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Special Article

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Guideline for the Antibiotic Use in Acute Gastroenteritis

Youn Jeong Kim[1,*], Ki-Ho Park[2,*], Dong-Ah Park[3,*], Joonhong Park[4,*], Byoung Wook Bang[5,*], Seung Soon Lee[6,*], Eun Jung Lee[7,*], Hyo-Jin Lee[8,*], Sung Kwan Hong[9,*], and Yang Ree Kim[8]

[1]Division of Infectious Diseases, Department of Internal Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea
[2]Division of Infectious Diseases, Department of Internal Medicine, Kyung Hee University Hospital, Kyung Hee University School of Medicine, Seoul, Korea
[3]Division of Healthcare Technology Assessment Research, National Evidence-Based Healthcare Collaborating Agency, Seoul, Korea
[4]Department of Laboratory Medicine, Daejeon St. Mary's hospital, College of Medicine, The Catholic University of Korea, Daejeon, Korea
[5]Division of Gastroenterology, Department of Internal Medicine, Inha University College of Medicine, Incheon, Korea
[6]Division of Infectious Diseases, Department of Internal Medicine, Hallym University Chuncheon Sacred Heart Hospital, Hallym University College of Medicine, Chuncheon, Korea
[7]Division of Infectious Diseases, Department of Internal Medicine, Soonchunhyang University Seoul Hospital, Soonchunhyang University College of Medicine, Seoul, Korea
[8]Division of Infectious Diseases, Department of Internal Medicine, Uijeongbu St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Uijeongbu, Korea
[9]Division of Infectious Diseases, Department of Internal Medicine, CHA Bundang Medical Center, CHA University, Seongnam, Korea

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Corresponding Author:
Yang Ree Kim, MD, PhD
Division of Infectious Diseases, Department of Internal Medicine, Uijeongbu St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 271 Cheonbo-ro, Uijeongbu, Gyeonggi-do 11765, Korea.
Tel: +82-31-820-3798
Fax: +82-31-820-3334
E-mail: yrkim@catholic.ac.kr

*These authors contributed equally to this manuscript.

ORCID iDs
Yang Ree Kim
https://orcid.org/0000-0002-3585-3690

Conflict of Interest
No conflicts of interest.

ABSTRACT

Acute gastroenteritis is common infectious disease in community in adults. This work represents an update of 'Clinical guideline for the diagnosis and treatment of gastrointestinal infections' that was developed domestically in 2010. The recommendation of this guideline was developed regarding the following; epidemiological factors, test for diagnosis, the indications of empirical antibiotics, and modification of antibiotics after confirming pathogen. Ultimately, it is expected to decrease antibiotic misuse and prevent antibiotic resistance.

Keywords: Infectious diarrhea; Traveler's diarrhea; Antibiotic

INTRODUCTION

Gastroenteritis refers to infection in the stomach and intestines, and most cases of acute gastroenteritis present as acute-onset diarrhea. Diarrhea is usually defined as passage of abnormally liquid or unformed stools at an increased amount and frequency. When diarrhea is caused by a source of infection and is accompanied by nausea, vomiting, and abdominal pain, it is referred to as infectious diarrhea. However, the microorganism causing the infection is rarely confirmed in clinic. Diarrhea is defined as acute if it lasts for 14 days or less, which is the case for most infectious diarrhea. In patient samples collected

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through 'Sentinels in acute infectious diarrhea surveillance' in Korea conducted by the Korea Centers for Disease Control and Prevention (KCDC), bacterial pathogens were isolated from 11.5 - 23.7% of samples between 2012 and 2016. In 2017, bacteria tested in the surveillance project (*Salmonella* spp., *Escherichia coli, Shigella* spp., *Vibrio parahaemolyticus, Vibrio cholerae, Campylobacter* spp., *Clostridium perfringens, Staphylococcus aureus, Bacillus cereus, Listeria monocytogenes,* and *Yersinia enterocolitica*) were isolated in 1,376 of 9,344 samples collected at 70 participating institutions, thus at a rate of 14.7%, which showed that bacteria do not account for a high number of cases of acute diarrhea. In general, acute gastroenteritis improves spontaneously and does not require antibiotic treatment. Inappropriate use of antibiotics may cause antibiotic-associated diarrhea or other complications and may also lead to antibiotic resistance in the long term. Although the Korean Society for Antimicrobial Therapy published 'Clinical guideline for the diagnosis and treatment of gastrointestinal infections' in 2010, updates are required to reflect recent changes. Therefore, this guideline was developed in order to provide clinical recommendations based on the newest evidence on empirical antibiotic therapy for suspected acute gastroenteritis, which is commonly seen in clinic, and on targeted antibiotic treatment for cases with confirmed bacterial growth, with an ultimate aim to decrease antibiotic misuse and to prevent the rise of antibiotic-resistant bacterial strains.

DEVELOPMENT OF CLINICAL GUIDELINE

1) Committee on clinical guideline

The committee comprised one chairperson (Yang Ree Kim, College of Medicine, The Catholic University of Korea) and six committee members (Youn Jeong Kim, College of Medicine, The Catholic University of Korea; Ki-Ho Park, Kyung Hee University School of Medicine; Seung Soon Lee, Hallym University College of Medicine; Eun Jung Lee, Soonchunhyang University College of Medicine; Hyo-Jin Lee, College of Medicine, The Catholic University of Korea; and Sung Kwan Hong, CHA University College of Medicine) recommended by the Korean Society for Antimicrobial Therapy and the Korean Society of Infectious Diseases, one member (Byoung Wook Bang, Inha University College of Medicine) recommended by the Korean Society of Gastroenterology, one member (Joonhong Park, College of Medicine, The Catholic University of Korea) recommended by the Korean Society of Clinical Microbiology, and one expert in clinical guidelines (Dong-Ah Park, National Evidence-Based Healthcare Collaborating Agency).

2) Target and scope of the guideline

The present guideline is for community-acquired infectious diarrhea and traveler's diarrhea in adults with the exception of *Clostridioides difficile* infection and immune-suppressed patients. Moreover, the guideline focused on the use of antibiotics in treatment. Although antidiarrheal agents and probiotics were included, intravenous hydration was excluded. The guideline was designed so that various specialists, resident physicians, government officials, and general practitioners treating acute gastroenteritis patients at hospitals and clinics of various sizes can easily refer to the guideline.

3) Selection of key questions

The committee selected a total of 10 key questions, and questions on intervention were organized based on the populations of interest, intervention, comparison and outcome (PICO) format.

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4) Literature search and selection of clinical guidelines

To search for guidelines on antibiotic use in acute gastroenteritis published after 2010, 'acute gastroenteritis', 'acute colitis', 'infectious colitis', 'infectious diarrhea', 'travelers' diarrhea', 'food-borne', and 'water-borne' were used as the keywords for search; 'guideline' and 'recommendation' were used as keywords to search for guidelines and were combined with other keywords through AND. The search was conducted on MEDLINE and EMBASE, which are international electronic databases, on KoreaMed and KMbase, which are Korean electronic databases, and on NGC, GIN, and KoMGI, which are databases on clinical practice guidelines. Two committee members independently selected clinical guidelines and came to an agreement. First, unrelated literature was excluded based on a review of titles and abstracts, and second, guidelines that satisfied the selection criteria were selected. The exclusion criteria were established based on a mutual agreement (**Fig. 1**).

5) Evaluation of clinical guidelines and review of recency

For the four clinical guidelines selected through the aforementioned process, two committee members (per guideline) evaluated the quality of the guidelines through K-AGREE II and calculated the scores for each domain (**Table 1**). The guidelines that had scores above 50% in Domain 3, Rigor of Development, were selected. The clinical guideline on gastrointestinal diseases developed in 2010 did not have a high score in Rigor of Development; however, as it is the only guideline developed in Korea, it was used for adaptation. After reviewing the recency of the guidelines selected for adaptation, additional evidence was collected on PubMed and KoreaMed for each key question.

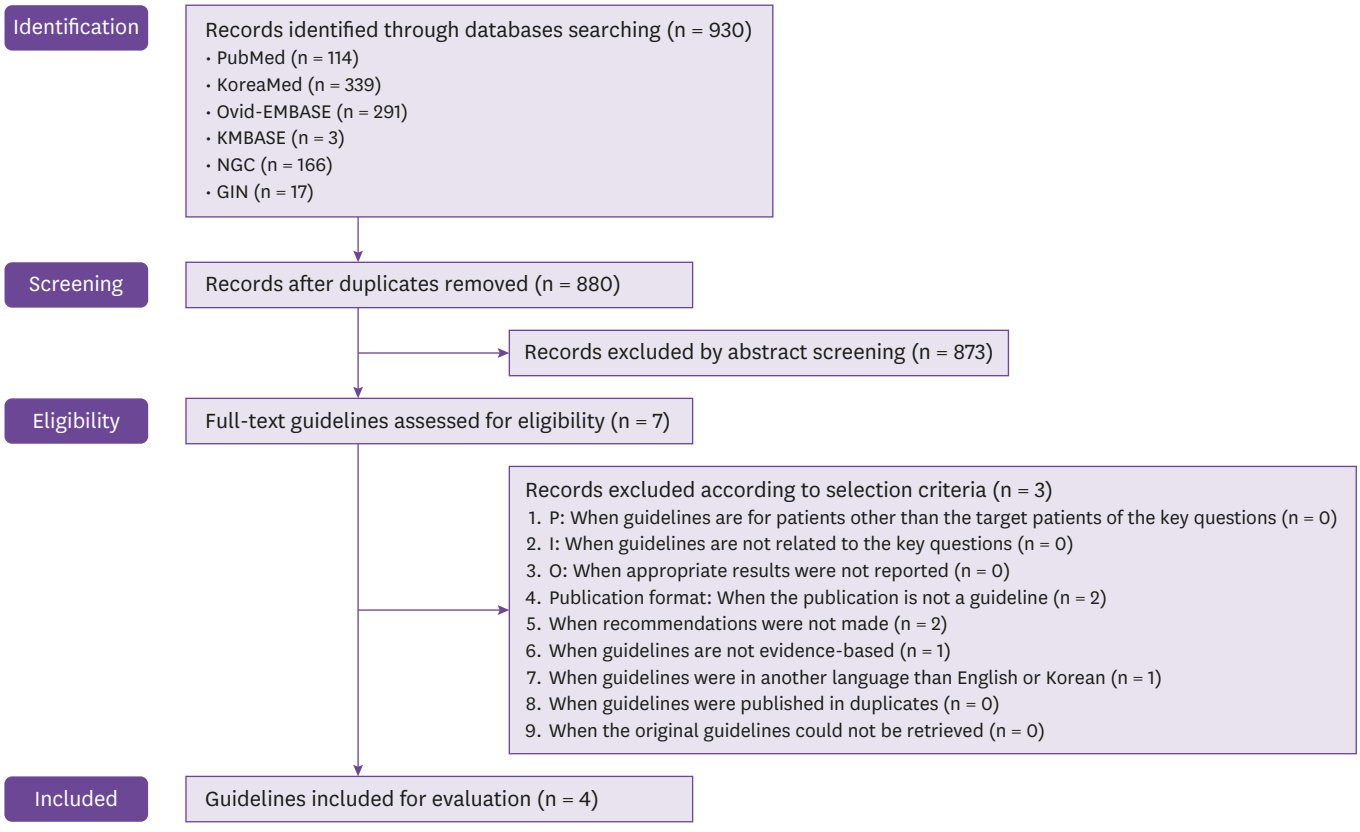

Figure 1. Search strategies and details for each database.
NGC, national guideline clearinghouse; GIN, guidelines international network.

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Table 1. Score for each domain in quality evaluation

Domain	Evaluative criteria	Guideline A[a]	Guideline B[b]	Guideline C[c]	Guideline D[d]
1	Scope and Purpose	96%	78%	69%	79%
2	Stakeholder Involvement	57%	70%	52%	57%
3	Rigor of Development	87%	63%	73%	52%
4	Clarity of Presentation	93%	100%	100%	99%
5	Applicability	47%	22%	39%	15%
6	Editorial Independence	94%	100%	94%	48%

[a]Shane AL, Mody RK, Crump JA, Tarr PI, Steiner TS, Kotloff K, Langley JM, Wanke C, Warren CA, Cheng AC, Cantey J, Pickering LK. 2017 Infectious Diseases Society of America clinical practice guidelines for the diagnosis and management of infectious diarrhea. Clin Infect Dis 2017;65:e45-80.
[b]Riddle MS, Connor BA, Beeching NJ, DuPont HL, Hamer DH, Kozarsky P, Libman M, Steffen R, Taylor D, Tribble DR, Vila J, Zanger P, Ericsson CD. Guidelines for the prevention and treatment of travelers' diarrhea: a graded expert panel report. J Travel Med 2017;24:S63-80.
[c]Riddle MS, DuPont HL, Connor BA. American College of Gastroenterology(ACG) clinical guideline: diagnosis, treatment, and prevention of acute diarrheal infections in adults. Am J Gastroenterol 2016;111:602-22.
[d]The Korean Society of Infectious Diseases, Korean Society for Chemotherapy, The Korean Society of Clinical Microbiology. Clinical guideline for the diagnosis and treatment of gastrointestinal infections. Infect Chemother 2010;42:323-61.

6) Preparation of the guideline and determination of the grade of recommendation

For each key question, the initial draft of the guideline included the actual guideline, grade of recommendation, and background. The committee members prepared the initial draft based on tables comparing the four selected guidelines and relevant evidence for each key question and also considered evidence that was used in review of recency. After the initial draft was prepared, the grade of recommendation and the background for the recommendations were described. The overall quality of evidence used for recommendations for each key question was evaluated as 'high', 'moderate', 'low', and 'very low'. When the key question had no supporting evidence, when evidence could be assumed based on expert agreement, and when recommendations were absolutely necessary despite a lack of evidence, the level of evidence of the recommendations was categorized as 'expert opinion'. The grade of recommendation was evaluated as 'strong recommendation (strong)' or 'weak recommendation (weak)' upon consideration of the balance of desirable and undesirable outcome, quality of evidence, belief in patient value and preference, cost of treatment, and use of resources. The committee held meetings to discuss and reach agreement on the recommendations and grade of recommendation.

(1) Grade of recommendation

① Strong: It is best that most or all individuals receive the services outlined in the recommendation. The benefit clearly outweighs the cost or risk, or the cost or risk clearly outweighs the benefit.
② Weak: It may not be best for all individuals to receive the services outlined in the recommendation. The decision should be made based on patient value, preference, and circumstances. The level of evidence is low, or there is no clear difference in risks and benefits.

(2) Level of evidence

① High: Almost no other study will change the level of trust in the estimates of the effects.
② Moderate: Other studies may influence the committee's trust in the estimates of the effects, and the level of trust may also change.
③ Low: Other studies may significantly influence the committee's trust in the estimates of the effects, and the level of trust may also change.
④ Very low: The committee does not trust the calculated estimates of the effects.

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⑤ Expert opinion: Although there is no supporting evidence, the committee has determined through official expert meetings that the recommendation is clinically appropriate at present.

7) Review by external experts

Through a meeting held on January 11, 2019, opinions on the guideline was gathered from physicians with their own clinical practice and specialists in infectious diseases, gastroenterology, and clinical microbiology. The guideline was also reviewed and approved by the Korean Academy of Family Medicine, Korean Society of Infectious Diseases, Korean Society of Gastroenterology, Korean Society of Clinical Microbiology, and Korean Society for Antimicrobial Therapy.

8) Limitations and future tasks of the guideline

The guideline was developed based on Korean and international clinical practice guidelines and recent literature available at the time of development. If new drugs are developed or if significant changes are observed in antibiotic resistance of pathogenic bacteria, the guideline may be updated.

9) Support

The guideline was supported as a Policy Research Project by the KCDC in 2018 (research project number 2018-E2803-00). The committee members who participated in developing this guideline were not influenced by any means by government organizations, academic societies, pharmaceutical companies, or other for-profit institutions.

SUMMARY OF GUIDELINE

Recommendation		Grade of recommendation	Level of evidence
(KQ1) What clinical and epidemiological characteristics are associated with the diagnosis and treatment of adult patients with suspected acute infectious diarrhea?			
1	Thoroughly investigate epidemiological characteristics, including clinical manifestation and history of exposure.	Strong	Moderate
2	If diarrhea is observed in patients who work at childcare services, long-term residences, restaurants, group meal services, or swimming pools or those who work with close patient contact, investigate the possibility of group outbreaks.	Strong	High
3	If fever or bloody diarrhea is also present, test for *Salmonella*, *Shigella*, and *Campylobacter*.	Strong	Low
4	Enteric fever should only be considered ① if fever and diarrhea or fever alone is present, ② if the patient traveled to other countries with ongoing epidemics of enteric fever, and ③ if the patient consumed food prepared by individuals who were recently exposed to the pathogen in an area with an ongoing epidemic	Strong	Moderate
5	If there is a clinical possibility of Shiga toxin-producing bacteria, such as epidemiological possibility and afebrile bloody diarrhea or abdominal pain, Shiga toxin should be tested.	Strong	Moderate
6	If large amounts of 'rice water-like' diarrhea are present with travel history in the past three days to areas with the ongoing cholera epidemic, conduct stool tests for cholera.	Strong	Low
7	If diarrhea persists for more than 14 days in travelers, parasitic infections should be evaluated.	Strong	Moderate
8	If patients used antibiotics within 8 - 12 weeks of the onset of diarrhea, *C. difficile* should be tested.	Strong	Moderate
9	Evaluate for extraintestinal complications of the infection.	Strong	Moderate
(KQ2) Which tests are helpful in identifying the pathogen in adult patients with suspected acute infectious diarrhea?			
(KQ2-1) Is stool test necessary for the diagnosis of acute infectious diarrhea? Which tests are appropriate?			
1	If bloody or mucoid stool, severe abdominal pain or tenderness, or diarrhea with septic findings are present, conduct stool test to test for *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, *C. difficile*, and Shiga toxin-producing *E. coli* (STEC).	Strong	Moderate
2	Although acute watery diarrhea or uncomplicated traveler's diarrhea in adults improves within days without antibiotics in most cases, consider non-culture tests in addition to traditional stool tests when pathogens should be identified.	Low	Expert opinion
3	Conduct stool tests for *Vibrio*, norovirus, and rotavirus upon consideration of symptoms or epidemiological relevance.	Strong	Moderate

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Recommendation		Grade of recommendation	Level of evidence
4	If there is a risk or suspicion of an outbreak of diarrhea, conduct stool tests.	Strong	Moderate
5	Since traditional stool tests (culture, microscopic analysis, and antigen analysis) often cannot identify pathogens responsible for acute diarrheal diseases, consider the molecular diagnosis.	Strong	Very low
6	Since panel-based multiplex molecular analysis for diarrhea detects DNA regardless of the survival of microorganisms, consider clinical situations in interpreting the results.	Strong	Low
(KQ2-2) Is stool leukocyte or lactoferrin test helpful in the clinical diagnosis of acute infectious diarrhea in adults?			
1	Stool leukocyte or lactoferrin test is not recommended in identifying the cause of acute infectious diarrhea.	Strong	Moderate
(KQ2-3) Are laboratory tests (complete blood count, chemistry, serology, culture) helpful in diagnosing acute infectious diarrhea or predicting complications?			
1	Blood cultures are helpful in diagnosing patients with suspected infectious diarrhea in the following cases: ① patients with septic findings, ② suspected enteric fever, ③ systemic infectious symptoms, ④ immune-suppressed patients, ⑤ high-risk situations, such as hemolytic anemia, ⑥ patients with fever of unclear etiology who have travel history to areas with endemic enteric fever or contact history with individuals who traveled to area with endemic enteric fever.	Strong	Moderate
2	Widal test is not recommended for diagnosis of pathogens causing enteric fever	Strong	Moderate
3	If infectious diarrhea is suspected, total white cell count and differential count may be helpful in determining whether it is bacterial.	Weak	Low
4	Repeat hemoglobin, platelet count, electrolytes, blood urea nitrogen/creatinine to detect early findings of hemolytic uremic syndrome or renal damage may help in predicting complications in patients infected with *E. coli* 0157 or other STEC. Moreover, peripheral blood smear to confirm red blood cell fragments is helpful when the hemolytic uremic syndrome is suspected.	Strong	High
(KQ2-4) Is computed tomography (CT) helpful in diagnosing or predicting complications of acute infectious diarrhea?			
1	CT may be helpful in diagnosing complications, such as aortitis, infectious aneurysm, peritonitis, intestinal perforation, and toxic megacolon, when fever continues despite appropriate antibiotic treatment in elderly patients with invasive *Salmonella enterica* or *Yersinia* infections or when patients have atherosclerosis.	Weak	Low
2	CT may be helpful in differential diagnosis of acute infectious diarrhea and non-infectious diarrhea.	Weak	Low
(KQ2-5) Is endoscopy helpful in diagnosis of infectious diarrhea?			
1	Endoscopy is not recommended in most acute and chronic infectious diarrhea patients.	Strong	Very low
2	Endoscopy or sigmoidoscopy should be considered in acute diarrhea patients without improvement, in persistent unexplained diarrhea in acquired immune deficiency syndrome patients, persistent diarrhea in patients who have anal sexual intercourse, and persistent diarrhea in patients with recent travel history.	Strong	Low
3	Duodenal aspiration may be considered when *Giardia*, *Strongyloides*, *Cystoisospora*, or *Microsporidia* infection is suspected.	Weak	Low
(KQ3) What are indications for empirical antibiotic therapy for acute infectious diarrhea and which antibiotics should be used?			
1	In general, antibiotic treatment is not recommended for most cases of acute watery diarrhea.	Strong	Low
2	Empirical antibiotic therapy can be considered in the following cases: ① If bloody or mucoid stool and fever, or Shigellosis symptoms (frequent scant bloody stools, fever, cramping abdominal pain, and tenesmus) are present and ② in traveler's diarrhea accompanied by high fever above 38.5℃ or septic findings.	① Weak ② Low	① Expert opinion ② Low
3	Antibiotic treatment is recommended for immune-suppressed patients with bloody diarrhea.	Strong	Low
4	For empirical antibiotic therapy, use fluoroquinolone antibiotics or azithromycin upon consideration of the distribution and antibiotic sensitivity of pathogens in local communities or areas where the patient traveled.	Strong	High
5	Rifaximin may be used for suspected infection with non-invasive bacteria without bloody diarrhea.	Low	Low
6	The use of antibiotics is not recommended for patients with suspected STEC infection.	Strong	Moderate
(KQ4) How should antibiotics be modified when the bacterial strain causing acute infectious diarrhea is identified?			
1	When the bacteria and antimicrobial susceptibility results are identified, antibiotics should be modified accordingly.	Strong	High
2	For infectious diarrhea caused by *Campylobacter*, the use of azithromycin is recommended.	Strong	High
3	For nontyphoidal salmonellosis, antibiotic treatment is not recommended with the exception of infants less than 3 months of age, patients over 50 with suspected atherosclerosis, immune-suppressed patients, patients with valvulopathy, and patients with significant joint diseases.	Weak	Low
4	Azithromycin, ciprofloxacin, or ceftriaxone is recommended for shigellosis.	Strong	High
5	Doxycycline is recommended for *Vibrio cholerae* infections, and ciprofloxacin, azithromycin, and ceftriaxone may also be used.	Strong	High
(KQ5) Do anti-diarrheal agents decrease the duration of symptoms in acute infectious diarrhea?			
1	Bismuth subsalicylates provide symptomatic improvement by regulating the amount of stool in mild or moderate acute diarrhea.	Strong	High
2	Loperamide is helpful in shortening the duration of symptoms of acute watery diarrhea in otherwise healthy adults.	Weak	Moderate

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Recommendation		Grade of recommendation	Level of evidence
3	Loperamide should not be used for children below the age of 18.	Strong	Moderate
4	Loperamide should be avoided when there is a possibility of toxic megacolon or when fever continues.	Strong	Low
5	Loperamide may improve symptoms in traveler's diarrhea with appropriate antibiotic treatment.	Strong	Moderate
(KQ6) Do probiotics decrease the duration of symptoms in acute infectious diarrhea?			
1	Probiotics decrease the symptoms and duration of acute infectious diarrhea in otherwise healthy adult and pediatric patients.	Weak	Moderate
2	Probiotics are not recommended to prevent traveler's diarrhea.	Weak	Low

RECOMMENDATIONS FOR EACH KEY QUESTION

KQ1. What clinical and epidemiological characteristics are associated with the diagnosis and treatment of adult patients with suspected acute infectious diarrhea?

Recommendation		Grade of recommendation	Level of evidence
1	Thoroughly investigate epidemiological characteristics, including clinical manifestation and history of exposure.	Strong	Moderate
2	If diarrhea is observed in patients who work at childcare services, long-term residences, restaurants, group meal services, or swimming pools or those who work with close patient contact, investigate the possibility of group outbreaks.	Strong	High
3	If fever or bloody diarreha is also present, test for *Salmonella*, *Shigella*, and *Campylobacter*.	Strong	Low
4	Enteric fever should only be considered ① if fever and diarrhea or fever alone is present, ② if the patient traveled to other countries with ongoing epidemics of enteric fever, and ③ if the patient consumed food prepared by individuals who were recently exposed to the pathogen in an area with an ongoing epidemic	Strong	Moderate
5	If there is a clinical possibility of Shiga toxin-producing bacteria, such as epidemiological possibility and afebrile bloody diarrhea or abdominal pain, Shiga toxin should be tested.	Strong	Moderate
6	If large amounts of 'rice water-like' diarrhea are present with travel history in the past three days to areas with ongoing cholera epidemic, conduct stool tests for cholera.	Strong	Low
7	If diarrhea persists for more than 14 days in travelers, parasitic infections should be evaluated.	Strong	Moderate
8	If patients used antibiotics within 8 - 12 weeks of the onset of diarrhea, *C. difficile* should be tested.	Strong	Moderate
9	Evaluate for extraintestinal complications of the infection.	Strong	Moderate

Infectious diarrhea has different causes and incidence in different countries based on the level of public health, lifestyle, and diet. Korea has a surveillance system on gastrointestinal infections characterized by vomiting and diarrhea at 196 surveillance institutions including tertiary hospitals, hospitals with more than 200 beds, and public hospitals. Of the 15,717 pathogens isolated in 2017, 9,276 cases were viral (59.0%), most of which were caused by norovirus and rotavirus, and 6,373 were bacterial (40.5%) caused by *Salmonella, Clostridium perfringens*, and *Campylobacter*; 68 were caused by protozoa (0.4%), most of which were caused by *Giardia lamblia* [1]. In the United States, food-borne outbreaks were caused by norovirus in most cases, followed by *Salmonella*, between 2009 and 2015 [2]. Enteric fever includes typhoid fever caused by *Salmonella enterica* subspecies *enterica* serovar Typhi (*Salmonella typhi*) and paratyphoid fever caused by *Salmonella enterica* subspecies *enterica* serovar Paratyphi (*Salmonella paratyphi*) A, B, and C. Enteric fever is most common in Central Asia and South East Asia, and is also observed in other Asian countries, Africa, Latin America, and Oceania [3]. The most common serotype of *Salmonella* in Korea between 1998 and 2007 were *Salmonella typhi*, *Salmonella enterica* subspecies *enterica* serovar Enteritidis (*Salmonella enteritidis*), and *Salmonella enterica* subspecies *enterica* serovar Typhimurium (*Salmonella typhimurium*) [4]. *Salmonella* causes food- or water-borne gastroenteritis in Korea. Although its incidence is on a decreasing trend, typhoid fever introduced from other countries has increased owing to increases in travels to other countries and foreign nationals living in Korea [5].

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Since possible pathogens can be estimated based on epidemiological characteristics in patients with suspected acute infectious diarrhea (**Table 2**), food consumption (undercooked meat, eggs, shellfish, and milk), consumption of unsterilized water, contact with pets, contact with other infected individuals, history of stay at group facility, travel history, underlying diseases, sexual history, and occupation should be confirmed. *Vibrio* spp. and norovirus are common causes of diarrhea after consumption of uncooked seafood or shellfish, and diarrhea after consumption of uncooked meat or poultry may be caused by Shiga toxin-producing *Escherichia coli* (STEC) (beef), *C. perfringens* (beef and poultry), *Salmonella* (poultry), *Campylobacter* (poultry), *Yersinia* (pork and pork intestine), *Staphylococcus aureus* (poultry). When patients consumed unpasteurized milk, their diarrhea may be accountable to *Salmonella, Campylobacter, Yersinia enterocolitica, S. aureus* toxin, *Cryptosporidium*, or STEC, and *Salmonella* or *Shigella* contamination is common in eggs. Water can cause infectious diseases directly through consumption or indirectly through contamination of food or dishes [2]. Consumption of unsterilized water may lead to *Campylobacter*, *Cryptosporidium*, *Giardia*, *Shigella*, *Salmonella*, or STEC infection, and *Cryptosporidium* or other water-borne infections are possible after swimming at pools. In Korea, there was an outbreak of acute diarrhea in 67 patients that used a pool in 2008; in six patients with severe diarrhea, norovirus was identified in three patients. Since norovirus with a similar RNA sequence was also detected in samples of groundwater, the outbreak was reported to have been caused by contaminated groundwater [6]. Diarrhea in prisons can be accounted for by norovirus, *C. difficile*, *Shigella, Cryptosporidium, Giardia, Salmonella*, STEC, and rotavirus, and diarrhea in childcare services may have been caused by rotavirus,

Table 2. Epidemiologic factors associated with pathogens of diarrhea

Epidemiological factors		Possible pathogens
Food-related	Food at hotel or restaurant	Norovirus, nontyphoidal *Salmonella*, *Clostridium perfringens*, *Bacillus cereus*, *Staphylococcus aureus*, *Campylobacter*, ETEC, STEC, *Listeria*, *Shigella*, *Cyclospora cayetanensis*, *Cryptosporidium*
	Unpasteurized milk	*Salmonella*, *Campylobacter*, *Yersinia enterocolitica*, *S. aureus toxin*, *Cryptosporidium*, STEC, *Brucella* (goat milk products), *Mycobacterium bovis*, *Coxiella burnetii*
	Raw or uncooked meat or poultry	STEC (meat), *C. perfringens* (meat, poultry), *Salmonella* (poultry), *Campylobacter* (poultry), *Yersinia* (pork, pork intestine), *S. aureus* (poultry), *Trichinella* (pork, wild animal meat)
	Fruits or vegetables	STEC, nontyphoidal *Salmonella*, *Cyclospora*, *Cryptosporidium*, Norovirus, Hepatitis A, *Listeria monocytogenes*
	Uncooked eggs	*Salmonella*, *Shigella*
	Shellfish	*Vibrio*, Norovirus, Hepatitis A, *Plesiomonas*
Exposure or contact	Consumption of unsterilized water	*Campylobacter*, *Cryptosporidium*, *Giardia*, *Shigella*, *Salmonella*, STEC, *Plesiomonas shigelloides*
	Swimming at a pool	*Cryptosporidium*
	Prisons	Norovirus, *C. difficile*, *Shigella*, *Cryptosporidium*, *Giardia*, STEC, Rotavirus
	Childcare services	Rotavirus, *Cryptosporidium*, *Giardia*, *Shigella*, STEC
	Recent antibiotic use	*C. difficile*, multi-drug-resistant *Salmonella*
	Travel history to areas with poor public health	*Escherichia coli* (enteroaggregative, enterotoxigenic, enteroinvasive), *Shigella*, *Salmonella* Typhi, nontyphoidal *Salmonella*, *Campylobacter*, *Vibrio cholerae*,*Entamoeba histolytica*, *Giardia*, *Blastocystis*, *Cyclospora*, *Cystoisospora*, *Cryptosporidium*
	Contact with pets that have diarrhea	*Campylobacter*, *Yersinia*
	Contact with pig stool	*Balantidium coli*
	Contact with poultry	Non-typhoidal *Salmonella*
	Visits to farms or zoos	STEC, *Cryptosporidium*, *Campylobacter*

ETEC, enterotoxigenic *E. coli*; STEC, Shiga toxin-producing *E. coli*.

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Cryptosporidium, Giardia, Shigella, or STEC. *C. difficile* may be accountable if the patient has recent history of antibiotic use. Infectious diarrhea is caused by different common bacteria in patients of different ages; for infants of 6 - 18 months, rotavirus is common, whereas nontyphoidal *Salmonella* is common for patients younger than 3 months or patients older than 50 with atherosclerosis. *Shigella* should be considered first for patients aged 1 - 7 years, and *Campylobacter* should be considered for young adults. Traveler's diarrhea is a common disease associated with travelling and is observed in 30 - 70% of travelers depending on the area and season; it is most commonly caused by *E. coli*, *Campylobacter jejuni*, *Shigella*, and *Salmonella*. South East Asia, Central Asia, India, Africa, Mexico, and Latin America are high-risk areas of traveler's diarrhea.

Although causative bacteria may not cause significant differences in clinical manifestations of acute diarrhea, possible pathogens may be considered based on characteristic symptoms (**Table 3**). *Salmonella, Campylobacter, Yersinia,* or *Shigella* should be considered first if persistent fever and systemic symptoms are present [7]. *Yersinia* has symptoms similar to those of acute appendicitis, thus necessitating differential diagnosis [7, 8]. Rotavirus and norovirus often cause watery diarrhea, and *Shigella*, *C. jejuni*, *Salmonella*, STEC, and enteroinvasive *E. coli* (EIEC) often cause bloody diarrhea [7]. For food-related outbreaks, the possible pathogen can be estimated based on the incubation period. Short incubation periods of 1 - 6 hours are estimated to have been caused by consumption of toxins, so *S. aureus* or *Bacillus cereus* producing emetic toxin is suspected. *C. perfringens* or *B. cereus* producing diarrheal toxin are suspected for incubation periods of 8 - 16 hours, and Enterotoxigenic *E. coli* (ETEC), *Salmonella*, *Shigella*, and *Vibrio cholerae* may be suspected for incubation periods of 16 - 72 hours [7, 8]. If there is a travel history to areas with cholera epidemics with large amounts of 'rice water-like' diarrhea, the possibility of cholera should be considered. Since 1990, around 10 cases of cholera have been reported annually in Korea; in 2017, all five cases were introduced from other countries (four from the Philippines and one from India) [9].

STEC is highly toxic and can cause a hemolytic uremic syndrome in young children and elderly patients. Moreover, it is important in the perspective of public health as it spreads easily. It can cause infections in small numbers below 10^2 colonies, so infections may arise easily secondary to contaminated food or environment [7]. Although STEC O157:H7 is the most common serotype that causes infections in humans worldwide, non-O157 STEC can also cause symptoms. In 2011, there were outbreaks of enteritis caused by STEC O104:H4 in Germany and France; of the 3,816 cases in Germany, 22% had hemolytic uremic syndrome [10, 11]. According to 20 years of epidemiological investigation of STEC O157:H7 between

Table 3. Clinical findings associated with pathogens of diarrhea

Clinical findings	Possible pathogens
Bloody diarrhea	STEC, *Shigella*, *Salmonella*, *Campylobacter*, *Entamoeba histolytica*, non-cholera *Vibrio*, *Yersinia*, *Balantidium coli*, *Plesiomonas*
Chronic diarrhea	*Cryptosporidium*, *Giardia lamblia*, *Cyclospora cayetanensis*, *Cystoisospora belli*, *Entamoeba histolytica*
Abdominal pain	STEC, *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, Non-cholera *Vibrio*, *Clostridioides difficile*
Severe abdominal pain and bloody diarrhea, mild or no fever	STEC, *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia enterocolitica*
Abdominal pain with fever (similar to appendicitis)	*Yersinia enterocolitica*, *Yersinia pseudotuberculosis*
Nausea and vomiting lasting ≤24 hours	*S. aureus* toxin or *Bacillus cereus* (emetic toxin)
Vomiting, 2–3 days of non-bloody diarrhea	Norovirus

STEC, Shiga toxin-producing *E. coli*.

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Table 4. Extraintestinal complications associated with pathogens of diarrhea

Clinical findings	Possible pathogens
Postinfectious irritable bowel syndrome	*Campylobacter*, *Salmonella*, *Shigella*, STEC, *Giardia*
Hemolytic uremic syndrome	STEC, *Shigella dysenteriae* serotype 1
Erythema nodosum	*Yersinia*, *Campylobacter*, *Salmonella*, *Shigella*
Guillain-Barre syndrome	*Campylobacter*
Reactive arthritis (Reiter's syndrome)	*Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, rarely *Giardia*, *Cyclospora cayetanensis*
Intestinal perforation	*Salmonella*, *Campylobacter*, *Yersinia*, *Entamoeba histolytica*
Aortitis, osteomyelitis	*Salmonella*, *Yersinia*

STEC, Shiga toxin-producing *E. coli*.

1982 and 2002 in the United States, hemolytic uremic syndrome was found in 4% of 8,598 cases, with mortality of 0.5% [12]. Although research on STEC has been lacking in Korea, a previous report suggested that STEC was identified in 0.19% of 17,148 diarrhea patients in Kwangju between 2004 and 2018 [13]. Diarrhea appears approximately 2 - 12 days after consumption of STEC, and symptoms vary between mild and bloody diarrhea, with around 90% of patients experiencing bloody stool [14]. The symptoms are often accompanied by abdominal pain and generally start as non-bloody diarrhea and progress to be bloody 1-3 days later; bloody diarrhea is more common in STEC O157:H7 infections than in non-O157 STEC [15, 16]. Hemolytic uremic syndrome may arise in 5 - 13 days of diarrhea.

Although most cases of traveler's diarrhea improve spontaneously, 10% of patients may have persistent diarrhea for several weeks to months. Here, parasitic infections, the most common of which is *Giardia*, should be considered [17]. When afebrile bloody diarrhea and abdominal pain are present after traveling to areas with epidemics of bacteria that produce Shiga toxin, STEC infection can be suspected [18].

Extraintestinal complications (**Table 4**) of enteritis, such as the following, require caution: *Yersinia, Campylobacter, Salmonella,* and *Shigella* may cause erythema nodosum; *Campylobacter* may cause Guillain-Barre syndrome; STEC or *Shigella dysenteriae* serotype 1 may cause hemolytic uremic syndrome; *Salmonella*, *Shigella*, *Campylobacter*, and *Yersinia* may cause reactive arthritis, commonly referred to as Reiter's syndrome, or intestinal perforation; and *Salmonella* and *Yersinia* may cause aortitis or osteomyelitis. Postinfectious irritable bowel syndrome is also a well-known complication of infectious enteritis. This should be considered when patients present with chronic diarrhea or abdominal pain after infectious diarrhea or traveler's diarrhea [19, 20]; the condition is characterized by persistent gastrointestinal symptoms even after loss of infectious causes, owing to persistent, permanent changes to gastrointestinal functions after infectious enteritis. Although the symptoms improve in most cases within one year, they sometimes persist for several years, in which case assessment by a gastroenterologist is necessary. A study reported that irritable bowel syndrome developed in 9.2% of patients with bacterial enteritis confirmed through cultures within three months and in 12.3% of the patients within six months [21].

Since other epidemiological data on infectious diarrhea are lacking outside of the sentinel surveillance of gastrointestinal infections in Korea, more Korean research is warranted in this regard.

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KQ2. Which tests are helpful in identifying the pathogen in adult patients with suspected acute infectious diarrhea?

KQ2-1. Is the stool test necessary for diagnosis of acute infectious diarrhea? Which tests are appropriate?

	Recommendation	Grade of recommendation	Level of evidence
1	If bloody or mucoid stool, severe abdominal pain or tenderness, or diarrhea with septic findings are present, conduct stool test to test for *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, *C. difficile*, and Shiga toxin-producing *E. coli* (STEC).	Strong	Moderate
2	Although acute watery diarrhea or uncomplicated traveler's diarrhea in adults improves within days without antibiotics in most cases, consider non-culture tests in addition to traditional stool tests when pathogens should be identified.	Low	Expert opinion
3	Conduct stool tests for *Vibrio*, norovirus, and rotavirus upon consideration of symptoms or epidemiological relevance.	Strong	Moderate
4	If there is a risk or suspicion of outbreak of diarrhea, conduct stool tests.	Strong	Moderate
5	Since traditional stool tests (culture, microscopic analysis, and antigen analysis) often cannot identify pathogens responsible for acute diarrheal diseases, consider molecular diagnosis.	Strong	Very Low
6	Since panel-based multiplex molecular analysis for diarrhea detects DNA regardless of the survival of microorganisms, consider clinical situations in interpreting the results.	Strong	Low

In general, acute watery diarrhea improves spontaneously without particular treatment. Stool tests are necessary when pathogens should be confirmed from a public health perspective due to risks of further progression of the disease or risks of outbreaks.

Since it is difficult to identify responsible pathogens based on clinical symptoms of infectious diarrhea, *in vitro* diagnostic tests should be conducted on stool samples to identify the pathogens. *In vitro* tests of microorganisms include bacterial and viral culture, parasite/parasitic egg smears, enzyme-based immunological assays such as viral antigen test (norovirus and rotavirus), parasitic antigen test (*Giardia* and *Entamoeba histolytica*), and bacterial toxin test (*C. difficile*), as well as recently introduced molecular microbiological tests. Various pathogens can cause acute infectious diarrhea, and *in vitro* tests are limited in terms of the complexity and cost. Therefore, only highly pathogenic bacteria, such as *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, *C. difficile*, STEC, and *Vibrio* et al., are selectively cultured, and only certain viruses, such as norovirus and rotavirus, are tested in enzyme-based immunological assays; here, although enzyme-based immunological assays take a short amount of time, they have relatively low sensitivity and specificity [22].

For usual bacterial cultures, fresh stool is seeded onto culture media to detect *Salmonella*, *Shigella*, and *C. jejuni*. Acute diarrhea caused by *Y. enterocolitica*, *C. difficile*, *Vibrio*, or STEC is tested additionally when there is clinical suspicion. To detect *Y. enterocolitica*, samples are seeded on cefsulodin-irgasan-novobiocin (CIN) medium for culture at room temperature; samples are seeded on thiosulfate citrate bile salt sucrose (TCBS) medium for *Vibrio* and on sorbitol-MacConkey medium for STEC. When diarrhea persists for more than two weeks, *Giardia* is often responsible; for diagnosis, protozoa is confirmed in stool smear or cyst antigens are confirmed through immunological assays. Bacteria that cause acute diarrhea through toxins include ETEC, STEC, *Clostridium botulinum, C. difficile, B. cereus,* and *S. aureus*. STEC and *C. difficile* can also be tested through commercialized immunological test or molecular microbiological kits.

Fresh stool is preferred for bacterial tests for acute diarrhea, and rectal swabs may also be used. Rectal swabs are transported in modified Stuart transport medium. All samples should be delivered to the laboratory within two hours as delays in delivery may lead to drops in stool pH, thus suppressing the growth of some bacteria including *Shigella*. If timely delivery

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to the laboratory is difficult, the samples may be refrigerated for a short period of time and transported on ice. If samples should be delivered to over long distances to contracted testing institutions, the samples should be deep-frozen on dry ice (–70°C).

Panel-based multiplex molecular analysis for diarrhea employs polymerase chain reaction (PCR), which is widely used for molecular microbiological analyses, to use DNA from samples to simultaneously test for various pathogens causing diarrhea, such as bacteria, viruses, and parasites, and often has a higher sensitivity compared to conventionally used culture tests [23, 24]. Therefore, it is useful in detecting pathogens causing acute infectious diarrhea, which are often not found easily through conventional stool culture [25, 26]. According to a previous report, when multiplex molecular analysis and conventional diagnostic test were compared for detection of viruses, bacteria, and parasites in 1,758 stool samples collected from 1,516 patients, molecular analysis identified pathogens in 530 samples (30%) whereas conventional test identified pathogens in only 324 samples (18%) [22]. Another study comparing multiplex molecular analysis and conventional tests (culture to identify bacteria and electron microscopy to identify viruses) reported that molecular analysis identified pathogenic viruses in many samples that were negative in electron microscopy and multiplex molecular analysis had high sensitivity to many bacteria that were not detected in culture, including enteropathogenic *E. coli* (EPEC hereafter), enteroaggregative *E. coli* (EAEC hereafter), and non-O157 STEC. Overall, multiplex molecular analysis (60/135, 44.4%) identified pathogens in more than double of cases identified by conventional tests (24/135, 17.8%) [23].

Recently, microfluidic devices that enable sample pre-processing, mixing, isolation, and analysis to be performed on one chip have been developed and have been applied as nucleic acid-based point-of-care assays, where the high sensitivity and specificity of nucleic acid amplification are maintained with simultaneous nucleic acid extraction within short amounts of time [27, 28]; these assays have been very useful in early diagnosis of infectious diarrhea.

However, since molecular tests identify the presence of DNA from microorganisms, they cannot distinguish between live and dead bacteria. Therefore, the tests may come out as positive even after treatment, and pathogenic colonies or normal gut flora may also lead to positive results. For these reasons, clinical situations should be considered when interpreting the results. Further research is also required on the cost-effectiveness and South Korean data on the utility of panel-based multiplex molecular analysis.

KQ2-2. Is stool leukocyte or lactoferrin test helpful in clinical diagnosis of acute infectious diarrhea in adults?

Recommendation		Grade of recommendation	Level of evidence
1	Stool leukocyte or lactoferrin test is not recommended in identifying the cause of acute infectious diarrhea.	Strong	Moderate

Most acute inflammatory diarrhea is caused by *Campylobacter, C. difficile*, enterohemorrhagic *E. coli* (EHEC hereafter), EIEC, *Salmonella*, *Shigella*, and *Yersinia*, and non-inflammatory diarrhea is caused by *Clostridium* food poisoning, ETEC, *Staphylococcus*, *Vibrio cholerae*, viruses (norovirus and rotavirus), and parasites (*Giardia* and *Cryptosporidium*) [8]. Most pathogens causing non-inflammatory diarrhea cause diarrhea through toxins but do not cause inflammation in intestinal mucosa; therefore, leukocytes or occult blood is rarely found in stool. Although stool leukocyte or lactoferrin test is not widely used in acute diarrhea patients in Korea, they are screening tests used for diagnosis of intestinal inflammation abroad. Since neutrophils in stool denature with time, the tests should be conducted in a timely manner. If stool leukocyte

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test is positive, it is highly likely that the diarrhea is of inflammatory origin, and the test is often negative in viral, parasitic, or toxin-caused diarrhea. However, stool leukocytes are only occasionally observed in inflammatory diarrhea, are not uniformly distributed, and have limited sensitivity. Moreover, although stool smears are used for differential diagnosis of invasive infections, the smears often result in false positives or negatives. Lactoferrin does not denature during transport or pre-processing and can thus be used as an alternative marker to stool leukocytes. However, since lactoferrin is also present in inflammatory enteritis of non-infectious etiologies, differential diagnosis from infectious inflammatory diarrhea is necessary [29], and it is not used commonly in clinical laboratories.

KQ2-3. Are laboratory tests (CBC, chemistry, serology, culture) helpful in diagnosing acute infectious diarrhea or predicting complications?

	Recommendation	Grade of recommendation	Level of evidence
1	Blood cultures are helpful in diagnosing patients with suspected infectious diarrhea in the following cases: ① septic findings, ② suspected enteric fever, ③ systemic infectious symptoms, ④ immune-suppressed patients, ⑤ high-risk situations, such as hemolytic anemia, ⑥ patients with fever of unclear etiology who have travel history to areas with endemic enteric fever or contact history with individuals who traveled to an area with endemic enteric fever.	Strong	Moderate
2	Widal test is not recommended for diagnosis of pathogens causing enteric fever	Strong	Moderate
3	If infectious diarrhea is suspected, total white cell count and differential count may be helpful in determining whether it is bacterial.	Weak	Low
4	Repeat hemoglobin, platelet count, electrolytes, blood urea nitrogen/creatinine to detect early findings of hemolytic uremic syndrome or renal damage may help in predicting complications in patients infected with *E. coli* 0157 or other STEC. Moreover, peripheral blood smear to confirm RBC fragments is helpful when the hemolytic uremic syndrome is suspected.	Strong	High

When infectious diarrhea is suspected, blood culture may be helpful in identifying the pathogen in patients with septic findings, patients with suspected enteric fever, and suppressed patients with fever [30, 31]. Non-typhoidal *Salmonella, Campylobacter, Shigella, Listeria*, non-cholera *Vibrio*, and *Yersinia* may cause invasive infections and infectious diarrhea in many immune-suppressed patients, and blood culture may be employed to identify the pathogen and test for antibiotic sensitivity [32-36]. In order to confirm bacteremia, cultures of blood samples drawn from different sites should be conducted in 2-3 repeats. It is advisable to collect 20ml of samples, and the cultures should be done prior to antibiotic use [37]. Recently developed automated blood culture instruments, such as BacT/ALERT 3D automated microbial detection system, perform automated reads of each culture bottle at regular, short intervals to generate rapid test results; these instruments also have very high sensitivity at 95 - 98%.

The Widal test detects agglutinin, which responds to *Salmonella* O (somatic) antigens and H (flagella) antigens, for rapid serological diagnosis of enteric fever. Since it is cheap and simple, it was widely used previously, but it is no longer recommended due to its low specificity and sensitivity to enteric fever [30, 38]. The Widal test results should be interpreted upon consideration of the past history of enteric fever, vaccination history, and antigen levels in healthy individuals in community [39]. Increased vaccination against enteric fever and other infections by *S. enterica* may decrease the specificity of Widal test, and cross-reaction may also be observed in non-*Salmonella* infections (*e.g.*, malaria, dengue fever, and brucellosis) in areas with endemics of enteric fever [38, 40]. There also are significant deviations in agglutinin levels in healthy populations in community; this is because the level may change with time and vary depending on how endemic enteric fever is in a given area [30].

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Peripheral total and differential white cell count may be helpful in diagnosing whether infectious diarrhea is of bacterial, viral, or parasitic etiology. When infectious diarrhea is caused by bacteria, total leukocyte and neutrophil count often increase. In bacterial sepsis, total leukocyte and platelet count may decrease below the normal range. The leukemoid reaction may be observed in shigellosis. If infectious diarrhea is of viral etiology, the total white cell count may be within normal range with increases in lymphocyte fraction, and eosinophil count may increase in parasitic infections. Monocytes may increase in intracellular pathogenic infections such as *Salmonella* infections.

Since hemolytic uremic syndrome arises with time in infectious diarrhea, single complete blood count (CBC) is not enough for evaluation of its risks. Hemoglobin levels close to normal ranges may indicate dehydration. If platelet count decreases for 1 - 14 days from the onset of diarrhea, the risk of hemolytic uremic syndrome increases. If platelet count increases or stabilizes in patients in recovery, CBC monitoring can be discontinued. Patients with increasing serum creatinine, blood pressure, and body fluid volume should be closely monitored, and treatment for acute renal failure should be considered [41].

KQ2-4. Is computed tomography (CT) helpful in diagnosing or predicting complications of acute infectious diarrhea?

	Recommendation	Grade of recommendation	Level of evidence
1	CT may be helpful in diagnosing complications, such as aortitis, infectious aneurysm, peritonitis, intestinal perforation, and toxic megacolon, when fever continues despite appropriate antibiotic treatment in elderly patients with invasive *Salmonella enterica* or *Yersinia* infections or when patients have atherosclerosis.	Weak	Low
2	CT may be helpful in differential diagnosis of acute infectious diarrhea and non-infectious diarrhea.	Weak	Low

Although aortitis and infectious aneurysm are very rare, they often have unfavorable prognosis and are caused by Gram-positive bacteria including *Staphylococcus, Enterococcus*, and *Streptococcus pneumoniae*. However, they also may occur as complications of acute infectious diarrhea; *Salmonella* infections may lead to abdominal aortitis, and the incidence is high in individuals at high risks of atherosclerosis. CT enables rapid diagnosis of aortitis, aortic dissection, and hematoma of vascular walls [42]. *Yersinia* infection may cause complications, including bacteremia, mesenteric lymphadenitis, endocarditis, and infectious aneurysm, and these complications are common in patients with diabetes, chronic liver disease, poor nutrition status, and tumor, as well as in elderly patients. When bacteria are identified in blood cultures, CT may be helpful in diagnosis of aortitis [35, 43]. Infectious abdominal aneurysm has been reported following *Campylobacter* infection, particularly *Campylobacter fetus* infection. Although this is a very rare condition, there is a high risk of rupture. Therefore, early diagnosis is very important for prognosis, and surgical treatment is necessary along with antibiotic treatment [44].

Acute diarrhea may also be present in inflammatory bowel diseases and ischemic enteritis, and CT may help in the differential diagnosis of these. On radiological findings, hyperplasia of bowel walls may lead to 'empty lumen sign' in infectious diarrhea, as well as relatively less 'fat stranding' compared to inflammatory bowel disease or ischemic enteritis. 'Fat stranding', 'comb' sign, fistula, or abscess may be found in inflammatory bowel diseases. Ischemic enteritis often invades the sigmoid colon or splenic flexure, and mesenteric infiltration is a major radiological finding. These CT findings may help in differential diagnosis of the cause of acute diarrhea [45]. Different changes in the intestinal wall thickness caused by inflammation may be observed depending on the cause. If the infection invades the small intestine, the intestinal wall may be normal on CT or may only show mild edema. Infection by *E. coli* O157 or enteritis caused by *C. difficile* infection is characterized by severe hyperplasia of colon wall on CT [46-48].

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KQ2-5. Is endoscopy helpful in diagnosis of infectious diarrhea?

	Recommendation	Grade of recommendation	Level of evidence
1	Endoscopy is not recommended in most acute and chronic infectious diarrhea patients.	Strong	Very Low
2	Endoscopy or sigmoidoscopy should be considered in acute diarrhea patients without improvement, in persistent unexplained diarrhea in acquired immune deficiency syndrome patients, persistent diarrhea in patients who have anal sexual intercourse, and persistent diarrhea in patients with recent travel history.	Strong	Low
3	Duodenal aspiration may be considered when *Giardia*, *Strongyloides*, *Cystoisospora*, or *Microsporidia* infection is suspected.	Weak	Low

Although acute infectious diarrhea is common in healthy individuals, most cases do not require tests or treatment as they recover spontaneously within short period. Likewise, endoscopy to evaluate the cause of diarrhea is also not recommended [49]. Diarrhea is categorized into acute (less than 14 days), persistent (14 - 29 days), and chronic (30 days or longer) [50], and endoscopy is recommended for acute diarrhea without improvement, persistent diarrhea of unclear etiology in AIDS patients, and persistent diarrhea associated with anal sexual intercourse [29]. Endoscopy may also be helpful in persistent diarrhea after traveling to tropical or subtropical regions.

Sigmoidoscopy is sufficient for differential diagnosis of acute diarrhea. Although colonoscopy does not play a significant role in the diagnosis of acute infectious diarrhea and is thus not recommended, it may be considered if other conditions, such as colon cancer, are suspected. Even when colonoscopy is used, strong laxatives should be avoided whenever possible, and the test should be done with light enema. Endoscopy may be used to confirm inflammation state of colon mucosa and to differentially diagnose various types of enteritis through biopsy at different sites [51, 52]; endoscopy is particularly useful in diagnosis of CMV enteritis and *C. difficile* enteritis [53]. Moreover, intestinal juice may be aspirated during endoscopy to obtain useful information for differential diagnosis of enteritis. A previous study reported that bacterial culture of intestinal juice aspirated during endoscopy and stool culture had a 91.2% concordance rate, thus suggesting that intestinal juice aspiration may be useful in the diagnosis [54]. In general, endoscopy is more useful for differential diagnosis of chronic diarrhea than acute diarrhea, and it is particularly helpful for diagnosis of Giardiasis, celiac disease, Crohn's disease, Whipple's disease, and eosinophilic gastroenteritis [53]. Since acute infectious diarrhea is mostly caused by lower gastrointestinal tract infections, gastroscopy is not recommended for this; however, gastroscopy may still be useful for a subset of patients. If trophozoite is found in duodenal biopsy and aspiration, Giardiasis can be diagnosed [55, 56], and duodenal aspiration is also useful for suspected *Strongyloides*, *Cystoisospora*, or *Microsporidia* infection [57].

KQ3. What are indications for empirical antibiotic therapy for acute infectious diarrhea and which antibiotics should be used?

	Recommendation	Grade of recommendation	Level of evidence
1	In general, antibiotic treatment is not recommended for most cases of acute watery diarrhea.	Strong	Low
2	Empirical antibiotic therapy can be considered in the following cases: ① If bloody or mucoid stool and fever, or Shigellosis symptoms (frequent scant bloody stools, fever, cramping abdominal pain, and tenesmus) are present and ② in traveler's diarrhea accompanied by high fever above 38.5℃ or septic findings.	① Weak ② Low	① Expert opinion ① Low
3	Antibiotic treatment is recommended for immune-suppressed patients with bloody diarrhea.	Strong	Low
4	For empirical antibiotic therapy, use fluoroquinolone antibiotics or azithromycin upon consideration of distribution and antibiotic sensitivity of pathogens in local communities or areas where the patient traveled.	Strong	High
5	Rifaximin may be used for suspected infection with non-invasive bacteria without bloody diarrhea.	Low	Low
6	The use of antibiotics is not recommended for patients with suspected STEC infections.	Strong	Moderate

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Acute watery diarrhea is often viral in etiology (norovirus, rotavirus, and adenovirus). Even when bacterial in etiology, the symptoms often improve spontaneously without treatment, and treatment does not necessarily shorten the duration of symptoms. Considering the side effects and cost of antibiotics as well as antibiotic resistance, antibiotic treatment does not offer much benefit [58]. Therefore, antibiotic treatment is not recommended with the exception of special cases, including immune-suppressed patients. Diarrhea can be classified as mild, moderate, and severe. Mild diarrhea is defined as bearable and is characterized by three or less loose bowel movements per day; patients can still travel or engage in other activities as scheduled. Moderate diarrhea is characterized by four or more bowel movements per day, and patients travel or activity plans are interfered by diarrhea. Severe diarrhea is defined as six or more bowel movements per day, and it interferes with daily activities and prevents planned trips or other activities. All bloody diarrhea is defined as severe [59]. When empirical antibiotic therapy was used for moderate traveler's diarrhea, the treatment was found to decrease the duration of diarrhea by 1.5 days on average [58, 60, 61], and by 16 - 30 hours for severe traveler's diarrhea [58].

Salmonella, *Campylobacter*, *Shigella*, and STEC are the most common pathogenic bacteria causing acute bloody diarrhea. Multiple randomized controlled studies demonstrated that empirical antibiotic therapy in these patients lead to 1-day reduction in the duration of symptoms compared to placebo treatment. However, antibiotic treatment increases the time for excretion of *Salmonella*, and can also cause the excretion of fluoroquinolone-resistant *Campylobacter*. Therefore, considering the benefits and risks of treatment, empirical antibiotic therapy is not recommended for most patients except immune-suppressed patients and those with severe infections. Although no evidence supporting that antibiotic use is clearly beneficial could be found, this guideline considered clinical environment in South Korea as well as expert opinions for the following recommendation: antibiotic use can be considered if bloody or mucoid stool and fever, or Shigellosis symptoms (frequent scant bloody diarrhea fever, cramping abdominal pain, and tenesmus) are present and in traveler's diarrhea accompanied by high fever above 38.5°C or septic findings (**Fig. 2**).

Selection of antibiotics for empirical antibiotic therapy of acute infectious diarrhea should consider the distribution and antibiotic sensitivity of pathogens in local communities or areas where the patient traveled. Although fluoroquinolone antibiotics, including ciprofloxacin and levofloxacin, have been recommended for first-line therapy, resistance against these antibiotics has increased recently. Moreover, fluoroquinolone antibiotics have risks of serious side effects, such as ligament inflammation, ligament rupture, peripheral neuropathy, and central nervous system side effects, and thus require caution.

In some areas, macrolides, such as azithromycin, is recommended due to increased resistance of *Campylobacter* to fluoroquinolone. In Europe in 2012, *Campylobacter* infections were three times more common than nontyphoidal *Salmonella* infections [62], and ciprofloxacin resistance of *Campylobacter* was reported to be as high as 44% in some European countries [63]. Fluoroquinolone resistance of *Campylobacter* has also been reported to be high in Mexico (56%) and Thailand (>92%) [64, 65]. Considering these, macrolides including azithromycin may be considered for empirical antibiotic therapy in areas where *Campylobacter* is common and has high resistance to fluoroquinolone.

According to the KCDC's analysis of 3,526 samples isolated from infectious diarrhea patients in 2014, *Salmonella* species accounted for 13.5%, and *Campylobacter* species accounted for 6.1% [66]. Moreover, 29% (63/218) of *Campylobacter* have been reported to be resistant to

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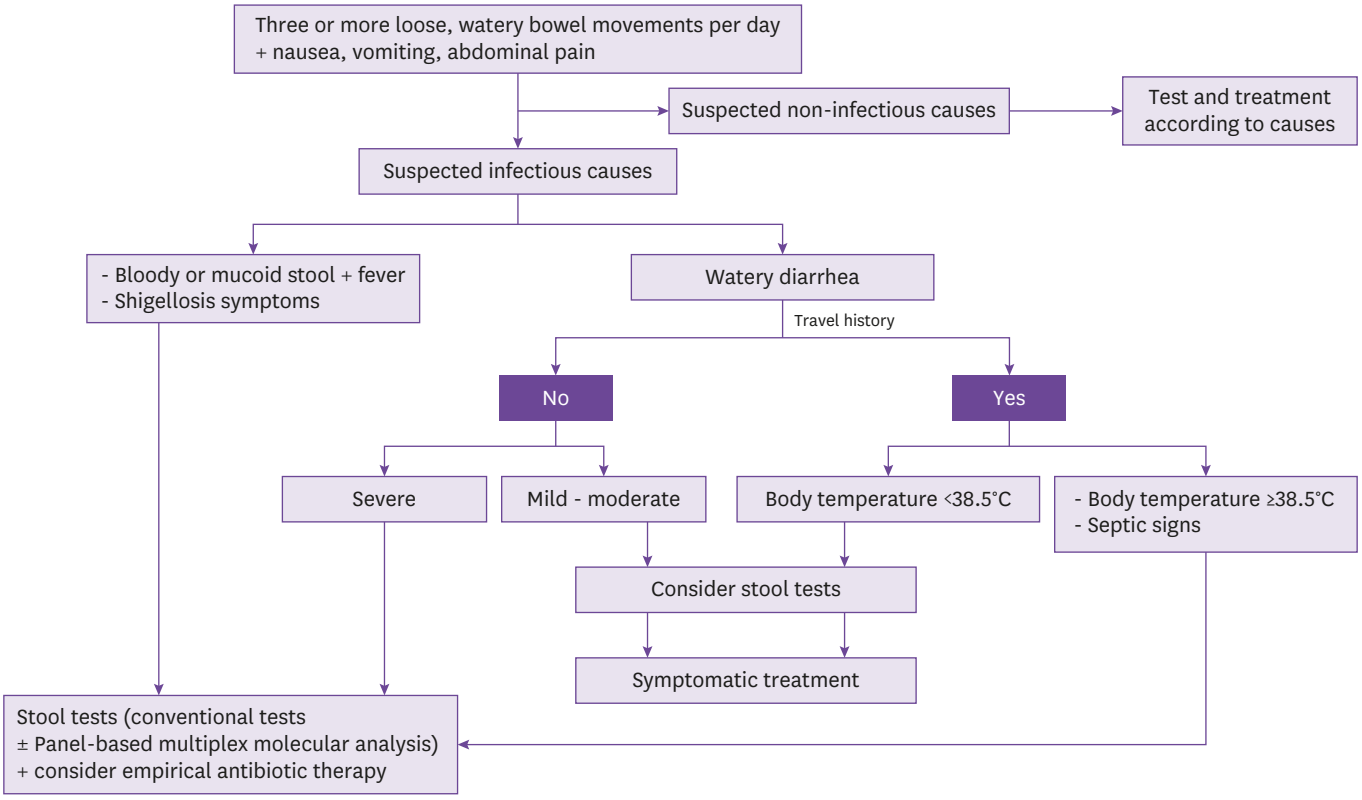

Figure 2. Algorithm for treatment of infectious diarrhea.
- Mild: Diarrhea is bearable, and the patient is capable of travelling or other activities as planned.
- Moderate: Diarrhea interferes planned travels or other activities.
- Severe: Diarrhea interferes with daily activities and prevents planned travels or other activities.

fluoroquinolones although this report was made from a single institution [67]. Therefore, the percentage of *Campylobacter* and increase in fluoroquinolone resistance should be considered in infectious diarrhea in South Korea, and the use of macrolides, such as azithromycin, should also be considered.

Since rifaximin is a non-absorbable rifamycin derivative, it is relatively safe. It shortened the duration of symptoms compared to placebo in a randomized controlled trial [68], and its effects were comparable to those of fluoroquinolones [69, 70]. Rifaximin is often effective against *E. coli* and less effective against invasive bacteria, such as *Campylobacter*, *Salmonella*, and *Shigella*. In particular, resistance is an issue in *Campylobacter*. Therefore, rifaximin is not recommended in areas where invasive bacteria are common or in patients with suspected infection with invasive bacteria (bloody diarrhea).

In studies employing animal models and *in vitro* models of STEC infection, fluoroquinolone and trimethoprim-sulfamethoxazole (TMP/SMX) antibiotics were associated with increased secretion of Shiga toxin, but fosfomycin, azithromycin, and rifaximin did not increase the excretion of Shiga toxin [71-73]. Recent meta-analyses of STEC patients did not show a significant correlation between antibiotic use and hemolytic uremic syndrome [74, 75]. However, when the analysis was repeated only on studies with low risk of bias and appropriate definition of the hemolytic uremic syndrome, the risk of hemolytic uremic syndrome doubled when antibiotics were used [75]. Therefore, the use of antibiotics is not recommended for patients with suspected or confirmed STEC infections.

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For empirical antibiotic therapy, single administration or three-day regimen is recommended for most uncomplicated cases. However, a previous study suggested that five-day regimen, rather than single administration or three-day regimen, is more effective in gastroenteritis caused by *Shigella dysenteriae* [76].

KQ4. How should antibiotics be modified when the bacterial strain causing acute infectious diarrhea is identified?

	Recommendation	Grade of recommendation	Level of evidence
1	When the bacteria and antimicrobial susceptibility results are identified, antibiotics should be modified accordingly.	Strong	High
2	For infectious diarrhea caused by *Campylobacter*, the use of azithromycin is recommended.	Strong	High
3	For nontyphoidal salmonellosis, antibiotic treatment is not recommended with the exception of infants less than 3 months of age, patients over 50 with suspected atherosclerosis, immune-suppressed patients, patients with valvulopathy, and patients with significant joint diseases.	Weak	Low
4	Azithromycin, ciprofloxacin, or ceftriaxone is recommended for shigellosis.	Strong	High
5	Doxycycline is recommended for *Vibrio cholerae* infections, and ciprofloxacin, azithromycin, and ceftriaxone may also be used.	Strong	High

Although multiple randomized controlled trials showed significant decreases in the duration of symptoms of *Campylobacter* gastroenteritis with antibiotic treatment, the degree of significance was not great. A meta-analysis showed that treatment with fluoroquinolone or macrolide shortened the duration of symptoms by 1.32 days [77]. Azithromycin was more effective in decreasing the excretion of bacteria than ciprofloxacin in diarrhea observed in American soldiers deployed to Thailand; this finding seems to have been related to the high *Campylobacter* prevalence and fluoroquinolone resistance in the area [78]. Since antibiotic use increases recurrence and prolongs bacterial excretion in nontyphoidal salmonellosis, it is not recommended in most cases [79]. According to a randomized controlled trial on pediatric patients with *Salmonella* enteritis, bacteriological recurrence was observed in 53% of cases treated with ampicillin or amoxicillin, but no recurrence was found in the placebo control group. Moreover, 38% of patients with bacteriological recurrence had symptomatic recurrence [79]. This seems to be because antibiotic treatment in this population of patients damages the gut flora. In a meta-analysis on 767 patients in 12 studies, antibiotic treatment did not yield significant benefit in symptomatic improvement and duration in adult nontyphoidal salmonellosis patients who were otherwise healthy [80]. In cases where there is a high risk of bacteremia or high risks of complications from gastrointestinal infection, antibiotics may be used. When the KCDC analyzed 219 bacterial strains of nontyphoidal *Salmonella* clinically isolated between 2006 and 2008, the resistance to ampicillin, nalidixic acid, ciprofloxacin, and TMP/SMX was 49%, 50%, <1%, and 8%, respectively. The use of azithromycin, ciprofloxacin, or ceftriaxone is recommended for shigellosis. Although TMP/SMX or ampicillin may be used when isolated bacteria are sensitive, a Korean study reported a high resistance rate. In 67 strains of *Shigella sonnei* isolated in Jeollanam-do in 1999 - 2000, the resistance to trimethoprim, sulfonamide, nalidixic acid, and ampicillin was 100%, 99%, 70%, and 49%, respectively, but no resistance to cefotaxime or ciprofloxacin was observed [81].

KQ5. Do anti-diarrheal agents decrease the duration of symptoms in acute infectious diarrhea?

	Recommendation	Grade of recommendation	Level of evidence
1	Bismuth subsalicylates provide symptomatic improvement by regulating the amount of stool in mild or moderate acute diarrhea.	Strong	High
2	Loperamide is helpful in shortening the duration of symptoms of acute watery diarrhea in otherwise healthy adults.	Weak	Moderate
3	Loperamide should not be used for children below the age of 18.	Strong	Moderate
4	Loperamide should be avoided when there is a possibility of toxic megacolon or when fever continues.	Strong	Low
5	Loperamide may improve symptoms in traveler's diarrhea with appropriate antibiotic treatment.	Strong	Moderate

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Antidiarrheal agents include intestinal motility inhibitors, adsorbents, and intestinal secretion inhibitors. Intestinal secretion or motility inhibitors may be helpful in decreasing the frequency or duration of diarrhea for symptomatic improvement of acute infectious diarrhea patients with moderate symptoms [82].

Bismuth subsalicylates, which are intestinal secretion inhibitors, decrease the frequency of diarrhea and improve nausea and abdominal pain within 24 hours of treatment in acute diarrhea patients. They are effective in improving the symptoms of traveler's diarrhea and are particularly helpful in preventing symptoms in ETEC enteritis [83, 84]. Coformulations with bismuth subnitrate are available in Korea for acute diarrhea patients. Racecadotril is an enkephalinase-specific inhibitor, which is a secretion inhibitor that decreases diarrhea without influence on intestinal motility. It is effective in diarrhea in pediatric patients and had similar effects as loperamide in acute diarrhea in adults [85-87].

Loperamide inhibits intestinal motility to decrease the movement of intestinal contents and promote the absorption, thereby decreasing diarrhea. It also suppresses the secretion of intestinal mucosal secretion, which contributes to decreasing diarrhea [88, 89]. It shortens the duration by 1 day, and decreases amount and frequency of watery diarrhea in otherwise healthy adults. Meta-analyses have reported that side effects outweigh treatment effects in pediatric patients, especially those younger than 3, patients with poor nutrition, patients with moderate or severe dehydration, patients with systemic symptoms, and patients with bloody diarrhea. Side effects include intestinal obstruction, abdominal distension, lethargy, and even death [90]. Loperamide may be used with antibiotics for fast symptomatic improvement of traveler's diarrhea. Although the treatment effects are not clear, it helps to decrease the symptoms and is known to be relatively safe with few reports of side effects. When a meta-analysis compared single use of antibiotics and combined use of loperamide (4 mg administration initially, additional administration of 2 mg with each episode of diarrhea, up to 16 mg per day), clinical improvement was greater in the combined treatment group 24 hours after the start of treatment, and the duration of diarrhea was also shorter in the combined treatment group after treatment. The treatment failure rate was also lower in the combined treatment group. In terms of the safety, the two groups did not differ significantly without any major side effects. When the effects of loperamide in traveler's diarrhea was compared to those of bismuth subsalicylates, the effects were greater in the group receiving loperamide, and there was no significant difference in side effects [61, 91, 92]. When loperamide is used in acute diarrhea, constipation may arise. When used in severe intestinal inflammation, megacolon can arise, and the duration of symptoms may increase. Therefore, the use of loperamide should be avoided when there is a possibility of megacolon or when fever persists from severe inflammatory responses. In particular, for enteritis caused by *C. difficile* or *C. perfringens*, loperamide should not be used as it may lead to toxic megacolon or intestinal expansion. The side effects were more common when loperamide was used on its own without appropriate antibiotic treatment [93-95].

Adsorbents, such as kaolin, pectin, charcoal, and attapulgite, do not decrease the frequency or duration of diarrhea and, thus, are not recommended in infectious diarrhea [96, 97].

KQ6. Do probiotics decrease the duration of symptoms in acute infectious diarrhea?

Recommendation		Grade of recommendation	Level of evidence
1	Probiotics decrease the symptoms and duration of acute infectious diarrhea in otherwise healthy adult and pediatric patients.	Weak	Moderate
2	Probiotics are not recommended to prevent traveler's diarrhea.	Weak	Low

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The World Health Organization defined probiotics as live microorganisms that are beneficial for the host when administered in adequate amounts [98]. Theoretically, the administration of beneficial bacteria in acute infectious diarrhea suppresses the proliferation of harmful bacteria and thus treats or prevents acute infectious diarrhea. Many studies have been conducted on probiotics in pediatric patients with acute bacterial diarrhea, and most studies found that probiotics were effective in decreasing the duration and frequency of acute infectious diarrhea [98, 99]. In a Cochrane analysis of 63 studies on 8,014 patients with acute infectious diarrhea, most of whom were pediatric patients, the groups receiving probiotics had diarrhea for one day less on average compared to control groups, and the frequency of bowel movements on day 2 of administration was 0.8/day less in the probiotics groups than in the control groups. *Lactobacillus* GG and *Saccharomyces boulardii* were the most commonly used probiotics in these studies [100]. However, since less studies have been conducted on adult patients than on pediatric patients with acute infectious diarrhea, it is difficult to draw conclusion on the effects in adults. Moreover, as many probiotics studies had different definition of diarrhea, cause of diarrhea, interpretation of results, methods, and probiotic strains, it is difficult to compare their effects [101]. According to research conducted on adults, when *Enterococcus* SF 68 was administered per os in 211 patients, the duration of diarrhea was 1.69 days in the group receiving the treatment and 2.81 days in the control group. At day 4 of treatment, diarrhea resolved in all patients in the treatment group whereas it persisted in 15.2% of patients in the control group; in other words, probiotics were found to decrease the duration of acute infectious diarrhea [102]. Similarly, when *Enterococcus* SF 68 was administered in 123 adult patients with acute diarrhea, diarrhea improved in 87.2% of patients in the treatment group on day 4 of treatment, compared to 59.5% improvement observed in the control group, and no side effects of probiotics were reported [103]. However, Mitra AK et al. administered enterococcus SF 68 to 183 acute bacterial diarrhea patients for 3 days and observed no decrease in the duration and frequency of bowel movement [104]. Although probiotics have been covered by the public health insurance in South Korea for pediatric patients with acute infectious diarrhea, antibiotic-associated diarrhea, and necrotizing enteritis since 2011, the same coverage does not apply for adults (notice number 2011-74). Probiotics are known to be safe with very little side effects, but caution is still required as cases of fungemia or bacteremia from probiotics have been reported in immune-suppressed patients [105].

It is difficult to conclude that certain probiotic strains are superior to others in acute infectious diarrhea. Since the effects of probiotics are strain-specific, it is also difficult to apply the findings of a study to other closely related species [106]. Moreover, research on dose-dependent effects is lacking, and the results indicated no correlation between dose and treatment effects [107]. However, in five out of six studies where different doses of probiotics were administered, dose-dependent increases in probiotics in stool were observed, indicating a recovery in stool [107]. Research is also lacking in comparison of single and combined therapy in acute infectious diarrhea [108].

Although research has been conducted to evaluate acute infectious diarrhea in adults in the context of recent travels, it is difficult to interpret the results due to different research environments, variability in probiotic strains, and short follow-up duration [12]. Moreover, two meta-analyses showed preventive efficacy against traveler's diarrhea, the prophylactic use of probiotics is not recommended due to insufficient evidence [109, 110]. (**Table 5**)(**Table 6**)

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Table 5. Empirical antibiotics in acute infectious diarrhea

Antibiotic	Dose	Duration
Ciprofloxacin	500 mg PO twice daily or	3 days
	500 mg PO once daily	3 days
	750 mg PO	Single dose
Levofloxacin	500 mg PO	3 days
Azithromycin	500 mg PO	3 days
	1,000 mg PO	Single dose
Rifaximin	200 mg PO three times daily	3 days

PO, per os.

Table 6. Recommended antibiotics by pathogen

Pathogen	First-line antibiotics	Second-line antibiotics
Campylobacter	Azithromycin	Ciprofloxacin[b]
Non-typhoidal *Salmonella*	Usually not indicated[a]	NA
Salmonella enterica Typhi or Paratyphi	Ceftriaxone or ciprofloxacin	Ampicillin[b], TMP/SMX[b], or azithromycin
Shigella	Azithromycin, ciprofloxacin[b], or ceftriaxone	TMP/SMX[b] or ampicillin[b]
Vibrio cholerae	Doxycycline	Ciprofloxacin, azithromycin, or ceftriaxone
Non-choleraic *Vibrio*	Noninvasive disease: usually not indicated	Noninvasive disease: usually not indicated
	Invasive disease: ceftriaxone + doxycycline	Invasive disease: TMP/SMX + aminoglycoside

[a]Ceftriaxone, ciprofloxacin, TMP/SMX, or amoxicillin may be used when there is a risk of invasive infections.
[b]Has a high risk of resistance in South Korea and may be used based on sensitivity test results. Caution is required when sensitivity is unknown (*e.g.*, only positive PCR results).
NA, not available; TMP/SMX, trimethoprim-sulfamethoxazole.

SUPPLEMENTARY MATERIAL

Guideline Korean version.

Supplementary material can be found with this article on-line https://icjournal.org/src/sm/ic-51-217-s001.pdf.

Supplementary

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