

SYSTEMATIC REVIEW

Should Antibiotic Treatment or Surgery be First-Line for Acute Uncomplicated Appendicitis? A Systematic Review

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Abstract

Background: Acute appendicitis is the sudden inflammation of the vermiform appendix. It is the most common abdominal emergency. Appendectomy, performed open or laparoscopically, has been the mainstay in the treatment of uncomplicated appendicitis. This technique has numerous advantages, namely the impossibility of recurrence. The use of antibiotic-only treatment for acute appendicitis has associated benefits and risks. Procedure specific complications of appendectomy such as wound infections and incisional hernias can be avoided. This treatment option is gaining popularity amongst patients due to these potential benefits.

Aim: To determine whether appendectomy or antibiotic treatment is superior as first-line treatment for acute uncomplicated appendicitis.

Methods: Several databases were searched to identify published literature relevant to this field of study. The databases used were Cochrane Library, Medline, and PubMed. Articles that reported on trials utilising antibiotics or surgery for the treatment of acute uncomplicated appendicitis were selected and further screened to ensure that they were randomised controlled trials, 'English full-text articles' that were published in peer-reviewed journals from the years 2010-2021. Other types of research studies such as case reports and meta-analyses alongside studies that involved participants aged 16 or younger were excluded.

Results: The initial search identified a total of 124 studies. Of these studies, 47 duplicates were excluded and the remaining 77 underwent title and abstract screening. From this screening, 20 studies were identified for a full-text study, which led to the inclusion of 10 papers for this review. On review of these studies, all 10 of these random controlled trials compared the outcomes between antibiotics and surgical intervention for the treatment of acute uncomplicated appendicitis.

Conclusions: There is insufficient evidence to suggest that antibiotic therapy should replace appendectomy as first-line treatment for acute uncomplicated appendicitis. However, while antibiotic therapy failed to meet the criteria for superiority compared with appendectomy in several major studies, consideration should be given to the other advantages of antibiotic therapy, especially in resource-poor countries, where it can be used to free up hospital beds for emergencies that warrant greater care and intervention.

Keywords: Acute uncomplicated appendicitis, Appendectomy, Antibiotic therapy

Introduction

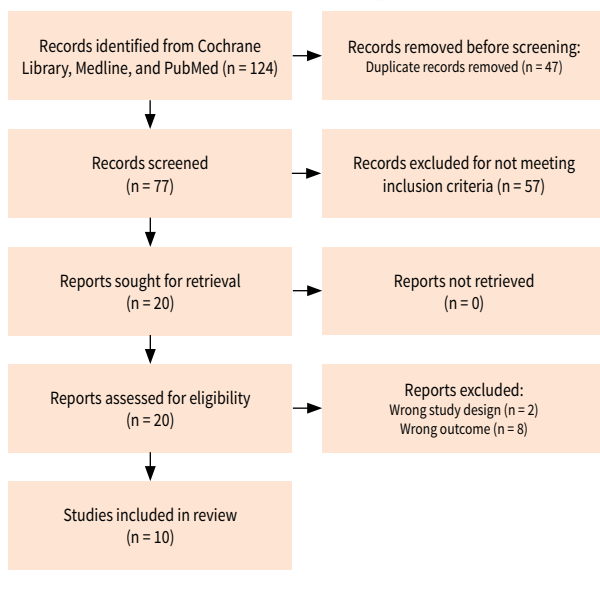
Appendicitis is the sudden inflammation of the vermiform appendix. It is the most common abdominal emergency, accounting for an estimated 17.7 million cases and over 33,400 deaths in 2019¹. The incidence of appendicitis, although stable in most western countries, is suggested to be rising rapidly in newly industrialised countries, underscoring the importance of developing novel treatments².

Appendectomy, performed open or laparoscopically, has long been the mainstay in the treatment of uncomplicated acute appendicitis. First performed in the late 19th century, this technique is described to

have numerous advantages, namely the impossibility of recurrence³. It is considered to be a relatively safe procedure with a mortality rate of 0.8 per 1000 for acute uncomplicated appendicitis⁴. However, the incidence of postoperative complications such as wound infections and the formation of intra-abdominal masses have been reported in as high as 40% of all appendectomy patients⁵. Furthermore, surgical intervention may not be feasible due to patient co-morbidities, or a patient's preferences given the assumption of higher associated costs and longer duration of absence from work⁶.

The use of antibiotics-only treatment for acute appendicitis was first described by Harrison in 1953 and

Figure 1. PRISMA Chart Highlighting Inclusion/Exclusion of Articles at Different Stages of the Review



has associated benefits and risks⁷. Procedure specific complications of appendectomy such as wound infections or incisional hernias can be avoided, with the potential trade-offs being higher rates of recurrence and associated readmission for appendectomy⁸. Given the potential benefits, it is no surprise that this treatment option is gaining popularity amongst patients, with a 2021 survey finding that 49.2% of patients preferred antibiotic-only treatment for acute uncomplicated appendicitis⁹. Through critical analysis of several existing studies, this systematic review will contribute further insight into the outcomes of antibiotic treatment for uncomplicated acute appendicitis in comparison to surgery and draw firmer conclusions for their use. Its implications may also have potentially life-saving role in resource poor countries.

Methods

Several databases, including Cochrane Library, Medline, and PubMed, were used because of their relevance to this field of study. The search terms used in each database were as follows: (antibiotics) AND (surgery OR appendectomy) AND (acute uncomplicated appendicitis).

In this systematic review, we only included randomised controlled trials (RCTs) that investigated the effects of antibiotic treatment or surgery for first-line treatment of acute uncomplicated appendicitis. Other types of research studies such as case reports and meta-analyses alongside studies that involved participants aged 16 or younger were excluded. Only 'English full-text articles' published in peer-reviewed journals from the years 2010–2021 were included.

In total, 124 papers were obtained through the initial search and imported into Covidence for a thorough screening process comprising three major components. Every article in each component was screened by two independent reviewers to ensure eligibility according

to the predetermined criteria. Any disagreements on an article were resolved by a third independent reviewer.

Results

The initial search identified a total of 124 studies. Of these studies, 47 duplicates were excluded and the remaining 77 underwent a title and abstract screening. From this screening, 20 studies were identified for a full-text analysis, which led to the inclusion of 10 papers for this review. On review of these studies, we identified 10 RCTs which met our inclusion criteria. The remaining articles were excluded as they were either not published yet, followed the wrong patient population or were the wrong study design. **Figure 1** details the number of studies that were included/excluded at each stage of the review.

We selected RCTs because they are the highest quality of evidence. Nevertheless, we recognise that all studies have a risk of bias. Regarding the 10 studies that were included within our review, they are all RCTs that compared the outcomes between antibiotics and surgical intervention for the treatment of acute uncomplicated appendicitis. **Tables 1–2** summarises the key data in each study.

Discussion

This review compared antibiotic treatment and appendectomy for acute uncomplicated appendicitis by examining the recurrence rate (only relevant in the antibiotics group), length of stay, quality of life, complication rate, acceptance of each treatment, and cost.

Advantages of Antibiotics vs. Surgery

Antibiotics treatment had several major advantages, most notably significantly lower overall complication rates compared to appendectomy^{6,8,12}.

Appendectomy does involve a risk of postoperative complications in approximately 2–23% of patients, with 3% of patients developing adhesions related to the appendectomy leading to hospital readmission in the following 10 years¹⁴. Salminen et al. described complications like surgical site infection, incisional hernias, abdominal or incisional pain, or obstructive symptoms in 24.4% of the surgical group and 6.5% in the antibiotics group within 5 years¹⁰. Thus, in terms of the complication rate, antibiotics may be superior to appendectomies. In the Antibiotic Therapy versus Appendectomy for the treatment of Uncomplicated Acute Appendicitis (APPAC) trial, the commonest cause of morbidity in the appendectomy group was related to wound infections.

Due to significant investments of time, cost, and training involved, laparoscopic appendectomies are more common in areas that are able to afford these investments. This study suggests antibiotics may be more useful in resource-limited areas¹⁰. Antibiotic treatment was also associated with significantly lower total costs, in terms of overall social costs and sick leave (3.6 days shorter)^{10,11,13}, and even after adjusting for age and sex¹³.

According to Prechal et al. there is a high level of acceptance of antibiotic treatment among acute

Table 1. Studies included in the review

Reference	Study Design	Number of Participants	Primary Outcome(s)	Secondary Outcome(s)	Results (Group A = Cohort receiving surgery, Group B = Cohort receiving antibiotics)
(2018) ¹⁴	RCT	45	The primary outcome was the success rate (resolution of symptoms within 2 weeks and no need for further treatments).	Secondary outcomes were complication rate; negative appendectomy rate (only in surgical arm); and long-term outcomes within a year as recurrence.	In group A, all participants obtained the primary outcome (success), however there were negative secondary outcomes which were noted for five patients; two of which presented with negative appendectomies and the remaining three with wound infections. On the contrary, within group B, the treatment failed for 16.8% of the patients. Furthermore, one of the patients experienced relapse at 30 days.
(2017) ¹²	RCT	130	Outcomes such as hospital stay, complications, recurrence within one year and patient's satisfaction were examined.	Outcomes such as hospital stay, complications, recurrence within one year and patient's satisfaction were examined.	Regarding hospital stay, Group A had an average stay of 2.02 +/- 0.85 days, versus 6.28 +/- 2.44 days in group B. Furthermore in regards to recurrence within 1 year, group A was found to be 1.54% versus group B which was 27.69%. Additionally, in group A, 96.92% of patients were satisfied, compared to 67.64% patients in group B. However, regarding complications, group B had a 3.08% complication rate when compared to 15.38% in group A.
(2017) ¹⁷	RCT	227	Outcomes that were examined included duration of pain (in hours), duration of hospital stay, conversion to surgery, duration of days for absence from work, and negative appendectomies.	N/A	The duration of pain and analgesic consumption was much higher in group B in comparison to group A for the first 2 days after surgery. However, the intensity of pain started to decrease after 2 days in group A and 4 days in group B. There were no noted differences in the 1 month follow up. Furthermore, the duration of hospital stay was longer for group B than group A. Additionally, the mean cost therapy was more expensive in group B when compared to group A. On the other hand, group A experienced much more infections than group B.
(2021) ¹¹	RCT	186	The primary end-point for the trial evaluated the success rate of antibiotic treatment only for acute uncomplicated appendicitis at 1-year follow-up. In the operative arm, the primary endpoint was defined as successful appendectomy, which was expected to be 100%.	Secondary end-points included a comparison of quality of life, cost and length of stay between the 2 study groups.	There was a significantly better EQ-VAS quality of life score in group A compared with group B at 3 months, 94.3 vs 91.0, and at 12 months 94.5 vs 90.4. The accumulated 12-month sickness days was 3.6 days shorter for the group B when compared to group A, 5.3 vs 8.9 days. The mean length of stay in hospital for both groups was not significantly different, 2.3 vs 2.8 days. However, the mean total cost was significantly higher for group A in comparison to group B, €4,816 vs €3,077.
(2017) ¹⁵	RCT	124	The primary endpoint was treatment success, defined as no secondary appendectomy during follow-up and no recurrent appendicitis treated conservatively (primary antibiotic group), or successful appendectomy, defined as performed appendectomy (primary appendectomy group).	Secondary endpoints were duration of hospitalization, pain intensity (measured on a numeric rating scale, NRS), incidence and type of complications (according to the Clavien-Dindo classification), and duration of absence from work (only in the primary antibiotic group).	Treatment success at 1 year was 77.1% in group B and 100% for Group A. The initial hospital stay was significantly shorter in group B compared to group A, with a mean of 3.6 vs. 4.8 days. After 1 year, the cumulative hospital stay was not different between groups.

Table 2. Studies included in the review (Cont.)

Reference	Study Design	Number of Participants	Primary Outcome(s)	Secondary Outcome(s)	Results (Group A = Cohort receiving surgery, Group B = Cohort receiving antibiotics)
(2015) ⁸	RCT	530	The primary end point for patients in the antibiotic group was resolution of acute appendicitis, resulting in discharge from the hospital without the need for surgical intervention and no recurrent appendicitis during a minimum follow-up of 1 year (treatment efficacy). Treatment success in the appendectomy group was defined as a patient successfully undergoing an appendectomy.	Secondary end points included overall post-intervention complications, late recurrence (after 1 year) of acute appendicitis after conservative treatment, length of hospital stay and the amount of sick leave used by the patient, post-intervention pain scores (VAS score range, 0-10; a score of 0 indicates no pain and 10 indicates the worst possible pain), and the use of pain medication. Post-intervention complications included clinical wound infection (surgical site infection) occurring within 30 days after the operative procedure as diagnosed by a surgeon or with a positive bacterial culture, 19 other general postoperative complications (eg, pneumonia), adverse effects of the antibiotic treatment (eg, diarrhea), incisional hernia, possible adhesion-related problems (eg, bowel obstruction), and persistent abdominal or incisional pain.	In Group A there was a success rate of 99.6%, however in group B 27.3% were forced to undergo appendectomy within 1 year of initial presentation for appendicitis.
(2017) ¹⁸	RCT	530	The primary endpoint in the antibiotic group was resolution of acute appendicitis, resulting in discharge from the hospital without the need for surgical intervention and absence of recurrent appendicitis during 1 year. In the operative group, treatment success was defined as successful appendectomy.	Secondary outcomes included overall post-intervention complications, late recurrence (after 1 year) of acute appendicitis following conservative treatment, length of hospital stay and duration of sick leave, post-intervention pain scores and use of pain medication. The present study focuses on all secondary outcomes with an effect on the overall societal costs in the context of evaluating the economic effects of both randomized treatment options with a 1-year follow-up.	In group A, the overall societal costs were 1.6 times higher than those in group B. Additionally, those in group A were prescribed significantly more sick leave than those in group B, 17.0 versus 9.2 days respectively. When the age and sex of the patient as well as the hospital were controlled for simultaneously, the operative treatment generated significantly more costs in all models.
(2018) ¹⁰	RCT	530	N/A	Pre-specified secondary end points reported at 5-year follow-up included late (after 1 year) appendicitis recurrence after antibiotic treatment, complications, length of hospital stay, and sick leave.	The cumulative incidence of appendicitis recurrence was 34.0% at 3 years, and 37.1% at 5 years. Of the 85 patients in group B who subsequently underwent appendectomy for recurrent appendicitis, 76 had uncomplicated appendicitis, 2 had complicated appendicitis, and 7 did not have appendicitis. At 5 years, the overall complication rate was 24.4% in group B. There was no difference between groups for length of hospital stay, but there was a significant difference in sick leave (11 days more for group A).
(2020) ¹³	RCT	530	N/A	Post-hoc secondary end points of post-intervention QOL (EQ-5D-5L) and patient satisfaction and treatment preference were evaluated.	The quality of life between both groups was similar. Patients in group A were more satisfied in the treatment than patients in group B (68% very satisfied, 21% satisfied, 6% indifferent, 4% unsatisfied, and 1% very unsatisfied in group A and 53% very satisfied, 21% satisfied, 13% indifferent, 7% unsatisfied, and 6% very unsatisfied in group B). There was no difference in patient satisfaction after successful antibiotic treatment compared with appendectomy.
(2011) ¹⁴	RCT	243	The primary binary endpoint was the occurrence of peritonitis within 30 days of initial treatment. Appendectomy done within 30 days of treatment initiation in the antibiotic group was not a primary endpoint if complicated appendicitis with peritonitis was not identified at surgery.	Secondary endpoints were the number of days with a post-intervention visual-analogue-scale pain score > 4 (on a 0-10 scale), 15 lengths of hospital stay and absence from work (total days including any additional hospital stays), incidence of complications other than peritonitis within 1 year (postoperative wound abscess, incisional hernia, adhesive occlusion), and recurrence of appendicitis after antibiotic treatment (appendectomy done between 30 days and 1 year of follow-up, with a confirmed diagnosis of appendicitis).	30-day post-intervention peritonitis was significantly more frequent in group B than group B, 8 vs 2% respectively.

uncomplicated appendicitis patients and only 1 patient in this study opted for surgical treatment after evidence-based disclosure of the advantages and disadvantages of both treatments¹⁵. Additionally, studies exist that show that uncomplicated appendicitis could resolve in the first few days of antibiotic treatment, questioning the need for invasive surgery in this cohort of patients¹⁰.

Disadvantages of Antibiotics vs. Surgery

The major downside of antibiotic treatment that is circumvented with appendicectomy is the possibility of appendicitis recurrence, as evidenced by many studies^{8,10,11}. The rate for secondary appendicectomy post-antibiotic treatment was 27.3% within 1 year and was 39.1% within 5 years in the APPAC trial¹⁰. Antibiotics were also associated with longer hospital stays^{8,12,13}, though possibly due to predefined protocols in place to ensure patient safety.

In the 2011 RCT by Vons et al. comparing amoxicillin plus clavulanic acid with appendicectomy, antibiotic treatment failed to meet the criteria for non-inferiority to emergency appendicectomy for acute uncomplicated appendicitis due to significantly higher rates of 30-day post-intervention peritonitis in the antibiotics group (8%) compared to the appendicectomy group (2%)¹⁴. However, this may be due to many reasons, including errors during inclusion and randomisation, difficulty in differentiating between complicated and uncomplicated appendicitis even with multiple-detector CT scans, and antibiotic resistance among the causative bacterial⁴. Importantly, the presence of appendicoliths was associated with significantly increased risk of complicated appendicitis and failure of antibiotic treatment, and on the exclusion of the subgroup of patients with appendicoliths (which was not in their exclusion criteria), results showed no significant difference in 30-day post-intervention peritonitis rates between the antibiotics and surgery groups¹⁴.

Furthermore, Sippola et al. concluded that long-term patient quality of life was similar for both interventions, but patients who had antibiotic therapy and later had appendicectomy were less satisfied and 33% of these patients would not choose antibiotics as their primary treatment again¹³.

Thus antibiotic therapy may be inferior to appendicectomy as first-line treatment of acute uncomplicated appendicitis in terms of appendicitis remission, post-intervention peritonitis rates and long-term patient satisfaction.

Strengths, Limitations and Biases

A strength of this review is the qualitative approach in analysing existing literature due to the heterogeneity between the studies in terms of their procedures, methods, criteria, outcomes, and so on.

However, there are several limitations in the studies reviewed. There was difficulty in recruiting patients in several studies^{8,16}, possibly due to open appendicectomy being the mainstay of treatment⁸, which potentially reduced the power of the studies and made them inadequate to support the primary and secondary outcomes. Additionally, given that acute appendicitis,

especially if complicated, is considered a medical emergency, this might have posed difficulties during the research process¹⁶.

Another limitation is the possible bias that may be introduced if all patients with suspected complicated appendicitis underwent primary appendicectomy, such as in the study by Prechal 2019¹⁵. Also, there was difficulty in performing a randomised double-blinded placebo-controlled trial in some studies like the APPAC trial, where they were unable to blind participants, clinicians, and research assessors⁸.

Furthermore, the choice of antibiotics differed between studies, some of which may not be the most appropriate for the patient. Amoxicillin and clavulanic acid used in the trial by Vons et al.¹⁴ only provide limited coverage for *E. coli*, a major part of gut flora, and the efficacy of antibiotics may also be undermined by the rising incidences of resistant bacteria⁸.

Conclusion

Antibiotic therapy as a first-line treatment option over appendicectomy in acute uncomplicated appendicitis has many tangible benefits for patients and the healthcare system. It also has some disadvantages compared to appendicectomy. The advantages include shorter initial hospital stays and significantly lower total costs, in terms of overall societal cost and sick leave. Antibiotic therapy was also associated with significantly lower rates of complications post-intervention. However, antibiotic therapy was also associated with a higher rate of recurrence and significantly higher rates of peritonitis post-intervention. Although antibiotic treatment failed to meet the criteria for noninferiority compared with appendicectomy in several major studies⁸, consideration should still be given to the other advantages of antibiotic use, especially in resource-poor countries, to free up hospital beds for emergencies that warrant greater care and intervention, and in the cohort of patients with uncomplicated appendicitis who may not require surgical intervention as much as those with complicated appendicitis.

Further studies may be warranted to identify the best antibiotic regimens in the treatment of acute uncomplicated appendicitis, as well as further stratification of patients to be channelled through different treatment regimens for optimal outcomes. Depending on their presentation, some patient cohorts may not need invasive interventions like appendicectomies, some may benefit from different antibiotic combinations, and some may derive the greatest benefit from surgical intervention. ◀

Declarations

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Liz Birdie Ong Shi Yun is a section editor with the TSMJ. This article was anonymised following submission and subsequently reviewed and accepted by an independent team of editors and peer reviewers as per the TSMJ's peer review and article acceptance protocol.

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