Antibiotic Administration Can Be an Independent Risk Factor for Therapeutic Delay of Pediatric Acute Appendicitis

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Objectives: Little is known about the relationship between prior treatment with antibiotics and delay of diagnosis and treatment in pediatric acute appendicitis (AA). We have defined a situation requiring more than 48 hours from the onset of symptoms to surgery in pediatric AA as "therapeutic delay." The aim of this study was to investigate the risk factors contributing to therapeutic delay in pediatric AA.

Methods: We conducted a retrospective chart review of AA children operated on between 2003 and 2008 at tertiary-care pediatric and perinatal hospitals. Univariate and multivariate logistic regressions were analyzed to determine independent risk factors of therapeutic delay in pediatric AA.

Results: The duration between the onset of symptoms and surgery was more than 48 hours (therapeutic delay) in 50 patients (25%, group A) and 48 hours or less in 151 patients (75%, group B). The patients in group A had a significantly higher frequency of diarrhea (48% vs 12%; $P < 0.0001$). The percentages of children who had previously received antibiotics were more frequent in group A (46% vs 8%; $P < 0.0001$). The median C-reactive protein levels (72 vs 7 mg/L; $P < 0.0001$) and frequency of perforation (60% vs 13%; $P < 0.0001$) were statistically significantly higher in group A. A multivariate analysis demonstrated that the independent risk factors of therapeutic delay were history of receiving antibiotics (odds ratio [OR], 5.8; 95% confidence interval [CI], 2.3–15.5), diarrhea (OR, 5.2; 95% CI, 2.1–13.1), and elevated C-reactive protein levels (OR, 4.5; 95% CI, 1.9–10.8).

Conclusions: Prior treatment with antibiotics was an independent risk factor for therapeutic delay in pediatric AA.

Key Words: acute appendicitis, antibiotics, therapeutic delay

(*Pediatr Emer Care* 2012;28: 792–795)

In children, acute appendicitis (AA) is the most common cause of acute abdomen requiring emergency surgery.[1] It is more difficult to diagnose in children than in adults. Mistaken diagnosis and therapy in children between 6 and 17 years of age with AA frequently result in litigation against emergency physicians.[2,3] Although AA should have a favorable outcome, the delay in diagnosis can lead to perforated appendicitis, increased morbidity, complications, and length of hospital stay.[4]

Many previous studies have revealed risk factors of perforation in children, with more than a 36- to 48-hour delay of diagnosis after AA onset, including diffuse abdominal tenderness, elevated white blood cell (WBC) counts or C-reactive protein (CRP) levels, and abscess or fecalith formation on radiological findings.[5–10] However, the reasons for the delay in diagnosis and treatment of AA in children have not been clarified. We have defined a situation requiring more than 48 hours from the onset of symptoms to surgery in pediatric AA as "therapeutic delay" and sought to investigate the risk factors associated with it.

METHODS

Setting

The National Center for Child Health and Development is a tertiary-care pediatric and perinatal hospital in Tokyo. Approximately 35,000 children annually visit the emergency department (ED) of the hospital. Emergency department physicians, a radiologist, a surgeon, and anesthesiologists are on duty 24 hours a day.

Patients

The study enrolled 201 children, aged 2 to 17 years, who visited our ED and received emergency appendectomy between March 2002 and April 2008. We divided the patients into the following 2 groups according to the duration from onset to surgery: group A (>48 hours) and group B (≤48 hours).

Acute appendicitis was clinically diagnosed based on physical examinations by surgeons and ultrasonographic findings by radiologists. Computed tomography (CT) was conducted in 49 cases. Definitive diagnosis was made according to operative and pathological findings.

Data Collection

This retrospective study was approved by the ethical committee of our hospital. We extracted the following information from medical records: patient characteristics (age and sex), medical history (presence or absence of abdominal pain, diarrhea, and vomiting), the day of presentation (weekday or weekend), antibiotic administration, physical findings, blood test results (WBC counts and CRP levels), diagnostic imaging findings, operative and pathological findings, duration of symptoms (from onset to surgery), and outcomes after operation (complications and length of hospital stay). When patients visited the ED more than once before surgery, data from the final visit were analyzed. The time of day when a physician initially examined a patient was precisely noted. The exact time of operation was determined from the surgical records.

All patients were examined by ultrasonography. Computed tomography scan was performed only when the appendix was not identified or intra-abdominal abscess was suspected after ultrasonography. Perforation of the appendix and abscess were determined through surgical operation and pathological examinations.

Statistical Analysis

Data were analyzed using JMP7 (SAS Institute Inc, Cary, NC). In univariate analysis, continuous variables were compared

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Disclosure: The authors declare no conflict of interest.

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ISSN: 0749-5161

by the Mann-Whitney test, and categorical variables by χ^2 analysis. A logistic regression was used to determine independent risk factors of therapeutic delay. The variables that were considered clinically important or proven to significantly correlate with therapeutic delay in univariate analysis were entered into the regression model for a multivariate analysis. Continuous variables were converted to categorical variables by using a cutoff point that maximized the Youden index. The Youden index yields the value that maximizes the sensitivity and specificity of any continuous variable, enabling choice of an appropriate cutoff point for dichotomization. Odds ratios were corrected to approximate relative risks using the Zhang method of correction. In addition, we conducted univariate analysis again, concerning the risk factor that was determined through multivariate analysis.

RESULTS

A total of 201 consecutive patients aged 2 to 17 years who received appendectomy were studied. Table 1 summarizes patient demographic characteristics, symptoms, and clinical findings. There were 50 patients (25%) whose duration of symptoms was more than 48 hours (group A) and 151 patients (75%) whose duration of symptoms (the duration from onset to surgery) was 48 hours or less (group B).

There was no statistical difference in the male-female ratio or the day of presentation, but the patients in group A were significantly younger than those in group B (median age, 9 vs 11 years; $P = 0.0094$). The frequency of abdominal pain was similar in both groups, but the frequency of diarrhea was higher in group A (48% vs 12%; $P < 0.0001$). The number of children who had previously received antibiotics was also significantly higher in group A (46% vs 8%; $P < 0.0001$). As for laboratory examinations, there was no difference in the median WBC counts, but the median CRP level was significantly higher in group A (72 vs 7; $P < 0.0001$). In the surgical findings, the frequency of perforation (60% vs 13%; $P < 0.0001$) and abscess formation (44% vs 3%; $P < 0.0001$) was significantly higher in group A. As clinical outcomes, the incidence of postoperative complications was higher in group A (22% vs 7%; $P = 0.0075$), and the average length of hospital stay in group A (median, 9 days) was significantly longer than that in group A (6 days; $P < 0.0001$).

The multivariate model found having initially received antibiotics, presence of diarrhea, and elevated CRP levels were the risk factors independently associated with therapeutic delay with statistical significance.

We further analyzed the influence of the most significant factor (ie, history of receiving antibiotics) by dividing patients into the following 2 groups: group C (having received antibiotics) and group D (no history of antibiotic treatment). The patients in group C were significantly younger and contained more girls than group D (median, 9 vs 11 years; $P = 0.01$). Although the frequency of abdominal pain and peritoneal signs was similar in both groups, the frequency of diarrhea was significantly higher in group C (41% vs 16%; $P = 0.0025$). The median CRP level was significantly higher in group C (mean, 7.4 vs 0.9; $P < 0.0001$), although there was no difference in median WBC count between the 2 groups. The number of patients whose appendix could not be identified by ultrasonography and who received CT scan was significantly larger in group C (44% vs 20%; $P = 0.0045$). Moreover, the occurrence of perforated appendicitis (50% vs 19%; $P = 0.0004$) and abscess formation (41% vs 7%; $P < 0.0001$) was higher in group C. Overall, duration of symptoms (median, 56 vs 25 hours; $P < 0.0001$) and length of hospital stay (median, 9 vs 6 days; $P = 0.0015$) were longer, and the postoperative complication rate was higher in group C (27% vs 7%; $P = 0.0014$) (Tables 2 and 3).

DISCUSSION

We set out to determine whether antibiotic administration before definitive diagnosis and history of diarrhea are possible risk factors for therapeutic delay in AA children. Some previous studies have suggested that a history of diarrhea may be a risk

TABLE 1. Characteristics of Patients With AA

	Group A >48 h (n = 50)	Group B ≤48 h (n = 151)	Total (n = 201)	*P*
Male	27 (54)	95 (62)	122 (60)	0.3166
Median age, y	9 (3–15)	11 (2–17)	11 (2–17)	0.0094
ED visits on weekend	9 (18)	31 (20)	40 (19)	0.8387
Abdominal pain as a primary symptom	42 (84)	140 (92)	182 (90)	0.0918
Diarrhea	24 (48)	18 (12)	42 (21)	<0.0001
Vomit	33 (66)	90 (60)	123 (61)	0.5045
Prior treatment with antibiotics	23 (46)	13 (8)	36 (17)	<0.0001
RLQ pain	27 (54)	91 (60)	118 (58)	0.5080
RLQ tenderness	37 (74)	128 (84)	165 (82)	0.0925
Peritoneal sign	43 (86)	137 (90)	180 (89)	0.4228
Median WBC count, $\times 10^9$/L	14 (3.2–24.2)	15 (6.8–27.7)	15 (3.2–27.7)	0.2795
Median CRP, mg/L	72 (0–360)	7 (0–23)	1.2 (0–360)	<0.0001
Appendix enlargement in US	37 (74)	127 (84)	164 (81)	0.1397
Rupture	30 (60)	20 (13)	50 (24)	<0.0001
Intra-abdominal abscess	22 (44)	6 (3)	28 (13)	<0.0001
Gangrenous appendicitis	31 (62)	54 (35)	85 (42)	0.0016
Complication	11 (22)	11 (7)	22 (10)	0.0075
Duration of hospital stay, d	9 (4–28)	6 (4–19)	7 (4–28)	<0.0001

Values are numbers (%) or median (range).

RLQ indicates right lower quadrant; US, ultrasonography.

TABLE 2. Adjusted Risk of Therapeutic Delay

Characteristics	Odds Ratio	95% Confidence Interval	*P*
Prior treatment with antibiotic	5.8	2.3–15.5	<0.01
Diarrhea	5.2	2.1–13.1	<0.01
CRP >50 mg/L	4.5	1.9–10.8	<0.01
Age <6 y	1.1	0.3–3.5	0.82
Abdominal pain as a primary symptom	0.8	0.2–3.4	0.83
RLQ tenderness	0.4	0.1–1.2	0.12

RLQ indicates right lower quadrant.

factor for diagnostic delay of AA in children. We additionally found that prior treatment with antibiotics was also a risk factor for therapeutic delay.

The prescription of antibiotics for pediatric outpatients in Japan differs fundamentally from patterns in other countries. In Japan, primary care physicians tend to frequently prescribe antibiotics for febrile pediatric patients. This is considered to be due to the Japanese nationwide insurance system, under which everyone has generally affordable access to antibiotic medication.[11] In addition, the O-157 outbreak in 1996 might be related to the antibiotic overprescription for children with diarrhea.[12]

Although a few studies have suggested some relationship between prior treatments with antibiotics and clinical diagnostic delay of AA, therapeutic delay has not been investigated. All of our patients received surgical treatment; therefore, diagnosis of AA was defined by pathological examinations of surgical specimen. Thus, the diagnosis of AA in this study can be more definitive than that of the previous studies. Taken together, the finding of this study can overcome the uninvestigated aspects of previous studies.[13–17]

We believed there were several reasons why prior treatment with antibiotics became a risk factor of therapeutic delay in pediatric AA. First, misdiagnosis of appendicitis could be considered. In the present study, children receiving antibiotics showed significantly higher frequency of diarrhea than did children not receiving antibiotics. It was difficult to distinguish whether children with preexisting diarrhea received antibiotics, or children had diarrhea because of antibiotics, because this study was a retrospective trial. However, several investigators have reported that acute gastroenteritis diarrhea is the most common misdiagnosis of AA. The presence of gastroenteritis evokes diarrhea, which may lead to misdiagnosis and diagnostic delay in AA children.[13–15] This study was conducted in a tertiary hospital, and most patients visited our ED after they had visited primary care clinics. The duration from the symptomatic onset to the ED visit was significantly longer, and the time to physician's referral or to the patient's ED visit was longer, in children receiving antibiotics. As a result, these atypical clinical courses caused a situation in which further laboratory or imaging studies and active observation with AA in mind were difficult to perform.[16]

The second possible reason was that antibiotics blunted the clinical signs of appendicitis. Some studies about diagnostic delay reported that the children receiving antibiotics present nonspecific symptoms and poorly localized signs, which delays diagnosis and leads to higher perforation and complication rates.[17–21] Furthermore, many studies comparing AA with perforation and without perforation reported differences in laboratory results (significantly elevated WBC count and CRP in perforated appendicitis), as well as clinical symptoms (iliac pain and peritoneal signs).[4–10,22] In our study, higher CRP levels were also observed in children receiving antibiotics, which strongly correlated with the higher incidence of gangrenous appendicitis and perforated appendicitis in children receiving antibiotics. However, there were no differences in clinical symptoms or signs (iliac pain and peritoneal sign) between children receiving antibiotics and those not receiving antibiotics. We therefore speculated that modification and even obfuscation

TABLE 3. Comparison of Patients Between With and Without Prior Treatment With Antibiotics

	Group C With Antibiotics (n = 36)	Group D Without Antibiotics (n = 165)	Total (n = 201)	*P*
Median age, y	9 (4–17)	11 (2–13)	11 (2–17)	0.0100
Male	16 (44)	106 (64)	122 (60)	0.0376
Diarrhea	15 (41)	27 (16)	42 (21)	0.0025
RLQ pain	21 (58)	97 (58)	118 (58)	1.0000
Peritoneal sign	34 (94)	146 (88)	180 (89)	0.3796
RLQ tenderness	30 (83)	135 (81)	165 (82)	1.0000
Median WBC count, $\times 10^9$/L	13 (3.4–25)	15 (3.2–27)	15 (3.2–27.7)	0.2163
Median CRP, mg/L	74 (0–190)	9 (0–360)	12 (0–36)	<0.0001
Identification of appendix in US	21 (58)	143 (86)	164 (81)	0.0002
CT	16 (44)	33 (20)	49 (24)	0.0045
Rupture	18 (50)	32 (19)	50 (24)	0.0004
Intra-abdominal abscess	15 (41)	13 (7)	28 (13)	<0.0001
Gangrenous appendicitis	24 (66)	61 (36)	85 (42)	0.0014
Complications	10 (27)	12 (7)	22 (10)	0.0014
Duration of hospital stay, d	9 (24)	6 (4–28)	7 (4–28)	0.0015
Duration from onset to ED visit, h	47 (2–435)	14 (0.5–240)	17 (0.5–435)	<0.0001
Duration from onset to surgery, h	56 (8–215)	25 (6–646)	27 (6–646)	<0.0001

Values are numbers (%) and median (range).

RLQ indicates right lower quadrant; US, ultrasonography.

of the clinical findings of appendicitis by antibiotics, which have been discussed in previous studies,[18–21] might have been involved in the present cases.

The third reason was related to the difficulty of diagnostic imaging. Children receiving antibiotics showed lower rates of ultrasonographic appendix identification and required significantly more CT scans than did children not receiving antibiotics. This might be because children receiving antibiotics had a higher incidence of appendix perforation and abscess formation. When the appendix was perforated and abscess was formed, identification of the appendix by ultrasonography becomes difficult. Furthermore, advanced perforated appendicitis showed clinical symptoms more representative of acute abdomen than AA, and the patients were required to be investigated by CT scan to determine the causes of acute abdomen. Children receiving antibiotics consequently required more imaging studies to establish a diagnosis of appendicitis.

Many risk factors related to perforation in pediatric appendicitis have been reported, and duration of symptoms for more than 36 to 48 hours (ie, therapeutic delay) has been identified as one of the important risk factors.[6,8,9,23] To the best of our knowledge, this is the first study that has investigated the risk factors of therapeutic delay and suggested that prior treatment with antibiotics is an independent risk factor, using univariate and multivariate analyses. The 3 reasons discussed above might be complexly intertwined in the background of therapeutic delay. We propose that it is important for physicians to consider the history of antibiotic therapy when children present clinical signs and symptoms of possible AA.

This study has some limitations. This was a retrospective study conducted in a tertiary-care pediatric hospital, and all patients were surgically treated cases. This may limit the generalizability of our findings. In addition, severe cases could be referred from other hospitals or clinics to our hospital intensively, and antibiotics could be used selectively in severe cases. Thus, it cannot be denied that antibiotics might be a confounding factor. Multicenter prospective studies are needed to eliminate these limitations.

In conclusion, we suggest that prior treatment with antibiotics is an independent risk factor of therapeutic delay in pediatric AA. Therefore, all pediatric physicians should investigate prior treatment with antibiotics when considering AA as a differential diagnosis. If a child is on antibiotics, close observation and further investigation should be performed.

ACKNOWLEDGMENTS

The authors thank Drs Shuichi Ito and Akihiko Saito for critical discussion and Dr Shunsuke Nosaka for radiological support and Drs Ryuta Suzuki, Yasutaka Kuniyoshi, and Minoru Tashiro for their contribution in the planning of this study. The authors also thank Prof J. Patrick Barron of the Department of International Medical Communication of Tokyo Medical University for his review of the manuscript.

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