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

Shungo Yukumi, Kei Ishimaru, Hideaki Suzuki, Masamitsu Morimoto, Chika Sato, Yukiyo Kaneko and Yoshikazu Kubo

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

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
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%), cepham (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

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**Table 1.** Patient Data.

| Procedure                  | 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
Two strains of aerobic bacteria were detected in 15 (28%) cases. The number of cultured strains of aerobic bacteria showed no problematic antibiotic resistance. All bacteria in this group were susceptible to CMZ except Clostridium, 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 anaerobic 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 Pseudomonas.

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-

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**Table 2. Cultured Strains of Aerobic Bacteria.**

| Bacteria            | Number of strain (number of case) | 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
resistant. In cases where ESBL-producer or fluoroquinolone-positive cocci are not commercially available in Japan, 30% were not described in previous studies. However, their frequencies in Japan or other Asian countries.

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.

### Table 3. Cultured Strains of Anaerobic Bacteria.

| Bacteroides | Peptostreptococcus | Clostridium | Fusobacterium | Shewanella | Enterobacter | Prevotella |
|-------------|--------------------|------------|---------------|------------|--------------|-----------|
| 3 (3)       | 3 (3)              | 2 (2)      | 1 (1)         | 1 (1)      | 1 (1)        | 22 (15)   |
| 11/11 (100%)| 3/3                | 3/3        | 1/1           | 1/1        | 1/1          | 22/22 (100%)|
| 11/11 (100%)| 3/3                | 3/3        | 1/1           | 1/1        | 1/1          | 22/22 (100%)|
| 3/11 (27%)  | 2/3 (67%)          | 3/3        | 1/1           | 1/1        | 1/1          | 13/22 (59%)|
| 7/11 (63%)  | 3/3                | 3/3        | 1/1           | 1/1        | 1/1          | 18/22 (82%)|

**Susceptibility**

| Carbapenem | TAZ/PIPC | CLDM | CMZ |
|-------------|----------|------|-----|
| 11/11 (100%)| 3/3      | 3/3  | 3/3 |
| 11/11 (100%)| 3/3      | 3/3  | 3/3 |
| 3/11 (27%)  | 2/3 (67%)| 3/3  | 3/3 |
| 7/11 (63%)  | 3/3      | 3/3  | 3/3 |

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

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