JOURNAL OF THE
ANUS, RECTUM AND COLON
dx.doi.org/10.23922/jarc.2022-016
http://journal-arc.jp

Original Research Article

Appropriate Antibiotic Selection during the in-hospital Waiting Period for Surgery for Appendicitis

Shungo Yukumi[1)3)], Kei Ishimaru[5)], Hideaki Suzuki[1)], Masamitsu Morimoto[1)], Chika Sato[2)3)], Yukiyo Kaneko[6)] and Yoshikazu Kubo[3)4)]

1) Departments of Surgery, National Hospital Organization Ehime Medical Center, Toon, Japan
2) Departments of Respiratory Medicine, National Hospital Organization Ehime Medical Center, Toon, Japan
3) Infection Control Team, National Hospital Organization Ehime Medical Center, Toon, Japan
4) Departments of Gastroenterology, National Hospital Organization Ehime Medical Center, Toon, Japan
5) Department of Minimally Invasive Gastroenterology, Ehime University Medical School, Toon, Japan
6) Department of Nursing, National Hospital Organization Osaka Minami Medical Center, Kawachinagano, Japan

Abstract

Objectives: Acute appendicitis is a common disease that often requires emergency surgery. However, recently, not all cases are treated as an urgent operation, but surgery may be delayed to when medical resources are abundant to perform the operation safely. In such cases, preoperative antibiotics are administered during the waiting period. Though the choice is empiric, an appropriate choice is needed to avoid emergency surgery. Guidelines for the choice of antibiotics recognized as international standards cannot be applied in Asia due to the high rate of extended-spectrum β-lactamase (ESBL) producers or fluoroquinolone-resistant *Escherichia coli*. The purpose of this study was to determine the optimal antibiotic during the in-hospital waiting period for patients with appendicitis scheduled for surgery.

Methods: Bacterial culture results and antibiotic susceptibility were retrospectively examined in 106 cases who underwent surgery for appendicitis.

Results: Bacterial cultures were positive in 53 cases (50%). Twenty-six strains of *E. coli* were identified. Of these, four (15%) were ESBL producers, and seven (27%) were fluoroquinolone resistant. Twenty-two strains of anaerobic bacteria were identified. Carbapenems and tazobactam/piperacillin were effective for all. The rates of susceptibility to clindamycin (CLDM) and cefmetazole (CMZ) were 59% and 82%, respectively.

Conclusions: In Japan, from the point of view of reducing carbapenem use, CMZ must be considered a first-choice drug during the in-hospital waiting period for appendectomy.

Keywords

appendicitis, antibiotics, ESBL, fluoroquinolone resistance

J Anus Rectum Colon 2022; 6(4): 259-263

Introduction

Acute appendicitis is a common disease. The lifetime risk is reported to be 7%-8%[1]. Performing early laparoscopic surgery is said to shorten the hospital stay[2]. Despite a pervasive need for urgent surgery, the lack of capacity for emergency surgery often prevents its performance. Though a short 12-24-h in-hospital delay does not increase the risk of

Corresponding author: Kei Ishimaru, kei.ishimaru@gmail.com
Received: March 30, 2022, Accepted: June 16, 2022

Table 1. Patient Data.

n = 106	
Age, mean (median, range)	49 (50, 14–92)
Gender	
Male	61
Female	45
Preoperative inflammatory index	
WBC (/ml)	12.4 (12.5, 2.8–24.1)
CRP (mg/dl)	4.5 (0.6, 0–30.9)
Pre-operative in-hospital stay	2 (2, 0–11)
Simple	63 (59%)
Complicated	43 (41%)
Necrosis	33
Perforation	10
Abscess	11
Procedure	
Open appendectomy	29 (27%)
Laparoscopic appendectomy	72 (68%)
Ileocecal resection	5 (5%)

WBC white blood cell count, *CRP* C-reactive protein

perforation[3], and the delay can help service provision through the avoidance of nighttime operations and increased access to daytime technological resources[4], the operations may be delayed a few days when the patient's state is stable. Appropriate antibiotic selection is required to avoid the deterioration of patients during this waiting period.

Antibiotic selection in acute appendicitis is often empiric because a culture specimen cannot be taken unless we access the peritoneal cavity, except in cases of bacteremia. *Escherichia coli*, streptococci, and anaerobic bacteria are known as common causative bacteria in appendicitis. In Japan, there is no guideline for antibiotics in acute appendicitis. Guidelines or references that are widely accepted around the world such as SIS-IDSA[5], WSES[6] guideline, or the Sanford Guide cannot be applied in Japan and other Asian countries due to the high rates of extended-spectrum β-lactamase (ESBL) producer and fluoroquinolone-resistant *E. coli* in this area. Under these conditions, clinicians must choose broad-spectrum agents such as carbapenems to treat appendicitis.

The purpose of this study was to determine the appropriate antibiotic to administer while waiting to perform appendectomy with reference to bacterial culture data and antibiotic susceptibility tests in a retrospective case series. These results will help us select empirical antibiotics and provide a basis for reducing inappropriate use of broad-spectrum agents during the waiting period before operation.

Methods

Data were retrospectively collected from the registry of Ehime Medical Center. The study protocol was approved by the Review Board of the National Hospital Organization Ehime Medical Center. Written informed consent was waived because this was a retrospective study. Cases that underwent appendectomy or ileocecal resection for appendicitis at Ehime Medical Center from April 01, 2014, to March 31, 2022, were identified.

Since there were no criteria for antibiotic selection and operation timing in our institution, the choice of antibiotics and the timing of the operation depended on the decision of the physicians in charge of the first visit or the surgeons in charge of the operation.

The following parameters were evaluated: (1) preoperative characteristics, including age, sex, white blood cell count (WBC), serum C-reactive protein level (CRP), antibiotic administration status, time from diagnosis to surgery; (2) surgical procedure, including open or laparoscopic, appendectomy, or ileocecal resection; (3) histological or clinical classification of appendicitis, including exudative, phlegmonous, gangrenous, perforated, or abscess forming; and (4) bacterial cultures with antibiotic susceptibility, including specimens of bacterial cultures obtained by aspirating the peritoneal fluid or abscess intraoperatively. In some cases, they were obtained by swabbing the lumen of the excised appendix specimen. The aspirated fluid or abscess was placed into a sterilized Spitz tube, and the swabbed specimens were placed in transport medium immediately. Further, they were sent to the hospital laboratory, and were inoculated on blood, chocolate, and MacConkey agar for aerobic bacteria and Brucella HK agar for anaerobic bacteria. The automated VITEK 2 system (bioMerieux, Inc., Durham, NC, USA) was used to identify pathogens and perform antibiotic susceptibility tests of aerobic bacteria. Anaerobic specimens were transferred to an external laboratory for identification and antibiotic susceptibility tests (SRL, Inc. Matsuyama, Ehime, Japan). Based on the susceptibility reports, antibiotics considered to be effective were then identified.

Results

In the period studied, 106 patients underwent surgery for appendicitis (Table 1). Patients' ages ranged between 14 and 92 years (mean 49, median 50 years), and 61 (58%) patients were men. Bacterial culture was positive in 53 cases (50%). The WBC count and CRP ranged between 2,800 and 24,100/μl (mean 12,400/μl, median 12,500/μl) and between 0 and 30.9 mg/dl (mean 4.5 mg/dl, median 0.6 mg/dl), respectively.

In all patients, intravenous antibiotics were administered from the day of admission. The initial antibiotic was carbapenem in 46 (43%), cephem (CEPs) with or without metronidazole (MNZ) in 59 (56%), and tazobactam/piperacillin (TAZ/PIPC) in 1 (1%). Of the cases in which CEPs were selected, 20 were third- or fourth-generation cephalosporins

Table 2. Cultured Strains of Aerobic Bacteria.

Bacteria	Number of strain (number of case)	Susceptibility				
	N = 46	TAZ/PIPC	CMZ	3rd/4th CEPs	Carbapenem	Fluoroquinolone
E. coli	21 (19)	21/21	21/21	17/21 (81%)	21/21	15/21 (71%)
ESBL producer	4/21 (4)	4/4	4/4	0/4	4/4	1/4 (25%)
Fluoroquinolone resistant	6/21 (6)	6/6	6/6	3/6	6/6	0/6
Enterococcus	14 (14)	14/14	—	—	6/14 (43%)	14/14
Streptococcus	11 (11)	11/11	—	11/11	11/11	11/11
Klebsiella	5 (5)	5/5	5/5	5/5	5/5	5/5
Pseudomonas	3 (3)	3/3	0/3	3/3	2/3	3/3

TAZ/PIPC tazobactam/piperacillin, *CMZ* cefmetazole, *3rd/4th CEPs* 3rd- or 4th-generation cephem

(in combination with MNZ) in 12, and 37 were CMZ. The carbapenem usage rate was 76% during the period between 2014 and 2017, but it dropped to 22% since 2018. There was no difference in the trends of strains identified by bacterial culture between these two periods.

The preoperative in-hospital waiting period ranged between 0 and 11 days (mean 2 days, median 2 days). Preoperative antibiotics were given at least once to 17 cases who underwent surgery within 24 h of their visit. Three cases were clinically judged to be exacerbated or unable to wait based on their physical findings during the in-hospital waiting period and required emergency surgery. Meropenem (MEPM) was administrated from the start of treatment since these three cases had poor risk or localized peritonitis. One case underwent surgery 12 h after admission, and the remaining two underwent surgery on the second day. A total of 72 cases (68%) underwent laparoscopic appendectomy, and 29 (27%) underwent open appendectomy. Ileocecal resection was required in five cases (5%). Considering intraoperative and pathological findings, 43 cases were diagnosed with complicated appendicitis, including 10 with perforations, 11 with abscess formations, and 33 with histological necrosis of the appendix. Surgical site infection occurred in three cases. All of them were residual abscesses and required conservative treatment with antibiotics.

Overall, bacterial cultures were positive in 53 cases (50%) (Table 2). The culture-positive rate was 44% (28/63) in simple appendicitis and 63% (27/43) in complicated appendicitis. The positive rate increased from 39% to 58% since 2018. *Escherichia coli*, *Enterococcus, Streptococcus*, *Klebsiella*, and *Pseudomonas* were identified in 24 (45%), 17 (32%), 12 (23%), 7 (13%), and 6 (11%) cases, respectively. Two strains of *E. coli* were identified in two cases. Four strains (15%) of *E. coli* were ESBL producers, and 7 (27%) were fluoroquinolone resistant. Twenty-two strains of anaerobic bacteria were detected in 15 (28%) cases. The number of cultured strains of *Bacteroides*, *Clostridium*, *Peptostreptococcus*, and *Fusobacterium* was 11, 3, 3, and 2, respectively. Two strains of *Bacteroides* were identified in one case. *Bacillus*, *Eubacterium*, *Achromobacter*, *Serratia*, *Eikenella*, and *Citrobacter* were also identified, but they were excluded from this study, because it was unclear that they were causative of appendicitis and should be the target of antimicrobial therapy. No significant difference was observed in the strains cultured between simple appendicitis and complicated appendicitis using Fisher's exact test. However, the culture-positive rates of anerobic bacteria in simple and complicated appendicitis were 17% and 42%, respectively, and the rate tended to be higher in complicated appendicitis ($p = 0.068$). In the three exacerbated cases, bacterial cultures were positive, with *Bacteroides* identified in two cases that were pathologically gangrenous appendicitis. The remaining case was pathologically phlegmonous appendicitis, and *Pseudomonas* was identified.

Overall, 15% (4/26) of the *E. coli* were ESBL producers, and 27% (7 cases) were fluoroquinolone resistant. Other aerobic bacteria showed no problematic antibiotic resistance. All bacteria in this group were susceptible to CMZ except *Pseudomon*as.

Table 3 presents the results of susceptibility tests. In the anaerobic group, 59% and 82% were susceptible to clindamycin (CLDM) and CMZ; 64% of *Bacteroides* (8/11) and 33% of *Clostridium* (1/3) showed CLDM resistance. The CMZ resistance rate of *Bacteroides* was 36% (4/11). Other anaerobic bacterial strains were susceptible to CMZ. A strain of *Klebsiella* was resistant to carbapenem. Eight strains of enterococcus were not susceptible to carbapenem and were thought to have natural resistance. Information about susceptibility to MNZ was not available in this study, because it was not included in the antibiotic susceptibility test kit during the study period.

Discussion

Acute appendicitis is one of the most common abdominal surgical emergencies. Urgent operation is always required, but in stable patients, an in-hospital delay of 12-24 h will not increase the risk of perforation or of poor out-

Table 3. Cultured Strains of Anerobic Bacteria.

	Number of strain (number of case)	Susceptibility			
		Carbapenem	TAZ/PIPC	CLDM	CMZ
Bacteroides	11 (10)	11/11 (100%)	11/11 (100%)	3/11 (27%)	7/11 (63%)
Peptostreptococcus	3 (3)	3/3	3/3	3/3	3/3
Clostridium	3 (3)	3/3	3/3	2/3 (67%)	3/3
Fusobacterium	2 (2)	2/2	2/2	2/2	2/2
Shewanella	1 (1)	1/1	1/1	1/1	1/1
Enterobacter	1 (1)	1/1	1/1	1/1	1/1
Prevotella	1 (1)	1/1	1/1	1/1	1/1
	22 (15)	22/22 (100%)	22/22 (100%)	13/22 (59%)	18/22 (82%)

TAZ/PIPC tazobactam/piperacillin, *CLDM* clindamycin, *CMZ* cefmetazole

comes[7,8]. However, given the capacity for emergency surgery or human and physical resources, early surgery is not always feasible. In the present study, 35% (33 cases) were operated after an in-hospital stay of 3 or more days.

The choice of initial antibiotics during the in-hospital waiting period is important. The target bacteria often remain unknown when the initial antibiotic is selected, so that patients are treated empirically without culture data. However, inappropriate antibiotic selection could lead to progression to general peritonitis or perforation during the preoperative in-hospital period, which then requires emergency surgery.

Guidelines accepted worldwide, such as SIS-IDSA[5] and the WSES guideline[6], recommend beta-lactam/beta-lactamase inhibitor combinations, third-/fourth-generation CEPs, or fluoroquinolone combined with MNZ or ertapenem (ETP) for normal-risk, non-perforated patients. ETP is not commercially available in Japan. The frequency of ESBL producers and quinolone-resistant *E. coli* is reported to be high in Japan and Asia, so that CEPs or these agents are often ineffective. Therefore, these guidelines cannot be applied in Japan and Asia. In 2015, the WHO adopted the antimicrobial resistance (AMR) Global Action Plan (GAP)[9]. The prevalence of ESBL in the West Pacific and Southern Asia (46%, 22%) is reported to be higher than that in Europe and the Americas (4% and 2%)[10]. The proportion of fluoroquinolone-resistant *E. coli* in Japan was 37.4% in 2015 and 38.3% in 2016[10]. In Asia, the proportion is reported to be relatively higher (6%-33%) than in other regions (Europe 1%-23%, North America 3%-9%)[11].

The frequency of ESBL producers and the proportion of fluoroquinolone-resistant *E. coli* were not as high as described in previous studies. However, their frequencies in the present study, about 15% and 30%, respectively, were not low. In cases where ESBL-producer or fluoroquinolone-resistant *E. coli* is associated with appendicitis, incorrect initial antibiotic selection may interfere with in-hospital waiting. Third- and fourth-generation CEPs or fluoroquinolone-based regimens seem to not be appropriate as a first choice in Japan or other Asian countries.

Culture results may not directly reflect the causative organism, since it is difficult to obtain a sample before antibiotic administration. Furthermore, the pathogenic mechanism of appendicitis remains unknown, so the cultured organism and the causative organism may not coincide. For these reasons, it is quite difficult to identify the true causative organism. The increase in the culture-positive rate in the latter reviewed period may be due to the reduction of MEPN utilization. However, it did not appear that postoperative complication, including surgical site infection, increased during this period.

Broad-spectrum agents such as carbapenem or TAZ/PIPC may be required for very limited cases during the waiting period before operation in appendicitis. The main targets for appendicitis are considered to be facultative and aerobic Gram-negative organisms and anaerobic organisms[12]. Based on the present results, these organisms were almost completely susceptible to MEPN and TAZ/PIPC. However, from the perspective of AMR GAP, abuse of these agents must be avoided. On the other hand, CEPs or fluoroquinolone combined with MNZ, accepted as the global standard, is not always effective in Asia due to the high proportion of antimicrobial-resistant *E. coli*.

CMZ or another cephamycin can be a promising candidate as an initial antibiotic for appendicitis in countries where it is commercially available and with high ESBL-producing and fluoroquinolone-resistant *E. coli*. CMZ is an antibiotic that is classified in the cephamycin group. It has a narrower spectrum than carbapenems, but it is effective against ESBL producers[13]. It is known to show good activity against *Bacteroides*, *Clostridium*, and anaerobic Gram-positive cocci[14]. CMZ was active against all ESBL-producing and fluoroquinolone-resistant *E. coli* strains in the present study. Against anaerobic bacteria identified in the present study, the susceptibility rate to CMZ was above 80% and proved higher than that to CLDM. From the perspective of reducing carbapenem use, TAZ/PIPC may be considered for severe or high-risk cases, and CMZ may be considered as monotherapy for general risk cases.

Conclusion

CMZ demonstrated complete activity against ESBL-producing and fluoroquinolone-resistant *E. coli.* The susceptibility of anaerobic bacteria was also relatively high. Though the present study was based on a retrospective case series, and the result is not conclusive, CMZ may be considered a first-choice drug during the in-hospital waiting period for appendectomy in cases with average risk in whom *Pseudomonas* infection is unlikely to be a problem.

Conflicts of Interest

There are no conflicts of interest.

Author Contributions

Shungo Yukumi, Kei Ishimaru, Hideaki Suzuki, Masamitsu Morimoto, Chika Sato, and Yukiyo Kaneko wrote the main text. Shungo Yukumi and Kei Ishimaru prepared Table 1-3. All authors checked the entire manuscript.

Approval by Institutional Review Board (IRB)

Approval code; 04-21 Ehime Medical Center

References

1. Stewart B, Khanduri P, McCord C, et al. Global disease burden of conditions requiring emergency surgery. Br J Surg. 2014 Jan; 101 (1): e9-22.
2. Decadt B, Sussman L, Lewis MP, et al. Randomized clinical trial of early laparoscopy in the management of acute non-specific abdominal pain. Br J Surg. 1999 Nov; 86(11): 1383-86.
3. United Kingdom National Surgical Research Collaborative, Bhangu A. Safety of short, in-hospital delays before surgery for acute appendicitis: multicentre cohort study, systematic review, and meta-analysis. Ann Surg. 2014 May; 259(5): 894-903.
4. Drake FT, Mottey NE, Farrokhi ET, et al. Time to appendectomy and risk of perforation in acute appendicitis. JAMA Surg. 2014 Aug; 149(8): 837-44.
5. Solomkin JS, Mazusuki JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Disease Society of America. Clin Infect Dis. 2010 Jan; 50 (2): 133-64.
6. Sartelli M, Chichom-Mefire A, Labricciosa FM, 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 Jul; 12:29.
7. van Dijk ST, van Dijk AH, Dijkgraaf MG, et al. Meta-analysis of in-hospital delay before surgery as a risk factor for complications in patients with acute appendicitis. Br J Surg. 2018 Jul; 105(8): 933-45.
8. Alore EA, Ward JL, Todd SR, et al. Population-level outcomes of early versus delayed appendectomy for acute appendicitis using the American College of Surgeons National Surgical Quality Improvement Program. J Surg Res. 2018 Sep; 229:234-42.
9. Takerahara F, Nishiura H. Global action plan on antimicrobial resistance. BMC Public Health. 2019 Apr; 19(1): 426.
10. Karanika S, Karantanos T, Arvanitis M, et al. Fecal colonization with extended-spectrum beta-lactamase-producing enterocbacteriaceae and risk factors among healthy individuals. Clin Infect Dis. 2016 Aug; 63(3): 310-8.
11. Stapleton AE, Wagenlehner FME, Mulgirigama A, et al. Escherichia coli resistance to fluoroquinolones in community-acquired uncomplicated urinary tract infection in women: A systematic review. Antimicrob Agents Chemother. 2020 Sep; 64(10).
12. Jeon HG, Ju HU, Kim GY, et al. Bacteriology and changes in antibiotic susceptibility in adults with community-acquired perforated appendicitis. PLOS ONE. 2014 Oct; 9(10): e111144.
13. Fukuchi T, Iwata K, Kobayashi S, et al. Cefmetazole for bacteremia caused by ESBL-producing Enterobacteriaceae comparing with carbapenems. BMC Infect Dis. 2016 Aug; 16(1): 427.
14. Cornick NA, Jacobus NV, Gorbach SL. Activity of cefmetazole against anaerobic bacteria. Antimicrob Agents Chemother. 1987 Dec; 31(12): 2010-2.