

Original Article



Nationwide Analysis of Antimicrobial Prescription in Korean Hospitals between 2018 and 2021: The 2023 KONAS Report

I Ji Yun ^{1,*}, Hyo Jung Park ^{2,3,*}, Jungmi Chae ^{4,*}, Seok-Jae Heo ⁵,
Yong Chan Kim ^{6,†}, Bongyoung Kim ^{7,†}, and Jun Yong Choi ⁶

¹Department of Pharmacy, Yongin Severance Hospital, Yonsei University College of Medicine, Yongin, Korea

²Department of Pharmaceutical Services, Samsung Medical Center, Seoul, Korea

³School of Pharmacy, Sungkyunkwan University, Suwon, Korea

⁴Health Insurance Review and Assessment (HIRA) Assessment Policy Institute, Wonju, Korea

⁵Division of Biostatistics, Department of Biomedical Systems Informatics, Yonsei University College of Medicine, Seoul, Korea

⁶Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea

⁷Department of Internal Medicine, Hanyang University College of Medicine, Seoul, Korea

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ABSTRACT

Background: Data on antimicrobial use at the national level are crucial for establishing domestic antimicrobial stewardship policies and enabling medical institutions to benchmark each other. This study aimed to analyze antimicrobial use in Korean hospitals.

Materials and Methods: We investigated antimicrobials prescribed in Korean hospitals between 2018 and 2021 using data from the Health Insurance Review and Assessment. Primary care hospitals (PCHs), secondary care hospitals (SCHs), and tertiary care hospitals (TCHs) were included in this analysis. Antimicrobials were categorized according to the Korea National Antimicrobial Use Analysis System (KONAS) classification, which is suitable for measuring antimicrobial use in Korean hospitals.

Results: Among over 1,900 hospitals, PCHs constituted the highest proportion, whereas TCHs had the lowest representation. The most frequently prescribed antimicrobials in 2021 were piperacillin/β-lactamase inhibitor (9.3%) in TCHs, ceftriaxone (11.0%) in SCHs, and cefazedone (18.9%) in PCHs. Between 2018 and 2021, the most used antimicrobial classes according to the KONAS classification were 'broad-spectrum antibacterial agents predominantly used for community-acquired infections' in SCHs and TCHs and 'narrow spectrum beta-lactam agents' in PCHs. Total consumption of antimicrobials decreased from 951.7 to 929.9 days of therapy (DOT)/1,000 patient-days in TCHs and 817.8 to 752.2 DOT/1,000 patient-days in SCHs during study period; however, no reduction was noted in PCHs (from 504.3 to 527.2 DOT/1,000 patient-days). Moreover, in 2021, the use of reserve antimicrobials decreased

Received: Jan 22, 2024

Accepted: Apr 15, 2024

Published online: Jun 10, 2024

Corresponding Authors:

Yong Chan Kim, MD, PhD

Division of Infectious disease, Department of Internal Medicine,
Yongin Severance Hospital, Yonsei University College of Medicine, 363
Dongbaekjukjeon-daero, Giheung-gu, Yongin-si, Gyeonggi-do 16995, Korea.
Tel: +82-31-5189-8761, Fax: +82-31-5189-8567
Email: AMOMJ@yuhs.ac

Bongyoung Kim, MD, PhD

Department of Internal Medicine, Hanyang University College of
Medicine, 222-1 Wangsimni-ro, Seongdong-gu, Seoul 04763, Korea.

Tel: +82-2-2290-8357, Fax: +82-2-2298-9183

Email: sobakas@hanyang.ac.kr

*These authors equally contributed as first author.

†These authors equally contributed as corresponding author.

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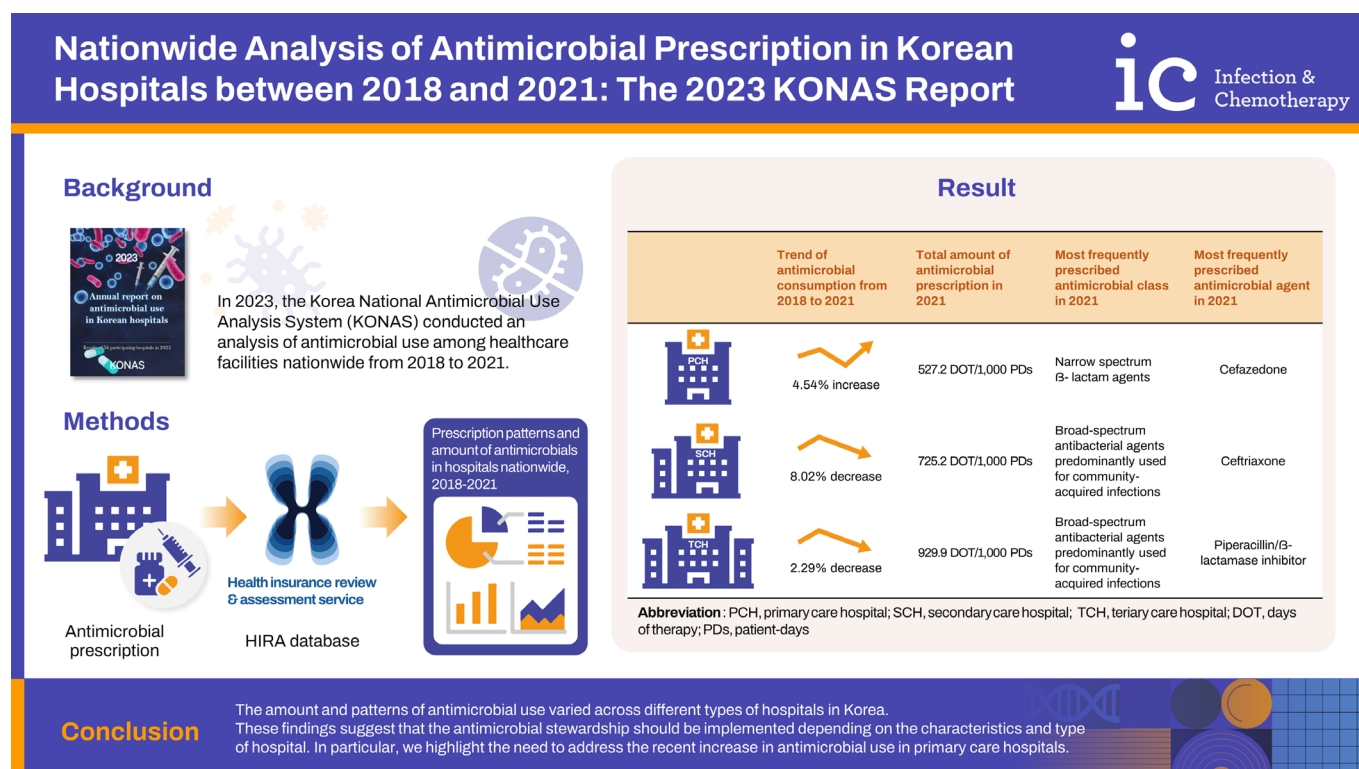
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from 13.6 to 10.7 DOT/1,000 patient-days in TCHs and from 4.6 to 3.3 DOT/1,000 patient-days in SCHs. However, in PCHs, the use increased from 0.7 to 0.8 DOT/1,000 patient-days.

Conclusion: This study confirmed that antimicrobial use differed according to hospital type in Korea. Recent increases in the use of total and reserve antimicrobials in PCHs reflect the challenges that must be addressed.

Keywords: Anti-bacterial agents; Antimicrobial stewardship; Hospitals; Korea

GRAPHICAL ABSTRACT



INTRODUCTION

The use of antimicrobials has increased substantially over the past years [1]. According to a recent study, the per-capita consumption of “Watch” antimicrobials (antimicrobials recommended only for specific infectious diseases as per the Access, Watch, and Reserve [AWaRe] classification) increased from 26.2% in 2000 to 90.9% in 2015 [2]. This increase in antimicrobial use has resulted in increased incidence of antimicrobial-resistant bacteria, leading to extended hospital stays, increased mortality rates, and increased healthcare costs [3-5]. Despite the global spread of antimicrobial resistance, the development of new antimicrobials to combat antimicrobial-resistant

bacteria, which pose a significant threat to public health, has been limited [6, 7]. According to a global report on antimicrobial resistance by Jim O’Neill, 10 million individuals could lose their lives, and 100 trillion USD of economic production could be at risk by 2050 due to this problem [8]. In this context, antimicrobial stewardship programs (ASPs) are important for minimizing antimicrobial misuse and abuse and facilitating the appropriate use of antimicrobials [9, 10].

ASPs refer to a series of multidisciplinary activities aimed at promoting the appropriate use of antimicrobials. This can enhance patient outcomes and minimize adverse drug reactions while reducing the emergence

of antimicrobial-resistant bacteria [11]. Monitoring and reporting antimicrobial use are crucial in ASPs, which have been emphasized by the United States (US) and Korea [12, 13]. Such monitoring and reporting tasks enable the quick detection of changes in antimicrobial usage patterns, prompt identification of issues, and development of interventions. Furthermore, this process not only aids in preventing antimicrobial misuse and abuse but also allows for the analysis of the relationship between antimicrobial use and the emergence of antimicrobial-resistant bacteria [14].

In 2016, the Korean government implemented a national action plan for antimicrobial resistance. A national-level antimicrobial use and resistance monitoring system was proposed as a key strategy for the national action plan, and the Korea National Antimicrobial Use Analysis System (KONAS) was established to monitor antimicrobial usage [15]. The KONAS monitors antimicrobial usage within healthcare facilities in Korea and provides in-depth analysis results, enabling healthcare facilities to independently assess their antimicrobial use and patterns. Moreover, these data can be used to analyze trends and compare results among facilities. The ultimate goal of KONAS is to enable individual healthcare facilities to engage in antimicrobial stewardship activities using such benchmarks.

In 2023, KONAS conducted an in-depth and extensive analysis of antimicrobial use among healthcare facilities nationwide from 2018 to 2021. This study aimed to provide insights into the direction of national ASPs in Korea.

MATERIALS AND METHODS

1. Study design and setting

This study retrospectively analyzed antimicrobial prescription data in Korea between 2018 and 2021. According to the medical service act, healthcare facilities in Korea are broadly divided into clinics, primary care hospitals (PCHs), secondary care hospitals (SCHs), and tertiary care hospitals (TCHs). Typically, clinics treat patients in an outpatient setting. PCHs are healthcare facilities with at least 30 beds capable of providing inpatient care. SCHs are defined as hospitals with 100 or more beds and employ specialists in essential medical domains. TCHs are designated by the Minister of Health and Welfare to satisfy certain criteria (availability of specialists for each of the 20 or more medical specialties and training of physicians seeking to become specialists)

and provide advanced medical care for high-acuity conditions. In the present analysis, we included PCHs, SCHs, and TCHs and excluded clinics and long-term care hospitals.

2. Ethics statement

This study was approved by the Hanyang University Institutional Review Board (approval number: 2024-05-029). Given the study's retrospective design and use of anonymized data, the requirement for written informed consent from patients was waived.

3. Data collection (antimicrobial prescriptions)

Antimicrobial use was analyzed based on claims data from the Health Insurance Review and Assessment (HIRA). All oral and injectable antimicrobials are prescription drugs in Korea. The country features a national health insurance system under the social security system. Information such as prescription details (name, ingredients, and duration of prescription), patient demographic characteristics, diagnosis, and length of stay (LOS) were collected via HIRA. The HIRA database contains information on approximately 98% of the population [16]. Data on claims represent claims of reimbursement submitted by healthcare facilities for insurance-covered medical services; therefore, they do not include information related to services not included in insurance coverage. In the present study, we collected and reviewed antimicrobial prescription claims for inpatients submitted between January 1, 2018, and December 31, 2021. We collected data on antimicrobials classified as J01 (systemic antimicrobial substances), A07AA09 (oral vancomycin), and J02 (systemic antifungal agents) as per the World Health Organization (WHO) Anatomical Therapeutic Chemical classification system, and the data included information regarding antimicrobials prescribed when inpatients were discharged.

4. Analysis of antimicrobial use

To intuitively review the antimicrobials prescribed by healthcare facilities in Korea and develop effective management strategies, we analyzed antimicrobial usage according to the KONAS classification systems (Table 1). The KONAS classification was established based on expert consensus through a Delphi survey of an expert panel in 2019 [17]. It is considered an appropriate classification system for monitoring antimicrobial usage among Korean healthcare facilities. Furthermore, we conducted an analysis of the usage patterns of aztreonam, colistin, daptomycin, linezolid, and tigecycline among the reserve

Table 1. KONAS antimicrobial classification

Category	Antimicrobials
Broad-spectrum antibacterial agents predominantly used for hospital-onset infections	Amikacin (IV), Cefepime, Cefoperazone/sulbactam, Cefpirome, Ceftazidime, Doripenem, Imipenem, Imipenem and cilastatin, Meropenem, Piperacillin/sulbactam, Piperacillin/tazobactam, and Tobramycin (IV)
Broad-spectrum antibacterial agents predominantly used for community-acquired infections	Aztreonam, Cefcapene, Cefdinir, Cefditoren, Cefetamet, Cefixime, Cefodizime, Cefotaxime, Cefpiramide, Cefpodoxime, Ceftizoxime, Ceftriaxone, Ciprofloxacin, Ertapenem, Gemifloxacin, Levofloxacin, Lomefloxacin, Moxifloxacin, Norfloxacin, Ofloxacin, Tosufloxacin, and Zabofloxacin
Antibacterial agents predominantly used for resistant Gram-positive infections	Daptomycin, Linezolid, Teicoplanin, and Vancomycin (IV)
Narrow spectrum β -lactam agents	Amoxicillin/clavulanate, Amoxicillin/sulbactam, Ampicillin, Ampicillin/sulbactam, Benzathine benzylpenicillin, Benzylpenicillin, Cefaclor, Cefadroxil, Cefalexin, Cefamandole, Cefazedone, Cefazolin, Cefbuperazone, Cefmetazole, Cefminox, Cefotetan, Cefotiam, Cefoxitin, Cefprozil, Cefradine, Cefroxadine, Ceftezole, Cefuroxime, Flomoxef, Nafcillin, and Sultamicillin
Antifungal agents predominantly used for invasive candidiasis	Anidulafungin, Caspofungin, Fluconazole, and Micafungin
Antibacterial agents predominantly used for resistant Gram-negative infections	Ceftolozane/tazobactam, Colistin, and Tigecycline

KONAS, Korea National Antimicrobial Use Analysis System; IV, intravenous agent.

antimicrobials in the 2021 AWaRe classification. These antimicrobials are covered by the National Health Insurance Service from 2018 to 2021. The AWaRe classification system, developed by the WHO in 2017, aims to promote appropriate antimicrobial usage worldwide and delay the emergence of antimicrobial resistance. Reserve antimicrobials are considered as a last resort in the treatment of serious infections due to their activity against multidrug-resistant or broad-spectrum-resistant bacteria [18].

5. Statistical analysis

Characteristics of the participating hospitals from 2018 to 2021 were presented as count (percentage). The top 20 most prescribed antimicrobials in 2021 were presented as proportion by hospital type. Antimicrobial consumption between 2018 and 2021 was summarized using days of therapy/1,000 patient-days according to the KONAS classification. The linear regression was used to identify linear increasing or decreasing trends for reserved antimicrobial consumption. All statistical analyses were

conducted using R software (version 4.3.3; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

1. Characteristics of national hospitals recorded between 2018 and 2021

Table 2 shows the nationwide characteristics of healthcare facilities (PCHs, SCHs, and TCHs) between 2018 and 2021. More than 1,900 facilities were included in the analysis each year, and the proportion of facilities by size and type was similar across the study period. By hospital size, the majority of facilities each year had less than 100 beds (48.7–50.3%). According to hospital type, PCHs accounted for the majority of facilities (81.2–81.4%) and TCHs accounted for the fewest (2.1–2.3%).

2. Top 20 antimicrobials prescribed in 2021

In TCHs, the top 20 antimicrobials accounted for 76.4% of all antimicrobial usage. The most frequently prescribed

Table 2. Characteristics of the participating hospitals

Year	2018	2019	2020	2021
No. of hospitals	1,946	1,941	1,974	1,962
Hospital size				
<100	947 (48.7%)	951 (49.0%)	988 (50.1%)	987 (50.3%)
100–299	769 (39.5%)	766 (39.5%)	763 (38.7%)	753 (38.4%)
300–599	141 (7.2%)	142 (7.3%)	141 (7.1%)	139 (7.1%)
600–899	60 (3.1%)	54 (2.8%)	54 (2.7%)	57 (2.9%)
900–1,199	18 (0.9%)	18 (0.9%)	19 (1.0%)	17 (0.9%)
$\geq 1,200$	11 (0.6%)	10 (0.5%)	9 (0.5%)	9 (0.5%)
Hospital type				
Tertiary care	42 (2.2%)	42 (2.2%)	42 (2.1%)	45 (2.3%)
Secondary care	319 (16.4%)	323 (16.6%)	326 (16.5%)	322 (16.4%)
Primary care	1,585 (81.4%)	1,576 (81.2%)	1,606 (81.4%)	1,595 (81.3%)

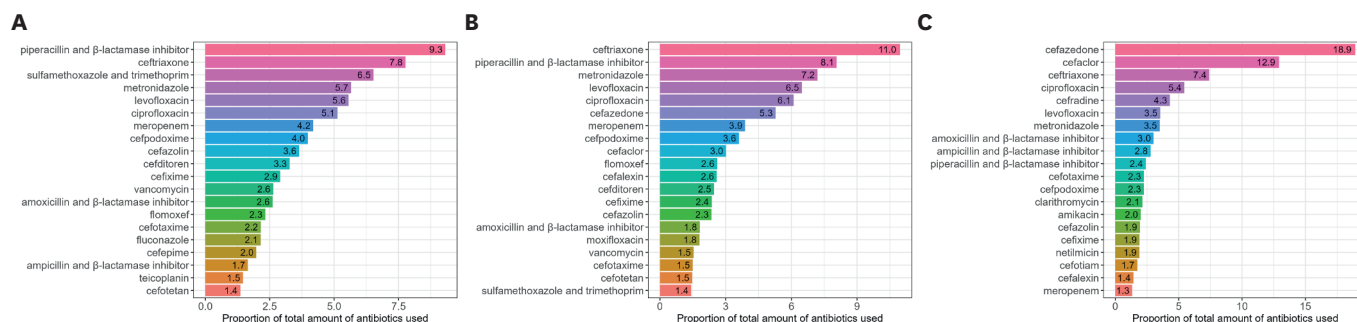


Figure 1. The top 20 most frequently prescribed antimicrobials in 2021. (A) Tertiary care hospitals, (B) secondary care hospitals, and (C) primary care hospitals.

antimicrobial was piperacillin/ β -lactamase inhibitor (9.3%), followed by ceftriaxone and trimethoprim-sulfamethoxazole (Fig. 1A). In SCHs, the top 20 antimicrobials accounted for 76.6% of all antimicrobials used. The most frequently prescribed antimicrobial was ceftriaxone (11.0%), followed by piperacillin/ β -lactamase inhibitor and metronidazole (Fig. 1B). In PCHs, the top 20 antimicrobials accounted for 82.9% of all antimicrobials used. The most frequently prescribed antimicrobial was cefazidone (18.9%), followed by cefaclor and ceftriaxone (Fig. 1C). The types of antimicrobials frequently prescribed for PCHs differed from those prescribed for SCHs and TCHs.

Patients from all hospitals were classified into pediatric (<15 years) and adult (≥ 15 years) groups. The most frequently prescribed antimicrobial among adults was ceftriaxone (8.9%), and that among pediatric patients was ampicillin/ β -lactamase inhibitor (11.1%) (Supplementary Fig. 1).

3. Antimicrobial classes used between 2018 and 2021

TCHs had the largest total antimicrobial usage every year, followed by SCHs and PCHs (Fig. 2). Between 2018 and 2021, antimicrobial usage in TCHs and SCHs has decreased since 2019. In PCHs, antimicrobial usage decreased in 2020 but increased again in 2021. According to the KONAS classification, antimicrobial usage patterns were similar across years within each hospital type. The most frequently prescribed antimicrobials were 'broad-spectrum antibacterial agents predominantly used for community-acquired infections' in TCHs and SCH, and 'narrow-spectrum β -lactam agents' in PCHs, every year. Statistical analyses for the trend of antimicrobial use were presented in Supplementary Table 1.

The use of antimicrobials in 2018 and 2019 was more than two-fold higher in pediatric patients than in adult patients. Even in 2020 and 2021, when antimicrobial use among the

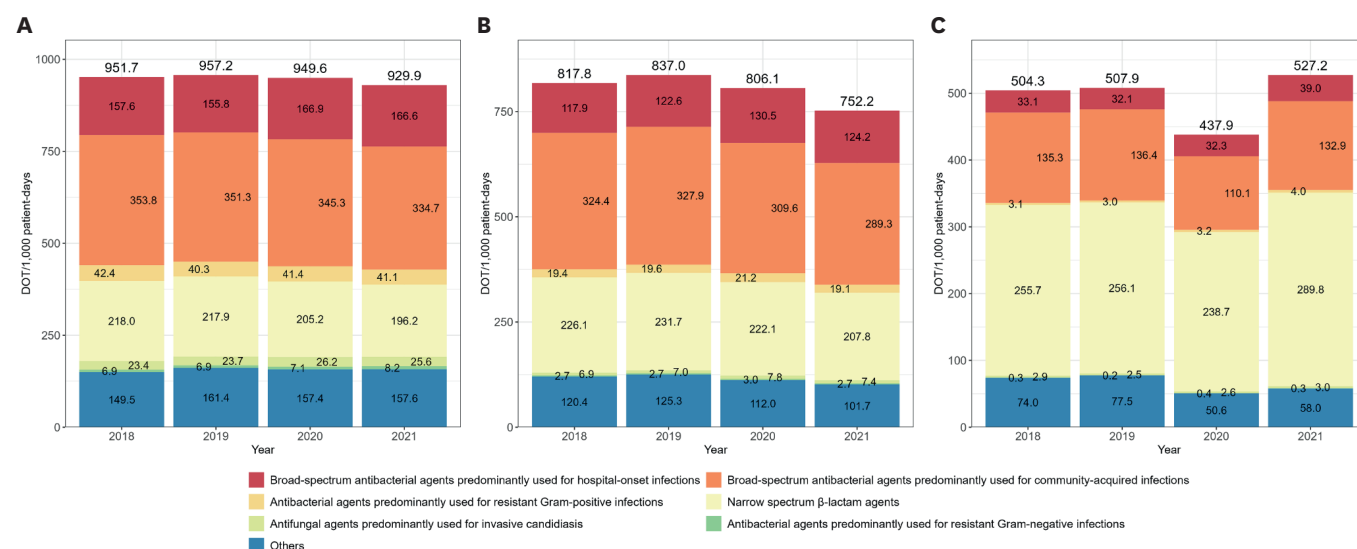


Figure 2. Antimicrobial consumption according to the KONAS classification between 2018 and 2021. (A) Tertiary care hospitals, (B) secondary care hospitals, and (C) primary care hospitals. KONAS, Korea National Antimicrobial Use Analysis System; DOT, days of therapy.

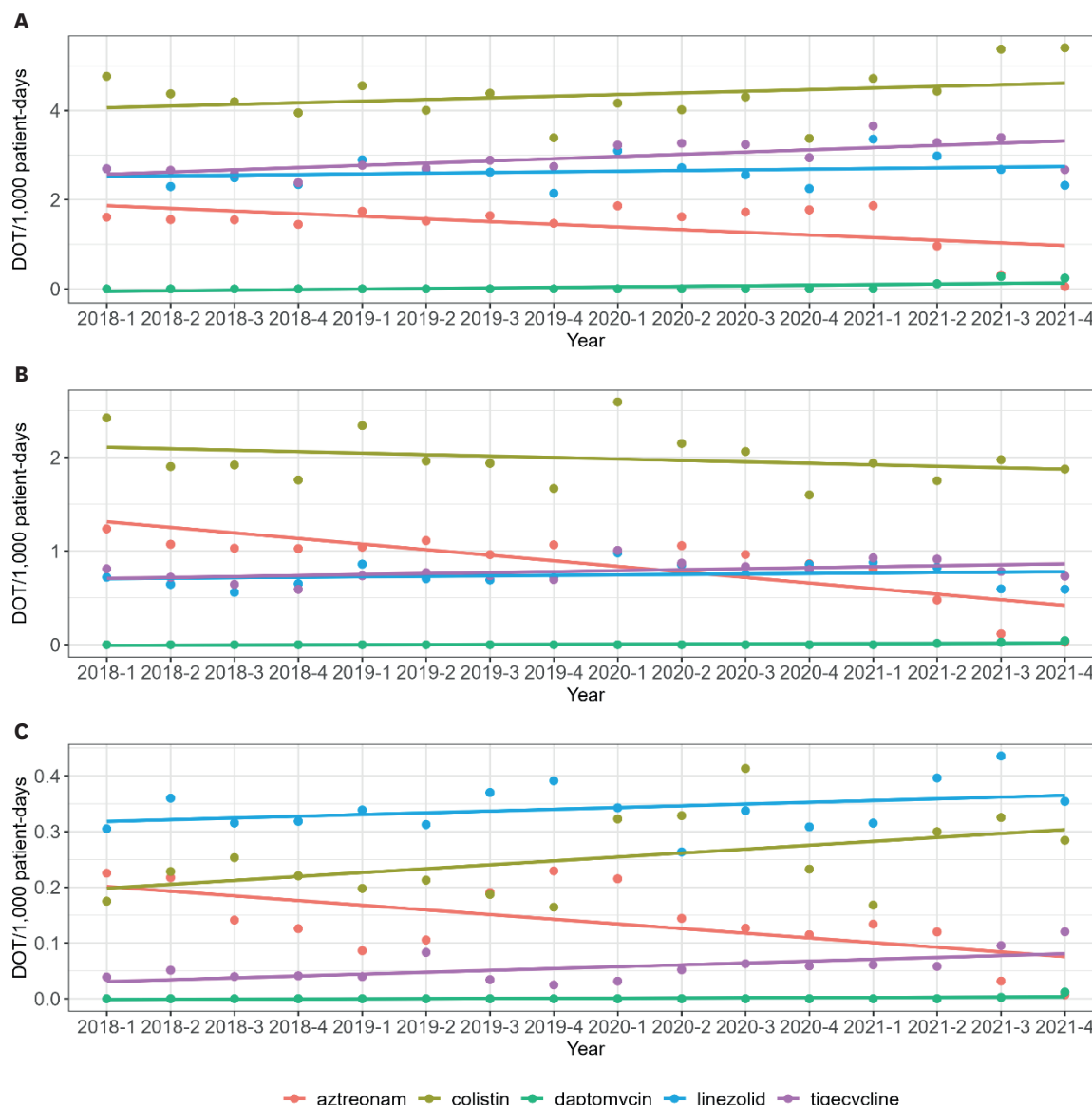


Figure 3. Reserved antimicrobial consumption between 2018 and 2021. (A) Tertiary care hospitals, (B) secondary care hospitals, and (C) primary care hospitals. DOT, days of therapy.

pediatric population substantially decreased, the usage in pediatric patients remained higher than that in adults (Supplementary Fig. 2).

4. Reserve antimicrobials

Between 2018 and 2021, the usage of reserve antimicrobials was highest in TCHs, followed by SCHs and PCHs (Fig. 3). In 2021, the amounts of reserve antimicrobial use were 12.05, 3.81, and 0.8 days of therapy/1,000 patient-days in TCHs, SCHs, and PCHs, respectively. The most frequently used reserve antimicrobial was colistin in TCHs and SCHs (Fig. 3A and 3B), whereas linezolid was the most commonly

used antimicrobial in PCHs (Fig. 3C). In the second half of 2020, daptomycin was first introduced in Korea, and its use increased across all types of hospitals in 2021. In contrast, the use of aztreonam decreased considerably by 2021 because of the discontinuation of its supply. Statistical analyses for the trend of antimicrobial use were presented in Supplementary Table 2.

DISCUSSION

National-level data on antimicrobial usage and usage patterns are fundamental for establishing ASP policies

in Korea. These data also provide a valuable reference to promote the appropriate use of antimicrobials among healthcare providers. In this study, we used data from the HIRA claims database to analyze antimicrobial use in over 1,900 healthcare facilities across the country from 2018 to 2021. Specifically, we provided antimicrobial usage data by hospital type and age group, thereby enabling the analysis of antimicrobial usage tailored to the characteristics of healthcare facilities.

The coronavirus disease 2019 (COVID-19) pandemic has had a substantial impact on healthcare field worldwide, particularly on antimicrobial usage [19-21]. During the early days of the pandemic, there were concerns regarding the increasing use of antimicrobials and the consequent emergence of drug-resistant microbes [22]. However, in Korea, antimicrobial usage decreased in 2020, soon after the COVID-19 outbreak, particularly in PCHs. A possible explanation for this decrease is outlined as follows. The incidence and spread of communicable diseases attributed to respiratory viruses have decreased because of non-pharmaceutical interventions (NPIs) such as social distancing, use of face masks, and strict hand hygiene practices [23, 24]. In Korea, respiratory viral infections are predominantly treated in clinics and PCHs, often leading to antimicrobial prescriptions. Therefore, it is presumed that the NPIs implemented in 2020 would have had a more pronounced impact on antimicrobial usage in PCHs. For the same reasons mentioned above, it is estimated that the decline in antimicrobial usage during the pandemic was more prominent in pediatric patients than in adult patients (**Supplementary Fig. 2**).

In our study, the antimicrobial usage in PCHs was lower than that in TCHs and SCHs. However, while antimicrobial usage in TCHs and SCHs has gradually decreased, the usage in PCHs has continued to increase every year, except in 2020. Furthermore, a notable upward trend was recorded in the use of reserve antimicrobials in the PCHs. However, the use of reserve antimicrobials decreased in both TCHs and SCHs. This trend may be due to a shortage of infectious disease specialists or pharmacists capable of managing antimicrobial use in these institutions. Infectious disease specialists in Korea are scarce, numbering approximately 0.6 specialists per 100,000 population, which is considerably lower than in the US (2.4 specialists per 100,000 population) and Japan (0.9 specialists per 100,000 population) [25]. The lack of specialized personnel responsible for ASPs is even more pronounced in smaller hospitals. Therefore, robust hospital leadership

and national support are essential to implement ASPs and reduce antimicrobial use in small hospitals.

According to the 2021 HIRA report on the appropriateness of medication coverage, the rate of antimicrobial prescriptions for acute upper respiratory infections is higher among infants and young children (0-6 years) (38.9%) than that among adults (35.9%), and this trend has been captured over three consecutive years since 2019. In fact, at the first outpatient visit of a pediatric patient with acute pharyngitis, a combined treatment of penicillin and beta-lactamase was prescribed in 47.2% of cases [26]. In our study, antimicrobial prescriptions for pediatric patients comprised less than 10% of all antimicrobial prescriptions. However, the antimicrobial usage was higher among pediatric patients than among adult patients (**Supplementary Fig. 2**), which highlights the importance of active antimicrobial stewardship for the pediatric population.

According to a 2021 Korea Disease Control and Prevention Agency report, the proportion of methicillin-resistant *Staphylococcus aureus*-among blood isolates of *S. aureus* in 2021 continued to decrease, reaching 45.2% of all infections, compared to trends since 2016 [27]. However, there was no significant change in the usage of antibacterial agents predominantly used for resistant Gram-positive infections during the period of 2018-2021. Furthermore, there was an upward trend in the usage of broad-spectrum antimicrobials predominantly used for hospital-onset infections, such as meropenem, piperacillin and β -lactamase inhibitor, and cefepime in TCHs, SCHs and PCHs (**Supplementary Table 3**). These findings suggest that implementing a feedback into use of certain antibiotics may prove beneficial in antimicrobial stewardship efforts.

This study has several limitations. First, we could not analyze the quality of antimicrobial prescriptions because the data from the HIRA claims database did not contain information about clinical test results and the timing of antimicrobial usage. However, we conducted a cross-sectional and longitudinal study using data from the HIRA claims database, which provided insights into the current antimicrobial usage and trends among healthcare facilities nationwide. Second, the data on antimicrobial usage included antimicrobials prescribed to inpatients at the time of their discharge. PCHs in Korea primarily treat community-acquired infections; therefore, the patient LOS is short, with frequent prescriptions of oral

antimicrobials at discharge. Hence, the antimicrobial use in these facilities might have been overestimated. Third, national policies may have affected antimicrobial usage. Health authorities designated certain hospitals as COVID-19 hospitals during the pandemic for the admission of patients with moderate COVID-19 [28, 29]. Although concurrent bacterial infections were recorded in only 5-10% of patients with COVID-19 in the early days of the COVID-19 pandemic, more than 75% of patients were prescribed antimicrobials [30]. According to one study using the National Health Insurance System database, antimicrobials were prescribed to 27.3% of patients with COVID-19 in Korea, from December 1, 2019 to December 31, 2020. In particular, 73.8-87.6% of patients with severe or critical illness received antimicrobial treatment [31]. It is speculated that elevated levels of inflammatory markers or abnormal chest X-ray findings among COVID-19 patients prompted physicians to prescribe antimicrobials, and the same phenomenon may have occurred in many PCHs designated as COVID-19 hospitals in Korea. Fourth, we could not track changes in the incidence of drug-resistant bacteria according to antimicrobial usage. Further research is required in this area. Lastly, this study did not include clinics and long-term care hospitals, which account for a significant portion of Korean medical institutions. Investigating the antimicrobial use in clinics and long-term care hospitals would be helpful for developing effective national ASPs.

The results of this study demonstrated that the amount and patterns of antimicrobial use varied across different types of hospitals in Korea. These findings suggest that the management of antimicrobials varies depending on the characteristics and type of hospital. In particular, we highlighted the need to address the recent increase in antimicrobial use in PCHs via national antimicrobial stewardship policies.

ACKNOWLEDGEMENTS

We would like to thank the KONAS participating hospitals and commissioners for their support of this project.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Antimicrobial consumption according to the KONAS classification between 2018 and 2021

Supplementary Table 2

Reserved antimicrobial consumption between 2018 and 2021

Supplementary Table 3

Consumption of broad-spectrum antimicrobials predominantly used for hospital-onset infections between 2018 and 2021

Supplementary Figure 1

The top 20 most frequently prescribed antimicrobials in 2021. (A) Adults (≥ 15 years) and (B) children (< 15 years).

Supplementary Figure 2

Antimicrobial consumption according to the KONAS classification between 2018 and 2021. (A) Adult (≥ 15 years) and (B) children (< 15 years).

ORCID iDs

I Ji Yun 
<https://orcid.org/0009-0009-4773-2165>
 Hyo Jung Park 
<https://orcid.org/0000-0002-3875-0224>
 Jungmi Chae 
<https://orcid.org/0000-0003-2634-1738>
 Seok-Jae Heo 
<https://orcid.org/0000-0002-8764-7995>
 Yong Chan Kim 
<https://orcid.org/0000-0001-5081-7906>
 Bongyoung Kim 
<https://orcid.org/0000-0002-5029-6597>
 Jun Yong Choi 
<https://orcid.org/0000-0002-2775-3315>

Funding

This research was supported by the Korea National Institute of Health (KNIH) research project (project No.2022-ER2210-01).

Conflict of Interest

JYC is editorial board and BK is associate editor of *Infect Chemother*; however, they did not involve in the peer reviewer selection, evaluation, and decision process of this article. Otherwise, no potential conflicts of interest relevant to this article was reported. This research was supported by the Korea National Institute of Health (KNIH) research, but it was not involved in the contents of this study.

Author Contributions

Conceptualization: YCK, BK, JYC. Data curation: IJY. Formal analysis: YCK, SJH. Investigation: IJY, HJK, JC. Methodology: YCK, BK, JYC. Software: JC. Validation: IJY, YCK. Visualization: IJY, YCK. Writing the original draft: IJY, HJK, JC. Writing, reviewing, and editing: YCK, BK.

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