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A Survey of Antimicrobial Stewardship Programs in Korea, 2015

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The study was conducted to evaluate the Antibiotic Stewardship Program (ASP) in Korean hospitals compared with the previous two surveys in 2006 and 2012. The information on ASPs was collected through an online-based survey sent by e-mail to 192 infectious diseases specialists in 101 Korean hospitals in September 2015. Fifty-four hospitals (53.5%, 54/101) responded to the online survey. One infectious diseases specialist was employed in 30 (55.6%) of the 54 hospitals, and they were in charge of ASPs in hospitals with the program. Fifty of the 54 hospitals (92.6%) had ASPs and the same number of hospitals was conducting a preauthorization-of-antibiotics-use program. Although most hospitals adopted preauthorization strategies for more antibiotics in 2015 than in 2012 (median 14 in 2015; 13 in 2012), a limited number of antibiotics were under control. The number of per oral and parenteral antibiotics available in hospitals in 2015 decreased compared to 2006 and 2012. The number of hospitals performing a retrospective or prospective qualitative drug use evaluation of antibiotic use increased from 2006 to 2015. Manpower in charge of antibiotic stewardship in most hospitals was still very limited and ASPs heavily depended on preauthorization-of-antibiotics-use programs in this survey. In conclusion, there leaves much to be desired in ASPs in Korea in 2015.

Keywords: Stewardship; Antimicrobial; Antibiotic; Korea; 2015

INTRODUCTION

Multi-drug resistance (MDR), caused by an excessive antibiotic use, is considered to be a present threat to public health, and an emerging crisis (1). Unfortunately the pace of antimicrobial drug development has slowed markedly in the last 30 years, and there has been a significant decrease in the development and approval of new antimicrobial agents (2). Many experts suggest reducing antibiotic misuse as an approach for overcoming the threat posed by antibiotic-resistant infections (1). Infections by resistant organisms not only result in increased morbidity and mortality but also dramatically increase healthcare costs (3). According to a study conducted in the US, the medical costs attributable to antimicrobial-resistant infections ranged from $18,588 to $29,069 per patient (4). With the aim of improving antibiotic use in healthcare facilities, an antimicrobial stewardship program (ASP) has been developed. An ASP is a set of multidisciplinary activities focusing on the proper use of antimicrobials to provide optimal patient outcomes, reduce the risk of adverse effects, promote cost-effectiveness, and lower or stabilize levels of resistance (5).

Currently many Korean hospitals employ ASPs. According to two previous surveys in 2006 and 2012, their operation was entirely oriented to preauthorization-of-antibiotics-use programs (6,7). This study was conducted to examine the changing pattern of ASPs in Korea.

MATERIALS AND METHODS

The study was conducted in September 2015 among 192 infectious diseases (ID) specialists who work in 101 secondary or tertiary hospitals in Korea. The online-based survey linked to each e-mail collected information about the general profile of each hospital, its antimicrobial management committee (AMC), and strategies of the ASPs. One answer was accepted from each hospital. The data from similar surveys of ASPs in Korea in 2006 (6) and 2012 (7) which contained similar questions with the present survey, targeting the ID specialists, were used for comparison.

Antibiotics in this study included antibacterial agents, antifungal agents and antiviral agents except antiretroviral agents, excluding antiparasitic agents and antituberculous agents.

We classified the strategies of the ASPs into three categories: education and guidelines for antibiotic use, restriction on antibiotic use and drug use evaluation (DUE). Qualitative DUE is defined as a system of systematic, criteria-based evaluation of drug use that will help ensure that antibiotics are used appropriately; quantitative review of antimicrobial consumption as a measurement system of total amount of antimicrobial use.

The factors determining preauthorization-requiring antibiotics were calculated by a priority weighting method (e.g. 1st, 6 point; 2nd, 5 point; 3rd, 4 point; 4th, 3 point; 5th, 2 point; 6th, 1 point).

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was used for statistical analyses. Categorical variables were analyzed by the χ^2 test or Fisher's exact test. A P value of < 0.05 was considered to be statistically significant.

RESULTS

Demographic information of hospitals

Fifty-four (53.5%, 54/101) hospitals responded to the 2015 online survey. In terms of the number of in-patient beds, most of the hospitals had 501-1,000 beds (63.6%, 35/54), while 21.8% (12/54) had 200-500 beds, and 12.7% (7/54) had more than 1,001 beds. One ID specialist (excluding fellows in training) was employed in the majority of the hospitals (55.6%, 30/54), while 29.6% (16/54) had two, 5.6% (3/54) had three or four, and 1.9% (1/54) had five or six (Table 1).

Looking at the hospitals participating in this survey, forty-eight (88.9%, 48/54) hospitals were concordant with the participants of either the survey of 2012 or 2006 (27.8% [15/54] participated in both 2012 and 2006; 16.7% [9/54] in 2012; 25.9% [14/54] in 2006).

Antimicrobial management committee (AMC)

An AMC was present in 92.6% (50/54) of the responding hospitals, and a figure was similar to those in the 2006 and 2012 surveys (92.7%, 38/44 in 2006; 87.5%, 35/40 in 2012, $P = 0.864$) (Table 1). Of the AMCs, 32.0% (16/50) held a meeting every 6 months and whenever there was an issue, 26.0% (13/50) did so quarterly, 14.0% (7/50) annually, and 4.0% (2/50) monthly. Significantly more AMCs in 2012 and 2015 took charge of determining antibiotics which require preauthorization (18.4%, 7/38 in 2006; 65.7%, 23/35 in 2012; 58.0%, 29/50 in 2015, $P < 0.001$) and DUE of antibiotics (18.4%, 7/38 in 2006; 38.7%, 19/35 in 2012; 40.0%, 20/50 in 2015, $P = 0.006$) than in 2006. Additionally, AMCs introduced new antibiotics (76.0%, 38/50), provided antibiotic use guidelines (46.0%, 23/50), dealt with antibiotic insurance claims (24.0%, 12/50), and analyzed antibiotic-resistance rates (14.0%, 7/50). The performance interval of these tasks was similar to the 2006 and 2012 surveys (data not shown).

Number of prescribed antibiotics in each hospital

Fifty-three hospitals (98.1%, 53/54) responded to the question about number of prescribed antibiotics. The number of parenteral antibiotics present in the hospitals was as follows: ≤ 40 in 6 of 53 hospitals (11.3%), 41-50 in 13 (24.5%), 51-60 in 15 (28.3%), 61-70 in 8 (15.1%), 71-80 in 5 (9.4%), 81-90 in 3 (5.7%), and ≥ 91 in 3 (5.7%). In terms of per oral antibiotics present in the hospitals was as follows: ≤ 40 in 17 of 53 hospitals (32.1%), 41-50 in 15 (28.3%), 51-60 in 9 (17.0%), 61-70 in 1 (1.9%), 71-80 in 5 (9.4%), 81-90 in 1 (1.9%), and ≥ 91 in 5 (9.4%). Comparing the proportion of hospitals containing > 60 parenteral or per oral antibiotics among 2006, 2012 and 2016 survey, a decreasing trend was observed: 55.7% (24/43) in 2006, 22.5% (6/37) in 2012, and 22.6% (12/53) for per oral antibiotics ($P < 0.001$); 50% (21/42) in 2006, 35% (11/37) in 2012, 25.9% (19/53) in 2015 for parenteral anti-

Table 1. Demographic information from the study hospitals: a comparison of the 2006, 2012 and 2015 surveys

Demographic parameters	No. (%) of hospitals			*P* value
	2006 (n = 44)	2012 (n = 40)	2015 (n = 54)	
No. of in-patient beds in the hospitals				0.148
200-500	3 (6.8)	3 (7.5)	12 (22.2)	
501-1,000	33 (75.0)	31 (77.5)	35 (64.8)	
> 1,000	8 (18.2)	6 (15.0)	7 (13.0)	
No. of infectious diseases specialists				0.864
1		20 (50.0)	30 (55.6)	
2		12 (30.0)	16 (29.6)	
3		3 (7.5)	3 (5.6)	
4		3 (7.5)	3 (5.6)	
5		0 (0)	1 (1.9)	
6		1 (2.5)	1 (1.9)	
7		1 (2.5)	0 (0)	
No. of laboratory microbiology specialists				-
0			18 (33.3)	
1			31 (57.4)	
2			4 (7.4)	
3			1 (1.9)	
No. of pediatric infectious diseases specialists				-
0			33 (61.1)	
1			20 (37.0)	
3			1 (1.9)	
Presence of antimicrobial management committee				0.864
Yes	38 (92.7)	35 (87.5)	50 (92.6)	
No	3 (3.65)	5 (12.5)	4 (7.4)	
No reply	3 (3.65)	0 (0)	0 (0)	

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biotics (P = 0.187).

Strategies of ASPs

Fifty hospitals (92.6%, 50/54) had ASPs in this survey, similar to 2006 (95.5%, 42/44) and 2012 (87.5%, 35/40) (P = 0.397).

Table 2 presents the data in detail. In education and guidelines for antibiotic use, 60.0% (30/50) had some documented guidelines for antimicrobial use in 2015 (38.1%, 16/53 in 2006; 68.6%, 24/35 in 2012, P = 0.064), and 68.0% (34/50) had education programs for doctors about antimicrobial use (83.3%, 35/42 in 2006; 80.0%, 28/35 in 2012, P = 0.202). Twelve percent (6/50) provided a printed document for proper antibiotic use.

As for restriction on antibiotic use, 32.0% (16/50) adopted the strategy of selected reporting of antibiotic susceptibility results in 2015 (16.7% [7/42] in 2006, 20.0% [7/35] in 2012, P = 0.194), twenty-six hospitals (52.0%) operated an automatic stop order (40.5%, 17/42 in 2006, P = 0.270), and 18.0% (9/50) had formulary restrictions (23.8%, 10/42 in 2006; 20.0%, 7/35 in 2012, P = 0.787). In addition, fifteen hospitals had a strategy for controlling inappropriate antibiotic combination therapies, and 23 limited long-term antibiotics usage without appropriate clinical justification.

In terms of qualitative DUE, a significant trend of increase was observed both in retrospective and prospective methods. However, feedback to prescriber after DUE did not increase from 2006 to 2015.

Preauthorization-of-antibiotic-use programs

All hospitals with ASPs were conducting preauthorization-of-antibiotic-use programs. The spectrum of antibiotics was the most important factor (mean value 4.89), followed by possibility of development of resistant pathogens (mean value 4.81), insurance coverage (mean value 4.12), price (mean value 3.23), literature review (mean value 2.62), and adverse effect (mean value 3.23).

Table 3 summarizes detailed data on the programs. All hospitals with preauthorization-of-antibiotic-use programs had computerized systems for control (100%, 50/50). The proportion of hospitals with computerized system was higher than in 2006 and 2012 (P < 0.001). The main department determining antibiotics which require preauthorization was the division of ID in 30.0% (15/50), AMC in 58.0% (29/50), pharmacy board in 8.0% (4/50), and drug department in 4.0% (2/50) in this study. Twenty-six of 50 hospitals (52.0%) approved preauthorization-required antibiotics use by consultation (case by case approach) while 48.0% (24/50) used automated algorithms. In all the hospitals in this survey, division of ID had a primary responsibility for approval for preauthorization-required antibiotics use compared with 72.5% in 2012 (P < 0.001).

A half of hospitals (50.0%, 25/50) permitted the use of preauthorization-required antibiotics for a few days before authorization (79.5%, 35/44 in 2006; 30.0%, 12/40 in 2012, P < 0.001), 24.0% (12/50) began restriction from the first prescription (15.9%, 7/44 in 2006; 25.0%, 10/40 in 2012, P = 0.527) and 20.0% (10/50) began restriction from intervention by the department of primary responsibility for approval (0%, 0/44 in 2006; 5.0%, 2/40 in 2012, P = 0.002). In the present survey, none of the hospitals reported they had antimicrobial cycling systems.

Fig. 1 shows the change of hospital proportions according to preauthorization-required antibiotics from 2006 to 2015. Hospitals in 2015 adopted preauthorization strategies for more antibiotics than in 2012 (number of preauthorization-required antimicrobials, median [range] were 14 [5.0-42.0] in 2015; 13 [9.5-20.0] in 2012). Most carbapenems such as imipenem, meropenem, doripenem and ertapenem were controlled by the preauthorization system in most hospitals, and increasing numbers of hospitals required a preauthorization for their use. Glycopeptides, such as vancomycin and teicoplanin, which have been the most frequently controlled antibiotics, needed approval in 98% of the hospitals (100%, 43/43 in 2006; 85.0%, 34/40 in

Table 2. Strategies of antimicrobial stewardship programs (ASPs): a comparison of the 2006, 2012 and 2015 surveys

Stewardship programs	No. (%) of hospitals			*P* value
	2006 (n = 42)	2012 (n = 35)	2015 (n = 50)	
Education and guidelines for antibiotic use				
Any documented guidelines for antimicrobial use	16 (38.1)	24 (68.6)	30 (60.0)	0.064
Education programs for doctors about antimicrobial use	35 (83.3)	28 (80.0)	34 (68.0)	0.202
Printed documents for proper antibiotic use			6 (12.0)	-
Restriction on antibiotics use				
Selected reporting of antimicrobial susceptibility results	7 (16.7)	7 (20.0)	16 (32.0)	0.194
Automatic stop order	17 (40.5)		26 (52.0)	0.270
Formulary restriction	10 (23.8)	7 (20.0)	9 (18.0)	0.787
Restriction on inappropriate antibiotic combination therapy			15 (30.0)	-
Restriction on long-term antibiotic use			23 (46.0)	-
Drug use evaluation				
Qualitative drug use evaluation of antimicrobials, retrospective review	4 (9.5)	10 (28.6)	19 (38.0)	0.011
Qualitative drug use evaluation of antimicrobials, prospective monitoring	4 (9.5)		13 (26.0)	0.043
Quantitative review of antimicrobial consumption			25 (50.0)	-
Feedback to prescriber after drug use evaluation	13 (31.0)	10 (28.6)	12 (24.0)	0.708

Table 3. Preauthorization-of-antibiotic-use programs: a comparison of the 2006, 2012 and 2015 surveys

Programs or systems	No. (%) of hospitals		2015 (n = 50)	*P* value
	2006 (n = 44)	2012 (n = 40)		
Computerized system for control	26 (59.1)	34 (85.0)	50 (100.0)	< 0.001
Cumulative number of updates for computerized system				
0			6 (12.0)	
1-2			26 (52.0)	
≥ 3			16 (32.0)	
No answer			2 (4.0)	
The greatest obstacle against update for computerized system				
Compatibility with existing programs			9 (18.0)	
Shortage of manpower			32 (64.0)	
Shortage of technical support			6 (12.0)	
Other			1 (2.0)	
No answer			2 (4.0)	
The main department determining antibiotics which require preauthorization				
Infectious disease		9 (22.5)	15 (30.0)	0.424
Antimicrobial management committee		17 (42.5)	29 (58.0)	0.144
Pharmacy board		4 (10.0)	4 (8.0)	1.000
Drug department		0 (0)	2 (4.0)	0.501
Others		10 (25.0)	0 (0)	< 0.001
Approval of preauthorization-required antibiotics use				
Consulting the department of primary responsibility (case by case approach)			26 (52.0)	
Automated algorithm			24 (48.0)	
The department of primary responsibility for approval of preauthorization-required antibiotics use				
Infectious disease		29 (72.5)	50 (100.0)	< 0.001
Pediatrics		1 (2.5)	0 (0)	0.444
Others		6 (15.0)	0 (0)	0.006
No answer		4 (10.0)	0 (0)	0.036
Timing of antibiotic preauthorization commencement				
From the first prescription	7 (15.9)	10 (25.0)	12 (24.0)	0.527
No restriction for a few days	35 (79.5)	12 (30.0)	25 (50.0)	< 0.001
From intervention by the department of primary responsibility for approval	0 (0)	2 (5.0)	10 (20.0)	0.002
Others	1 (2.3)	6 (15.0)	3 (6.0)	0.076
No answer	1 (2.3)	10 (25.0)	0 (0)	< 0.001

2012, $P = 0.004$). Tigecycline, which was recently introduced to the market, needed approval prior to being used in all the hospitals. Another newly introduced antibiotic, linezolid, also needed approval in most hospitals, but there was no significant difference from the 2006 and 2012 surveys (93.0%, 40/43 in 2006; 82.5%, 33/40 in 2012; 92.0%, 46/50 in 2015, $P = 0.235$). However, the proportion of hospitals requiring preauthorization for cefepime, ceftazidime, piperacillin/tazobactam, and aztreonam remained relatively low and did not show a change from 2006 to 2012. Among antifungal agents, the number of hospitals requiring preauthorization before use of liposomal amphotericin B and voriconazole increased from 2006 through 2015 ($P = 0.032$ and $P = 0.002$, respectively).

Compliance of other departments with ASPs

When we asked the other departments' compliance with ASPs, most hospitals answered yes (70.4%, 38/54). The reason for a low compliance was ignorance (56.3%, 4/16), followed by prescribers' stubbornness (25.0%, 4/16) and lack of interest (18.7%, 3/16) in hospitals answering a low compliance with ASPs. The hospitals were employing several policies to improve compliance: private conversations with the staff of other departments (57.4%, 31/54), education of other departments (31.5%, 17/54), giving a disadvantage for repeated inappropriate antibiotic use (24.1%, 13/54), and holding conferences about antibiotic use with other departments (16.7%, 9/54). No hospital offered incentives for appropriate antibiotic use.

Microbiologic culture report systems and therapeutic drug monitoring (TDM)

Active reporting systems for cultures of microorganisms were established at more hospitals in 2015 than in 2012 (55.0%, 22/40 in 2012 vs. 75.9%, 41/54 in 2015, $P = 0.033$). Cell phone messages (80.5%, 33/41) were used most frequently, followed by telephones (12.2%, 5/41), and computer networks (7.3%, 3/41). The specimens subject to active reporting were limited to blood (97.6%, 40/41) and cerebrospinal fluid (39.0%, 16/51) in most hospitals.

Forty-three of the 54 hospitals (79.6%) were performing therapeutic drug monitoring (TDM) (Table 4). TDM was applied to vancomycin (97.7%, 42/43), amikacin (37.2%, 16/43), gentamicin (27.9%, 12/43), and voriconazole (14.0%, 6/43). These frequencies were not significantly different from those in 2012. The departments in charge of the service were laboratory medicine (46.5%, 20/43), the drug department (37.2%, 16/54), and

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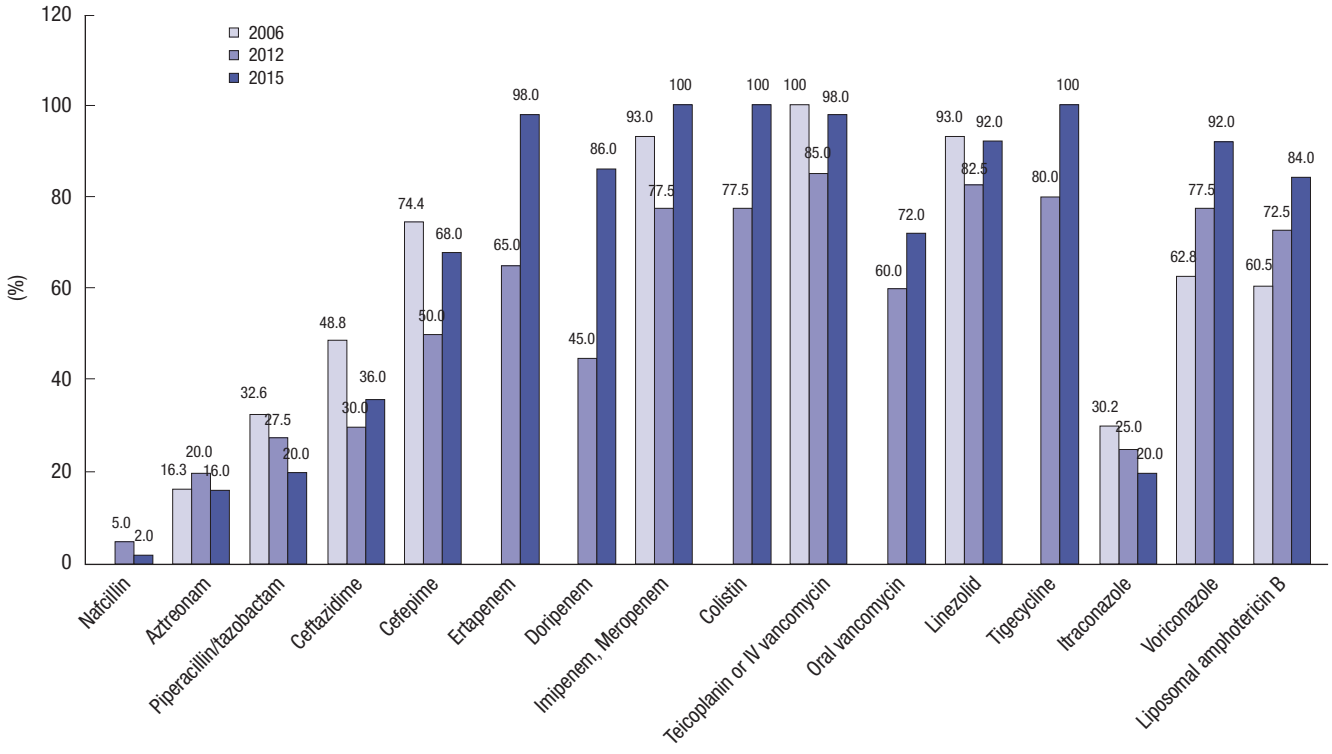

Fig. 1. The change of hospital proportions according to preauthorization-required antibiotics: a comparison of the 2006 (n=43), 2012 (n=40) and 2015 (n=50) surveys.

Table 4. Therapeutic drug monitoring (TDM)

Drug monitoring	No. (%) of hospitals		*P* value
	2012 (n = 20)	2015 (n = 43)	
Type of antibiotics			
Vancomycin	20 (100.0)	42 (97.7)	1.000
Amikacin	8 (40.0)	16 (37.2)	0.832
Gentamicin	8 (40.0)	12 (27.9)	0.337
Voriconazole	1 (5.0)	6 (14.0)	0.415
Department in charge (multiple response)			
Laboratory medicine	10 (10.0)	20 (46.5)	0.796
Drug department	14 (70.0)	16 (37.2)	0.015
Infectious disease	4 (20.0)	5 (11.6)	0.448
Method of requesting			
TDM order code		22 (51.2)	
Consulting the department in charge		17 (39.5)	
Automatically linked to codes of drug level measurement		3 (7.0)	
Automatically linked to codes of antibiotic prescription		1 (2.3)	

ID (11.6%, 5/43). The methods for requesting TDM were as follows: use of an existing TDM order code (51.2%, 22/43), consulting the department in charge (39.5%, 17/43), automatically linked to codes of drug level measurement (7.0%, 3/43), and automatically linked to codes of antibiotic prescription (2.3%, 1/43).

DISCUSSION

Although the importance of antimicrobial stewardship is being emphasized in many countries, research on such programs is limited in Korea. This is the third nationwide survey of ASPs in Korea followed by the surveys in 2006 and 2012. The survey enabled us to evaluate the changes in ASPs in Korean hospitals. Despite increasing numbers of ID specialists, there were still 4 hospitals that did not operate ASPs, and the proportion had not changed significantly from 2006 to 2015.

According to Infectious Disease Society of America (IDSA) guidelines, it is essential that the antimicrobial stewardship team include an ID physician and a clinical pharmacist with ID training, and that both of these individuals be recompensed appropriately for their time. They also recommend to include a clini-

cal microbiologist, an information systems specialist, an infection control professional, and a hospital epidemiologist in the ASP team (8). Since clinical pharmacists are not readily available in Korea, ID specialists have to fulfill the core role of leading the committee (5). Most hospitals with 500-800 beds in this study employ one ID specialist for antibiotic stewardship, and there is no proper reward for all the activities involved in ASPs in the domestic medical insurance system. Therefore, systematic support from the government is imperative (5,8) as well as further adoption of the automated algorithm method for preauthorization-of-antibiotic-use programs (9,10).

The hospitals adopt a variety of strategies for antimicrobial stewardship; however, they are rather reluctant to perform other activities rather than the preauthorization-of-antibiotics-use program. In terms of education and guidelines for appropriate antibiotic use, many papers reported the importance of education and feedback: Wilf-Miron et al. (11) showed that the volume of antibiotic prescription by primary physicians who received peer group interventions was reduced, and Davey et al. (12) demonstrated the effect of restrictions on antibiotic use was compromising gradually with the passage of time. According to a study in Korea, one of the main factors leading to prescription of inappropriate antibiotic combinations is a lack of knowledge; hence bad habits can be corrected by education and feedback (13).

Activities promoting reduction on antibiotic consumption sector were even more limited. Most hospitals failed to have proper strategies, and only 18.0% had formulary restrictions on antibiotics. One bright point concerned the number of available antibiotics in each hospital: there was a marked decline in the number of antibiotics in use, and this was more prominent for per oral antibiotics (hospitals with more than 60 antibiotics: 55.7%, 24/43 in 2006; 22.5%, 6/37 in 2012; 22.6%, 12/53, $P < 0.001$). Many experts suggested designating individual drugs or selected formulary agents within a drug class in order to reduce the number of antibiotics with overlapping actions, as a strategy to prevent drug abuse and misuse (14,15). Although only few hospitals (18.0%, 9/50) have adopted a formulary restriction strategy compared to American hospitals (88.0% in 2010) (16), this decline indicates that hospitals have changed their policy with respect to the minimum number of required antibiotics.

At present most hospitals in Korea focus on preauthorization-of-antibiotic-use programs for carrying out ASPs. Studies have shown a decrease in antibiotic consumption as a result of such programs (9,17), and antimicrobial resistant patterns of pathogens improved when certain types of antibiotic were prescribed less (18,19). However, the scope of preauthorization programs necessarily varied depending on the number of antibiotics under control and the type of antibiotic control program (control of unnecessary combinations of antibiotics, length of antibiotic use for specific diseases, the purpose of antibiotic use, etc.). Considering the lack of ID specialists and the even fewer clinical pharmacists with ID training in hospitals, the scope of preauthorization-of-antibiotic-use is inevitably limited in most hospitals in Korea.

In general, ASPs in Korea achieved an improvement in several areas over a number of years; for example, a remarkably higher rate of computerization and increased number of antibiotics which require preauthorization. However, a major part of antibiotic use is not under control. According to a recent report, the total consumption of antibiotics for systemic use increased from 21.68 (DDD per 1,000 people per day) in 2008 to 23.12 (DDD per 1,000 people per day) in 2012, and the trend of increased use was more prominent for 3rd generation cephalosporins and fluoroquinolone, which did not require preauthorization (20). In fact, antibiotics which were controlled in most hospitals, such as carbapenems, glycopeptides, colistin, linezolid and tigecycline, represented a small proportion of the total consumption of systemic antibiotics (0.65%, 0.151/23.12 DDD per 1,000 people per day in 2012) (20).

We have some limitations in this study. First, the participants were not exactly the same as the previous two studies, which potentially could be a selection bias. Second, we only surveyed ID specialists in this study, and the results may have limitations in terms of representation. Considering the growing number of ID specialists working in the secondary hospitals, we think that the results of this survey represent the present situation of ASP in Korea.

In conclusion, ASPs are operated mainly by ID physicians in most hospitals in Korea, and the programs still depend on preauthorization-of-antibiotic-use. The most important requirements for appropriate operation of ASPs in Korea are reinforcement of manpower capable of performing ASPs, and national-level support.

DISCLOSURE

The authors have no potential conflicts of interest to disclose.

AUTHOR CONTRIBUTION

Conception and coordination of the study: Kim B, Kim J, Kim SW, Pai H. Data review: Kim B, Pai H. Statistical analysis: Kim B. Manuscript preparation: Kim B, Pai H. Critical review of the manuscript: Pai H. Manuscript approval: all authors.

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