



## Appendectomy versus Conservative Antibiotics Treatment for Non-Complicated Acute Appendicitis: A Meta-Analysis of Randomized Controlled Trials

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### Abstract

**Purpose:** In this meta-analysis, we compared the safety and efficacy of antibiotic treatment with appendectomy for the primary treatment of uncomplicated acute appendicitis.

**Methods:** A comprehensive search was conducted using MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials to identify randomized controlled trials that compared antibiotic treatment with appendectomy in uncomplicated acute appendicitis. The primary outcome measure was the initial treatment failure rate. Secondary outcomes included the overall treatment failure rate, length of primary hospital stay, time for sick leave, and cost.

**Results:** In total, 1,480 patients from 6 randomized controlled trials (751 undergoing antibiotic treatment, 729 undergoing appendectomy) were included in the final analysis. Overall treatment efficacy in the antibiotic group was 0.77 (95% CI, 0.68 to 0.84;  $P_{\text{chi}^2} < 0.001$ ;  $I^2 = 81.51\%$ ) versus 0.91 (95% CI, 0.81 to 0.96;  $P_{\text{chi}^2} < 0.001$ ;  $I^2 = 80.23\%$ ) in the appendectomy group. There were no differences with regard to overall treatment efficacy (Risk ratio (RR), 0.88; 95% CI, 0.74 to 1.04;  $P_{\text{chi}^2} < 0.001$ ;  $I^2 = 90.98\%$ ; NNT=6), complication rate (Risk ratio(RR), 1.56; 95% CI, 0.48 to 5.05;  $P_{\text{chi}^2} = 0.008$ ;  $I^2 = 71.21\%$ ; NNT=186), hospital stay (mean difference(MD), -0.05; 95% CI, -0.65 to 0.55;  $P_{\text{chi}^2} < 0.001$ ;  $I^2 = 98.24\%$ ), time for sick leave (MD, -4.36; 95% CI, -12.00 to 3.28;  $P_{\text{chi}^2} < 0.001$ ;  $I^2 = 99.45\%$ ) and cost (MD, -12230.46; 95% CI, -17086.77 to -7374.15;  $P_{\text{chi}^2} = 0.321$ ;  $I^2 = 0.00\%$ ).

**Conclusion:** Antibiotic treatment is effective and safe as primary treatment for patients with uncomplicated acute appendicitis. Therefore, antibiotic treatment could be considered as an alternative option in the treatment of patients with acute uncomplicated appendicitis.

**Keywords:** Acute appendicitis; Appendectomy; Antibiotic; Meta-analysis

### Introduction

Acute appendicitis is one of the most common surgical emergencies and early appendectomy has been regarded as the gold standard of therapy since Mc Burney recommended immediate appendectomy in every case of presumed acute appendicitis in order to avoid potential fatal outcome in the pre-antibiotic era [1]. Even though appendectomy has been the mainstay for appendicitis, Coldrey reported treating 471 patients with antibiotics in 1956, relatively soon after antibiotics were available [2]. However, although an initial nonsurgical approach for complicated appendicitis has been relatively widely accepted, mainly on the basis of tradition rather than evidence, the role of antibiotic treatment in acute uncomplicated appendicitis may have been over looked. Non-complicated acute appendicitis is defined as absence of any of criteria of complicated appendicitis with peritonitis: extra luminal gas, periappendiceal fluid, or disseminated intraperitoneal fluid. The rationale of appendectomy in acute appendicitis has its origins in the assumption that nonperforated appendicitis progresses to perforation, with intra luminal appendiceal obstruction as the main cause [3,4]. However, since the beginning of the 20<sup>th</sup> century, many researchers entertained an infectious cause for appendicitis [5-8]. If infection were the prevailing etiology of acute appendicitis, it would be logical to treat it with antibiotics rather than appendectomy. Several randomized controlled trials have been performed and these have also been subjected to meta-analysis [9-14]. Each of these meta-analyses had several limitations such as including withdrawn trial since publication, non-randomized trial, or omitting some published randomized controlled trials, and without definite evidence of superiority, Appendectomy remains the standard approach for treating appendectomy

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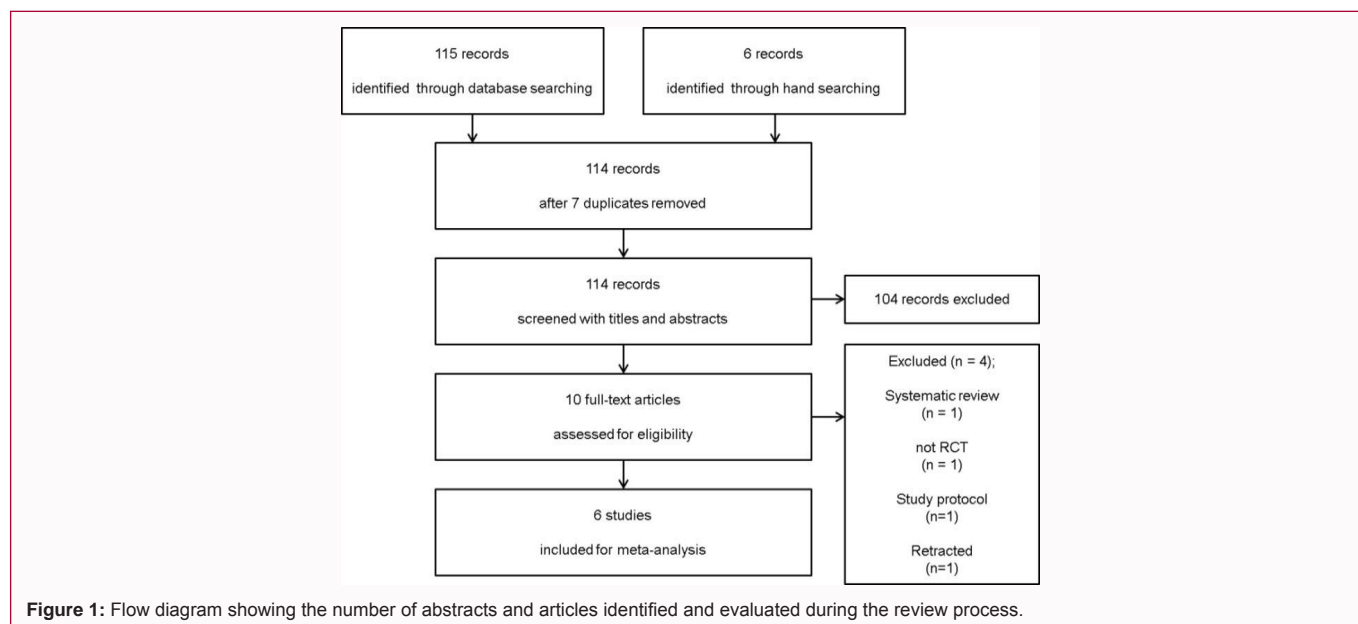
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[15-19]. The meta-analysis presented here provides a valid and up-to-date summary of the relevant literature, including a recently published randomized controlled trial and excluding retracted publication, and publication that is unclear if the patients were randomized. The aim of this meta-analysis for randomized controlled trials was to compare the safety and efficacy of antibiotic treatment with appendectomy for the primary treatment of uncomplicated acute appendicitis.

## Materials and Methods

The present systematic review and meta-analysis was registered in PROSPERO (CRD42016038179) and was conducted following the guideline with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [20].

### Literature search

Two authors (KH and LSE) independently carried out database searches in April 2016 using OVID-MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), and Google Scholar. There were no language limitations in our study. The reference lists of the identified literatures and eligible articles were also searched manually. The following Mesh search headings were used: “complicated appendicitis,” “perforated appendicitis,” “appendiceal abscess,” “appendiceal mass,” “conservative treatment,” “acute appendectomy,” “interval appendectomy,” “comparative study,” and “treatment outcome.” The above terms and their combinations were also searched as text words. The search strategy, which included a combination of free text, Medical Subject Headings and Emtree terms, is described in the Appendix.

### Study selection

The study’s inclusion and exclusion criteria were determined before systematic search. Randomized controlled trials (RCTs) were included that compared surgery (either laparotomy or laparoscopy) with antibiotic therapies alone for the treatment of patients with non-complicated acute appendicitis. Review articles, case reports, case-series, letters to the editor, commentaries, proceedings, laboratory science studies, and any other non-relevant studies were excluded. Two authors (CGJ and SSW) independently scanned the titles and abstracts of the reports identified via the search strategies described

above. If a report was determined eligible from the title or abstract, the full paper was retrieved. Potentially relevant studies chosen by at least one author were retrieved, and full-text versions were evaluated. Two authors (CGJ and SSW) discussed their opinion to arrive at a consensus as to whether a study should be included or excluded. Disagreement over inclusion or exclusion was settled in discussion with a third investigator (LSE).

### Outcome measure

We recorded clinical outcomes according to the intention to treat analysis where available. The primary outcome measure of this meta-analysis was initial treatment efficacy. Treatment efficacy was defined as a patient who was treated successfully with antibiotics without treatment failure. For antibiotics treatment, success was defined as definite improvement without need for surgery and subsequent hospital discharge without an operation. Therefore, initial treatment failure in the antibiotic group was defined as performance of an appendectomy within 48 hrs after initial hospitalization with antibiotics and on the contrary, initial treatment efficacy was defined as completeness of antibiotics treatment with no appendectomy within 48 hrs after initial hospitalization. The secondary outcome measures were overall treatment efficacy, complicated appendicitis, and complication, length of primary hospital stay, sick leave, and costs. Overall treatment failure and efficacy were determined during follow-up period of up to one year. Overall treatment efficacy was defined as no appendectomy during follow-up period of up to one year after antibiotics treatment. For surgical treatment, treatment success was defined as patients who were successfully treated with appendectomy. Complicated appendicitis was defined as perforated or gangrenous appendicitis. Complications included any antibiotic-related or surgery-related morbidity such as abscess formation, ileus, wound infection, and so on.

### Data extraction

All interrelated data from the included studies were independently extracted and entered into standardized forms by two authors (CYS, KH), and then cross-checked. Any discrepancy was resolved through discussion. If an agreement could not be reached, the dispute was resolved with the aid of a third investigator (LSE). The standardized

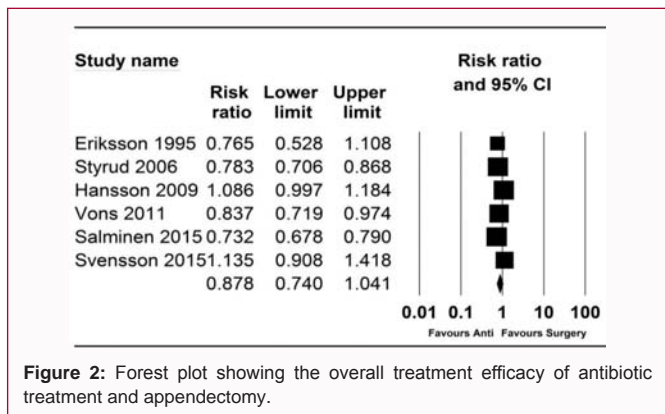


Figure 2: Forest plot showing the overall treatment efficacy of antibiotic treatment and appendectomy.

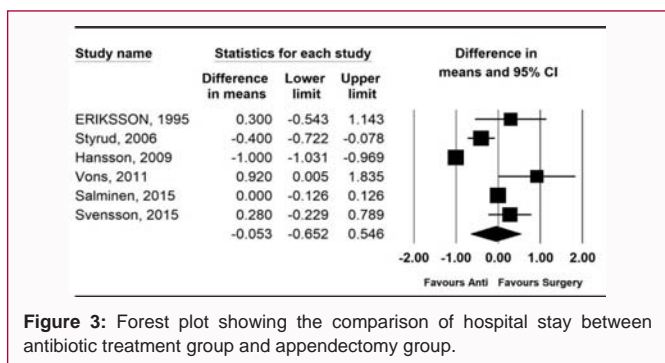


Figure 3: Forest plot showing the comparison of hospital stay between antibiotic treatment group and appendectomy group.

form included the following items: (1) title, (2) name of first author, (3) name of journal, (4) year of publication, (5) study design, (6) registration of clinical trial, (7) competing interest, (8) country, (9) risk of bias, (10) inclusion criteria, (11) exclusion criteria, (12) sex, (13) age, (14) number of patients, (15) diagnosis, (16) regimen of antibiotic used, (17) type of surgery performed, (18) primary and secondary outcome, (19) complication of intervention, (20) hospital stay, (21) time for sick leave, and (22) total cost. The data were initially extracted from tables or text. In cases involving missing or incomplete data, an attempt was made to contact the study authors to obtain the relevant information.

**Risk of bias assessment**

The quality of studies was independently assessed by two authors (CGJ and SSW) using the tool of “risk of bias” according to the software Review Manager (Version 5.3, The Cochrane Collaboration, Oxford, UK). Quality was evaluated using the following potential sources of bias: sequence generation, allocation concealment, blinding of participants or outcome assessor, incomplete data, and selective reporting. The methodology for each study was graded as “high”, “low”, or “unclear”, which reflected a high risk of bias, low risk of bias, or uncertain bias, respectively.

**Statistical analysis**

We conducted this meta-analysis by Review Manager (Version 5.3, The Cochrane Collaboration, Oxford, UK) and Comprehensive Meta-Analysis software (Version 2.0; Biostat, Englewood, NJ, USA). Two authors (KH and LSE) independently input all data into the software. The pooled Risk Ratio (RR) or mean difference (MD) and their 95% Confidence Intervals (CIs) were calculated for each outcome. We used the chi-squared test for homogeneity and the I<sup>2</sup> test for heterogeneity. A level of 10% significance (P<0.1) for the chi-squared statistic or an I<sup>2</sup> greater than 50% was considered to indicate considerable heterogeneity. If the P-value for chi-square

test was >0.10 and the I<sup>2</sup> value was <50%, a fixed effects model was selected. In the cases for which the I<sup>2</sup> value was >50%, a random effects model was used [21,22]. Since, the total number of studies that showed substantial heterogeneity was less than 10; t-statistics (the Hartung-Knapp-Sidik-Jonkman method) were used instead of Z-test in all random effects analysis to lower the error rate [23]. We also conducted sensitivity analysis in terms of heterogeneous outcomes. If the reported data were median (P<sub>25</sub>-P<sub>75</sub>), median (range), or mean (standard error of mean), then mean and standard deviation were calculated from these values [24]. We calculated the number needed to treat (NNT) using a 95% CI based on the absolute risk reduction as an estimate of the overall clinical impact of the intervention [25]. Publication bias was assessed by Begg’s funnel plot and Egger’s linear regression test and a P value <0.05 was used to identify the presence of a publication bias, or funnel plots for each data set were visually assessed for asymmetry. If a publication bias was present, a trim-and-fill analysis was performed to evaluate the effect of that bias [26].

**Ethics approval and consent to participate**

This meta-analysis was approved by the Institutional Review Board in Chung-Ang University Hospital in Seoul, South Korea. No ethical approval or patient consent was required because all analyses were based on previous published studies.

**Results**

The search of OVID-MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL), produced 115 studies, and 6 in manual research. After adjusting for duplicates, 114 studies remained. Of these, 104 studies were discharged, because reviewing the title and abstracts indicated that these studies were not of interest. The full texts of the remaining 10 studies were reviewed in detail and 4 studies were excluded for the following reasons: systematic review (n=1), lack of evidence of randomization (n=1), study protocol (n=1) and retracted article (n=1) [17,27-29]. Thus, 6

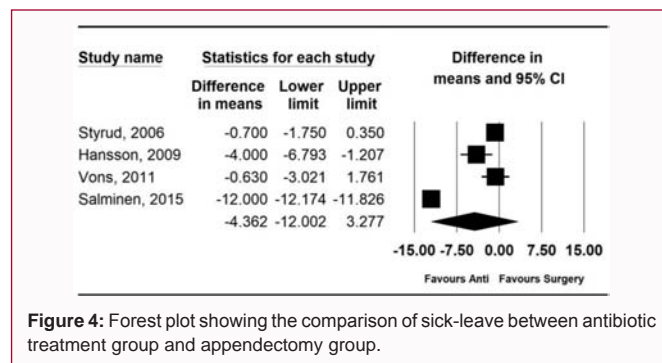


Figure 4: Forest plot showing the comparison of sick-leave between antibiotic treatment group and appendectomy group.

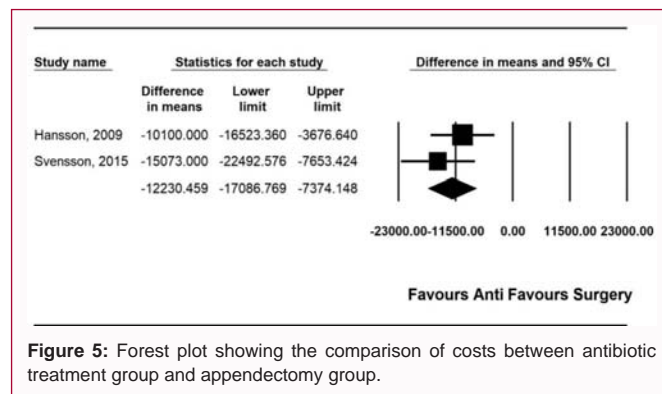


Figure 5: Forest plot showing the comparison of costs between antibiotic treatment group and appendectomy group.

**Table 1:** Descriptive Summary of Six Randomized Trials.

	Eriksson [9]	Styrud [10]	Hansson [11]	Vons [12]	Salminen [13]	Svensson [14]
Location	Sweden	Sweden	Sweden	France	Finland	Sweden
No. participants						
antibiotics	20	128	202	120	257	24
appendectomy	20	124	167	119	273	26
Sex (M/F)						
antibiotics	14-Jun	128/0	103/99	73/47	155/102	14-Oct
appendectomy	13-Jul	124/0	92/75	70/49	174/99	Dec-14
Age (yrs, range)						
antibiotics	27.8 (18-53)	N/A (18-50)	38 (N/A)	31 (N/A)	33.0 (26-47)	12.2 (5.9-15.0)
appendectomy	35.0 (19-75)		38 (N/A)	34 (N/A)	35.0 (27-46)	11.1 (6.2-14.8)
Diagnosis	clinical universal US and CRP	clinical CRP	clinical selective US and CT scan	clinical universal CT scan	clinical universal CT scan	clinical universal US and CT scan
Exclusion	Children	Children, Women	Children	Children	Children	Adult
Intention-to-treat analysis	Yes	Yes	Yes	Yes	Yes	Yes
Laparoscopic technique (n)	N/A	8 (6.5%)	N/A	79 (66.4%)	15 (5.5%)	26 (100%)
Regimen of antibiotics	Cefotaxime 2 g q 12 h + tinidazole 80 mg q d intravenously for 2 days	Cefotaxime 2 g q 12 h + tinidazole 80 mg q d intravenously for 2 days	Cefotaxime 1 g q 12 h + metronidazole 500 mg intravenously for 1 days	Amoxicillin/clavulanic acid (3g/day for weighing <90 kg; 4g/day for >90 kg) given intravenously to patients with nausea or vomiting and orally to others. Total 8 days	Ertapenem 1g qd intravenously for 3 days	Meropenem 10 mg/kg q 8 h + metronidazole 20 mg/kg qd intravenously for 2 days
	Ofloxacin 200 mg q 12 h + tinidazole 500 mg q 12 h orally for 8 days	Ofloxacin 200mg q 12h + tinidazole 500 mg q 12 h orally for 8 days	Ciprofloxacin 500 mg q 12 h + metronidazole 400 mg q 8h orally for 9 days		Levofloxacin 500 mg qd + metronidazole 500 mg q 8 h orally for 7 days	Ciprofloxacin 20 mg/kg q 12 h + metronidazole 20 mg/kg qd orally for 8 days
Normal appendix in appendectomy group (n)	3 (15%)	4 (3.2%)	13 (14.1%)	N/A	2 (0.7%)	0
Perforated appendix in appendectomy group (n)	1 (5%)	8 (6.5%)	44 (26.3%)	21 (17.6%)	2 (0.7%)	5 (19.2%)
Follow up schedule (days)	6,10,30	7,42,365	30,365	15,30,90,180,365	7,60,365	30,90,365
Follow up (months)	7	12	12	12	12	12
Recurrence in antibiotic group (n)	7 (35%)	16 (12.5%)	14 (6.9%)	39 (32.5%)	57 (22.2%)	9 (37.5%)
Time to recurrence (months)	7	4	1/3 within 10days, 2/3 between 3 and 16 mo	N/A	3.4	N/A
Minimum required hospitalization (days)						
antibiotics	2	2	1	no minimum	2	2
appendectomy	no minimum	no minimum	N/A	no minimum	no minimum	no minimum

NA: Not Available

studies with a total of 1,480 patients, of whom 751 patients received antibiotic therapy while 729 patients underwent appendectomy, were included in the final analysis as having met the inclusion criteria and were included in this systematic review and meta-analysis (Figure 1).

### Study description of the trials

A description and summary of each trial's methodology is shown in Table 1. All studies had only two arms, antibiotics or appendectomy. Because of the nature of the treatment arms, none of the studies was blinded. The studies were conducted mainly in Sweden with the exception of one in France and one in Finland

[9-12,14]. Five studies are performed for adult patients except for one study which was conducted in children [9-13]. Selection of the patients in two studies was mainly on clinical grounds, while in recently performed three studies computed tomography scans were obtained from all [10-12,14]. There were differences in the choice of antibiotic, antibiotic dosage, and duration of antibiotic therapy. The details including number of patients, diagnosis and management are summarized in Table 1.

### Risk of bias

The random sequence generation method was clearly described



**Table 2:** Risk of bias.

	Random Sequence generation	Allocation concealment	Blinding	Missing data	Selective reporting	Clinical trial registry	COI
Eriksson3 1995	Unclear	Unclear	No	Unclear	Unclear	Not described	Unclear
Styrud4 2006	Unclear	Yes	No	Unclear	Unclear	Not described	Described
Hansson5 2009	No (Birth date)	No	No	Yes	Yes	Described	Described
Vons6 2011	Yes	Yes	No	Yes	Yes	Described	Described
Salminen7 2015	Yes	Yes	No	Yes	Yes	Described	Described
Svensson82015	Yes	Unclear	No	Yes	Yes	Described	Described

in three studies and one study allocated the patients using birth date which meant that those with an uneven date of birth were allocated to antibiotics and those with an even date of birth to appendectomy group [11-14]. The method for allocation concealment was described in three studies [10,12,13]. Four RCTs were registered in clinical trial, and conflict of interest was described in five studies [10-14]. The overall risks of bias are shown in Table 2.

### Initial and overall treatment efficacy

The initial treatment efficacy in the antibiotic group was 0.78 (95% CI, 0.68 to 0.85;  $P_{\text{chi}^2} < 0.001$ ;  $I^2 = 82.16\%$ ). The overall treatment efficacy in the antibiotic group was 0.77 (95% CI, 0.68 to 0.84;  $P_{\text{chi}^2} < 0.001$ ;  $I^2 = 81.51\%$ ) vs. 0.91 (95% CI, 0.81 to 0.96;  $P_{\text{chi}^2} < 0.001$ ;  $I^2 = 80.23\%$ ) in the appendectomy group. However, the combined result showed no evidence of difference for overall treatment efficacy between the two groups (Risk ratio (RR), 0.88; 95% CI, 0.74 to 1.04;  $P_{\text{chi}^2} < 0.001$ ;  $I^2 = 90.98\%$ ; NNT=6) (Figure 2).

### Complicated appendicitis

Among 172 patients who underwent appendectomy due to the failure of antibiotic treatment, 37 patients (21.5%) were pathologically diagnosed as perforated or gangrenous appendicitis (Event Rate (ER) 0.23; 95% CI, 0.14 to 0.34;  $P_{\text{chi}^2} = 0.071$ ;  $I^2 = 50.75\%$ ). Of the 729 patients who underwent appendectomy, 137 (18.8%) patients had pathological diagnosis of perforated or gangrenous appendicitis (ER 0.23; 95% CI, 0.14 to 0.34;  $P_{\text{chi}^2} = 0.071$ ;  $I^2 = 50.75\%$ ). The combined result showed no evidence of difference for complicated appendicitis between the two groups (Risk ratio (RR), 1.73; 95% CI, 0.76 to 3.94;  $P_{\text{chi}^2} = 0.001$ ;  $I^2 = 76.01\%$ ; NNT=-29).

### Complications

The complication rate was compared between groups in five studies [9-13]. The combined results showed no evidence of difference (Risk Ratio (RR), 1.56; 95% CI, 0.48 to 5.05;  $P_{\text{chi}^2} = 0.008$ ;  $I^2 = 71.21\%$ ; NNT=186). The pooled complication rate in the antibiotics group was 0.13 (95% CI, 0.006 to 0.25;  $P_{\text{chi}^2} < 0.001$ ;  $I^2 = 73.20\%$ ).

### Hospital stay

The hospital stay was compared in all included studies [9-14]. The combined results showed no evidence of difference (MD, -0.05; 95% CI, -0.65 to 0.55;  $P_{\text{chi}^2} < 0.001$ ;  $I^2 = 98.24\%$ ). On performing sensitivity analysis with removing Hansson's study, heterogeneity was decreased and hospital stay became shorter in the surgery group than the antibiotics group, but was still insignificant (MD, 0.06; 95% CI, -0.26 to 0.38;  $P_{\text{chi}^2} = 0.022$ ;  $I^2 = 64.89\%$ ) (Figure 3) [11].

### Sick leave

Sick leave was compared in four studies [10-13]. There were no differences between the groups in days for sick leave (MD, -4.36; 95% CI, -12.00 to 3.28;  $P_{\text{chi}^2} < 0.001$ ;  $I^2 = 99.45\%$ ). On performing sensitivity

analysis with removing which defined duration of disability, and which showed greatest difference between groups, significance did not change significance did not change (MD, -5.59; 95% CI, -14.37 to 3.19;  $P_{\text{chi}^2} < 0.001$ ;  $I^2 = 99.78\%$ , MD, -1.47; 95% CI, -3.28 to 0.33;  $P_{\text{chi}^2} = 0.384$ ;  $I^2 = 0.00\%$ ). (Figure 4) [12,13].

### Cost

Cost was compared in two studies [11,14]. The combined results showed that the cost was lower in the antibiotics group than in the appendectomy group (MD, -12230.46; 95% CI, -17086.77 to -7374.15;  $P_{\text{chi}^2} = 0.321$ ;  $I^2 = 0.00$ ) (Figure 5).

### Publication bias

There was no evidence of publication bias detected by Egger's linear regression test and funnel plot. There was no P-value of Egger's regression test showing  $< 0.05$ , which is indicative of publication bias.

## Discussion

This meta-analysis of six randomized controlled trials including 1,480 patients, of whom 751 patients received antibiotic therapy and 729 patients underwent appendectomy, has demonstrated that there was no significant difference in overall treatment efficacy for uncomplicated appendicitis between the antibiotic group and the appendectomy group. The overall treatment efficacy of the antibiotic group was 0.77 (95% CI, 0.68 to 0.84;  $P_{\text{chi}^2} < 0.001$ ;  $I^2 = 81.51\%$ ) and that of the appendectomy group was 0.91 (95% CI, 0.81 to 0.96;  $P_{\text{chi}^2} < 0.001$ ;  $I^2 = 80.23\%$ ) (Risk (RR), 0.88; 95% CI, 0.74 to 1.04;  $P_{\text{chi}^2} < 0.001$ ;  $I^2 = 90.98\%$ ; NNT=6), and there were no significant differences in either complications, length of hospital stay, or incidence of complicated appendicitis. This meant that there was no increased risk of developing complicated appendicitis even if the patients underwent appendectomy after recurrence despite antibiotics treatment, suggesting that in the primary treatment of uncomplicated appendicitis, antibiotic treatment is as safe an option as appendectomy. To date, several meta-analyses have been published. However, most of these meta-analyses had several limitations, such as including withdrawn trial, non-randomized trial, or omitting some published randomized controlled trials [15-19]. Therefore, conflicting results were offered, and without definite evidence of superiority, appendectomy was thought to be the standard approach for treating uncomplicated appendicitis [17]. When compared with previous meta-analyses, the present meta-analysis included only relevant randomized trials, and a recently published trial [9-14]. There are several theoretical advantages to antibiotics treatment over appendectomy. First, non-operative management for uncomplicated appendicitis could not result in any surgery-related morbidity. Second, there is an absence of incisional pain in the patients treated non-operatively, and this could lead to less pain medication, and shorter sick-leave. Furthermore, several authors reported that

recurrence after antibiotics treatment can be treated efficiently with the administration of a second course of antibiotics [30,31]. However, it could be controversial to conclude that antibiotic therapy was one of the standard treatments for uncomplicated appendicitis, because of several protocol design limitations in the included randomized controlled trials, such as the loose criteria chosen for the definition of acute appendicitis, type and duration of antibiotic treatment, unclear determination of the primary endpoint, and highly restrictive selection. First, acute appendicitis was diagnosed based on clinical examination without confirmation by radiology, or ultrasonography of the right iliac fossa [9-11]. Because of the absence of morphological investigation in the surgical group of two large trials, 10% to 15% of patients did not have appendicitis, and about 40% of patients had complicated appendicitis, which should be excluded [10,11]. Another limitation was the absence of consensus for the selection of antibiotics and duration of the treatment. The route, type and timing of antibiotics administration were variable between the studies. One study administered oral antibiotics as the first line treatment, with the intravenous route only used in patients with nausea and vomiting [12]. The intervention durations of intravenous antibiotics were various, from 24 hr to 72 hrs. The type of antibiotics was also variable, with three studies using a combination of  $\beta$ -lactam (third-generation cephalosporins) and nitroimidazole antibiotics, two using a carbapenem antibiotic, and one using a combination of  $\beta$ -lactam antibiotics [9-14]. The rate of *Escherichia coli* resistant to third-generation cephalosporins is from 10% to 15% in Europe and the United States, and carbapenem is not considered as a first-line antibiotic for uncomplicated antibiotics [32,33]. To be effective treatment, although the antibiotics must provide broad-spectrum coverage for all the pathogens that might cause appendicitis, broad-spectrum antibiotics have the potential problem of a risk of developing antibiotic resistance, hence, future trials should be conducted to determine adequate antibiotics with a more restricted antibacterial spectrum. The next limitation is that the primary end point was not stated or unclear, and if it was stated, the definition for the same end point differed from trial to trial [9-11]. In particular, in the appendectomy group, the definition of treatment efficacy was not obvious. Two studies defined normal appendix on pathology as the treatment failure in the appendectomy group because they regarded normal appendix as significant complication or not appropriate surgical indication [11,14]. Since patients were randomized, the same rate of negative appendicitis could be expected in both antibiotics and appendectomy treatment group. And by considering negative appendicitis only in the appendectomy group as a treatment failure, the results may favor the antibiotics treatment. Since the limits of the Relative Risk confidence interval are closed to 1, considering negative appendicitis only in one group or in both groups may change the conclusion. The relatively large proportions of patients lost to follow-up by 1 year in two trials were also problematic. Another limitation is that most of the appendectomies were performed using an open operative approach [10,11]. Nowadays, for uncomplicated appendicitis, laparoscopic appendectomy has become the preferred method with less pain, shortened hospital stay, faster return to normal activity, and fewer wound infections and the European Association for Endoscopic Surgery (EAES), the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) and World Society of Emergency Surgery (WSES) have recommended laparoscopic surgery as the gold standard [3-7]. Considering that the most common cause of morbidity in the surgical group of this meta-analysis related to wound infection, the complication rate of the

appendectomy group might become lower, if the appendectomy was performed using laparoscopy [34-36]. Furthermore, recently there have been several reports that laparoscopic appendectomy can be performed successfully on an outpatient basis. In this regard, future trials should compare antibiotics group and laparoscopic appendectomy group with an admission basis or with an outpatient basis [37-39]. The high rate of protocol violation is also a limitation. In one study, 50% of patients allocated to antibiotic treatment underwent appendectomy immediately after randomization [11]. The recurrence rates may not be representative of the true recurrence rates after antibiotic therapy because of the relatively short follow-up of within one year. Unfortunately, there are still no follow-up data extending beyond 1 year after conservative management. Further long-term surveillance for the antibiotic group is required to establish the true recurrence rate. The obvious advantage of surgery is the complete and long-term avoidance of further appendicitis. The present meta-analysis showed that 28.8% of the patients, i.e., about one of three patients, experienced readmission and surgery after antibiotics treatment. Despite the evidence reinforcing the safety and efficacy of primary antibiotic therapy for the patients with uncomplicated appendicitis this treatment has not yet gained widespread acceptance. Also, it should be considered that the general lifetime risk of 6.7% to 8.6% for acute appendicitis persists in antibiotics group patients [15,40,41]. The low rate of false-negative appendectomies also shows that unnecessary appendectomies are rare in these times of improved diagnostic tools. Therefore, to establish antibiotics treatment as a first line alternative treatment for uncomplicated appendicitis, further study of risk factors for recurrence after antibiotics treatment, and to decrease treatment failure should be performed. Regardless of limitations of already published randomized controlled studies, our study applied rigorous methodology, excluding withdrawn article and non-randomized trial, and including omitted study in other meta-analyses, to compare safety and efficacy of the antibiotic treatment with appendectomy as a primary treatment of uncomplicated acute appendicitis.

## Conclusion

Despite the above limitations, this meta-analysis reveals that antibiotic therapy could be considered as an alternative option in the treatment of patients with acute uncomplicated appendicitis. If the patient is willing to accept initial failure or a subsequent recurrence, and forgoing appendectomy, antibiotic treatment can be recommended. However, to be established as the gold standard of treatment, further well-organized randomized controlled trials should be performed.

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