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

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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
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 1. Patient Data.

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

WBC white blood cell count, CRP C-reactive protein
Bacteria | Number of strain (number of case) | TAZ/PPC | 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
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/PPC tazobactam/piperacillin, CMZ cefmetazole, 3rd/4th CEPs 3rd- or 4th-generation cepheid

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-
resistant low. In cases where ESBL-producer or fluoroquinolone-
positive cocci[14]. CMZ was active against all ESBL-producing and fluoroquinolone-resistant E. coli strains in the
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.

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 cephemycan 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 cephemycin 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].

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.

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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