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의학석사 학위논문

Stepwise Expansion of Antimicrobial Stewardship Programs and Its Impact on Antibiotic Use and Resistance Rates at a Tertiary Care Hospital in Korea

단일 3차 의료기관에서 항생제 사용관리 프로그램의 단계적 확대가 항생제 사용량과 내성률에 미친 영향 분석

2023년 2월

서울대학교 대학원

의학과 내과학전공

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이 논문을 의학석사 학위논문으로 제출함

2022년 10월

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신동훈의 석사 학위논문을 인준함

2023년 1월

위 원 장 ______________________ (인)

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위 원 ______________________ (인)

국문초록

단일 3차 의료기관에서 항생제 사용관리 프로그램의 단계적 확대가 항생제 사용량과 내성률에 미친 영향 분석

배경: 항생제 스튜어드십 프로그램(Antimicrobial stewardship program; ASP)의 핵심 전략을 미국 질병통제예방센터가 발간하였으나, 인력이 부족한 의료 기관에서는 적용하기 어려울 수 있다. 따라서 자원이 제한된 상급종합병원에서 ASP의 단계적 확대가 항생제 사용량과 5가지 세균의 내성률에 미치는 영향을 조사하고자 한다.

방법: 일개 상급종합병원에서 시행한 ASP 활동들을 핵심 전략에 따라 정리하였다. 또한, 2010년 1월부터 2019년 12월까지 입원했던 모든 환자의 항생제 처방량과 모든 임상 검체의 배양 결과를 후향적으로 수집하였다. 추세 분석을 위해 2-sided correlated seasonal Mann-Kendall nonparametric tests를 시행하였다.

결과: 10년간 다양한 ASP 활동들을 정착시켰고, 그동안 총 항생제 사용량은 days of therapy per 1000 patient-days (DOT) 기준 617.49에서 550.81로 약 10.80%가 유의하게 감소하였다 (P < 0.01). 광범위 항생제 중에선 glycopeptide (DOT: 22.88 to 18.81; P < 0.01)와 fluoroquinolone (FQ, DOT: 65.29 to 46.15; P < 0.01)의 사용량이 유의하게 감소한 반면, 3세대 cephalosporin (3rd generation cephalosporin; 3GC)의 사용량은 유의한 변화가 없었다 (DOT: 115.04 to 108.86; P = 0.48). 또, 전체 carbapenem 사용량은 유의한 변화가 없었으나 (DOT: 21.10 to 20.42; P = 1.00), ertapenem 사용량은 증가하였다 (DOT: 8.97 to 12.91; P = 0.02). *Staphylococcus aureus*의 methicillin 내성률은 지속적으로 감소하였고 (내성률 [%]: 55.4 to 45.5; P < 0.01). *Escherichia coli*의 3GC 내성률 (내성률 [%]: 18.9 to 37.1; P < 0.01), FQ 내성률 (내성률 [%]:

41.4 to 53.7; $P < 0.01$)은 유의하게 증가하였다. 반면, *Klebsiella pneumoniae*의 3GC 내성률 (내성률 [%]: 22.3 to 26.5; $P = 1.00$)은 유의하게 증가하지 않았고, *Pseudomonas aeruginosa*의 3GC 내성률 (내성률 [%]: 15.8 to 12.3; $P = 0.01$), FQ 내성률 (내성률 [%]: 29.5 to 23.1; $P = 0.01$)은 유의하게 감소하였다.

결론: 인력이 제한된 상황에서도 ASP의 핵심 전략에 근거한 단계적 확대가 총 항생제 사용량을 줄이는데 효과적이었다.

주요어 : 항생제 스튜어드십 프로그램, 핵심 전략, 항생제 사용량, 항생제 내성

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Chapter 1. Introduction

1.1. Study background

Antimicrobial resistance (AMR) has been a global issue since decades. The increase in antibiotic use in the past has exerted selective pressure on susceptible bacteria, leading to the rise of AMR (1). Previous studies have reported that 30%–50% of antibiotic prescriptions in hospitals are inappropriate, and broad-spectrum antibiotics are overprescribed (2, 3). Antibiotic misuse has led to increased AMR rates, resulting in significant morbidity and mortality (4). In addition to infection prevention and control, aggressive antimicrobial stewardship programs (ASP) to ensure optimal antibiotic use is urgently needed to reduce AMR rates (5).

To optimize the use of antibiotics, the United States Centers for Disease Control and Prevention (CDC) encouraged all hospitals in the United States to implement ASP and outlined the core elements of hospital-based ASP (6). The core elements of ASP consist of 7 parts, which are described in [Table 1] (7).

[Table 1] Core elements of hospital antibiotic stewardship programs

Hospital leadership commitment	Dedicate necessary human, financial, and information technology resources.
Accountability	Appoint a leader or co-leaders, such as a physician and pharmacist, responsible for program management and outcomes.
Pharmacy expertise	Appoint a pharmacist, ideally as the co-leader of the stewardship program, to help lead implementation efforts to improve antibiotic use.
Action	Implement interventions, such as prospective audit and feedback or preauthorization, to improve antibiotic use.
Tracking	Monitor antibiotic prescribing, impact of interventions, and other important outcomes, like *C. difficile* infections and resistance patterns.
Reporting	Regularly report information on antibiotic use and resistance to prescribers, pharmacists, nurses, and hospital leadership.
Education	Educate prescribers, pharmacists, nurses, and patients about adverse reactions from antibiotics, antibiotic resistance, and optimal prescribing.

First, the senior leadership of the hospital, especially the chief medical officer, chief nursing officer, and director of pharmacy, should support the ASP team. They are recommended to make an environment in which the ASP team can dedicate time and technology resources. Then, a physician and a pharmacist responsible for managing the ASP are appointed as a leader or co-leaders. In addition, there are pharmacists specializing in ASP, which give expertise in the proper use of antibiotics. The ASP team takes responsibility and introduces new ASP actions in the hospital. They track outcomes of the introduced ASP actions, such as antibiotic use data, resistance patterns, and the incidence of *Clostridioides difficile* infection. The next process of ASP consists of the periodic reports of this data, promotion of the importance of ASP to clinicians, and making changes in antibiotic prescription through education.

Some hospitals applied the CDC guidelines and successfully reduced the duration of antibiotic use, length of hospital stay, and rate of *C. difficile* infection (8, 9). In addition, treatment failures and adverse effects caused by unnecessary antibiotic use could be reduced through optimizing the use of antibiotics (8). However, in many countries, including Korea, it is difficult to apply the core elements at a national level due to low compliance by clinicians, lack of expertise, and absence of an appropriate reward structure (10).

Here, we summarize the findings from a tertiary care hospital with limited resources where the core elements of ASP were successfully implemented for over a decade and analyze the effect of the ASP on antibiotic use and AMR rates of five pathogens.

1.2. Hypothesis

Stepwise implementation of the core elements of an ASP would be effective in preventing an increase in the use of antibiotics.

Chapter 2. Methods

2.1. Study population and data collection

This study was conducted at Seoul National University Bundang Hospital (SNUBH), a tertiary care teaching hospital established in 2003 with approximately 900 beds, which has been increased to over 1300 beds in 2013. We retrospectively collected data regarding antibiotic prescription and culture results of all patients hospitalized between January 2010 and December 2019. This study was approved by the Institutional Review Board of SNUBH (No. X-2101-663-902), and the requirement for obtaining written informed consent was waived due to the retrospective nature of the study.

2.2. Hospital leadership and stepwise implementation of the ASP at SNUBH

The ASP implemented at SNUBH has been summarized in [Table 2].

[Table 2] Antimicrobial stewardship activities performed for hospitalized patients at Seoul National University Bundang Hospital until December 2019

ASP core elements	Examples	Initiation
Hospital leadership	Staff involved in ASP activities (on a part-time basis)[a] with over 1300 beds - 2 ID physicians (1 internist and 1 pediatrician) - 3 ID physicians (2 internists and 1 pediatrician) - 4 ID physicians (3 internists and 1 pediatrician)	 May 2003 March 2009 March 2011
	CDSS launched	September 2003
	Pharmacy & therapeutics committee (11) • Establishment of a subcommittee for antibiotics • Promotion to ASP committee • Establishment of a new subcommittee for therapeutic drug monitoring of antibiotics	 September 2003 November 2018 September 2019
Accountability	• Creation of an ASP team consisting of ID specialists, pharmacists, and microbiology laboratory staff • Regular handshake stewardship for the hematology unit	November 2018 March 2006
Pharmacy expertise	• ID training for the pharmacists • Designation of one full-time ID pharmacist for ASP activities	March 2013 May 2019

Action	**Preauthorization** • Restricted antibiotic approval only, such as broad-spectrum antibiotics (e.g. carbapenems, glycopeptides, and polymyxins), antifungals (e.g. newer azoles, and liposomal amphotericin-B), and antivirals (e.g. ganciclovir) • Post-prescription review and feedback through automatic consultation of ID physicians.	 May 2003 August 2011
	Prospective audit and feedback • Electronic alerts with automatic consultation of ID physicians for patients with positive blood cultures (12) • Prevention of redundant combinations of metronidazole or clindamycin with other anti-anaerobic antibiotics (13) • Prospective review of nine antibiotics: azithromycin, cefoxitin, clindamycin, colistimethate, sulfamethoxazole/trimethoprim, anidulafungin, fluconazole, voriconazole, and acyclovir • Intravenous to oral conversion of administration of fluoroquinolone and metronidazole (14) • "Shorter is better" campaign targeting antibiotics prescribed for more than 2 weeks, and all in-hospital long-term antibiotic prescriptions were monitored daily.	 August 2011 July 2013 July 2014 August 2015 August 2018
	Facility-specific treatment guidelines • Shortening of duration of antibiotic administration for surgical antibiotic prophylaxis via the clinical pathway (15) - less than 5 days - less than 3 days - less than 2 days • Biannual updating of facility-specific guidelines for solid organ transplantation in collaboration with the transplantation teams	 June 2003 November 2009 April 2015 April 2009 Last updated in 2019
	Pharmacologic intervention • Vancomycin loading using the computerized CDSS • Renal dosing guidance - computerized dosing recommendations (16) - dosing pamphlets released to the prescribers • Daily alerts, particularly for the pharmacists, using an ASP review sheet in the electronic medical record (11)	 July 2016 April 2006 July 2020 November 2016

	- intravenous to oral conversion - inappropriate dosing according to indications and renal function - drug interactions and adverse events	
	Rapid diagnostics • Multiplex polymerase chain reaction performed in patients with bacteremia with clusters of gram-positive cocci (18)	February 2012
Tracking	**Antibiotic use measures** • Monitoring surgical antibiotic prophylaxis • Monitoring antibiotic administration data from the clinical database (defined daily dose, day of therapy, and length of therapy per 1000 patient-days) • Hospital-wide point prevalence survey on the appropriateness of antibiotic prescription	October 2007 July 2014 August 2018
	Outcome measures • Biweekly meetings with the staff at the microbiology laboratory and infection control office - changed to weekly meetings • Daily morning conference with the pharmacists	May 2003 March 2017 March 2013
Reporting	• Regular report on antibiotic resistance rates for important clinical isolates by newsletter • Regular report on antibiotic use • Regular report on the proportion of clinical consultations for therapeutic drug monitoring of antibiotics administered for over 7 days	December 2004 April 2009 December 2019
Education	• Education programs for physicians and pharmacists about antibiotic choice, dosage, and treatment duration for common infections such as pneumonia, urinary tract infection, and skin and soft tissue infection • Educational materials developed by elective course internal medicine residents and shared with other physicians • Annual ASP symposium for health-system pharmacists	March 2016 March 2016 October 2019

ASP: antimicrobial stewardship program; ID: infectious disease; CDSS: Clinical decision support system

[a] Part-time basis is a concept as opposed to full-time equivalents, and full-time equivalents are defined as working 52 hours per week for ASP-related activities according to the labor laws in Korea.

At first, only one internist and one pediatrician specialized in infectious diseases (ID) were involved in developing the ASP at SNUBH with over 900 beds in 2003. As the hospital expanded, the number of ID physicians also increased, and from 2011, 4 physicians for over 1300 beds were included in the ASP team. A team consisting of ID physicians, pharmacists, infection control nurses, and microbiology laboratory staff was involved on a part-time basis in the ASP. Although the team was not recognized as an official department initially, they held meetings every or every other week with all members, and ID physicians and pharmacists met every morning for decision making about the ASP, and finally they became an official team in November 2018. Previously, the ASP team did not have full-time medical personnel, but from March 2019, a full-time ID pharmacist was officially appointed as a co-leader.

The first action performed as a part of the ASP was preauthorization of restricted antibiotics, such as broad-spectrum antibacterial agents, antifungals, and antivirals. Since August 2011, as the number of ID physicians increased, we implemented a system in which ID physicians were automatically consulted before the restricted antibiotics were prescribed. If the prescription was approved by an ID physician, antibiotics could be administered for 7 days, and in the absence of a decision by an ID physician, antibiotics could be prescribed for 3 days for urgent use. If the ASP team determined that the antibiotic use was inappropriate, they recommended an alternative treatment in their consultation note, and the pharmacy did not prepare the prescribed antibiotics. At the same time, when the results of blood culture indicated bacteremia, ID physicians were also automatically consulted, and the ASP team recommended the type and duration of antibiotics to be administered (12).

Next, the duration of routine perioperative antibiotic prophylaxis was first changed to less than 5 days, then the duration was gradually decreased to 3 days, 2 days, and 24 hours. This was reflected in the clinical decision support systems (CP) (15). CP typically comprises detailed sets of orders that describe how a patient should be cared for, from the time of admission to discharge, and the dose and duration of prophylactic antibiotics for each CP are tailored down to a specific surgery type. If a physician propose a new CP for a surgery, the proposed CP is reviewed by the ASP team. Also, this was made possible by the implementation of the national hospital evaluation program for arthroplasty, gastrectomy, and hysterectomy, which began in 2007 (17). The application of antibiotic prophylaxis guidelines was subsequently extended to other surgeries.

In addition, as part of the pharmacist-based ASP, the concurrent administration of antianaerobic antimicrobials were monitored daily except weekends, and clinicians were recommended to modify the prescription (13). A redundant antianaerobic combination was defined as the concurrent administration of either metronidazole or clindamycin and an antibiotics with antianaerobic activity, such as cephamycins, beta-lactam/beta-lactamase inhibitors, moxifloxacin, carbapenem, or tigecycline. If the indication of the combination was not appropriate, like treating *C. difficile* infection, and toxic shock syndrome, the pharmacist made a consultation note on the electronic medical records by using a text template without incentive or disincentive to follow the recommendation.

After the establishment of these relatively simple activities, more aggressive ASP activities were gradually added with the consent of the clinicians. For example, the ID pharmacists, as ASP co-leaders, performed additional activities to reduce the use of redundant intravenous fluoroquinolones (FQ) (14). Every 2 to 3 times a week, the ID pharmacist tracks intravenous FQ use and if the case needs intervention, left a note of recommendation for the intervention in the electronic medical record. The note included the primary site of infection, purpose of antimicrobial administration, and treatment period. Also, the information on oral equivalent dose and drug interactions was included. Moreover, as part of a “shorter is better” campaign, all in-hospital antibiotic prescriptions with a duration of more than 14 days were monitored daily. The ID pharmacist assessed them for appropriateness and advised the physicians to discontinue administration in cases where it was plausible.

In recent years, to educate and inform clinicians about ASP activities with the aim of long-term reduction of antibiotic prescription, ID specialists regularly provide lectures to residents and clinicians about antibiotic choice, dosage, and treatment duration for common infections such as pneumonia, urinary tract infection, and skin and soft tissue infection. Additionally, a booklet on antibiotic dosage according to renal function was created and distributed to clinicians. The status and outcomes of these ASP activities are tracked and discussed with all the ID physicians and pharmacists every morning.

2.3. Definitions

Data regarding antibiotic use were extracted from clinical data warehouse (19), particularly for the following six classes of broad-spectrum antibiotics that are associated with AMR (20): 3GC, fourth-generation cephalosporins, beta-lactam/beta-lactamase inhibitors, FQ, glycopeptides, and carbapenems. Antibiotic use was quantified as days of therapy (DOT) per 1000 patient-days. The antibiotic resistance rate of five nosocomial pathogens, including *Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa,* and *Acinetobacter baumannii,* were analyzed using WHONET program (21). To avoid duplication, the first isolate of all clinical samples (e.g. blood, sputum, urine, genital swab, and wound swab) from each patient was included. Antimicrobial susceptibility was determined using the disk-diffusion method or VITEK 2 (bioMe´rieux, Marcy L'etoil, France). Each isolate was classified as resistant or non-resistant according to the Clinical and Laboratory Standards Institute criteria (22). The proportion of isolates of each bacteria species resistant to antibiotics was assessed as follows: *S. aureus* (oxacillin), *E. coli* and *K. pneumoniae* [3GC (cefotaxime or ceftazidime), and FQ (ciprofloxacin)], and *P. aeruginosa* and *A. baumannii* [3GC (ceftazidime), FQ, and carbapenems].

2.4. Comparisons with Korean national data

To compare the use of antibiotics at SNUBH with that at the national level, we reviewed the Korean National Health Insurance Service (NHIS) database. The NHIS is the sole health insurance provider in Korea and is responsible for all hospitalization-related costs. We randomly extracted data regarding 40% of all antibiotic-related claims data for hospitalized patients at Korean tertiary care hospitals from 2010 to 2019. Antibiotic use was converted into DOT per 1000 patient-days using annual inpatient data. Data on the AMR rate at Korean general hospitals with over 100 beds from 2010 to 2016 were obtained from the national surveillance program, the Korean Antimicrobial Resistance Monitoring System (KARMS) (23) and that from 2017 to 2019 were obtained from Korea Global Antimicrobial Resistance Surveillance System (Kor-GLASS) (24). Antibiotic-resistant pathogens isolated from clinical samples at designated hospitals were investigated for each year, and the changes in AMR rate were compared between SNUBH and the nationwide data.

2.5. Statistical analysis

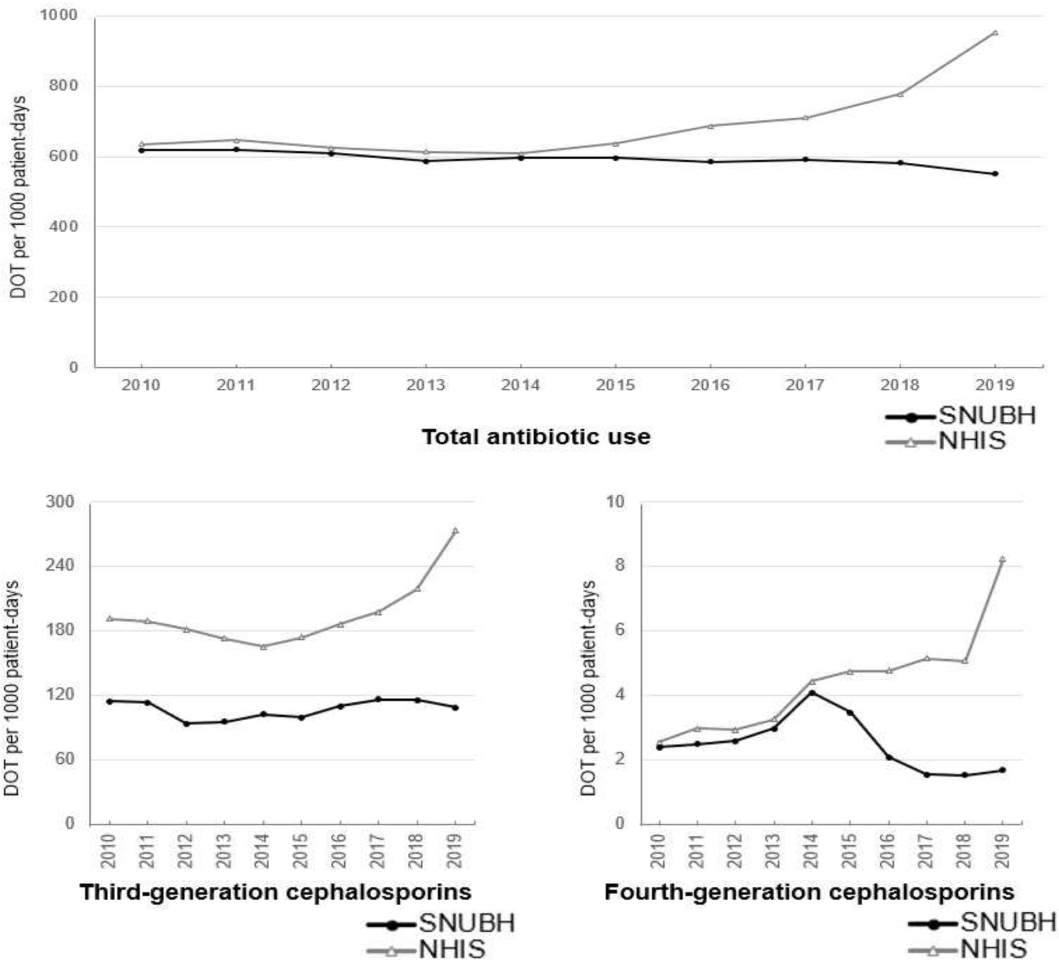
The trends of antibiotic use and AMR rates were analyzed using nonparametric two-sided correlated seasonal Mann - Kendall tests, and $P < 0.05$ means that the trend tended to statistically significantly increase or decrease. The magnitude of change per year was estimated using the Sen's method (25). Statistical analyses were performed using R version 4.1.1 (R Core Team, Vienna, Austria) and Python statistical software version 3.7.4 (Python Software Foundation, Oregon, the United States).

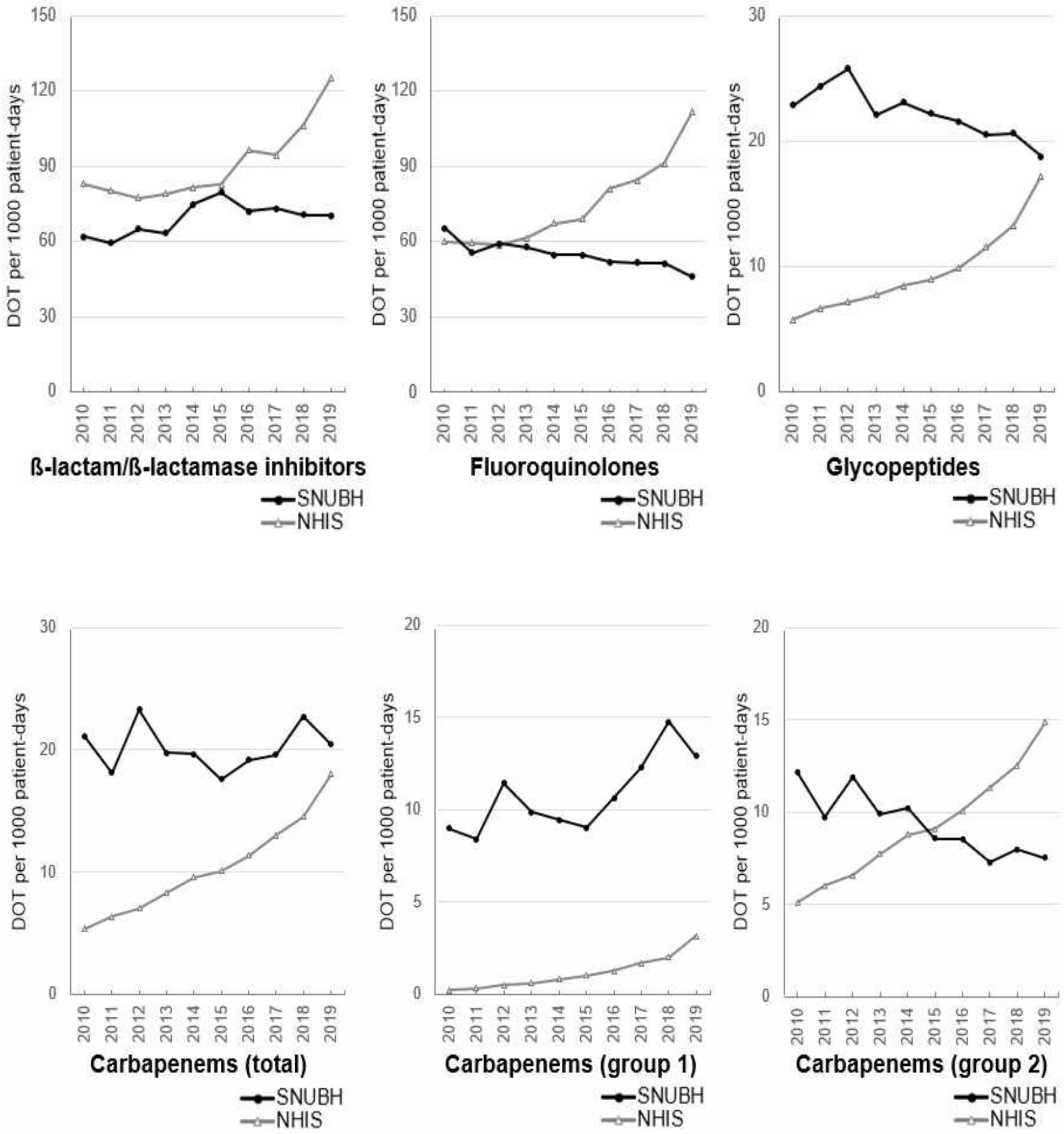
Chapter 3. Results

3.1. Antibiotic use

[Fig. 1] shows the DOT with antibiotics per 1000 patient-days over the course of 10 years at SNUBH. Total antibiotic use significantly decreased by approximately 10.80% from 2010 to 2019 (Mann - Kendall tests, $P < 0.01$, [Table 3 and 4]).

[Fig. 1] Trends of antibiotic use (days of therapy per 1000 patient-days) at Seoul National University Bundang Hospital from 2010 to 2019.





DOT: days of therapy; SNUBH: Seoul National University Bundang Hospital; NHIS: National Health Insurance Service

[a] Carbapenems (group 1): ertapenem; Carbapenems (group 2): meropenem, imipenem-cilastatin, and doripenem.

[Table 3] Comparison between antibiotic use (days of therapy per 1000 patient-days) at Seoul National University Bundang Hospital and in National Health Insurance Service data[a] from 2010 to 2019

Antibiotics	Data	Year									
		2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
All antibacterial agents	SNUBH	617.49	618.92	608.28	587.00	596.28	596.27	585.71	591.00	582.34	550.81
	NHIS	635.44	645.37	623.69	613.47	608.42	636.31	686.99	710.86	777.37	952.02
Third-generation cephalosporins	SNUBH	115.04	113.85	93.77	95.60	102.86	99.94	110.17	116.41	115.77	108.86
	NHIS	191.78	189.06	181.66	172.94	165.78	174.56	186.53	197.91	219.30	273.67
Fourth-generation cephalosporins	SNUBH	2.40	2.50	2.59	2.97	4.09	3.47	2.09	1.56	1.53	1.69
	NHIS	2.55	2.98	2.93	3.27	4.44	4.75	4.77	5.15	5.08	8.23
ß-lactam/ß-lactamase inhibitors	SNUBH	62.01	59.46	65.09	63.42	74.77	79.67	72.01	73.25	70.70	70.28
	NHIS	83.08	80.04	77.51	79.00	81.64	82.56	96.30	94.41	106.35	125.00
Fluoroquinolones	SNUBH	65.29	55.60	59.15	57.88	54.81	54.82	52.05	51.55	51.42	46.15
	NHIS	60.21	59.39	58.58	61.60	67.28	69.05	81.01	84.41	91.16	111.82
Glycopeptides	SNUBH	22.88	24.42	25.79	22.08	23.10	22.20	21.60	20.55	20.65	18.81
	NHIS	5.79	6.67	7.17	7.72	8.48	8.99	9.87	11.55	13.31	17.24
Carbapenems[b]	SNUBH	21.10	18.09	23.30	19.73	19.64	17.57	19.16	19.56	22.70	20.42
	NHIS	5.33	6.32	7.03	8.31	9.56	10.10	11.32	12.98	14.50	18.01
Group 1	SNUBH	8.97	8.39	11.43	9.85	9.45	9.01	10.61	12.29	14.75	12.91
	NHIS	0.22	0.31	0.47	0.59	0.80	1.02	1.24	1.67	1.98	3.15
Group 2	SNUBH	12.13	9.70	11.87	9.88	10.19	8.56	8.55	7.27	7.95	7.51
	NHIS	5.11	6.01	6.56	7.72	8.77	9.08	10.08	11.31	12.52	14.86

SNUBH: Seoul National University Bundang Hospital; NHIS: National Health Insurance Service

[a] The NHIS is the sole health insurance provider in Korea and is responsible for all hospitalization-related costs. We reviewed 40% of all antibiotic-related claim data of patients admitted to Korean tertiary care hospitals.

[b] Group 1 carbapenem: ertapenem. Group 2 carbapenem: meropenem, imipenem-cilastatin, and doripenem.

[Table 4] Mann - Kendall test and Sen's slope[a] for antibiotic use at Seoul National University Bundang Hospital and in National Health Insurance Service data from 2010 to 2019

Antibiotics	Data	Mann - Kendall test		Sen's slope (95% CI)
		Tau	*P*	
All antibacterial agents	SNUBH	−0.78	<0.01	−5.29 (−8.51 to −3.46)
	NHIS	0.56	0.03	23.87 (0.17 to 42.24)
Third-generation cephalosporins	SNUBH	0.20	0.47	1.20 (−1.19 to 4.03)
	NHIS	0.33	0.21	4.53 (−3.45 to 11.97)
Fourth-generation cephalosporins	SNUBH	−0.29	0.28	−0.12 (−0.29 to 0.16)
	NHIS	0.91	<0.01	0.37 (0.23 to 0.63)
ß-lactam/ß-lactamase inhibitors	SNUBH	0.33	0.21	1.35 (−0.66 to 2.51)
	NHIS	0.64	0.01	3.76 (0.93 to 6.18)
Fluoroquinolones	SNUBH	−0.87	<0.01	−1.58 (−2.13 to −0.85)
	NHIS	0.87	<0.01	5.16 (3.01 to 6.76)
Glycopeptides	SNUBH	−0.69	0.01	−0.56 (−0.87 to −0.28)
	NHIS	1.00	<0.01	0.88 (0.64 to 1.32)
Carbapenems[b]	SNUBH	−0.02	1.00	−0.03 (−0.41 to 0.59)
	NHIS	1.00	<0.01	1.17 (1.00 to 1.46)
Group 1	SNUBH	0.60	0.02	0.51 (0.16 to 0.95)
	NHIS	1.00	<0.01	0.23 (0.17 to 0.33)
Group 2	SNUBH	−0.73	<0.01	−0.51 (−0.71 to −0.26)
	NHIS	1.00	<0.01	0.93 (0.84 to 1.15)

CI: confidence interval; SNUBH: Seoul National University Bundang Hospital; NHIS: National Health Insurance Service

[a] Trend analyses were performed using nonparametric two-sided correlated seasonal Mann - Kendall tests, with $P < 0.05$ indicating that the trend statistically significantly increased or decreased. The magnitude of change per year was estimated using Sen's method.

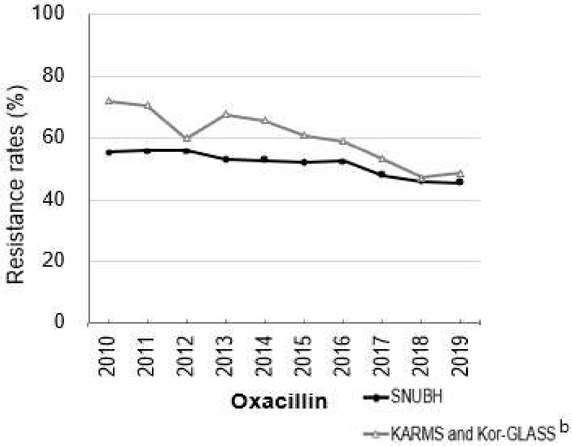
[b] Group 1 carbapenem: ertapenem. Group 2 carbapenem: meropenem, imipenem-cilastatin, and doripenem.

Glycopeptide (P < 0.01) and FQ (P < 0.01) use gradually decreased, while 3GC (P = 0.48) and fourth-generation cephalosporin (P = 0.29) and beta-lactam/beta-lactamase inhibitors (P = 0.21) use did not significantly change. There was no significant change in carbapenem use, although the use of the group 1 carbapenem (ertapenem) increased (P = 0.02). Total antibiotic use was lower in SNUBH data than in NHIS data, and the difference between them widened further, with SNUBH 42.14% lower than NHIS in 2019. In addition, the use of every broad-spectrum antibiotic except 3GC continuously increased at other Korean tertiary care hospitals. Although glycopeptide and carbapenem use were higher in SNUBH data than in NHIS data, all kinds of broad-spectrum antibiotic prescriptions except group 1 carbapenem showed no increase, and at least maintained a stable level at SNUBH.

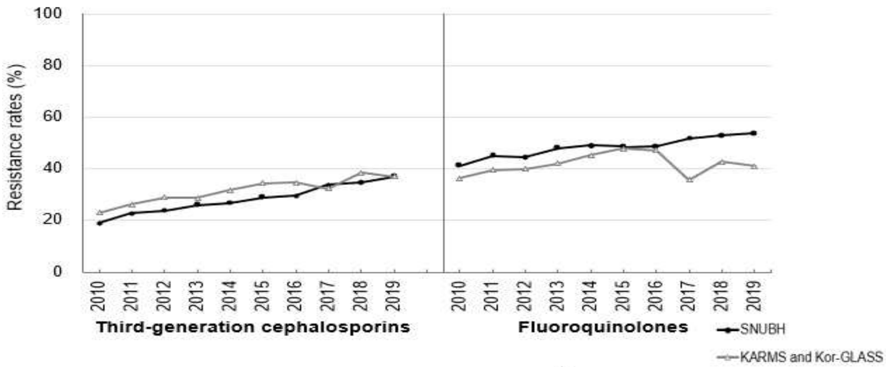
3.2. AMR rates

[Fig. 2] shows the change in AMR rates by bacterial species. At SNUBH, the methicillin-resistance rate of *S. aureus* significantly decreased (Mann - Kendall tests, P < 0.01, [Table 5 and 6]).

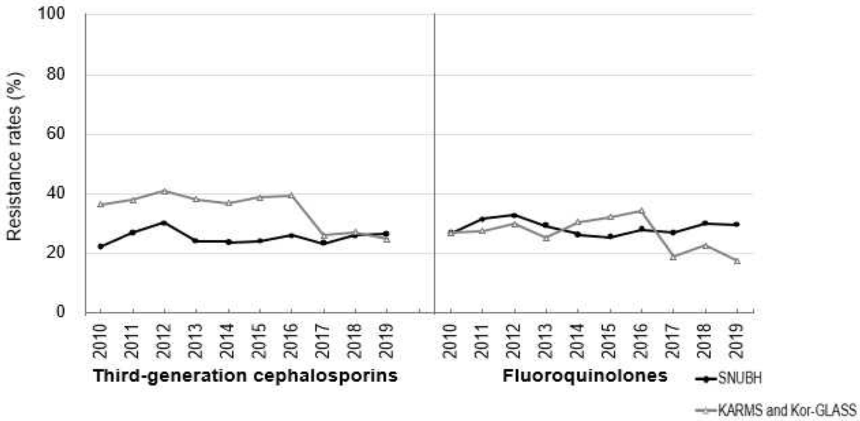
[Fig. 2] Changes in antibiotic resistance rates at Seoul National University Bundang Hospital from 2010 to 2019[a].



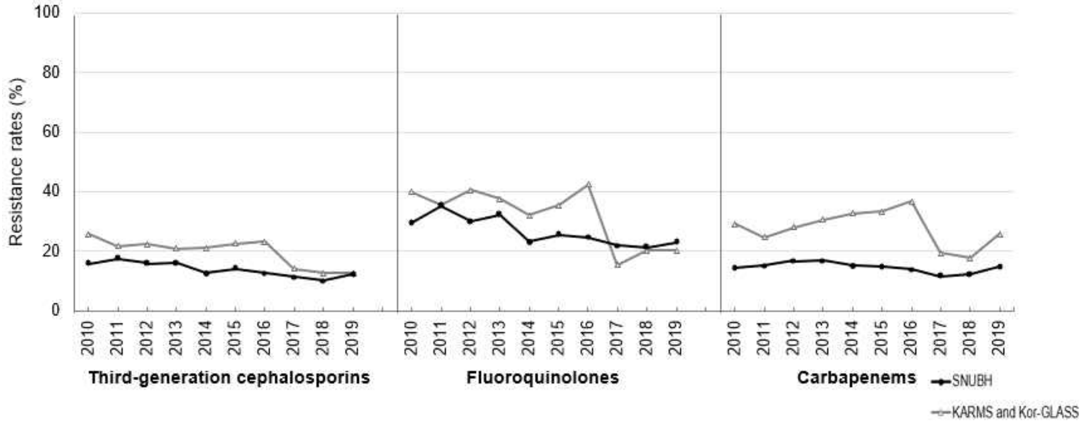
Staphylococcus aureus



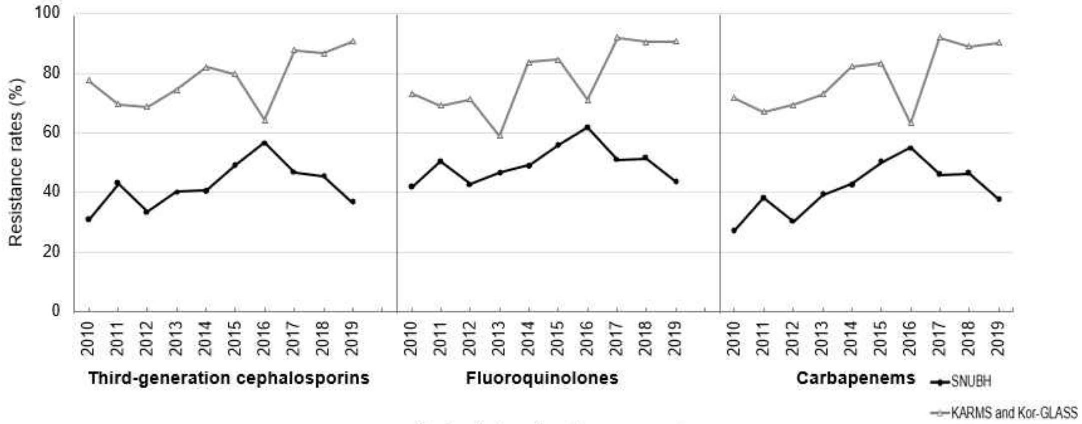
Escherichia coli [c]



Klebsiella pneumoniae [c]



Pseudomonas aeruginosa



Acinetobacter baumannii

SNUBH: Seoul National University Bundang Hospital; KARMS: Korean Antimicrobial Resistance Monitoring System; Kor-GLASS: Korea Global Antimicrobial Resistance Surveillance System

[a] Antimicrobial susceptibility was determined using the disk-diffusion method or VITEK 2 (bioMe´rieux, Marcy L'etoil, France). Each isolate was classified into resistant or non-resistant according to the Clinical and Laboratory Standards Institute criteria. The proportions of isolates of each bacteria species resistant to the following antibiotics were assessed: oxacillin, third-generation cephalosporins (cefotaxime or ceftazidime), fluoroquinolones (ciprofloxacin), and carbapenems (imipenem).

[b] Data on the AMR rate at Korean general hospitals with over 100 beds from 2010 to 2016 were obtained from KARMS, and that from 2017 to 2019 were obtained from Kor-GLASS.

[c] The proportions of carbapenem-resistant *E. coli* and *K. pneumoniae* at SNUBH remained less than 1.14%.

[Table 5] Comparison between antimicrobial resistance rates (%) at Seoul National University Bundang Hospital and those in the Korean Antimicrobial Resistance Monitoring System data from 2010 to 2019[a]

Bacteria	Antibacterial agents	Data	Period									
			2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
S. aureus	Oxacillin	SNUBH	55.4	55.8	55.8	53.0	52.7	52.0	52.5	47.9	45.9	45.5
		KARMS	72.0	70.6	60.0	67.7	65.7	60.9	58.9	53.2	47.1	48.6
E. coli[b]	Third-generation cephalosporins	SNUBH	18.9	22.7	23.8	25.9	26.8	28.9	29.6	33.9	34.7	37.1
		KARMS	23.1	26.3	29.0	28.7	31.8	34.5	34.6	32.4	38.6	37.1
	Fluoroquinolones	SNUBH	41.4	45.1	44.4	48.1	49.2	48.6	48.7	52.0	52.9	53.7
		KARMS	36.3	39.5	40.0	42.1	45.2	47.8	47.1	35.8	42.7	41.1
K. pneumoniae[b]	Third-generation cephalosporins	SNUBH	22.3	26.9	30.4	24.1	23.9	24.2	26.0	23.3	26.0	26.5
		KARMS	36.5	37.9	41.0	38.1	36.9	38.7	39.5	26.1	27.1	24.9
	Fluoroquinolones	SNUBH	26.8	31.5	32.8	29.3	26.4	25.5	27.9	26.9	30.2	29.9
		KARMS	26.9	27.6	30.0	25.3	30.6	32.2	34.3	18.9	22.7	17.6
P. aeruginosa	Third-generation cephalosporins	SNUBH	15.8	17.6	16.0	16.1	12.6	14.1	12.7	11.5	10.2	12.3
		KARMS	25.7	21.8	22.5	20.9	21.1	22.6	23.2	14.1	12.7	12.6
	Fluoroquinolones	SNUBH	29.5	35.4	30.0	32.4	23.3	25.6	24.8	22.0	21.4	23.1
		KARMS	40.0	35.7	40.6	37.6	32.1	35.5	42.4	15.4	20.4	20.3
	Carbapenems	SNUBH	14.3	15.3	16.9	17.0	15.3	14.8	13.9	11.6	12.2	14.8
		KARMS	29.2	24.7	28.1	30.6	32.7	33.3	36.7	19.5	17.8	25.8
A. baumannii	Third-generation cephalosporins	SNUBH	30.7	42.9	33.6	40.3	40.7	49.2	56.7	46.8	45.5	36.8
		KARMS	77.6	69.6	68.8	74.4	82.0	79.7	64.3	87.7	86.7	90.8
	Fluoroquinolones	SNUBH	41.7	50.4	42.7	46.7	49.1	55.8	61.8	51.1	51.4	43.6
		KARMS	73.2	69.3	71.3	59.0	83.7	84.6	71.0	92.1	90.5	90.8
	Carbapenems	SNUBH	27.2	38.2	30.4	39.2	42.8	50.1	55.1	46.1	46.4	37.7
		KARMS	71.7	67.1	69.5	73.0	82.2	83.4	63.2	92.1	89.0	90.3

SNUBH: Seoul National University Bundang Hospital; KARMS: Korean Antimicrobial Resistance Monitoring System

[a] Antimicrobial susceptibility was determined using the disk-diffusion method or VITEK 2 (bioMe´rieux, Marcy L'etoil, France). Each isolate was classified as resistant or non-resistant, according to the Clinical and Laboratory Standards Institute criteria. The proportions of isolates of each bacteria species resistant to the following antibiotics were assessed: oxacillin, third-generation cephalosporins (cefotaxime or ceftazidime), fluoroquinolones (ciprofloxacin), and carbapenems (imipenem). National surveillance data on antibiotic resistance rates from 2010 to 2016 at Korean general hospitals with over 100 beds were obtained from KARMS, and that from 2017 to 2019 were obtained from Korea Global Antimicrobial Resistance Surveillance System.

[b] The proportions of carbapenem-resistant *E. coli* and *K. pneumoniae* at SNUBH remained less than 1.14%.

[Table 6] Mann - Kendall test and Sen's slope[a] for antimicrobial resistance rates (%) at Seoul National University Bundang Hospital and those in the Korean Antimicrobial Resistance Monitoring System data from 2010 to 2019[b]

Bacteria	Antibacterial agents	Data	Mann - Kendall test		Sen's slope (95% CI)
			Tau	*P*	
S. aureus	Oxacillin	SNUBH	−0.85	<0.01	−1.24 (−1.60 to −0.67)
		KARMS	−0.82	<0.01	−2.75 (−3.63 to - 1.63)
E. coli	Third-generation cephalosporins	SNUBH	1.00	<0.01	1.90 (1.55 to 2.05)
		KARMS	0.82	<0.01	1.60 (1.06 to 2.00)
	Fluoroquinolones	SNUBH	0.87	<0.01	1.22 (0.90 to 1.50)
		KARMS	0.29	0.28	0.53 (−0.70 to 2.08)
K. pneumoniae	Third-generation cephalosporins	SNUBH	−0.02	1.00	−0.04 (−0.77 to 0.50)
		KARMS	−0.29	0.28	−1.29 (−2.40 to 0.32)
	Fluoroquinolones	SNUBH	−0.02	1.00	−0.10 (−0.90 to 0.75)
		KARMS	−0.16	0.59	−0.65 (−1.98 to 1.15)
P. aeruginosa	Third-generation cephalosporins	SNUBH	−0.64	0.01	−0.75 (−1.15 to −0.37)
		KARMS	−0.51	0.05	−1.38 (−1.68 to −0.10)
	Fluoroquinolones	SNUBH	−0.64	0.01	−1.40 (−2.12 to −0.57)
		KARMS	−0.47	0.07	−2.19 (−3.80 to 0.30)
	Carbapenems	SNUBH	−0.39	0.15	−0.37 (−0.85 to 0.10)
		KARMS	−0.02	1.00	−0.33 (−1.72 to 2.10)
A. baumannii	Third-generation cephalosporins	SNUBH	0.33	0.21	1.45 (−0.78 to 3.55)
		KARMS	0.47	0.07	2.40 (−0.80 to 3.33)
	Fluoroquinolones	SNUBH	0.38	0.15	0.94 (−0.85 to 2.82)
		KARMS	0.51	0.05	2.63 (0.30 to 4.16)
	Carbapenems	SNUBH	0.47	0.07	1.60 (−0.06 to 4.58)
		KARMS	0.56	0.03	2.88 (1.20 to 4.17)

CI: confidence interval; SNUBH: Seoul National University Bundang Hospital; KARMS: Korean Antimicrobial Resistance Monitoring System

[a] Trend analyses were performed using nonparametric two-sided correlated seasonal Mann - Kendall tests, with $P < 0.05$ indicating that the trend statistically significantly increased or decreased. The magnitude of change per year was estimated using Sen's method.

[b] National surveillance data on antibiotic resistance rates from 2010 to 2016 at Korean general hospitals with over 100 beds were obtained from KARMS, and that from 2017 to 2019 were obtained from Korea Global Antimicrobial Resistance Surveillance System.

The rates of resistance to 3GC and FQ increased in *E. coli* ($P < 0.01$), whereas the rates were not significantly changed in *K. pneumoniae* ($P = 1.00$), and decreased in *P. aeruginosa* ($P = 0.01$). The proportion of carbapenem-resistant *A. baumannii* (CRAB) seems to be increased, but the trend was not statistically significant ($P = 0.07$).

The trend of methicillin-resistant *S. aureus* (MRSA) colonization was consistently lower, and that of 3GC- and FQ-resistant *E. coli* colonization was higher in the SNUBH data than in the KARMS and Kor-GLASS data. Although the carbapenem resistance rate of *A. baumannii* in the SNUBH data was 40% lower than that in the KARMS data in 2010, the difference between the two rates decreased over time.

Chapter 4. Discussion

The ASP team at SNUBH not only introduced new activities one by one but also ensured that they were continued. With the implementation of strong ASP at SNUBH, not only total antibiotics but also broad-spectrum antibiotics prescriptions except group 1 carbapenem showed no increase as compared to the nationwide trend. Although AMR rates of 3GC-resistant *E. coli* increased like nationwide data, that of other important pathogens did not increase at SNUBH.

There are a few studies on the application and outcomes of ASP implementation. Although most of them were single-center studies, they showed that the use of antibiotics (especially carbapenems) and rates of carbapenem-resistant *P. aeruginosa* (CRPA) and CRAB reduced after ASP implementation (26, 27). However, many countries with insufficient medical resources are finding it difficult to realize the necessity and cost-effectiveness of ASP. Limited human and fiscal resources are regarded as the main barriers to ASP implementation in the Asia-Pacific region (28). Despite such environmental constraints, when ASP was combined with infection control, it reduced not only antibiotic consumption, but also hospital-acquired infection rates without worsening clinical outcomes (29). While Korea is a relatively high-income country, there is insufficient support for ASP: only one ID physician per 372 beds was involved in the ASP on a part-time basis, and there were less than 300 ID physicians among the 50 million population (30, 31). Moreover, each ID physician performs various roles, including diagnosis and treatment of ID, outpatient-based antibiotic therapy administration, infection prevention and control, education, research, planning a response to emerging ID, and ASP. At SNUBH, although the ASP team had only one full-time worker (an ID pharmacist), antibiotic prescription was maintained at a low level. Based on these results, we attempted to formulate an appropriate ASP implementation model with limited resources.

For implementing new ASP activities, inter-departmental teamwork involving pharmacists, laboratory medicine physicians, and infection control nurses as well as support from the senior leadership are vital. To increase clinician compliance, we gradually expanded the ASP activities based on small successes. For example, the duration of routine perioperative antibiotic prophylaxis was changed to less than 5 days, and this was reflected in the clinical decision support systems, as shown in a previous study (32). After checking that the rate of surgical site infections did not increase, the duration was gradually decreased to 3 days, 2 days, and 24 hours, with the consent of surgeons (15). Moreover, it was relatively simple and intuitional to reduce redundant combinations of metronidazole or clindamycin with other anti-anaerobic antibiotic agents, and it allowed clinicians to recognize the importance of ASP (13). Based on these successes, we expanded the monitoring of specific antibiotic use, resulting in changes such as modification of the FQ administration route from intravenous to oral, and intervention for all long-term (over 2 weeks) antibiotic prescriptions.

The designation of an ID pharmacist as a co-leader was important for maintaining the expanded ASP. The addition of new activities alongside the continuation of existing ASP activities led to a steady decrease in total antibiotic use. As there are only a few pharmacists available to lead hospital ASPs in Korea, there is an urgent need to provide support for human resource development. To further train ID pharmacists and improve their expertise, various certification programs about ASP including academic societies need to be introduced in Korea.

In this study, the proportion of MRSA decreased, which might have been related to decreased FQ use, as mentioned in a previous study (33). Although the reason remains unclear, this trend has been observed worldwide (34). Nevertheless, the use of glycopeptides has not declined globally (35) or in other tertiary care hospitals in Korea. Therefore, the decrease in glycopeptide use at SNUBH was not only due to a decreased rate of MRSA but also due to several ASP activities. For example, preauthorization of glycopeptides and using routine multiplex polymerase chain reaction in patients with bacteremia with gram-positive cocci in clusters resulted in a reduction of the duration of vancomycin administration (18). Thus, regardless of the decreased rate of MRSA, aggressive ASP interventions are required to avoid unnecessary glycopeptide use in patients with conditions such as community-acquired pneumonia and neutropenic fever (36, 37).

3GC and beta-lactam/beta-lactamase inhibitors were used to treat most of the common infections such as hepatobiliary and gastrointestinal tract infection, skin and soft tissue infection, urinary tract infection, and pneumonia. Although these antibiotics were not restricted or monitored if used for less than 2 weeks, their use did not significantly increase at SNUBH, possibly because education about the optimal empirical antibiotic therapy for common infections was periodically provided to physicians. Since the ASP team cannot monitor the prescription of each antibiotic, ASP activities with a low work burden, such as education, should be consistently provided.

Although the use of carbapenems, particularly group 2 carbapenems, did not significantly change, ertapenem use increased at SNUBH, possibly due to an increase in resistance to 3GC (especially in *E. coli*). Replacing group 2 carbapenems with ertapenem for empirical antibiotic therapy in critically ill patients might help to reduce CRPA and CRAB colonization; however, previous studies on this strategy have obtained conflicting results (38). At SNUBH, the rate of colonization with CRPA did not increase. Furthermore, the absolute rate of CRAB colonization remained lower than those calculated from the data of the KARMS and Kor-GLASS. However, since the rate of colonization with CRAB increased despite no increase in carbapenem use at SNUBH, additional ASP strategies are needed for reducing CRAB colonization, and further prospective trials on this topic are needed.

One of the limitation of the study is that it is difficult to explain the causal relationship between strict ASP and decreasing AMR rates. [Table 7] summarizes several studies showing the significant association between antibiotic use and AMR rates.

[Table 7] Studies showed the significant association between antibiotic use and antibiotic resistance rates

Reference, year	Setting for use of antibiotics	Organisms	Findings
Goossens H, et al. (39), 2005	Outpatient	*Streptococcus pneumoniae*	The significant Spearman correlations was shown between antibiotic use for outpatient in Europe and antibiotic resistance of *S. pneumoniae*.
Gagliotti C, et al. (40), 2006	Outpatient	*Streptococcus pyogenes*	A significant association between the number of macrolide prescriptions for children and erythromycin resistance of *S. pyogenes* was shown, and recent prescription of a macrolide is a predictor of erythromycin resistance.
Gagliotti C, et al. (41), 2007	Outpatient	*Escherichia coli*	Prescription of fluoroquinolones during the previous 6 months was associated independently with the emergence of ciprofloxacin-resistant *E. coli* in the urine samples of outpatients.
Kärpänoja P, et al. (42), 2008	Inpatient	*Streptococcus pneumoniae*	Among the *S. pneumoniae* isolates, a statistically significant connection was found between regional trimethoprim-sulfamethoxazole consumption and resistance.
Schneider-Lindner V, et al. (43), 2009	Inpatient	*Staphylococcus aureus*	Risk for community-acquired methicillin-resistant *S. aureus* increased with number of antimicrobial drug prescriptions in the previous year, and odds ratio was highest for fluoroquinolones and macrolides.
Bergman M, et al. (44), 2009	Outpatient	*Escherichia coli*	Statistically significant associations were found for nitrofurantoin use versus nitrofurantoin resistance, cephalosporin use versus nitrofurantoin resistance, amoxicillin use versus fluoroquinolone resistance, and fluoroquinolone use versus ampicillin resistance of *E. coli* isolates, mainly from urine samples.
Lee DS et al. (45), 2010	Outpatient and inpatient	*Escherichia coli*	The prevalence of ESBL-producing *E. coli* was significantly related to cefaclor medication.
Altunsoy A, et al. (46), 2011	Inpatient	*Escherichia coli, Klebsiella, Pseudomonas, Acinetobacter*	A negative correlation was observed between the ceftriaxone consumption and the prevalence of ceftriaxone resistant *E. coli* and *Klebsiella* spp. The decreased use of carbapenems was correlated with decreased carbapenems-resistant *Pseudomonas* spp. and *Acinetobacter* spp.
Sun L, et al. (47), 2012	Antibiotic prescription data from retail pharmacies	*Escherichia coli, Staphylococcus aureus*	Antibiotic resistance of *E. coli* was significantly correlated with 1 month lagged antibiotic prescriptions for aminopenicillins and fluoroquinolones. Ciprofloxacin-resistant Methicillin-resistant *S. aureus* were also significantly correlated with a 1-month lag fluoroquinolone prescriptions.
Megraud F, et al. (48), 2013	Outpatient	*Helicobacter pylori*	A significant association was found between quinolone use and the proportion of levofloxacin resistance of *H. pylori* and between the use of long-acting macrolides and clarithromycin resistance.

Although the sample size of the studies, target antibiotics, and antibiotic-resistant bacteria are all different, there is a significant relationship between antibiotic use and antibiotic resistance, which is also confirmed in the meta-analysis results (49). However, in SNUBH, the trends of AMR rates of most pathogens were similar to those calculated from KARMS and Kor-GLASS data, even though we could decrease or at least avoid an increase in the use of broad-spectrum antibiotic agents. To reduce AMR rates, several factors other than antibiotic use should be also controlled, such as infection control practices (50), regional increase in AMR, and agricultural use of antibiotics. It is not enough to implement an ASP at one institution, and a nationwide strategy would be needed. In particular, changing the insurance system to induce fewer antibiotic prescriptions for outpatients that account for about 80.9% of the total antibiotic prescription in Korea (51), and introducing a system to monitor and regulate the use of veterinary antibiotics would be helpful based on previous guidelines (52).

This study has other limitations. Since the study was retrospective and various ASP-related activities were performed together, the specific effect of each activity could not be distinguished. However, these activities can be expected to ultimately be effective in reducing antibiotic use and antibiotic resistance rates based on past experience (53). In addition, the nationwide data and SNUBH data cannot be directly compared because the surveillance systems are different. Also, although antibiotic use in SNUBH and that in other tertiary care hospitals were compared, in hospitals smaller than SNUBH, clinicians may prefer to prescribe different types of antibiotics, which could lead to have bias. However, the trend of changes in antibiotic use and AMR rates could be compared.

In conclusion, stepwise implementation of the core elements of an ASP outlined by the United States Centers for Disease Control and Prevention was effective in preventing an increase in the total use of antibiotics despite a lack of sufficient manpower. Therefore, beginning with basic activities, step-by-step expansion, and long-term multi-disciplinary teamwork can improve the success and sustainability of an ASP model even in settings with limited resources.

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Abstract

Stepwise Expansion of Antimicrobial Stewardship Programs and Its Impact on Antibiotic Use and Resistance Rates at a Tertiary Care Hospital in Korea

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Background: To optimize antibiotic use, the United States Centers for Disease Control and Prevention outlined core elements of antimicrobial stewardship programs (ASP). However, they are difficult to implement in countries with limited-resources. We report on the successful implementation of a series of ASP with insufficient number of infectious diseases specialists.

Methods: We retrospectively collected data regarding antibiotic prescription and culture results of all patients admitted to a tertiary care teaching hospital (SNUBH) from January 2010 to December 2019. Trend analyses were performed using nonparametric two-sided correlated seasonal Mann–Kendall tests.

Results: Total antibiotic agent usage significantly decreased with

ASP implementation at SNUBH since 2010 (days of therapy per 1000 patient-days [DOT]: 617.49 to 550.81; P < 0.01). Also, glycopeptide (DOT: 22.88 to 18.81; P < 0.01) and fluoroquinolone (FQ, DOT: 65.29 to 46.15; P < 0.01) use gradually decreased. Third-generation cephalosporins (3GC; DOT: 115.04 to 108.86; P = 0.48) and carbapenem use (DOT: 21.10 to 20.42; P = 1.00) did not significantly change. Furthermore, the rate of colonization with methicillin-resistant *Staphylococcus aureus* showed a consistently decreasing trend (Antimicrobial resistance [AMR] rate [%]: 55.4 to 45.5; P < 0.01). Although that with 3GC- (AMR rate [%]: 18.9 to 37.1; P < 0.01) and FQ-resistant *Escherichia coli* (AMR rate [%]: 41.4 to 53.7; P < 0.01) significantly increased, that of 3GC resistant-*Klebsiella pneumoniae* did not increase (AMR rate [%]: 22.3 to 26.5; P = 1.00). Also, that of 3GC- (AMR rate [%]: 15.8 to 12.3; P = 0.01) and FQ-resistant *Pseudomonas aeruginosa* (AMR rate [%]: 29.5 to 23.1; P = 0.01) significantly decreased.

Conclusions: Stepwise implementation of core ASP elements was effective in reducing total antibiotic use despite a lack of sufficient manpower.

keywords : antimicrobial stewardship program, core elements, antibiotic use, antibiotic resistance

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