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REVIEW

Antibiotic therapy for acute uncomplicated appendicitis: a systematic review and meta-analysis

Daniela Prechal[1] · Fuad Damirov[2] · Maurizio Grilli[3] · Ulrich Ronellenfitsch[4]

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Abstract

Purpose Appendectomy has been the gold standard for every form of appendicitis. In recent years, though, it has repeatedly been claimed that for acute uncomplicated appendicitis, antibiotic therapy can be an equivalent treatment. The aim of this meta-analysis was to determine if antibiotic therapy is a safe and effective alternative to appendectomy for acute uncomplicated appendicitis.

Methods In a systematic literature review, relevant databases were searched for randomized studies comparing appendectomy with antibiotic treatment for uncomplicated acute appendicitis. Two independent reviewers performed study selection and data extraction. The primary endpoint was the successful treatment of appendicitis. Secondary endpoints were pain intensity, duration of hospitalization, absence from work, and the incidence of complications.

Results Five randomized controlled studies ($n = 1430$ patients) fulfilled the inclusion criteria. Of the 727 patients treated initially with antibiotics, 272 (37.4%) underwent secondary appendectomy within 1 year (treatment effectiveness: 62.6% compared to 96.3% in the surgical group, RR 0.65, 95% CI 0.55–0.76, $p < 0.00001$). Neither duration of hospital stay (MD 0.11 days, 95% CI: − 0.22–0.43, $p = 0.53$) nor the probability of complication-free treatment (RR 1.08, 95% CI: 0.97–1.22, $p = 0.16$) were significantly different between the two treatments. Absence from work was significantly shorter in the antibiotic group (MD − 2.49 days, 95% CI: − 4.59–− 0.40, $p = 0.02$).

Conclusions This meta-analysis shows that appendectomy is more effective than antibiotic therapy for definitive cure of acute uncomplicated appendicitis. However, since the incidence of complications does not differ between the two treatments, antibiotic therapy might be a reasonable alternative for selected patients.

Keywords Antibiotic therapy · Acute uncomplicated appendicitis · Conservative treatment · Non-operative treatment · Meta-analysis · Systematic review

Introduction

The lifetime risk of appendicitis is 8.6% for males and 6.7% for females [1]. Appendicitis is one of the most frequent specific underlying causes in patients presenting to emergency departments with abdominal pain [2, 3]. For a long time, every form of appendicitis was an unconditional indication for appendectomy [4]. A conservative approach to treatment of acute appendicitis without complications was first described in 1953 by Harrison [5] and in 1959 by Coldrey et al. [6]. Coldrey reported on 471 patients treated with antibiotics with low mortality (0.2%) and low recurrence rate (14.4%) [6]. In recent years, antibiotic therapy for acute uncomplicated appendicitis (i.e., appendicitis without perforation, peritonitis, abscess, or coprolite) has repeatedly been promoted as equivalent and safe treatment alternative. Both appendectomy and

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✉ Ulrich Ronellenfitsch
ulrich.ronellenfitsch@uk-halle.de

[1] Medical Faculty Heidelberg, Im Neuenheimer Feld 672, 69120 Heidelberg, Germany

[2] Department of Surgery, Medical Faculty Mannheim of the University of Heidelberg, University Medical Center Mannheim, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany

[3] Department of Library and Information Sciences, Medical Faculty Mannheim of the University of Heidelberg, University Medical Center Mannheim, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany

[4] Department of Visceral, Vascular and Endocrine Surgery, University Hospital Halle (Saale), Ernst-Grube-Str. 40, 06120 Halle (Saale), Germany

antibiotic therapy have benefits and associated risks. One clear advantage of antibiotic therapy is that procedure-specific postoperative complications, such as wound infections, intestinal adhesions, or incisional hernias, can be avoided [7]. Furthermore, conservative therapy spares patients from anesthesia-associated risks, which may play a particular role in comorbid patients. Further advantages of antibiotic therapy are the potentially shorter hospitalization, a presumed shorter duration of absence from work and lower costs [8]. On the other hand, the main risk associated with antibiotic therapy is its failure. Primary uncomplicated appendicitis could turn into a complicated form, and appendiceal perforation with peritonitis or perityphlitic abscess and possibly sepsis can occur, requiring secondary, often more invasive surgery, at worst leading to irreversible morbidity or mortality. Furthermore, there is the risk of recurrent appendicitis. Another risk of widespread antibiotic therapy for appendicitis is the development of antibiotic resistance [9].

Several randomized controlled trials have compared antibiotic therapy with appendectomy for acute uncomplicated appendicitis [8, 10–13]. Results and potential degree of bias differ between the single trials. A Cochrane systematic review with meta-analysis summarized the evidence published until 2011 [14]. However, it also included quasi-randomized trials of inferior evidence level. After publication of this review, the results of the hitherto largest randomized controlled trial on antibiotic therapy of uncomplicated acute appendicitis became available [8]. Therefore, we decided to summarize the most up-to-date evidence on the topic by means of a new systematic review with meta-analysis.

Methods

The systematic review and meta-analysis were carried out in line with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15] (Fig. 1) and according to a pre-specified protocol. The selection of studies and data extraction were performed independently by two investigators (FD, DP) at all stages. Cases of disagreement were resolved by a third investigator (UR).

Selection process and identification of the relevant studies

For the selection of studies, the following electronic databases were searched (see Online Resource 1 for a detailed search strategy according to the PICO scheme): PubMed, Cochrane Library, Web of Science Core Collection, Cinahl, ClinicalTrial.gov (study registry), ICTRP (study registry). The time period November 1965 to January 2016 was considered; the search had no limitations regarding language of publication. Identified studies were checked with regard to title and abstract. If the study met the inclusion criteria, or if this could not be determined from the abstract alone, the full text was retrieved and assessed.

Inclusion criteria

Randomized controlled trials with the following criteria were included into the meta-analysis: patients ≥ 18 years with acute uncomplicated appendicitis, i.e., without signs of perforation, peritonitis, abscess, or coprolite, which compared antibiotic therapy, i.e., any kind of treatment with oral or intravenous antimicrobial medication, with surgical therapy, i.e., any form of appendectomy.

Studies including patients with clinical signs of perforation or peritonitis or suspicion of a tumor or abscess were not included. Studies that compared different forms of appendectomy (e.g., laparoscopic vs. open) and studies performed exclusively among children or minors (age < 18 years) were also not considered. Only studies reporting at least one of the endpoints mentioned below were selected.

Endpoints

The primary endpoint was the successful treatment of acute appendicitis. In patients treated with antibiotics, successful treatment was defined as absence of a later need for surgical intervention (appendectomy) and absence of recurrent appendicitis, diagnosed by the criteria defined in the single study, during the follow-up period defined by each study. In patients treated with surgery, successful treatment was defined as performed appendectomy.

Secondary endpoints were the incidence and type of complications, duration of hospitalization, duration of absence from work, and pain intensity.

Data extraction

The following data were extracted from the studies according to pre-defined criteria using a standardized data extraction sheet:

- general information: title, authors, contact address, date of publication, place of publication
- study design: mode of randomization, single-center vs. multicenter, duration of follow-up
- patient sample: number of patients in each study arm, age, sex
- used diagnostic procedures: computed tomography (CT scan), sonography, laboratory (C-reactive protein (CRP), hemoglobin, creatinine, leukocytes, temperature)
- form of treatment: antibiotic therapy: which antibiotics were used for how long; surgery: laparoscopic or open appendectomy

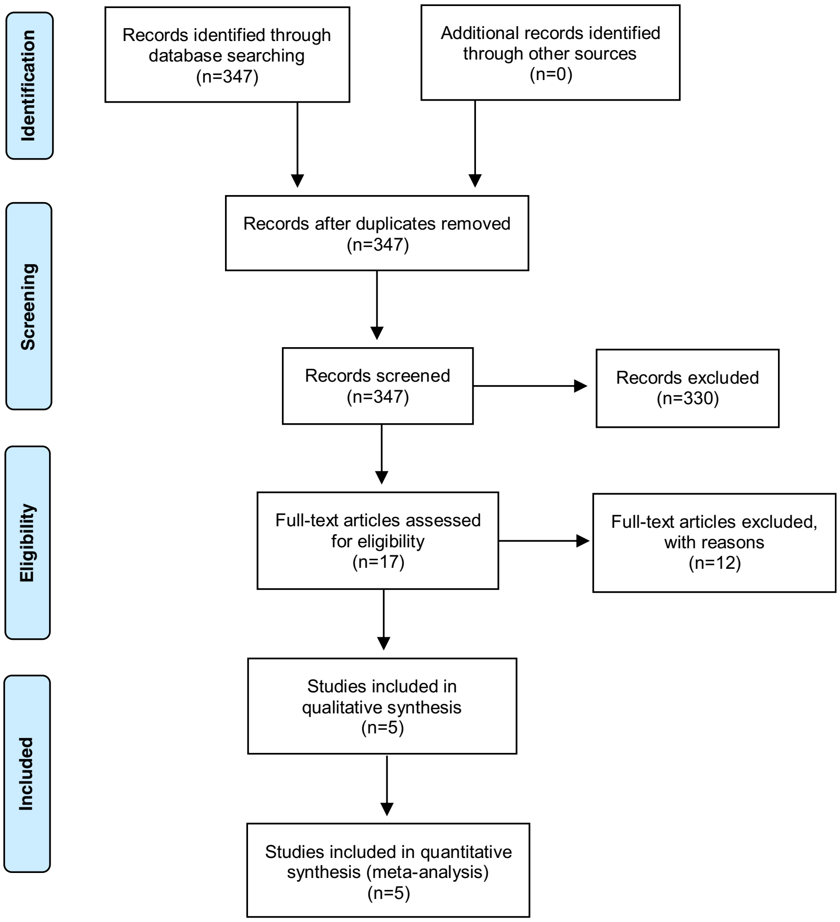


Fig. 1 Flow chart-process of study selection

- outcomes: successful treatment (see above), pain intensity, duration of hospitalization, duration of absence from work, incidence of complications

Evaluation of the methodological quality of the included studies

In order to evaluate possible bias of the included studies, the risk of bias tool of the Cochrane Collaboration was used [16]. Studies were evaluated with regard to selection bias, performance bias, detection bias, and attrition bias. From these domains, a total risk of bias was determined with the following levels: low risk of bias, high risk of bias, or unclear risk of bias.

Statistical analyses

For statistical analyses, the ReviewManager 5.3 software provided by the Cochrane Collaboration was used (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Data entry was verified by an independent reviewer (UR).

A p value of < 0.05 was considered statistically significant. For dichotomous variables, the relative risk with a 95% confidence interval (95% CI) was calculated. For continuous variables, the mean difference with a 95% CI was calculated. All meta-analyses were performed using a random-effect model. I^2 was used to quantify heterogeneity between the individual studies. Following the recommendations of the Cochrane Collaboration [17], I^2 values were interpreted as follows:

- I^2 = 0–40% negligible heterogeneity
- I^2 = 30–60% moderate heterogeneity
- I^2 = 50–90% substantial heterogeneity
- I^2 = 75–100% considerable heterogeneity

Results

Literature review

The results of the literature review are shown in Fig. 1. A total of 347 publications were identified from searching the databases. After assessment of titles and abstracts, 17 publications were selected and their full text retrieved. Based on the full text article, five publications [8, 10–13] fulfilled all inclusion criteria and were selected for the meta-analysis. See Online Resource 2 (Table 1) for details of study characteristics.

In total, the selected studies comprised 1430 patients, 727 of whom were treated with antibiotics and 703 of whom were treated with surgery. There was no relevant difference in patient characteristics between the different studies and between the single arms of the studies. The study by Styrud et al. [11] included only male patients. In all included studies, the diagnosis of acute appendicitis was made based on physical examination, laboratory results, temperature, ultrasound and CT scan (mandatory in the studies by Vons and Salminen [8, 12], optional in the study by Hansson [10]; in the studies by Styrud and Eriksson [11, 13] nothing was reported about CT scans). Appendectomy in the surgery group was laparoscopic in 101/536 patients, (18.8%) and open in 435/536 patients (81.2%) (Hansson et al. [10] did not report the number of patients operated laparoscopically). In all studies, the duration of follow-up was at least 1 year with the exception of Eriksson et al. [13]. In this study, all patients were followed until there were normal ultrasound findings of the appendix or surgery was needed. The mean follow-up period in this study was 13.2 months [13].

Outcomes

Successful therapy

All studies reported the number of patients with treatment success, as per our definition of the primary outcome, in both groups. Of 727 patients in the antibiotic group, 455 (62.6%) were treated successfully within the follow-up period of 1 year, which was pre-defined in all included studies [8, 10–12] with the exception of Eriksson et al. [13]. Of 703 patients in the surgical group, 677 (96.3%) patients were treated successfully. Treatment success was significantly more frequent in the surgical group (Fig. 2).

I^2 statistics indicated considerable heterogeneity between the single studies.

Complications

Considering any complication, as reported by the single studies, there was a non-significantly lower incidence in the antibiotic than in the surgical group. Complications occurred in 74/727 (10.2%) patients primarily treated with antibiotics and 126/703 (17.9%) patients primarily treated surgically (Fig. 3). The majority of postoperative complications were wound infections. In the group primarily treated with antibiotics, these occurred in 16/599 (2.7%) patients (16/241 (6.6%) patients who underwent secondary appendectomy). In the primary surgery group, they occurred in 33/565 (5.8%) patients (the study by Styrud et al. [11] was excluded from this analysis because only the overall complication rate, and not the incidence of wound infections was given). Other complications such as intra-abdominal abscess, bowel obstruction, incisional pain, and enterocolitis were less frequent in both groups. Three cases of incisional hernias have been reported during the follow-up period of the trials, two in the antibiotic group in patients who underwent secondary appendectomy [8] and one in the surgical group [10].

No statistically significant differences were found between both groups for complications among patients who eventually underwent appendectomy (Fig. 4) (22/153 (14.4%) in the antibiotic group and 71/536 (13.3%) in the surgical group). For this outcome, the study by Hansson et al. [10] was excluded from the analysis because only the incidence of complications in all patients, and not specifically in patients who underwent surgery, was given. I^2 statistics indicated considerable heterogeneity between the single studies.

Duration of hospital stay

All studies reported the length of the primary hospital stay, not taking into account possible re-admissions during the follow-up period. The mean length of hospital stay was 3.0 days in the surgical group and 3.03 days in the antibiotic group (Fig. 5). The mean difference was not significant. I^2 statistics indicated substantial heterogeneity between the single studies. Vons et al. [12] was the only study which reported the overall hospital stay including readmissions up to 1 year. It found a non-significant longer stay in the antibiotic group (mean stay 3.96 vs. 3.04 days, $p = 0.08$). To maintain consistency, this study was excluded from the meta-analysis for length of hospital stay. Also, the study by Salminen et al. [8] was excluded from the analysis because no standard deviations were given. In this study, the median length of primary hospital stay was 3.0 days in both groups [8].

	Antibiotic therapy		Surgery			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Eriksson 1995	12	20	20	20	10.9%	0.61 [0.43, 0.87]
Hansson 2009	83	202	142	167	19.4%	0.48 [0.40, 0.58]
Salminen 2015	187	257	272	273	24.5%	0.73 [0.68, 0.79]
Styrud 2006	97	128	124	124	23.5%	0.76 [0.69, 0.84]
Vons 2011	76	120	119	119	21.7%	0.63 [0.55, 0.73]
Total (95% CI)		**727**		**703**	**100.0%**	**0.65 [0.55, 0.76]**
Total events	455		677			

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 27.23$, df = 4 ($P < 0.0001$); $I^2 = 85\%$
Test for overall effect: $Z = 5.50$ ($P < 0.00001$)

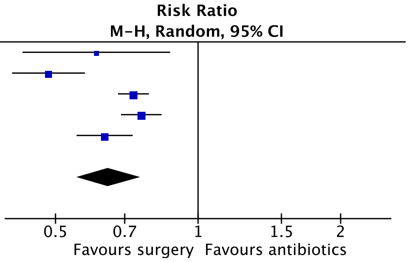
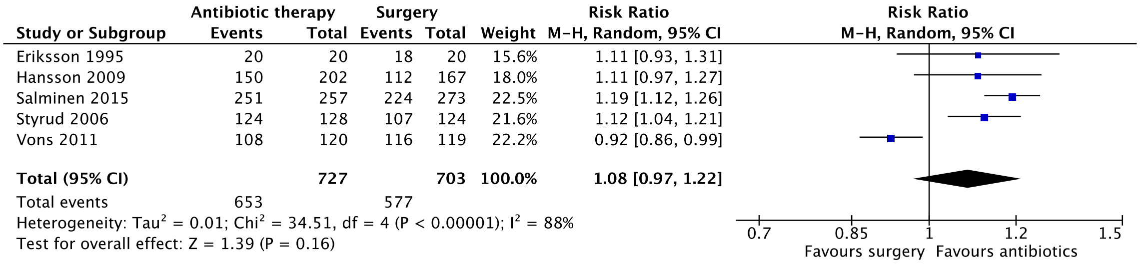


Fig. 2 Forest plot-successful therapy



Study or Subgroup	Antibiotic therapy Events	Antibiotic therapy Total	Surgery Events	Surgery Total	Weight	Risk Ratio M-H, Random, 95% CI
Eriksson 1995	20	20	18	20	15.6%	1.11 [0.93, 1.31]
Hansson 2009	150	202	112	167	18.0%	1.11 [0.97, 1.27]
Salminen 2015	251	257	224	273	22.5%	1.19 [1.12, 1.26]
Styrud 2006	124	128	107	124	21.6%	1.12 [1.04, 1.21]
Vons 2011	108	120	116	119	22.2%	0.92 [0.86, 0.99]
Total (95% CI)		**727**		**703**	**100.0%**	**1.08 [0.97, 1.22]**
Total events	653		577			

Heterogeneity: Tau^2 = 0.01; Chi^2 = 34.51, df = 4 (P < 0.00001); I^2 = 88%

Test for overall effect: Z = 1.39 (P = 0.16)

Fig. 3 Forest plot-complication-free treatment

Length of absence from work

Four studies reported the length of absence from work [8, 10–12]. The results showed a significantly shorter absence in the antibiotic than in the surgical group (Fig. 6).

I^2 statistics indicated considerable heterogeneity between the single studies.

The study by Salminen et al. [8] was excluded from the analysis because no standard deviations were given. In this study, the median length of absence from work was 19.0 days in the surgical group and 7.0 days in the antibiotic group [8].

Pain intensity

Three studies reported pain intensity of both treatment groups using the visual analog scale (VAS) [8, 12, 13]. Two studies reported the duration of pain [10, 12], and in one study [11], neither pain intensity nor duration of pain were reported. Both pain intensity and duration of pain were less, respectively, shorter in patients treated with antibiotics, except in the study by Hansson et al. [10]. In this study, the duration of abdominal pain was longer in the antibiotic group than in the surgical group during 1-year follow-up (mean 39 days vs. 30 days).

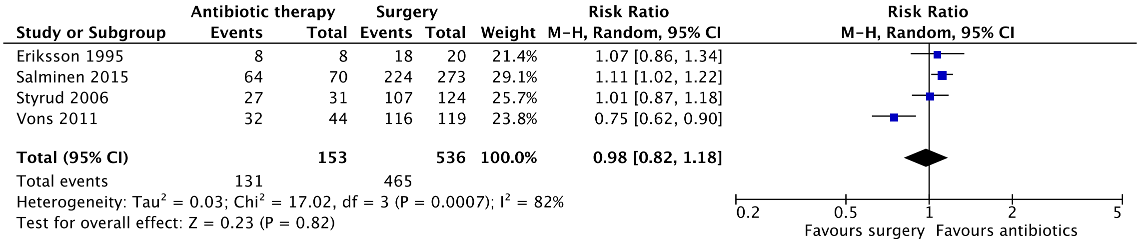
In the study by Salminen et al. [8], the median pain intensity was 5.0 in the antibiotic group and 6.0 in the surgical group. At hospital discharge, the median pain intensity was 2.0 in the antibiotic group and 3.0 in the surgical group. At 1 week and 2 months, the median pain intensity was 1.0 and 1.0 in the antibiotic group and 2.0 and 1.0 in the surgical group, respectively. In this study, no standard deviation was given. In the study by Eriksson et al. [13], the mean pain intensity after 24 h of hospitalization was 32 mm in the surgical group and 9 mm in the antibiotic group. Six days after discharge, the mean pain intensity was 11 mm in the surgical group and 0 mm in the antibiotic group. Both times, there was significantly less pain in patients treated with antibiotics.

In the study by Hansson et al. [10], the mean duration of postoperative abdominal pain was 6 days in the antibiotic group and 9 days in the surgical group during the hospital stay and within 1 month after discharge. Vons et al. [12] reported a mean pain score of 6.4 ± 2.1 in the surgical group and 6.3 ± 1.9 in the antibiotic group. The median duration of pain (VAS > 4) did not differ between the two groups (mean 1.70 ± 1.07 days in the surgical group and 1.63 ± 1.35 days in the antibiotic group).

Critical appraisal of included studies (risk of bias)

An overview of the individual risk of bias of the single studies is shown in Figs. 7 and 8.

Three of the five included studies reported randomization with sealed envelopes, resulting in a low risk of selection bias [8, 11, 12]. In one study, the randomization procedure was not reported, and thus, the risk of selection bias remained unclear [13], and for one study [10], the risk was considered high because of pseudo-randomization by date of birth. The risk of performance bias was considered unclear for all studies [8, 10–13], because there was no blinding of study participants and physicians. In all studies [8, 10–13], the risk of detection bias was considered high because there was no blinding of physicians. A high risk of attrition bias was considered for one study [10] because the numbers reported in tables and in the text were inconsistent and drop-out was unexplained or not reported. Also, the numbers in the text and its corresponding tables contradicted each other. In one study, the risk of attrition bias was unclear [11], and for three other studies [8,

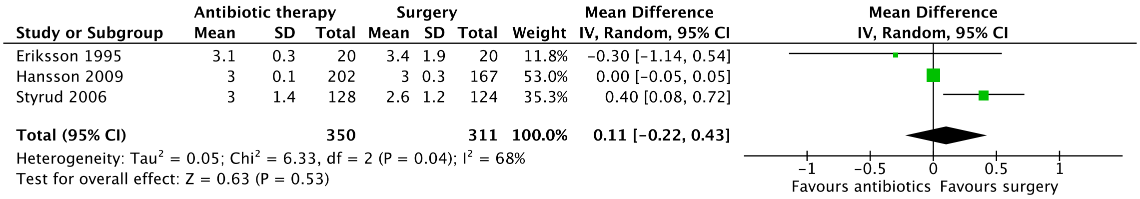


Study or Subgroup	Antibiotic therapy Events	Antibiotic therapy Total	Surgery Events	Surgery Total	Weight	Risk Ratio M-H, Random, 95% CI
Eriksson 1995	8	8	18	20	21.4%	1.07 [0.86, 1.34]
Salminen 2015	64	70	224	273	29.1%	1.11 [1.02, 1.22]
Styrud 2006	27	31	107	124	25.7%	1.01 [0.87, 1.18]
Vons 2011	32	44	116	119	23.8%	0.75 [0.62, 0.90]
Total (95% CI)		**153**		**536**	**100.0%**	**0.98 [0.82, 1.18]**
Total events	131		465			

Heterogeneity: Tau^2 = 0.03; Chi^2 = 17.02, df = 3 (P = 0.0007); I^2 = 82%

Test for overall effect: Z = 0.23 (P = 0.82)

Fig. 4 Forest plot-complication-free treatment based on the number of patients who underwent appendectomy



Study or Subgroup	Antibiotic therapy Mean	SD	Total	Surgery Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Eriksson 1995	3.1	0.3	20	3.4	1.9	20	11.8%	−0.30 [−1.14, 0.54]
Hansson 2009	3	0.1	202	3	0.3	167	53.0%	0.00 [−0.05, 0.05]
Styrud 2006	3	1.4	128	2.6	1.2	124	35.3%	0.40 [0.08, 0.72]
Total (95% CI)			**350**			**311**	**100.0%**	**0.11 [−0.22, 0.43]**

Heterogeneity: $\text{Tau}^2 = 0.05$; $\text{Chi}^2 = 6.33$, df = 2 (P = 0.04); $I^2 = 68\%$
Test for overall effect: Z = 0.63 (P = 0.53)

Fig. 5 Forest plot-duration of hospital stay

12, 13], it was considered low. Three studies [10, 11, 13] were considered at high risk of reporting bias because of a lack of predefined endpoints or for changing the primary endpoint for publication of results [10]. In two studies, the risk of reporting bias was considered low [8, 12].

Discussion

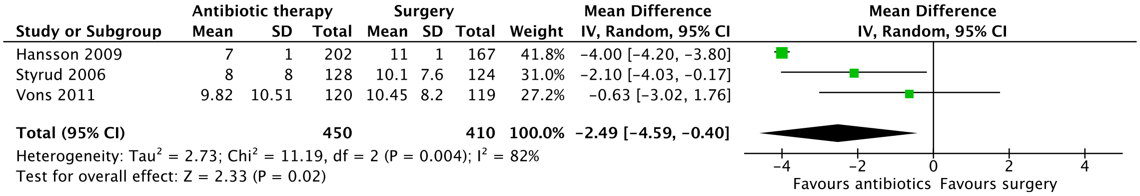
This systematic review with meta-analysis summarizes the available high-level evidence from randomized controlled trials comparing antibiotic and surgical treatment of acute uncomplicated appendicitis. The evaluation of the included studies shows that treatment success was higher in the surgical group than in the antibiotic group, in which more than a third of patients required appendectomy for initially persistent appendicitis or recurrent appendicitis within 1 year from the initial antibiotic treatment. The length of absence from work was significantly shorter in the antibiotic group, the incidence of complications and the duration of hospital stay did not differ significantly between the two groups.

The obvious advantage of surgery is that it constitutes a definite cure for appendicitis with only a rather hypothetical risk of "stump appendicitis" in cases in whom the appendix is not entirely removed [18]. In contrast, in patients receiving antibiotic treatment, the risk of recurrent appendicitis persists for their lifetime, even if the initial episode of appendicitis is successfully treated. There are no reliable estimates how high this lifetime risk is and what temporal patterns recurrent appendicitis follows. In the largest and most recently published randomized controlled trial included in our meta-analysis [8], 5.8% of patients receiving antibiotics had a persistent first episode of appendicitis and required appendectomy still during the initial hospital admission, whereas 21.4% of patients had recurrent appendicitis which led to appendectomy during subsequent re-admission within 1 year of initial presentation. This indicates that the lifetime risk of recurrent appendicitis after antibiotic treatment is of relevant magnitude and that recurrence tends to occur early.

An important finding is that in our meta-analysis, the overall risk of complications was not significantly different between the two treatment groups. This holds true both when all patients in the respective group serve as denominator, but also when analyzing only patients who did undergo surgery. Therefore, one can conclude that antibiotic treatment of appendicitis is safe. It does not expose patients to a higher risk of complications either from the antibiotic treatment itself (e.g., allergic reactions, enterocolitis), from the appendicitis (e.g., intraabdominal abscess, sepsis) or from the actual operation (e.g., wound infections, intestinal adhesions). Consequently, the attribute for antibiotic treatment of appendicitis as potentially dangerous therapy when compared to surgery does not hold true. However, long-term effects of widespread antibiotic treatment such as drug resistance both in the individual patient and the population at large [9] are not accounted for in any published studies on the approach. The regimens of antibiotics and treatment duration varied between studies, and one study [8] used a combination of levofloxacin, metronidazole, and ertapenem, the latter being a broad-spectrum antibiotic usually reserved for severe infection with potentially resistant bacteria [19].

Proponents of conservative treatment for appendicitis claim that the approach is associated with shorter hospital stays, earlier return to work, and lower cost. The meta-analysis did not show any difference in length of hospital stay between the two approaches. This can probably at least partially be attributed to defined treatment protocols in the single trials with preset days for discharge in both arms.

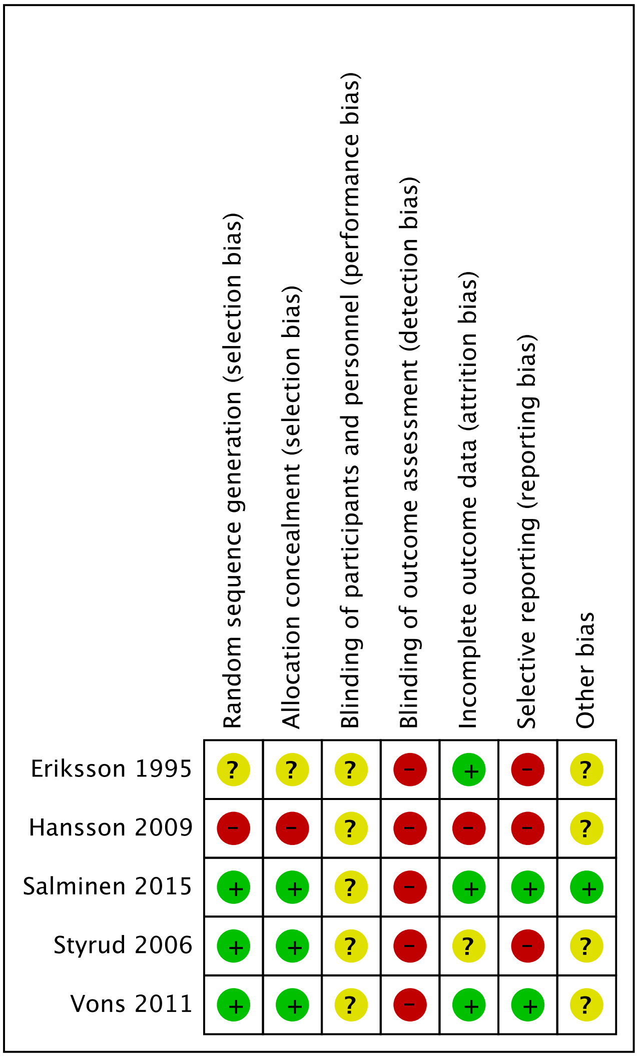
In the study by Vons et al., patients were discharged after resolution of pain, fever, and any digestive symptoms [12]. To ensure safety, in the study by Salminen et al. [8], the minimum length of hospital stay of patients treated with antibiotics was 3 days [20]. In the study by Styrud et al., patients who underwent appendectomy were discharged when their condition was deemed satisfactory, and patients who received



Study or Subgroup	Antibiotic therapy Mean	SD	Total	Surgery Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Hansson 2009	7	1	202	11	1	167	41.8%	−4.00 [−4.20, −3.80]
Styrud 2006	8	8	128	10.1	7.6	124	31.0%	−2.10 [−4.03, −0.17]
Vons 2011	9.82	10.51	120	10.45	8.2	119	27.2%	−0.63 [−3.02, 1.76]
Total (95% CI)			**450**			**410**	**100.0%**	**−2.49 [−4.59, −0.40]**

Heterogeneity: $\text{Tau}^2 = 2.73$; $\text{Chi}^2 = 11.19$, df = 2 (P = 0.004); $I^2 = 82\%$
Test for overall effect: Z = 2.33 (P = 0.02)

Fig. 6 Forest plot-length of sick leave



	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Eriksson 1995	?	?	?	−	+	−	?
Hansson 2009	−	−	?	−	−	−	?
Salminen 2015	+	+	?	−	+	+	+
Styrud 2006	+	+	?	−	?	−	?
Vons 2011	+	+	?	−	+	+	?

Fig. 7 Risk of bias analysis

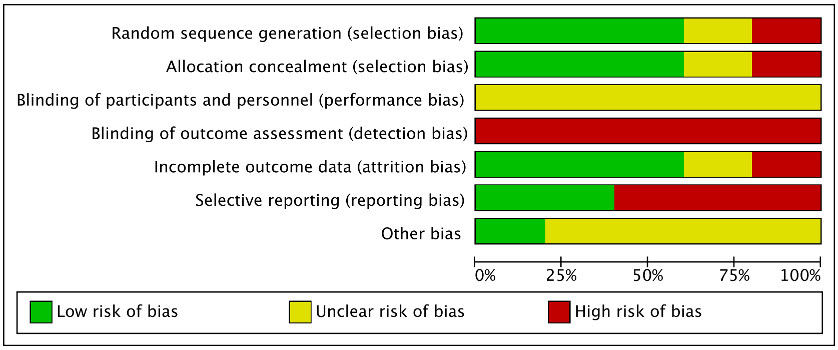
antibiotics were discharged after 2 days [11]. According to the study protocol by Hansson et al., patients treated conservatively received intravenous antibiotics for 24 h. Provided clinical status had improved, patients were discharged the following morning [10]. In the study by Eriksson et al., patients treated with antibiotics were discharged after 2 days and operated patients when conditions were satisfactory [13].

However, only the study by Vons et al. [12] accounted for subsequent inpatient episodes of recurrent appendicitis and reported the overall length of hospital stay including readmissions up to 1 year. Thus, the results of the meta-analysis are biased in favor of antibiotic treatment. Absence from work was significantly shorter in patients treated with antibiotics than in the surgical group. The mean difference was 2.49 days. An economic secondary analysis of the largest trial included in our analyses showed that productivity losses were considerably higher in patients treated with primary surgery compared to those treated with primary antibiotics [21]. This may probably not be socio-economically relevant. Only one [10] of the studies included in our meta-analyses reported a comparison of costs between both groups in the respective original publication. It showed lower costs for conservative treatment than for operative treatment. However, this analysis considered only costs relating to the initial hospital admission and disregarded subsequent re-admissions due to recurrent appendicitis. Therefore, its results are biased in favor of antibiotic treatment.

Appendiceal neoplasia often mimics symptoms of acute appendicitis, and thus, some cases are misdiagnosed [22]. A population-based study from Finland found that 3.24% of patients diagnosed with complicated acute appendicitis and 0.87% of patients diagnosed with uncomplicated acute appendicitis [23] actually had appendiceal neoplasia. Treatment of these patients with antibiotics might have severe consequences in terms of late diagnosis and risk of metastasis. This needs to be considered another disadvantage of antibiotic treatment.

Quality of life plays an important role when comparing two differential treatment approaches. This holds particularly true when it comes to deciding between a medical and a surgical treatment. For many people, surgery and the associated anesthesia, even when it comes to “routine” operations as is the case for appendectomy, are considered stressful and affecting. For such patients, surgery might potentially have a higher impact on quality of life than a drug therapy, even when the outcome is good and no complications are encountered. On the other side, there might be patients who rate their quality of life lower after conservative treatment because of a persisting risk of recurrent appendicitis. Several studies showed that

Fig. 8 Risk of bias, graphical overview



patient preferences on the choice of treatment for appendicitis differ in relation to socioeconomic factors and medical history [24, 25]. These differing preferences will certainly affect quality of life as a function of the treatment the patient has received. Unfortunately, none of the randomized trials published so far has assessed patient preferences and quality of life.

This meta-analysis has some methodological limitations which need to be considered in its interpretation. In contrast to previous meta-analyses [26], we chose to include only randomized controlled trials. This enhances the validity of our results, but at the same time excludes potentially relevant information from non-randomized studies. Even though all included studies are randomized controlled trials, some of them still have a considerable risk of bias, as assessed with a specific tool. This might inevitably bias the results of the meta-analysis. As demonstrated by high I^2 values, statistical heterogeneity between the included trials was substantial for most outcomes. Therefore, summary measures must be regarded with caution. Besides statistical heterogeneity, there is relevant heterogeneity in the clinical design of the single trials. They used different tools for the diagnosis of appendicitis. Physical examination and laboratory results were uniformly used, but not all studies applied imaging such as ultrasound and CT for diagnosis. Moreover, the antibiotic regimen varied between the studies so the best choice for first-line antibiotic therapy of uncomplicated appendicitis remains unclear. Most patients in the trials underwent open appendectomy. Nowadays, in many industrial countries, laparoscopic has replaced open appendectomy as standard treatment. There is evidence that the incidence of wound infections is lower for laparoscopic appendectomy [27]. Therefore, the incidence of complications in the surgery arms of the included trials might be an overestimation compared to more recent cohorts operated laparoscopically.

Compared to the previous meta-analysis by Wilms et al. [14], our analysis was able to provide more detailed results and has thus wider implications for clinical practice. This was achieved through the inclusion of the hitherto largest randomized controlled trial and a different approach in the analyses. Wilms et al. focused their analysis on the formal proof of non-inferiority by looking at primary treatment success. While the probability of primary treatment success was in both groups similar to our results, the authors regarded their results as inconclusive due to large confidence intervals overlapping the non-inferiority boundary. Moreover, they did not specifically examine the outcome and morbidity of patients who underwent secondary appendectomy following primary antibiotic treatment. Therefore, they were unable to evaluate potential risks of primary antibiotic treatment.

In summary, our meta-analysis showed that antibiotic therapy of uncomplicated acute appendicitis comes with a need for subsequent appendectomy in more than a third of patients. Therefore, appendectomy should still be considered the first-line therapy for the disease. However, antibiotic treatment is not associated with a higher incidence of complications than appendectomy. In particular, secondary appendectomy does not lead to more surgical complications. Consequently, antibiotic therapy can be recommended without jeopardizing patient safety. During individual decision-making regarding the treatment of patients with uncomplicated appendicitis, physicians should try to explore patients' preferences [24, 25] and provide unbiased and impartial information on the advantages and risks of both therapeutic approaches, allowing for an informed shared decision in line with the patient's own needs and expectations [28].

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Addiss DG, Shaffer N, Fowler BS, Tauxe RV (1990) The epidemiology of appendicitis and appendectomy in the United States. Am J Epidemiol 132(5):910–925
2. Fagerstrom A, Paajanen P, Saarelainen H, Ahonen-Siirtola M, Ukkonen M, Miettinen P, Paajanen H (2017) Non-specific abdominal pain remains as the most common reason for acute abdomen: 26-year retrospective audit in one emergency unit. Scand J Gastroenterol 52(10):1072–1077. https://doi.org/10.1080/00365521.2017.1342140
3. Cervellin G, Mora R, Ticinesi A, Meschi T, Comelli I, Catena F, Lippi G (2016) Epidemiology and outcomes of acute abdominal pain in a large urban emergency department: retrospective analysis of 5,340 cases. Ann Transl Med 4(19):362. https://doi.org/10.21037/atm.2016.09.10
4. Sakorafas GH, Mastoraki A, Lappas C, Sampanis D, Danias N, Smyrniotis V (2011) Conservative treatment of acute appendicitis: heresy or an effective and acceptable alternative to surgery? Eur J Gastroenterol Hepatol 23(2):121–127. https://doi.org/10.1097/MEG.0b013e32834233b6
5. Harrison PW (1953) Appendicitis and the antibiotics. Am J Surg 85(2):160–163
6. Coldrey EJJICS (1959) Five years of conservative treatment of acute appendicitis. J Int Coll Surg 32(3):255–261
7. Kapischke M, Friedrich F, Hedderich J, Schulz T, Caliebe A (2011) Laparoscopic versus open appendectomy–quality of life 7 years after surgery. Langenbeck's Arch Surg 396(1):69–75. https://doi.org/10.1007/s00423-010-0715-1
8. Salminen P, Paajanen H, Rautio T, Nordström P, Aarnio M, Rantanen T, Tuominen R, Hurme S, Virtanen J, Mecklin JP, Sand J, Jartti A, Rinta-Kiikka I, Grönroos JM (2015) Antibiotic therapy vs appendectomy for treatment of uncomplicated acute appendicitis: the APPAC randomized clinical trial. Jama 313(23):2340–2348. https://doi.org/10.1001/jama.2015.6154
9. Elder DP, Kuentz M, Holm R (2016) Antibiotic resistance: the need for a global strategy. J Pharm Sci 105(8):2278–2287. https://doi.org/10.1016/j.xphs.2016.06.002
10. Hansson J, Korner U, Khorram-Manesh A, Solberg A, Lundholm K (2009) Randomized clinical trial of antibiotic therapy versus appendicectomy as primary treatment of acute appendicitis in unselected patients. Br J Surg 96(5):473–481. https://doi.org/10.1002/bjs.6482

11. Styrud J, Eriksson S, Nilsson I, Ahlberg G, Haapaniemi S, Neovius G, Rex L, Badume I, Granström L (2006) Appendectomy versus antibiotic treatment in acute appendicitis. A prospective multicenter randomized controlled trial. World J Surg 30(6):1033–1037. https://doi.org/10.1007/s00268-005-0304-6
12. Vons C, Barry C, Maitre S, Pautrat K, Leconte M, Costaglioli B, Karoui M, Alves A, Dousset B, Valleur P, Falissard B, Franco D (2011) Amoxicillin plus clavulanic acid versus appendicectomy for treatment of acute uncomplicated appendicitis: an open-label, non-inferiority, randomised controlled trial. Lancet 377(9777):1573–1579. https://doi.org/10.1016/s0140-6736(11)60410-8
13. Eriksson S, Granstrom L (1995) Randomized controlled trial of appendicectomy versus antibiotic therapy for acute appendicitis. Br J Surg 82(2):166–169
14. Wilms IM, de Hoog DE, de Visser DC, Janzing HM (2011) Appendectomy versus antibiotic treatment for acute appendicitis. Cochrane Database Syst Rev (11):Cd008359. https://doi.org/10.1002/14651858.CD008359.pub2
15. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, Clarke M, Devereaux PJ, Kleijnen J, Moher D (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 339:b2700. https://doi.org/10.1136/bmj.b2700
16. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA (2011) The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Bmj 343:d5928. https://doi.org/10.1136/bmj.d5928
17. Ryan R (2016) Cochrane Consumers and Communication Review Group. 'Heterogeneity and subgroup analyses in Cochrane Consumers and Communication Group reviews: planning the analysis at protocol stage. http://cccrg.cochrane.org/sites/cccrg.cochrane.org/files/public/uploads/heterogeneity_subgroup_analyses_revising_december_1st_2016.pdf. Accessed 28 Jan 2019
18. Roberts KE, Starker LF, Duffy AJ, Bell RL, Bokhari J (2011) Stump appendicitis: a surgeon's dilemma. Jsls 15(3):373–378. https://doi.org/10.4293/108680811x13125733356954
19. Zhanel GG, Johanson C, Embil JM, Noreddin A, Gin A, Vercaigne L, Hoban DJ (2005) Ertapenem: review of a new carbapenem. Expert Rev Anti-Infect Ther 3(1):23–39
20. Paajanen H, Gronroos JM, Rautio T, Nordstrom P, Aarnio M, Rantanen T, Hurme S, Dean K, Jartti A, Mecklin J-P, Sand J, Salminen P (2013) A prospective randomized controlled multicenter trial comparing antibiotic therapy with appendectomy in the treatment of uncomplicated acute appendicitis (APPAC trial). BMC Surg 13:3 1471–2482 (Electronic)
21. Sippola S, Gronroos J, Tuominen R, Paajanen H, Rautio T, Nordstrom P, Aarnio M, Rantanen T, Hurme S, Salminen P (2017) Economic evaluation of antibiotic therapy versus appendicectomy for the treatment of uncomplicated acute appendicitis from the APPAC randomized clinical trial. Br J Surg 104(10):1355–1361. https://doi.org/10.1002/bjs.10575
22. Shaib WL, Assi R, Shamseddine A, Alese OB, Staley C 3rd, Memis B, Adsay V, Bekaii-Saab T, El-Rayes BF (2017) Appendiceal mucinous neoplasms: diagnosis and management. Oncologist 22(9):1107–1116. https://doi.org/10.1634/theoncologist.2017-0081
23. Lietzen E, Gronroos JM, Mecklin JP, Leppaniemi A, Nordstrom P, Rautio T, Rantanen T, Sand J, Paajanen H, Kaljonen A, Salminen P (2019) Appendiceal neoplasm risk associated with complicated acute appendicitis-a population based study. Int J Color Dis 34(1):39–46. https://doi.org/10.1007/s00384-018-3156-x
24. Hanson AL, Crosby RD, Basson MD (2018) Patient preferences for surgery or antibiotics for the treatment of acute appendicitis. JAMA Surg 153(5):471–478. https://doi.org/10.1001/jamasurg.2017.5310
25. Kadera SP, Mower WR, Krishnadasan A, Talan DA (2016) Patient perspectives on antibiotics for appendicitis at one hospital. J Surg Res 201(2):253–257. https://doi.org/10.1016/j.jss.2015.11.016
26. Harnoss JC, Zelienka I, Probst P, Grummich K, Muller-Lantzsch C, Harnoss JM, Ulrich A, Buchler MW, Diener MK (2017) Antibiotics versus surgical therapy for uncomplicated appendicitis: systematic review and meta-analysis of controlled trials (PROSPERO 2015: CRD42015016882). Ann Surg 265(5):889–900. https://doi.org/10.1097/sla.0000000000002039
27. Guller U, Hervey S, Purves H, Muhlbaier LH, Peterson ED, Eubanks S, Pietrobon R (2004) Laparoscopic versus open appendectomy: outcomes comparison based on a large administrative database. Ann Surg 239(1):43–52. https://doi.org/10.1097/01.sla.0000103071.35986.c1
28. Ubbink DT, Hageman MG, Legemate DA (2015) Shared decision-making in surgery. Surg Technol Int 26:31–36