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Special Article

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Korean Guidelines for Use of Antibiotics for Intra-abdominal Infections in Adults

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ABSTRACT

The guidelines are intended to provide practical information for the correct use of antibiotics for intra-abdominal infections in Korea. With the aim of realizing evidence-based treatment, these guidelines for the use of antibiotics were written to help clinicians find answers to key clinical questions that arise in the course of patient care, using the latest research results based on systematic literature review. The guidelines were prepared in consideration of the data on the causative pathogens of intra-abdominal infections in Korea, the antibiotic susceptibility of the causative pathogens, and the antibiotics available in Korea.

Keywords: Intraabdominal infections; Anti-bacterial agents; Practice guideline

INSTRUCTIONS FOR USE OF GUIDELINES

The guidelines aim to present the basic principles for the use of antibiotics in patients with intra-abdominal infections in consideration of the current domestic situation. The guidelines are not intended to be applied uniformly to all patients but to be a reference for physicians who directly treat patients, considering the different circumstances of each patient. Therefore, the guidelines cannot be used as a standard for evaluating the adequacy of the final judgments made by clinicians. The guidelines can be used for personal treatment and education, but not for commercial intent or purpose of reviewing the adequacy of insurance reimbursement. To use them for purposes other than medical treatment and education, approval must be sought by submitting a written request to the Committee of Clinical Practice Guidelines.

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INTRODUCTION

Intra-abdominal infection broadly includes cases of inflammation of organs caused by exposure to microorganisms in the abdominal cavity. Peritonitis is an inflammation of the peritoneum that surrounds the abdominal cavity and the organs contained therein, which can be classified differently depending on the cause (**Table 1**) [1-4]. Based on the classification according to the cause [2, 5], primary intra-abdominal infection is an infection of unknown cause due to spontaneous intra-abdominal invasion of bacteria and is mainly caused by a single microorganism in infants, children, patients with liver cirrhosis, patients on peritoneal dialysis, and immunosuppressed patients [4]. Secondary intra-abdominal infection includes a process of infection that gradually penetrates the abdominal cavity, such as perforation of the gastrointestinal tract and intestinal necrosis, with polymicrobial infection observed commonly. It can be subdivided into community-acquired infections and healthcare-associated infections [2, 3]. Tertiary intra-abdominal infection mainly occurs when secondary intra-abdominal infection persists or recurs, and is mainly caused by pathogenic microorganisms. In general, it often occurs after surgery for the treatment of secondary peritonitis, including occurrence due to causative bacteria with low virulence in immunosuppressed patients [1, 4] (**Table 1**).

According to the clinical severity, it can be classified into mild, moderate, and severe; severe includes cases with an Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) score ≥15 [1, 4]. In the most common classification based on anatomical location into complicated and uncomplicated intra-abdominal infections, a complicated intra-abdominal infection is defined as an abscess or peritonitis due to the spread of infection beyond the gastrointestinal tract into the abdominal cavity, and an uncomplicated intra-abdominal infection is defined as inflammation that is localized to a single organ while maintaining anatomical distinction, usually referring to an inflammatory lesion within the wall of the gastrointestinal tract [1, 2]. **Table 1** shows the definition of the terms used in the guidelines [2, 5]. Furthermore, a new classification based on three criteria: (1) community-acquired/early healthcare-associated infections (less than seven days of inpatient care) or late healthcare-associated infections (more than seven days of inpatient care)/recent antibacterial treatment history; (2) severity; and (3) presence or absence of anatomical destruction, is proposed [5]. This is a classification for the selection of an appropriate empirical antibiotics and is worth considering, but most studies and guidelines adopt a simpler classification for community-acquired and healthcare-associated infections [6-8]. The guidelines have taken the initiative to classify infections into two settings: community-acquired and healthcare-associated. Considering the limitation in antibiotic selection based on the simple classification of community-acquired and healthcare-associated infections, it is intended to evaluate the risk of multiple drug resistance organisms (MDRO), in addition to

Table 1. Classification and common pathogens of peritonitis

Type	Subtype	Definition	Microbiology
Uncomplicated	Primary	Due to bacterial translocation or hematogenous seeding No break in integrity of the GI tract	Monomicrobial: Enteric Gram-negatives, *Enterococcus*, or streptococci
Complicated	Secondary	Microscopic or macroscopic perforation	Polymicrobial; Enteric Gram-negatives, Gram-positive cocci (*Enterococcus*, etc.), and enteric anaerobes
	Tertiary	Persistent or recurrent development after treatment of secondary peritonitis	Nosocomial organisms; enterococci, staphylococci; resistant Gram-negative bacilli, and yeast
Peritoneal dialysis associated		Seeding of the peritoneum due to dialysis catheter	Usually monomicrobial; skin flora, *Staphylococcus aureus*, yeast
Tuberculous		Peritonitis due to reactivation of *Mycobacterium tuberculosis* in the peritoneum	*Mycobacterium tuberculosis*

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the abovementioned classification, taking the approach of considering the "risk of MDRO." Peritoneal dialysis catheter-associated peritonitis or tuberculous peritonitis, often observed in Korea, is classified as a special type of peritonitis (**Table 1**).

The main causative bacteria differ depending on the location of the organ where the infection started in the abdominal cavity, the amount of exposed bacteria, and the ratio of anaerobic bacteria increase from the upper gastrointestinal tract toward the lower gastrointestinal tract [9]. As for gastric perforation, infections are commonly caused by *Lactobacilli* spp. or *Streptococcus* spp.; In case of small intestine perforation, infections are commonly caused by *Lactobacilli* spp., *Escherichia coli,* or *Enterococcus faecalis*; and when considering large intestine perforation, infections are commonly caused by *Bacteroides* spp. or *Bifidobacterium bifidum* [10]. Patients may develop limited peritonitis or inflammation of the global peritoneum and progress to sepsis and septic shock. Inappropriate antibiotic treatment leads to a poor prognosis, and timely use of antibiotics and antibiotic treatment consistent with the identification and susceptibility of the bacteria improves the prognosis [2, 6, 11]. Therefore, the estimation and evaluation of the appropriate causative agent and the use of antibiotics are very important in clinical practice.

1. Background and Purpose

Guidelines for the use of antibiotics for intra-abdominal infections in Korea were published in 2010 as the "Guidelines for Treatment of Gastrointestinal Infections" [12]. These guidelines were of a wider scope than the "Guidelines for the Antibiotic Use in Adults with Intra-abdominal Infections." The Committee of Clinical Practice Guidelines has selected intra-abdominal infection as the disease for guideline development.

Revision of antibiotic treatment guidelines for intra-abdominal infections is necessary due to changes in the pathogens that cause the infections, in particular, the increase in antibiotic-resistant strains and the development of new antibiotics. With the recent publication of a multicenter study on the causative pathogens of intra-abdominal infections in Korea [13], it is intended to propose a new set of guidelines for the use of antibiotics in Korea. The guidelines also aim to serve the purpose of antibiotic stewardship by promoting proper use of antibiotics to reduce abuse or misuse, thereby reducing the induction of antibiotic resistance, costs, and adverse effects while improving the clinical prognosis [14].

2. Scope

The guidelines present the basic principles of antibiotic use for patients with suspected intra-abdominal infections in consideration of the current situation in Korea. Peritonitis, intra-abdominal abscesses, gallbladder infections, and biliary tract infections were mainly described; pancreatic infections and liver abscesses were not included. Tuberculous peritonitis is a separate topic and will be dealt with in the future in the treatment area of extrapulmonary tuberculosis. Periodic revisions will be made according to changes in the domestic situation.

3. Establishment of the Committee of Clinical Practice Guidelines

In 2021, eight experts recommended by the Korea Society for Antimicrobial Therapy and the Korean Society of Infectious Diseases participated in the making of these guidelines.

4. Literature Search Method

The literature related to antibiotic treatment of intra-abdominal infections in adults was searched systematically and previous clinical guidelines were also reviewed.

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The main search databases for establishing clinical practice guidelines were PubMed (www.pubmed.gov) and Embase (www.embase.com), and domestic studies were searched on KMBase (www.kmbase.medric.or.kr) and KoreaMed (www.koreamed.org). The literature search was conducted systematically by a literature search expert in January 2022, and a highly sensitive search was conducted by combining controlled language (MeSH terms for PubMed and Cochrane Library, Emtree terms for Embase) and natural language for each key question. Selected references were reviewed, and a total of 174 references were cited.

5. Key Question Setting and Consensus-building Processes

The clinical practice guidelines were developed around key questions to aid clinicians in finding answers to major clinical questions that may arise during the course of antibiotic treatment for patients with intra-abdominal infections. In consideration of the domestic situation, a total of nine key questions were finally selected through the coordination of the opinions of the Committee of Clinical Practice Guidelines. The nominal group technique (NGT) was used to draw consensus, reaching an agreement among the members.

6. Strength of Recommendations and Quality of Evidence

The expert panel specified the quality of evidence and the strength of the recommendations using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE, http://www.gradeworkinggroup.org) method. The quality of evidence was classified as high, moderate, low, and very low, and the strength of the recommendations was classified as strong and weak (**Table 2**, **Fig. 1**).

7. External Expert Evaluation

Based on the guideline recommendations prepared through the internal meetings of the Committee of Clinical Practice Guidelines, the second evaluation opinion of the expert group was collected. The discussed content was revised and supplemented through additional internal meetings of the Committee of Clinical Practice Guidelines. In addition, the opinions of other expert groups were collected to complete the guidelines. These guidelines were reviewed and endorsed prior to publication by the Korea Society for Antimicrobial Therapy and the Korean Society of Infectious Diseases.

Table 2. 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: Belief 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.

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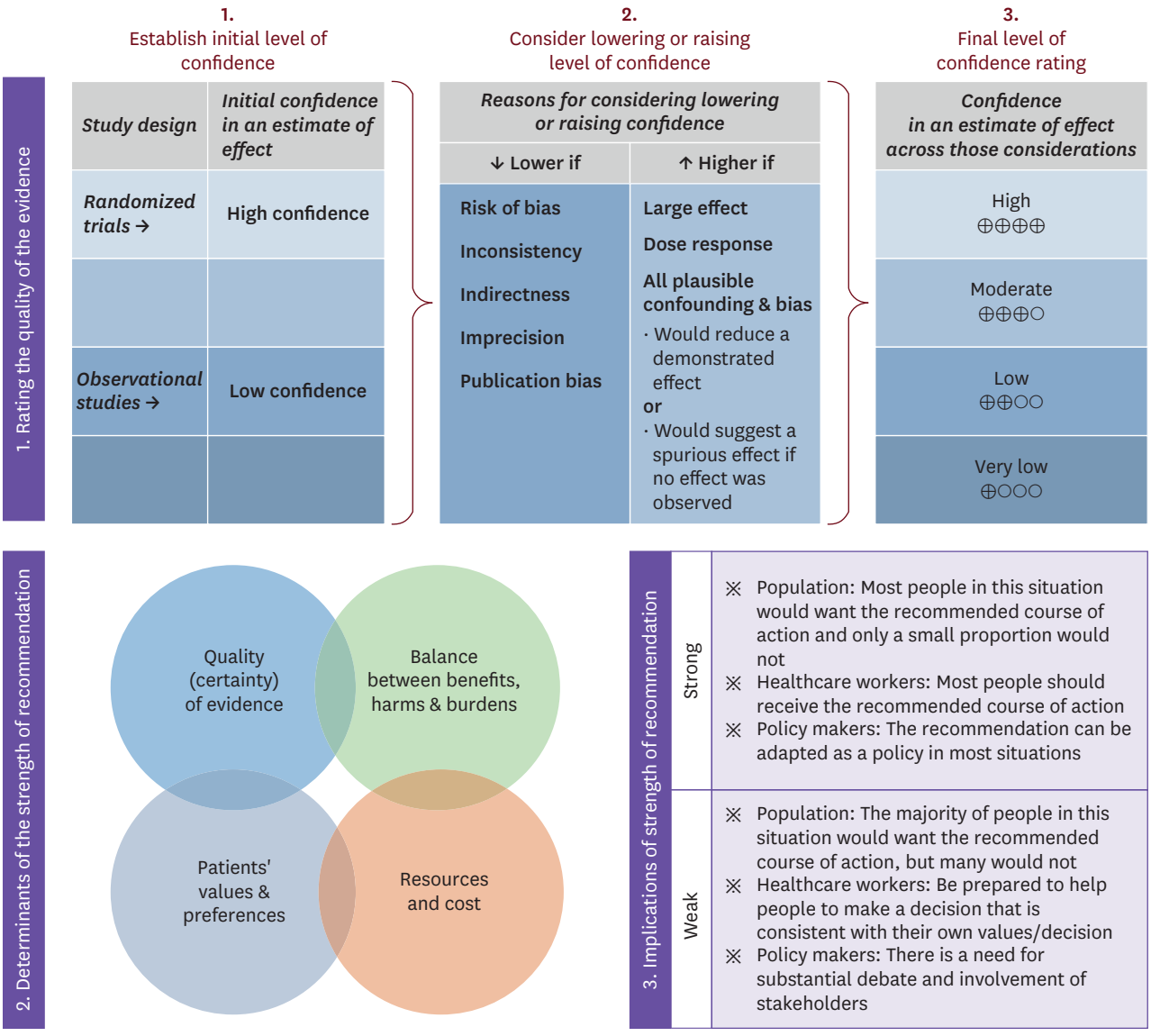

Figure 1. Grading of Recommendations Assessment, Development, and Evaluation (GRADE; http://www.gradeworkinggroup.org).

8. Glossary of Terms and Abbreviations

In the guidelines, related academic terms were written in Korean based on the sixth edition of the medical glossary (published by the Korean Medical Association, revised in March 2020). If the meaning of a term was not clearly conveyed in Korean, it was indicated in Korean with the English term written in parentheses. Terms that could not be expressed in Korean, such as pathogen names, proper nouns, drug names, and units, were written in English.

RECOMMENDATIONS

1. Summary of Key Questions

1) What are the main causes of primary and complicated intra-abdominal infections?
2) What are the empirical antibiotic treatments for primary peritonitis?

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3) What are the empirical antibiotic treatments for complicated peritonitis?
4) What are the main causes of gallbladder and biliary tract infections?
5) What are the empirical antibiotic treatments for gallbladder and biliary tract infections?
6) What risk factors should be considered for antibiotic-resistant bacteria?
7) Is treatment tailored to the susceptibility of the bacteria identified in the abdominal cavity and biliary drainage duct necessary?
8) What is the appropriate duration of antibiotic treatment for an intra-abdominal infection?
9) Is treatment necessary for *Candida* spp. isolated from a culture of intra-abdominal specimen?

Recommendations for Key Questions

Key Question 1: What are the main causes of primary and complicated intra-abdominal infections?

1. The most common causative bacteria for intra-abdominal infection are *Enterobacteriaceae*, and *Escherichia coli* and *Klebsiella pneumoniae* should be considered (quality of evidence at moderate, strength of recommendation at strong).
2. For healthcare-associated intra-abdominal infections, the possibility of extended-spectrum ß-lactamase (ESBL)-producing bacteria, carbapenem-resistant bacteria, *Enterococcus* spp., or *Candida* spp. should be considered (quality of evidence at moderate, strength of recommendation at weak).

Primary intra-abdominal infections account for approximately 1% of all intra-abdominal infections [15, 16]. About 70% of primary intra-abdominal infections occur in patients with cirrhosis and the remaining 30% in immunosuppressed patients [17]. One study identified the causative bacteria in only approximately 35% of patients with primary intra-abdominal infection, as culture tests were performed on only about half of them [17]. In general, approximately 60% of infections are caused by Gram-negative bacteria, and less than 5% are caused by fungi. Since the mechanism of development mainly involves the translocation of intestinal bacteria, the most common causative agent is *E. coli*, followed by *K. pneumoniae*, *Staphylococcus aureus*, *E. faecalis*, and *E. faecium* [18]. Approximately 35% of primary intra-abdominal infections in patients with cirrhosis are caused by MDRO, and the number of cases responding to initial empirical antibiotic therapy is decreasing [19].

Representative studies on the causative bacteria of complicated intra-abdominal infections include the complicated intra-abdominal infections worldwide observational study (CIAOW) by Sartelli et al. and the extended prevalence of infection in the intensive care unit (EPIC) II study by Waele et al. [20, 21]. CIAOW was a multicenter observational study of adult patients who underwent surgery or procedures for complicated intra-abdominal infections at 68 medical institutions between 2012 and 2013 [20]. A total of 1,898 patients were included, with community-acquired infections accounting for 86.7% and healthcare-associated infections accounting for the remaining 13.3%. While 43.6% had generalized peritonitis, 56.4% had intra-abdominal abscess or focal peritonitis, with an overall mortality rate of 10.5%. The EPIC II study in 2007 enrolled 1,392 adult patients with complicated intra-abdominal infections treated in 1,265 intensive care units in 75 countries, with an overall mortality rate of 24.4% [21]. In both the CIAOW and EPIC II studies, the most common causative bacteria were aerobic Gram-negative bacteria, which were identified in 63% and 48% of the cases, respectively. It was followed by aerobic Gram-positive bacteria in 22.7% and 28.4%, anaerobic bacteria in 7.7% and 11.3%, and fungi in 6.4% and 10.1% cases, respectively [20, 21].

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In the CIAOW study, *E. coli* (57.3%) was the most common aerobic Gram-negative bacteria, followed by *Klebsiella* spp. (15.7%), *Pseudomonas* spp. (7.7%), *Enterobacter* spp. (6.7%), and *Proteus* (4.9%) [20]. In the EPIC II study, the most common causative agent was *E. coli* (34.1%), followed by *Pseudomonas* spp. (13.9%), *Klebsiella* spp. (13.7%), *Enterobacter* spp. (12.4%), *Proteus* spp. (7.6%), and *Acinetobacter* spp. (5.7%) [21]. As for aerobic Gram-positive bacteria identified in the CIAOW study, *Enterococcus* spp. (56.6%) was the most common, followed by *Streptococcus* spp. (22.8%) and *S. aureus* (10.2%) [20]. In the EPIC II study, the most common causative aerobic Gram-positive bacteria were *Enterococcus* spp. (56.6%), followed by *S. aureus* (15.0%) and *Streptococcus* spp. (13.9%) [21]. While the most common causative anaerobic bacteria were *Bacteroides* spp. (75.2%) in the CIAOW study, it was *Clostridium* spp. (64.4%) in the EPIC II study [20, 21].

The major causative bacteria of complicated intra-abdominal infections may differ depending on the patient characteristics, clinical courses, healthcare-associated factors, and antibiotic resistance patterns in the region, in addition to the anatomical location where the infections have started in the abdominal cavity. Despite the limited data on complicated intra-abdominal infections only, the most cited data on the causative bacteria of intra-abdominal infections, including biliary tract infections, are the results of the Study for Monitoring Antimicrobial Resistance Trends (SMART). [22]. The most common causative bacteria of intra-abdominal infection are *Enterobacteriaceae*, accounting for 68.3% to 89.5%, with *E. coli* and *K. pneumoniae* being the most common. *Enterobacter cloacae* or *Pseudomonas aeruginosa* are commonly identified as well, and *Acinetobacter baumannii* has also been prevalent recently in Asia [23-25]. According to a study involving 2,189 clinical isolates from 2002 to 2010 from patients with intra-abdominal infections in the Asia-Pacific region, the most common causative agent was *E. coli* (48.5%), followed by *K. pneumoniae* (20.2%), *P. aeruginosa* (10.5%), *A. baumannii* (5.0%), and *E. cloacae* (4.6%) [26]. In the studies that analyzed 3,420 clinical isolates from 2002 to 2009 in China and 2,417 clinical isolates from 2006 to 2010 in Taiwan, the types of the five most common causative bacteria were not different [23, 27]. Meanwhile, in American and European studies including strains collected from 2005 to 2007, *Proteus mirabilis* was commonly identified instead of *A. baumannii* [28], and a study in Singapore identified *Enterococcus* spp. as the main causative agent instead of *A. baumannii* [29].

According to the results of SMART from 2005 to 2010, the global incidence of ESBL-producing *Enterobacteriaceae* was 23% in 2005, 27% in 2006, 38% in 2007, 32% in 2008, 35% in 2009, and 29% in 2010, which was relatively higher than the results confirmed at around 10% in Europe and North America during the same period [29]. From 2002 to 2010 in the Asia-Pacific region, the prevalence of ESBL-producing bacteria among *E. coli* and *K. pneumoniae* isolated from intra-abdominal infections was 28.2% and 22.1%, respectively, and it was 25.9% and 24.5%, respectively, in Korea, similar to the average [30]. The resistance rate of these domestic ESBL-producing *Enterobacteriaceae* was lower than that in China, Thailand, and Vietnam but higher than that in Australia, New Zealand, Hong Kong, Malaysia, Singapore, and Taiwan [30]. In the data after 2010, the prevalence of ESBL-producing bacteria among *E. coli* and *K. pneumoniae* isolated from intra-abdominal infections was 40.8% and 26.9%, respectively, in the Asia-Pacific region. In the United States, the prevalence was 9.7% and 12.7%, in Europe, 11% and 23%, and in Latin America, 31.2% and 41.2%, respectively [31]. The ESBL strain in the SMART study refers to several clinical specimens, but the recent domestic ESBL-positive rate cultured in blood reported 37.4% (40/107) of those with blood diseases [32]. Another domestic study showed that the frequency of resistance varied depending on whether the infection is community-acquired or healthcare-associated [33].

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The prevalence of carbapenem-resistant infections, which has recently become a problem, is also increasing in healthcare-associated intra-abdominal infections. According to the results of SMART in the Asia-Pacific region, where a total of 52 healthcare institutions in 11 countries participated between 2002 and 2010, imipenem resistance rates among *E. coli* and *K. pneumoniae* isolated from intra-abdominal infection were confirmed to be 0.3% and 0.8%, respectively [30]. On the other hand, for *P. aeruginosa* and *A. baumannii*, the imipenem resistance rate was confirmed to be 38.0% and 79.0%, respectively, since 2010. In the United States, it was reported to be 24.0% and 39.0% and in the Middle East, it was reported to be 25.0% and 92.0%, respectively [31]. MDRO was found more commonly in healthcare-associated than in community-acquired infections [34], and *Enterococcus* spp., *Candida* spp., *Pseudomonas* spp., *A. baumannii*, methicillin-resistant *S. aureus* (MRSA), and vancomycin-resistant enterococcus (VRE) were also more commonly isolated in tertiary intra-abdominal infections associated with healthcare-associated infections [35].

Domestic data on the epidemiology of causative bacteria for intra-abdominal infections are limited. According to the results of a multicenter study, in which a total of 2,114 clinical isolates from six participating university hospitals in Korea from 2016 to 2018 were analyzed, aerobic Gram-negative bacteria (62.6%), aerobic Gram-positive bacteria (33.7%), fungi (2.8%), and anaerobic bacteria (0.9%) were commonly isolated, with a high isolation rate of Gram-positive bacteria in healthcare-associated infections (**Fig. 2**) [13]. Although it was difficult to identify the causative bacteria of complicated intra-abdominal infections by dividing the them, as these data accounted for the largest proportion of biliary tract infections, the most common causative bacteria were *E. coli* (23.8%), *Enterococcus* spp. (23.1%), and *Klebsiella* spp. (19.8%) (**Fig. 2**) [13]. *In E. coli* and *Klebsiella* spp., the proportion of ESBL-producing bacteria was 39.8% and 17.7%, respectively, and the imipenem resistance rate was 0.2% and 1.2%, respectively [13]. *In P. aeruginosa* and *A. baumannii*, the imipenem resistance rate was 77% and 37%, respectively (**Fig. 3**) [13].

The anaerobic isolation rate and antibiotic susceptibility results are important factors for empirical antibiotic selection for intra-abdominal infections in Korea [36]. In 2012, in the analysis data of 268 anaerobic bacteria isolated from patients with intra-abdominal infections at three tertiary hospitals in Korea, the most common causative bacteria were identified as *Bacteroides fragilis* and *Clostridium* spp., and *B. fragilis* was highly susceptible to piperacillin/tazobactam, imipenem, and meropenem (**Fig. 4**) [37]. Afterwards, from 2014 to 2016, the results of domestic antibiotic susceptibility to anaerobic bacteria isolated from patients with intra-abdominal infections in Korea also showed that most *B. fragilis* strains were susceptible to piperacillin/tazobactam, imipenem, and meropenem (**Fig. 4**) [38]. Anaerobic bacteria have low resistance to metronidazole in Korea and abroad (**Fig. 4**) [5, 37-39]. When selecting antibiotics for anaerobic bacteria in Korea, the antibiotics mentioned in **Table 3** are considered effective, and understanding and knowledge of the resistance level of domestic anaerobic bacteria against them are important to reduce the overuse of antibiotics against anaerobic bacteria. In other words, this serves as a guideline in making efforts not to use excessive antibiotics (**Fig. 4**). Although it is missing from the anti-anaerobic antibiotics in **Table 3**, tigecycline, often introduced as a drug that can be used for intra-abdominal infections in clinical practice guidelines, is reported to be relatively effective against anaerobic bacteria (the minimum inhibitory concentration at which 90% of the isolates were inhibited (MIC_{90}) against *B. fragilis* was 2 - 4 μg/mL and the MIC_{90} against *Peptostreptococcus* spp. was 0.125 - 0.25 μg/mL) [40]. Therefore, it seems that tigecycline does not need to be combined with metronidazole when treating intra-abdominal infections.

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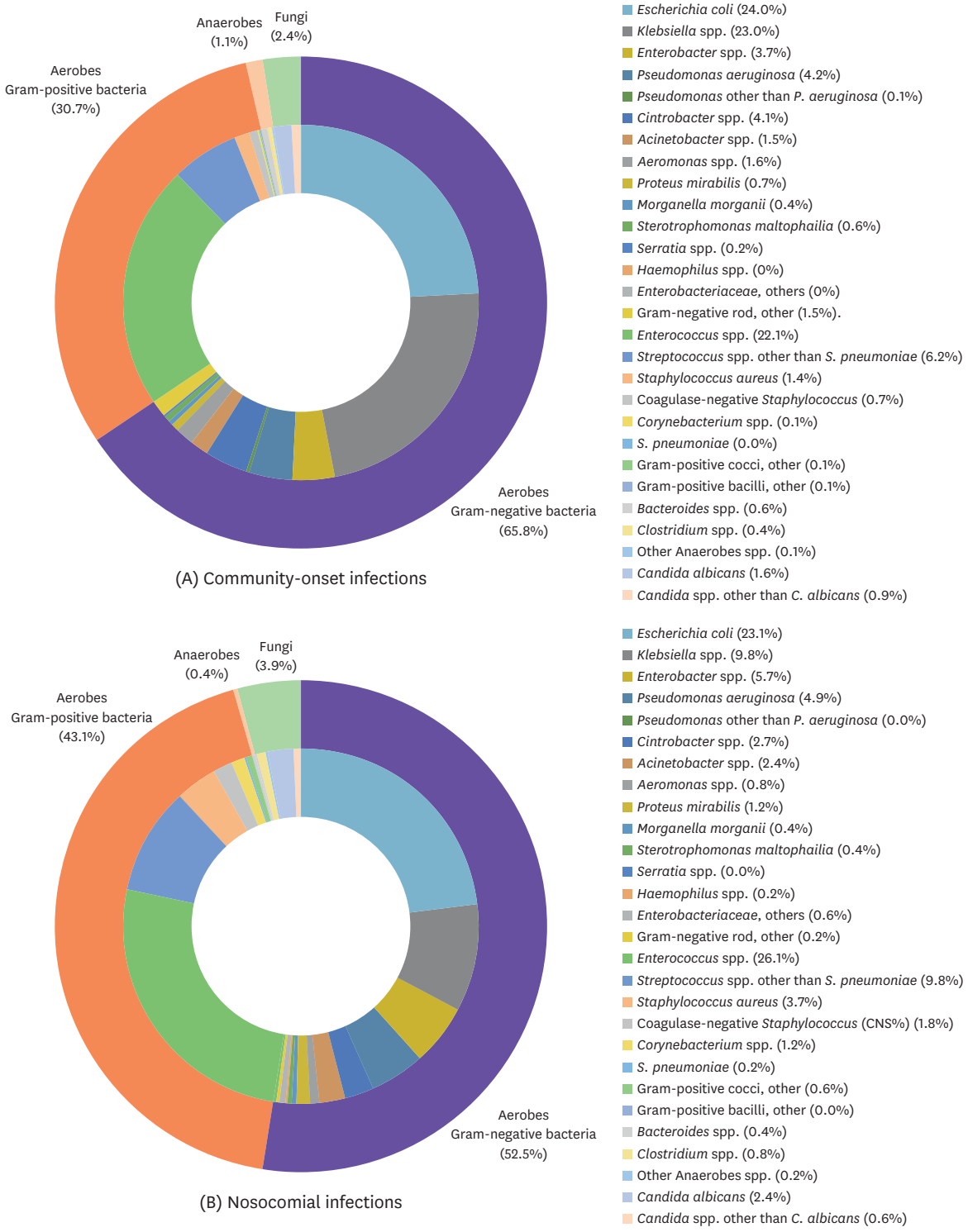

Figure 2. Microorganisms isolated from patients with intraabdominal infection in Korea; (A) community-onset and (B) nosocomial.

The patients most likely to be detected with *Enterococcus* spp. were those with healthcare-associated infections or postoperative infections among complicated intra-abdominal infections, severe immunosuppression, recurrent infections, and long-term antibiotic use [41]. Patients detected with *Enterococcus* spp. had a worse prognosis than those without *Enterococcus*

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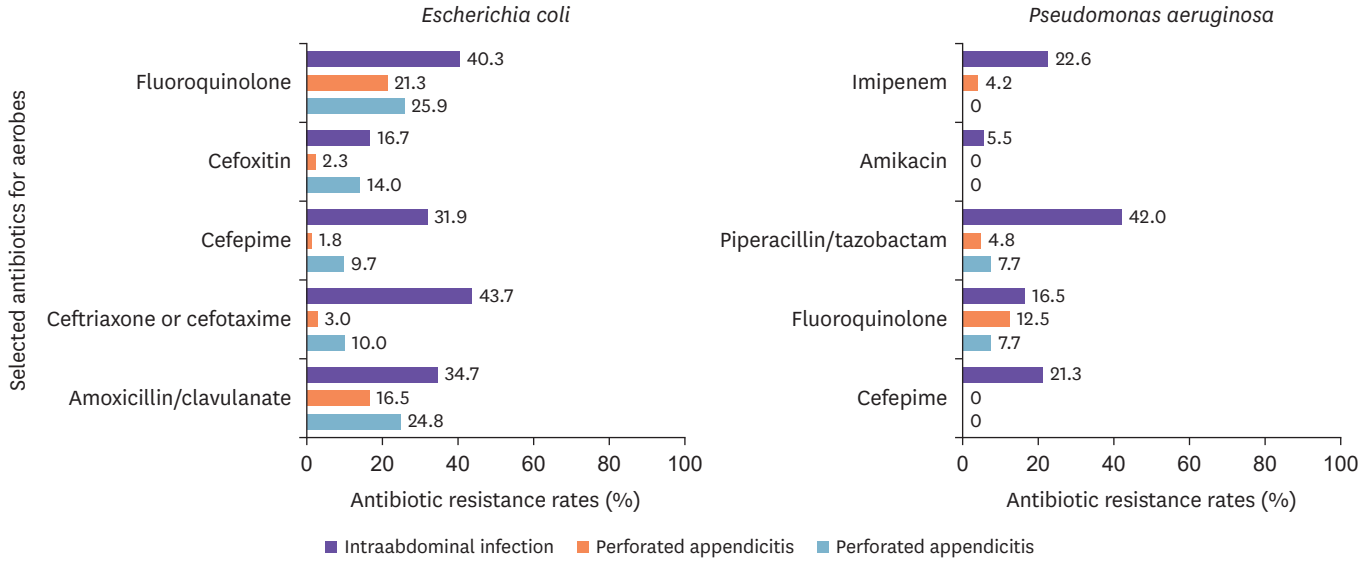

Figure 3. Resistance rates of major aerobic causative bacteria of complicated peritonitis in Korea. ***: [57], **: [58], *: [13].

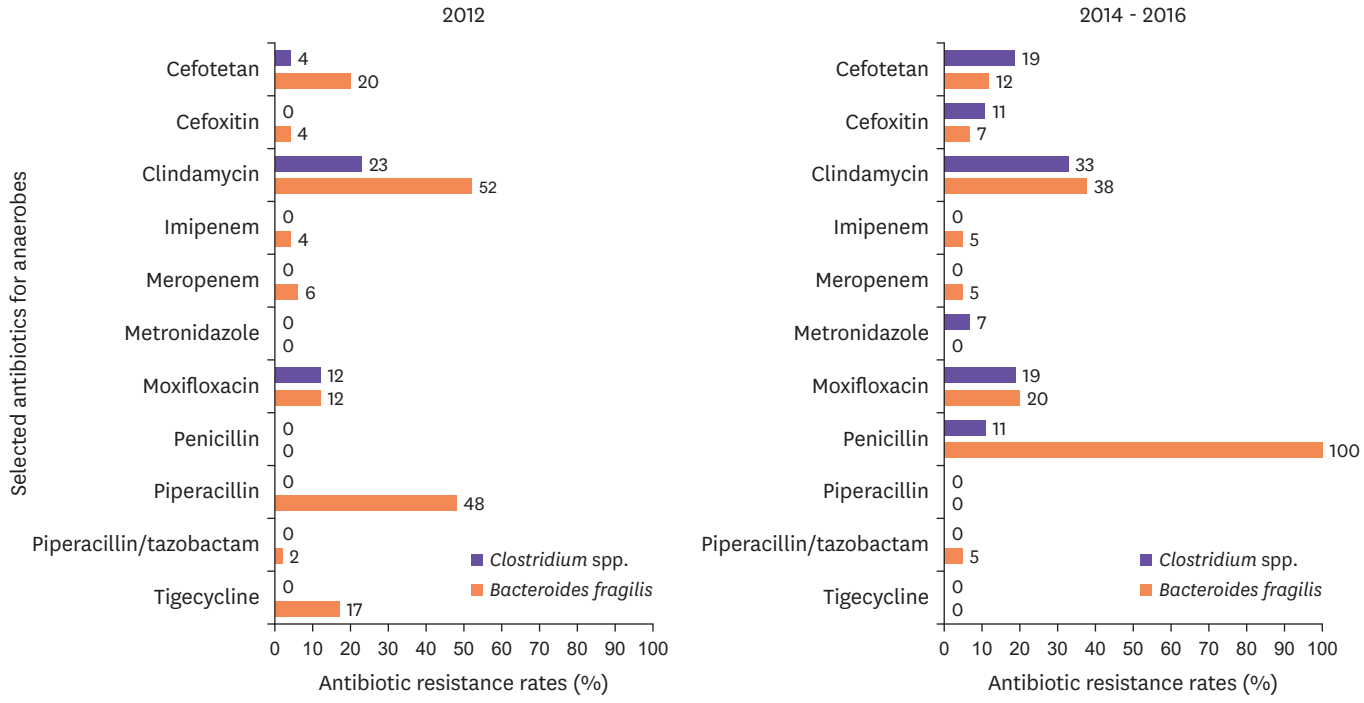

Figure 4. Comparison of antibiotic resistance rates of *Bacteroides fragilis* and *Clostridium* spp. by hospital [37, 38].

spp. [41, 42]. Intra-abdominal infections caused by MRSA are rare, but the elderly, patients with significant underlying medical conditions, recent hospitalization or surgery, antibiotic therapy, or colonization of MRSA are considered high-risk groups for MRSA infections [6]. Intra-abdominal infections caused by *Candida* spp. are uncommon in community-acquired infections. However, since it is highly likely to occur in healthcare-associated infections, postoperative infections, and severely immunosuppressed patients, it is possible that APACHE II score ≥15, recent antibiotic treatment history, upper gastrointestinal surgery, postoperative cardiopulmonary insufficiency, pancreatitis that has undergone surgical treatment, and yeast

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Table 3. Indications for susceptibility testing of anaerobic bacteria in Korea

Primary agents
Amoxicillin-clavulanate
Ampicillin-sulbactam
Piperacillin-tazobactam
Clindamycin
Metronidazole
Ertapenem
Imipenem
Meropenem, doripenem
Supplementary agents
Cefoxitin
Cefotetan
Ampicillin
Penicillin
Ceftizoxime
Ceftriaxone
Piperacillin
Moxifloxacin

confirmed in Gram staining of abdominal cavity-related clinical specimens are associated with intra-abdominal infections by *Candida* spp. [6, 43].

Key Question 2: What are the empirical antibiotic treatments for primary peritonitis?

1. The most important criteria for the selection of empirical antibiotics for primary peritonitis are the common causative bacteria and its antibiotic susceptibility, and since there are differences between countries and regions, they should be considered first (quality of evidence at moderate, strength of recommendation at strong).
2. Since the most common causative bacteria of primary peritonitis are *Enterobacteriaceae*, including *E. coli*, and *K. pneumoniae*, third-generation cephalosporins (cefotaxime or ceftriaxone) are preferred as empirical antibiotics (quality of evidence at moderate, strength of recommendation at strong).
3. With a high risk of isolating antibiotic-resistant bacteria, such as healthcare-associated infections, empirical antibiotic treatment with a broader antimicrobial spectrum, such as piperacillin/tazobactam, is considered, taking into account cephalosporin-resistant *Enterobacteriaceae* and *Enterococcus* spp. (quality of evidence at moderate, strength of recommendation at strong).
4. Empirical antibiotic treatment with carbapenems (such as meropenem, imipenem, and doripenem) is generally not recommended and used for specific treatment after identification of the causative organism (quality of evidence at moderate, strength of recommendation at weak).

Spontaneous bacterial peritonitis, the most common form of primary peritonitis, is peritonitis with no apparent cause that requires intra-abdominal surgery. The diagnosis is usually based on an increase in absolute polymorphonuclear leukocyte count (≥250 cells/mm^3) in an ascites test. However, even when the white blood cell count is <250 cells/mm^3, it is diagnosed as peritonitis with bacteria cultured in ascites.

In the selection of empirical antibiotics, the most important criteria are the common causative bacteria and its antibiotic susceptibility results; since there are differences between countries and regions, they should be considered first [3, 5]. The failure rate of empirical

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antibiotic treatment is increasing due to the recent increase in antibiotic resistance [44, 45]. The types of available antibiotics and insurance reimbursement standards also differ from country to country, greatly affecting the selection of antibiotics. Immediately after performing the peritoneal fluid culture test, antibiotics effective on common causative bacteria should be empirically started, and in severe patients, blood culture tests should be additionally performed [1, 5, 13].

Since the most common causative agents of primary peritonitis are *Enterobacteriaceae*, including *E. coli* and *K. pneumoniae*, third-generation cephalosporins (cefotaxime or ceftriaxone) are preferred as empirical antibiotics (**Fig. 5**) [5, 46]. In clinical situations of cholestasis due to cirrhosis or stones in the biliary tract, cefotaxime is preferred over ceftriaxone. The dose of cefotaxime (2 g) should be administered at 8-hour intervals if renal function is normal, and the adjusted if renal function decreases. Ceftriaxone is administered at 2 g every 24 hours without renal dose adjustment.

It is necessary to select empirical antibiotics by distinguishing between community-acquired infections and medical-related infections (including nosocomial infections) and determining risk factors for multidrug-resistant bacteria (**Fig. 3-5**) [5, 47-49]. As for early hospital-acquired infections that occur during inpatient care of less than seven days, empirical antibiotics can be selected in anticipation of a pattern of antibiotic resistance similar to community-acquired infections [5]. As for insufficient clinical response, it is a good option to quickly move on to antibiotic treatment considering resistant bacteria. For a high risk of medical-related infection, a drug with a wider antibacterial range, such as piperacillin/tazobactam, is first considered, taking into account treatment including cephalosporin-resistant *Enterobacteriaceae* and *Enterococcus* spp. In general, piperacillin/tazobactam, which has broad antibacterial activity against anaerobic bacteria, *Enterococcus* and *Pseudomonas*, is not preferred as empirical antibiotics for primary peritonitis (**Fig. 5**) [6].

In general, different antibiotics are not selected according to the type of underlying diseases [5]. In Korea, empirical antibiotic treatment using carbapenems (meropenem, imipenem, and doripenem) is generally not recommended and is used for specific treatment after the causative organism is identified [50]. However, it can be empirically administered to severe patients with unstable vital signs, such as septic shock (**Fig. 5**) [5, 50]. As for sepsis caused by peritonitis and in severe cases, empirical antibiotics should be administered as soon as possible (within one hour) for the causative agent to be considered [1, 6, 29, 51]. Inappropriate use of antibiotics in sepsis and critically ill patients leads to poor prognosis [29, 52]. However, the diagnosis of sepsis requires a cautious approach as it is easy to induce excessive use of antibiotics in terms of antibiotic stewardship [53].

Fluoroquinolones, metronidazole, and aminoglycoside are not recommended for empirical treatment of primary peritonitis [6], and they are recommended for specific treatment after bacterial identification. It should be remembered that aminoglycosides have no effect on anaerobic bacteria and are therefore not an easy drug of choice for intra-abdominal infection (**Table 3**) [3]. In patients with type 1 hypersensitivity to β-lactams, fluoroquinolones can be used empirically (**Fig. 5**) [8]. As for hypersensitivity to β-lactams, special attention should be paid to type 1 hypersensitivity or similar hypersensitivity reactions. History-taking is more important than antibiotic skin reactions, and mild allergies should not be avoided [54]. Consulting an allergist when necessary may reduce the risk [54]. Tigecycline is not recommended for primary uncomplicated peritonitis [6]. In a previous study, in the empirical treatment of hospital-

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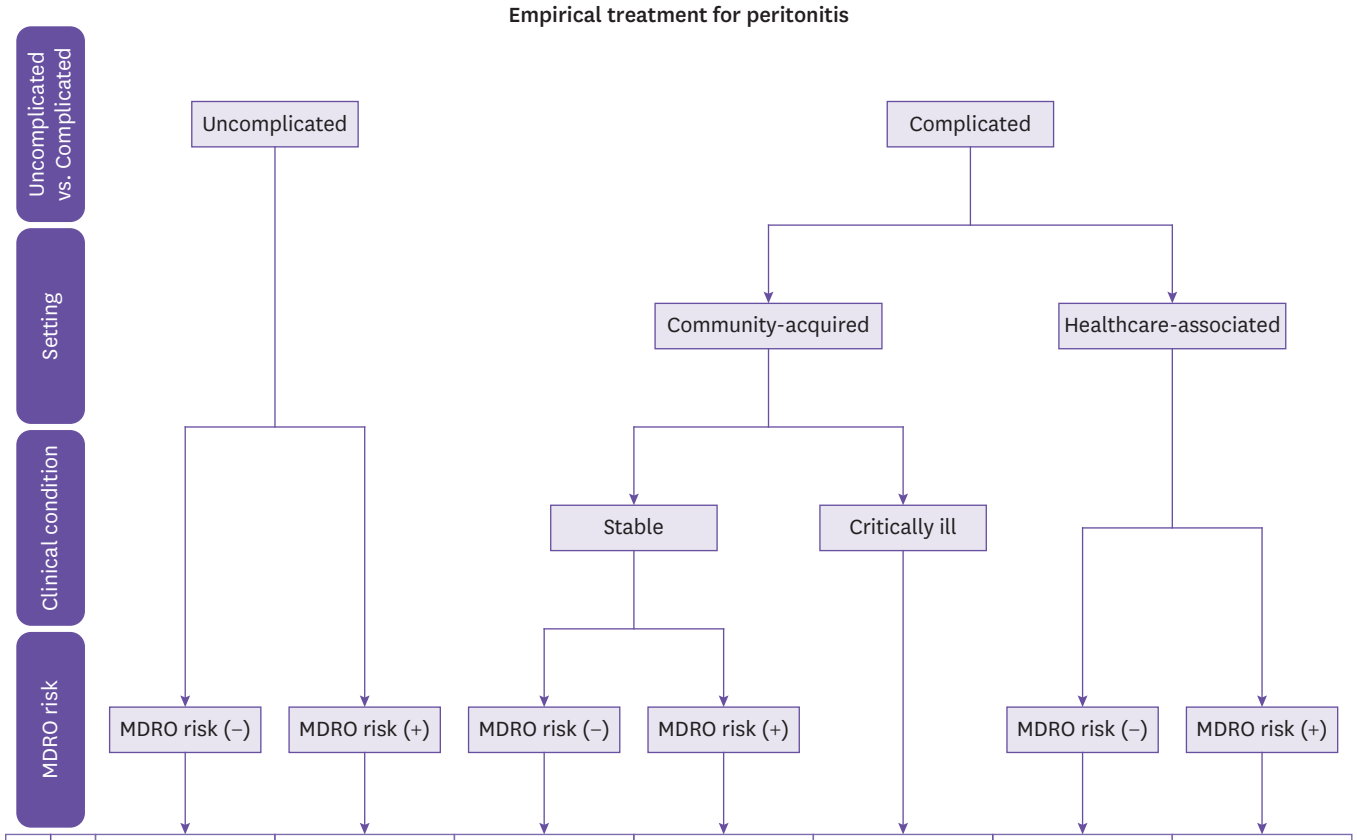

Examples of empiric antibiotic choices		Category 1	Category 2	Category 3	Category 4	Category 5	Category 6	Category 7
	preferred choice	3rd generation cephalosporins, ciprofloxacin or levofloxacin for β-lactam allergy	Piperacillin /tazobactam	3rd cephalosporins + metronidazole, cefamycins (cefoxitin etc.)	Tigecycline, piperacillin /tazobactam, ertapenem	Piperacillin /tazobactam, meropenem, imipenem /cilastatin, doripenam	Piperacillin /tazobactam	Meropenem, imipenem /cilastatin, doripenem ± aminoglycosides
	for β-lactam hypersensitivity	Ciprofloxacin or levofloxacin	Tigecycline, ceftazidime (for penicillin hypersensitivity)	Ciprofloxacin + metronidazole or levofloxacin + metronidazole	Tigecycline, ceftazidime or cefepime + metronidazole (for penicillin hypersensitivity), carbapenems (for penicillin and cephalosporin hypersensitivity)	Ceftazidime or cefepime + metronidazole (for penicillin hypersensitivity), carbapenems (for penicillin and cephalosporin hypersensitivity), tigecycline	Ciprofloxacin ± metronidazole or levofloxacin ± metronidazole, ceftazidime or cefepime ± metronidazole (for penicillin hypersensitivity), carbapenems (for penicillin and cephalosporin hypersensitivity)	Tigecycline, ceftazidime or cefepime ± metronidazole (for penicillin hypersensitivity), carbapenems (for penicillin and cephalosporin hypersensitivity)

MDRO: Multidrug resistant organisms, critically ill: APACHE II score ≥15

Figure 5. Schema for empirical antibiotic treatment of uncomplicated and complicated peritonitis.

acquired primary peritonitis, the combined treatment of meropenem and daptomycin showed better treatment results than ceftazidime alone [46], but it is not recommended to apply this in terms of insurance claim standards and antibiotic stewardship in Korea. Antifungal drugs are not empirically used in community-acquired peritonitis (**Fig. 5**) [8].

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Antibiotic treatment should be adjusted according to the results of ascites and blood culture tests and the susceptibility of the causative bacteria [5]. If peritonitis persists for a long time, blood and ascites cultures should be repeated and antibiotics should be adjusted [45].

Key Question 3: What are the empirical antibiotic treatments for complicated peritonitis?

1. In the selection of empirical antibiotics for complicated peritonitis, the most important criteria are the common causative bacteria and its antibiotic susceptibility results, and since there are differences between countries and regions, they should be considered first (quality of evidence at moderate, strength of recommendation at strong).
2. For clinically stable cases of community-acquired complicated peritonitis, cefoxitin may be used; ceftriaxone, cefotaxime, or a combination of cefuroxime and metronidazole may be used (quality of evidence at moderate, strength of recommendation at weak). When allergic to β-lactams antibiotics, a combination of ciprofloxacin and metronidazole may be used (quality of evidence at high, strength of recommendation at strong).
3. In community-acquired complicated peritonitis, ertapenem, tigecycline, or piperacillin/tazobactam may be used when clinically stable but at risk of infection with MDRO (quality of evidence at high, strength of recommendation at strong).
4. Piperacillin/tazobactam, meropenem, imipenem/cilastatin, or doripenem may be used for severe cases of community-acquired complicated peritonitis (quality of evidence at high, strength of recommendation at strong). Ceftazidime or a combination of cefepime and metronidazole may be used (quality of evidence at moderate, strength of recommendation at weak). A combination of ceftolozane/tazobactam or ceftazidime/avibactam with metronidazole may be considered (quality of evidence at high, strength of recommendation at weak).
5. For healthcare-associated complicated peritonitis (including tertiary peritonitis), piperacillin/tazobactam, meropenem, doripenem, and imipenem/cilastatin, which are effective broad-spectrum antibiotics against *P. aeruginosa*, can be used, and amikacin can be combined (quality of evidence at moderate, strength of recommendation at weak).
6. For healthcare-associated complicated peritonitis (including tertiary peritonitis), the risk of infection with *Enterococcus* spp., MRSA, and *Candida* spp., is evaluated, and when cultured, recommended as definitive treatment and not as empirical treatment (quality of evidence at moderate, strength of recommendation at strong).
7. Concomitant empirical combination therapy of aminoglycoside with β-lactams is not recommended (quality of evidence at moderate, strength of recommendation at strong).

Empirical antibiotics for the treatment of complicated peritonitis should be selected in consideration of the severity of the disease, the rate of antibiotic resistance of major strains in the community, and the risk of infection by resistant bacteria (**Fig. 3-5**) [29, 55]. The existing guidelines for community-acquired complicated peritonitis classified severity into "mild or moderate" and "severe" [1, 9, 12] or into "hemodynamically stable" and "hemodynamically unstable" [3, 55], and further mentioned the possibility of infection with MDRO [4]. In these guidelines, the severity of the disease and the risk of MDRO were applied together, and the empirical antibiotic selection criteria for community-acquired complicated peritonitis were categorized into stable, stable but at risk of infection with MDRO (**Table 4**), and severe conditions, presenting a schema for empirical antibiotic use (**Fig. 5**). Cases with an APACHE II score of 15 or higher were evaluated as severe, and others were evaluated as stable [1, 4].

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Table 4. Risk factors of multidrug resistance for the selection of empirical therapy against peritonitis (with more than one risk factor)

Postoperative peritonitis
Tertiary peritonitis
Antibiotic treatment for other illness
MDRO colonization in the previous three months
Drug-based immunosuppression
Prolonged hospitalization or stay in long-term care facilities
Previous intensive care unit stay

MDRO, multidrug-resistant microorganisms.

For community-acquired complicated peritonitis with stable patient status, cefoxitin, or a combination of third-generation cephalosporins (ceftriaxone, cefotaxime) with metronidazole may be used [2, 39]. Some guidelines recommend using a single agent, such as ertapenem or tigecycline, even under stable conditions [1, 2, 9, 39, 56]. In Korea, it should be considered when there is a risk, rather than when there is no risk, of resistant bacteria (**Fig. 5**). As a result of an antibiotic susceptibility test in 2012 on strains isolated from local community-acquired perforating appendicitis, cefoxitin susceptibility of *E. coli* was 86% and ciprofloxacin susceptibility was 74.1% (**Fig. 3**) [57]. In another study published in 2014, the antibiotic susceptibility of cefoxitin and ciprofloxacin was 97.7% and 78.7%, respectively (**Fig. 3**) [58]. In the antibiotic susceptibility results of strains isolated from community-acquired intra-abdominal infection in patients in 2019, the most recent domestic data, the susceptibility of *E. coli* was 83.3% to cefoxitin, showing a low susceptibility of 59.7% to ciprofloxacin, 56.3% to ceftriaxone, and 68.1% to cefepime (**Fig. 2**). [13]. In Korea, a susceptibility of 67.3% (72/107) reported in *E. coli*, which was recently identified in bacteremia in patients with hematological malignancy [32]. This suggested that empirical selection of fluoroquinolone antibiotics was difficult in Korea. Based on guidelines that did not recommend the use of empirical antibiotics when the resistance rate in a community-acquired infection was 10% or higher, the combined use of fluoroquinolone and metronidazole, which was recommended in the 2010 domestic guidelines, was changed to limit its use to patients who were allergic to β-lactams antibiotics (**Fig. 5**) [1, 6, 8, 52]. In the case of cefoxitin, it may be a good choice in the domestic situation where the ratio of ESBL-producing strains is increasing, but caution is needed as the resistance rate is increasing in recent susceptibility results (**Fig. 5**) [13]. Although there have been foreign data and recommendations on the effectiveness of moxifloxacin in intra-abdominal infections [2, 5], it is not recommended as empirical antibiotics considering the high resistance to fluoroquinolone and increased resistance to moxifloxacin in anaerobic bacteria in Korea (**Fig. 5**) [37, 38]. Although foreign guidelines sometimes describe clindamycin as empirical antibiotics for intra-abdominal infection with anaerobic bacteria, it cannot be used as empirical antibiotics based on domestic resistance rate data (**Fig. 5**) [37, 38]. As for other anti-anaerobic antibiotics, when the effectiveness of recommended empirical antibiotics is evaluated based on domestic data, the list of empirical antibiotic recommendations is subject to change in the future according to the change in resistance rate.

The recommended empirical antibiotics for severe conditions include ceftolozane/tazobactam and metronidazole or the combined use of ceftazidime/avibactam and metronidazole [55, 59]. However, considering the domestic health insurance claim standards, it is difficult to actively apply it, and the recommendation strength is presented as weak. As for cephalosporins effective against *P. aeruginosa*, which were previously recommended, cefepime susceptibility was 100% [57], 100% [58], and 78.8% (**Fig. 3**) [13] in domestic data, and ceftazidime susceptibility was 77.6% in one report (**Fig. 3**) [13]. Overseas guidelines suggested that ceftazidime be used when it was difficult to use other

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recommended antibiotics [6], and in most cases, the use of carbapenem-class antibiotics was suggested with a high quality of evidence and strong recommendations. Although these guidelines suggest the use of cephalosporins effective for *P. aeruginosa* with a moderate quality of evidence and a weak recommendation, they are subject to change depending on the results of future domestic epidemiological investigations.

As for healthcare-associated complicated peritonitis, it is recommended to empirically select an antibiotic with a broad antimicrobial range as much as possible, and then adjust it according to the results of antibiotic susceptibility [1, 3, 55]. Some guidelines suggested that empirical antibiotics could be selected even in the case of healthcare-associated complicated peritonitis by classifying them into "mild or moderate" and "severe" subjects [3, 4]. In Korea, there is no difference in the list of available antibiotics in consideration of the application criteria for health insurance claim. Therefore, the empirical antibiotics for healthcare-associated and hospital- or surgery-associated complicated peritonitis are presented together without separate classification.

Antimicrobial activity against *P. aeruginosa* should be considered for the empirical treatment of medical-related complicated peritonitis. Piperacillin/tazobactam is mainly recommended when the possibility of infection by multidrug-resistant bacteria is low, and meropenem, imipenem/cilastatin, or doripenem is recommended mainly when there is a possibility of multidrug-resistant bacterial infection [60]. In consideration of renal function, aminoglycosides, especially amikacin, can be used in combination as needed [8]. In domestic data, amikacin showed a high susceptibility of 97.4% in *E. coli* and 94.5% in *P. aeruginosa*, and it can be expected to be effective enough for use as empirical antibiotics (**Fig. 3**) [13]. However, empirical combination therapy of aminoglycosides with β-lactams is not recommended [1]. In severe intra-abdominal infections, there was no difference in treatment prognosis in a randomized controlled study between using β-lactams alone and in combination with aminoglycosides [61]. Therefore, the incorporation of aminoglycosides in intra-abdominal infection should be considered limitedly in consideration of renal function, susceptibility, and severity of the identified strain [1, 62].

The combined use of ceftolozane/tazobactam or ceftazidime/avibactam with metronidazole may be considered as carbapenem replacement therapy for multidrug-resistant Gram-negative bacteria [3, 6].

Other causative bacteria to be considered in the treatment of healthcare-associated complicated peritonitis include *Enterococcus spp*., MRSA, and *Candida spp.* Among the causative bacteria of healthcare-associated complicated peritonitis, the proportion of *Enterococcus* spp. is 21.0 – 35.0%, which is higher than that of community-acquired peritonitis [63]. In particular, the risk of infection by *Enterococcus* spp. is high in immunosuppressed patients with healthcare-associated peritonitis, postoperative peritonitis, recurrent peritonitis, recent use of broad-spectrum antibiotics, heart valve diseases, or endovascular prosthesis [9]. In foreign countries, vancomycin or teicoplanin can be used as antibiotics with antimicrobial activity against *Enterococcus* spp. [6]. The use of empirical vancomycin for *Enterococcus* is often not recommended [1], and the use of empirical vancomycin or teicoplanin is restricted considering the fact that *Enterococcus* is not highly virulent (**Fig. 5**). It is appropriate to use in addition to drugs for Gram-negative bacteria and anaerobic bacteria by looking at the sampling process and clinical course of *Enterococcus* in the treatment (targeted) selection. The clinical value of *Enterococcus* detection in the draining ducts over time is low compared to detection in specimens obtained during initial surgery and procedures.

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As for MRSA, the major risk factors for pathogen acquisition include old age, severe underlying diseases, past hospitalization or surgery, recent antibiotic exposure, and MRSA colonization or infection history. With these risk factors, the use of vancomycin or teicoplanin can be considered in overseas guidelines and studies, and the use of linezolid, daptomycin, and tigecycline can also be considered [1, 2, 6, 9, 59]. However, in Korea, the initial use of empirical antibiotics for MRSA is difficult to recommend in terms of health insurance claims and antibiotic stewardship, and vancomycin or teicoplanin is used as definitive treatment after MRSA is identified. If treatment fails, the use of linezolid, daptomycin, or tigecycline should be considered.

Among the causative bacteria of medical-related complicated peritonitis, yeast accounts for 11.0 – 33.0%, which is higher than that of community-acquired peritonitis [63]. In complicated peritonitis due to upper gastrointestinal perforation, the risk of infection increases with repeated intestinal perforation, long-term broad-spectrum antibiotic use, and pre-existing *Candida* colonization [6, 8]. If yeast is confirmed as *Candida*, echinocandin can be used for severe conditions, and fluconazole can be used for stable conditions. However, considering the domestic antibiotic insurance coverage criteria, fluconazole can be used as the first definitive treatment at this time, and it is necessary to consider the change to antifungal drugs such as echinocandin along with the final identification of the fungal species, the results of the antifungal drug susceptibility test, and the clinical response.

Even in complicated peritonitis, if sepsis is accompanied as in primary peritonitis, empirical antibiotics should be administered as soon as possible (within one hour) toward the causative bacteria considered [6, 51].

Key Question 4: What are the main causes of gallbladder and biliary tract infections?

1. The major causative bacteria of gallbladder and biliary tract infections include *E. coli, K. pneumoniae, Enterobacter, P. aeruginosa, Enterococcus* spp., and *Bacteroides* (quality of evidence at moderate, strength of recommendation at strong).
2. Biliary tract infections by multidrug-resistant Gram-negative bacteria and *Enterococcus* spp. have increased (quality of evidence at moderate, strength of recommendation at weak).

The most common causative bacteria of biliary tract infections, such as acute cholecystitis or cholangitis, are a group of *Enterobacteriaceae* originating from the gastrointestinal tract. The distribution of causative bacteria may vary depending on epidemiological characteristics such as nosocomial infection or the anatomical state of the biliary tract. Gram-negative bacteria such as *E. coli, K. pneumoniae,* and *Enterobacter* are the main causative aerobic bacteria, and *P. aeruginosa* also causes associated infections. *Enterococcus* and *Streptococcus* are common Gram-positive bacteria, and *Enterococcus* is a major cause of biliary tract infections caused by healthcare-associated infections or immunosuppressed patients such as those who have undergone liver transplantation. *Enterococcus* or polymicrobial infections are more common in patients who have received biliary stents. Anaerobic bacteria such as *Bacteroides*, *Fusobacterium*, and *Clostridia* are common causes in patients with a history of biliary tract surgery or bile duct-intestinal anastomosis. [1, 7, 13, 64-68].

Although there are differences between regions and healthcare institutions, the detection of multidrug-resistant Gram-negative bacteria such as ESBL or carbapenemase-producing strains is increasing in intra-abdominal infections, including biliary tract infections, which is a risk

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factor for organ failure and death [13, 24, 64, 69-72]. Compared to the past, the isolation rate of *Enterococcus* from biliary tract infections and the resistance rate of *Enterococcus* to ampicillin and vancomycin have increased [7, 13, 67]. Among anaerobic bacteria, *Bacteroides*, the main causative bacteria, have a high resistance rate to clindamycin according to domestic reports but a low resistance rate to cefoxitin compared to foreign countries, which needs to be considered when selecting an empirical treatment for biliary tract infections (**Fig. 4**, **5**) [1, 7, 30, 73].

While healthcare-related infections, use of biliary catheters, or exposure to antibiotics are known to be major risk factors for biliary tract infections caused by MDRO, recent studies report that MDRO have also been isolated from community-acquired infections [71, 74]. In a study on patients with acute cholangitis that occurred in 2006 - 2012 in Korea, 30.4% of the causative bacteria were ESBL-producing *E. coli*, and the frequency was particularly high in hospital-acquired infections. [75]. In a study on biliary tract infections from 2007 to 2016 based on data from the Health Insurance Review and Assessment Service, the frequency of infections caused by ESBL-producing bacteria showed a tendency to continuously increase [76]. In the 2016 - 2018 intra-abdominal infection study conducted at six university hospitals in Korea, the common causative bacteria of biliary tract infections were *E. coli* (31.9%), *K. pneumoniae* (25.4%), and *Enterococcus* (36.4%). In this study, 39.8% of *E. coli* and 17.7% of *K. pneumoniae* were ESBL-producing strains, and 39% of *Enterococcus* showed ampicillin resistance and 12.8%, vancomycin resistance (**Fig. 3**) [13].

Several previous studies have reported intensive care unit admission, abdominal invasive procedures, and use of biliary catheters as independent risk factors for acquiring carbapenem-resistant *Enterobacteriaceae* [77-79]. In a domestic study on acute cholangitis that occurred between 2000 and 2009, 3.5% (13/376 cases) of causative bacteria were carbapenemase-producing strains [72]. In a study on bloodstream infection by carbapenemase producing carbapenem-resistant *Enterobacteriaceae* (CP-CRE) in Korea from 2015 to 2016 conducted by the Korea Disease Control and Prevention Agency, 15% (20/131 cases) of CP-CRE bacteremia were caused by biliary tract infection [80]. Although domestic reports on the distribution of CP-CRE in biliary tract infections are rare, caution is needed depending on the incidence of CP-CRE in healthcare institutions and risk factors of patients.

Key Question 5: What are the empirical antibiotic treatments for gallbladder and biliary tract infections?

1. In patients with mild or moderate acute cholangitis or cholecystitis, cefuroxime, cefotaxime, or ceftriaxone should be selected as empirical antibiotics (quality of evidence at moderate, strength of recommendation at strong).
2. It is recommended to choose antibiotics with an anti-anaerobic effect for bile duct-intestinal anastomosis, such as cefotaxime or ceftriaxone in combination with metronidazole, and cephamycin (cefoxitin, cefmetazole, etc.) (quality of evidence at moderate, strength of recommendation at strong).
3. In patients with severe acute cholangitis or cholecystitis, anti-Pseudomonal antibiotics are recommended, such as ceftazidime or cefepime in combination with metronidazole, piperacillin/tazobactam, meropenem, and imipenem/cilastatin (quality of evidence at moderate, strength of recommendation at weak).
4. In terms of antibiotic stewardship, empirical treatment with vancomycin or teicoplanin should be considered in hemodynamically unstable patients or those with septic shock (quality of evidence at moderate, strength of recommendation at weak).

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In the treatment of acute cholecystitis or cholangitis, treatment for the causative lesion (drainage, surgery, etc.) is essential. Surgical treatment should be considered first in acute cholecystitis without complications, and the role of antibiotics has not yet been established. The priority is to remove the lesion that causes blockage, such as gallstones [7]. If surgery cannot be performed, even for acute cholecystitis without complications, antibiotics are administered for therapeutic purposes if the patient is elderly, clinically serious, debilitated, or immunosuppressed [81]. If there are complications such as gallbladder perforation or emphysema or necrotizing cholecystitis, antibiotics should be administered for therapeutic purposes. Acute cholangitis is a disease with high mortality and requires antibiotic administration.

Administration of second- or third-generation cephalosporins is recommended for mild or moderate community cholangitis or cholecystitis. Ampicillin/sulbactam is a drug that has been frequently used for intra-abdominal infections, but recently, the ampicillin/sulbactam susceptibility of *E. coli* has significantly decreased. While overseas clinical practice guidelines sometimes recommend it as an empirical treatment [59], it is no longer recommended as such in Korea (**Fig. 5**). With susceptibility confirmed, ampicillin/sulbactam may be used as definitive therapy. First-generation cephalosporin has also been recommended as a treatment in overseas guidelines [1, 7], but considering the current state of antibiotic resistance in Korea, where the resistance rate of *E. coli* or *K. pneumoniae* is close to 50%, the use of first-generation cephalosporin as empirical antibiotics for acute cholecystitis or cholangitis is not appropriate. Fluoroquinolone antibiotics are also recommended to be administered only when susceptibility to cultured isolates is known, as resistance to antibiotics is increasing significantly in the community [1, 64].

In acute cholangitis after bile duct-intestinal anastomosis, regardless of symptoms or severity, administration of antibiotics with antibacterial effects against anaerobic bacteria is required. In particular, antibiotics effective against *Bacteroides* spp. should be selected. As *Bacteroides* spp. isolated from intra-abdominal infection have high clindamycin resistance, clindamycin is no longer recommended as a treatment, and a combination therapy with metronidazole is recommended. In addition, it may be considered to change to β-lactams antibiotics with antibacterial activity against *Bacteroides* spp., and administration of cephamycin such as cefoxitin and cefmetazole may be considered [7]. United States guidelines no longer recommend cefoxitin because of the high resistance rate of *Bacteroides* spp. [1, 82]. This is due to an increase in cefoxitin-resistant *B. fragilis* and some older foreign clinical studies related thereto [83, 84]. As the resistance rate in Korea is relatively low, with possible clinical usefulness, the recommendation may change depending on the tracking of the resistance rate in the future (**Fig. 4**, **5**).

For severe community-acquired acute cholecystitis or cholangitis, empirical antibiotics with anti-Pseudomonal effects are recommended until the causative agent is identified. In previous studies, it has been reported that about 20% of acute cholecystitis or cholangitis is caused by *P. aeruginosa* [64]. In a recently published large-scale study, however, *P. aeruginosa* was found in 1.1% to 3.1% of blood culture isolates and 2.5% to 3.6% of bile cultures isolated from patients with acute cholangitis, respectively [85]. However, considering the virulence of *P. aeruginosa*, failure to include it in empirical antibacterial therapy can lead to high mortality. In severe infections, it is recommended to include anti-Pseudomonal antibiotics.

S. aureus is not a common isolate of acute cholangitis or cholangitis, and less than 1% of *S. aureus* has been isolated from the blood and bile of patients with acute cholangitis in the

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study [3]. Therefore, empirical treatment for MRSA is not recommended. Vancomycin is recommended when drug-resistant Gram-positive bacteria such as MRSA or *Enterococcus* have colonized or there is a concern for multidrug-resistant Gram-positive bacterial infections.

Enterococcus is another important pathogen to consider in severe community cholangitis or cholecystitis. There is a foreign guideline that suggests vancomycin administration may be considered to include *Enterococcus* in the antimicrobial range until culture results are obtained in patients with severe community-acquired acute cholangitis or cholecystitis [1, 8, 59]. However, in Korea, it is necessary to consider the empirical vancomycin administration when the vital signs are unstable or septic shock is accompanied, in terms of antibiotic stewardship.

When *Enterococcus* is detected in bile culture, treatment may be possible even with cephalosporin, which has no antibacterial activity against *Enterococcus*, due to the low virulence of *Enterococcus*. Even if the isolation of *Enterococcus* from clinical specimens continues after treatment for other bacteria, clinical improvement is often achieved. Therefore, there is no need to empirically administer antibiotics for *Enterococcus* except for postoperative infections, immunosuppressed patients, and healthcare-related infections in patients with heart valve disease or endovascular prostheses. If there is no clinical improvement with *Enterococcus* continuously detected or repeatedly detected in blood culture, and if only *Enterococcus* is detected or the number of *Enterococcus* detected is large and clinically serious, it requires antibiotic administration.

Since 2010, there have been few clinical studies on antibiotic therapy for patients with medically related acute cholangitis or cholecystitis. Research in this field is needed at home and abroad. As for cholangitis, a number of infections caused by antibiotic resistant bacteria have been reported worldwide [7]. In particular, there has been an increase in ESBL-producing *E. coli* and *Klebsiella* spp. even in community infections. Therefore, with periodic monitoring of the regional prevalence of ESBL or CP-CRE [7], reporting a high resistance rate, new drugs such as carbapenems, piperacillin/tazobactam, tigecycline, amikacin, ceftazidime/avibactam, and ceftolozane/tazobactam may also be used to treat these resistant strains [7]. National and regional susceptibility monitoring is important for rational empirical antibiotic selection [7].

Key Question 6: What risk factors should be considered for antibiotic-resistant bacteria?

1. In order to select appropriate empirical antibiotics in clinical practice, risk factors for antibiotic-resistant bacterial infection should be considered (quality of evidence at high, strength of recommendation at strong).
2. Choosing appropriate antibiotics in consideration of risk factors for resistant bacteria is also very important in terms of public health and socioeconomics (quality of evidence at high, strength of recommendation at strong).

Risk Factors for Antibiotic-resistant Strains

Antibiotic-resistant bacteria are increasing worldwide, making it difficult to select empirical antibiotics [14, 86, 87]. Antibiotic resistance threatens the treatment of infectious diseases and increases mortality [86]. Therefore, it is essential to identify antibiotic resistance-related factors and to deal with them appropriately [88]. Furthermore, antibiotics need to be used in consideration of antibiotic stewardship, and the guidelines for antibiotic use are important for this purpose [14].

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Various antibiotic-resistant bacteria are emerging, and the representative bacteria are *Enterococcus, S. aureus, K. pneumoniae, A. baumannii, P. aeruginosa,* and *Enterobacter spp.*, abbreviated as "ESKAPE" [89]. As for the independent risk factors for each antibiotic-resistant strain, MRSA infection is associated with a history of broad-spectrum antibiotic use, pressure sores, prostheses [90], a history of fluoroquinolone use [91], and intranasal or skin colonization of MRSA [92].

Risk factors for intra-abdominal infections caused by VRE include long-term hospitalization, treatment with glycopeptides or broad-spectrum antibiotics [90], and a history of VRE colonization [7], and intra-abdominal infections of the liver and biliary tract in patients after liver transplantation [6]. Empirically, antibacterial treatment for VRE is not recommended, and antibiotic treatment with susceptibility should be considered for definitive treatment [1]. For definitive treatment for VRE, tigecycline, linezolid, or daptomycin may be considered. The usual dose of tigecycline is 100 mg once, followed by a daily dose of 50 mg, but a daily dose of 200 mg has recently been recommended for VRE [93]. For definitive treatment for VRE, the usual dose (600 mg twice a day injected) of linezolid is appropriate at a MIC ≤1 μg/mL, but an increase in the dose should be considered when it is higher [94].

Risk factors for infections with antibiotic-resistant Gram-negative bacteria are known to include urethral tube insertion, excessive use of antibiotics, use of a contaminated humidifier [90], history of broad-spectrum antibiotic use, long-term inpatient care, repeated invasive intra-abdominal procedures, history of colonization or infection by antibiotic-resistant Gram-negative bacteria, and diabetes [6, 95]. In addition, the number of antibiotics used before, the site of infection, infection in the previous three months [96], ventilator treatment, long-term inpatient care, chronic disease [97], admission to the intensive care unit, malignant disease, transplantation requiring immunosuppressive medication, and age of 65 years or older may also be included [98]. In particular, admission to the intensive care unit is a major risk factor for the colonization of MDRO [99, 100].

Intra-abdominal infections by ESBL-producing *Enterobacteriaceae* are associated with infection by or carriers of this strain in other sites, admission to a long-term care facility, gastrostomy tube insertion, chronic renal failure, antibiotic administration within 30 days, and length of inpatient care prior to infection [101].

CRE infection occurs mainly in patients with enteric CRE carriers or on dialysis due to end-stage renal disease [102]. Previous inpatient care, gastroscopy, carbapenem administration, and aminoglycoside use were also considered risk factors [103]. The appearance of carbapenem-resistant bacteria has also been reported to be increased by the use of glycopeptide [104]. In domestic data, risk factors for ESBL and CRE infection were hospital-acquired infection, biliary tract and bile duct-related procedures, or implants [72]. Other antibacterial agents of choice for CRE may include tigecycline, amikacin, and colistin. Recently, domestic CRE resistance to tigecycline was reported to be 70.7% (29/41) and 31.0% (26/84) to colistin [105]. Since tigecycline is recommended as a treatment for intra-abdominal infections, it may be considered an appropriate option for antibiotic selection when CRE is identified intra-abdominally, showing susceptibility.

In intra-abdominal infections, the rate of antibiotic resistance of the causative pathogen varies from region to region. Regions with a high rate of antibiotic resistance of *Enterobacteriaceae* are the Asia-Pacific region, Africa, and the Middle East, especially Southeast

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Asia [34, 106, 107]. People returning from traveling to these areas are more likely to carry antibiotic-resistant *Enterobacteriaceae.*

Intra-abdominal Infections (IAI)

Risk factors for intra-abdominal infections caused by MDRO include liver cirrhosis, immunosuppression, exposure to ceftazidime, previously used antibiotics, biliary tract procedures, hospital-acquired infections, and shock [108]. Other cases included those who were hospitalized within three months and received antibiotic treatment for two days or more, were hospitalized for five days or more, and had reoperation at intervals of five days or more [8, 109]. Data from other studies have shown that antibiotic treatment within seven days prior to surgery, patients with severe underlying cardiovascular disease, leukocytes <4,000/mm^3 or >12,000/mm^3, healthcare-acquired complicated intra-abdominal infections, and inadequate source control were also relevant [110]. In particular, the following six were presented as risk factors for MDRO in the standard guidelines published in France: history of treatment with third-generation cephalosporin or fluoroquinolone within three months; identification of ESBL-producing intestinal flora or ceftazidime-resistant *P. aeruginosa* within three months; hospital admissions in other areas within 12 months; admission to a long-term care facility; history of failure in treatment with third-generation cephalosporin, fluoroquinolone, or piperacillin/tazobactam; and re-infection within two weeks after using piperacillin/tazobactam for more than three days [8].

Pancreatic fistula and the use of fluoroquinolones after surgery were identified as risk factors for MDRO infection after pancreaticoduodenectomy [111]. Risk factors for infection with bacteria resistant to third-generation cephalosporins in intra-abdominal infections include antibiotic use within 90 days, immunosuppression, inpatient care within 90 days, surgery, and invasive procedures [4].

Patients with Cirrhosis

In patients with liver cirrhosis, antibiotic-resistant bacterial infections increase according to the misuse of antibiotics [112], the frequency of inpatient care, and the need for invasive procedures [113], and vary according to various antibiotic prescriptions and policies in each country [114]. Hospital-acquired infections, admission to the intensive care unit, and recent inpatient care were identified as risk factors for the development of MDRO infections in patients with cirrhosis [115]. Factors including women, high Child Pugh score, ascites, dialysis, and prophylactic oral antibiotic administration and rifaximin use for spontaneous bacterial peritonitis were statistically significantly associated with VRE infection [116]. Prior antibiotic exposure and previous invasive procedures were risk factors for bloodstream infection caused by MDRO in patients with cirrhosis [117].

Spontaneous Bacterial Peritonitis (SBP)

Risk factors for MDRO infection in SBP include hospital-acquired infections, prolonged prophylactic administration of norfloxacin, severe liver failure, previous infection with MDRO, and recent treatment with β-lactams [113]. Although the administration of norfloxacin is most widely recommended for the prevention of SBP in international guidelines, it is causing an increase in fluoroquinolone resistance [19, 118-120]. On the other hand, Piano et al. reported that antibiotics used prophylactically in patients with cirrhosis were not associated with the development of a resistance [18]. The issue of prophylactic antibiotic administration in patients with cirrhosis is unresolved [121]. In another study, MDRO infections in patients with SBP were associated with the use of antibiotics, including

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prophylactic antibiotics; hospital-acquired infections; recent history of MDRO infections; recent inpatient care; use of healthcare; and upper gastrointestinal bleeding in patients with liver cirrhosis [19, 122, 123].

Antibiotic treatment with β-lactams prior to 90 days and a history of invasive gastrointestinal procedure were risk factors for third-generation cephalosporin-resistant bacterial infections in SBP [124]. In the Mayo Clinic study, nosocomial infection, recent antibiotic use, and hepatocellular carcinoma were identified as factors [125]. In secondary bacterial peritonitis, exposure to broad-spectrum antibiotics and hospital stay for more than five days were other risk factors for infection with antibiotic-resistant bacteria [126].

Biliary Tract Infection

Acute cholangitis is associated with a high risk of infection with *E. faecalis* and *E. faecium* in patients with prior endoscopic sphincterotomy (EST), presence of a stent in the biliary tract, prior cholecystectomy, and previous admission to an intensive care unit. It is recommended to select antibiotics in consideration of the intrinsic resistance of the *Enterococcus* strain [68]. In another study, the only risk factor associated with MDRO infections in patients with acute cholangitis was the presence of a stent in the bile duct [127].

In biliary tract infection, increased aspartate aminotransferase (AST) level, antibiotic use within 90 days, absolute neutrophil count, biliary tract surgery, and hemoglobin level were suggested as factors associated with MDRO infections [128]. In another study, prior appendectomy, antibiotic use within three months, and biliary intestinal anastomosis or sphincterotomy were also identified as risk factors [129]. In Korea, risk factors for biliary tract infection caused by ESBL-producing strains were male sex, old age, underlying diseases, biliary tract treatment history, and use of antibiotics, especially carbapenem, within 90 days [76].

Conclusions on Risk Factors for Antibiotic Resistance

To summarize several reports, the risk factors to consider for intra-abdominal infections caused by antibiotic-resistant bacteria are recent antibiotic exposure history, hospital-acquired infections, underlying diseases (especially liver cirrhosis), clinical symptoms (septic shock, immunosuppressed state, neutropenia, and low hemoglobin level), old age, biliary procedure or surgery, multidrug-resistant bacteria carrier, and history of living in a nursing facility. Therefore, empirical antibiotics should be selected in full consideration of these risk factors and the results of Gram staining and previous culture tests.

Although there are many risk factors for MDRO in intra-abdominal infection, the risks used in the guidelines for empirical antibiotic selection include postoperative peritonitis, tertiary peritonitis, antibiotic treatment history due to other diseases, MDRO colonization confirmed in the intestinal tract, immunosuppression due to drug treatment, long-term inpatient care, admission to long-term care facilities, and admission to the intensive care unit (**Fig. 5**, **Table 4**) [59].

Key Question 7: Is treatment tailored to the susceptibility of the bacteria identified in the abdominal cavity and biliary drainage duct necessary?

1. Acquisition of intra-abdominal specimens for microbiological evaluation of the infection site is always recommended for critically ill patients and those with healthcare-associated infections or community-acquired infections (previous antibacterial treatment) at risk of antibiotic-resistant pathogen infections (quality of evidence at moderate, strength of

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recommendation at strong).
2. Appropriate clinical specimens should be collected prior to antibiotic administration, and the results should be interpreted carefully. In the absence of clinical signs of infection, antibiotic treatment tailored to the susceptibility of bacteria colonized in drains is generally not required (quality of evidence at low, strength of recommendation at weak).
3. As for intra-abdominal or biliary tract infections that are not well controlled or worsening in clinical situations, culture tests using drainage tubes are not as useful as abscesses or invasive cultures, but antibiotic treatment considering the bacteria found is a reasonable option (quality of evidence at low, strength of recommendation at weak).
4. Controlling the source of infection is more important in determining the prognosis than performing antibiotic treatment considering the susceptibility of the pathogens (colonization or true pathogen) cultured in the drainage tube (quality of evidence at low, strength of recommendation at strong).

Acquisition of intra-abdominal specimens for microbiological evaluation of the infection site is always recommended for critically ill patients and those with healthcare-associated infections or community-acquired infections (previous antibacterial treatment) at risk of antibiotic-resistant pathogen infections [49]. A suitable intra-abdominal sample is peritoneal fluid or tissue from the site of infection [49]. Sufficient abdominal fluid/tissue volume (usually at least 1 - 2 mL of fluid) should be collected, processed to maintain sterility, and transported to the microbiology laboratory using a transport system [49]. In the laboratory, intra-abdominal specimens should be subjected to Gram staining, aerobic and anaerobic culture, and antibiotic susceptibility testing [49].

Acute cholangitis is usually caused by a combination of factors such as obstruction of bile flow and bacterial colonization in the biliary tract. Restoring biliary flow is key to the treatment, but antibiotics play an important role in the management of cholangitis [7]. In particular, the administration of effective antibiotics in severe infections is more important than in mild infections [130]. Careful and appropriate antibiotic use and early step-down or termination of antibiotic therapy are necessary to reduce antibiotic resistance [7].

Common causative bacteria of acute cholangitis are *Enterococcus* spp., *Enterobacteriaceae* (*E. coli* and *Klebsiella* spp.) [7, 130], and most of these results are obtained from incubation in the bile drainage ducts. They become contaminated over time by the normal flora of the skin and gut [130]. Thereafter, the frequency of antibiotic resistance increases due to medical-related infections [7].

Surgical site infection after pancreatic head resection is a major risk factor for acute cholecystitis, and bacterial bile is the main cause. Intraoperative bile duct aspiration improves the culture positivity rate and increases the possibility of selecting appropriate antibiotics in patients undergoing pancreatectomy compared to collecting bile duct samples with cotton swabs [131].

Appropriate clinical specimens should be obtained prior to antibiotic administration, and the results should be interpreted carefully. In the absence of clinical signs of infection, antibiotic treatment tailored to the susceptibility of bacteria colonized in drains is not required [132]. Culturing the contents of an indwelling catheter should not be performed as it usually simply indicates drainage catheter colonization [133, 134]. As for intra-abdominal or biliary tract infections that are not well controlled or worsening in clinical situations, culture tests using

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drainage tubes are not as useful as abscesses or invasive cultures, but antibiotic treatment for the bacteria found seems to be a reasonable option. However, there are few clinical data on the clinical significance of antibiotic treatment tailored to the susceptibility of the bacteria cultured in the drainage tube. Control of infectious source is important for the treatment of intra-abdominal infections [2, 7, 49].

Key Question 8: What is the appropriate duration of antibiotic treatment for an intra-abdominal infection?

1. In uncomplicated acute colonic diverticulitis, clinical course observation without antibiotic administration is considered first (quality of evidence at moderate, strength of recommendation at weak).
2. In acute or gangrenous appendicitis without perforation or acute or gangrene cholecystitis, antibiotic treatment is recommended within 24 hours if the surgical treatment is successful (quality of evidence at high, strength of recommendation at strong).
3. If the lesion is properly removed from the intra-abdominal infection, four days (96 h) of antibiotic treatment is recommended (quality of evidence at high, strength of recommendation at strong).
4. In intra-abdominal infections without the lesion removed, usually five to seven days of antibiotic treatment are maintained until 48 hours after clinical status is normalized (for example, alleviation of fever, normalization of white blood cell count, and recovery of gastrointestinal motility) (quality of evidence at moderate, strength of recommendation at strong). If there is no improvement with initial antibiotic treatment in complicated intra-abdominal infections, consider identifying and removing the lesion (quality of evidence at low, strength of recommendation at weak).

Insufficient antibiotic treatment increases treatment failure rates for infectious diseases as well as mortality [6, 135, 136]. On the other hand, unnecessarily long-term antibiotic therapy can increase unnecessary medical costs and cause adverse reactions such as super-infection, *Clostridioides difficile* infections, and organ damage [137].

Antibiotic treatment duration for patients with intra-abdominal infection is recommended based on the site of infection, clinical severity, removal of the lesion, and treatment response. In general, for patients with intra-abdominal infection with well-controlled infectious lesions, an antibiotic treatment period of 7 days or less is appropriate [6, 82]. Recommendations for antibiotic administration following intra-abdominal infection are as follows.

Local diseases such as traumatic bowel injury operated within 12 hours, upper gastrointestinal perforation operated within 24 hours, non-perforated appendicitis, cholecystitis, intestinal obstruction, and intestinal infarction are diseases in which the lesion of inflammation or infection is completely removed by surgery [1, 6]. For these cases, the main goal of antibiotic treatment is prevention of surgical site infections, not treatment of established infections. There was no difference in the incidence of infectious diseases according to the period of antibiotic administration in a comparative study between the group with antibiotic administration for 24 hours and the group with antibiotic administration for five days, with no need to exceed the antibiotic administration for 24 hours [6, 138-140].

In uncomplicated acute colonic diverticulitis, clinical course observation without antibiotic administration is considered first. Several retrospective and randomized clinical studies

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revealed that patients without perforation and in normal immune status recover well without antibiotic administration [141-145].

In acute or gangrenous appendicitis without perforation or acute or gangrene cholecystitis, antibiotic treatment is recommended within 24 h. As a result of a randomized study with a single-administration group (92 patients, infection rate of 6.9%), three-time administration group (94 patients, infection rate of 6.4%), and five-day administration group (83 patients, infection rate of 3.6%) before surgery for acute appendicitis, evaluating the postoperative infection rate, there was no significant difference among the groups, and on the contrary, the incidence of antibiotic-related complications was significantly higher in the five-day administration group than in the single-administration group [146]. In the cholecystitis study, there was no significant difference in the postoperative infection rates between the one-day antibiotic administration group (207 patients) and the five-day administration group (207 patients) before and after surgery (17% and 15%, respectively) [147].

If the lesion is adequately removed from the intra-abdominal infection, four days (96 hours) of antibiotic treatment is recommended. In a prospective multicenter study in which 111 patients with peritonitis were randomized to the three-day ertapenem and the five-day ertapenem treatment groups after surgery to analyze the progress, the treatment success rates of the three-day treatment group and the five-day treatment group were 92.9% and 89.6%, respectively, and there was no significant difference between the two treatment groups as the causative bacteria eradication was 95.3% and 93.7%, respectively [148]. In the 2008 – 2013 Study to Optimize Peritoneal Infection Therapy (STOP-IT) study conducted in 518 patients with complicated intra-abdominal infections in the United States, the postoperative progress such as the surgical site infection rate, intra-abdominal infection recurrence, and mortality within 30 days was compared and analyzed in the groups that received antibiotics four days after surgery (257 patients) and that received antibiotics for up to 48 hours upon confirming alleviation of fever, normalization of white blood cell count, and normalization of gastrointestinal motility after surgery (260 patients, up to 10 days of antibiotic administration). The average value of the patient APACHE II scores did not show a significant difference between the four-day treatment group and the control group, with surgical site infection rates of 21.8% and 22.3%, respectively. The median duration of antibiotic administration was 4.0 days (quartiles 4.0 - 5.0) and 8.0 days (quartiles 5.0 - 10.0), respectively, showing a significant difference between the two groups, but there were no significant differences in the surgical site infection, intra-abdominal infection recurrence, and mortality rates [149].

Even in complicated intra-abdominal infections without the lesion removed, the antibiotic treatment period can be shortened to five to seven days through clinical parameters such as use of an antipyretic, white blood cell normalization, and gastrointestinal motility recovery [150, 151]. If clinical conditions do not normalize after five to seven days of antibiotic treatment, abdominal computed tomography, examination to identify potential lesions, and removal of lesions are considered to find out the possible cause of treatment failure. In tertiary intra-abdominal infection, it is usually necessary to continue antibiotic administration until the lesion is controlled [152].

In patients with secondary bacteremia after intra-abdominal infection, antibiotic treatment can be reduced to seven days if the bacteremia is resolved after adequate lesion removal. In the results of a comparative analysis study on the period of bacteremia treatment conducted in Canada in the early 2000s, for secondary bacteremia, there was no significant difference in

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the clinical cure rate, microbiological cure rate, or survival rate between the short-term (five to seven days) antibiotic administration group and the long-term (seven to 21 days) antibiotic administration group [153-155].

Clinicians tend to stick with the traditional approach of continuing antibiotic therapy until clinical improvement is evident. For most acute intra-abdominal infections, antibiotic administration is maintained for an average of 10 to 14 days, and the period of antibiotic administration is extended, especially for severe conditions [156, 157].

A randomized controlled study conducted in 21 intensive care units in France from 2011 to 2015 compared the effectiveness and safety of eight-day antibiotic treatment and 15-day antibiotic treatment in critically ill patients who developed intra-abdominal infections after surgery [158]. The study results concluded that an eight-day short administration was adequate, with equivalence established in terms of 45-day mortality. In both treatment groups, there was no difference in the length of stay in the intensive care unit and hospital, the appearance of MDRO, or the occurrence of reoperation. Prolonged antibiotic treatment up to 15 days was not associated with clinical benefit [155]. Interestingly, according to a case study of 2,552 complicated intra-abdominal infections in the United States from 1997 to 2010, excessive duration of antibiotic therapy (eight days or longer) for complicated intra-abdominal infections was associated with subsequent infections elsewhere outside the abdomen and increased mortality [158]. In selecting the period of antibiotic use, not only the severity of the primary disease but also other complex factors such as the occurrence of other secondary infections due to prolonged antibiotic use, resistance development, and superinfection should be considered as well.

In some specific patients, it may not be appropriate to reduce the duration of antibiotics used to treat intra-abdominal infections. There are still insufficient data to evaluate the duration of antibiotic treatment in patients with intra-abdominal infections receiving immunosuppressants or developing sepsis or septic shock [149, 152].

Key Question 9: Is treatment necessary for Candida spp. isolated from a culture of intra-abdominal specimen?

1. When *Candida* spp. is isolated from intra-abdominal infection-associated clinical specimens, treatment with antifungal agents (echinocandin, fluconazole, voriconazole) should be considered in the following cases: upper gastrointestinal perforation or recurrent intestinal perforation; healthcare-associated intra-abdominal infection due to pancreatitis, treated surgically; unstable hemodynamic parameters; and recent administration of broad-spectrum antibiotics (quality of evidence at moderate, strength of recommendation at weak).
2. For patients with healthcare-associated intra-abdominal infections, administration of empirical antifungal agents (echinocandin) may be considered when yeast is identified in Gram staining of intra-abdominal clinical specimens, with unstable hemodynamic parameters (quality of evidence at moderate, strength of recommendation at weak).
3. In general, the administration of antifungal agents to patients with intra-abdominal infections is recommended as a definitive treatment (quality of evidence at moderate, strength of recommendation at weak). For definitive treatment after pathogen identification, it is recommended to request an antifungal susceptibility test (quality of evidence at moderate, strength of recommendation at weak).

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The most commonly isolated fungus from intra-abdominal infections is *Candida* spp. Although *Candida* spp. is a normal intestinal flora, it is mainly isolated from clinical specimens of patients with healthcare-associated intra-abdominal infections [159, 160]. In other words, tertiary intra-abdominal infection or secondary intra-abdominal infection in which the source of infection is not sufficiently controlled surgically may cause intra-abdominal infection by fungi.

When *Candida* spp. is isolated from intra-abdominal clinical specimens of patients with intra-abdominal infections, there is no clear clinical criterion for distinguishing a true infection [161, 162], but a clinical prediction model or biomarkers through blood tests such as 1,3-ß-D-glucan, mannan antigen, anti-mannan antibodies, and *C. albicans* germ tube antibodies may be used [160, 163]. Whether the specimen is an early specimen of peritonitis or one detected in the late drainage duct is also important for giving clinical significance and treatment, with a fungus detected in the early specimen being more meaningful for treatment.

As a result of analyzing 481 patients with intra-abdominal candidiasis in 13 medical institutions in several European countries, factors significantly associated with mortality were age, APACHE II score, secondary peritonitis, septic shock, and failure to control intra-abdominal infectious agents [159]. In particular, in patients with intra-abdominal infection accompanied by septic shock, the mortality rate was more than 60%, regardless of whether antifungal treatment was performed in patients whose intra-abdominal infectious agents were not controlled [159]. Another study analyzed 180 patients with secondary peritonitis, reporting that intra-abdominal *Candida* infection with septic shock was associated with a high mortality rate. In particular, a significant association with death was confirmed when yeasts were identified in intra-abdominal specimens of patients with postoperative intra-abdominal infections [164]. Based on this, the high-risk groups associated with intra-abdominal infections caused by *Candida* spp. include individuals with healthcare-associated infections or postoperative infections; severely immunosuppressed patients; those with APACHE II score ≥15; individuals with a history of antibiotic treatment for more than 48 hours; patients who have undergone upper gastrointestinal surgery; patients with cardiopulmonary insufficiency after surgery; those with surgically treated pancreatitis; and those with yeast confirmed in Gram staining of intra-abdominal clinical specimens [6, 43, 165]. According to the results of a multicenter study that collected data from a total of 1,571 patients with intra-abdominal infections at six university hospitals in Korea from 2016 to 2018, the isolation of *Candida* spp. from clinical specimens related to intra-abdominal infection was identified as one of the factors significantly associated with mortality [166].

The isolation of *Candida* spp. from clinical specimens related to postoperative peritonitis or healthcare-associated intra-abdominal infection is often associated with negative treatment outcomes. Although isolation of *Candida* spp. from clinical specimens is an indirect indicator of poor prognosis, antifungal therapy is usually recommended [1, 6, 9, 160, 164, 167]. However, in general, antifungal agents are not recommended for non-severe cases of community-acquired intra-abdominal infections [1, 6, 9, 167, 168].

Although there is little evidence on the timing of antifungal drug administration, there was no significant difference in treatment outcomes between prophylactic or empirical use and definitive use in previous studies [73, 169-171]. Therefore, for preemptive antifungal treatment, antifungal administration may be considered for *Candida* spp. colonies isolated from various clinical specimens in immunosuppressed patients or those with recurrent or postoperative intra-abdominal infections [9, 167].

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With respect to the type of antifungal agents, there were no randomized trials examining differences between echinocandins, polyenes, and triazoles [172]. However, in general, polyene antifungal agents are recommended when it is difficult to use echinocandins or triazole antifungal agents due to frequent adverse effects [15, 173]. Considering factors such as antifungal resistance, echinocandin or voriconazole is recommended for severe infections, and fluconazole can be administered for non-severe infections [1, 6, 167, 173].

The local susceptibility data for *Candida* spp. need to be considered for the empirical use of antifungal agents. Most *C. albicans* and *C. parapsilosis* isolated from domestic blood were susceptible to fluconazole, whereas about 50% of *C. glabrata* were not [174]. For definitive treatment, it is recommended to request an antifungal susceptibility test [174].

CONCLUSION

1. Limitations of These Guidelines and Suggestions

There are still areas that require clear evidence and discussion regarding the treatment of intra-abdominal infections. Even in Korea, since the epidemiological characteristics of the causative pathogens for intra-abdominal infections change dynamically over time, periodic collection of clinical data is required. To collect more accurate causative pathogens information, a standardized culture test through an aseptic procedure considering anaerobic bacteria before antibiotic administration should be actively performed. These data are required to initially determine the appropriate empirical antibiotic therapy. On the other hand, more prospective randomized clinical studies are needed to determine the risk assessment and stratification method regarding the severity of intra-abdominal infections and domestic risk factors for MDRO infections.

Although clinical experience is accumulating overseas, domestic clinical studies on new antibiotics, limited in use in Korea, are required to determine their exact roles. With an increase in the number of immunosuppressed patients, the effect of underlying diseases on the treatment of intra-abdominal infections should be investigated. There is still a lack of further studies on the clinical significance and appropriate timing for treatment of *Enterococcus*, coagulase-negative *Staphylococcus*, MRSA, and *Candida* spp. Furthermore, additional studies on the optimal treatment period and use of antibiotics are needed.

Based on these data, establishing and implementing the principles of a reasonable antibiotic management program for patients with intra-abdominal infections in Korea will improve the treatment outcomes of patients while reducing antibiotic resistance by reducing the use of broad-spectrum antibiotics. Currently, guidelines are being developed based on the content focused on causative pathogen-based antibiotic treatment; in the future, it may be possible to consider various methods of controlling infectious sources, develop a method to quickly identify the causative agent at an early stage, or establish a precise antibiotic treatment strategy linked with an individualized treatment strategy according to the mechanism of intra-abdominal infection from a broader perspective, such as the microbiome.

2. Conflict of Interest

The Committee of Clinical Practice Guidelines, which participated in the preparation of the guidelines, stated that the development process was not affected in any way by government agencies, pharmaceutical companies, hospitals, or interest groups.

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3. Plan for Revision of Guidelines

These guidelines will be periodically revised to reflect the results of major recent research at home institutions, as well as abroad, to ensure the applicability of the guidelines for the domestic situation.

SUPPLEMENTARY MATERIAL

Guideline Korean version

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