ABSTRACT

Background: This study evaluated the antimicrobial susceptibility of pathogens isolated from Korean patients with intraabdominal infections (IAIs).

Methods: This multicenter study was conducted at 6 university-affiliated hospitals in Korea between 2016 and 2018. All patients with microbiologically proven IAIs were retrospectively included, while patients with spontaneous bacterial peritonitis or continuous ambulatory peritoneal dialysis peritonitis were excluded. Identification and antimicrobial susceptibility testing were performed using automated microbiology systems.

Results: A total of 2,114 non-duplicated clinical isolates were collected from 1,571 patients. Among these pathogens, 510 (24.1%) were isolated from nosocomial infections, and 848 isolates (40.1%) were associated with complicated IAIs. The distribution of the microorganisms included aerobic gram-negative (62.6% of isolates), aerobic gram-positive (33.7%), anaerobic (0.9%), and fungal (2.8%) pathogens. The most common pathogens were Escherichia coli (23.8%), followed by Enterococcus spp. (23.1%) and Klebsiella spp. (19.8%). The susceptibility rates of E. coli and Klebsiella spp. to major antibiotics were as follows: amoxicillin/clavulanate (62.5%, 83.0%), cefotaxime (61.4%, 80.7%), ceftriaxone (63.7%, 83.1%), ceftazidime (65.3%, 84.3%), ciprofloxacin (56.4%, 86.3%), piperacillin/tazobactam (99.0%, 84.8%), amikacin (97.4%, 98.3%), and imipenem (99.8%, 98.8%). The susceptibility rates of Enterococcus spp. to ampicillin were 61.0%, amoxicillin/clavulanate, 63.6%; ciprofloxacin, 49.7%; imipenem, 65.2%; and vancomycin, 78.2%. The susceptibility rates of Pseudomonas aeruginosa and Acinetobacter spp. to imipenem were 77.4% and 36.7%, respectively.

Conclusion: Enterococcus spp. with susceptibility to limited antibiotics was one of the main pathogens in Korean IAIIs, along with E. coli and Klebsiella spp., which were highly susceptible to imipenem, amikacin, and piperacillin/tazobactam. Meanwhile, the low susceptibilities of E. coli or
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Author Contributions
Conceptualization: Yoon YK, Kim SW. Data curation: Yoon YK, Kim J, Moon C, Lee MS, Hur J, Lee H. Formal analysis: Yoon YK. Investigation: Yoon YK. Resources: Kim J, Moon C, Lee MS, Hur J, Lee H. Writing - original draft: Yoon YK. Writing - review & editing: Kim SW.

INTRODUCTION
While not uncommon, intraabdominal infections (IAIs) can have potentially serious complications and poor outcomes, particularly if inappropriately managed.1-4 IAIs are complex disease entities with a wide spectrum of pathological conditions ranging from uncomplicated appendicitis to generalized peritonitis. IAIs are caused by a diversity of microbes, most commonly enteric organisms.5-7 Appropriate antibiotic therapy and timely source control are essential to improve prognosis and minimize collateral damage caused by antimicrobial-resistant bacteria.8-10 Recent epidemiologic studies have shown increasing interest in issues related to antimicrobial resistance in patients with IAIs.10-15 Multidrug-resistant microorganisms are widespread worldwide, with significant geographical variations in pathogen diversity.12-14 Extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae are problematic for both community-acquired and nosocomial infections. Hospitalized patients are often at a risk for IAIs caused by carbapenem-resistant Enterobacteriaceae and carbapenem-resistant Pseudomonas aeruginosa and Acinetobacter species along with vancomycin-resistant enterococci (VRE).2,15 These problems of antimicrobial resistance complicate the decision-making process when choosing appropriate antibiotic therapy.8,16 The selection of empirical antibiotics based on accurate knowledge of potentially causative microorganisms increases the probability of making the right choice. Data on the distribution and antimicrobial susceptibility of pathogens isolated from patients with IAIs are of particular value for the implementation of an evidence-based antimicrobial stewardship program. However, no multicenter survey has determined the distribution and antimicrobial susceptibility of IAI-causative pathogens in Korea. Therefore, the current study investigated the microbiological profile and prevalence of antimicrobial-resistant organisms isolated from patients with IAIs in Korea, with a particular focus on Enterobacteriaceae resistant to third-generation cephalosporins, fluoroquinolones, and carbapenems, as well as non-fermentative gram-negative bacilli resistant to carbapenems, during the last 3 years to guide IAI antimicrobial therapy.

METHODS
Study design and patients
This multicenter, non-interventional cohort study was conducted at 6 university-affiliated hospitals located in 4 cities (Seoul, Guri, Busan, and Daegu) in Korea from January 2016 to December 2018. The primary aim of the study was to investigate the epidemiology and antibiotic susceptibility of microorganisms isolated from clinical specimens obtained from patients with IAIs.

Our study was based on a retrospective chart review of microorganisms isolated from consecutive adult patients (aged ≥ 18 years) with a clinical diagnosis of IAI in whom the causative pathogens

Klebsiella spp. to amoxicillin/clavulanate, advanced-generation cephalosporins, and ciprofloxacin should be considered when determining empirical antibiotic therapy in clinical practice.

Keywords: Intraabdominal Infections; Antimicrobial Susceptibility; Epidemiology
had been elusive. First, data on all microorganisms isolated from patients in each participating hospital during the study period were listed. Then, the IAI-causative microorganisms were screened by the investigator in each participating hospital. IAI-causative microorganisms were defined as pathogens identified from intraabdominal fluid or tissue samples obtained from an aseptically placed drain in the intraabdominal space, such as closed suction drainage system, open drain, T-tube drain, computed tomography-guided drainage, or during invasive procedures for diagnosis or treatment. Specific microorganisms involved in spontaneous bacterial peritonitis or continuous ambulatory peritoneal dialysis peritonitis were excluded from our analysis. Isolates obtained from abdominal drains or drainage bottles, superficial wounds, blood, or perianal abscess were also excluded from our analysis. The organisms were considered clinically significant at the discretion of the investigators. Microbiological and clinical data for each isolate were recorded on a case report form based on the patients’ medical records.

A single patient could harbor more than one microorganism during the study period. All microorganisms isolated from a patient were separately included in the analysis. In cases of multiple isolates of the same microorganism from a patient during the study period, only the first was included in the analysis.

Data collection and definitions

IAIs were clinically diagnosed in patients who presented with rapid-onset abdominal pain and signs of local and systemic inflammation (pain, tenderness, fever, tachycardia, and tachypnea). The diagnosis of postoperative IAIs was made based on the definitions stated in the guidelines from the National Nosocomial Infections Surveillance system. Electronic medical records were also reviewed to collect relevant demographic and clinical information such as demographic characteristics, IAI type (complicated or non-complicated), IAI extent, infection origin, and microbiological data.

Nosocomial IAIs were defined as infections that were absent on hospitalization but that occurred after 48 hours of admission in patients hospitalized for a reason other than IAI. The remaining IAIs were classified as community-onset IAIs. Uncomplicated IAIs were defined as infections contained within a single organ of origin, whereas complicated IAIs were defined as infections that extended beyond the source organ and into the peritoneal cavity through the anatomic disruption. Postoperative IAIs were considered nosocomial infections. The remaining IAIs were categorized as community-onset IAIs.

Microbiological evaluation

Species identification and drug susceptibility testing of the isolates were performed in each participating hospital using VITEK II (BioMérieux, Hazelwood, MO, USA) or MicroScan WalkAway 96 plus (Siemens Healthcare Diagnostics Inc., CA, USA) systems based on the standard criteria defined by the Clinical and Laboratory Standards Institute (CLSI). Escherichia coli and Klebsiella spp. were screened for an ESBL phenotype (ceftazidime or cefotaxime minimum inhibitory concentration >1 μg/mL) and confirmed as ESBL producers using combination clavulanate-based testing according to the method from the CLSI.

Statistical analysis

Data are presented as frequencies (proportion) or means ± standard deviation, as appropriate. Categorical variables were compared using χ² or Fisher’s exact tests. IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA) was used for all statistical analyses. Statistical significance was defined as P < 0.05.
**Ethics statement**
The study protocol was reviewed and approved by the Institutional Review Board (IRB) of the Korea University Anam Hospital (IRB registration No. 2019AN0128). The investigators requested formal approval of the protocol by the regional ethics committee, if required. Because this research was a retrospective chart review study, informed consent was waived.

**RESULTS**

**Patients and characteristics of IAIs**
During the study period, 2,114 isolates from 1,571 patients (60.4% men, 67.0 ± 15.7 years) with microbiologically proven IAI were identified. Among 1,571 patients, community-onset IAIs and nosocomial IAIs were identified in 1,207 (76.8%) and 364 (23.2%) patients, respectively. Uncomplicated and complicated IAIs were observed in 966 (61.5%) and 605 (38.5%) patients, respectively. The most common primary focus of IAIs was the biliary tract, including the gallbladder (51.2%), followed by the liver (13.7%), colon or rectum (13.0%), gastroduodenum (6.3%), and appendix (4.9%). The distribution of lesion extent included localized inflammation (27.2%), localized abscess (47.5%), localized peritonitis (7.4%), diffuse suppurative peritonitis (12.2%), and combined complicated infection (5.7%). Among 2,114 isolates, 1,604 (75.9%) were collected from community-onset IAIs and 510 (24.1%) were collected from nosocomial IAIs. Among these isolates, 848 (40.1%) and 1,266 (59.9%) were associated with complicated and non-complicated IAIs, respectively. The lesion extent and sources of specimens in community-onset and nosocomial infections are summarized in Table 1. Diffuse suppurative peritonitis was more common in nosocomial IAIs than in community-onset IAIs. More than half of the IAI specimens were collected from biliary tracts, including the gallbladder (Table 1).

**Table 1. Characteristics of IAIs according to community-acquired and nosocomial infections**

| Parameters                        | Total (n = 2,114) | Community-onset infections (n = 1,604) | Nosocomial infections (n = 510) | P value |
|-----------------------------------|-------------------|---------------------------------------|--------------------------------|---------|
| **Type of IAIs**                  |                   |                                       |                                |         |
| Complicated                       | 848 (40.1)        | 450 (28.1)                            | 398 (78.0)                     | < 0.001 |
| Non-complicated                   | 1,266 (59.9)      | 1,154 (71.9)                          | 112 (22.0)                     |         |
| **Extent of IAIs**                |                   |                                       |                                | < 0.001 |
| Localized inflammation            | 579 (27.4)        | 523 (32.6)                            | 56 (11.0)                      |         |
| Localized abscess                 | 978 (46.3)        | 747 (46.6)                            | 231 (45.3)                     |         |
| Localized peritonitis             | 162 (7.7)         | 114 (71)                              | 48 (9.4)                       |         |
| Diffuse suppurative peritonitis   | 271 (12.8)        | 148 (9.2)                             | 123 (43.1)                     |         |
| Combined complicated infection    | 124 (5.9)         | 72 (4.5)                              | 52 (10.2)                      |         |
| **Specimen sources**              |                   |                                       |                                | < 0.001 |
| Gastrointestinal tract            | 136 (6.4)         | 49 (3.1)                              | 87 (17.1)                      |         |
| Small intestine                   | 112 (5.3)         | 932 (58.1)                            | 150 (29.4)                     |         |
| Colorectal                        | 294 (13.9)        | 130 (8.1)                             | 164 (32.2)                     |         |
| Appendix                           | 119 (5.6)         | 102 (6.4)                             | 17 (3.3)                       |         |
| Liver                             | 248 (11.7)        | 238 (14.8)                            | 10 (2.0)                       |         |
| Biliary tract                     | 1,082 (51.2)      | 932 (58.1)                            | 150 (29.4)                     |         |
| Pancreas                           | 51 (2.4)          | 35 (2.2)                              | 16 (3.1)                       |         |
| Retroperitoneum                   | 10 (0.5)          | 8 (0.5)                               | 2 (0.4)                        |         |
| Other                             | 62 (2.9)          | 48 (3.0)                              | 14 (2.7)                       |         |

Data are presented as number (%).
IAIs = intraabdominal infections.
*Biliary tract infections such as acute cholecystitis and acute cholangitis.
Distribution of the major pathogens isolated from IAIs

The distribution of the microorganisms was aerobic gram-negative (62.6%), aerobic gram-positive (33.7%), anaerobic (0.9%), and fungal (2.8%) pathogens. The most commonly identified pathogens were *E. coli* (23.8%), followed by *Enterococcus* spp. (23.1%), *Klebsiella* spp. (19.8%), and *Streptococcus* spp. other than *S. pneumoniae* (7.1%).

The distribution of microorganisms differed between community-onset and nosocomial IAIs (Table 2). Nosocomial IAIs had higher proportions of aerobic gram-positive bacteria (*P* < 0.001) and lower proportions of aerobic gram-negative bacteria (*P* < 0.001) than those in community-onset IAIs. There were significant differences in the isolation frequencies of *Klebsiella* spp. (*P* < 0.001) and *Streptococcus* spp. other than *S. pneumoniae* (*P* = 0.006) between the 2 groups, unlike *E. coli* (*P* = 0.689) and *Enterococcus* spp. (*P* = 0.065). The most commonly identified pathogens of nosocomial IAIs were *Enterococcus* spp. (26.1%), followed by *E. coli* (23.1%), *Streptococcus* spp. (10.0%), and *Klebsiella* spp. (9.8%), while those of community-onset IAIs were *E. coli* (24.0%), followed by *Klebsiella* spp. (23.0%), *Enterococcus* spp. (22.1%), and *Streptococcus* spp. (6.2%) (Table 2).

Table 2. Distributions of the most common microorganisms isolated from patients with IAIs

| Microorganisms                      | Total (n = 2,114) | Community-onset infections (n = 1,604) | Nosocomial infections (n = 510) | *P* value |
|-------------------------------------|------------------|---------------------------------------|--------------------------------|-----------|
| **Aerobes**                         |                  |                                       |                                |           |
| Gram-negative bacteria              | 1,323 (62.6)     | 1,055 (65.8)                          | 268 (52.5)                     | < 0.001   |
| *Escherichia coli*                  | 503 (23.8)       | 385 (24.0)                            | 118 (23.1)                     | 0.689     |
| *Klebsiella* spp.                   | 419 (19.8)       | 369 (23.0)                            | 50 (9.8)                       | < 0.001   |
| *Enterobacter* spp.                 | 88 (4.2)         | 59 (3.7)                              | 29 (5.7)                       | 0.044     |
| *Pseudomonas aeruginosa*            | 93 (4.4)         | 68 (4.2)                              | 25 (4.9)                       | 0.525     |
| *Pseudomonas* other than *P. aeruginosa* | 1 (0.01)   | 1 (0.1)                               | 0                              | 1.000     |
| *Citrobacter* spp.                  | 80 (3.8)         | 66 (4.1)                              | 14 (2.7)                       | 0.158     |
| *Acinetobacter* spp.                | 36 (1.7)         | 24 (1.5)                              | 12 (2.4)                       | 0.193     |
| *Aeromonas* spp.                    | 30 (1.4)         | 26 (1.6)                              | 4 (0.8)                        | 0.164     |
| *Proteus mirabilis*                 | 17 (0.8)         | 11 (0.7)                              | 6 (1.2)                        | 0.266     |
| *Morganella morganii*               | 9 (0.4)          | 7 (0.4)                               | 2 (0.4)                        | 0.712     |
| *Sterotrophomonas maltophilia*      | 12 (0.6)         | 10 (0.6)                              | 2 (0.4)                        | 0.742     |
| *Serratia* spp.                     | 3 (0.1)          | 3 (0.2)                               | 0                              | 1.000     |
| *Haemophilus* spp.                  | 1 (0.01)         | 0                                     | 1 (0.2)                        | 0.241     |
| *Enterobacteriaceae, other*         | 3 (0.1)          | 0                                     | 3 (0.6)                        | 0.046     |
| *Gram-negative rod, other*          | 25 (1.2)         | 24 (1.5)                              | 1 (0.2)                        | 0.018     |
| **Aerobes**                         |                  |                                       |                                |           |
| Gram-positive bacteria              | 713 (33.7)       | 493 (30.7)                            | 220 (43.3)                     | < 0.001   |
| *Enterococcus* spp.                 | 488 (23.1)       | 355 (22.1)                            | 133 (26.1)                     | 0.065     |
| *Streptococcus* spp. other than *S. pneumoniae* | 150 (7.1) | 100 (6.2)                            | 50 (9.8)                       | 0.006     |
| *Staphylococcus aureus*             | 42 (2.0)         | 23 (1.4)                              | 19 (3.7)                       | 0.001     |
| *Coagulase-negative Staphylococcus* | 20 (0.9)         | 11 (0.7)                              | 9 (1.8)                        | 0.036     |
| *Corynebacterium* spp.              | 8 (0.4)          | 2 (0.1)                               | 6 (1.2)                        | 0.003     |
| *S. pneumoniae*                     | 1 (0.01)         | 0                                     | 1 (0.2)                        | 0.241     |
| Gram-positive cocci, other           | 5 (0.2)          | 2 (0.1)                               | 3 (0.6)                        | 0.094     |
| Gram-positive bacilli, other         | 2 (0.1)          | 2 (0.1)                               | 0                              | 1.000     |
| **Anaerobes**                       |                  |                                       |                                |           |
| Anaerobes, total                    | 19 (0.9)         | 17 (1.1)                              | 2 (0.4)                        | 0.278     |
| *Bacteroides* spp.                  | 10 (0.5)         | 9 (0.6)                               | 1 (0.2)                        | 0.467     |
| *Clostridium* spp.                  | 7 (0.3)          | 7 (0.4)                               | 0                              | 0.207     |
| Anaerobes, other                    | 2 (0.1)          | 1 (0.1)                               | 1 (0.2)                        | 0.424     |
| **Fungi**                           |                  |                                       |                                |           |
| Fungi, total                        | 59 (2.8)         | 39 (2.4)                              | 20 (3.9)                       | 0.075     |
| *Candida albicans*                  | 43 (2.0)         | 27 (1.7)                              | 16 (3.1)                       | 0.043     |
| *Candida* spp. other than *C. albicans* | 16 (0.8) | 12 (0.7)                           | 4 (0.8)                        | 1.000     |

Data are presented as number (%). IAIs = intraabdominal infections.
The most common causative isolates differed according to the IAI origin (Table 3). Gram-positive bacteria were the most common pathogens in IAIs of the upper gastrointestinal tract compared with gram-negative bacteria in the lower gastrointestinal tract. *Klebsiella pneumoniae* and *Enterococcus* spp. were the most commonly isolated pathogens in patients with IAIs of the liver and pancreaticobiliary tract, respectively.

**Antimicrobial susceptibilities of major pathogens isolated from IAIs**

The antimicrobial susceptibility profiles of the most common gram-negative bacteria are detailed in Table 4. The most active antibiotics against Enterobacterales were amikacin (susceptibility rates ranging from 97.4% to 100%), ertapenem (92.2% to 99.5%), imipenem (94.3% to 99.8%), and tigecycline (94.9% to 99.0%). The susceptibility rate to ciprofloxacin was as low as 56.4% in *E. coli* but was 86.3% in *K. pneumonia*, 94.3% in *Enterobacter* spp., and 82.3% in *Citrobacter* spp. The susceptibility rates of ß-lactam/ß-lactamase inhibitors to piperacillin/tazobactam and amoxicillin/clavulanate were 99.0% and 62.5%, respectively, in *E. coli* and 84.8% and 83.0%, respectively, in *Klebsiella* spp. With respect to cephalosporins, the susceptibility rates to cefoxitin, cefotaxime, ceftazidime, and cefepime were 82.7%, 61.4%, 63.7%, and 65.3%, respectively, in *E. coli* and 88.1%, 80.7%, 83.1%, and 84.3%, respectively, in *Klebsiella* spp. In *P. aeruginosa*, the susceptibility rates to amikacin, ciprofloxacin, imipenem, and ceftazidime were 94.5%, 83.5%, 77.4%, and 73.3%, respectively, while the rates to piperacillin/tazobactam was as low as 58.0%. In *Acinetobacter* spp., the susceptibility rates to amikacin, ampicillin/sulbactam, piperacillin/tazobactam, and imipenem were less than 50% (Table 4).

Table 4 shows the susceptibility rates to major antimicrobial agents against community-onset and nosocomial isolates of the gram-negative bacteria most frequently recovered from IAIs. Overall, the susceptibility rates to most antibiotics were higher in microorganisms isolated from community-onset IAIIs than in those isolated from nosocomial IAIIs. In *E. coli* and *Klebsiella* spp., the susceptibility rates to cefotaxime, cefepime, ciprofloxacin, and piperacillin/tazobactam differed by more than 10% between the 2 groups, whereas the rates to amikacin and imipenem did not (Table 4). The tigecycline susceptibility rate for *Klebsiella* spp. isolated from nosocomial IAIIs was 10.1% lower than that for isolates from community-onset IAIIs. However, the *E. coli* susceptibility rates to tigecycline were similar between the 2 groups (Table 4).

On comparison between ESBL-producer and non-ESBL-producer *E. coli* and *Klebsiella* spp., the susceptibility rates to imipenem, amikacin, and tigecycline were above 90% in both groups. The susceptibility rates to cefotaxin and piperacillin/tazobactam in ESBL-producing *E. coli* were 73.2% and 77.4%, respectively, whereas those in ESBL-producing *Klebsiella* spp. were 66.2% and 41.3%, respectively (Table 5).

The antimicrobial susceptibility profiles of the most common gram-positive bacteria are described in Table 6. Considering the susceptibility rates of gram-positive bacteria to major
Table 4. Antimicrobial susceptibilities of aerobic gram-negative bacteria according to CO and N infections

| Antibiotics | Escherichia coli (n = 503) | Klebsiella spp. (n = 419) | Enterobacter spp. (n = 88) | Citrobacter spp. (n = 80) | Pseudomonas aeruginosa (n = 93) | Acinetobacter spp. (n = 36) |
|-------------|---------------------------|---------------------------|---------------------------|---------------------------|-------------------------------|-----------------------------|
|             | Total                     | CO (n = 385, 76.5%)       | N (n = 118, 23.5%)        | Total                     | CO (n = 66, 82.5%)           | N (n = 14, 17.5%)            |
|             | (n = 503)                 | (n = 369, 93.6%)          | (n = 50, 10.0%)           | (n = 57, 66.3%)           | (n = 29, 33.7%)              | (n = 14, 77.5%)              |
| AMP/SM      | 62/139                    | 49/103                    | 13/36                     | 79/95                     | 71/79                         | 8/16                        |
|             | (44.6)                    | (47.6)                    | (36.1)                    | (83.2)                    | (89.9)                        | (50.0)                      |
|             |                            | (16.0)                    | (18.2)                    | (18.2)                    | (20.0)                        | (0)                         |
| AMX/CA      | 210/336                   | 164/251                   | 46/85                     | 185/223                   | 162/184                       | 23/39                       |
|             | (62.5)                    | (65.3)                    | (54.1)                    | (81.0)                    | (88.0)                        | (59.0)                      |
|             |                            | (14.4)                    | (18.2)                    | (14.8)                    | (4.2)                         | (2.0)                       |
| TZP         | 49.5/500                  | 312/364                   | 91/115                    | 290/342                   | 272/393                       | 33/49                       |
|             | (99.0)                    | (91.2)                    | (79.1)                    | (84.8)                    | (86.7)                        | (101)                       |
|             |                            | (9.2)                     | (20.8)                    | (5.3)                     | (20.7)                        | (0)                         |
| IPM         | 488/499                   | 382/382                   | 116/117                   | 417/416                   | 363/366                       | 50/50                       |
|             | (99.8)                    | (100)                     | (99.1)                    | (98.8)                    | (98.6)                        | (101)                       |
|             |                            | (0.2)                     | (0.9)                     | (1.2)                     | (1.4)                         | (0)                         |
| MPM         | 130/131                   | 96/96                     | 34/35                     | 103/103                   | 86/86                         | 17/17                       |
|             | (99.2)                    | (100)                     | (97.1)                    | (100)                     | (100)                         | (100)                       |
|             |                            | (0.8)                     | (2.9)                     | (1.4)                     | (5.8)                         | (3.7)                       |
| EPM         | 417/419                   | 325/326                   | 92/93                     | 35/35/36                 | 309/351                       | 41/41                       |
|             | (99.5)                    | (99.7)                    | (98.9)                    | (98.3)                    | (98.1)                        | (100)                       |
|             |                            | (0.5)                     | (1.1)                     | (2.1)                     | (2.0)                         | (0)                         |
| CFX         | 407/492                   | 314/377                   | 93/115                    | 373/405                   | 323/357                       | 34/48                       |
|             | (82.7)                    | (83.3)                    | (89.9)                    | (88.1)                    | (90.5)                        | (70.8)                      |
|             |                            | (17.3)                    | (1.5)                     | (1.9)                     | (2.2)                         | (30.2)                      |
| CTX         | 269/428                   | 271/225                   | 58/113                    | 305/378                   | 277/281                       | 28/40                       |
|             | (61.4)                    | (64.9)                    | (51.3)                    | (80.7)                    | (82.0)                        | (70.0)                      |
|             |                            | (38.6)                    | (49.7)                    | (20.0)                    | (20.0)                        | (30.0)                      |
| CFC         | 60/112                    | 45/80                     | 15/32                     | 53/66                     | 46/65                         | 7/10                        |
|             | (53.6)                    | (56.3)                    | (73.1)                    | (60.0)                    | (60.7)                        | (70.0)                      |
|             |                            | (49.0)                    | (42.1)                    | (40.0)                    | (40.0)                        | (40.0)                      |
| CAZ         | 316/496                   | 254/379                   | 62/117                    | 344/414                   | 352/365                       | 32/49                       |
|             | (63.7)                    | (67.0)                    | (52.0)                    | (65.3)                    | (65.3)                        | (53.2)                      |
|             |                            | (37.3)                    | (48.0)                    | (35.7)                    | (35.7)                        | (47.0)                      |
| FEP         | 324/496                   | 238/379                   | 66/117                    | 350/465                   | 375/366                       | 33/49                       |
|             | (65.3)                    | (68.3)                    | (56.4)                    | (94.3)                    | (86.6)                        | (67.3)                      |
|             |                            | (34.7)                    | (4.7)                     | (1.7)                     | (3.4)                         | (33.1)                      |
| AMK         | 481/494                   | 370/379                   | 111/116                   | 408/415                   | 365/366                       | 48/50                       |
|             | (97.4)                    | (97.9)                    | (95.7)                    | (98.3)                    | (98.6)                        | (96.0)                      |
|             |                            | (2.6)                     | (2.1)                     | (3.7)                     | (4.0)                         | (4.0)                       |
| GEN         | 341/447                   | 258/333                   | 83/114                    | 343/379                   | 307/338                       | 36/41                       |
|             | (76.3)                    | (77.5)                    | (72.8)                    | (80.5)                    | (80.8)                        | (87.8)                      |
|             |                            | (23.7)                    | (27.2)                    | (19.5)                    | (12.2)                        | (12.2)                      |
| CIP         | 281/498                   | 228/382                   | 53/116                    | 82/95                     | 325/366                       | 32/50                       |
|             | (56.4)                    | (59.7)                    | (45.7)                    | (86.3)                    | (88.8)                        | (64.0)                      |
|             |                            | (43.6)                    | (54.3)                    | (16.0)                    | (16.0)                        | (36.0)                      |
| TIG         | 48.5/500                  | 379/382                   | 171/118                   | 39/40/41                 | 347/381                       | 43/50                       |
|             | (99.0)                    | (99.0)                    | (99.2)                    | (94.9)                    | (94.1)                        | (96.0)                      |
|             |                            | (0.0)                     | (0.8)                     | (0.9)                     | (0.9)                         | (4.0)                       |

The data are presented as number of susceptible/total number (%).
antibiotics, vancomycin, tigecycline, and linezolid were most consistently active in vitro in both community-onset and nosocomial infections (Table 6). However, even in community-onset IAIIs, the susceptibility rates to ampicillin/sulbactam and ciprofloxacin in Enterococcus spp. and those to clindamycin and ciprofloxacin in Staphylococcus aureus were less than 70% (Table 6). The prevalence of methicillin-resistant S. aureus and VRE was 21.8% and 59.5%, respectively.

**DISCUSSION**

To our knowledge, this is the first multicenter study on IAIIs in Korea to describe the microbiological distribution and antimicrobial susceptibility patterns of pathogens isolated from patients with IAIIs. In this descriptive study, Enterococcus spp. was the second most common isolate in patients with IAIIs, accounting for 23.1% of isolates. These enteric microorganisms frequently show multidrug resistance to various antibiotics recommended as empirical antibiotics.

In the present study, the 3 most common pathogens in community-onset IAIIs were *E. coli* (24.0%), *Klebsiella* spp. (23.0%), and *Enterococcus* spp. (22.1%), whereas those in nosocomial...
IAIs were Enterococcus spp. (26.1%), E. coli (23.1%), and Streptococcus spp. (10.0%). Previous studies mainly focused on gram-negative bacteria have reported Enterobacteriaceae to be the major pathogens involved in complicated IAIs. In contrast, our study included both uncomplicated and complicated IAIs to report the microbiological distribution of IAIs, observing a relatively high composition ratio of gram-positive pathogens, particularly Enterococcus spp. The heterogeneity of study populations with various IAI origins can also affect the microbiologic profile of pathogens associated with IAIs (Table 3). Although clinicians in real-world settings commonly encounter Enterococcus isolates while treating IAIs, the necessity of empirical and directed antimicrobial agents against Enterococcus spp. continues to be debated. Some studies have suggested that the isolation of Enterococcus in patients with IAIs results in treatment failure or increased mortality, while others demonstrated no association with mortality. Furthermore, some studies have shown equivalent therapeutic effects among empiric antibiotic regimens, regardless of the antimicrobial activity against enterococci. At present, prominent guidelines recommend empirical anti-enterococcal therapy for patients with nosocomial IAIs and severe community-acquired IAIs.

Our findings reveal a much smaller proportion of anaerobes than previously reported (0.9% vs. 7.7%–22.9%), although one study reported a similar proportion. Several guidelines on the management of complicated IAIs have indicated the role of intraabdominal culture and susceptibility testing. However, they did not provide detailed culture methods to identify anaerobic bacteria. Considering the increasing prevalence of antibiotic resistance in anaerobes, regional susceptibility patterns are crucial for the empirical treatment of anaerobic infections.

The guidelines from the World Society of Emergency Surgery suggest amoxicillin/clavulanate and cefotaxime or ciprofloxacin in combination with metronidazole as appropriate regimens for mild-to-moderate community-acquired IAIs. Moreover, cefepime in combination with metronidazole has been recommended for high-risk community-acquired IAIs. In the present study, however, we observed poor susceptibility rates of < 70% to amoxicillin/clavulanate (62.5%), cefotaxime (61.4%), ceftazidime (63.7%), cefepime (65.3%), and ciprofloxacin (56.4%) among E. coli isolates and good susceptibility rates of ≥ 80% to cefoxitin (82.7%), piperacillin/tazobactam (99.0%), ertapenem (99.5%), imipenem (99.8%), meropenem (99.2%), amikacin (97.4%), and tigecycline (99.0%) in both community-onset IAIs and nosocomial IAIs. In both nosocomial and community-onset IAIs, increased Enterobacteriaceae resistance to cefotaxime along with high resistance rates to cefepime undermine the rationale for the use of extended-spectrum cephalosporins as empirical therapy for IAIs in Korea. However, carbapenem monotherapy and amikacin-based combination therapy are expected to have broad-spectrum activity against bacterial pathogens of IAIs, and thus, the clinical value of cefoxitin mentioned in the guidelines for the diagnosis and management of complicated IAIs by the Infectious Diseases Society of America should be evaluated clinically. In addition, active bacterial culture and susceptibility testing may be useful in guiding pathogen-directed therapy to ensure appropriate antibiotic therapy and minimize excessive exposure to broad-spectrum antibiotics with step-down therapy. Among Klebsiella spp. isolated from community-onset IAIs, good susceptibility rates of ≥ 80% to all antibiotics tested were observed (Table 4). In contrast, among isolates from nosocomial IAIs, the susceptibility rates to amoxicillin/clavulanate, cefepime, ciprofloxacin, and piperacillin/tazobactam were < 70%, whereas those to amikacin, imipenem, ertapenem, and tigecycline were ≥ 80%.
The main resistance problems are currently represented by ESBL-producing Enterobacteriaceae, CRE, and carbapenem-resistant non-fermentative bacteria. In our study, ESBL-producing strains accounted for 39.8% of *E. coli* spp. and 17.7% of *Klebsiella* spp. Data from the Study for Monitoring Antimicrobial Resistance Trends from 2005 to 2010 also showed that the Asia–Pacific region consistently had the highest ESBL positivity rates of 23%–38% for *E. coli* and *K. pneumoniae*, respectively, in IAI isolates. The susceptibility rates of the *P. aeruginosa* and *Acinetobacter* spp. isolates to imipenem were 77.4% and 36.7%, respectively, which were similar to those mentioned in previous reports. As the susceptibilities of *P. aeruginosa* and *Acinetobacter* spp. isolates to imipenem were less than 80% in nosocomial IAIs, antimicrobial coverage of the potential pathogens of nosocomial IAIs may become more convoluted.

To reduce carbapenem resistance, carbapenem-sparing therapy has been proposed for infections caused by ESBL-producing Enterobacteriaceae. In our findings, the high susceptibility rates of ESBL-producing *E. coli* to piperacillin/tazobactam (77.4%), cefoxitin (73.2%), amikacin (93.9%), and tigecycline (99.0%) (Table 5) suggest that these antibiotics may be acceptable alternatives to imipenem (99.5%). However, the low susceptibility rates of ESBL-producing *Klebsiella* spp. to piperacillin/tazobactam (41.3%) and cefoxitin (66.2%) and reduced activity against ESBL-producing *E. coli* with a high inoculum of bacteria may impede the general use of piperacillin/tazobactam and cefoxitin against ESBL producers.

Ciprofloxacin and amoxicillin/clavulanate, previously recommended for mild-to-moderate community-acquired IAIs, were active against less than 60% of *E. coli* isolates in vitro, as shown in previous studies. Therefore, their roles as empirical antibiotics even for community-acquired IAIs are limited. However, their role as directed antibiotics should be guaranteed to control the emergence of antimicrobial resistance.

Our study has several limitations. First, the limitations pertain mostly to the study’s retrospective design. In particular, data on the community-onset versus nosocomial nature of the infections were determined retrospectively using the length of stay as a surrogate marker. Second, because centralized microbiological analysis of the strains in a reference laboratory was not available, complete susceptibility data could not be elucidated. However, all microbiological laboratories are periodically accredited under the Korean Laboratory Accreditation Program developed by the Korean Society of Laboratory Medicine. Third, the IAI-causative pathogens in this study were initially selected based on objective criteria. However, the clinical significance of the microorganisms was determined by researchers at each participating institution.

In conclusion, the results of this study demonstrate the prevalent antimicrobial resistance patterns among pathogens isolated from patients with IAIs in Korea, which are inconsistent with the international guidelines for IAIs. The establishment of local guidelines for IAIs is required according to more basic data reflecting the national situation.

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REFERENCES

1. Lopez N, Kobayashi L, Coimbra R. A comprehensive review of abdominal infections. World J Emerg Surg 2011;6(1):7.
2. Sartelli M, Catena F, Ansaloni L, Coccolini F, Corbella D, Moore EE, et al. Complicated intra-abdominal infections worldwide: the definitive data of the CIAOW Study. World J Emerg Surg 2014;9(1):37.
3. Torer N, Yorganci K, Elker D, Sayek I. Prognostic factors of the mortality of postoperative intraabdominal infections. Infection 2010;38(4):255-60.
4. Merlino JI, Malangoni MA, Smith CM, Lange RL. Prospective randomized trials affect the outcomes of intraabdominal infection. Ann Surg 2001;233(6):859-66.
5. Menichetti F, Sganga G. Definition and classification of intra-abdominal infections. J Chemother 2009;21 Suppl 1:3-4.
6. Shirah GR, O’Neill PJ. Intra-abdominal Infections. Surg Clin North Am 2014;94(6):1319-33.
7. Marshall JC, Innes M. Intensive care unit management of intra-abdominal infection. Crit Care Med 2003;31(8):2228-37.
8. Mazuski JE, Tessier JM, May AK, Sawyer RG, Nadler EP, Rosengart MR, et al. The Surgical Infection Society revised guidelines on the management of intra-abdominal infection. Surg Infect (Larchmt) 2017;18(1):1-76.
9. Sartelli M, Chichom-Mefire A, Labricciosa FM, Hardcastle T, Abu-Zidan FM, Adesunkanmi AK, et al. The management of intra-abdominal infections from a global perspective: 2017 WSES guidelines for management of intra-abdominal infections. World J Emerg Surg 2017;12(1):29.
10. Solomkin JS, Mazuski JE, Bradley JS, Rodvold KA, Goldstein EJ, Baron EJ, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Surg Infect (Larchmt) 2010;11(1):79-109.
11. Syue LS, Chen YH, Ko WC, Hsueh PR. New drugs for the treatment of complicated intra-abdominal infections in the era of increasing antimicrobial resistance. Int J Antimicrob Agents 2016;47(4):250-8.
12. Chang YT, Coombs G, Ling T, Balaji V, Rodrigues C, Mikamo H, et al. Epidemiology and trends in the antibiotic susceptibilities of Gram-negative bacilli isolated from patients with intra-abdominal infections in the Asia/Pacific region, 2010–2013. Int J Antimicrob Agents 2017;49(6):734-9.
13. Ko WC, Hsueh PR. Increasing extended-spectrum beta-lactamase production and quinolone resistance among gram-negative bacilli causing intra-abdominal infections in the Asia/Pacific region: data from the Smart Study 2002–2006. J Infect 2009;59(2):95-103.
14. Huang CC, Chen YS, Toh HS, Lee YL, Liu YM, Ho CM, et al. Impact of revised CLSI breakpoints for susceptibility to third-generation cephalosporins and carbapenems among Enterobacteriaceae isolates in the Asia-Pacific region: results from the Study for Monitoring Antimicrobial Resistance Trends (SMART), 2002–2010. Int J Antimicrob Agents 2012;40 Suppl:S4-10.
15. De Waele J, Lipman J, Sakr Y, Marshall JC, Vanhems P, Barrera Groba C, et al. Abdominal infections in the intensive care unit: characteristics, treatment and determinants of outcome. BMC Infect Dis 2014;14(1):420.
16. Waele JJ. What every intensivist should know about the management of peritonitis in the intensive care unit. Rev Bras Ter Intensiva 2018;30(1):9-14.
17. Centers for Disease Control and Prevention. National Healthcare Safety Network (NHSN) patient safety component manual. https://www.cdc.gov/nhsn/pdfs/pscmanual/pscmanual_current.pdf. Updated 2019. Accessed October 18, 2019.
18. Sartelli M, Catena F, Abu-Zidan FM, Ansaloni L, Biffl WL, Boermeester MA, et al. Management of intra-abdominal infections: recommendations by the WSES 2016 consensus conference. *World J Emerg Surg* 2017;12(1):22.

19. National Nosocomial Infections Surveillance System. National Nosocomial Infections Surveillance (NNIS) system report, data summary from January 1992 through June 2004, issued October 2004. *Am J Infect Control* 2004;32(8):470-85.

20. Kim J, Kang CI, Gwak GY, Chung DR, Peck KR, Song JH. Clinical impact of healthcare-associated acquisition in cirrhotic patients with community-onset spontaneous bacterial peritonitis. *Korean J Intern Med* 2018. DOI: 10.3904/kjim.2017.231.

21. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing*. 26th ed. CLSI Supplement M100S. Wayne, PA: CLSI; 2016.

22. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing*. 25th ed. CLSI Supplement M100-S25. Wayne, PA: CLSI; 2015.

23. Sudaharan S, Kanne P, Vemu L, Chavali P, Desmukha SR, Nagari B. Bacteriological profile of intra-abdominal infections in a tertiary care hospital. *Iran J Microbiol* 2018;10(4):208-14.

24. Zhang H, Yang Q, Liao K, Ni Y, Yu Y, Hu B, et al. Update of incidence and antimicrobial susceptibility trends of *Escherichia coli* and *Klebsiella pneumoniae* isolates from Chinese intra-abdominal infection patients. *BMC Infect Dis* 2017;17(1):776.

25. Zhang H, Yang Q, Liao K, Ni Y, Yu Y, Hu B, et al. Antimicrobial susceptibilities of aerobic and facultative gram-negative bacilli from intra-abdominal infections in patients from seven regions in China in 2012 and 2013. *Antimicrob Agents Chemother* 2015;60(1):245-51.

26. Sanders JM, Tessier JM, Sawyer R, Dellinger EP, Miller PR, Namias N, et al. Does isolation of *Enterococcus* affect outcomes in intra-abdominal infections? *Surg Infect (Larchmt)* 2017;18(8):879-85.

27. Harbarth S, Uckay I. Are there patients with peritonitis who require empiric therapy for *Enterococcus*? *Eur J Clin Microbiol Infect Dis* 2004;23(2):73-7.

28. Tarchini G. Empirical enterococcal coverage for complicated intra-abdominal infection. *Clin Infect Dis* 2010;51(6):757-8.

29. Burnett RJ, Haverstock DC, Dellinger EP, Reinhart HH, Bohnen JM, Rotstein OD, et al. Definition of the role of *Enterococcus* in intra-abdominal infection: analysis of a prospective randomized trial. *Surgery* 1995;118(4):716-21.

30. Kaffarnik MF, Urban M, Hopt UT, Utzolino S. Impact of *Enterococcus* on immunocompetent and immunosuppressed patients with perforation of the small or large bowel. *Technol Health Care* 2012;20(1):37-48.

31. Sotto A, Lefrant JY, Fabbro-Peray P, Muller L, Tafuri J, Navarro F, et al. Evaluation of antimicrobial therapy management of 120 consecutive patients with secondary peritonitis. *J Antimicrob Chemother* 2002;50(4):569-76.

32. Gauzit R, Péan Y, Barth X, Mistretta F, Lalaude O; Top Study Team. Epidemiology, management, and prognosis of secondary non-postoperative peritonitis: a French prospective observational multicenter study. *Surg Infect (Larchmt)* 2009;10(2):119-27.

33. Claridge JA, Banerjee A, Kelly KB, Leukhardt WH, Carter JW, Haridas M, et al. Bacterial species-specific hospital mortality rate for intra-abdominal infections. *Surg Infect (Larchmt)* 2014;15(3):194-9.

34. Tan A, Rouse M, Kew N, Qin S, La Paglia D, Pham T. The appropriateness of ceftriaxone and metronidazole as empirical therapy in managing complicated intra-abdominal infection-experience from Western Health, Australia. *PeerJ* 2018;6:e5383.
35. Khan S, Gupta DK, Khan DN. Comparative study of three antimicrobial drugs protocol (Ceftriaxone, Gentamicin/Aminoglycosides and Metronidazole) versus two antimicrobial drugs protocol (Ceftriaxone and Metronidazole) in cases of intra-abdominal sepsis. *Kathmandu Univ Med J (KUMJ)* 2005;3(1):55-63.

36. Ohlin B, Cederberg A, Forsell H, Solhaug JH, Tveit E. Piperacillin/tazobactam compared with cefuroxime/metronidazole in the treatment of intra-abdominal infections. *Eur J Surg* 1999;165(9):875-84.

37. Teppler H, McCarroll K, Gesser RM, Woods GL. Surgical infections with *Enterococcus* outcome in patients treated withertapenem versus piperacillin-tazobactam. *Surg Infect (Larchmt)* 2002;3(4):337-49.

38. Montravers P, Lepape A, Dubreuil L, Gauzit R, Pean Y, Benchimol D, et al. Clinical and microbiological profiles of community-acquired and nosocomial intra-abdominal infections: results of the French prospective, observational EBIIA study. *J Antimicrob Chemother* 2009;63(4):785-94.

39. Sóki J, Hedberg M, Patrick S, Bálint B, Herczeg R, Nagy I, et al. Emergence and evolution of an international cluster of MDR *Bacteroides fragilis* isolates. *J Antimicrob Chemother* 2016;71(9):2441-8.

40. Byun JH, Kim M, Lee Y, Lee K, Chong Y. Antimicrobial susceptibility patterns of anaerobic bacterial clinical isolates from 2014 to 2016, including recently named or renamed species. *Ann Lab Med* 2019;39(2):190-9.

41. Schuetz AN. Antimicrobial resistance and susceptibility testing of anaerobic bacteria. *Clin Infect Dis* 2014;59(5):698-705.

42. Kurup A, Liu KH, Ren J, Lu MC, Navarro NS, Farooka MW, et al. Antibiotic management of complicated intra-abdominal infections in adults: the Asian perspective. *Ann Med Surg (Lond)* 2014;3(3):85-91.

43. Kiratisin P, Chongthaleong A, Tan TY, Lagamayo E, Roberts S, Garcia J, et al. Comparative in vitro activity of carbapenems against major gram-negative pathogens: results of Asia-Pacific surveillance from the COMPACT II study. *Int J Antimicrob Agents* 2012;39(4):311-6.

44. Liu YM, Chen YS, Toh HS, Huang CC, Lee YL, Ho CM, et al. In vitro susceptibilities of non-Enterobacteriaceae isolates from patients with intra-abdominal infections in the Asia-Pacific region from 2003 to 2010: results from the Study for Monitoring Antimicrobial Resistance Trends (SMART). *Int J Antimicrob Agents* 2012;40 Suppl:S117.

45. Bouxom H, Fournier D, Bouiller K, Hocquette D, Bertrand X. Which non-carbapenem antibiotics are active against extended-spectrum β-lactamase-producing Enterobacteriaceae? *Int J Antimicrob Agents* 2018;52(1):100-3.

46. López-Cerero L, Picón E, Morillo C, Hernández JR, Docobo F, Pachón J, et al. Comparative assessment of inoculum effects on the antimicrobial activity of amoxicillin-clavulanic and piperacillin-tazobactam with extended-spectrum beta-lactamase-producing and extended-spectrum beta-lactamase-non-producing *Escherichia coli* isolates. *Clin Microbiol Infect* 2010;16(2):132-6.

47. Guet-Revillet H, Emirian A, Groh M, Nebbad-Lechani B, Weiss E, Join-Lambert O, et al. Pharmacological study of cefoxitin as an alternative antibiotic therapy to carbapenems in treatment of urinary tract infections due to extended-spectrum β-lactamase-producing *Escherichia coli*. *Antimicrob Agents Chemother* 2014;58(8):4899-901.