics was expressed in terms of defined daily dose (DDD) following the guidelines of the anatomical therapeutic chemical classification system by the World Health Organization.^[14]

Hospital types were classified according to the Korean healthcare delivery system. Clinics and primary hospitals are considered primary medical institutions, but they have different numbers of hospital beds: clinics have less than 30 beds or have not an admission bed while primary hospitals have 30 to 100 beds. Secondary hospitals are the referral centers for primary medical institutions and have more than 100 beds and operate nine mandatory departments (internal medicine, general surgery, pediatrics, obstetrics and gynecology, radiology, anesthesiology, laboratory medicine, psychiatry, and odontology). Tertiary hospitals are the referral centers for primary and secondary medical institutions and have more than 500 beds and operate the same nine mandatory departments mentioned above. In addition, tertiary hospitals are required to have a resident training system for each department.

2.3. Statistical analysis

We performed linear regression analysis of annual measurements to assess the trends of antibiotic usage over time using the SAS enterprise guide, version 6.1 (SAS Institute Inc., Cary, NC). Statistical significance was defined with a *P* value < .05.

The average antibiotic usage for APN treatment was input into the biogeographical information system software program DIVA-GIS 7.5 to evaluate the county-wise distribution. In total, 251 county-level administrative districts were used as spatial units of analysis. To assess the overall spatial correlation, Moran's index (*I*) was calculated for the distribution of average antibiotic usage for APN treatment using R Statistical Package (Institute for Statistics and Mathematics, Vienna, Austria, v3.1.2, www.R-project.org). Moran's *I* is a measure that enables the detection of the spatial autocorrelation of a county with its adjacent county. The values range from -1 (indicating perfect dispersion) to +1 (perfect correlation). A zero value indicates a random spatial pattern. Cluster analysis was performed using spatial and spacetime scan statistic (SaTScan) software, version 9.0 (Martin Kulldorff, Boston, MA), which uses a continuous Poisson model to identify the hotspot of average antibiotic usage for APN. SaTScan scans across the study region with a candidate area (scan window) of various sizes. For each window, the likelihood (based on the Poisson distribution of county data in this case) is calculated, and the candidate area with the maximum likelihood defines the most likely cluster.

2.4. Ethics statement

The study protocol was approved by the Institutional Review Board (IRB) of Hanyang University Hospital (IRB number: 2016-01-032), and the requirement for written informed consent from patients was waived.

Table 1
Average antibiotic usage for the treatment of acute pyelonephritis by administration route (unit: DDD).

	2010	2011	2012	2013	2014	P-value
Parenteral						
Tertiary	6.15	6.94	7.38	7.74	8.02	.004
Secondary	5.19	5.52	5.66	5.96	6.41	.002
Hospital	4.47	4.57	4.93	4.93	5.25	.007
Clinics	6.13	6.45	5.86	5.86	5.69	.121
Per oral						
Tertiary	6.99	6.78	6.49	6.32	6.19	.001
Secondary	5.80	5.87	5.71	5.68	5.55	.042
Hospital	4.70	4.92	5.00	5.07	4.87	.323
Clinics	3.77	3.95	4.28	4.12	3.84	.695

3. Results

Between 2010 and 2014, 208,652 APN events were identified in Korea (39,831 in 2010, 40,414 in 2011, 41,553 in 2012, 42,414 in 2013, and 44,440 in 2014).

3.1. Antibiotic usage patterns for APN according to hospital type

The average antibiotic usage per inpatient event was 11.3 DDD, which increased steadily throughout the study period (10.8 DDD in 2010, 11.1 DDD in 2011, 11.3 DDD in 2012, 11.5 DDD in 2013, and 11.7 DDD in 2014, $P=.002$). The average antibiotic usage was the highest among patients admitted to tertiary hospitals (13.8 DDD), followed by patients admitted to secondary hospitals (11.5 DDD), clinics (10.0 DDD), and primary hospitals (9.8 DDD).^[11]

Table 1 shows the average antibiotic usage according to the administration route. The average parenteral antibiotic usage was the highest in tertiary hospitals (7.25 DDD), followed by clinics (6.01 DDD), secondary hospitals (5.77 DDD), and primary hospitals (4.84 DDD). The usage of parenteral antibiotics increased significantly during the study period in tertiary hospitals ($P=.004$), secondary hospitals ($P=.002$), and primary hospitals ($P=.007$). The usage of oral antibiotics decreased significantly during the study period in tertiary hospitals ($P=.001$) and secondary hospitals ($P=.042$).

As for the class of antibiotic used for APN treatment in tertiary hospitals, third-generation (3G) cephalosporins and fluoroquinolones (FQs) were the most frequently prescribed antibiotics, comprising 41.9% (5.78 DDD) and 29.1% (4.02 DDD) of the total antibiotics used, respectively. Similarly, 3G cephalosporins and FQs were the most frequently prescribed antibiotics in APN patients in secondary (45.2% and 29.0%, respectively) and primary hospitals (37.3% and 27.2%, respectively). In clinics, first-generation cephalosporins and FQs were the most frequently prescribed antibiotics, comprising 29.2% (2.92 DDD) and 24.4% (2.44 DDD) of the total antibiotics used, respectively.

There was a significant increasing trend in antibiotic usage among all hospital types, except clinics. Table 2 and Supplement 1 (Available at: <http://links.lww.com/MD/E750>) show the differences in the change in the trend of antibiotic usage among hospital types (Table 2, Supplement 1, Available at: <http://links.lww.com/MD/E750>). Increase usage of 3G cephalosporins and carbapenems was observed in almost all types of hospitals. In comparison, the usage of FQs and aminoglycosides decreased in some types of hospitals (Fig.1).

3.2. Antibiotic usage patterns for APN treatment according to region

Antibiotic usage for APN treatment in the various administrative districts of Korea ranged from 5.0 to 19.4 DDD/event. Geographic analyses revealed a high relative risk of antibiotic prescription for APN treatment in some regions (Fig. 2).

Considering the antibiotics commonly prescribed for APN patients, we found some hotspots for each antibiotic (Fig. 3, Supplement 2, <http://links.lww.com/MD/E750>). In some southern regions, 3G cephalosporins were highly prescribed; FQs and aminoglycosides were highly prescribed in some centrally located regions of the Korean peninsula. The hotspots for carbapenem usage included Seoul and Gyeonggi province cluster and Busan cluster; these regions include the capital city and the second biggest city in Korea, respectively.

4. Discussion

Analyzing data from various viewpoints is necessary for establishing a proper ASP. This study provides specific data about the current status of antibiotic usage in Korea and can help policy makers identify the primary target for intervention. To the best of our knowledge, this is the first study describing antibiotic usage patterns according to hospital type and region in Korea.

The most frequently used antibiotics for APN treatment were 3G cephalosporins and FQs in all hospital types. These have been accepted as first-line empirical antibiotics for APN according to guidelines published jointly by several professional societies in Korea.^[10] In addition, these antibiotics are available in the oral form, facilitating easy prescription by physicians in outpatient settings as well.

Interestingly, we found that the administration of FQs decreased in some hospital types while 3G cephalosporin usage increased in almost all hospital types during the study period. Although most antibiotics for the treatment of APN had not been chosen based on culture results in small- to middle-sized hospitals, the physicians may have been aware of the increasing resistance of microorganisms to FQs due to several educational programs. Furthermore, safety concerns that have been raised since the late 1990s may have led to restrictions on the use of FQs.^[15] In 2008, the US Food and Drug Administration added “black box” warning labels on FQs regarding the increased risk of tendinitis and tendon rupture; this may have influenced physicians’ prescribing behaviors and thus, the preference of empirical antibiotics for APN treatment may have switched from FQs to 3G cephalosporins.^[16]

Table 2
Average antibiotic usage for the treatment of acute pyelonephritis by class (unit: DDD).

	2010	2011	2012	2013	2014	P-value
First-generation cephalosporins						
Tertiary hospitals	0.25	0.25	0.22	0.18	0.16	.011
Secondary hospitals	0.37	0.26	0.22	0.19	0.19	.028
Primary hospitals	0.90	0.81	0.75	0.66	0.50	.002
Clinics	3.15	3.29	2.99	2.76	2.37	.030
Second-generation cephalosporins						
Tertiary hospitals	0.69	0.60	0.64	0.50	0.50	.046
Secondary hospitals	0.77	0.67	0.54	0.58	0.63	.222
Primary hospitals	0.94	0.85	0.76	0.65	0.74	.061
Clinics	0.86	0.88	0.86	0.90	0.73	.325
Third-generation cephalosporins						
Tertiary hospitals	5.55	6.07	5.83	5.72	5.75	.947
Secondary hospitals	4.69	4.99	5.17	5.44	5.61	.000
Primary hospitals	2.69	3.19	3.76	4.13	4.37	.001
Clinics	1.07	1.19	1.36	1.71	1.83	.003
Fourth-generation cephalosporins						
Tertiary hospitals	0.19	0.17	0.18	0.14	0.18	.540
Secondary hospitals	0.03	0.04	0.04	0.04	0.06	.027
Primary hospitals	0.00	0.01	0.01	0.01	0.02	.060
Clinics	0.00	0.00	0.00	0.00	0.00	–
Aminoglycosides						
Tertiary hospitals	0.01	0.01	0.00	0.01	0.00	.499
Secondary hospitals	0.01	0.01	0.00	0.01	0.01	.127
Primary hospitals	0.07	0.06	0.07	0.04	0.03	.024
Clinics	0.89	0.67	0.71	0.44	0.38	.013
Beta-lactam/beta-lactamase inhibitors						
Tertiary hospitals	0.66	0.64	0.79	0.84	0.81	.059
Secondary hospitals	0.56	0.63	0.62	0.65	0.71	.025
Primary hospitals	0.88	0.87	0.84	0.82	0.82	.007
Clinics	0.85	0.86	0.82	0.83	0.81	.072
Carbapenems						
Tertiary hospitals	0.66	0.92	1.09	1.47	1.78	.001
Secondary hospitals	0.29	0.45	0.63	0.74	0.92	.000
Primary hospitals	0.11	0.15	0.20	0.28	0.39	.003
Clinics	0.01	0.01	0.01	0.04	0.07	.042
Fluoroquinolones						
Tertiary hospitals	4.13	4.06	3.95	4.04	3.93	.108
Secondary hospitals	3.50	3.53	3.36	3.27	3.08	.014
Primary hospitals	2.82	2.72	2.67	2.62	2.48	.003
Clinics	2.07	2.47	2.57	2.62	2.47	.188
Penicillins						
Tertiary hospitals	0.19	0.19	0.22	0.24	0.25	.013
Secondary hospitals	0.09	0.06	0.04	0.04	0.05	.078
Primary hospitals	0.13	0.09	0.09	0.06	0.05	.011
Clinics	0.45	0.58	0.42	0.23	0.32	.156
Trimethoprim/sulfamethoxazole						
Tertiary hospitals	0.18	0.15	0.16	0.13	0.17	.662
Secondary hospitals	0.09	0.07	0.07	0.07	0.08	.334
Primary hospitals	0.06	0.07	0.08	0.09	0.08	.158
Clinics	0.05	0.08	0.04	0.06	0.07	.504
Total						
Tertiary hospitals	13.1	13.7	13.9	14.1	14.2	.014
Secondary hospitals	11.0	11.4	11.4	11.6	12.0	.008
Primary hospitals	9.2	9.5	9.9	10.0	10.1	.010
Clinics	9.9	10.4	10.1	10.0	9.5	.315

Simultaneously, an increase in the use of carbapenems was observed in most hospital types during the study period. One of the plausible reasons is the increasing number of extended-spectrum beta-lactamase-producing *E. coli*. The resistance rate of

E. coli to 3G cephalosporins increased from 8.3% in 2010-2011 to 33.6% in 2017 to 2018 among patients with community-acquired APN.^[17,18] Based on this situation, physicians tended to switch to carbapenems if APN symptoms did not improve with

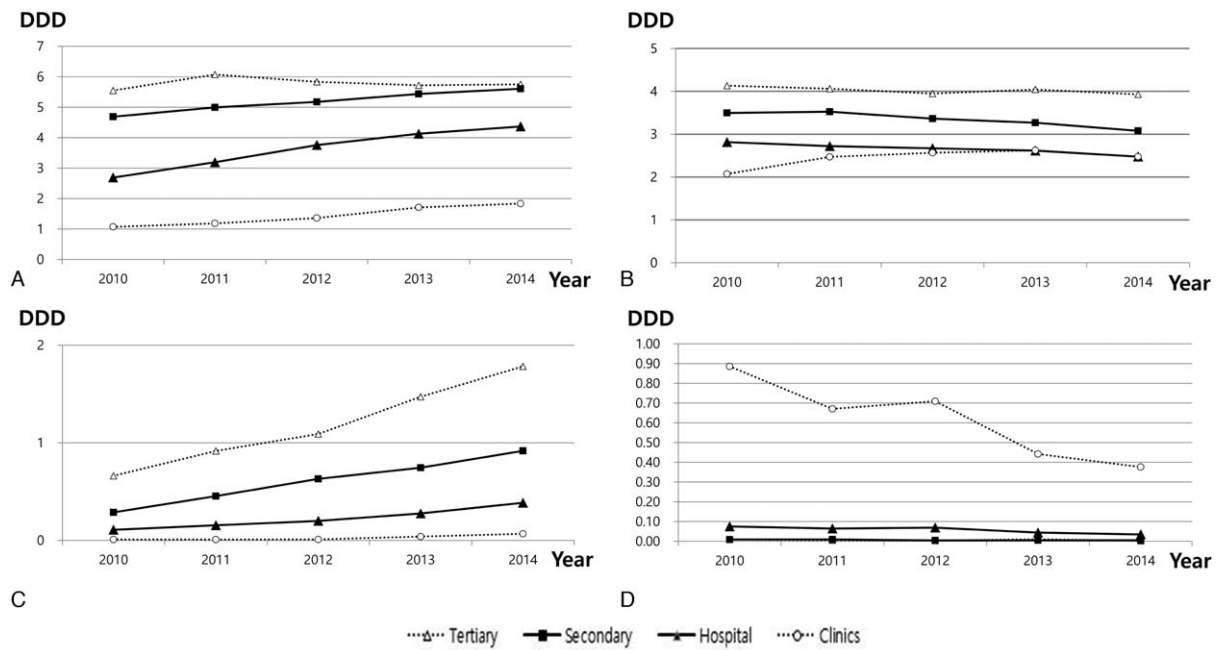


Figure 1. Average antibiotic usage for the treatment of acute pyelonephritis in Korea according to hospital type. A) Third-generation cephalosporins; B) fluoroquinolones; C) carbapenems; and D) aminoglycosides.

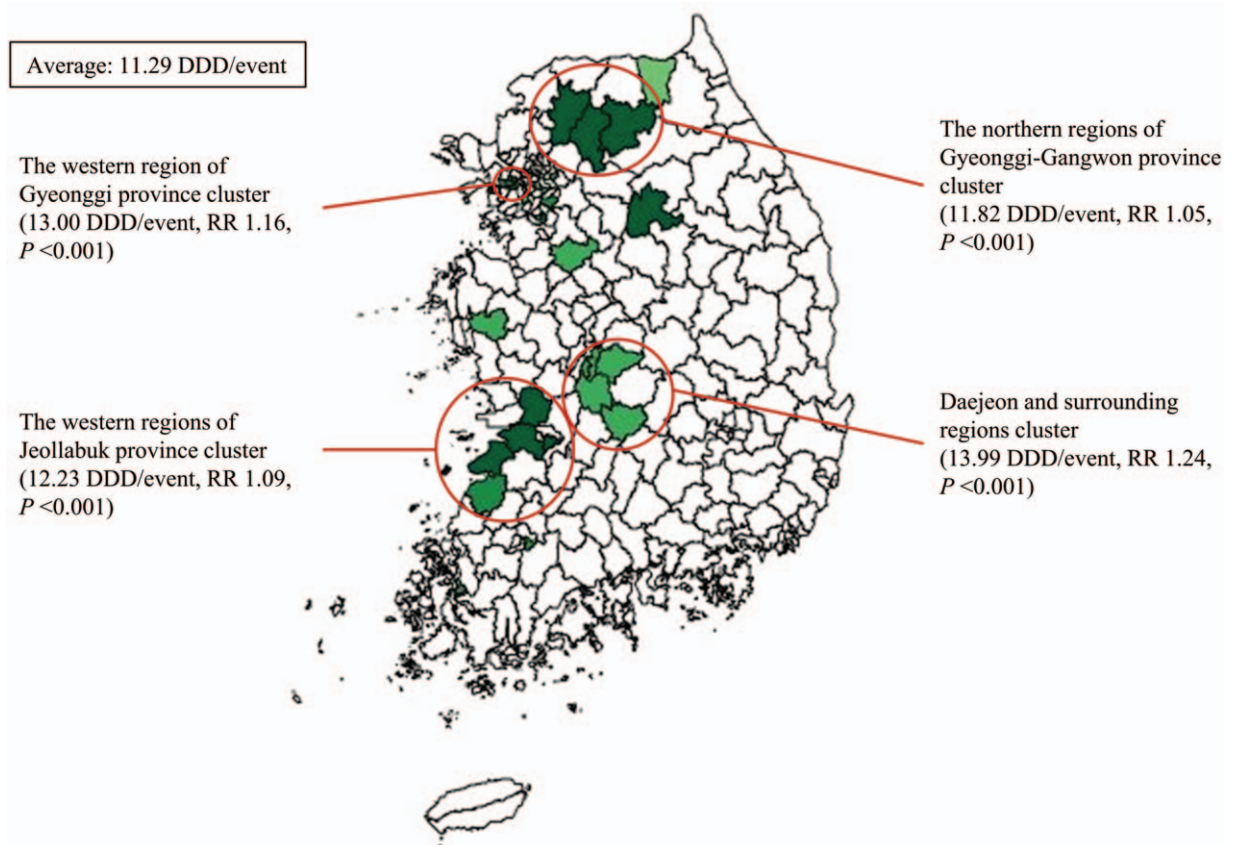


Figure 2. Mapping of clusters with high average antibiotic usage for the treatment of acute pyelonephritis in Korea.

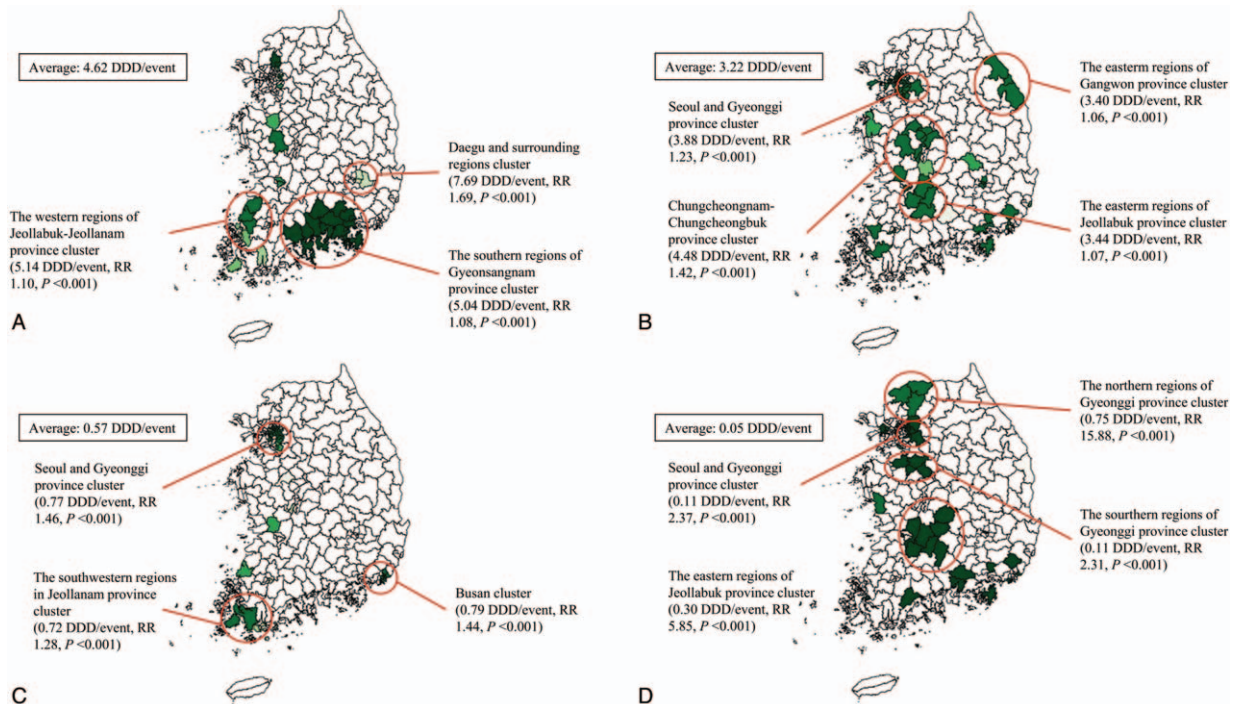


Figure 3. Mapping of clusters with high average antibiotic usage for the treatment of acute pyelonephritis in Korea according to antibiotic class. A) Third-generation cephalosporins; B) fluoroquinolones; C) carbapenems; and D) aminoglycosides.

the use of empirical antibiotics within 2 to 3 days, regardless of the culture results. Given that carbapenems are one of the last-resort antibiotics against multidrug-resistant gram-negative pathogens, a carbapenem-saving strategy, such as the use of piperacillin/tazobactam, should be considered for the treatment of patients with less severe APN.^[19,20]

A poor response to empirical antibiotics may also have led to the use of parenteral antibiotics. We found that the preference for parenteral antibiotics increased during the study period in almost all types of hospitals. Unexpectedly, the average parenteral antibiotic usage was higher in clinics than in secondary or primary hospitals in this study. This difference may be due to differences in sample size, as approximately 2000 patients were admitted to clinics per year during the study period, which is far less than the number of patients admitted to other types of hospitals (data not shown).

A couple of factors may be responsible for the varying antibiotic prescribing patterns among hospital types. First, the severity of APN or patient characteristics may vary among hospital types. Patients visiting secondary or tertiary hospitals tend to show more severe clinical manifestations and have more comorbidities than those visiting clinics or primary hospitals. Second, the HIRA criteria for insurance payments may have influenced the physicians' antibiotic prescribing patterns. Although several professional societies recommend 3G cephalosporins and FQs as first-line empirical antibiotics for APN,^[9,10] these antibiotics are considered second-line antibiotics in the treatment of a majority of common infectious diseases by the HIRA (for insurance claims).^[21] Fearing the rejection of health insurance claims, physicians in small hospitals could be reluctant to use 3G cephalosporins or FQs, which may explain the high prescription rate of first-generation cephalosporins, which are

not recommended for APN treatment, in clinics.^[9,10] Further investigation is necessary to identify the exact cause for the difference in antibiotic prescription patterns among hospital types.

Interestingly, the current study also showed regional differences in antibiotic usage for APN treatment. Previous studies have reported geographic differences in antibiotic prescriptions. In the US, a variation was observed in antibiotic usage among elderly Medicaid enrollees.^[22] An observational study performed in Europe found that antibiotic prescription patterns in emergency departments were highly variable among European countries, even for the same infectious diseases.^[23] It was reported that population factors such as age, sex, race, and economic status could cause such geographic differences.^[24] Of these factors, race would not have caused the geographic differences noted in our study. Otherwise, our data were not sufficient to determine whether age, sex, or economic status could have caused these differences.

One may wonder if there were any regional differences in the antibiotic resistance of uropathogenic *E. coli*, which may be responsible for the geographic differences in antibiotic prescription patterns. However, our previous study showed no such differences (Supplement 4, <http://links.lww.com/MD/E751>).^[18]

The variation in the distribution of hospital types among regions may be another possible explanation for regional difference in antibiotic usage for APN treatment. For instance, the total antibiotic usage would be high in regions with a high proportion of secondary or tertiary hospitals.

We speculate that variations in a physician's attitude may be a more significant factor for causing difference in antibiotic usage for the same infectious diseases. Although the characteristics of patients in each region could not be analyzed, there were

geographic differences in average medical costs and length of hospital stay for APN treatment, in addition to the differences in antibiotic prescription patterns (Supplement 3, <http://links.lww.com/MD/E750>). In fact, a physician's preference seems to impact the preferences of other physicians. A study from northern Israel showed that in primary physicians, the volume of antibiotic prescriptions reduced after peer group meetings and discussions.^[25] Another study from the United States showed that the rate of inappropriate antibiotic prescriptions by primary care physicians for upper respiratory tract infections decreased from 19.9% to 3.7% after they received a presentation on antibiotic prescription rates.^[26] According to a systematic review, apprehension about adverse outcomes, tolerance of risk and uncertainty, hierarchy, and social team dynamics were the most frequently reported determinants for antibiotic prescriptions.^[27] Further studies on the impact of physician behavior on antibiotic usage are necessary.

The main strength of this study was the documentation of differences in antibiotic prescribing patterns for the treatment of the same infectious disease according to different settings. In addition, the present study was based on the most representative health data in Korea. Our results were based on a large sample size and clearly showed the differences in antibiotic usage patterns according to hospital type and region.

Despite the strengths mentioned above, this study has a few potential limitations. First, we could not access the data on clinical features of the patients due to the nature of the data source. The severity of the disease or degree of antimicrobial resistance may have influenced the differences in antibiotic usage patterns. Second, only the primary discharge diagnosis of APN was included for analyses. Some APN cases may have been coded as secondary diagnoses made during hospitalization, such as gram-negative sepsis and adult respiratory distress syndrome. Third, detailed information on the total treatment duration and amount of each antibiotic used was not available as the amount of antibiotics consumed was measured only in terms of DDD. Therefore, antibiotic usage may have been underestimated in this study because this metric cannot reflect reduced dosing in patients with renal dysfunction. Finally, the analyzed data are from 2010-2014 and do not reflect the current situation well.

5. Conclusions

Despite the mentioned limitations, our results are a reasonable indicator of the differences in antibiotic usage according to hospital type and region. In conclusion, the antibiotic usage patterns for APN treatment in Korea differ depending on the hospital type and region.

Author contributions

Conceptualization: Bongyoung Kim
Data curation: Bongyoung Kim, Rangmi Myung
Formal analysis: Bongyoung Kim, Rangmi Myung
Funding acquisition: Bongyoung Kim
Investigation: Bongyoung Kim, Rangmi Myung
Methodology: All authors
Project administration: Bongyoung Kim
Resources: Bongyoung Kim
Software: Rangmi Myung, Jun Hee Han
Supervision: Bongyoung Kim

Validation: All authors

Visualization: Rangmi Myung, Jun Hee Han

Writing – original draft: Bongyoung Kim, Rangmi Myung

Writing – review & editing: Bongyoung Kim

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