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Comparison of Antibiotic Therapy and Appendectomy for Acute Uncomplicated Appendicitis in Children
A Meta-analysis

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IMPORTANCE Antibiotic therapy for acute uncomplicated appendicitis is effective in adult patients, but its application in pediatric patients remains controversial.

OBJECTIVE To compare the safety and efficacy of antibiotic treatment vs appendectomy as the primary therapy for acute uncomplicated appendicitis in pediatric patients.

DATA SOURCES The PubMed, MEDLINE, EMBASE, and Cochrane Library databases and the Cochrane Controlled Trials Register for randomized clinical trials were searched through April 17, 2016. The search was limited to studies published in English. Search terms included *appendicitis*, *antibiotics*, *appendectomy*, *randomized controlled trial*, *controlled clinical trial*, *randomized*, *placebo*, *drug therapy*, *randomly*, and *trial*.

STUDY SELECTION Randomized clinical trials and prospective clinical controlled trials comparing antibiotic therapy with appendectomy for acute uncomplicated appendicitis in pediatric patients (aged 5-18 years) were included in the meta-analysis. The outcomes included at least 2 of the following terms: success rate of antibiotic treatment and appendectomy, complications, readmissions, length of stay, total cost, and disability days.

DATA EXTRACTION AND SYNTHESIS Data were independently extracted by 2 reviewers. The quality of the included studies was examined in accordance with the Cochrane guidelines and the Newcastle-Ottawa criteria. Data were pooled using a logistic fixed-effects model, and the subgroup pooled risk ratio with or without appendicolith was estimated.

MAIN OUTCOMES AND MEASURES The primary outcome was the success rate of treatment. The hypothesis was formulated before data collection.

RESULTS A total of 527 articles were screened. In 5 unique studies, 404 unique patients with uncomplicated appendicitis (aged 5-15 years) were enrolled. Nonoperative treatment was successful in 152 of 168 patients (90.5%), with a Mantel-Haenszel fixed-effects risk ratio of 8.92 (95% CI, 2.67-29.79; heterogeneity, P = .99; I^2 = 0%). Subgroup analysis showed that the risk for treatment failure in patients with appendicolith increased, with a Mantel-Haenszel fixed-effects risk ratio of 10.43 (95% CI, 1.46-74.26; heterogeneity, P = .91; I^2 = 0%).

CONCLUSIONS AND RELEVANCE This meta-analysis shows that antibiotics as the initial treatment for pediatric patients with uncomplicated appendicitis may be feasible and effective without increasing the risk for complications. However, the failure rate, mainly caused by the presence of appendicolith, is higher than for appendectomy. Surgery is preferably suggested for uncomplicated appendicitis with appendicolith.

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Supplemental content

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Acute appendicitis is one of the most common pediatric emergencies.[1] Since 1889, when McBurney[2] first reported appendectomy as the treatment for acute appendicitis, surgical intervention has been the standard treatment strategy for acute appendicitis.[3,4] After appendicitis is diagnosed, further management is determined by whether the inflamed appendix is intact (uncomplicated), has developed perforation and/or gangrene, or has developed into an appendiceal mass or abscess (complicated).[5] Since 1995, investigators[6-8] have observed that patients presenting with uncomplicated appendicitis or well-formed abscess do not necessarily need urgent surgical intervention. However, with improved surgical technology, the low threshold for operative intervention has led to a risk for high rates of negative appendectomy findings, with unnecessary surgery-related morbidity. Improved computed tomography and ultrasonography, among other diagnostic tools, allow for accurate diagnosis of acute appendicitis and preoperative differentiation of perforated and nonperforated appendicitis.[9,10] Problems arising in clinical practice along with the advances of diagnostic imaging tools have made physicians rethink and investigate the application of nonoperative management with antibiotics in patients with appendicitis.

Several randomized clinical trials (RCTs) have proven the effectiveness and safety of nonoperative treatment for acute appendicitis in adult patients with uncomplicated disease,[7,8,11-14] with success rates ranging from 63% to 85%. Meta-analyses and systematic reviews of such trials[15-19] have yielded supportive conclusions. However, owing to specific anatomical and pathophysiologic features of children, the clinical scenario of acute appendicitis in pediatric patients is different from that in adults, and treatment decisions for children are more difficult.[6] Results from previous systematic reviews and meta-analyses of adult patients are not applicable to pediatric patients. The exact clinical guidance for whether nonoperative treatment or appendectomy should be used for pediatric patients with acute appendicitis depends on results from large studies with pediatric patients.

Some recent studies[20,21] suggest that antibiotic treatment may be a valid alternative to appendectomy in uncomplicated pediatric appendicitis. However, the sample sizes of those studies were relatively small, and the conclusions were inconsistent. The present meta-analysis aimed to compare antibiotic treatment with appendectomy for the treatment of uncomplicated acute appendicitis in pediatric patients, with particular reference to safety and efficacy.

Key Points

Question Are antibiotics as initial treatment appropriate for uncomplicated acute appendicitis in pediatric patients?

Findings In this meta-analysis of 5 studies (including 404 patients), antibiotic treatment was safe and effective in 152 of 168 pediatric patients (90.5%), but the risk for treatment failure increased significantly in patients with appendicolith.

Meaning Antibiotic treatment can be used as primary treatment in pediatric patients presenting with acute uncomplicated appendicitis without appendicolith.

Methods

Study Selection

Randomized clinical trials and prospective controlled trials comparing antibiotic treatment with appendectomy for nonperforated acute appendicitis in pediatric patients (aged 5-18 years) were eligible for inclusion. Eligible studies were required to report at least 2 of the following outcomes: success rate of antibiotic treatment and appendectomy (successful treatment was defined as no complications and no recurrences within 1 month after hospital discharge), complications, readmissions, length of stay, total cost for hospital stay, and number of days with disability. We limited the eligibility to English-language studies.

Search Strategy

To identify studies and determine eligibility, 2 of us (L.H. and Y.Y.) independently searched the PubMed, MEDLINE, EMBASE, and Cochrane Library databases and the Cochrane Controlled Trials Register for RCTs comparing antibiotic treatment with appendectomy for acute appendicitis until April 17, 2016. Search terms included *appendicitis*, *antibiotics*, *appendectomy*, *randomized controlled trial*, *controlled clinical trial*, *randomized*, *placebo*, *drug therapy*, *randomly*, and *trial*, which were all used in combination with the Boolean operators AND, OR, and NOT. The search terms were input as free text. Titles and abstracts were examined by both authors, and full manuscripts were obtained to finalize eligibility. Reference lists of eligibility studies were also examined to identify additional studies.

Data Extraction

We defined the primary outcome as success rate in each group. The secondary outcomes measured were time from assignment to discharge, cost, and complications that were reported by all studies, including complicated appendicitis and postoperative complications.

Risk for Bias

The quality of cohort studies was measured by a score system and assessed in accordance with the Newcastle-Ottawa criteria.[22] The total scores ranged from 0 (worst) to 9 (best) for cohort studies, with a score of at least 6 indicating high quality. The quality of RCT studies was assessed using the Cochrane Collaboration's risk for bias assessment tool,[23] which evaluated the selection bias (random-sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), and reporting bias (selective outcome reporting). Each criterion was assessed as low risk for bias, high risk for bias, or uncertain risk for bias.

Statistical Analysis and Exploration of Heterogeneity

Statistical analyses were completed using RevMan software (version 5.3; Cochrane Collaboration). We used pooled risk ratios for primary outcomes and pooled standard mean differences for secondary outcomes to evaluate the rates of complications and other outcome measures in the antibiotic and appendectomy groups. We used the Mantel-Haenszel (M-H) method to combine the summary statistics and assessed the statistical heterogeneity by using the I^2 method with the χ^2 test to calculate *P* values. The potential for publication bias was evaluated by visually inspecting funnel plots. Statistical heterogeneity was assessed using the I^2 statistic. Higher I^2 values indicate increased heterogeneity. The results were reported with 95% CIs, and *P* values, where appropriate, and the 5% level ($P < .05$) was considered to indicate statistical significance.

Results

The online search identified 527 articles, as shown in eFigure 1 in the Supplement. After screening the titles, abstracts, and trial registries, we excluded 459 records. A total of 68 full-text manuscripts were examined. We included 6 trials in the qualitative synthesis and 5 trials in the meta-analysis. The cohort study[24] was excluded because the same group of patients was reported in another study by the same authors with a longer follow-up period (eFigure 1 in the Supplement). Four single-center prospective nonrandomized controlled trials[25-28] and 1 single-center RCT[29] were included.

We summarized the characteristics of the 5 included studies. A total of 404 unique patients with uncomplicated acute appendicitis were assigned to the antibiotic treatment group (n = 168) or the appendectomy group (n = 236). Diagnosis of suspected acute appendicitis was obtained from the history, clinical signs, radiographic evidence, and laboratory tests for increased levels of inflammatory markers (**Table** and eTable 1 in the Supplement). In all 5 studies, computed tomography or ultrasonography was used to confirm the diagnosis. All patients who received an appendectomy had the diagnosis confirmed by pathologic findings, and no negative appendectomies were performed. Patients suspected of having complicated appendicitis during the preoperative examination were excluded in all the studies.

Randomization was performed using a computer-based randomization program (Simin [version 6.0; Institute of Child Health]) that allowed complete concealment of the randomization sequence in Svensson et al.[29] In the 4 other studies,[25-28] assignments were conducted by parental choice. None of these studies masked the patients, clinicians, outcome assessors, or data analysts. Three studies[25,26,29] documented a median follow-up period of 1 year. Tanaka et al[27] reported a median follow-up period of 4.3 years. However, Mahida et al[28] described a median follow-up period of 4.7 months, in which the planned follow-up visits were 2 to 5 days, 10 to 14 days, 30 days, 6 months, and 1 year after hospital discharge. All the studies reported dropouts and withdrawals. Loss to or unavailability for follow-up at 1 year was described in 3 studies, varying from 0% to 23%, and was similar in both groups in each study. In a Japanese study,[27] patients who were treated at other hospitals were excluded.

Primary Outcome

Success Rate of Treatment

The primary outcome of this meta-analysis was the success rate of treatment. Treatment success was defined in the antibiotic group as resolution of symptoms without the need for surgery within 48 hours or recurrence of appendicitis within 1 month after treatment initiation. In the appendectomy group, treatment success was considered as an operation without negative appendectomy findings and/or reoperation.

In the antibiotic group, 16 of 168 patients (9.5%) presented with initial failures of antibiotic treatment; 11 patients proceeded to have an appendectomy within 48 hours, and 5 patients experienced recurrence of appendicitis after 1-month follow-up. All 16 patients were pathologically diagnosed with appendicitis, with 3 of them having perforated appendicitis. In the appendectomy group, no negative appendectomy findings (0 of 236 patients) were observed, whereas 1 patient experienced a major complication that needed reoperation. Six minor complications were reported by Tanaka et al[27] and Minneci et al[26] (details not given), and all of them were treated conventionally. Nonoperative treatment was successful in 152 of 168 patients (90.5%), with a risk ratio of failure of 8.92 (M-H fixed-effects 95% CI, 2.67-29.79; heterogeneity, $P = .99$; $I^2 = 0\%$) (**Figure 1**).

Failure Rate Associated With Appendicolith

Four studies[25,27-29] reported the presence of appendicolith, with 3 studies[27-29] noting that appendicolith was associated with a high rate of treatment failure; 30 patients with appendicolith were allocated to the antibiotic group, and 19 patients with appendicolith received initial appendectomy. In the study by Hartwich et al,[25] no fecalith-associated complications occurred in the antibiotic or the surgery group. Minneci et al[26] excluded patients with appendicolith in study criteria. We performed a subgroup analysis based on the presence of appendicolith, which showed an increased risk for initial fails and recurrent appendicitis (**Figure 2**), with a risk ratio of 10.43 (M-H fixed-effects 95% CI, 1.46-74.26; heterogeneity, $P = .91$; $I^2 = 0\%$), and a lower risk in patients without appendicolith (eFigure 2 in the Supplement), with a risk ratio of 7.87 (M-H fixed-effects 95% CI, 1.80-34.33; heterogeneity, $P = .88$; $I^2 = 0\%$).

Recurrence of Appendicitis Within 1 Year

Of the 168 patients allocated to the antibiotic treatment group, 45 patients (26.8%) underwent appendectomy with 1-year follow-up. Twenty-seven patients (16.1%) were diagnosed with appendicitis using histopathologic findings; 6 of these 27 patients had recurrence of appendicitis within 30 days, and all 6 patients were counted in the initial statement of treatment failure. Moreover, 8 of 45 patients were diagnosed as having a normal appendix by histopathologic findings. Seven of these patients underwent appendectomy because of recurrent symptoms, and 1 asymptomatic patient underwent appendectomy at parental request. Minneci et al[26] reported 7 recurrent appendicitis cases. In the study of Svensson et al,[29] 7 patients received interval appendectomy after discharge; 1 patient was diagnosed with recurrent appendicitis by histopathologic findings, and the other 6 patients underwent appendectomy with a histopathologically normal appendix. Mahida et al[28] and Tanaka et al[27] reported 1 and 16 recurrent appendicitis cases after discharge, respectively. Furthermore, Hartwich et al[25]

Table. Characteristics of the 5 Included Studies

Source	Study Design	Participants	Intervention		Outcomes		Funding and Conflict of Interest Statement
			Antibiotics	Appendectomy	Primary	Secondary	
Minneci et al,[26] 2016	Single-center prospective nonrandomized controlled trial	Patients (n = 102) aged 7-17 y; diagnosis of acute appendicitis (uncomplicated); findings indicative of acute appendicitis in the history, inflammatory markers (WBC count), and imaging; no appendicolith	24-h IV PIP or 24-h IV CIP + MTR, then oral AMX for 10 d	IV antibiotics and laparoscopic appendectomy within 12 h	Success rates of nonoperative management (4 of 37 initial failures in the antibiotic group and 1 of 65 in the appendectomy group)	Appendicitis-related medical care, length of hospital stay, complications, disability days, HRQOL scores, total appendicitis-related costs	Funding: Research Institute at Nationwide Children's Hospital and grant UL1TR001070 from the National Center for Advancing Translational Sciences. No conflict of interest was reported.
Svensson et al,[29] 2014	Single-center randomized (pilot) trial	Patients (n = 50) aged 5-15 y; diagnosis of acute nonperforated appendicitis; findings indicative of nonperforated appendicitis in the history, inflammatory markers (WBC count and CRP level) and imaging; appendicolith in 12 patients	MEM, 10 mg/kg, + IV MTR, 20 mg/kg TID, for 48 h, then oral CIP, 20 mg/kg BID, + MTR, 20 mg/kg QD, for 8 d	Laparoscopic appendectomy within 12 h; complicated appendicitis received postoperative antibiotic	Resolution of symptoms without significant complications (2 of 24 with initial failures in antibiotic group and none in appendectomy group)	Length of stay in hospital, complications, recurrent appendicitis within 1 y, total costs	Funding: Crown Princess Lovisa's Foundation, the Hirsch Foundation. No conflict of interest was reported.
Hartwich et al,[25] 2016	Single-center prospective nonrandomized controlled trial	Patients (n = 74) with mean (SD) age 12.6 (0.6) y; clinical diagnosis of acute uncomplicated appendicitis made by history, physical examination, inflammatory markers, and imaging (US or/and MRI) findings; appendicolith in 4 children	IV PIP, 100 mg/kg TID or QID, then oral AMX, 50 mg/kg per d in 3 divided doses for 7 d	Immediate appendectomy; no details of antibiotic use	Success rates of nonoperative treatment (3 of 24 initial failures in antibiotic group; none in appendectomy group)	Complications (at 1 y), recurrence (at 1 y), length of stay, cost-utility	No funding or conflict of interest was reported.
Mahida et al,[28] 2016	Single-center prospective nonrandomized controlled trial	Patients (n = 14) aged 9-15 y; diagnosis of acute appendicitis (uncomplicated) with appendicolith); diagnosis made by clinical history and examination (US, CT, and blood test) findings	IV PIP for 24 h or IV CIP + MTR for 24 h, then oral AMX, for 7 d	Urgent appendectomy and IV PIP	Success rates of nonoperative management (2 of 5 initial failures in antibiotic group, none in appendectomy group)	Complications, recurrence	Funding: intramural funding from the Research Institute at Nationwide Children's Hospital (NIH5T32HL098039-03) and grant UL1TR001070 from the National Center for Advancing Translational Sciences. No conflict of interest was reported.
Tanaka et al,[27] 2015	Single-center prospective nonrandomized controlled trial	Patients (n = 164) aged 6-15 y; diagnosis of acute appendicitis (uncomplicated); diagnosis made by physical examination, blood test, and imaging findings; appendicolith in 19 patients	IV CMZ, 100 mg/kg per d for 48 h, then AMP, 200 mg/kg per d + CAZ, 150 mg/kg per d or MEM /IMP, 60 mg/kg per d + GEN, 5 mg/kg per d were used	Laparoscopic appendectomy within 48 h; IV antibiotics used until 48 h after surgery	Success rates of nonoperative treatment (5 of 78 initial failures in antibiotic group; none in appendectomy group)	Complications, recurrence, length of stay, cost	No funding information mentioned in article. No conflict of interest was reported.

Abbreviations: AMP, ampicillin sodium; AMX, amoxicillin; BID, 2 times per day; CAZ, ceftazidime; CIP, ciprofloxacin hydrochloride; CMZ, cefmetazole sodium; CT, computed tomography; GEN, gentamicin sulfate; HRQOL, health-related quality of life; IMP, imipenem; IV, intravenous; MEM, meropenem; MRI, magnetic resonance imaging; MTR, metronidazole hydrochloride; PIP, piperacillin sodium–tazobactam sodium; QD, every day; QID, 4 times per day; TID, 3 times per day; US, ultrasonography; WBC, white blood cell.

reported 4 instances of appendectomy in the antibiotic group during the follow-up period; 2 were for recurrence of appendicitis, whereas the other 2 were appendectomy with normal appendix. Moreover, patients with appendicolith had a higher rate of recurrent appendicitis than did patients without appendicolith (10 of 30 [33.3%] vs 17 of 138 [12.3%]).

Secondary Outcomes

Complication

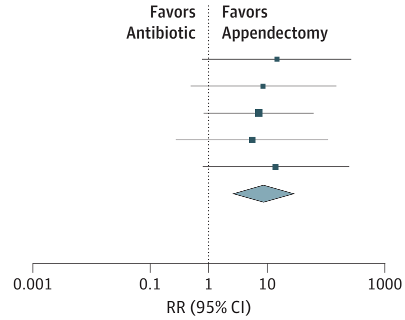
Complication in the antibiotic group was defined as perforation, abscess, gangrene, and/or postoperative complications after the interval appendectomy. In the appendectomy group, complications were defined as postoperative complications,

Figure 1. Forest Plot Showing Risk Ratio (RR) in Failure Rate in the Antibiotic vs Appendectomy Groups

	Antibiotic Therapy		Appendectomy			
Source	No. of Events	Total No.	No. of Events	Total No.	RR (95% CI)	Weight, %
Hartwich et al,[25] 2016[a]	3	24	0	50	14.28 (0.77-265.91)	13.8
Mahida et al,[28] 2016	2	5	0	9	8.33 (0.48-145.91)	15.7
Minneci et al,[26] 2015[b]	4	37	1	65	7.03 (0.82-60.56)	30.4
Svensson et al,[29] 2014	2	24	0	26	5.40 (0.27-107.09)	20.1
Tanaka et al,[27] 2015[c]	5	78	0	86	12.11 (0.68-215.58)	19.9
Total	**16**	**168**	**1**	**236**	**8.92 (2.67-29.79)**	100.0

Heterogeneity: $\chi^2_4 = 0.30$ ($P = .99$), $I^2 = 0\%$

Test for overall effect: $z = 3.56$ ($P < .001$)



Risk ratios were calculated using the Mantel-Haenszel method to combine summary statistics, and data were pooled using a fixed-effects model.

[a] Events were defined as initial failure of treatment.

[b] Two initial treatment failures and 2 recurrences of appendicitis occurred within 30 days.

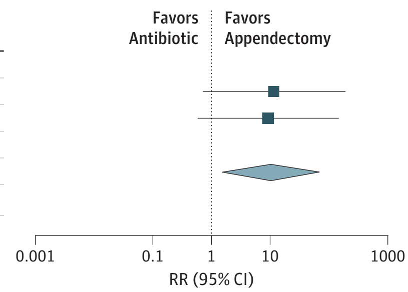
[c] One initial treatment failure and 4 recurrences of appendicitis occurred within 30 days.

Figure 2. Subgroup Forest Plot Showing Risk Ratio (RR) in Failure Rate in Patients With Appendicolith in the Antibiotic Therapy vs Appendectomy Groups

	Antibiotic Therapy		Appendectomy			
Source	No. of Events	Total No.	No. of Events	Total No.	RR (95% CI)	Weight, %
Hartwich et al,[25] 2016[a]	0	1	0	3	Not estimable	
Mahida et al,[28] 2016	3	5	0	9	11.67 (0.72-188.99)	49.7
Svensson et al,[29] 2014	3	5	0	7	9.33 (0.59-148.60)	50.3
Tanaka et al,[27] 2015[b]	9	19	0	0	Not estimable	
Total (included)[c]	**15 (6)**	**30 (11)**	0	**19**	**10.43 (1.46-74.26)**	**100**

Heterogeneity: $\tau^2 = 0.00$, $\chi^2_1 = 0.01$ ($P = .91$), $I^2 = 0\%$

Test for overall effect: $z = 2.34$ ($P = .02$)



Risk ratios were calculated using the Mantel-Haenszel method to combine summary statistics, and data were pooled using a fixed-effects model.

[a] Events were defined as failure rate at 1-year follow-up.

[b] No data were available in the appendectomy group.

[c] Patients with incomplete data were excluded from the analysis.

including ileus, surgical site infection, or other postoperative readmissions for appendectomy. A forest plot (eFigure 3 in the Supplement) shows a risk ratio of 0.65 (M-H fixed-effects 95% CI, 0.18-2.37; heterogeneity, $P = .51$; $I^2 = 0\%$). No statistically significant difference was detected in the prevalence of complications between the antibiotic and appendectomy groups.

Cost

Three of 5 studies reported cost in the antibiotic and appendectomy groups.[25,26,29] Initial cost refers to the cost of initial inpatient stay, whereas the total cost includes all the appendicitis-associated costs. Moreover, the initial or total cost decreased in the antibiotic treatment group (eFigure 4 in the Supplement and **Figure 3**). The mean difference between treatment groups in initial cost in US $1000 was −$0.70 (inverse variance fixed-effects 95% CI, −$0.89 to −$0.51; heterogeneity, $P < .001$; $I^2 = 100\%$) and in total cost in US $1000 was −$1.31 (inverse variance fixed-effects 95% CI, −$1.69 to −$0.92; heterogeneity, $P = .72$; $I^2 = 0\%$).

Hospital Stay and Disability Days

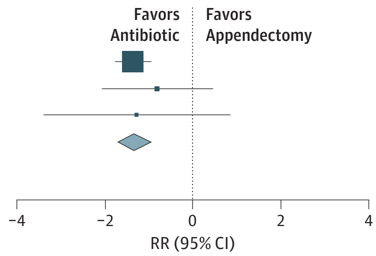
The length of hospital stay was reported in 3 studies.[26,27,29] The forest plot showed a significantly longer hospital stay in the antibiotic group than in the appendectomy group (eFigure 5 in the Supplement); with a mean difference of 14.32 hours (inverse variance fixed-effects 95% CI, 7.49-21.15 hours; heterogeneity, $P = .16$; $I^2 = 46\%$). Furthermore, Minneci et al[26] reported the mean length of disability as 8 days (interquartile range, 5-18 days) in the antibiotic group and 21 days (interquartile range, 15-25 days) in the appendectomy group ($P < .001$).

Discussion

Although well studied in adult patients, the feasibility and safety of antibiotic treatment vs appendectomy for acute appendicitis in pediatric patients remain uncertain, with no pediatric patient-based meta-analysis available. The current

Figure 3. Forest Plot Showing Mean Difference in Total Cost in Antibiotic Therapy vs Appendectomy Groups

	Antibiotic Therapy, US $1000		Appendectomy, US $1000			
Source	Mean (SD)	Total, No.	Mean (SD)	Total, No.	Mean Difference (95% CI)	Weight, %
Hartwich et al,[25] 2016	2.771 (0.816)	24	4.13 (0.909)	50	−1.36 (−1.77 to −0.95)	87.5
Minneci et al,[26] 2015	4.219 (3.912)	37	5.029 (0.656)	65	−0.81 (−2.08 to 0.46)	9.2
Svensson et al,[29] 2014	3.929 (4.79)	24	5.203 (2.359)	26	−1.27 (−3.39 to 0.85)	3.3
Total		85		141	**−1.31 (−1.69 to −0.92)**	**100.0**
Heterogeneity: χ^2_2 = 0.65, (*P* = .72), I^2 = 0%						
Test for overall effect: *z* = 6.63 (*P* < .001)						



Mean differences were calculated using the inverse variance method with fixed effects.

meta-analysis compared primarily the 2 different treatment strategies for pediatric patients with acute appendicitis. Five prospective clinical controlled trials were included, with 404 pediatric patients enrolled; the efficacy and safety were evaluated in antibiotic treatment and appendectomy. The results showed that the initial success rate of antibiotic treatment was as high as 90.5%, with a risk for complications comparable to that for appendectomy. Antibiotic treatment was associated with higher risk for failure compared with urgent appendectomy; 45 of 168 patients (26.8%) received interval appendectomy because of treatment failure (10 patients), histopathologically confirmed recurrence (27 patients), or a parent's demand (8 patients) during the 1-year follow-up.

We conducted a quality assessment on all the included studies (eTable 2 in the Supplement). All 4 cohort studies used the Newcastle-Ottawa criteria and scored at least 7, suggesting that all the studies achieved moderate or high quality. One RCT was rated as high quality by the Cochrane Collaboration's risk for bias assessment tool[23] in accordance with the following criteria: adequate generated random sequence, not double-blinded for patients and physicians, none of the patients were lost to follow-up during at least the 1-year follow-up period, and a low risk for selective reporting.

Accurate diagnosis of acute appendicitis and differentiating uncomplicated from complicated appendicitis are of essential importance in evaluating the treatment options. In some early studies, the misdiagnosis rate of patients with suspected appendicitis was greater than 15%,[30] with higher percentages in pediatric patients. Fortunately, the advancement of imaging studies has reduced the negative appendectomy rate. As shown in our review, the diagnosis of appendicitis was supported by results of a physical examination, blood tests, abdominal ultrasonography, or computed tomography in all studies. None of the 236 initial surgical procedures resulted in a negative appendectomy finding as determined by histopathologic results.

Although the combination of clinical manifestation and radiologic examination has a high level of accuracy in detecting the presence of appendicitis, differentiation between uncomplicated and complicated or perforated appendicitis may be uncertain before the operation. Early or uncomplicated appendicitis usually entails a recent onset (<48 hours), a relatively lower white blood cell count (<180 000/μL [to convert to 10^9 per liter, multiply by 0.001]), absence of pan-peritonitis, and abscess or phlegmon or fluid collection at imaging. In this meta-analysis, 4 studies[25-28] used stringent inclusion criteria that excluded patients with symptom duration longer than 48 hours or a white blood cell count of greater than 180 000/μL; use of these criteria helped decrease the risk for complicated appendicitis. In the RCT by Svensson et al,[29] a small proportion of patients presented with a long symptom duration and high white blood cell count, although the time to perforation and its clinical manifestation were variable; these factors may have affected the efficiency of nonoperative treatment. Furthermore, the final histologic examination revealed 3 cases of gangrenous appendicitis and 2 cases of perforated appendicitis in the appendectomy group; 1 patient in the antibiotic group, returning after an initial resolution in symptoms, was found to have perforated appendicitis.

The presence of appendicolith is another major concern when considering the application of nonoperative treatment for acute appendicitis. Appendicolith may lead to obstruction of the appendix lumen. Approximately 10% of patients with appendix inflammation are diagnosed with appendicolith, which often occurs in children or young adults.[31] Many studies[14,32-34] reported that the presence of appendicolith was associated with high risk (≤40%) for complicated appendicitis. Some studies[35,36] also showed that the presence of appendicolith may increase the risk for recurrent appendicitis. In the 5 studies included in this meta-analysis, Minneci et al[26] defined the presence of fecalith as an exclusion criterion, and the 4 other studies[25,27-29] reported the presence of appendicolith in the included patients. Mahida et al[28] focused on patients with acute appendicitis and appendicolith, but the study ended midway because of a high failure rate of antibiotic treatment and a high rate of complicated appendicitis found in the surgical group. In the study by Svensson et al,[29] 3 of 5 patients with appendicolith (60%) in the antibiotic group finally received appendectomy. In the study of Tanaka et al,[27] 9 of 19 patients with appendicolith (47%) experienced failure of initial antibiotic treatment compared with 24% of patients who did not. The increased risk for nonoperative treatment failure was confirmed in our subgroup analysis, with a risk ratio of 10.43 (M-H fixed-effects 95% CI, 1.46-74.26; heterogeneity, $P = .91$; $I^2 = 0\%$). Altogether, 15 of 30 patients with appendicolith (50%) in the antibiotic group underwent appendectomy. Therefore, considering the available evidence, researchers have found the application of nonoperative treatment for acute appendicitis with appendicolith to be inappropriate. Larger clinical trials are needed to further reveal precise indicators to guide the treatment of acute appendicitis with appendicolith.

The type and duration of antibiotic treatment may also influence the outcomes. Three studies[25,26,28] reported that a combination of piperacillin sodium and tazobactam sodium and a combination of oral ampicillin sodium and clavulanate potassium were used as the main therapeutic agents in the antibiotic group. Svensson et al[29] used meropenem, oral ciprofloxacin hydrochloride, and metronidazole hydrochloride. Tanaka et al[27] reported a sequence in which cefmetazole sodium was the initial treatment, and when symptoms were not alleviated, a combination of sulbactam sodium and ampicillin and ceftazidime sodium were used. Other possible treatments included meropenem or a combination of imipenem and cilastatin, as well as gentamicin sulfate. All patients were primarily treated with third-generation cephalosporins, carbapenems, or penicillins. All classes of drugs were effective broad-spectrum antibiotics, and previous guidelines suggested the use of effective antibiotics in the treatment of intra-abdominal infections.[37] Four studies[26-29] reported that prophylactic antibiotics were administered intravenously until 48 hours after surgery, which may have influenced the outcomes in the appendectomy group. In the study by Hartwich et al,[25] the perioperative administration of antibiotics was not clearly elucidated. Although all the studies focused on antibiotic therapy, the type, duration, and dose were different in various studies, and no standard criteria were determined for the antibiotic treatment of appendicitis. The use of antibiotics based on clear criteria needs to be determined in additional studies.

Increased length of hospital stay has been an issue regarding the efficacy of antibiotic use as the primary treatment for appendicitis. The lengths of hospital stay in antibiotic groups varied among different studies,[26,27,29] depending on the regimen and type of antibiotic prescribed. Meta-analyses showed significantly longer hospital stays in the nonoperative treatment group; 2 studies stipulated 24 hours[26] or 48 hours[29] of intravenous antibiotic treatment, and the patients were discharged only when tolerating a regular diet. In the trial by Tanaka et al,[27] the patients were hospitalized with continuous intravenous injection of antibiotics until total clinical relief was achieved. This relatively strict standard of discharge in clinical trials may partially explain the longer hospital stays in the antibiotic group; such time in a real-life setting can be reduced. Moreover, the number of disability days was fewer for patients treated with antibiotics than for patients who underwent surgery in the trial by Minneci et al.[26]

The cost of initial inpatient stay was lower for nonoperative treatment in our meta-analysis (mean difference [in US $1000], −$0.70; inverse variance fixed-effects 95% CI, −$0.89 to −$0.51; heterogeneity, $P < .001$; $I^2 = 100\%$). Furthermore, because of the high success rate in all the included studies, the total appendicitis-associated cost of attempting nonoperative treatment in uncomplicated appendicitis is lower after taking treatment failure, recurrence, and elective appendectomy rates into account (mean difference [in US $1000], −$1.31; inverse variance fixed-effects 95% CI, −$1.69 to −$0.92; heterogeneity, $P = .72$; $I^2 = 0\%$). However, primary failure and recurrent appendicitis are associated with high total cost for patients with these situations. In the trial by Hartwich et al,[25] the mean (SD) costs of urgent appendectomy, successful antibiotic treatment, recurrent appendicitis, interval appendectomy, and initial failure of antibiotic treatment were $4130 ($909), $1365 ($247), $5046 ($1952), $5702 ($933), and $8049 ($205), respectively. To increase efficiency, a cautious selection of patients when considering nonoperative treatment in acute appendicitis is very significant.

The avoidance of appendectomy is one of the most important advantages of nonoperative treatment. Of note, in the trials by Svensson et al[29] and Hartwich et al,[25] patients in the antibiotic group undergoing interval appendectomy because of recurrent symptoms or parental request with no evidence of appendicitis in histologic examination had significantly increased hospital stays and costs. The necessity of interval appendectomy after successful nonoperative treatment for uncomplicated appendicitis is limited. In the retrospective study by Puapong et al,[38] 61 patients with acute appendicitis underwent successful nonoperative management, and only 5 (8%) developed recurrent appendicitis. Moreover, in a systematic review that focused on complicated appendicitis,[39] the risk for recurrence in patients who did not undergo interval appendectomy was similar to the risk for morbidity associated with interval appendectomy. In our review, the true recurrence rate (confirmed by histopathologic examination) after successful antibiotic treatment is 27 of 168 patients (16.1%) during the 1-year follow up, and 10 of the patients with recurrence presented with appendicolith. However, results from our meta-analysis showed that nonoperative treatment was not suggested for patients with appendicolith. The recurrence rate can be further reduced if patients with appendicolith are excluded from nonoperative treatment in future studies or in clinical practice. In summary, because the recurrence rate is low after initial successful antibiotic treatment for uncomplicated appendicitis, interval appendectomy could only serve as a backup intervention.

Limitations

One of the major limitations of this study is that only 1 RCT and 4 prospective cohort studies were included. Nonetheless, all included studies were of high quality in accordance with the Newcastle-Ottawa criteria or the Cochrane Collaboration's risk for bias assessment tool (eTable 2 in the Supplement). A 1-year follow-up period was reported in 4 studies. However, Mahida et al[28] ended their study because of a high failure rate in the group receiving antibiotics; the mean follow-up period in their study was 4.7 months, which may have led to a risk for bias.

Conclusions

This meta-analysis provided valuable evidence regarding the outcomes of antibiotic treatment vs appendectomy as initial treatment for pediatric patients with acute uncomplicated appendicitis. The results from the present study show that antibiotic treatment is feasible and effective, with a high rate of success; the risk for treatment failure is higher than that for appendectomy; the presence of appendicolith increases the rate of failure of antibiotic treatment; and initial treatment with antibiotics alone is not associated with increased complications. The cost of the initial hospital stay and total appendicitis-related cost of antibiotic treatment were significantly lower than those of urgent appendectomy. The presence of appendicolith is the main cause for the failure of antibiotic treatment. Surgery is preferably suggested for uncomplicated appendicitis with appendicolith, but the patients who could be cured by conservative treatment need to undergo more detailed clinical evaluation. Larger clinical trials are needed to reveal more precise indications to guide the treatment of acute appendicitis with appendicolith.

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