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The efficacy of combined therapy with metronidazole and broad-spectrum antibiotics on postoperative outcomes for pediatric patients with perforated appendicitis

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Abstract

The aim of this study was to evaluate the efficacy of combined therapy with metronidazole and broad-spectrum antibiotics for patients with perforated appendicitis who underwent surgical intervention.

Broad-spectrum antibiotic therapy is warranted in the treatment of perforated appendicitis. Metronidazole has been used as anaerobic antimicrobial therapy. However, few studies about the use of metronidazole in perforated appendicitis have been reported.

The medical records of 249 patients treated with metronidazole combined with broad-spectrum antibiotics following perforated appendicitis surgery were reviewed retrospectively and compared with the medical records of 149 patients treated only with broad-spectrum antibiotics. Propensity score matching was performed to adjust for selected baseline variables. Clinical outcomes, including postoperative complications and length of hospital stay, were compared between the 2 groups.

No differences were found between the use of combined therapy with metronidazole and the use of solely broad-spectrum antibiotic agents with regard to postoperative duration of intravenous antibiotic treatment (6.8 ± 1.3 vs 7.9 ± 2.1 days, respectively, $P = .18$), inflammation variables at POD 5 (white blood cell [WBC] [risk ratio [RR], 1.06; 95% confidence interval [CI], 0.67–1.93, $P = .15$] and C-reactive protein [CRP] [RR, 1.18; 95% CI, 0.73–2.25, $P = .36$]) (Table 2), and the mean postoperative length of hospital stay (LOS) (RR, 0.68, 95% CI, 0.41–0.94, $P = .41$). There were also no differences in the incidence of postoperative complications, including the intra-abdominal or pelvic abscess rate (7[7.1%] vs 9[9.2%], respectively, $P = .40$), the incidence of wound infection (14 [14.3%] vs 15[15.3%], respectively, $P = .50$), and the 30-day readmission rate (9[9.2%] vs 12[12.2%], respectively, $P = .32$).

Regarding overall postoperative outcomes and complications, our study demonstrated no beneficial clinical effects of metronidazole administration in patients with perforated appendicitis who underwent surgical intervention. Therefore, metronidazole is not indicated when broad-spectrum antibiotics such as aminopenicillins with β-lactam inhibitors or carbapenems and select cephalosporins are used.

Abbreviations: CRP = C-reactive protein, ERT = ertapenem, LOS = length of hospital stay, PCT = procalcitonin, POD = postoperative days, PS = propensity score, RR = risk ratio, WBC = white blood cell.

Keywords: broad-spectrum antibiotic, metronidazole, perforated appendicitis, postoperative complications

1. Introduction

Appendicitis is the most common surgical emergency among the pediatric population. Despite the widespread prevalence of appendicitis, there is little consensus regarding the management of this disease.[1,2] There is considerable variability in the choice, duration, and route of administration of antibiotics for both simple and complicated appendicitis.[3,4] Appendicitis is associ-

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ated with a wide range of pathogens, including aerobic and anaerobic bacteria. Therapy is often instituted empirically with coverage of anaerobes[5] because anaerobic bacteria exist in the intestinal flora. For adults and older children, combination therapies with metronidazole and broad-spectrum antibiotics are reported to be effective in the treatment of complicated intra-abdominal infections.[6] The diversity of the intestinal bacterial population in pediatric patients and infants is different from that in adults. Although anaerobic organisms account for 8% to 11% of bacteremia episodes in adults, they have rarely been isolated from pediatric patients at the onset of appendicitis. Thus, the usage of metronidazole in addition to broad-spectrum antibiotics in adults might not apply to pediatric patients.[7] It is worthwhile to study the relationship of different antibiotic strategies to the outcomes of appendicitis treatment, especially for the pediatric population. Since the 1970s, metronidazole has been used as a standard therapy for trichomoniasis, anaerobic, and amebic infections worldwide, and resistance to metronidazole remains low.[8]

Recent data suggest that monotherapy with a broad-spectrum antibiotic may be as efficacious as, and potentially less costly than, standard multidrug therapy.[6] Monotherapy with ertapenem (ERT) is recommended for appendicitis[9] in both adult and pediatric patients. Although several randomized clinical trials (RCTs) have been done comparing the efficacy of combined therapy with metronidazole and carbapenem regimen,[10,11] systematic reviews or meta-analyses of these antibiotic therapies are limited. The relatively immature intestinal and immune systems of pediatric patients and infants make the intestinal bacterial population fundamentally different than in adults. To our knowledge, few studies evaluating antimicrobial therapy for complicated appendicitis among pediatric patients or infants have been reported. The aim of this study was to evaluate the effect of metronidazole therapy on postoperative perforated appendicitis in pediatric and infant populations. We evaluated and compared the clinical efficacy of these regimens in a retrospective manner. Both regimens are similarly effective, with similar rates of postoperative abscess formation and other complications.

2. Materials and methods

2.1. Patient population

This study is a retrospective review of pediatric patients with either perforated or abscessed appendicitis who underwent surgical intervention in our institutions from August 2013 to August 2016. Patients were eligible for entry into the study with the following inclusion criteria: under 5 years of age, no steroid or immunosuppressive medication administration, and normal renal and hepatic function. Exclusion criteria included patients with cardiac dysfunction, the presence of a penicillin allergy, and patients with ongoing respiratory infection. Additionally, patients treated in the intensive care unit (ICU) for more than 1 day were excluded to minimize differences in severity of illness in the study population. Five hundred eighteen patients under 3 years of age underwent an appendectomy for perforated appendicitis. Of those, 87 were excluded because of pretreatment with antibiotics and 62 for other exclusion criteria. A total of 369 patients met our inclusion criteria and were evaluated. The study protocol was approved by the local ethical committee and Institutional Review Board of the Children's Hospital of Chongqing Medical University (Approval No. 106/2012).

2.2. Clinical and bacteriologic assessments

According to criteria reported in previous studies, the qualified clinical records were reviewed for demographic variables, characteristics at enrollment, and postoperative surgical and nonsurgical outcomes, including complication rates, complication types, and total length of hospital stay (the number of days from the date of operation until the date of discharge). The primary outcome evaluated in this research was the normalization of inflammation variables after surgery, including white blood cell count and C-reactive protein (CRP) levels. The secondary outcomes evaluated were the return of bowel movement, restoration of physical activity, and postoperative complication rate. The laboratory tests, including white blood cell (WBC), CRP, and procalcitonin (PCT), were performed at pretreatment (within 24 hours prior to the start of therapy), and during treatment (day 5 or the day of IV/PO switch). Early ileus was defined as >1 episode of nausea or vomiting within the first 5 postoperative days. Late ileus was defined as sustained nausea or vomiting lasting >5 days after surgery and was confirmed by simple abdominal radiography. Wound complications included wound dehiscence, erythema, swelling, and purulent discharge. Infectious complications included pneumonia (which was confirmed with radiographs), abdominal, urinary, and systemic infection (oral temperature >38.5 °C); these complications were confirmed with microbiological culture. Major complications were defined as the need for repeat laparotomy for an intra-abdominal abscess, prolonged hospitalization, or severe clinical condition requiring transfer to the intensive care unit.

2.3. Medication

The same treatment protocol was carried out for all the patients in this study, including intraoperative cultures, surgical intervention, cessation of enteral feeding, and total parenteral nutrition. The choice of antibiotics depended on the patient's condition and surgeon's preference. The patients were divided according to whether or not metronidazole was used. Once the diagnosis of appendicitis was confirmed, IV antibiotics were started and continued until the WBC count and temperature had returned to normal, or a minimum of 5 days. Patients were discharged with oral amoxicillin-clavulanate if they had a leukocytosis on the day of discharge. They were discharged without oral antibiotics if the leukocyte count was normal. All patients received broad-spectrum antibiotic therapy with either piperacillin/tazobactam (100–150 mg/kg/d in 2 divided doses), ceftriaxone (100–150 mg/kg/dose in 2 divided doses), or cefoperazone sodium and sulbactam (100–150 mg/kg/dose in 2 divided doses). Patients in themetronidazole group also received metronidazole (30 mg/kg/dose in 2 divided doses) (Table 1).

2.4. Propensity score matching and statistical analysis

We performed a 1:1 propensity score matching analysis using SPSS 20.0 (IBM, Armonk, NY) or R 3.1.2 (The R Foundation for Statistical Computing, IBM, Armonk, NY) to minimize the potential confounding effect of selection bias between the metronidazole group and the broad-spectrum antibiotic group. A nonparsimonious multivariable logistic regression model was used with inclusion of the demographic and clinical variables with potential biases related to metronidazole usage. Matching without replacement was performed according to the estimated propensity score of each patient with no replacement, and a 0.1 caliper width. Our propensity score model discriminated well between the

Table 1

Summary of antibiotics used in this research.

	Metronidazole (249)	Broad-spectrum antibiotic (149)
Ceftriaxone, N (%)	173 (69.5)	44 (29.5)
Ticarcillin-clavulanate, N (%)	168 (67.5)	38 (25.5)
Piperacillin-tazobactam, N (%)	69 (27.7)	97 (65.1)
Cefoperazone-sulbactam, N (%)	0	14 (9.4)
Single therapy, N (%)	0	60 (40.3)
Double therapy, N (%)	249	89 (59.7)

metronidazole group and the broad-spectrum antibiotic group. The generalized additive model was used to check linear assumption in the PS model, thus matching 278 patients in the metronidazole treatment group to 278 patients in the broad-spectrum antibiotic treatment group. The characteristics of both the metronidazole group and the broad-spectrum antibiotic group were compared after PSM using SPSS 20.0 (IBM, Armonk, NY). Categorical and continuous variables were reported as frequencies (percentages) and means ± standard deviations, respectively. The difference between discrete variables was evaluated by a chi-square test or Fisher exact test, and then by estimation of the relative risk between the treatment groups. To compare abnormally distributed variables, normally distributed continuous variables were compared using the Student *t* test and the Mann–Whitney *U* test. A result was considered statistically significant if it had a P value <0.05 (a 2-tailed 95% confidence interval [CI]).

3. Results

3.1. Patient characteristics

The baseline characteristics of the patients according to metronidazole administration are summarized in Table 2. The primary clinical symptom reported was abdominal pain with tenderness, although other complaints were also reported as chief symptoms (fever, epigastric discomfort, vomiting, indigestion, or generalized abdominal pain); these symptoms were similar between the 2 groups. The patients receiving metronidazole had a slightly longer duration of clinical symptoms, which was statistically significant, suggesting that in this observational study, there were systematic differences in baseline characteristics between the patients in the metronidazole group and those in the broad-spectrum antibiotic group. There were no significant differences in other demographic features before PS-matching between the 2 groups, including sex distribution, and laboratory test results, including WBC, PCT, and CRP. In addition, there were no significant differences in the surgical approach (laparoscopic appendectomy vs open appendectomy) between the 2 groups with unmatched and propensity score-matched patients (Table 1). The duration of clinical symptoms was comparable after PS-matching. The operative magnitude was evaluated by measurement of operative time and estimated blood loss, and there were no differences between the 2 groups. Following PS-matching, the absolute standardized mean differences reduced from 0.01 to 0.10, indicating the variables were comparable between the patients in the metronidazole group and the patients in the broad-spectrum antibiotic group.

3.2. Postoperative outcomes

Approximately 56% of the patients were discharged on an oral antibiotic, which they received for a mean duration of 3.7 days. Postoperative duration of intravenous antibiotic treatment (Table 3) was not different between the metronidazole group and the broad-spectrum antibiotic group (6.8 ± 1.3 vs 7.9 ± 2.1 days, respectively, P = 0.18). Furthermore, there was no difference in total duration of antibiotic treatment (including both intravenous and oral antibiotic treatment) (9.2 ± 1.8 vs 9.3 ± 1.7days, respectively, P = 0.33) between the 2 groups. There was no difference in the rate of fever between the 2 groups in the first 5 postoperative days (Table 3). No significant differences were found in inflammation variables between the 2 groups at POD 5 (WBC [RR, 1.06; 95% CI, 0.67–1.93, P = .15] and CRP [RR, 1.18; 95% CI, 0.73–2.25, P = .36]) (Table 2). Laboratory

Table 2

Baseline characteristics of eligible patients and surgical parameters.

	Total population			Propensity matched population		
Treatment	Metronidazole (249)	Broad-spectrum antibiotic (149)	*P*	Metronidazole (98)	Broad-spectrum antibiotic (98)	*P*
Age, y	2.1 ± 0.8	2.2 ± 0.7	.31	2.0 ± 0.8	2.1 ± 0.7	.38
Duration of clinical symptoms, days, Mean ± SD	4.8 ± 2.5	3.9 ± 1.9	.03	4.3 ± 2.1	4.1 ± 2.0	.23
Clinical symptoms, N (%)						
Abdominal pain	238 (95.6)	142 (95.3)	.54	97 (99.0)	96 (98.0)	.50
Vomiting	126 (50.6)	73 (49.0)	.42	49 (50.0)	50 (51.0)	.50
Fever	191 (76.7)	112 (75.2)	.41	74 (75.5)	76 (77.5)	.43
Male:female	135:114	81:68	.53	53:45	53:45	.56
Abscess ≥2 cm, N (%)	113 (45.4)	68 (45.6)	.24	45 (45.9)	44 (44.9)	.35
WBC, 10^9/L	16.9 ± 3.7	17.3 ± 3.9	.31	17.0 ± 3.3	17.2 ± 3.4	.46
PCT (ng/mL, normal value: 0–0.5)	6.4 ± 2.8	6.7 ± 2.2	.17	6.5 ± 2.7	6.6 ± 2.1	.36
CRP (mg/L, normal value: 0–8)	20.8 ± 5.2	21.4 ± 4.8	.21	21.0 ± 4.3	21.2 ± 4.3	.39
Albumin (g/L, normal range, 35–50)	33.7 ± 4.9	34.2 ± 5.2	.33	33.9 ± 4.2	34.1 ± 4.7	.24
Surgical approach						
Laparoscopic appendectomy	68 (27.3)	36 (24.2)	.49	25 (25.5)	24 (24.5)	.87
Open appendectomy	181 (72.7)	113 (75.8)	.28	73 (74.5)	74 (75.5)	.50
Operative time, min	48 ± 17	52 ± 16	.18	49 ± 15	50 ± 15	.32
Operative blood loss, mL	16 ± 11	15 ± 9	.26	15 ± 11	15 ± 8	.43

CRP = C-reactive protein, PCT = procalcitonin, WBC = white blood cell.

Table 3

Outcome characteristics in the matched population (multivariate logistic regression).

Treatment	Metronidazole (98)	Broad-spectrum antibiotic (98)	*P*	Risk ratio (95% CI)
Feeding within POD3, N (%)	79 (80.6)	75 (76.5)	.30	1.28 (0.64–2.53)
Total antibiotic duration	9.2±1.8	9.3±1.7	.33	0.45 (0.32–0.73)
Fever (>37.5°C) on POD 5, N (%)	5 (5.1)	6 (6.1)	.50	0.82 (0.24–2.80)
Abdominal distension, N (%)	29 (29.6)	33 (33.7)	.34	0.84 (0.46–1.54)
Diarrhea, N (%)	43 (43.9)	41 (41.8)	.44	1.09 (0.62–1.91)
Postoperative LOS, days, Mean±SD	6.9±1.3	7.1±1.4	.41	0.68 (0.41–0.94)
WBC (10^9/L) on POD 5	8.9±2.5	8.7±3.1	.15	1.06 (0.67–1.93)
PCT (ng/mL, normal value: 0–0.5) on POD 5	0.8±0.3	0.9±0.6	.32	0.58 (0.43–0.89)
CRP (mg/L, normal value: 0–8) on POD 5	9.4±3.6	9.2±4.6	.36	1.18 (0.73–2.25)
Duration of IV antibiotics, days, Mean±SD	6.8±1.3	7.9±2.1	.18	0.56 (0.41–0.97)
Abscess drainage, N (%)	74 (75.5)	81 (82.7)	.15	0.65 (0.32–1.30)

CI=confidence interval, CRP=C-reactive protein, LOS=length of hospital stay, PCT=procalcitonin, POD=postoperative days, WBC=white blood cell.

analysis of liver and kidney function did not demonstrate any differences related to metronidazole treatment (data not shown). The mean postoperative length of hospital stay (LOS) was 6.9± 1.3 days in patients receiving metronidazole, which was comparable to the mean length of stay (7.1±1.4 days) in the broad-spectrum antibiotic group (RR, 0.68, 95% CI, 0.41–0.94, P=.41) (Table 3).

3.3. Postoperative complications

According to established criteria, the salient postoperative complication outcomes are summarized in Table 4. Twenty-seven percent of patients (27/98) in the metronidazole group experienced at least 1 complication, compared with 26.5% (26/98) in the broad-spectrum antibiotic group, with an odds ratio of 1.05 (95% CI, 0.56–1.98, P=.50) (Table 4). In the propensity-matched cohort, there were no statistically significant differences between the groups in the incidence of diarrhea or abscess, postoperative intra-abdominal or pelvic abscess rate (7[7.1%] vs 9[9.2%], respectively, P=.40), postoperative wound infection (14[14.3%] vs 15[15.3%], respectively, P=.50), and 30-day readmission rate (9[9.2%] vs 12[12.2%], respectively, P=0.32) (Table 4). An evaluation of intraoperative culture results in patients who developed an abscess did not suggest inadequate susceptibility as the cause of the abscess since the pathogens were sensitive to the postoperative antibiotic administered.

4. Discussion

After propensity score matching, we found no significant benefit of metronidazole treatment in pediatric patients with perforated appendicitis. Metronidazole treatment did not provide any improvement in postoperative complications, including surgical infections and ileus/bowel obstruction, which was associated with the length of postoperative hospital stay among all patients with perforated appendicitis.

Although simpler antibiotic regimens have recently been proposed, triple antibiotic therapy, including anaerobic antimicrobial therapy, for perforated appendicitis is still common practice in pediatric surgery.[12,13] In recent years, several studies have compared the efficacy of combined therapy with metronidazole to carbapenem alone in the treatment of intra-abdominal infections. Considering the anaerobic flora in young children, the benefits of empirical metronidazole anaerobic therapy for infants with perforated appendicitis is unknown. Our findings demonstrate that broad-spectrum antibiotic therapy (including piperacillin/tazobactam) is equivalent to a metronidazole combination regimen for children with perforated appendicitis; these results are consistent with previous studies that show that monotherapy with broad-spectrum agents (piperacillin/tazobactam) for intra-abdominal infections is equally efficacious as traditional triple therapy.[14] In our study, no difference in the incidence of abscess formation was found between the patients receiving broad-spectrum agents alone compared with those also receiving metronidazole. Finally, these results indicate the need for further research to investigate the optimal antibiotic therapy in pediatric patients with perforated appendicitis.

Over the study period, although anaerobic antimicrobial use changed dramatically with increased piperacillin–tazobactam usage and decreased clindamycin usage, metronidazole was used consistently. It is unclear if empiric coverage of anaerobic bacteria

Table 4

Postoperative complications in the matched population (chi-square test).

Treatment	Metronidazole (98)	Broad-spectrum antibiotic (98)	*P*	Odds ratio (95% CI)
Total complications (at least 1 complication), N (%)	27 (27.6)	26 (26.5)	.50	1.05 (0.56–1.98)
Total number of complications	52 (53.1)	49 (50.0)	.39	1.13 (0.65–1.98)
Surgical wound infection, N (%)	14 (14.3)	15 (15.3)	.50	0.92 (0.42–2.03)
Peritonitis or recurrent abscess, N (%)	7 (7.1)	9 (9.2)	.40	0.76 (0.27–2.13)
Sepsis, N (%)	2 (2.0)	2 (2.0)	.69	1.00 (0.14–7.25)
Pneumonia, N (%)	8 (8.2)	10 (10.2)	.40	0.78 (0.30–2.07)
Incision dehiscence, N (%)	1 (1.0)	2 (2.0)	.50	0.50 (0.04–5.55)
Late ileus, N (%)	19 (19.4)	17 (17.3)	.43	1.15 (0.56–2.36)
Re-admissions	9 (9.2)	12 (12.2)	.32	0.73 (0.29–1.81)

CI=confidence interval.

is necessary in the pediatric population based on the current practice guidelines and literature.[15,16] Many institutions report the use of broad-spectrum agents in addition to anti-anaerobic agents (e.g., metronidazole) in pediatric patients with appendicitis.[17–20] Combined therapy with metronidazole has been suggested to be superior to β-lactam-based regimens with regard to cure; however, a variety of β-lactam-based regimens were used.[21] The choice of antibiotic regimen should take into account the problem of antimicrobial resistance. Many anaerobic species besides *Bacteroides fragilis* (*B fragilis)* have acquired the ability to produce beta-lactamase, which is involved in antimicrobial resistance. The development of resistance by anaerobes to all known agents makes the selection of reliable empirical therapy difficult. Until now, there have been no published data regarding the propensity of microbes to develop resistance to metronidazole. It has been suggested that with the addition of avibactam, the antibiotic resistance rate among 316 anaerobic bacteria was 15.2%, compared with 37.7% with ceftazidime alone. Ceftazidime/avibactam activity against anaerobic bacteria is similar to that of ceftolozane/tazobactam, in that variable activity was achieved against *B fragilis*.[22] Consistent with this finding, the most broad-spectrum agents used here included a beta-lactamase inhibitor. Our current study supports the use of broad-spectrum agents for perforated appendicitis in pediatric patients to reduce the number of anaerobic organisms. The occurrence of an intra-abdominal abscess following appendectomy is a serious and life-threatening complication event. In the current study, intra-abdominal abscess formation was reported in 9 patients who received only broad-spectrum antibiotics (9.2%), compared with 7 patients receiving the combination regimen (7.1%, $P=.40$). Although it was only used in an adult, newer monotherapy using tigecycline has been reported to be similar to combined therapy with metronidazole in patients with intra-abdominal infections.[23,24] Our findings are consistent with another study that found a low incidence of intra-abdominal infections, with no significant difference found between moxifloxacin and ertapenem treatment in a small cohort study.[25]

One may postulate that bacteria in peritoneal fluid could be the causative organism for postoperative infectious complications. Contrary to this notion, the value of intraoperative culture is debatable because of the discordance between outcomes and antibiotic therapy tailored to these culture results.[26,27] In this study, due to the low rate of positive blood culture in patients with perforated appendicitis, an antibiotic regimen for sepsis was based on empiric therapy. It was quite difficult to identify the profile of pathogens after laparotomy in our study because only 4 strains were identified in positive blood cultures. Intraoperative cultures in those who developed an abscess did not suggest inadequate susceptibility, as the pathogens were sensitive to the postoperative antibiotic administered. Furthermore, because the gut ecosystem changes from an anaerobic to an aerobic system during open abdominal surgery, it becomes unsuitable for the growth of anaerobic bacteria, and the reduced mortality rate in perforated appendicitis may not be attributed solely to the anaerobic antimicrobial therapy.[28] Since infectious complications were not higher in the group that did not receive metronidazole, our findings may also be interpreted to indicate that anaerobic coverage using metronidazole is not a critical component of this regimen. Our data do not provide sufficient information about which anaerobic antimicrobial agent should be chosen empirically. This question could be answered by further investigation of complicated intra-abdominal infections in pediatric patients.

This study was limited by its retrospective, single-center design, and lack of randomization to initiate broad-spectrum antibiotics. Therefore, we could not completely avoid the risk of unobserved confounders. Selection of cases for metronidazole administration might have been biased by factors such as duration of symptoms and surgeon preference. We may have been inclined to use metronidazole in some patients who were prone to a longer duration of symptoms. To limit the influence of confounding variables on the actual effects of metronidazole, we performed propensity score matching analysis to generate similar baseline factors regarding metronidazole administration. Following the PS matching, the discrepancy is comparable, as indicated by the standardized mean differences and *P* value. However, we could not completely avoid variables that may affect this comparison. Despite these limitations, a relatively uniform pathology is encountered in young patients with perforated appendicitis, and source control is readily accomplished by widely accepted operative techniques. This enhances the probability that the differences observed between the groups are due to differences in antibiotic efficacy rather than source control.[9,18] In the case of perforated or abscessed appendicitis, important differences between antibiotic regimens might be identified to test the activity of metronidazole and other broad-spectrum agents, such as aminopenicillins with beta-lactam inhibitors or carbapenems and select cephalosporins.

In summary, clinical evidence from the present study suggests that pediatric perforated or abscessed appendicitis can be managed effectively with broad-spectrum antibiotic agents after appendectomy, although it is still controversial whether metronidazole is associated with benefits in this specific patient population. No difference was detected between the groups in terms of length of stay, readmission rate, abscess rate, and wound infection rate. Although there is no consensus about this broad-spectrum regimen, our experience with broad-spectrum agents for children with perforated appendicitis should be considered.

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