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Appropriateness of antibiotic prescriptions during hospitalization and ambulatory care: a multicentre prevalence survey in Korea

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ABSTRACT

Objectives: Antimicrobial resistance is one of the most urgent global health threats. The need for the qualitative evaluation of antibiotic use at the national level is increasing. To identify areas for improvement, we aimed to assess the prevalence and appropriateness of antibiotic prescriptions during hospitalization and ambulatory care in Korea.

Methods: The prevalence and appropriateness of antibiotic prescriptions on 29 August 2018 were assessed for 20 hospitals in Korea. Infectious disease specialists determined appropriateness. Except for antiviral and anti-tuberculosis agents, all antibacterial or antifungal agent prescriptions during hospitalization or ambulatory care were evaluated.

Results: The prevalence of antibiotic prescription was 14.1% (8,400/59 216 patients) on the study date. Antibiotics were prescribed for 50.8% of inpatients (6557/12 902), with two or more antibiotics prescribed for 27.4% (1798/6557) of patients. A total of 10 948 prescriptions (7999 therapeutic, 2105 surgical prophylaxes, and 844 medical prophylaxes) were included in the final analysis, and 27.7% of these were inappropriate. Surgical prophylaxis was inadequately prescribed most frequently (54.4%), followed by medical

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prophylaxis (29.5%) and therapeutic antibiotics (20.5%). The most common indications for therapeutic antibiotics were respiratory (29.1%, n=2332), gastrointestinal (22.4%, n=1791), and urinary tract infections (13.1%, n=1050). The most frequently prescribed antibiotics were cephalosporins (52.0%, n=5490), followed by beta lactam/beta lactamase inhibitors (13.7%, n=1373), fluoroquinolones (9.1%, n=957), and metronidazole (6.6%, n=699).

Conclusion: This was the first nationwide qualitative antibiotic prescription adequacy evaluation in Korea. A significant proportion of antibiotic prescriptions were inappropriate. Therefore, interventions for high-frequency infections and prescription antibiotics are needed.

1. Introduction

Antimicrobial resistance is one of the biggest public health problems, and available antibiotics are limited. Consequently, efforts to reduce antimicrobial resistance through the use of appropriate antibiotics are attracting worldwide attention [1]. The inappropriate use of antibiotics leads to treatment failure, increased medical costs/hospital periods, and *Clostridioides difficile* infection. Therefore, it is very important to ensure the appropriate use of antibiotics through antibiotic stewardship programs [2,3]. Accordingly, The Netherlands, Australia, and the United States do not only monitor antibiotic usage, but also conduct qualitative evaluations of actual antibiotic use. This is an attempt at qualitative monitoring for inappropriate antibiotic use [4–6].

Korea already has a unique public healthcare system run by the National Health Insurance Service (NHIS), which strictly limits reimbursement for inappropriate prescriptions, but this strategy is based only on the investigation of the mismatch between the prescription and the diagnostic code. Therefore, some more innovative antibiotic use policies have been implemented by the healthcare authorities. These include the introduction of the separation of pharmaceutical prescription and dispensation in 2000; quality assessment of prescriptions, including those for antibiotics for the treatment of acute upper respiratory tract infections, in ambulatory care in 2001, and public reporting of the results in 2006; quality assessment of the use of prophylactic antibiotics for surgery in 2007; and the code of conduct for ethical competition in the pharmaceutical trade in 2010 [7]. Through these, there have been improvements in the quantitative (reducing antibiotic administration period and usage) and qualitative (surgical preventive antibiotic type, first administration time change, etc.) use of antibiotics [8].

Several studies have been conducted to analyse antibiotic use through health insurance claim data or NHIS data [9,10]. However, no qualitative study has been conducted on the appropriateness of antibiotic prescriptions at the national level in Korea. This study aimed to plan future antimicrobial stewardship activity by conducting a national antibiotic prescription adequacy evaluation.

2. Materials and methods

2.1. Study design and setting

We conducted a cross-sectional one-day point prevalence study. One hundred and twenty-two hospitals (95 with a capacity of >500 beds and 27 with <500 beds) where adult or paediatric infectious disease specialists were working were considered. A total 20 hospitals were finally included based on the consideration of regional distribution, type, and the number of beds. The participating hospitals included two with more than 1000 beds, 14 with 500–1000 beds, and four with fewer than 500 beds. Ten were tertiary general hospitals, nine were general hospitals, and one was a long-term care hospital. Five hospitals were located in Seoul Metropolitan city, five in Gyeonggi, four in Gyeongsang, two in Chungcheong, two in Jeolla, one in Gangwon, and one in Jeju Province (Supplementary Fig. S1). The study was approved by the Institutional Review Board of each hospital. The requirement for an informed written consent from patients was waived because of the retrospective nature of the study.

2.2. Prevalence of antibiotic use and assessment of appropriateness

The adequacy evaluation was conducted targeting antibiotics prescribed on 29 August 2018. The prevalence of antibiotic use on the study date was calculated by dividing the number of patients who received antibiotics by the number of patients who were hospitalized (general ward and intensive care unit) or visited ambulatory care facilities or the emergency room.

Assessment of appropriate prescription on 29 August 2018 was conducted on the individual prescriptions of all antibiotics and antifungal agents prescribed. Antiviral, anti-tuberculosis, and antiparasitic drugs were excluded. Intravenous, intramuscular injection, and oral administration routes were included. Antibiotics administered for ointment, cleaning, and nebulization were excluded. Infants aged under 30 days were excluded from the evaluation. Antibiotics were classified as therapeutic antibiotics, medical prophylaxis, and surgical prophylaxis according to the purpose of the prescription.

2.3. Principles of appropriateness assessment

Appropriateness assessments were retrospectively conducted by adult or paediatric infectious disease specialists from each hospital. The data were collected via a web-based electronic case report form (e-CRF) from 16 September to 31 December 2018. In order to keep the evaluation criteria constant, an expert committee was formed to develop evaluation guidelines for maintaining the same evaluation criteria in determining appropriateness of antibiotic use (Supplementary Table S1). In the case of definitive treatment in which causative bacteria were identified, even if there was a narrow-spectrum antibiotics, it was considered an appropriate prescription. A total of nine adult and paediatric infectious disease experts were selected as panellists. The panellists developed appropriate assessment guidelines for a total of nine infectious disease categories: cardiovascular infections, skin and soft tissue infections, gastrointestinal infections, central nervous system infections, respiratory tract infections, urinary tract infections, febrile neutropenia, musculoskeletal infections, and acute otitis media for children. The guidelines developed by the expert panels stipulated the appropriate empirical antibiotics and examples of inappropriate prescription based on domestic/international guidelines, and consensus was reached in expert panel meetings. In the absence of

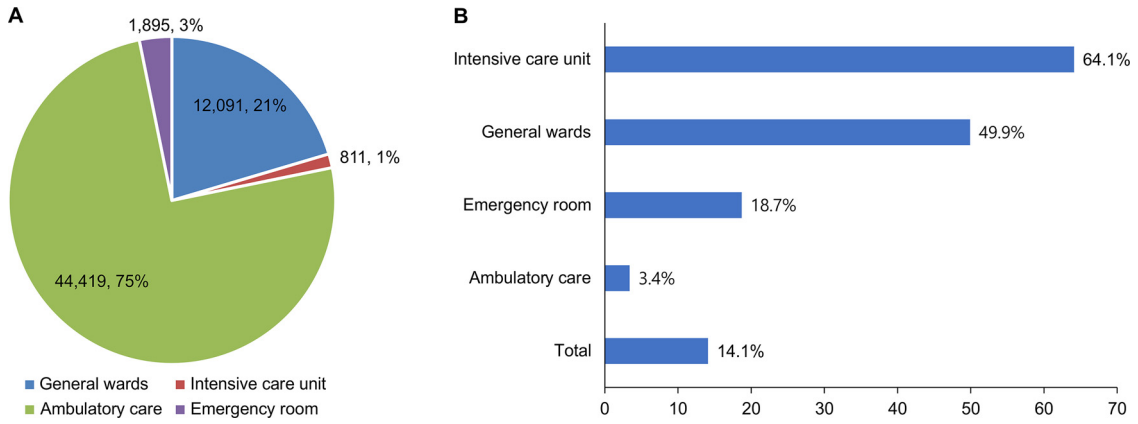

Fig. 1. Total patients and prevalence of antibiotic prescription according to location.

assessment guidelines for each disease, individual evaluators conducted the evaluation based on domestic and international guidelines and expert opinions of adult and paediatric infectious disease specialists.

The evaluation was made based on infectious disease–related diagnosis or medical records. If the evaluation was not available due to the lack of information in the medical records, the evaluation was based on the infectious disease diagnosis presumed by the evaluator, referring to the laboratory or image study results related to the antibiotic prescription. However, if the evaluator could not evaluate at all based on antibiotic prescription from the medical records and test results, it was concluded that the appropriateness of antibiotic prescription could not be evaluated.

2.4. Statistical analysis

Descriptive statistics were used to summarize findings. Continuous variables are expressed as the median and range. Categorical variables are expressed as percentages and proportions. Results were considered statistically significant if the two-sided *P* value was less than 0.05. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Prevalence of antibiotic prescription

On the study date (29 August 2018), 59 216 patients visited the hospital for ambulatory care or were hospitalized (general wards/intensive care unit or emergency room) (Fig. 1A). Of these patients, 14.1% (8400/59 216 patients) were prescribed antibiotics. More than two antibiotics were prescribed in 3.6% (n=2161) of the patients. Antibiotic prescription was most frequent in the intensive care unit (64.1%), followed by general wards (49.9%), the emergency room (18.7%), and outpatient care (3.4%) (Fig. 1B). The detailed prevalence of antibiotic prescription is shown in Supplementary Table S2.

3.2. Baseline information of antibiotic appropriateness evaluation

A total of 11 735 antibiotic appropriateness results were collected via the eCRF. Among these, 647 results were excluded because the reason for the prescription could not be determined by the evaluators. Furthermore, 140 results were excluded due to insufficient information. Thus, 10 948 antibiotic appropriateness results were included in the analysis. Most of the results were for antibacterial agents (10 623, 97%), with only 325 (3%) being for antifungal agents. The antibiotics were administered via intravenous injection in 7603 (69.7%) cases; orally, 3269 (30.0%) cases; and intramuscular injection, 34 (0.3%) cases. The purpose for the prescription was most commonly antibiotic therapy (7999, 73.1%), followed by surgical prophylaxis (2105, 19.2%) and medical prophylaxis (844, 7.7%).

3.3. Antibiotic appropriateness according to prescription purpose

Detailed results on the appropriateness of antibiotic prescription according to hospital type/prescription purpose are shown in Table 1. The median proportion of inappropriateness of antibiotic prescription for therapeutic purposes was 20.0% (range, 7.8%–38.8%) (Supplementary Fig. S2). Regarding inappropriate antibiotic prescription for therapeutic purposes, unrecommended use was most common (45.9%), followed by unnecessary use (36.7%) (Supplementary Table S3). Antibiotic prescription was most common during hospitalization (6234, 78.1%), followed by ambulatory care (1351, 16.9%) and emergency room visits (396, 5.0%). Inappropriate use of antibiotics was more frequently observed in ambulatory care than during hospitalization (30.9% vs 18.1%, $P < 0.001$) or emergency room visits (20.4%, $P < 0.001$) (Fig. 2A). Further, 29.5% of prescriptions for medical prophylaxis were inappropriate. The most common indications were transplantation and steroid use (137, 16.2%), followed by percutaneous endoscopic gastrostomy (PEG) (126, 14.9%). However, 54% (68/126) and 78.9% (30/38) of antibiotic prescriptions for PEG and dental procedures, respectively, were inappropriate (Supplementary Table S4). Furthermore, about one-half (54.4%) of the prescriptions for surgical prophylaxis were inappropriate. Inappropriate use was more frequent in surgical prophylaxis than in therapy or medical prophylaxis ($P < 0.001$) (Fig. 2B). Unnecessary and unrecommended use constituted 50.5% (573/1146) and 46.0% (527/1146), respectively, of inappropriate antibiotic use for surgical prophylaxis (Supplementary Table S5).

3.4. Therapeutic antibiotics by infectious disease syndrome group

Of the 7999 therapeutic antibiotic prescriptions, those for respiratory tract infections were the most common (n=2332, 29.1%). These were followed by prescriptions for gastrointestinal infections (n=1791, 22.4%), urinary tract infections (n=1050, 13.1%), and skin and soft tissue infections (n=848, 10.6%) (Table 2). Among the prescriptions for respiratory tract infections, 19.3% were inappropriate. Of the prescriptions for bacterial sinusitis and pharyngitis, 41.5% and 33.3%, respectively, were inappropriate. Regarding gastrointestinal infections, 25.2% and 23.0% of prescriptions for infectious colitis and pancreatitis, respectively, were inappropriate. The

Table 1
Appropriateness of antibiotic prescribing according to hospital type/prescription purpose

Purpose of prescription	Hospital type	Total antimicrobial prescription, n	Inappropriate prescription, n	Proportion of inappropriate prescription, % (95% CI)
Treatment	Tertiary general hospital	5320	1012	19.0 (18.0–20.1)
	General hospital	2653	616	23.2 (21.6–24.8)
	Long-term care hospital	26	8	30.8 (13.0–48.5)
	Total	7999	1636	20.5 (19.6–21.3)
Medical prophylaxis	Tertiary general hospital	668	149	22.3 (19.1–25.5)
	General hospital	176	100	56.8 (49.5–64.1)
	Total	844	249	29.5 (26.4–32.6)
Surgical prophylaxis	Tertiary general hospital	1446	755	52.2 (49.6–54.8)
	General hospital	659	391	59.3 (55.6–63.1)
	Total	2105	1146	54.4 (52.3–56.6)
Total	Tertiary general hospital	7434	1916	25.8 (24.8–26.8)
	General hospital	3488	1107	31.7 (30.2–33.3)
	Long-term care hospital	26	8	30.8 (13.0–48.5)
	Total	10 948	3031	27.7 (26.8–28.5)

CI, confidence interval.

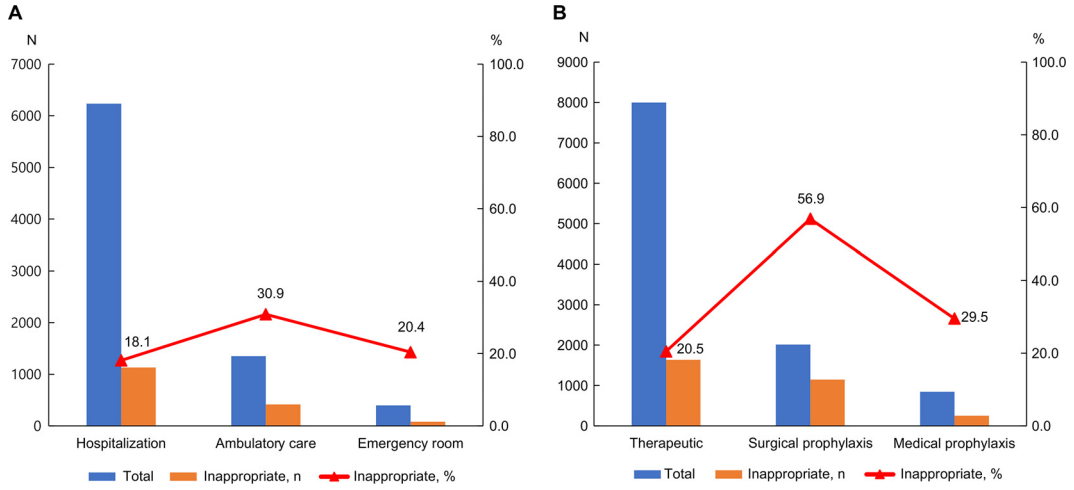

Fig. 2. Total antimicrobial use and inappropriate use proportion stratified by (A) prescribing site and (B) purpose of prescription.

Table 2
Appropriateness of antibiotic prescribing by infectious disease

Infectious diseases syndrome	Total prescription, n (%)	Inappropriate prescription, n	Proportion of inappropriate prescription, % (95% CI)
Respiratory tract infections	2332 (29.1)	449	19.3 (17.7–20.9)
Gastrointestinal infections	1791 (22.4)	251	14.0 (12.4–15.6)
Urinary tract infections	1050 (13.1)	152	14.5 (12.3–16.6)
Skin and soft tissue infections	848 (10.6)	228	26.9 (23.9–29.9)
Musculoskeletal infections	490 (6.1)	81	16.5 (13.2–19.8)
Febrile neutropenia	140 (1.7)	14	10 (5.0–15.0)
Primary bacteraemia	112 (1.4)	7	6.3 (1.8–10.7)
Central nervous system infections	89 (1.1)	10	11.2 (4.7–17.8)
Sexually transmitted infections	87 (1.1)	8	9.2 (3.1–15.3)
Cardiovascular infections	77 (0.9)	5	6.5 (1.0–12.0)
Otitis media in children	32 (0.4)	6	18.7 (5.2–32.3)
Tick-borne diseases	9 (0.1)	0	0.0 (0.0–0.0)
Protozoal diseases	5 (0.1)	0	0.0 (0.0–0.0)
Others[a]	1026 (12.8)	411	40.1 (37.1–43.1)
Total	7999 (100.0)	1636	20.5 (19.6–21.3)

CI, confidence interval.
[a] Not available due to absence of diagnostic category.

appropriateness of the antibiotic prescription for each infectious disease syndrome group is shown in Supplementary Table S6.

3.5. Frequent prescription antibiotics and appropriateness

Table 3 shows the frequent prescription antibiotics and their appropriateness. Third-generation cephalosporins were the most common antibiotics (n=2563, 24.3%), followed by first-generation cephalosporins (n=1380, 13.1%), beta-lactam/beta-lactamase inhibitors (n=1373, 13.0%), and second-generation cephalosporins (n=1075, 10.2%). Cephalosporin prescriptions (n=5490, 52.0%) accounted for more than half of all antibiotic prescriptions. Carbapenem and glycopeptides accounted for 5.2% (n=545) and 4.7% (n=498), respectively, of the prescriptions. As a single agent, cef-

Table 3
Result of the appropriateness of antibiotic prescribing by antibiotic classification

Antibiotic classification	Total prescription, n (%)	Inappropriate prescription, n	Proportion of inappropriate prescription, % (95% CI)
Third-generation cephalosporins	2563 (24.3)	836	32.6 (30.8–34.4)
First-generation cephalosporins	1380 (13.1)	367	26.6 (24.3–28.9)
Beta-lactam/beta-lactamase inhibitor	1373 (13.0)	254	18.5 (16.4–20.6)
Second-generation cephalosporins	1075 (10.2)	688	64.0 (61.1–66.9)
Fluoroquinolones	957 (9.1)	201	21.0 (18.4–23.6)
Metronidazole	699 (6.6)	162	23.2 (20.0–26.3)
Carbapenem	545 (5.2)	59	10.8 (8.2–13.4)
Glycopeptide	498 (4.7)	45	9.0 (6.5–11.6)
Macrolides	267 (2.5)	78	29.2 (23.8–34.7)
Sulphonamides/trimethoprim	262 (2.5)	23	8.8 (5.4–12.2)
Aminoglycosides	178 (1.7)	108	60.7 (53.5–67.9)
Fourth-generation cephalosporins	174 (1.6)	28	16.1 (10.6–21.6)
Penicillins	154 (1.5)	26	16.9 (11.0–22.8)
Tetracyclines	131 (1.2)	26	19.8 (13.0–26.7)
Lincosamide	97 (0.9)	39	40.2 (30.4–50.0)
Polymyxins	34 (0.3)	1	2.9 (–2.7 to 8.6)
Monobactams	28 (0.3)	18	64.3 (46.5–82.0)
Rifampin	26 (0.2)	2	7.7 (–2.6 to 17.9)
Tigecycline	18 (0.2)	0	0.0 (0.0–0.0)
Oxazolidinones	17 (0.2)	0	0.0 (0.0–0.0)
Non category[a]	90 (0.9)	34	37.8 (27.8–47.8)
Total	10 566 (100.0)	2995	28.3 (27.5–29.2)

[a] Non category included rifaximin (n=64), fosfomycin (n=24), fusidic acid (n=1), and nitrofurantoin (n=1).CI, confidence interval.

triaxone was the most common antibiotic, (n=1077) followed by piperacillin/tazobactam (n=819) and metronidazole (n=669). Cefazolin (379, 18.2%) was the most commonly used surgical prophylaxis antibiotic, followed by flomoxef (248, 11.9%), cefazedone (243, 11.6%), and ceftriaxone (117, 5.6%) (Supplementary Table S6).

4. Discussion

This study revealed that the prevalence of antibiotic prescription was 14.1%, and a significant proportion (27.7%) of the prescriptions were inappropriate. The prevalence of antibiotic use was concentrated among more than half of the inpatients, especially in the intensive care unit. Antibiotic use was least prevalent in ambulatory care, but most frequently inappropriate use was observed. Two-thirds of antibiotic prescriptions for surgical prophylaxis were inappropriate. In addition, we identified the most frequently used antibiotics, their appropriateness, and the indications for antibiotic use. This study was the first nationally representative qualitative antibiotic prescription adequacy evaluation in the Korea.

Antibiotics were prescribed for more than half of all hospitalized patients. However, only 3.4% of ambulatory care patients were prescribed antibiotics. This was lower than the approximately 10% reported in China and 13% in the United States [11–13]. However, the actual amount of antibiotics accounted for one-fourth of all antibiotics used. Approximately 30% of the prescriptions for ambulatory care patients were inappropriate, which was similar to the 23%–40% reported in the United States or the UK and lower than the 51%–61% reported in Japan or China [11–15]. Considering that most of the hospitals in this study were general and tertiary hospitals, it is estimated that the appropriateness of antibiotic prescription in primary care would be higher. The evaluation of antibiotic use in primary care hospitals where outpatient prescriptions are the mainstay should be considered, and intervention is required for inappropriate antibiotic use. In the present study, as the evaluation was limited to the hospitals where the infectious disease specialists worked, no attempt was made to evaluate antibiotic use in primary medical institutions.

Respiratory tract infection was the most common indication for antibiotic use (29.1%). Similar findings were reported in Australia and Saudi Arabia [5,16]. In the present study, the gastrointestinal tract was the second most common site of infection. Cholecystitis/cholangitis was the most common gastrointestinal infection. However, the proportion of inappropriate antibiotic use for cholecystitis/cholangitis was only 8.9%. Notably, more than 20% of antibiotic use for infectious colitis (25.2%) was inappropriate; pancreatitis, 23.0%; and spontaneous bacterial peritonitis, 21.6%. Even within the same infection site category (e.g., gastrointestinal infection), there was a considerable difference in the frequency of prescription and the proportion of inappropriate antibiotic use. Therefore, even in the same infection site category, it is essential that an intervention strategy be established according to the detailed results.

The evaluation in this study included antibiotic use for medical prophylaxis. The proportion of medical prophylaxis was only 7.9%, but inappropriate prescription was observed in one-third of the prescriptions. This inappropriate prescription frequency was much higher than that for therapeutic use (20.5%). This could be attributed to the lack of national guidelines for the prescription of medical prophylactic antibiotics and the lack of education. There is large room for improvement in medical prophylaxis: clear recommendations and guidelines should be provided. Furthermore, the evaluation of prescription adequacy at the national level should be continuously carried out for prophylactic antibiotics.

In Korea, clinical performance measurement in surgical antibiotic prophylaxis was implemented as part of a national hospital evaluation program in 2007. Clinical indicators for the program were antibiotic selection, timing of administration of the first dose, and duration. From 2007, there was significant quality improvement in the use of surgical antibiotic prophylaxis for the three clinical indicators [8]. Despite the former intervention by the national evaluation program, this study revealed that approximately 50% of surgical antibiotic prophylaxis was prescribed inappropriately. Second-generation cephalosporins (Cefotetan and Flomoxef) and third-generation cephalosporins (cephalosporins) were especially frequently and inappropriately prescribed. Appropriate selection of antibiotics should be more emphasized especially for second- and third-generation cephalosporins.

A strength of this study is the qualitative evaluation of more than 10 000 individual antibiotic prescriptions by infectious disease experts using consistent criteria developed by expert panels.

In addition, the scope of evaluation included not only hospitalized patients but ambulatory care patients. Furthermore, the study included antibiotic prescriptions for both therapeutic and medical/surgical prophylaxis purposes. The study also included the detailed classification of each infectious disease syndrome or antibiotic treatment indication. Therefore, this study paints the whole picture of antibiotic prescription patterns, with prescription adequacy results for acute-care hospitals in Korea.

There are limitations in thus study. First, the evaluation did not consider the duration of the antibiotic prescriptions. More accurate results will be known only after the evaluation of optimal antibiotic prescription, including the appropriate treatment duration as an evaluation criterion. Second, a total of 20 hospitals from around the country were included for representativeness. However, only one long-term care hospital was evaluated, and primary care hospitals were not evaluated. The evaluation of long-term care or primary care hospitals was difficult to include because there were no infectious disease experts who could conduct the evaluation. In the future, the prevalence and appropriateness of antibiotic prescriptions in long-term care or primary care hospitals should be evaluated. This would present an opportunity to manage antibiotic prescriptions and develop methods for implementation.

In conclusion, this research via infectious disease specialist evaluations revealed that 27.7% of antibiotic prescriptions were inadequate. Furthermore, the study clarified the dominant prescription purposes, diagnosed diseases, and prescribed antibiotics through detailed analysis. This national-level qualitative evaluation was very helpful in identifying target intervention diseases where inappropriate antibiotic use was frequently observed or target antibiotics according to antibiotic use purpose. Based on the results, it is vital for the Korean government to design a specific, long-term agenda to tackle antibiotic drug resistance from inadequate antibiotic prescription.

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Declaration of Competing Interests

None declared.

Ethic approval

This study was approved by the Institutional Review Board (IRB) of Soonchunhyang University Seoul Hospital (IRB no. 2019-12-016).

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jgar.2022.03.021.

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