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Special Article

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Guidelines on Implementing Antimicrobial Stewardship Programs in Korea

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ABSTRACT

These guidelines were developed as a part of the 2021 Academic R&D Service Project of the Korea Disease Control and Prevention Agency in response to requests from healthcare professionals in clinical practice for guidance on developing antimicrobial stewardship programs (ASPs). These guidelines were developed by means of a systematic literature review and a summary of recent literature, in which evidence-based intervention methods were used to address key questions about the appropriate use of antimicrobial agents and ASP expansion. These guidelines also provide evidence of the effectiveness of ASPs and describe intervention methods applicable in Korea.

Keywords: Antimicrobial stewardship program; Guidelines; Korea; Antimicrobial resistance

PREFACE

1. Background and purpose

Experts in the field have long claimed that antimicrobial stewardship programs (ASPs) are important for reducing or preventing antimicrobial resistance [1, 2]. Currently, there is mounting concern regarding antimicrobial resistance worldwide. Implementation of ASPs is one of the most important measures to address the emergence of antimicrobial resistance [2].

Infection & Chemotherapy

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How to use these guidelines
The purpose of these guidelines is to present basic principles for implementing antimicrobial stewardship programs (ASPs) in Korea. These guidelines can be used as a source of reference when medical facilities in Korea implement an ASP. The contents of these guidelines are not intended to be applied to all medical facilities in the same way. Instead, those in charge of ASP development at individual medical facilities should select the interventions that apply to their situation. These guidelines are designed to encourage and educate ASP managers at medical facilities in Korea in order to promote appropriate antimicrobial use and are not intended to be used for commercial or evaluation purposes.

Abbreviations

ASP	Antimicrobial stewardship program
CAP	Community-acquired pneumonia
C. difficile	*Clostridioides difficile*
CDI	*Clostridioides difficile* infection
DOT	Days of therapy
ED	Emergency department
ICU	Intensive care unit
MALDI-TOF	Matrix-assisted laser desorption/ionization time-of-flight
P. aeruginosa	*Pseudomonas aeruginosa*
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PK	Pharmacokinetics
S. aureus	*Staphylococcus aureus*

An ASP is defined as a program that supports the appropriate use of antimicrobial agents through promoting optimal antimicrobial use, including the choice of agents, treatment duration, and the route of administration [1, 3].

In 2007, guidelines were developed for medical facilities to systematically implement ASPs in the United States (US), which were revised in 2016 [1, 4]. As other countries have different healthcare systems and environments, the US guidelines have been adapted for use in different countries.

Implementation of an ASP can improve the clinical outcomes of patients and reduce the incidence of *Clostridioides difficile* infection (CDI) and adverse drug reactions, and reduce medical costs [1, 5]. There are many reports, including systematic literature reviews, providing evidence of a decreased incidence of antimicrobial resistance following implementation of ASPs [5, 6].

It is not easy for medical facilities in Korea to implement effective ASPs due to a shortage of professional human resources and a lack of appropriate monetary compensation [7, 8]. Nevertheless, a recent National Hospital Evaluation Program found that there is a need for medical facilities in Korea to implement appropriate ASPs. There is a need for guidelines to promote the use of evidence-based, efficient ASPs in the healthcare system in Korea. Thus, the Korean Society for Antimicrobial Therapy, the Korean Society of Infectious Diseases, and the Korean Society of Health-System Pharmacists collaborated to develop these guidelines for implementing ASPs in Korea.

2. Scope

Based on a systematic literature review, these guidelines provide evidence of the benefits of ASPs. In addition, the description is focused on ASP intervention methods that could be adapted for use in medical facilities in Korea, considering the current situation as of January 2021. These guidelines should be revised according to changes in the domestic situation.

3. Formation of the Antimicrobial Stewardship Program Guidelines Development Committee

In January 2020, a committee was formed to develop ASP guidelines. In order to develop evidence-based guidelines using a multidisciplinary approach, seven experts recommended by the Korean Society for Antimicrobial Therapy and the Korean Society of Infectious Diseases were appointed. Two pharmacist experts recommended by Korean Society of Health-System Pharmacist participated in the review process.

4. Systematic literature search and review

ASP-related literature was identified by means of a systematic literature search and existing clinical guidelines were reviewed. The main international databases used for the development of these guidelines included PubMed (www.pubmed.gov), the Cochrane Library (www.cochranelibrary.com), and Embase (www.embase.com), while Korean literature was searched using the Korean Medical Database (KMBase, kmbase.medric.or.kr) and the Research Information Sharing Service (Appendix 1of Supplementary material). Six information search experts conducted systematic literature searches. For each key question, a search was performed with a highly sensitive search strategy by combining the use of structured terms (MeSH terminology for PubMed and the Cochrane Library, and Emtree terminology for Embase) and natural vocabulary. The selected references were reviewed, and a total of 235 references were selected for citation (Appendix 2 of Supplementary material).

Infection & Chemotherapy

TDM	Therapeutic drug monitoring
US	United States of America
UTI	Urinary tract infection
VRE	Vancomycin-resistant enterococcus

Conflict of Interest
No conflicts of interest

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5. Selecting key questions and the process used to reach consensus

These guidelines were developed focusing on key questions, which would allow each medical facility to find interventions needed for the application of an ASP. Considering the Korean situation, the ASP guidelines development committee selected a total of nine key questions through discussion. Consensus was reached primarily by means of a nominal group technique process.

6. Strength of the recommendations and grading the quality of evidence

The expert panel classified the quality of evidence as high, moderate, low, or very low, and the strength of recommendations as strong or weak using the GRADE (grading of recommendations assessment, development and evaluation, http://www.gradeworkinggroup.org) method [9] (**Table 1**, **Fig. 1**).

7. Evaluation by external experts

Draft guidelines prepared following internal discussion by members of the ASP Guidelines Development Committee were reviewed by an expert group to obtain second opinions, and the contents were revised and supplemented during additional internal meetings of the ASP guidelines development committee. Additionally, opinions of other expert groups were included during the finalization process.

Korean Society for Antimicrobial Therapy, Korean Society of Infectious Diseases, Korean Society of Health-System Pharmacist and Korean Society for Healthcare-associated Infection Control and Prevention reviewed and endorsed the guideline prior to publication.

RECOMMENDATIONS

Summary of key questions

The nine key questions developed were:

1) What types of strategies (programs) can be used in an ASP (internationally and in Korea)?
   a) What are the key high-impact interventions for applying antimicrobial stewardship?
   b) What are the supplementary interventions for applying antimicrobial stewardship?

Table 1. Strength and quality of recommendations (GRADE system)

	Evaluation of the quality of evidence				Strength of recommendations
Study design	Initial grading of the quality of evidence	Consider lowering the grade if:	Consider raising the grade if:	Quality of evidence	
Randomized trials	High	Bias risk: Serious: −1 Highly serious: −2 Inconsistency: Serious: −1 Highly serious: −2	Effect size: Large: +1 Very large: +2 Positive relationship: Yes: +1	High: 4 points Moderate: 3 points Low: 2 points Very low: 1 point	Strong: Believed that benefits are clearly larger or smaller than the harms Weak: All non-strong recommendations
Observational study	Low	Indirectness: Serious: −1 Highly serious: −2 Imprecision Serious: −1 Highly serious: −2 Publication bias Strongly suspicious: −1	Confounding variables Raising the certainty of effect estimation: +1		

GRADE, grading of recommendations assessment, development and evaluation.

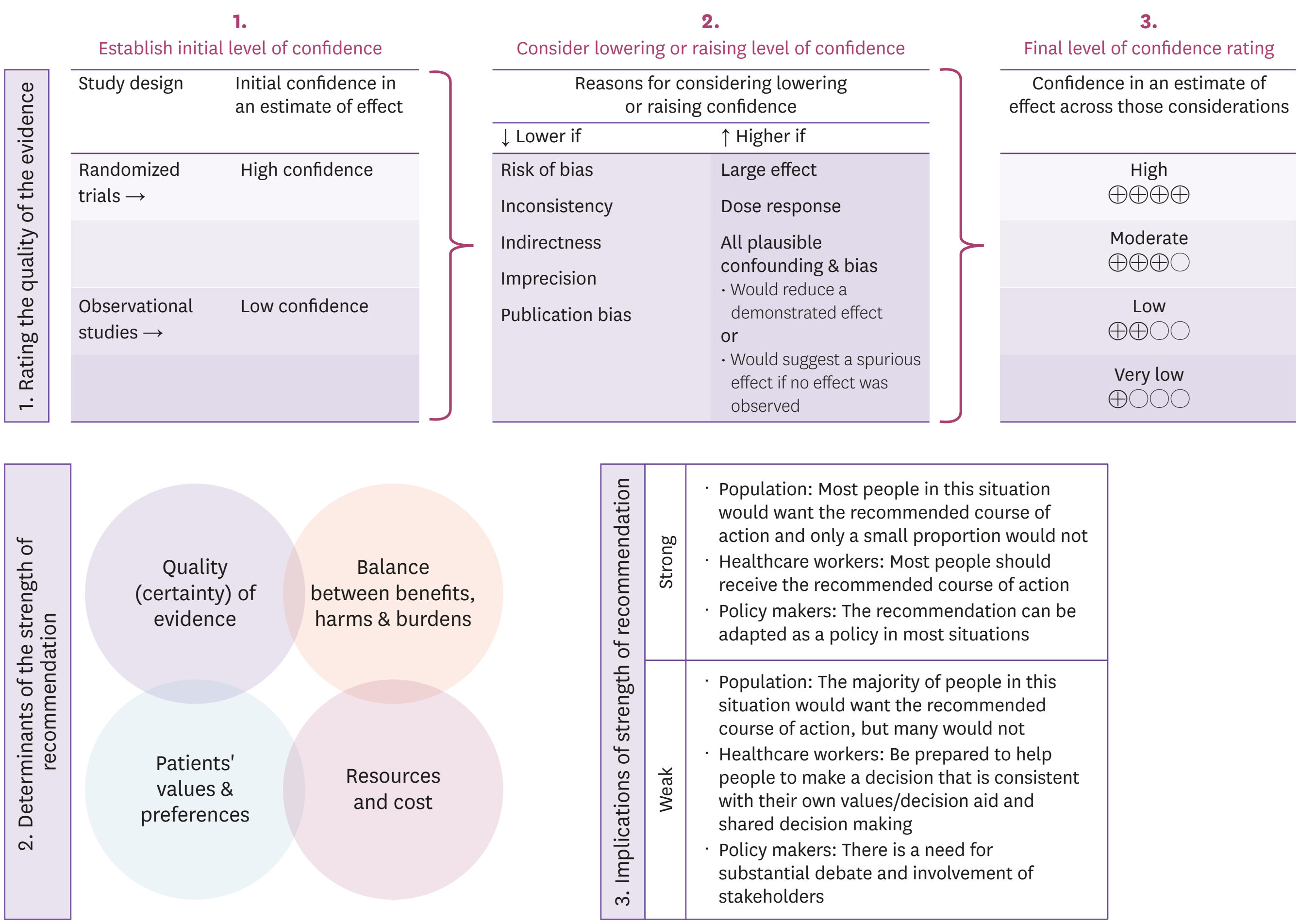

Figure 1. Approach and implication to the rating the quality of evidence and strength of recommendations using the grading of recommendations assessment, development and evaluation (GRADE) approach [9].

2) What are the core elements to assist healthcare facilities in effectively implementing an ASP?
3) How does one operate the team that manages the ASP?
4) Do ASPs decrease the amount and cost of antibiotic use?
5) What are the effects of ASPs on the clinical outcome (prognosis) of patients?
6) What are the effects of ASPs on the adverse effects (toxicity or allergy) of antibiotic use?
7) What are the effects of ASPs on the incidence of CDI?
8) Do ASPs decrease antimicrobial resistance?
9) What types of strategies (programs) can be applied for ASPs in smaller community hospitals and long-term care hospitals?

RECOMMENDED GUIDELINES FOR EACH KEY QUESTION

Key Question 1: What types of strategies can be applied in an antimicrobial stewardship program?

1. ASP key strategies can include a selective combination of restriction and preauthorization of antimicrobial agents or a prospective audit with feedback (quality of evidence: moderate; strength of recommendation: strong).

2. The control of antimicrobial agents through education should be accompanied by an active intervention using a prospective audit with feedback (quality of evidence: moderate; strength of recommendation: strong).

3. Practical guidelines and clinical pathways should be developed for each disease according to the characteristics of the medical facility, using a syndrome-based antimicrobial intervention approach (quality of evidence: low; strength of recommendation: strong).

4. A computerized clinical decision-support system should be utilized as part of a computerized antibiotic prescription system for antimicrobial control (quality of evidence: moderate; strength of recommendation: strong).

5. A collaborative relationship should be fostered between the antibiotic control team and the microbiology laboratory of each medical facility, which should include regular sharing of antimicrobial susceptibility results, a system for early diagnosis of infectious diseases, and systematic reporting of test results (quality of evidence: low; strength of recommendation: strong).

1. What are the key high-impact interventions for applying antibiotic stewardship?

The ASP development framework contains core strategies and supplementary strategies for the control of antimicrobial agents (**Table 2**) [4]. There are two active core strategies for evidence-based interventions regarding the use of antimicrobial agents, namely 1) antimicrobial restriction and preauthorization, or 2) a prospective audit with feedback. An antimicrobial restriction and preauthorization is a strategy by which the medical staff should obtain approval for the use of specific restricted antimicrobial agents before prescription to ensure appropriate antimicrobial use. A prospective audit with feedback is a strategy by which the manager evaluates the appropriateness of antimicrobial type, dosage,

Table 2. Important strategies for antimicrobial stewardship programs

Core strategies
Restriction and preauthorization
Prospective audit with feedback
Supplementary strategies
Handshake stewardship
Education
Guidelines and clinical pathways
Duration optimization for infectious syndromes
Targeted review of patients with specific infectious syndromes
Conversion from parenteral to oral therapy
Dosage optimization and therapeutic drug monitoring (with feedback)
Combination therapy
Streamlining or de-escalation of therapy
Clinical decision-support systems/computerized physician order entry
Monitoring antimicrobial resistance and drug usage
Selective antibiotic susceptibility reporting
Microbiological alerts and rapid diagnostic testing

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and duration of administration after the antimicrobial prescription. The antimicrobial intervention strategies should be selected considering the unique culture of the hospital, attitudes of medical staff, and the available resources, and the advantages and disadvantages of the core strategies.

Antimicrobial restriction and preauthorization of prescription (front-end program) has the advantage of enabling a manager to determine whether antimicrobial administration is required for patients before they are administered, which decreases unnecessary antimicrobial use, leading to a reduction of antimicrobial agent-related costs, and it can also increase the chance of initiating an appropriate empirical antimicrobial agent. In addition, it can induce a change in prescription patterns in the early stage.

In contrast, its disadvantages are that there are no complete culture test results available at the time of the decision, and there may be negative interaction caused by a conflictual relationship between the program managers and the prescribing clinician due to a loss of prescribing autonomy. In addition, it requires substantial human resources to deal with preauthorization requests after-hours, and may cause a delay in necessary antimicrobial administration. Due to a limited management effect on preauthorized antimicrobial agents, it can have a balloon effect a cause the use of other antimicrobials to increase. In addition, the effectiveness depends on the manager's proficiency.

Antimicrobial restriction and preauthorization of prescription are generally applied to certain antimicrobial agents. In a randomized controlled trial, it had no effect on mortality or the length of hospitalization, but significantly decreased the amount of antimicrobial use and the duration of administration [10]. A meta-analysis suggested that antimicrobial restriction and preauthorization of prescription is more effective for reducing the CDI incidence than the persuasion strategy for appropriate antimicrobial use [11]. However, the authorization proficiency of medical staff is highly important. It has been reported that an antibiotic control team with infectious disease specialists and clinical pharmacists responsible for antimicrobial agent restriction and preauthorization is associated with more appropriate antimicrobial recommendations and a greater treatment success rate than a program managed by infectious disease fellows [12]. Attention should be paid to the balloon effect whereby certain antimicrobial restrictions can boost the use of other antimicrobial agents. According to a previous study that implemented a preauthorization program for third-generation cephalosporins, the incidence of ceftazidime-resistant *Klebsiella* infection decreased, while imipenem use increased, which resulted in a higher incidence of imipenem-resistant *Pseudomonas aeruginosa* infections [13]. In a recent study conducted in Korea, it was reported that when antibiotic restrictions and prior approval in hospitals are stopped, antibiotic usage patterns rapidly returned to the patterns prior to the implementation of the program. Through antimicrobial restriction and preauthorization of prescription, the educational effect of encouraging prescribers to self-prescribe appropriate antibiotics is not expected to be significant [14].

Meanwhile, antimicrobial restriction and preauthorization of prescription should be operated 24 hours a day based on sufficient manpower, but it is difficult in reality. To alleviate the inconvenience and resistance of prescribers caused by restrictions on antibiotic prescriptions, various types of interventions have been applied to certain drugs and medical facilities in Korea, which include an antimicrobial restriction that is initiated after the basic microbiology data were obtained (*i.e.*, 3 - 5 days after a prescription), when it is possible to

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Infection & Chemotherapy

clinically evaluate the appropriateness of the prescription, or a method that restricts the corresponding antimicrobial agents from the beginning [15].

Prospective audit with feedback (back-end program) has the advantage that opinions regarding antimicrobial de-escalation and the duration of antimicrobial administration can be presented because there is relatively more clinical information at the time of evaluation. It also enables the formation of a positive relationship among medical staff members, which helps the manager to better understand why clinicians used certain specific antimicrobial agents. As the timing of the antimicrobial intervention can be set, it is relatively less burdensome for the program manager than the antimicrobial restriction and preauthorization of prescription program approach. On the other hand, it cannot prevent inappropriate antimicrobial use, and it can delay appropriate antimicrobial administration [16]. The acceptance rate may vary, depending on the medical staff in charge and the feedback methods. To lighten the burden of work, an antimicrobial prescription program or a computerized antimicrobial agent management program is required. In addition, it may take longer for the intervention effect to become apparent than with the antimicrobial restriction and preauthorization of prescription program approach [1].

Prospective audit with feedback can also improve the appropriateness of antimicrobial use without significantly affecting clinical outcomes, and decrease antimicrobial resistance and the CDI incidence [17-21]. Three randomized controlled trials have shown that a reduction in the antimicrobial administration period after the intervention [22-24]. One of the studies found a significantly shorter time to rehospitalization and an increased rehospitalization rate caused by recurrence of infection within 60 days [22], and another study also showed a higher frequency of appropriate antimicrobial use [23]. As prospective audit with feedback is also highly labor-intensive, a computerized audit system is useful. An intermittent intervention or prospective audit with feedback led by pharmacists, rather than a continuous operation of the program, has been shown to lower antimicrobial use when healthcare resources are limited [25]. In general, with prospective audits, prescriptions are reviewed approximately 72 hours after antibiotic administration. However, it has been reported that an audit of empirically prescribed antimicrobial agents within 48 hours after administration can improve mortality and significantly shorten the duration of antimicrobial administration [26].

Only a limited number of studies have compared the effects of antimicrobial restriction and preauthorization of prescription with prospective audits with feedback [27, 28]. According to a meta-analysis, antimicrobial restriction and preauthorization of prescription is more effective at reducing the amount of antimicrobial use 1 month after the intervention and the incidence of CDI and multidrug-resistant bacterial infections 6 months after the intervention compared to a prospective audit with feedback which is a persuasion-based intervention [27]. A study reported that, when an antimicrobial restriction and preauthorization of prescription strategy was changed to a prospective audit with feedback strategy, the amount of antimicrobial use and the length of hospitalization of patients significantly increased [28]. Antimicrobial restriction and preauthorization of prescription, and prospective audit with feedback are not mutually exclusive methods. Instead, they can be selectively combined depending on the hospital characteristics, human resources, other resources, and structure, and the specific antimicrobial agent or patient group.

2. What are the supplementary interventions for applying antibiotic stewardship?

Of various supplementary intervention methods, ***handshake stewardship***, recently proposed

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Infection & Chemotherapy

by Hurst et al. [29], is another unique comprehensive strategy, that builds trust and communicates through a rounding-based individual approach. The handshake stewardship entails prospective audit with feedback, in which an ASP team, composed of a pharmacist and a physician, reviews all prescribed antimicrobial agents without antimicrobial restriction or preauthorization, and immediately provides direct and individual feedback through rounding. The study focused on pediatric patients, and showed a reduction in vancomycin and meropenem use, and overall antimicrobial use. In an application of the handshake stewardship and a computerized prescription system, if all antimicrobial agents are controlled through rounding, the acceptance rate and guideline compliance of medical staff can be improved [30].

Prescriber education is a core element of ASPs, which can directly affect antibiotic prescription behaviors. Passive education methods include lectures, distribution of brochures about guidelines, and sending alert messages by E-mail. Passive education methods should be applied with active interventions in order to be effective [31, 32]. A meta-analysis found that, while the distribution of booklets by campaign or education by lecture was partially effective [17], the effect of the intervention was transient and lasted less than 1 year [33]. Education should be provided to various healthcare professionals, including physicians, pharmacists, physician assistants, nurses, nursing students, and residents, with a specific focus on medical students [34].

Development and implementation of ***practical guidelines and clinical pathways*** for each disease, according to the characteristics of the medical facility, can induce a change in antimicrobial prescription trends. Studies have shown that when guidelines for treating community-acquired pneumonia (CAP) and nosocomial pneumonia were widely distributed, clinical practice was improved, including the appropriateness of the initial empirical antimicrobial administration and the duration of antimicrobial administration, leading to a reduction of mortality and length of hospitalization, and a lowering of medical costs [35, 36]. When guidelines or unified clinical pathways are applied to an ASP, it is recommended the feedback be given to the medical staff. In two randomized controlled trials with pneumonia patients, interventions using guidelines or unified clinical pathways accompanied by feedback reduced inappropriate use of antimicrobial agents, raised compliance with the guidelines, and increased the frequency of correct dosage, without a significant change in the mortality rate or the length of hospitalization [37, 38]. To reflect such guidelines or clinical pathways to the prescription process, an order set and a checklist for best practice alert can be utilized [39].

Recently, an antimicrobial control intervention with ***duration optimization for infectious syndromes*** was developed based on evidence-based guidelines and various studies [40]. In studies of antimicrobial control intervention through duration optimization of antimicrobial administration in pneumonia patients [36, 41] and a meta-analysis, there were no differences in the effectiveness of treatment of CAP, hospital-acquired pneumonia, or ventilator-associated pneumonia between patients who received short-term and long-term antimicrobial treatment [42-44]. A randomized controlled trial showed similar results [41].

Recently, it has been reported that ***syndrome-based (disease-based) antimicrobial intervention control*** might be more effective for ASP than a prospective audit with feedback [45]. Syndrome-based antimicrobial intervention targeting patients with urinary tract infections (UTIs) or CAP can reduce antimicrobial use, unnecessary tests, and CDI incidence [46, 47].

Interventions that apply a ***unified clinical pathway*** can include ***changing intravenous antimicrobials to oral medications*** [48-50]. In randomized controlled trials of patients with CAP, changing to oral medication reduced the length of hospitalization, the duration of antimicrobial administration, medical costs, and complications associated with intravenous administration, without affecting the clinical outcomes [51, 52]. In a study in Korea, the use of intravenous antibiotics and the length of hospitalization for catheter-related UTIs was significantly reduced by switching from treatment with intravenous fluoroquinolone to oral medications [53]. Another study found that an intervention with the application of clinical pathways that used ertapenem or recommended ertapenem, instead of imipenem or meropenem reduced the incidence of carbapenem-resistant infections [54].

An ***optimized dose of antimicrobial administration*** that maximizes the treatment effect and minimizes the adverse effects is important for good clinical outcomes. Methods to administer an optimized dose of β-lactam antibiotics include practical guideline-based administration, ***therapeutic drug monitoring (TDM) of antimicrobial agents,*** utilization of dose-optimization software, and continuous or extended intravenous infusion [55]. Traditionally, TDM of antimicrobial agents has been applied to antimicrobial agents such as vancomycin and aminoglycosides that have a narrow therapeutic range mostly to minimize the risk of toxicity. In a randomized controlled trial, TDM of patients who received aminoglycosides reduced renal toxicity and medical costs [56], and another randomized controlled trial showed similar results for vancomycin [57]. Two meta-analyses found that the effectiveness of treatment of critically ill patients with multidrug-resistant infections was improved by intravenous administration of β-lactam antibiotics either continuously or over an extended period of infusion time [58, 59]. The French Pharmacist Association and the French Intensive Care Associations recommend that TDM is used whenever possible in severely ill patients and patients with renal failure who require treatment with β-lactam antibiotics, and also recommend that patients with non-fermenting gram-negative bacterial infections be treated with intravenous β-lactam antibiotics administered either continuously or over an extended period of infusion time [60]. The appropriate empirical antimicrobial dose should be carefully determined for each individual and recommended based on clinical practicality. However, only a limited number of studies on optimized antimicrobial dose targeting have been conducted in Korean patients.

Antimicrobial combination therapy can create synergism between antimicrobial agents and lead to a reduction in the incidence of multidrug-resistant infections, and can be used to expand the antimicrobial spectrum while awaiting the species identification and antimicrobial susceptibility results. Antimicrobial combination therapy is also useful for lowering the dose of toxic drugs and reducing the duration of antimicrobial administration [61]. Particularly, using antimicrobial combination therapy to treat severe infections can increase the chance of giving appropriate antimicrobial agents in the early stage of infection and lead to improved clinical outcomes [62]. In patients with infective endocarditis, antimicrobial combination therapy is recommended, with the drug combination depending on antimicrobial susceptibility test results [63, 64]. Previously developed antimicrobial agents for which licensing applications were suspended due to adverse effects, have recently been used in combination therapy for infectious diseases caused by multidrug-resistant microorganisms [65, 66]. However, it is unclear whether combination therapy is better than single-agent therapy in reducing the treatment failure rate [65, 66].

In antimicrobial combination therapy, ***antimicrobial streamlining*** or ***antimicrobial de-escalation*** means the suspension of one or more antimicrobial agents or the change to an antimicrobial

Infection & Chemotherapy

agent that shows a narrower antimicrobial spectrum. However, most combination therapies are initiated for patients with severe infectious disease, so it is difficult to streamline antimicrobial agents without evidence of their effectiveness. Thus, it is helpful to identify the causative bacteria and obtain antimicrobial susceptibility results as soon as possible [67]. Nevertheless, studies have shown that such strategies could reduce medical costs [68, 69].

A clinical decision-support system using a computerized antimicrobial prescription system decreases the amount of broad-spectrum antimicrobial use [70, 71]; helps to ensure prescription of an appropriate dose [72]; lowers antimicrobial resistance [71]; supports choosing appropriate antimicrobial agents [70]; alleviates prescription errors [73]; and reduces adverse effects, mortality, the length of hospitalization [74], and antimicrobial costs [72]. If medical staff enter antimicrobial prescription information in electronic medical records, the appropriateness of certain antibiotic prescriptions can be more effectively evaluated, and the time needed for management can be reduced [30, 75]. Recently, as mobile devices have been applied to the management of antimicrobial agents [76], personalized clinical decision-support software has been developed for smartphones, and access to intranet-based guidelines has become easier [77].

In addition, a collaborative relationship between the antibiotic control team and the microbiology laboratory should be fostered. Specifically, it is essential to know the ***facility-specific antimicrobial susceptibility*** pattern in order to develop guidelines for empirical antimicrobial treatment. Analysis of the antimicrobial susceptibility pattern should be stratified according to the location of the bed (intensive care unit [ICU] or general ward) [78], age of the patient [79], specimen type (blood, urinary, respiratory, and other specimens) [80], presence of underlying diseases [81], and the infection type (community-acquired or hospital-acquired) [82]. This information, together with information about the amount of antimicrobial use, should be shared periodically with clinical staff.

When the antimicrobial susceptibility results of patients are reported, a selective report of the ***specific antimicrobial susceptibility,*** is more helpful than providing the susceptibility results of all the antimicrobials tested, for choosing appropriate antimicrobial agents and controlling antimicrobial agent use [83, 84], particularly in patients with uncomplicated UTIs [85]. A sequential report can be provided, which lists the susceptibility result of the second antimicrobial agent if the organism is resistant to the primary antimicrobial agent [1].

Rapid diagnostic methods (for the diagnosis of specific respiratory virus infections) can help to avoid unnecessary tests, reduce unnecessary antimicrobial use, and help to select appropriate drugs such as antiviral agents [86]. Polymerase chain reaction (PCR) tests for respiratory viruses can decrease early administration of antiviral agents and unnecessary antimicrobial use [87]. Recently, a study of respiratory samples of patients with ventilator-associated pneumonia led to a reduction in use of a wide-spectrum antibiotics and improved the empirical antimicrobial appropriateness through the introduction of a test method that diagnosed 21 bacteria and 19 resistance genes within 5 hours using multiplex PCR [88].

If ***rapid diagnosis*** is used ***with traditional blood culture***, appropriate antimicrobial agents can be prescribed at an early stage of infection. The use of rapid diagnostic tests can also reduce recurrence of infection, mortality, length of hospitalization, and medical costs [89]. Particularly in environments where medical resources for antimicrobial intervention are limited, bacteremia cause by Gram-positive cocci can be tested rapidly and simply through

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GeneXpert MRSA/SA (Cepheid, Sunnyvale, CA, USA) or Verigene nucleic acid microarray assay (Nanosphere, Northbrook, IL, USA), which allow early administration of appropriate antimicrobial agents and reduced the length of hospitalization [90, 91]. Matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry can also enable early identification of pathogens and appropriate early antimicrobial administration [89]. A combination of multiplex PCR with MALDI-TOF mass spectrometry for patients with bacteremia can reduce the use of a broad range of antimicrobial agents and increase the appropriate use of antimicrobial agents [92]. However, other studies have found that rapid diagnostic tests had no significant benefits regarding improvement of antimicrobial use, early administration of an appropriate antimicrobial agent, or reduction of the length of hospitalization [93, 94].

In a study on ***biomarkers (such as procalcitonin) for suspending antimicrobial use*** combined with PCR for diagnosing respiratory virus infections, a computerized antimicrobial intervention based on alerts posted in electronic medical records reduced the amount of antimicrobial use [95].

Additional strategies, which should be customized to each medical facility, are shown in **Table 2.**

Key Question 2: What are the core elements to assist healthcare facilities in effectively implementing an antimicrobial stewardship program?

1. Core elements for implementing an ASP include leadership commitment, accountability, pharmacy expertise, action, tracking, reporting, and education. It is necessary to develop core elements relevant to the situation in Korea (quality of evidence: moderate; strength of recommendation: strong).
2. Core elements of the ASP should be chosen according to the size and function of the medical facility (quality of evidence: moderate; strength of recommendation: strong).

The US Centers for Disease Control and Prevention recommended that all acute care hospitals implement an ASP, considering the urgent need to improve antimicrobial use in hospitals and the benefits of an ASP and published the core elements of an effective hospital ASP in 2014 [96]. It proposed a range of core elements for different types of medical facility, including hospitals, outpatient hospitals, nursing homes or long-term care facilities, small-size acute care hospitals, and resource-limited settings. The core elements were classified based on facility size, staffing, and type of care. The common core elements were leadership commitment, accountability, pharmacy expertise, action, tracking, reporting, and education. In the US, 41% of hospitals were running core elements in 2014 in collaboration with the American Hospital Association, Quality Improvement Organization, and hospital accrediting organizations. This increased to 85% in 2018 [97]. After implementation of the core elements, the CDI incidence and antimicrobial use decreased [98, 99].

Leadership commitment

Leadership support is very important for the success of an ASP. Staff to perform ASP-related tasks and essential financial resources should be provided. ASP-related duties should be officially included in the job description of ASP staff, for whom adequate time should be provided to perform ASP-related tasks. Directors should receive reports on ASP actions

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Infection & Chemotherapy

and outcomes periodically and support system improvements. To encourage the leadership of the medical facility to support the human and financial resources required for an ASP, medical insurance should cover the cost of ASP-related activities. ASPs have benefits in terms of optimization of antimicrobial use, and minimization of the incidence of antimicrobial-resistant infections and CDI [6, 100]. In addition, ASPs reduce the use of hospital financial and medical resources, leading to reduced medical costs. These cost savings should be used to support ASP staff and the costs of running an ASP [101].

Accountability

Implementing an ASP requires leaders or co-leaders designated to be in charge of the program management and the outcomes. According to a hospital survey conducted by the National Healthcare Safety Network, 59% of the US hospitals were operating an ASP co-led by physicians and pharmacists in 2019 [102]. This is a desirable method for effective ASP operation because regular stewardship rounding by co-leaders and discussion with medical staff who prescribe antimicrobial agents leads to an improvement in antimicrobial use [29].

Pharmacy expertise

A pharmacist can operate an ASP highly effectively by actively participating in the program as a leader or co-leader [103]. It is important to select a pharmacist who can play a leading role in order to improve antimicrobial use. A pharmacist with an education in infectious diseases can be highly effective at improving antimicrobial and is often a good choice of leader in general hospitals and community hospitals. 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 and training.

Action

The two most effective intervention methods to improve antimicrobial use are prospective audit, feedback, and preauthorization [1]. Prospective audit and feedback can be implemented by external experts targeting antimicrobial use, which can be performed in various ways depending on their expertise. If there is an insufficient number of infectious disease experts, a review can be based on the treatment guidelines for common infections including CAP, UTIs, and skin and soft tissue infections, and real prescriptions. Feedback through the handshake stewardship can raise the effectiveness of prospective audit and feedback. Preauthorization is an intervention method that requires approval before antimicrobial use. This intervention method is helpful to increase the appropriateness of empirical antimicrobial agents in the early stage. If a medical facility develops and utilizes its treatment guidelines, prospective audit and preauthorization intervention methods may be more effective. Other methods include interventions based on common infectious diseases such as CAP, UTIs, and skin and soft tissue infections; interventions based on antimicrobial prescriptions such as antimicrobial timeout and penicillin allergy evaluations; pharmaceutical service team-based interventions; interventions based on microbiology test results; and nursing-based interventions.

Tracking

Tracking can be divided into the measurement of the amount of antimicrobial use, ASP outcome measurement, and process evaluation for quality improvement. The hospital or pharmacy information system should be used to measure the amount of antimicrobial use. In the US, various types of healthcare information technology companies help to report antimicrobial use options to the Nation Healthcare Safety Network [104]. They collect this information and provide almost all hospitals with antimicrobial use rates, reported as days of therapy (DOT). In addition, they also report the 'standardized antimicrobial administration ratio (a metric for comparing observed to predicted days of antimicrobial therapy)', enabling a comparison of antimicrobial use with other hospitals. The standardized antimicrobial administration ratio allows a comparison between the expected antimicrobial use and the actual antimicrobial use of the facility. Hospitals can obtain antimicrobial use information in the form of DOT or daily defined doses from the pharmacy information system. Daily defined doses are calculated by division of the total amount (grams) of antimicrobial agents purchased, ordered, prescribed, or administered during a certain period, by the value assigned by the World Health Organization, enabling the antimicrobial use of each hospital to be estimated [105]. Reduction of the incidence of CDI and antimicrobial resistance is an important goal of ASPs and monitoring the incidence of CDI and antimicrobial resistance is essential for evaluating ASP outcomes. Although cost-reduction should not be a primary measure of the success of an ASP, if cost savings are used to perform stewardship activities, it is useful to monitor cost savings. Evaluation of the quality improvement process can focus on specific interventions. Tracking the type and acceptance of prospective audit and feedback, can be useful for identifying areas that require more education and additional interventions. Treatment delays caused by preauthorization should be monitored. Other specific tracking methods include monitoring whether each hospital complies with treatment guidelines, whether antimicrobial timeout is performed, whether injectable antimicrobial agents are changed to oral agents, and whether two or more antimicrobial agents are unnecessarily administered together. The duration of antimicrobial administration should also be reviewed to determine whether it is appropriate.

Reporting and education

The ASP should regularly provide prescribers, pharmacists, nurses, and managers with updated information on dealing with national and local issues including antimicrobial resistance and its outcomes. Staff in the microbiology laboratory, the infection control department, and the medical epidemiology department in the hospital should collaborate in preparing reports on antimicrobial resistance. Information summarizing antimicrobial use and resistance, and ASP tasks should be regularly shared with the directors and the board of trustees of the hospital. Sharing the outcomes evaluations of medical drug use and the issues found during reviews of intervention with prescribers can motivate them to improve their antibiotic prescription practices.

Although education is a core element of comprehensive efforts to improve antimicrobial use in hospitals, education alone is insufficient. Education is most effective when combined with interventions and outcome measurement. Specifically, case-based education is highly effective, so prospective audit, feedback, and preauthorization are good methods for providing education on appropriate antimicrobial use. Education can be more effective if it is provided individually. Patient education is also an important component of ASPs. Patients should know the name of the antimicrobial agent with which they are being treated, and the reason for the treatment. Patients also should be informed about possible adverse effects and the signs and symptoms of adverse effects, and told to report any symptoms of adverse effects to prescribers. It is also desirable to involve patients in the development and review of educational materials for patients, and nurses play a critical role in patient involvement.

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Infection & Chemotherapy

Key Question 3: How does one operate the team that manages the antimicrobial stewardship program?

1. To successfully implement an ASP, physicians, pharmacists, nurses, microbiologists, infection control professionals, and information technology experts should collaborate (quality of evidence: moderate; strength of recommendation: strong).
2. Based on clinical experience, leadership experience, multidisciplinary relationships, and training courses, infectious disease and pediatric infectious disease specialists are well-equipped to lead a multidisciplinary ASP team (quality of evidence: moderate; strength of recommendation: strong).
3. A pharmacist is a core member of the ASP team and plays an important role in achieving the ASP goals (quality of evidence: moderate; strength of recommendation: strong).
4. Nurses, who play an important role in the treatment of patients and communication with physicians, should participate in the ASP team (quality of evidence: low; strength of recommendation: moderate).

An ASP requires participation of staff from multiple fields in the healthcare system infrastructure and collaboration with external partners. A key ASP component is routine collaboration of pharmacy, microbiology laboratory, clinical services, and the infection prevention teams. To successfully implement an ASP, the expertise of physicians, pharmacists, nurses, microbiologists, and infection control professionals should be utilized (**Fig. 2**) [106, 107].

Infectious disease and pediatric infectious disease specialists form the frontline for managing the diagnosis and treatment of complex infectious diseases, antimicrobial prescription, and effects of antimicrobial use. In clinical practice, infectious disease

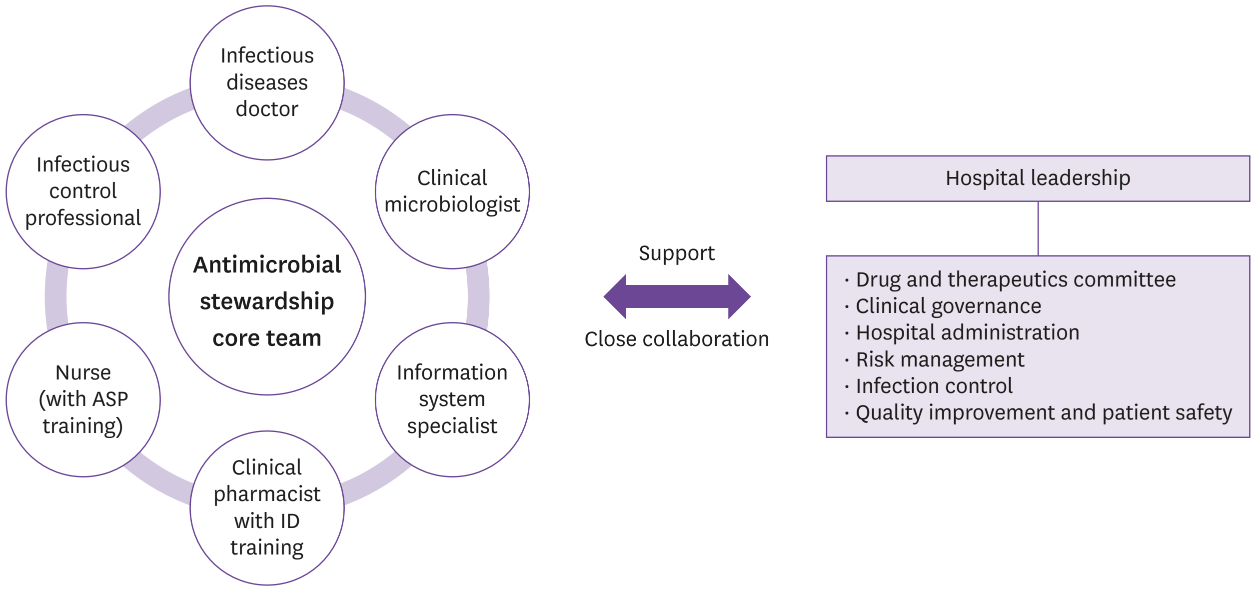

Figure 2. Core multidisciplinary experts comprising the ASP team [106, 107].
ASP, antimicrobial stewardship program; ID, infectious diseases.

Infection & Chemotherapy

doctors need to establish a strong relationship with the hospital managers and doctors in various other specialties to promote team-based treatment. The leadership skills of infectious disease doctors have been widely recognized because they play roles as hospital epidemiologists, infection control professionals, and quality improvement and patient safety officers. An ASP provides healthcare system-based guidelines for antimicrobial prescription using the local data on antimicrobial sensitivity and microbiology, and provides physicians with direct feedback on antimicrobial selection. Based on clinical experience, leadership experience, multidisciplinary relationships, and training courses, many infectious disease doctors are well-equipped to lead multidisciplinary ASP teams [106]. However, there are only 242 infectious disease doctors in Korea, distributed across 131 medical facilities, which is a ratio of one doctor per 372 beds [108]. Moreover, 2/3 of them work in the Seoul area, so many hospitals have no infectious disease doctors available to lead the ASP. There is an urgent need to train more infectious disease doctors. Staff from other disciplines can acquire the expertise to lead the ASP on behalf of infectious disease doctors through education.

A pharmacist, as a core member of the ASP team, supports the appropriate use of antimicrobial agents, including prospective audit through intervention and feedback, education, matrix development and tracking of antimicrobial use, use of rapid diagnostic tests, and the establishment of policies and protocols related to antimicrobial agents and infectious diseases [109]. Pharmacists play an extensive role in ASPs, and are important for achieving continuity of treatment, including inpatient and outpatient treatment, and long-term treatment. Considering the ongoing need for multidisciplinary collaboration, pharmacists can also play an important role in ensuring that all regulatory requirements of the ASP are met. Having antimicrobial prescriptions reviewed by a pharmacist, and consulting a pharmacist regarding antimicrobial prescriptions can reduce the amount of antimicrobial use. Thus, there should be policy support to include pharmacists in the ASP team [110]. In Korea, there are an insufficient number of pharmacists working in hospitals, so currently the pharmacists in the ASP team are not yet active. However, there are research results that effectively improved the use of antibiotics by pharmacists taking the lead in ASP activities using computerized programs [111, 112].

For successful application of an ASP, it is important to have multidisciplinary collaboration. Nurses have been reported to play an important role and to make a significant contribution [113]. In their work treating patients, nurses play a key role in the implementation of elements of the ASP. Nurses should be educated on antimicrobial resistance and the ASP before participating in ASP activities. It is important to include nurses in all ASP activities because they function as the most significant healthcare providers in routine patient treatment. Nurses play a particularly important role in the successful implementation of ASPs in long-term care facilities [114].

A clinical microbiologist is an essential member of the ASP team and can play a significant role in the promotion of appropriate antimicrobial use, monitoring resistant pathogens, and prevention of healthcare-related infection [115]. Rapid diagnostic technologies have the potential to shorten the required treatment time, improve treatments of patients, and should be applied after discussing with clinicians, clinical microbiologists, and the ASP team. The ASP team should help clinicians make appropriate use of the microbiology laboratory and to interpret antimicrobial sensitivity results. Collaboration between infection prevention program staff and ASP staff can maximize the efficiency and effectiveness of actions to prevent antimicrobial resistance. ASPs and infection prevention have common goals and

Infection & Chemotherapy

shared interventions. ASPs and infection prevention programs can both be effective for the prevention of infections caused by multidrug-resistant organisms, surgical site infections, and CDI, and education of staff regarding asymptomatic bacteriuria [116]. Integration of information technologies in the ASP can improve the efficiency and expand the scope of the ASP intervention. Information technologies promote ASP management including tracking and reporting antimicrobial use data and other indices [117]. Information technologies can provide prescribers with guidelines at the time of treatment using a clinical decision-support system and predictive analysis.

Key Question 4: Do antimicrobial stewardship programs decrease the amount and cost of antibiotic use?

1. Implementation of an ASP can reduce the amount of antimicrobial use and antimicrobial cost (quality of evidence: moderate; strength of recommendation: strong).
2. Antimicrobial prescription interventions that include prospective audit with feedback activities and introduction of restrictions on the use of certain antimicrobials can reduce the amount of antimicrobial use and antimicrobial cost (quality of evidence: moderate; strength of recommendation: strong).
3. Implementation of interventions (such as checklists, antibiotic time-out, the introduction of a computerized decision-support system for antimicrobial prescriptions) that promote appropriate prescription of antimicrobial agents can reduce the amount of antimicrobial use and antimicrobial cost (quality of evidence: moderate; strength of recommendation: strong).

Antimicrobial prescription interventions have been reported to reduce the amount and cost of antibiotic use in many countries [118-123]. Prospective audit with feedback, a key intervention, can reduce the amount of antimicrobial use regardless of the size of the type of facility. For example, a study conducted in a large hospital with approximately 1,100 beds in Sweden, found that an intervention in which an infectious disease specialist reviewed the medical records of inpatients in the medical ward who were receiving antimicrobial agents twice a week, and recommended changes to the antimicrobial agent use, led to a 27% reduction in total antimicrobial use [124]. In the US, a local community hospital with an average of less than 100 inpatients per day introduced empirical antimicrobial prescription guidelines that took into account the antimicrobial resistance rate in the local community and recommended antimicrobial agents after a prospective audit of major antimicrobial agents and a review of medical records. This was associated with a 10% reduction in antimicrobial use, and saved approximately $280,000 per year in medical costs [125]. In another study of patients who were admitted to a trauma and neurosurgery ICUs in a teaching hospital with 465 beds in Canada and prescribed antimicrobial agents, a physician and clinical pharmacist with infectious disease training reviewed the patients every weekday and recommended antimicrobial agents. This was associated with a 28% reduction in antimicrobial use [126].

Such prospective audit with feedback can be applied only to patients who were receiving certain antimicrobial agents which were targeted by the intervention [120, 127, 128]. When gram-positive bacteria with β-lactam resistance were not identified in patients within 96 hours after vancomycin administration in a university hospital of Korea, an infectious

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Infection & Chemotherapy

disease specialist directly contacted the prescribing doctor to ask them to stop using the antimicrobial agent. This resulted in a 15% reduction in vancomycin use [129]. However, most studies found that these effects on reduction of the amount and cost of antimicrobial agent use did not extend to antimicrobials that were not targeted by the intervention [130, 131]. In addition to interventions targeting certain antimicrobial agents, specific patient groups that are subject to prospective audit with feedback can be identified by various methods, depending on the hospital setting. Such interventions also generally reduce the amount of antimicrobial use and costs. In a hospital in Singapore, doctors in the ASP team reviewed empirical prescriptions of antimicrobial agents within 24 hours of administration. If there was no indication for antimicrobial use, they recommended suspension. When the recommendation was followed, this saved approximately SGD 10,817 (approximately 9,400,000 Korean Won) per patient [121]. In Korea, a hospital implemented a program in which a clinical pharmacist reviewed the records of patients who were being prescribed redundant anti-anaerobic antimicrobials and suspended unnecessary anti-anaerobic antimicrobial use. This led to a reduction of approximately 50% in prescriptions for metronidazole and clindamycin [132]. In another study conducted in Korea of inpatients were prescribed intravenous fluoroquinolone, an antimicrobial agent with a high bioavailability, it was recommended that the administration be changed to oral administration in patients who met certain conditions. This reduced the cost of fluoroquinolone use by 35% compared to a control group [53].

Antimicrobial restriction and preauthorization of prescriptions, another key intervention for antimicrobial prescription, is particularly useful as core a strategy for ASP implementation in Korean hospitals that have do not have sufficient human resources for ASP implementation [7, 8]. When restrictions were placed on the use of certain antimicrobials in adult patients who were admitted to a university hospital with approximately 860 beds in Korea, there was a reduction in the use of carbapenem, one of the restricted antimicrobial agents, and glycopeptides, which were widely used in ICU patients [133]. Restrictions on antimicrobial use were also found to be effective in a mid-size, 400-bed hospital with limited resources in Korea. Immediately after the implementation of restrictions on the use of certain antimicrobials, the use of carbapenem, a restricted microbial agent, and glycopeptides decreased [134]. Studies conducted in other countries have also found a reduction in antimicrobial use and costs following the implementation of antimicrobial restrictions and preauthorization of antimicrobial prescriptions. In a study conducted in four tertiary hospitals in Saudi Arabia, antimicrobial costs decreased by approximately 28% immediately after the program implementation [123]. In a study conducted in a large hospital in the US, the antimicrobial use of fluoroquinolone decreased from 173 DOT/1,000 patient-days to < 60 DOT/1,000 patient-days after introduction of a program for antimicrobial restriction and preauthorization of prescriptions targeting fluoroquinolone [135].

Interventions that encourage prescribers to make appropriate antimicrobial prescriptions on their own, can also lead to a reduction of antimicrobial use and costs. In a study conducted in the Netherlands, nine hospitals introduced an antimicrobial checklist and asked prescribers check it before antimicrobial prescription. This intervention not only improved the appropriateness of antimicrobial prescriptions, but also shortened the length of hospitalization and saved approximately 12 Euro per patient [118]. In a study conducted in a university hospital in Canada, an antibiotic timeout policy was implemented that required that residents reevaluate antimicrobial prescriptions twice a week. This led to a 46% reduction in the total antimicrobial costs of patients treated in the ward [136]. In

Korea, a large hospital introduced a computerized decision-support system for antimicrobial prescriptions, linked to a computerized prescription program to promote appropriate antimicrobial prescription. This reduced the use of the third-generation cephalosporins and aminoglycosides [137]. In a study conducted in Spain, guidelines for the appropriate use of antimicrobial agents were developed and distributed, and education for appropriate antimicrobial prescription was provided. This led to a reduction in antimicrobial use [138].

Remote antimicrobial interventions can also reduce antimicrobial use and costs. In a study in the US targeting a local community hospital, a clinical pharmacist reviewed inpatients who were receiving antimicrobial agents 2 to 3 times a week, and an infectious disease specialist reviewed it again through a remote system and sent recommendations. This led to a reduction of approximately 24% in a broad range of antimicrobials that were subject to the intervention, and a reduction in antimicrobial costs of approximately $143,000 per annum [139]. In a large children's hospital in the US, an infectious disease specialist and a clinical pharmacist reviewed all medical records of patients with antimicrobial prescriptions of a certain department for 3 to 4 hours and sent recommendations about appropriate antimicrobial use. Concurrently, they applied handshake stewardship and performed rounding with medical staff in the care team three times a week. This was associated with a reduction in antimicrobial prescriptions of approximately 27% in adults, and approximately 13% in pediatric patients [140].

Key Question 5: What are the effects of antimicrobial stewardship programs on the clinical outcome (prognosis) of patients?

1. ASP implementation improves the clinical prognosis of patients (quality of evidence: moderate; strength of recommendation: strong).
2. ASP implementation decreases the amount and costs of antimicrobial use without aggravating the clinical prognosis of patients (quality of evidence: moderate; strength of recommendation: strong).
3. To improve the clinical prognosis of patients, ASP interventions such as prospective audit with feedback for antimicrobial use should be introduced (quality of evidence: moderate; strength of recommendation: strong).
4. To improve the clinical prognosis of patients, various interventions, including TDM and change of intravenous administration to oral administration are needed (quality of evidence: moderate; strength of recommendation: strong).

The major goals of ASPs are to minimize unintended outcomes such as the generation of antimicrobial-resistant strains or adverse drug reactions by promoting the appropriate use of antimicrobial agents and to ultimately improve the clinical outcomes of patients [1, 141]. Several previous studies reported that inappropriate use of antimicrobial agents, particularly misuse and abuse of a broad range of antimicrobial agents, negatively affected clinical outcomes in addition to increasing the incidence of antimicrobial resistance [142-144]. Inappropriate antimicrobial use during early treatment is an important factor that adversely affects the prognosis of patients with severe infectious diseases [145]. Inappropriate initial antimicrobial use may increase the incidence of nosocomial infection and increase the length of hospitalization and mortality [146].

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Infection & Chemotherapy

Some studies have found that interventions that promote appropriate use of antimicrobial agents as part of an ASP, have led to improved clinical outcomes in addition to a reduction in the incidence of antimicrobial resistance [27, 107, 147, 148]. Particularly, when an infectious disease doctor makes recommendations for patient groups with severe infectious diseases, such as patients with sepsis, as a part of an ASP, the rates of the appropriate antimicrobial selection and de-escalation increase [149, 150]. In a 972-bed hospital in Japan, an ASP team composed of an infectious disease doctor and a pharmacist implemented a program that regularly performed a prospective audit with feedback for antimicrobial use every week, targeting patients with bacteremia and patients who had received antimicrobial agents for 7 days or longer. This led to a significant reduction in the in-hospital mortality of patients with bacteremia, particularly, the 30-day mortality and in-hospital mortality in patients with antimicrobial-resistant gram-negative bacteremia. In addition, the antimicrobial administration period in patients with Gram-negative bacteremia was also reduced [151]. In a study conducted in an 860-bed hospital in Singapore to evaluate a program that restricted inappropriate antimicrobial use and de-escalated a broad range of antimicrobial agents targeting patients who were receiving carbapenems, the patients of doctors who complied with adjusted prescription recommendations showed less use of carbapenems and a significant reduction in the 30-day mortality compared to the patients of doctors who did not comply with the recommendations, while there was no significant change in the length of hospitalization or the 30-day rehospitalization rate [152].

In ASPs, there are various methods to promote appropriate antimicrobial use: preauthorization of antimicrobial use or giving feedback after a prospective audit of antimicrobial use, restriction of the use of certain antimicrobial agents, development of antimicrobial prescription guidelines, and providing an antimicrobial prescription support program [1, 15]. During prospective audits of antimicrobial use, feedback if provided on diagnosis and treatment through investigation of etiologies in addition to providing recommendations regarding antimicrobial prescription. Accurate diagnosis and procedure to identify causative bacteria are enhanced during consultations with infectious disease experts, which helps to improve the clinical outcomes [153-155]. Studies have found decreases in the mortality rate decreased after implementation of ASPs that include TDM, change of intravenous administration to oral administration, and the restriction of a broad range of antimicrobial agents [156, 157]. In Singapore, a 1,500-bed hospital implemented an antimicrobial management program operated by a multidisciplinary team, in which the effects of various clinical recommendations made during stewardship activities on the prognosis of patients were evaluated in addition to the effects of antimicrobial agent-related measures. The study found that the patient group in which the doctor accepted the clinical recommendations had a significantly lower 30-day mortality rate than the group in which the doctor did not follow the recommendations. This could be due to the enhanced effort for appropriate antimicrobial prescription according to the patient's condition in addition to antimicrobial restriction during the implementation of the program [158].

There are few well-designed studies that have evaluated the long-term effects of ASPs after implementation, and there is a need for further studies. In Australia, the adult ICU of a tertiary hospital implemented an ASP from November 2005 to October 2015 that included developing guidelines for antimicrobial prescription; utilization of the designated prescription set; restriction of the list of antimicrobial agents that can be prescribed; regular rounding by a multidisciplinary team; de-escalation of antimicrobial agents; and monitoring of the prescription of gentamicin and vancomycin. During the study period, the severity-

Infection & Chemotherapy

adjusted mortality rate of the ICU patients decreased from 12.9% to 10.4%, the 30-day mortality rate of the patients with bacteremia decreased from 37.9% to 26.3%, although these decreases were not statistically significant [159].

Some before-and-after studies of an ASP implementation found that there was no significant effect on the all-cause mortality rate or infection-related mortality rate of patients, while there were changes in antimicrobial resistance and use [100, 157]. Many studies on the effect of restrictions on the use of a broad range of antimicrobials have found a reduction in antimicrobial use and costs but no significant reduction in the mortality rate [27, 100, 157, 160]. Two recent systematic reviews and meta-analyses of the effects of ASPs in Asian countries showed that the amount of antimicrobial use decreased after ASP implementation, while there was no significant change in inpatient mortality [156, 161]. Some studies have found changes (reductions or increases) in the length of hospitalization or the rehospitalization rate after ASP implementation, but in most studies these changes were not statistically significant[29, 50, 152, 160, 162, 163]. The results of studies of the effects of ASPs indicate that ASP implementation can achieve the goals of reduction in the amount of antimicrobial use and antimicrobial costs without a significant effect on clinical prognosis indicators such as the mortality rate, length of hospitalization, and the rehospitalization rate. These studies provide evidence that can dispel any concerns that ASP implementation could induce insufficient antimicrobial treatment, and have an adverse effect on clinical outcomes such as the mortality rate.

While many studies on the effect of ASP analyzed mortality rate, length of hospitalization, and the rehospitalization rate to evaluate the clinical prognosis of patients, these studies have generally had several limitations. Indicators such as the mortality rate or the length of hospitalization can be affected by various factors other than antimicrobial use, such as comorbidities and the severity of infection. In addition, a short study period and implementation of infection control guidelines or antimicrobial prescription-related policies prior to the implementation of the ASP can make it difficult to evaluate the effect of the new program. Variables such as a change in characteristics of the patient group during the study period, communication problems between doctors, and modification of infection control activities can also affect the effectiveness of the program, so careful planning is required for future studies of the clinical effects of ASPs [5].

Key Question 6: What are the effects of antimicrobial stewardship programs on the adverse effects (toxicity or allergy) of antibiotic use?

1. ASPs reduce the adverse effects of antimicrobial agents through monitoring therapeutic drug concentration (quality of evidence: moderate; strength of recommendation: strong).
2. ASPs can mitigate allergy caused by antimicrobial use (quality of evidence: low; strength of recommendation: weak).

Appropriate antimicrobial use is one of the most important aspects of patient safety. Of supplemental strategies for ASPs, the optimization of antimicrobial dose and administration period is an important strategy that can maximize therapeutic effects and minimize the adverse effects [4]. To optimize the dose of antimicrobials, the change in pharmacokinetics (PK) of patients and pharmacodynamics (PD) of the administered drugs should be understood [164, 165]. Methods that determine the best β-lactam antimicrobial dose based

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Infection & Chemotherapy

on information on the PK and PD include using a dose based on the guidelines, TDM of the antimicrobial agent, utilization of dose-optimization software, and administration of the drug at the dose that improved clinical outcomes in compared to a previous dose [55]. If penicillin and imipenem are administered to patients with impaired renal function without lowering the dose, this can lead to an excessive blood level, resulting in neuromuscular overexcitability, convulsions, and coma. In patients with impaired renal function, the dose of aminoglycosides and vancomycin also need to be adjusted and TDM is required due to their high renal toxicity [166]. As erythromycin, azithromycin, and clindamycin are metabolized mostly in the liver, care should be taken when administering them to patients with hepatic disorders [166]. A study found that periodic cycling of antimicrobial agents in order to reduce bacterial resistance did not increase antimicrobial-related adverse effects [167]. A study on renal toxicity conducted in Australia, found the 14% of antimicrobial agents administered to patients with creatinine levels of 120 μmol/L or higher, were given in inappropriate doses, and that patients with elevated creatinine level were more than three times more likely to be prescribed an inappropriate dose (odds ratio [OR]: 3.4) [168]. In France, a team of infectious disease experts developed ASP guidelines and applied them in a 960-bed university hospital in order to reduce the incidence of antimicrobial-related adverse effects through education, evaluation, and feedback. This resulted in a 73%-reduction in the incidence of renal toxicity in a year [169]. In Korea, a multicenter study was conducted in five general hospitals to investigate the incidence of adverse reactions to antimicrobial agents. Hospitals that implemented multidisciplinary ASPs that included pharmacists had a lower incidence of adverse reactions to antimicrobial agents than those with ASPs without pharmacists (8.9% *vs.* 14.7%, $P < 0.001$), and ASPs managed by a multidisciplinary teams that included pharmacists had a 38% lower incidence of adverse reactions to antimicrobial agents (OR: 0.62) [170].

If the dose of aminoglycosides is optimized following TDM rather than being administered at the standard dose, an appropriate concentration can be achieved within the therapeutic range in addition to cost saving [56, 171], and renal toxicity, length of hospitalization, and mortality rate can also be reduced [56, 172]. In addition, PK/PD-based administration such as once-daily administration was also effective for alleviating renal toxicity and even improved clinical outcomes in some studies [173, 174]. The renal toxicity of vancomycin can be reduced by changing the mode of administration [175], or by adjusting the dose according to the blood level through TDM [57].

The promotion of appropriate antimicrobial prescription by ASPs is not only cost-effective, but can also play an important role in promoting patient safety by reducing the incidence of adverse reactions to antimicrobial agents including the CDI incidence. Antimicrobial agents that have a high-risk of causing CDI include a broad range of agents including third-generation cephalosporins, fluoroquinolones, and clindamycin [176]. Many studies have found that ASPs that reduce the use of clindamycin [177-180] cephalosporins [178-183], or fluoroquinolones [178-182, 184], resulted in a reduction in the CDI incidence.

Antimicrobial agents are the most common cause of drug allergies in inpatients [185]. Penicillin is the most common cause of drug allergy in inpatients, with a reported prevalence of 10 - 15% in inpatients and 15 - 24% in patients who require antimicrobial treatment [185, 186]. One study found that, compared to patients who were not allergic to penicillin, patients who had an allergy to penicillin were exposed to a greater number of alternative antimicrobial agents and had a higher CDI incidence, methicillin-resistant *Staphylococcus*

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Infection & Chemotherapy

aureus and vancomycin-resistant Enterococcus (VRE) infection, and a longer hospitalization period [185]. When the skin test for penicillin allergies was performed correctly, the negative predictive value was 97 - 99%, and the positive predictive value was 50% [187]. Several studies have found that many patients predicted to have a penicillin allergy, were not allergic to penicillin on allergy skin testing and when the allergy history was correctly evaluated, and that penicillin and other β-lactam antimicrobial agents could be safely administered [186, 188]. It was because most patients who were allergic to penicillin and β-lactams, in comparison to patients without antimicrobial allergy, were examined without accurate evaluation so that they had no actual allergy to the corresponding drugs [189]. Rimawi et al. [190], administered β-lactam antimicrobial agents to 146 patients who were negative on a skin test for penicillin allergy, despite having a penicillin allergy history. Except for one patient, 145 patients showed no adverse effects of antimicrobial agents, indicating that over 99% of the allergy histories were incorrect [190].

The use of a structured drug allergy testing can be associated with improved ASP performance in terms of selection of the antimicrobial agent, reduction of alternative antimicrobial use, reduction in the length of hospitalization, medical cost saving, and improved compliance with clinical guidelines [186, 188]. Park et al. [191], reported that a collaboration between a trained pharmacist and an allergy specialist was associated with an increase in a β-lactam prescription to patients with a penicillin allergy history.

To effectively and successfully use first-line antimicrobial agents to patients reported to have an allergy to penicillin and β-lactams, ASPs should enhance the evaluation of allergies to antimicrobial agents by means of measures such as skin testing for penicillin allergy [1].

Key Question 7: What are the effects of antimicrobial stewardship programs on the incidence of *Clostridioides difficile* infection (CDI)?

1. ASP implementation reduces the CDI incidence (colitis) (quality of evidence: moderate; strength of recommendation: strong).

ASP implementation can enhance the treatment and safety of patients [192, 193]. Several studies have found that ASPs reduce the nosocomial CDI incidence. *C. difficile* is an enteropathogen that colonizes the intestine after antimicrobial treatment [194]. A severe infection can lead to intestinal perforation, and sepsis. It primarily affects older patients and has a case fatality rate of up to 10% [195].

An exposure history to antimicrobial agents always precedes CDI [192], to which a broad range of antimicrobial agents including the 3rd generation cephalosporin, fluoroquinolone, clindamycin are mostly related [176]. Restriction of exposure to such high-risk antimicrobial agents through ASPs is an effective method of preventing CDI. Many studies showed that ASPs can reduce the CDI incidence when clindamycin, a CDI-inducing high-risk drug, [177-180] or a broad range of antimicrobial agents, particularly cephalosporins [178-183] and fluoroquinolones [178-182, 184] were used. In a study by Climo et al. [177], clindamycin restriction was associated with a statistically significant reduction in clindamycin use and the CDI incidence (P <0.001) and an improvement of clindamycin sensitivity (P <0.001). In addition, the study was the first study demonstrating that CDI reduction could save on overall medical costs. Both in short-term outbreaks of CDI [178, 184] and facilities with endemic CDI

Infection & Chemotherapy

[17, 182], ASPs have been shown to be associated with a statistically significant reduction in the incidence of nosocomial CDI [17, 177-180, 182-184]. The decrease in the CDI incidence can extend over a period of as long as 7 years [17].

Other studies have consistently shown that the addition of antimicrobial restriction strategies to the existing infection control measures can reduce the CDI incidence [177, 178]. According to a report by Valiguette et al. [178], simple reinforcement of basic infection control measures was unable to reduce the CDI incidence. However, the CDI incidence was reduced by using local treatment guidelines; a prospective audit with feedback; and an antimicrobial intervention that reduced the use of second- and third-generation cephalosporins, clindamycin, macrolides, and fluoroquinolones, using a shorter antimicrobial administration period (P <0.007).

In addition, a study found that the CDI incidence decreased after implementation of a non-restrictive ASP in an emergency department (ED) [196]. The ED is an environment that has less continuity of treatment and frequently requires rapid decision-making without obtaining meaningful microbiological information due to high patient loads, rapid turnover rate [197], and frequent changes in medical staff, so it is difficult to apply an ASP that reduces inappropriate antimicrobial use in this setting [198, 199]. EDs are positioned between the community and the hospital, so that a selection of antimicrobial agents in the ED can affect antimicrobial use of both discharged patients and admitted patients [198]. Hence, it is important to implement appropriate ASPs in EDs. Savoldi et al. [196], collected epidemiological and clinical information for a year before implementing an intervention. Based on the information that they collected, they developed and distributed appropriate empirical antimicrobial treatment guidelines for the ED, followed by weekly education, prospective audit with feedback, active collaborative treatment of infectious diseases, randomized audit, and regular feedback for 3 years. As a result, antimicrobial use and medical costs decreased in the entire ward, and the CDI incidence was significantly lowered.

Many systematic literature reviews and meta-analyses have reported the effect of ASPs on the CDI incidence in inpatients [6, 11, 200]. In a meta-analysis of 16 studies, the effect of the antimicrobial intervention on CDI prevention and control was highlighted, and the ASP intervention strategy was outlined [11]. The authors reported a 52% reduction in CDI incidence after ASP implementation, and reported that ASPs were particularly effective among older patients who are particularly vulnerable to CDI and have a high CDI-related mortality rate. Davey et al. [200], analyzed 20 interrupted time-series studies and found that the ASPs reduced the CDI incidence by 49%. Another meta-analysis of 32 studies found that the CDI incidence was reduced by 32% after API implementation [6].

On the other hand, as the length of hospital stay increases, the frequency of intestinal colonization increases, which lead to in-hospital transmission. Thus, in order to reduce CDI, infection control including shortening of hospital stay and standard precautions should be implemented together with ASPs [201].

Infection & Chemotherapy

Key Question 8: Do antimicrobial stewardship programs decrease antibiotic (antimicrobial) resistance?

1. ASP implementation decreases antimicrobial resistance (quality of evidence: moderate; strength of recommendation: strong).
2. Prospective audit with feedback should be introduced together with antimicrobial restriction to reduce antimicrobial resistance (quality of evidence: moderate; strength of recommendation: strong).
3. To reduce antimicrobial resistance, ASPs should be implemented together with infection control measures (quality of evidence: moderate; strength of recommendation: strong).
4. Further studies are needed to evaluate the effect of ASPs on the reduction of antimicrobial resistance (quality of evidence: low; strength of recommendation: strong).

Multiple studies have reported that an increase in antimicrobial use is an important risk factor for colonization or infection by multidrug-resistant bacteria [202-204]. An ASP is an intervention to minimize unnecessary antimicrobial use through administering an appropriate dose of antimicrobial only to patients who need the specific antimicrobial agent for the optimal period of time [1]. Strategies for preventing the occurrence of multidrug-resistant bacterial infections and the spread of multidrug-resistant bacteria in the hospital should include systematic management of antimicrobial prescription through an ASP.

ASPs focused on the restriction of a broad range of antimicrobial prescriptions are routinely employed in clinical practice. Depending on the capacity of the medical facility, various methods including prospective audit with feedback, education of medical staff and patients, development of antimicrobial prescription guidelines, and an antimicrobial prescription support program have been used [1]. Particularly, providing medical staff with reports on the antimicrobial situation and antimicrobial sensitivity data of the medical facility as a part of an ASP has a synergistic effect on prevention of nosocomial infection and reduction of antimicrobial resistance. To achieve a reduction of antimicrobial resistance through the efficient implementation of an ASP, it is necessary to have multidisciplinary cooperation of various fields including infectious disease experts, the infection control team, the pharmacology team, relevant clinical departments, and the micribiology laboratory [205].

Many recently published studies have shown that ASP implementation had a reduction effect of antimicrobial use and selection pressure. Particularly, when a prospective audit with feedback for antimicrobial prescription and infection control activities are combined, can result in a significant reduction in antimicrobial resistance in a hospital. In a study conducted in a 1,000-bed tertiary hospital in Spain, a program was implemented including the development and application of the antimicrobial prescription guidelines, prospective audit of antimicrobial use, collaborative treatment with an infectious disease expert, feedback of medical staff about antimicrobial prescription, improvement of antimicrobial prescription behavior, and a financial incentive. One year after the implementation of the program, inappropriate prescription of antimicrobial agents decreased from 53% to 25.4%, and the total antimicrobial use in the hospital declined. This trend lasted for 5 years after the implementation of the program, during which the incidence of multidrug-resistant gram-negative bacterial infections and nosocomial candidiasis also significantly decreased

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[206, 207]. In a study conducted at an 800-bed university hospital in Korea, an infectious disease expert led a prescription restriction program for broad-spectrum antimicrobial agents including carbapenems and glycopeptides, and monitored duplicate prescription of anti-anaerobic antimicrobials. This resulted in a significant reduction in the use of restricted antimicrobial agents and third-generation cephalosporins, β-lactam/β-lactamase inhibitors, and fluoroquinolones. Moreover, the prevalence of resistance of *S. aureus* to ciprofloxacin and oxacillin and resistance of *P. aeruginosa* to carbapenem decreased in the ICU [133]. A hematological malignancy unit of a US hospital applied a program that included the initial empirical designation of antimicrobial agents and regular cycling for febrile neutropenia patients and empirical anti-VRE antimicrobial use following a clinical prediction rule of VRE infection. This resulted in a reduction in the use of carbapenem and daptomycin, and a statistically significant reduction in the incidence of VRE colonization and infection in the study patients [208].

According to recent several meta-analyses, the infection and colonization by multidrug-resistant gram-negative bacteria, methicillin-resistant *S. aureus*, and CDI incidence declined after the ASP implementation. ASPs were more effective when infection control interventions, including hand hygiene interventions, were combined [6, 11, 100, 157]. Similarly, a meta-analysis on the prevention of multidrug-resistant bacterial infections in ICUs found that the occurrence of multidrug-resistant gram-negative bacterial infections, particularly extended-spectrum beta-lactamase-producing bacterial infections, decreased markedly after infection control measures such as environmental cleaning or selective decolonization were implemented in combination with the ASP [209].

However, some studies have found that the implementation of ASPs did not reduce the prevalence of antimicrobial resistance [5, 107, 210]. A meta-analysis found that despite an increase in compliance with the antimicrobial prescription guidelines and a decrease in the antimicrobial administration period by more than 1 day on average, after ASP implementation, there was no significant reduction in mortality rate, length of hospitalization, or the prevalence of antimicrobial resistance [27]. According to a recent systematic literature review, some studies showed a reduction of in the incidence of nosocomial VRE infections after the implementation of programs that restricted the prescription of the third-generation cephalosporins, vancomycin, and clindamycin, whereas a prescription restriction strategy that preferentially selected ertapenem among carbapenems did not significantly lower the incidence of carbapenem-resistant *Acinetobacter baumannii* and *P. aeruginosa* infections [211-214]. Few studies found a significant change in the incidence of carbapenem-resistant *A. baumannii* infection after implementing restriction on the prescription of carbapenems, which suggests that it is difficult to inhibit the incidence of multidrug-resistant gram-negative bacterial infections, and the occurrence of major resistant strains, by prescription restriction programs that target only specific antimicrobial agents [54, 215, 216].

There are various limitations in studies that investigated the effect of ASP on antimicrobial resistance in medical facilities. It is difficult to control various factors affecting the incidence of antimicrobial resistance in the hospitals during the study period, particularly, a change in the infection control policy, an increase of patients with chronic or severe underlying diseases, and the inflow of antimicrobial-resistant strains from outside the hospital, which can affect the evaluation of the ASP effect. Although some studies observed a reduction of antimicrobial-resistant strains after the implementation of programs targeting antimicrobial

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restriction, most studies have reported the effects in terms of the amount of antimicrobial use or costs, while few studies have analyzed the effect on antimicrobial resistance as a primary objective. Most studies that provided evidence of a reduction in antimicrobial resistance were descriptive studies based on simple observation, while there were only a few studies that were adequately designed to evaluate the effect of the ASP such as randomized controlled trials and quasi-experimental studies [210]. ASPs can have varying effects on prescription behavior. For example, after the implementation of the program that restricts the prescription of certain antimicrobial classes, the use of alternative antimicrobial agents can increase. However, there are few long-term studies that evaluated the change in subsequent antimicrobial resistance or other adverse effects, so the relationship between ASPs and antimicrobial resistance requires further study.

Key Question 9: What types of strategies (programs) can be applied for antimicrobial stewardship programs in smaller community hospitals and long-term care hospitals?

1. As ASPs are effective, even small local community hospitals should introduce ASPs (quality of evidence: moderate; strength of recommendation: strong).
2. ASP interventions are recommended for long-term care hospitals (quality of evidence: moderate; strength of recommendation: strong).
3. It is important to prioritize the reduction of CDI through treatment of asymptomatic bacteriuria (quality of evidence: moderate; strength of recommendation: strong).
4. Small local community hospitals and long-term care facilities need to change the system and support expert training to promote the ASP (quality of evidence: low; strength of recommendation: weak).

All medical facilities need ASPs regardless of their size and main roles. Unlike large acute tertiary hospitals, local community hospitals with fewer resources may consider the implementation of an ASP as a lower priority. Thus, other approaches are required to implement the ASP. While making an effort to implement ASP core elements used in the acute hospitals, they need to employ different ASP interventions that are applicable only to small medical facilities [1, 217]. To promote active participation of medical staff who prescribe antimicrobial agents, ASP team leaders should enlist active support of the hospital directors [217]. In addition, they also need to trace and manage executable ASP indicators and periodically report them to the directors [217].

A study found a reduction in the incidence of *C. difficile* infection in a small hospital after implementing ASP activities, indicating a positive effect of the ASP [125]. However, the study was a pre-post comparison study, and difficult to conduct randomized controlled trials in small local community hospitals and long-term care facilities. Hence, there are limited data with a high quality of evidence regarding the effectiveness of ASPs in small local community hospitals and long-term care facilities. In the US, a small local community hospital reported a positive effect after a pharmacist-led ASP implementation [218]. However, the inclusion of pharmacists in ASPs is possible only in a limited number of large tertiary hospitals in Korea, so including pharmacists of small hospitals in ASP activities can only be considered as a long-term goal or a recommendation.

Infection & Chemotherapy

Older patients staying in long-term care facilities have a higher risk of infection [219, 220]. As life-expectancy increases, the demand for long-term care facilities continues to grow. For many reasons, antimicrobial agents are used extensively in long-term care facilities, of which approximately 50 - 75% are considered inappropriate or unnecessary [220-223]. Excessive use of antimicrobial agents can have a direct negative effect on the residents of long-term care facilities and promote the occurrence and spread of resistant bacteria [220, 221].

Antimicrobial use at the end of life in long-term care facilities can degrade the quality of life, extend the dying process, and cause unnecessary costs that are seldom or never of benefit to the residents [224].

A study with European countries reported that approximately 40% of antimicrobial use in long-term care facilities was for preventive purposes [220], of which UTIs accounted for 70 - 75% of cases, followed by respiratory infections (12-18%), and skin and wound infections (4%) [220].

Long-term care facilities should not only minimize antimicrobial selection pressure but also participate in an ASP program that improves the quality of treatment of their residents [221].

Asymptomatic bacteriuria is commonly found in residents of long-term care facilities, for which antimicrobial agents are frequently prescribed [225]. Although evidence clearly shows that there is no clinical merit for the treatment of asymptomatic bacteriuria using antimicrobial agents, antimicrobial agents are routinely prescribed in many facilities so that this should be a priority focus of ASPs. Previous studies have shown that ASPs can reduce the prevalence of inappropriate antibiotic use in long-term care facilities [225-228].

Compared to general acute hospitals, local community hospitals and long-term care facilities have relatively limited financial and human resources, so that the applicable ASP structure and human resources need to differ from those of general acute hospitals. These topics should be studied further [217].

An institutional strategy is required for the introduction of an ASP in long-term care facilities. According to a survey on the status of ASP implementation in long-term care facilities in Pennsylvania in the US in 2017, 47% of the all long-term care facilities had implemented an ASP [229]. Many medical facilities had recently implemented an ASP because an ASP became an accreditation requirement in 2017 [230]. An institutional strategy should be prepared for long-term care facilities in Korea, either after or at the same time as ASP implementation in general acute hospitals has been stabilized based on institutional support. According to a recent domestic survey, it was found that in order to introduce and revitalize ASP in local community medical institutions, it is urgent to provide support for manpower who can perform ASP and to prepare a system that can compensate the costs of ASP activities [231]. According to this survey, it was confirmed that not only the personnel in charge of ASP were absent in community medical institutions, but also actual ASP activities were not being performed [231].

In the aforementioned study in Pennsylvania of the US, pharmacists led approximately 80% of long-term care facilities to apply the ASP, whereas the ASP in collaboration with infectious disease departments was as low as 12.7% [229]. In the US, pharmacists usually lead the ASP in small local community hospitals, and its positive effects were reported [218, 232]. Given that pharmacists have limited participation in ASPs, even in acute tertiary hospitals, there are no case studies of pharmacist-led ASPs in small hospitals in Korea. Due to the lack of experts and an institutional system, there is no collaboration among mid-size to small hospitals in Korea in the implementation of ASPs. In Korea, the Infection Control Consulting Network has been established, which promotes expert consulting for infection control in mid-size to small hospitals (hospitals, long-term care facilities, and clinics that have less than 150 beds). However, the Infection Control Consulting Network has no support for the ASP interventions.

There have been recent reports of infectious disease doctors performing an ASP intervention that entailed remotely reviewing antimicrobial agents used for lower respiratory tract infections or cellulitis. The intervention was found to save a broad range of antimicrobial use and costs [139, 233, 234], and to reduce the CDI incidence [234, 235]. While this has a sufficient base of application in Korea, the law and regualational challenge should be overcome in the future.

Because of the extreme shortage of professionals such as infectious disease specialists who can effectively manage ASPs, strategies need to be developed to compensate for the lack of skilled human resources. For smooth consulting, issues of social infrastructure for remote care and reimbursement for medical treatment should also be addressed.

CONCLUSIONS

This guideline discusses core and supplementary ASP strategies, important elements for ASP, and the impacts of ASP. Each institution have to assess its clinical needs and available resources and individualize its ASP.

1. Limitations of these guidelines and contents to be added in the future

The most challenging part in the development of the ASP guidelines was that there were only a small number of good quality evidence-based studies on this topic. In addition, most clinical trials that were used as evidence for the recommendations contained in these guidelines were conducted in other countries because of the limited number of Korean studies. This should be taken into account when applying these guidelines in clinical practice. Even with the studies conducted in other countries, it was difficult to find results that provided a strong level of evidence. The effect of ASP strategies was evaluated mostly by comparative studies such as before-and-after intervention surveys and research on specific conditions. However, it is challenging to perform reliable randomized blind studies of this topic. In order to revise the guidelines to make them more applicable to Korea, it is desirable to conduct a studies in Korean health facilities in order to accumulate data.

It is not possible to prevent antimicrobial resistance without an ASP. Implementation of an ASP should lead to a reduction in the incidence of antimicrobial-resistant infections and the adverse effects of antimicrobial agents, and other positive clinical outcomes in clinical practice.

Lastly, the usefulness of these ASP guidelines will be assessed through the level of compliance with these clinical guidelines in clinical setting, and then factors preventing compliance should be analyzed and reflected in future revisions of these guidelines.

2. Conflict of interest

Although the Korea Disease Control and Prevention Agency developed these guidelines through the Policy Research Service Project, the Agency did not participate in the content

Infection & Chemotherapy

development for these guidelines. The ASP Guidelines Development Committee declares that there was no potential influence from any government agencies, pharmaceutical companies, hospital organizations, and interest groups during the development process.

3. Plans for revision of these guidelines

These guidelines will be revised periodically to keep them relevant to the situation in Korea by reflecting results of recent studies conducted both in Korea and in other countries.

SUPPLEMENTARY MATERIAL

Korean version of the guidelines.

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