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Original Article

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Optimal First-Line Antibiotic Treatment for Pediatric Complicated Appendicitis Based on Peritoneal Fluid Culture

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ABSTRACT

Purpose: Consensus is lacking regarding the optimal antibiotic treatment for pediatric complicated appendicitis. This study determined the optimal first-line antibiotic treatment for pediatric patients with complicated appendicitis based on peritoneal fluid cultures.
Methods: This retrospective study examined the cases of pediatric patients who underwent appendectomy for complicated appendicitis at our institution between 2013 and 2019. Peritoneal fluid specimens obtained during appendectomy were cultured for the presence of bacteria.
Results: Eighty-six pediatric patients were diagnosed with complicated appendicitis. Of them, bacteria were identified in 54 peritoneal fluid samples. The major identified bacteria were *Escherichia coli* (n=36 [66.7%]), *Bacteroides fragilis* (n=28 [51.9%]), *α-Streptococcus* (n=25 [46.3%]), *Pseudomonas aeruginosa* (n=10 [18.5%]), *Enterococcus avium* (n=9 [16.7%]), *γ-Streptococcus* (n=9 [16.7%]), and *Klebsiella oxytoca* (n=6 [11.1%]). An antibiotic susceptibility analysis showed *E. coli* was inhibited by sulbactam/ampicillin in 43.8% of cases versus cefmetazole in 100% of cases. Tazobactam/piperacillin and meropenem inhibited the growth of 96.9-100% of the major identified bacteria. *E. coli* (100% vs. 84.6%) and *P. aeruginosa* (100% vs. 80.0%) were more susceptible to amikacin than gentamicin.
Conclusion: Tazobactam/piperacillin or meropenem is a reasonable first-line antibiotic treatment for pediatric complicated appendicitis. In the case of aminoglycoside use, amikacin is recommended.

Keywords: Antibiotics; Complicated appendicitis; Culture; Pediatric; Peritoneal fluid

INTRODUCTION

Complicated appendicitis (CA) is the most common cause of pediatric intra-abdominal infections (IAI) outside the neonatal age group [1]. Antibiotic treatment for CA is used to reduce postoperative infectious complications, such as wound infection and intra-abdominal abscess (IAA). Moreover, it is important for the conservative management of interval appendectomy. However, consensus is lacking regarding optimal antibiotic treatment for

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Conflict of Interest
The authors have no financial conflicts of interest.

pediatric CA. In addition, the appropriate antibiotic treatment for pediatric CA can change depending on the era and the patient's residential area owing to the transition of pathogenic bacterial species or antibiotic susceptibility. Based on the results of intraoperative peritoneal fluid cultures obtained in a Japanese institute, this study aimed to determine the appropriate first-line antibiotic treatment for pediatric CA.

MATERIALS AND METHODS

We retrospectively reviewed the medical records of pediatric patients who underwent appendectomy at University of Tsukuba Hospital between January 1, 2013, and December 31, 2019. Patients who underwent interval appendectomy, had a history of antibiotic treatment for appendicitis, or were aged ≥16 years were excluded. All resected appendices were evaluated histopathologically. We defined gangrenous appendicitis and perforated appendicitis as CA based on the histopathological examination results. In this study, we analyzed the results of peritoneal fluid culture, which included the identification and antimicrobial susceptibility of any bacteria present. We also evaluated the number of patients with CA who had postoperative infectious complications, including wound infection or IAA.

Appendicitis was diagnosed on physical, blood, and imaging examinations, which included ultrasonography and/or abdominal contrast-enhanced computed tomography.

We performed transumbilical laparoscopic-assisted appendectomy for all patients with appendicitis. When the surgery was difficult to complete using a single port through the umbilicus, we added ports in the lateral and/or lower abdomen. None of the patients required conversion to open laparotomy within the study period. A specimen of peritoneal fluid was collected intraoperatively using a swab or aspiration. The peritoneal fluid was then cultivated and examined for bacterial presence. Thereafter, the culture was subjected to antimicrobial susceptibility testing in our hospital's clinical laboratory. The bacteria were cultured on blood agar, chocolate agar, Columbia anaerobic agar, bromothymol blue lactate agar, and CHROMagar. The antimicrobial susceptibility tests were performed according to the criteria of the Clinical and Laboratory Standards Institute. In this study, bacteria were classified as resistant if the antimicrobial susceptibility test results indicated that they had intermediate susceptibility or resistance.

During this study period, we used cefmetazole as the first-line postoperative antibiotic treatment for patients with nonperforated appendicitis [2] and a combination of meropenem and amikacin as the first-line postoperative antibiotic treatment for patients with perforated appendicitis. Wound infection was defined as a superficial incisional surgical site infection (SSI) or a deep incisional SSI [3]. IAA was defined as an abscess that occurred postoperatively in the abdominal cavity and required prolonged antibiotic treatment and/or additional surgical intervention.

The study was conducted in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects by the Ministry of Health, Labour and Welfare of Japan in 2014, in compliance with the 1964 Declaration of Helsinki (revised in 2013), and with the approval of our local institutional review board (approval number: R02-116; July 16, 2020).

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RESULTS

A total of 306 patients underwent appendectomy. Of them, 54 were diagnosed with non-acute appendicitis (those who underwent interval appendectomy or had a history of treatment for appendicitis), while the other 252 were diagnosed with acute appendicitis. Of the latter, 166 were diagnosed with uncomplicated appendicitis on the histopathological examination, while the other 86 were diagnosed with CA (49 with perforated appendicitis, 37 with gangrenous appendicitis). Among the patients with CA, at least one bacterium was identified in the peritoneal fluid samples of 54 (**Fig. 1**). The median age of these 54 patients was 10 years (range, 1-15); 32 (59.3%) of them were male (**Table 1**). Some bacterial species, especially anaerobic species, could not be identified using the culture techniques.

Escherichia coli was the most frequently identified bacterium (36/54 patients [66.7%]). One specimen was identified as extended-spectrum beta-lactamase (ESBL)-producing *E. coli*. *Bacteroides fragilis* (28/54 patients [51.9%]), *α-Streptococcus* (25/54 patients [46.3%]), *Pseudomonas aeruginosa* (10/54 patients [18.5%]), *Enterococcus avium* (9/54 patients [16.7%]),

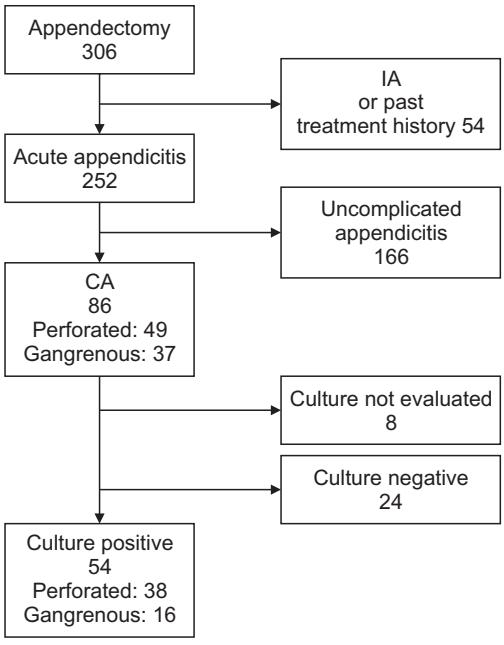

Fig. 1. Flow chart of patient groups.
CA: complicated appendicitis, IA: interval appendectomy.

Table 1. Demographic and clinical data of patients with complicated appendicitis

Patient data	Culture positive (n=54)	Culture negative (n=24)	Culture not evaluated (n=8)
Age (yr)	10 (1–15)	11 (5–15)	10.5 (5–14)
Sex			
Male	32 (59.3)	17 (70.8)	5 (62.5)
Female	22 (40.7)	7 (29.2)	3 (37.5)
Histopathological classification			
Perforated	38 (70.4)	3 (12.5)	2 (25.0)
Gangrenous	16 (29.6)	21 (87.5)	6 (75.0)
Infectious complications			
Wound infection	2 (perforated, 2; gangrenous, 0)	1 (perforated, 0; gangrenous, 1)	0
Intra-abdominal abscess	9 (perforated, 8; gangrenous, 1)	0	0

Values are presented as median (range), number (%), or number only.

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Table 2. Distribution of bacterial species in 54 patients with complicated appendicitis

Species	Positive patients
Escherichia coli	36 (66.7)
Bacteroides fragilis	28 (51.9)
α-Streptococcus	25 (46.3)
Pseudomonas aeruginosa	10 (18.5)
Enterococcus avium	9 (16.7)
γ-Streptococcus	9 (16.7)
Klebsiella oxytoca	6 (11.1)
β-Streptococcus	4 (7.4)
Haemophilus spp.	3 (5.6)
Klebsiella pneumoniae	2 (3.7)
Morganella morganii	2 (3.7)
Staphylococcus aureus	2 (3.7)
Others	9 (16.7)

Values are presented as number (%).

γ-Streptococcus (9/54 patients [16.7%]), and *Klebsiella oxytoca* (6/54 patients [11.1%]) were the major identified bacteria (**Table 2**).

The results of the antimicrobial susceptibility test of the seven major identified bacteria are shown in **Table 3**. For *E. coli*, the most frequently identified bacteria, cefmetazole (43/43 bacteria [100%]), tazobactam/piperacillin (31/32 bacteria [96.9%]), meropenem (33/33 bacteria [100%]), and amikacin (39/39 bacteria [100%]) demonstrated good inhibition of bacterial growth. The ESBL-producing *E. coli* were resistant to tazobactam/piperacillin. In contrast, sulbactam/ampicillin poorly inhibited the growth of *E. coli* (14/32 bacteria [43.8%]). Sulbactam/ampicillin (32/33 bacteria [97.0%]) and tazobactam/piperacillin (32/33 bacteria [97.0%]) inhibited *B. fragilis* growth. However, clindamycin poorly inhibited *B. fragilis* growth (11/36 bacteria [30.6%]) despite clindamycin being commonly used to suppress anaerobic bacteria. Tazobactam/piperacillin and meropenem inhibited the growth of 96.9-100% of the major identified bacteria. In terms of aminoglycoside, some bacteria were more susceptible to amikacin than gentamicin, including *E. coli* (amikacin 100% vs. gentamicin 84.6%) and *P. aeruginosa* (amikacin 100% vs. gentamicin 80%).

In terms of postoperative infectious complications in patients with CA, three of 86 patients (3.5%) had wound infections, while nine (10.4%) had IAA (**Table 1**). With regard to postoperative infectious complications of perforated appendicitis, wound infection occurred in two of 49 patients (4.1%), while IAA occurred in eight of 49 patients (16.3%).

Table 3. Antibiotic susceptibility of major identified bacteria in 54 patients with complicated appendicitis

Bacteria	Sulbactam/ampicillin	Tazobactam/piperacillin	Cefmetazole	Clindamycin	Meropenem	Amikacin	Gentamicin
Escherichia coli	14/32 (43.8)	31/32 (96.9)	43/43 (100)	2/2 (100)	33/33 (100)	39/39 (100)	33/39 (84.6)
Bacteroides fragilis	32/33 (97.0)	32/33 (97.0)	25/33 (75.8)	11/36 (30.6)	4/4 (100)	-	-
α-Streptococcus	24/25 (96.0)	-	-	12/19 (63.2)	27/27 (100)	-	-
Pseudomonas aeruginosa	R	11/11 (100)	R	R	11/11 (100)	10/10 (100)	8/10 (80.0)
Enterococcus avium	2/2 (100)	2/2 (100)	R	R	-	R	R
γ-Streptococcus	12/12 (100)	-	-	5/7 (71.4)	7/7 (100)	-	-
Klebsiella oxytoca	3/5 (60.0)	5/5 (100)	6/6 (100)	-	6/6 (100)	6/6 (100)	6/6 (100)

Values are presented as number (%).
R: natural resistance to antibiotics, -: data not evaluated.

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DISCUSSION

In the 1980s and 1990s, the administration of triple antibiotics (ampicillin, gentamycin, and clindamycin) was the "gold standard" for the treatment of CA [4-9]. Thereafter, the use of imipenem [10], ceftriaxone [11], and tazobactam/piperacillin [12] were reported. Two guidelines for the treatment of pediatric IAI, including CA, have been published to date [13,14]. In 2010, Solomkin et al. [13] recommended that broad-spectrum antimicrobial treatments for pediatric patients with complicated IAI include an aminoglycoside-based treatment, a carbapenem (imipenem, meropenem, or ertapenem), a β-lactamase-inhibitor/β-lactam combination (tazobactam/piperacillin or clavulanate/ticarcillin), or an advanced-generation cephalosporin (cefotaxime, ceftriaxone, or cefepime) with metronidazole. In 2017, Mazuski et al. [14] recommended cefotaxime, ceftriaxone plus metronidazole, or ertapenem as empiric antimicrobial therapy for community-acquired IAI in low-risk pediatric patients older than one month. They also recommend tazobactam-piperacillin, imipenem, or meropenem for empiric antimicrobial therapy of community-acquired IAI in high-risk pediatric patients older than one month. Thus, antibiotic treatment for pediatric patients with CA has changed over time, and a fixed treatment regimen has not been established. The purpose of perioperative antibiotic treatment for CA is to reduce infectious complications, including wound infection and IAA. The analysis of peritoneal fluid culture in patients with CA was reasonable because bacteria of postoperative infected wounds and IAA can also affect peritoneal fluid. Hopkins et al. [15] showed a significant relationship between resistance to empirical antimicrobials and postoperative infection in adults. The distribution of bacterial species and their antimicrobial resistance in patients with CA can differ depending on the era and the residential areas. Therefore, peritoneal fluid culture is useful for epidemiological surveys and first-line antibiotic therapy reevaluations [16].

Based on the results of this study, we determined the optimal antibiotic treatment for pediatric CA. In terms of the frequency of identified bacteria from peritoneal fluid cultures, antibiotics preferentially inhibited the growth of seven species (*E. coli*, *B. fragilis*, *α-Streptococcus*, *P. aeruginosa*, *E. avium*, *γ-Streptococcus*, and *K. oxytoca*) that were identified with high frequency in patients with CA (**Table 2**). In terms of natural resistance of *P. aeruginosa* and *E. avium* to antibiotics, it is inappropriate to administer a single dose of cefmetazole or third-generation cephalosporins, such as ceftriaxone or sulbactam/ampicillin, which cannot inhibit their growth. On our antibiotic susceptibility test, only 43.8% of *E. coli* samples, the most frequently identified bacteria in this study, were susceptible to sulbactam/ampicillin. Therefore, we believe that sulbactam/ampicillin cannot play a key role in the treatment of pediatric CA. In contrast, tazobactam/piperacillin inhibited the growth of *E. coli* except for the ESBL-producing *E. coli* samples. Moreover, tazobactam/piperacillin demonstrated good ability to inhibit the growth of other major identified bacteria. Meropenem inhibited the growth of all of the major identified bacteria except *E. avium*, whose susceptibility to meropenem was not evaluated in this study. Therefore, we concluded that tazobactam/piperacillin or meropenem can play a key role in the treatment of pediatric CA. Cefmetazole inhibited the growth of 100% of the *E. coli* samples. In Japan, cefmetazole is widely used as a perioperative antibiotic to prevent SSI in colorectal surgery [17,18]. Therefore, we believe that cefmetazole can play a key role in the treatment of pediatric uncomplicated appendicitis. In terms of aminoglycoside, amikacin better inhibited the growth of *E. coli* (100%) and *P. aeruginosa* (100%) than gentamicin (84.6% of *E. coli*, 80% of *P. aeruginosa*). Furthermore, from the viewpoint of reducing drug-induced hearing loss as a side effect of aminoglycoside antibiotics, we concluded that amikacin is superior to gentamicin when an

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aminoglycoside is selected for the treatment of pediatric CA. Clindamycin poorly inhibited the growth of *B. fragilis* (30.6%), the major anaerobic bacterial species identified in our study. Moreover, according to the nationwide surveillance of parental antibiotics in Japan in 2012, the pathogenic anaerobic bacteria *B. fragilis*, *Prevotella* spp., *Peptostreptococcus* spp., and *Fusobacterium* spp. were 53.7%, 34.7%, 13.2%, and 5.1% resistant to clindamycin, respectively [19]. Therefore, we stopped the use of clindamycin as a first-line antibiotic for the treatment of pediatric CA. The main purpose of postoperative antibiotic therapy for pediatric CA is to reduce the incidence of postoperative infections, particularly IAA. Several studies have reported the rate of postoperative IAA in patients with pediatric perforated appendicitis. In those reports, the postoperative incidence of IAA was 13-30% in cases of pediatric perforated appendicitis [20-22].

In our study, we used a combination of meropenem and amikacin as the first-line postoperative antibiotic treatment for treating patients with perforated appendicitis. Combination antibiotic therapy with carbapenem plus aminoglycoside is sometimes used in pediatric medicine with the expectation of synergistic effects [23]. The rate of IAA was 10.4% for CA and 16.3% for perforated appendicitis, which is lower than that reported in previous studies. In this decade, several studies have reported the antimicrobial resistance of bacteria in pediatric patients with CA based on intraoperative peritoneal fluid culture [16,22,24-26]. In those reports, *E. coli*, *Streptococcus*, *P. aeruginosa*, *Enterococcus* spp., and *B. fragilis* were frequently identified. The distribution of these major identified bacteria was similar to our results. In those studies, the rate of ESBL-producing *E. coli* among all identified *E. coli* species was 1.6-12.5%. In addition, *P. aeruginosa* was identified in the peritoneal fluid cultures of 4.3-32%. Therefore, based on the results of their studies, the authors suggested administering empiric antibiotic therapy for the treatment of pediatric CA.

In this study, we were unable to identify all the bacteria by their species; some, particularly anaerobic bacteria, were identified only by their Gram staining pattern. Moreover, the majority of microbial species in the human gastrointestinal tract are not cultivable [27]. Some authors recently reported on the microbiome of the appendix in patients with appendicitis using a culture-independent approach [27-30]. In those reports, bacteria that are normally found in the oral cavity were found in the appendix of a patient with appendicitis. In particular, *Fusobacterium* was suggested as an etiological agent of appendicitis [28-30]. We will further investigate the microbiome involved in appendicitis using a culture-independent approach to improve the treatment and clarify the etiology of pediatric appendicitis. Another limitation of this study was that we did not consider the problem of inducing drug-resistant bacteria as an adverse effect of broad-spectrum antibiotics. The use of these antibiotics can lead to the emergence of drug-resistant bacteria. Strict adherence to appropriate antibiotic indications, dosage, and duration of administration is needed. Moreover, we could not evaluate the significance of metronidazole because of the lack of resources in our institution. Finally, the study was retrospective in nature and comprised a small population because it was conducted at a single institute. However, because it was a single institutional study, we were able to collect high-quality retrospective data from the patients' medical charts. For example, we could distinguish between gangrenous and perforated appendicitis from CA, and we used a consistent procedure for the diagnosis, sample collection, and treatment during the study period.

In conclusion, we retrospectively reviewed the results of the peritoneal fluid cultures obtained intraoperatively from pediatric patients with CA. Based on our study results, piperacillin/

tazobactam or meropenem was a reasonable first-line antibiotic treatment for pediatric CA. In the case of aminoglycoside use, amikacin is recommended.

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