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ORIGINAL SCIENTIFIC REPORT

Antibiotics Versus Appendicectomy for the Treatment of Uncomplicated Acute Appendicitis: An Updated Meta-Analysis of Randomised Controlled Trials

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Abstract

Background Uncomplicated acute appendicitis has been managed traditionally by early appendicectomy. However, recently, there has been increasing interest in the potential for primary treatment with antibiotics, with studies finding this to be associated with fewer complications than appendicectomy. The aim of this study was to compare outcomes of antibiotic therapy with appendicectomy for uncomplicated acute appendicitis.

Method This meta-analysis of randomised controlled trials included adult patients presenting with uncomplicated acute appendicitis treated with antibiotics or appendicectomy. The primary outcome measure was complications. Secondary outcomes included treatment efficacy, hospital length of stay (LOS), readmission rate and incidence of complicated appendicitis.

Results Five randomised controlled trials with a total of 1430 participants (727 undergoing antibiotic therapy and 703 undergoing appendicectomy) were included. There was a 39 % risk reduction in overall complication rates in those treated with antibiotics compared with those undergoing appendicectomy (RR 0.61, 95 % CI 0.44–0.83, $p = 0.002$). There was no significant difference in hospital LOS (mean difference 0.25 days, 95 % CI −0.05 to 0.56, $p = 0.10$). In the antibiotic cohort, 123 of 587 patients initially treated successfully with antibiotics were readmitted with symptoms suspicious of recurrent appendicitis. The incidence of complicated appendicitis was not increased in patients who underwent appendicectomy after "failed" antibiotic treatment (10.8 %) versus those who underwent primary appendicectomy (17.9 %).

Conclusion Increasing evidence supports the primary treatment of acute uncomplicated appendicitis with antibiotics, in terms of complications, hospital LOS and risk of complicated appendicitis. Antibiotics should be prescribed once a diagnosis of acute appendicitis is made or considered.

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Abbreviations

LOS Hospital length of stay
IQR Interquartile range

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RR Risk ratio
CI Confidence interval

Introduction

Uncomplicated acute appendicitis has been managed traditionally by early appendicectomy due to the perceived risk of developing complicated appendicitis if prompt surgical treatment is not instigated. However, the development of this management strategy predated the discovery of antibiotics, and a large series of patients treated with antibiotic therapy in the 1950s reported reasonable success rates [1]. The shift in surgical technique from open to laparoscopic appendicectomy has resulted in reduced hospital length of stay (LOS), morbidity and earlier postoperative recovery [2–4], but irrespective of the technique, there are risks associated with appendicectomy, including surgical site and intraabdominal infections, incisional herniae and peritoneal adhesions. Appendicitis is a relatively common condition, with a lifetime incidence of approximately 9 % [5]. However, as only 20 % of patients present with complicated appendicitis [6], any change in management strategy for the vast majority presenting with uncomplicated acute appendicitis could have wide reaching effects.

There has, in recent times, been increasing interest in the potential for treatment of uncomplicated acute appendicitis using antibiotic therapy [7, 8], with several studies finding this treatment approach to be associated with fewer complications than operative intervention [9, 10]. Several studies have reported radiological and biochemical factors potentially predictive of successful conservative treatment of acute appendicitis [11–14], but these are not in widespread use. With the large number of broad-spectrum antibiotics available currently which may attenuate or cure the disease process, primary antibiotic therapy is becoming increasingly attractive. This has been further supported by several meta-analyses [15–17] which suggest a potential role for antibiotic therapy as a first line treatment strategy in uncomplicated appendicitis. A meta-analysis conducted by our group in 2012 [18] on four randomised controlled trials [19–22] found that antibiotics are both safe and effective as the primary treatment modality for uncomplicated acute appendicitis and suggested that this should be considered part of the therapeutic algorithm. However, the surgical community felt that more convincing studies and longer term results were required before this treatment strategy could be implemented in routine clinical practice [23]. Concerns also remain regarding the incidence of recurrent appendicitis [24] following non-operative management. The largest randomised controlled trial to date [25] has been published recently and has suggested that the majority of patients treated with intravenous antibiotics for uncomplicated acute appendicitis did not require subsequent appendicectomy for recurrent appendicitis during 1-year follow-up. However, the results of this trial did not meet the threshold for non-inferiority for antibiotic therapy when compared with appendicectomy. Despite this increasing evidence in support of antibiotics, there remains significant variability and lack of equipoise in attitudes towards the use of antibiotics as primary therapy for uncomplicated acute appendicitis in clinical practice [26].

The aim of this meta-analysis was to update the results of our previous meta-analysis [18] examining the safety and efficacy profiles of antibiotics versus appendicectomy for uncomplicated acute appendicitis and to determine if the strength of the recommendations of the previous meta-analysis was improved.

Methods

Search strategy

We performed a search for randomised controlled trials comparing appendicectomy with antibiotic therapy in adult patients (≥16 years old) presenting with uncomplicated acute appendicitis on PubMed, MEDLINE, Web of Science, Google™ Scholar and the Cochrane Controlled Trials Register. No language limit was placed on studies included, and we searched for trials published between 1 January 1966 and 31 July 2015. The keywords used included antibiotics, surgery, appendicectomy, appendicectomy, randomised controlled trial, controlled clinical trial, randomised, drug therapy, randomly and trial in combination with Boolean operators AND, OR and NOT. The bibliographies of all studies that met the inclusion criteria were also searched for other relevant articles and conference abstracts to ensure that study inclusion was as complete as possible. The meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [27].

Selection of articles

One author (KER) excluded articles on the basis of title and abstract details initially, following which we screened full text articles for suitability for inclusion. Studies were included if they were performed on adult patients who were diagnosed with uncomplicated acute appendicitis and randomised to treatment with either antibiotic therapy or appendicectomy, and if the study reported at least one relevant post-intervention clinical outcome. The diagnosis of appendicitis could be made by either clinical suspicion and laboratory analysis or imaging (ultrasound or computed tomography). We excluded non-randomised controlled trials, studies on paediatric patients and those that included patients with complicated appendicitis (local or contained perforation with an appendicular mass or abscess). Any studies in which the inclusion criteria were unclear were discussed with the senior author (DNL).

Data extraction

One author (KER) extracted the data, and these were checked by another (KKV). The primary outcome measure was post-intervention complications, and we reported all results on an intention-to-treat basis, where available. Secondary outcome measures considered were primary LOS, readmission rates and treatment efficacy. Other secondary outcome measures such as pain, analgesia requirements, incidence of post-intervention perforation and body temperature were documented when stated. A complication in the antibiotic group was defined as the 'incidence of perforated/gangrenous appendicitis or peritonitis and wound infection in patients who failed antibiotic therapy and subsequent appendicectomy' versus 'incidence of perforated appendicitis/peritonitis and wound infection' in the appendicectomy group. The LOS was defined in both groups as the number of days of inpatient admission for the primary hospital stay. Readmission in the antibiotic group was defined as 'patients who were readmitted for operations or antibiotic-related problems, such as diarrhoea and wound infections following surgery for failed antibiotic therapy, as well as those readmitted for recurrent symptoms'. In the appendicectomy group this was defined as 'patients who were readmitted with postoperative complications such as intraabdominal collections, adhesive obstruction and wound infections'. Finally, treatment efficacy in the antibiotic group was defined as a patient who was 'treated successfully with antibiotics only and had none of the following: failure of antibiotic therapy or symptom recurrence needing appendicectomy, and/or developing any post-therapeutic and postoperative complications'. In comparison in the appendicectomy group, this was defined as 'patients who were successfully treated with appendicectomy and had none of the following: no appendicitis on histology and/or developing any post-therapeutic and postoperative complications including readmissions'.

The authors of one randomised controlled trial were contacted to obtain mean and standard deviation data for LOS rather than the median and interquartile range included in the paper in order to include this in the meta-analysis [25].

Statistical analysis

We analysed the data and constructed the Forest plots using RevMan 5.3 [28] software. We calculated dichotomous variables as risk ratio (RR) with 95 % confidence intervals (CI) using Mantel–Haenszel random effects model due to the likely presence of variability in study design and methodology. We quoted continuous variables as mean difference and 95 % CI similarly using an inverse-variance random-effects model. We considered differences significant at $p < 0.05$ on two-tailed testing. We used the I^2 statistic to assess study heterogeneity and inconsistency [29]; <25 % was taken to represent low heterogeneity, 25–50 % as moderate heterogeneity and 50 % as high heterogeneity. We used GRADEpro software [30] to assess the quality of the evidence for each outcome. This incorporates a systematic evaluation of five domains for all studies included in each outcome evaluation: limitations of the study design and execution; inconsistency, indirectness and imprecision of results; and publication bias. This then grades the quality of evidence for each outcome for each treatment modality as low, medium or high.

Protocol registration

We registered the protocol for this meta-analysis with the PROSPERO database (www.crd.york.ac.uk/prospero): registration number CRD42015024133.

Results

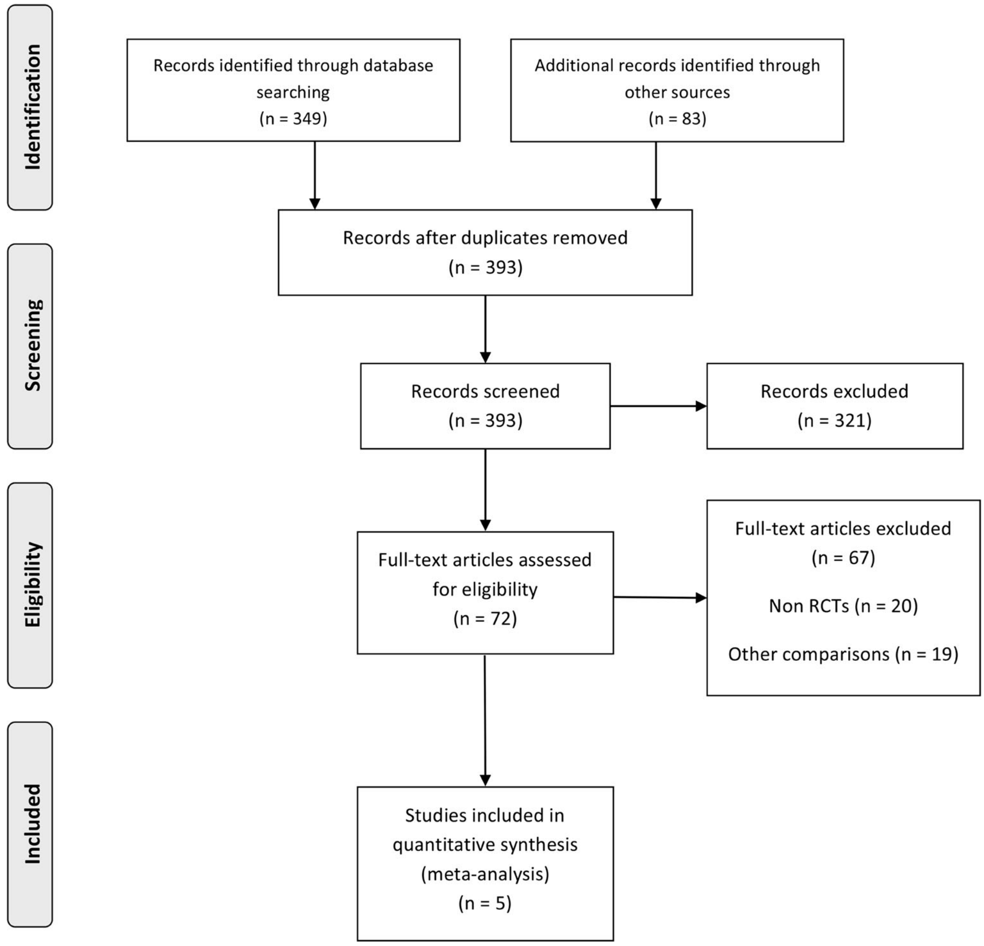
We found five [19–22, 25] of the 349 studies identified in the screening process eligible for inclusion (Fig. 1; Tables 1, 2). Two studies which met the inclusion criteria were excluded after closer review: one due to retraction of the study following publication [31] and one due to a lack of evidence of randomisation [32]. The risk of bias in the studies included in the meta-analysis was serious, and generally, quality of study evidence was low to moderate (Table 3).

The 5 studies included examined the outcomes of 1430 patients, of whom 727 received antibiotic therapy and 703 underwent appendicectomy. The treatment outcomes of those managed with antibiotics and appendicectomy are detailed in Figs. 2 and 3, respectively.

Complications

All studies reported on the primary outcome measure of complication rates. There was a 39 % risk reduction (RR 0.61, 95 % CI 0.44–0.83, $p = 0.002$) in complication rates in patients treated with antibiotics when compared with

Fig. 1 PRISMA diagram showing identification of relevant studies from initial search



those undergoing appendicectomy. When a subgroup analysis was performed excluding the single study which allowed cross-over of patients between groups [19], this risk ratio increased further, suggesting even greater benefit of antibiotic therapy (RR 0.52, 95 % CI 0.36–0.75, $p = 0.0005$).

Length of stay

Overall LOS (Fig. 4) was reported by all studies [19–22, 25], and there was no significant difference in this outcome by treatment modality (mean difference 0.25 days, 95 % CI −0.05 to 0.56, $p = 0.10$). However, when only studies which did not allow cross-over of patients were considered [20–22, 25], there was a significantly shorter LOS in patients treated with appendicectomy (mean difference 0.39 days, 95 % CI 0.18–0.59, $p = 0.0003$).

Treatment efficacy

Overall treatment efficacy in the antibiotic group at 1-year follow-up was 62.6 % ($n = 455/727$) versus 88.1 % in the appendicectomy group ($n = 619/703$). Salminen et al. [25] reported a successful treatment rate, at 1-year follow-up for those who received antibiotic therapy of 70.4 % ($n = 181/257$; 70 required appendicectomy up to one-year follow-up, 29 lost to follow-up, 1 died, 1 developed surgical site infection, 4 developed abdominal or incisional pain or obstructive symptoms) versus 81.0 % in those undergoing primary appendicectomy ($n = 221/273$; 24 developed surgical site infections, 2 developed incisional herniae, 23 developed abdominal or incisional pain or obstructive symptoms, 57 lost to follow-up, 1 died, 2 had no appendicitis on histology). This rate was similar to those of most previous studies (Vons et al. [20] 67.5 %; Styrud et al. [21] 75.8 %; Eriksson et al. [22] 65 %), with the exception of Hansson et al. [19] who found a treatment efficacy rate of 41.1 %, possibly related to the high cross-over rates in this study.

Complicated appendicitis

Of the 785 patients who underwent appendicectomy as the primary treatment, 133 (16.9 %) had perforated or

Table 1 Characteristics of included studies (updated from Varadhan KK, et al. BMJ 2012; 344:e2156 doi: 10.1136/bmj.e2156)

Eriksson et al. [22]	
Methods	Randomisation of patients admitted with history and clinical signs of acute appendicitis. Ultrasonography and laboratory tests—white blood cell count and C-reactive protein to identify patients with a high probability for acute appendicitis.
Participants	Patients with typical history and clinical signs, positive findings at ultrasound and either increased white blood cell count and C-reactive protein values or high C-reactive protein or white blood cell count on two occasions within a 4-h interval. Initial randomisation of 20 patients in each group, but one patient from the antibiotic group developed increased abdominal pain and generalised peritonitis, subjected to surgery and subsequent data were discounted.
Interventions	Conservative: Cefotaxime 2 g 12 hourly and tinidazole 800 mg for 2 days. Discharged after 2 days with oral ofloxacin 200 mg twice daily and tinidazole 500 mg twice daily for 8 days. Patients were excluded from the study in the event of increased abdominal pain and generalised peritonitis and subjected to surgery.
	Surgery: Treated with antibiotics for 24 h only in the event of bowel perforation or in cases of abdominal spillage. Discharged when conditions are satisfactory and when patients wished to return home. Histology obtained for all specimens.
	Follow-up: All patients were seen at 6, 10 and 30 days after admission and blood tested for white blood cell count and C-reactive protein, pain scores and temperature recorded. Abdominal & rectal examination on days 6 and 10. Stools examined for *Clostridium difficile* toxin at day 30. Ultrasound performed on days 10 and 30.
Outcomes	Pain scores (every 6 h using a visual analogue scale), morphine consumption, white blood cell count and temperature, positive diagnosis at surgery, hospital stay, wound infection, recurrent appendicitis.
Styrud et al. [21]	
Methods	Patients were asked to participate if appendicectomy was planned and those who agreed were subsequently randomised either to surgery or antibiotic therapy. Patients were monitored at the end of 1 week, 6 weeks and 1 year.
Participants	Male patients, 18–50 years of age, admitted to six different hospitals between years 1996 and 1999. No women were enrolled by decision of local ethics committee. Patients with suspected appendicitis with a C-reactive protein concentration of >10 mg/l and with no clinical signs of perforation.
Interventions	Antibiotics: Intravenous cefotaxime 2 g 12 hourly and tinidazole 800 mg daily for 2 days. Discharged after 2 days with oral ofloxacin 200 mg twice daily and tinidazole 500 mg twice daily for 10 days. If symptoms not improved within first 24 h, appendicectomy was performed. All conservatively treated patients with a suspected recurrence of appendicitis underwent surgery.
	Patients randomised to surgery were operated open or laparoscopically at the surgeon's discretion. All removed appendices were sent for histology.
Outcomes	Hospital stay, sick leave, diagnosis at operation, recurrences, complications.
Hansson et al. [19]	
Methods	Randomised controlled trial. Three hospitals included for the study, one hospital used only as a reference cohort for comparison with study and control groups at the other two hospitals. Allocation by date of birth (odd number-antibiotics group, even-surgery group). Questionnaire was sent to all patients after 1 and 12 months. Telephoned if no response.
Participants	369 patients with positive history, clinical signs, laboratory tests and in some cases, ultrasonography, computed tomography and gynaecological examination.
Interventions	Antibiotics: intravenous cefotaxime 1 g twice daily and metronidazole for at least 24 h. Patients when improved were discharged 24 h later with oral ciprofloxacin 500 mg twice day and metronidazole 400 mg three times a day for 10 days. If no improvement, intravenous treatment was prolonged.
	Surgery: Appendicectomy was performed according to author's usual practice, single dose antibiotic prophylaxis, open or laparoscopic technique and postoperative antibiotic treatment when the appendix was gangrenous or perforated.
	All specimens were sent for histological examination.
Outcomes	Treatment efficacy, complications, recurrences and reoperations, length of antibiotic therapy, abdominal pain after discharge from hospital, length of hospital stay and sick leave. The total costs for the primary hospital stay were analysed for each patient.
Vons et al. [20]	
Methods	Open-label, non-inferiority, randomised controlled trial in six academic centres.
Participants	All adults over 18 years with suspected acute appendicitis. Eligible participants had computed tomography diagnosis of uncomplicated appendicitis, using defined radiological criteria and randomised to appendicectomy or antibiotic therapy. Patients who were allergic to antibiotics or iodine, have been on antibiotics preceding to admission, receiving steroid or anticoagulants, have history of inflammatory bowel disease, pregnant, blood creatinine 200 μmol/L or more or inability to understand protocol or consent were excluded.

Table 1 continued

Interventions	Patients in both treatment groups were assessed twice a day following admission and were discharged after resolution of pain, fever and any digestive symptoms. All patients were seen on days 15, 30, 90, 180 and 360.
	Antibiotics: Intravenous or oral amoxicillin plus clavulanic acid (3 g per day if <90 kg or 4 g for patients >90 kg) for 48 h. Appendicectomy if no resolution of symptoms after 48 h. If resolution of symptoms, discharged with antibiotics and reviewed on day 8. Computed tomography performed if persistent pain or fever and possible appendicectomy. If not, antibiotics continued for another 8 days. If persistent symptoms on day 15, appendicectomy was performed.
	Surgery: Open or laparoscopic appendicectomy was done according to surgeon's standard practice. Amoxicillin plus clavulanic acid 2 g at induction of general anaesthesia. Antibiotics were given postoperatively only if complicated appendicitis. Histology was obtained for all specimens.
Outcomes	Primary endpoint: Occurrence of peritonitis within 30 days of initial treatment, diagnosed either at appendicectomy or postoperatively by computed tomography.
	Secondary endpoints: Number of days with a post-intervention visual analogue scale pain score ≥ 4, length of stay and absence from work, incidence of complications other than peritonitis within 1 year and recurrence of appendicitis after antibiotic treatment (appendicectomy done between 30 days and 1 year follow-up, with a confirmed diagnosis of appendicitis).
Salminen et al. [25]	
Methods	Open-label, non-inferiority, randomised controlled trial in six Finnish hospitals.
	Randomisation of patients admitted with CT-proven acute uncomplicated appendicitis to six Finnish hospitals between November 2009 and June 2012.
Participants	Patients aged 18–60 years admitted to the emergency department with clinical suspicion of acute uncomplicated appendicitis confirmed by CT scan were considered. Acute appendicitis was considered present when the appendiceal diameter exceeded 6 mm with wall thickening and at least one of the following; abnormal contrast enhancement of the appendiceal wall, inflammatory oedema, or fluid collections around the appendix. Patients with complicated appendicitis, defined as the presence of an appendicolith, perforation, abscess or suspicion of a tumour on the scan, were excluded.
	Initial randomisation of 530 patients by closed envelope technique to receive either antibiotic ($n = 257$) or appendicectomy ($n = 273$) treatment.
Interventions	Conservative: Single daily dose of intravenous ertapenem sodium (1 g/day) for 3 days with first dose administered in emergency department at presentation. Discharged after 72 h of intravenous therapy with 7 days of oral levofloxacin (500 mg once daily) and metronidazole (500 mg three times daily). Patients were excluded from the study if within 12–24 h they went on to develop progressive infection, perforated appendicitis or peritonitis at which point the patient underwent appendicectomy.
	Surgery: Open appendectomy via McBurney right lower quadrant muscle-splitting approach or laparoscopic appendicectomy. Prophylactic antibiotics (1.5 g cefuroxime and 500 mg metronidazole) were administered 30 min prior to incision. No further antibiotics were administered unless a wound infection was suspected postoperatively. Histological examination was performed on all specimens.
	Follow-up: All patients were seen daily during their hospital stays (days 0, 1, 2) and subsequently by telephone interviews at 1 week, 2 months and 1 year after the intervention. At 1 week and 2 months pain scores were obtained from a visual analogue scale, sick leave was registered, and the presence of wound infections and recurrent appendicitis was assessed. Patients were asked to contact the research hospital if they experienced any problems following treatment. For patients who were not contactable at final follow-up, a search of hospital records was performed to retrieve information regarding their treatment.
Outcomes	The primary outcome measure in the antibiotic group was resolution of acute appendicitis, with discharge from hospital without the requirement for surgical intervention and no recurrent appendicitis during 1-year follow-up. Treatment success in the appendicectomy group was defined as the patient successfully undergoing an appendicectomy.
	Secondary outcome measures were overall post-intervention complications, late recurrence of appendicitis (>1 year), hospital length of stay, sick leave taken, pain scores on a visual analogue scale, and the use of analgesics. Complications included surgical site infection within 30 days, adverse effects of antibiotic therapy, incisional hernia, adhesion-related problems and persistent abdominal or incisional pain.

gangrenous appendicitis diagnosed intraoperatively; 23 (2.9 %) had a normal appendix and other diagnoses were made in a further 20 (2.5 %). Excluding the Hansson study [19] due to high rates of cross-over, 32 of the 493 patients (6.5 %) who were randomised to antibiotic therapy went on to develop complicated appendicitis diagnosed intraoperatively following failure of antibiotic therapy during 1-year follow-up. Those treated primarily with antibiotics who went on to an appendicectomy for failure of treatment did not have a higher rate of complicated appendicitis than those who underwent appendicectomy as the primary treatment modality (10.9 vs. 17.9 %).

Salminen et al. [25] found an incidence of complicated appendicitis of 1.5 % ($n = 4/273$) in the appendicectomy group, all of which were diagnosed intraoperatively. Of these, two patients had perforated appendicitis and all had an appendicolith. In comparison, in the antibiotic cohort, 15 patients required appendicectomy during the index

Table 2 Summary of outcomes (updated from Varadhan KK, et al. BMJ 2012; 344:e2156 doi: 10.1136/bmj.e2156 [18])

Study	Number of patients, *n*		Age (years)		Successful treatment with intervention, *n*		Complication, *n*	
	Antibiotics	Surgery	Antibiotics	Surgery	Antibiotics	Surgery	Antibiotics	Surgery
Eriksson [22]	20	20	Mean (range): 27 (18–53)	Mean (range): 35 (19–75)	13	17	0	2
Styrud [21]	128	124	Range: 18–50; mean not reported	Range: 18–50; mean not reported	97	120	4	17
Hansson [19]	202	167	Mean (standard error of mean): 38 (1)	Mean (standard error of mean): 38 (1)	83	142	51	55
Vons [20]	120	119	Mean (standard deviation): 34 (12)	Mean (standard deviation): 38 (13)	81	119	3	12
Salminen [25]	257	273	Median (25th–75th percentile) 33 (26–47)	Median (25th–75th percentile) 35 (27–46)	181	221	8	28
Total	727	703			455	619	66	114

Study	Recurrences, *n*		Length of stay, mean (SD) (days)		Diagnoses in patients who had appendicectomy	
	Antibiotics	Surgery	Antibiotics	Surgery	Antibiotics	Surgery
Eriksson [22]	7	0	3.1 (0.3)	3.4 (1.9)	Appendicectomy: 8 (1 primary, 7 readmissions) 6 phlegmonous, 1 perforated	Appendicitis 17 (8 phlegmonous, 8 gangrenous, 1 perforated) 3 normal
Styrud [21]	16	0	3.0 (1.4)	2.6 (1.2)	Appendicectomy: 31 (15 primary + 16 readmissions) 1-primary had terminal ileitis; 12 perforated, 18 phlegmonous	Appendicitis: 120 (6 perforated, 1 gangrenous, 3 mesenteric adenitis, 1 no pathology)
Hansson [19]	15	0	3 (0.1)	3 (0.2)	119 patients had antibiotics and 83 others crossed over to surgery Appendicectomy: 21 (of 119) 9 appendicitis in index admission: 3 phlegmonous; 3 gangrenous, 3 perforated. (1-normal appendix, 1-surgically treatable) 12 of 15 recurrences had appendicectomy; 8 phlegmonous, 1 gangrenous, 3 perforated (3 treated with antibiotics)	83 crossed over to surgery from antibiotics (evaluated per protocol) Appendicectomy: 250 220 (128 phlegmonous, 42 gangrenous, 50 perforated) (Other diagnoses: 30) 3 other surgically treatable causes, 14 surgically non-treatable and 13 normal)
Vons [20]	30	0	3.96 (4.87)	3.04 (1.5)	44 had appendicectomy: 14 within 30 days (9 complicated, 4 uncomplicated, 1 normal) 30 days–1 year: 30 (3 complicated, 23 uncomplicated, 4 normal)	Appendicectomy: 119 (21 complicated appendicitis and 98 uncomplicated appendicitis)
Salminen [25]	55	0	3.2 (0.9)	2.8 (1.0)	15 had appendicectomy during primary hospital admission: 8 uncomplicated appendicitis, 7 complicated appendicitis 55 had appendicectomy after index admission at 1 year: 50 uncomplicated, 5 no appendicitis	Appendicectomy: 272 268 uncomplicated appendicitis, 4 complicated appendicitis 2 no evidence of appendicitis (1 had inflammation of lymphatic tissue, 1 had mucosal inflammation not extending to muscularis propria)
Total	123	0				

Table 3 GRADE Analysis (updated from Varadhan KK, et al BMJ 2012; 344:e2156 doi: 10.1136/bmj.e2156)

Question: Should antibiotics vs appendectomy be used for acute uncomplicated appendicitis?

Quality assessment							Summary of findings				
							Study event rates (%)		Relative effect (95 % CI)	Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	With appendicectomy	With antibiotics		Risk with appendicectomy	Risk difference with antibiotics (95 % CI)
Complications—All studies (critical outcome)											
1430 (5 studies) 1 years	Serious[a,b,c]	Serious[d]	No serious indirectness	No serious imprecision	Undetected	⊕⊕⊝⊝ Low[a,b,c,d] due to risk of bias, inconsistency	136/703 (19.3 %)	92/727 (12.7 %)	RR 0.62 (0.49–0.78)	193 per 1000	74 fewer per 1000 (from 43 fewer to 99 fewer)
Complications—Studies with no cross-over of patients (critical outcome)											
1061 (4 studies) 1 years	Serious[d]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	⊕⊕⊕⊝ Moderate[d] due to risk of bias	78/536 (14.6 %)	39/525 (7.4 %)	RR 0.52 (0.36–0.75)	146 per 1000	70 fewer per 1000 (from 36 fewer to 93 fewer)
Length of primary hospital stay—All studies (critical outcome; better indicated by lower values)											
1430 (5 studies) 1 years	Serious[a,b,c]	Serious[a]	No serious indirectness	No serious imprecision	Undetected	⊕⊕⊝⊝ Low[a,b,c] due to risk of bias, inconsistency	703	727	–		The mean length of primary hospital stay—all studies in the intervention groups was 0.04 higher (0.00–0.09 higher)
Length of primary hospital stay—studies with no cross-over of patients (critical outcome; better indicated by lower values)											
1061 (4 studies)	Serious[d]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	⊕⊕⊕⊝ Moderate[d] due to risk of bias	536	525	–		The mean length of primary hospital stay—studies with no cross-over of patients in the intervention groups was 0.39 higher (0.18–0.59 higher)
Risk of complicated appendicitis—all studies											
1430 (5 studies) 1 years	Serious[a,b,d]	Serious[a]	No serious indirectness	No serious imprecision	Undetected	⊕⊕⊝⊝ Low[a,b,d] due to risk of bias, inconsistency	135/703 (19.2 %)	61/727 (8.4 %)	RR 0.40 (0.31–0.53)	Study population 192 per 1000 Moderate	115 fewer per 1000 (from 90 fewer to 133 fewer) –
Risk of complicated appendicitis—studies with no cross-over of patients											
1061 (4 studies) 1 years	Serious[d]	Serious[e]	no serious indirectness	no serious imprecision	undetected	⊕⊕⊝⊝ Low[d,e] due to risk of bias, inconsistency	43/536 (8 %)	32/525 (6.1 %)	RR 0.78 (0.30–2.06)	80 per 1000	18 fewer per 1000 (from 56 fewer to 85 more)

[a] Incomplete data of patient numbers and events

[b] Randomisation by date of birth

[c] Cross-over of patients following randomisation (one study)

[d] Excluded female patients (one study)

[e] Definitions of outcome vary between trials

admission; however, just 7 of these had complicated acute appendicitis diagnosed at surgery, an incidence of 2.7 %. During 1-year follow-up, 55 patients who were initially successfully treated with antibiotics developed recurrent symptoms, all of whom underwent appendicectomy. There were no cases of complicated appendicitis in this cohort, with 50 patients having histologically uncomplicated appendicitis and 5 having a normal appendix.

Readmissions

In the whole cohort treated with antibiotics, 123 of 602 patients (20.4 %) were readmitted with symptoms suspicious of recurrent appendicitis. Of these, 120 went on to have an appendicectomy, and three were treated successfully with a further course of antibiotics. In those who had surgery during the follow-up period, nine patients had a normal appendix removed, and 111 had evidence of recurrent acute appendicitis.

Duration of sick leave

Length of sick leave was reported in four studies. Salminen et al. [25] found antibiotic treatment to be associated with a significant reduction in requirement for sick leave when compared with appendicectomy [median 7 days (IQR 7–12) versus 19 days (14–21), $p < 0.001$]. Hansson et al. [19] also found a significant reduction in sick leave in those treated with antibiotics in both the intention-to-treat (ITT) and per protocol (PP) analyses [ITT mean 7 days (SEM 1) vs. 11 (SEM 1), $p < 0.01$; PP 5 days (SEM 1) vs. 10 (1), $p < 0.01$].

Vons et al. [20] found no significant difference in 'duration of disability' which was defined as absence from work by treatment modality, nor did the study by Styrud et al. [21] which considered both overall time off work as well as sick leave.

Pain and temperature

Salminen et al. [25] found a significantly higher median (IQR) VAS pain score in the appendicectomy group at both discharge from hospital [3.0 (2–4) versus 2.0 (1–2), $p < 0.001$] and one-week follow-up [2.0 (1–3) versus 1.0 (1–1), $p < 0.001$]; however, this difference had disappeared at two-month follow-up [1.0 (1–1) versus 1.0 (1–1), $p = 0.40$]. Similarly, Erikkson et al. [22] reported a significant decrease in pain and analgesic requirement at days 6 and 10 in the antibiotic group. However, Vons et al. [20] found no significant difference in pain score between the groups [mean 2.70 (1.07) following appendicectomy versus 1.63 (1.35) in the antibiotic group]. In contrast, Hansson et al. [19] found a significantly shorter duration of pain following commencement of intervention (6 vs. 9 days in the surgical group, <0.05). In the year following intervention, there was no significant difference in the number of patients who experienced subjective abdominal pain (39 in the antibiotic group vs. 30 in the appendicectomy group, $p > 0.05$). This outcome was not reported in one study [25].

With regard to post-intervention temperature, Eriksson et al. [22] reported a significant decrease in patient temperature following antibiotic treatment versus appendicectomy. None of the other studies reported this outcome.

Discussion

This meta-analysis of five randomised controlled trials [19–22, 25] including 1430 patients, of whom 727 patients underwent antibiotic therapy and 703 appendicectomy, has demonstrated that antibiotic therapy for uncomplicated acute appendicitis is associated with a 39 % risk reduction in complications when compared with appendicectomy, with no significant difference seen in overall LOS. Those treated primarily with antibiotics who went on to have an appendicectomy for failure of treatment did not have a higher rate of complicated appendicitis than those who underwent appendicectomy as the primary treatment modality (10.9 % for antibiotics vs. 17.9 % for appendicectomy), suggesting that outcome is not worsened in those patients who undergo appendicectomy after "failed" antibiotic treatment. When only those studies which did not allow cross-over of patients were included in the meta-analysis [20–22, 25], the risk reduction in complications in favour of the antibiotic group was stronger (RR 0.52, 95 % CI 0.36–0.75, $p = 0.0005$); however, this patient cohort had a significantly longer overall LOS (mean difference 0.39 days, 95 % CI 0.18–0.59, $p = 0.0003$). The increase in LOS in patients treated with antibiotics was, to some extent, a result of the study protocols, and it is possible that the use of oral antibiotics may help shorten stay in the future.

The treatment efficacy associated with antibiotic therapy was similar in four studies [20–22, 25], ranging from 65 to 75.8 %, with a large reduction in this observed rate of efficacy in the single study which allowed high rates of cross-over between the treatment modalities [19]. When all patients included in the meta-analysis were considered, treatment efficacy in the antibiotic group at 1 year of follow-up was 62.2 % (Fig. 2). In comparison, the treatment efficacy rate for appendicectomy for these studies ranged between 85 and 100 %, with the overall efficacy rate of 88.1 %. The most recent study [25] stipulated a 24 % non-inferiority margin between the therapy modalities in light

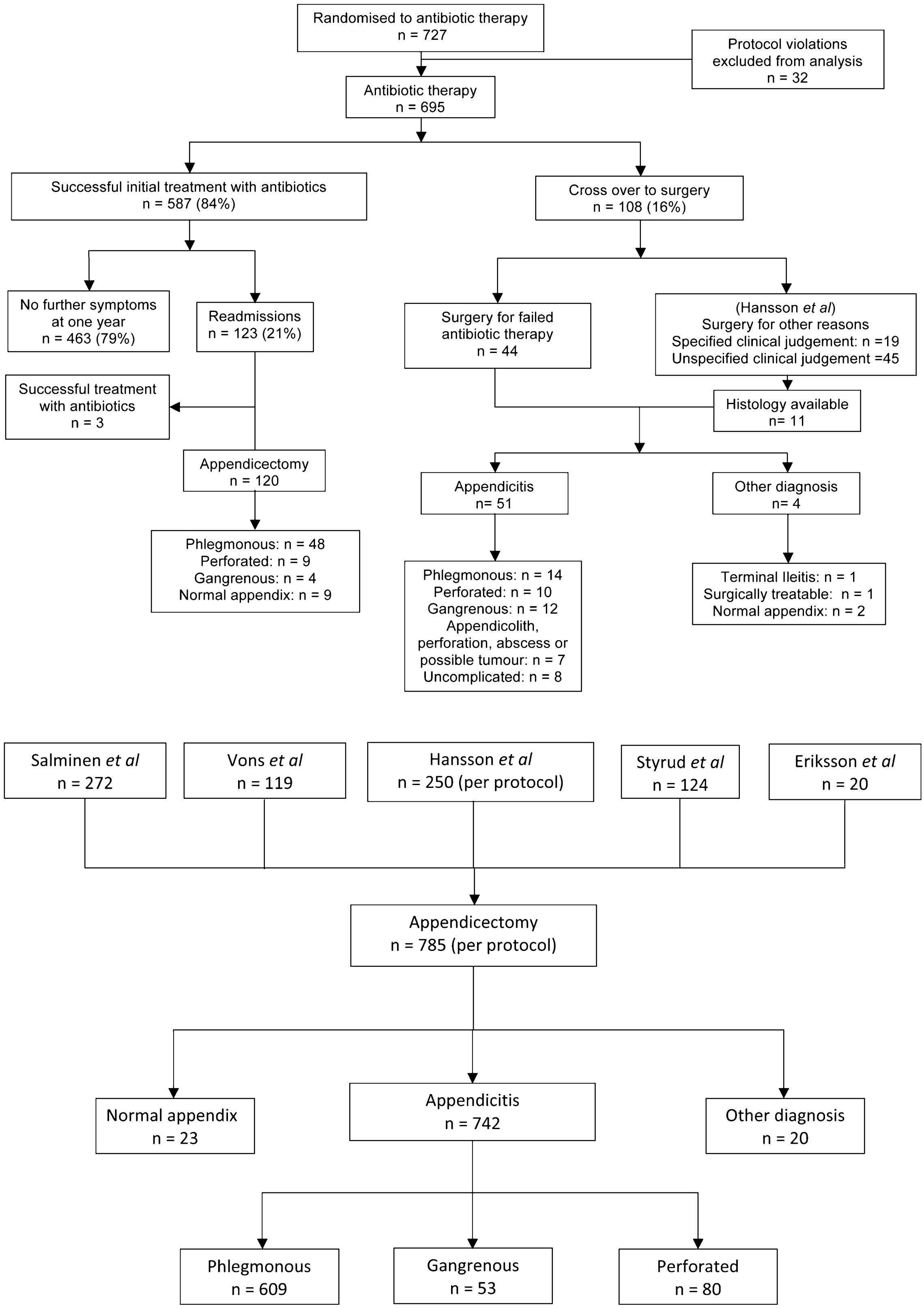
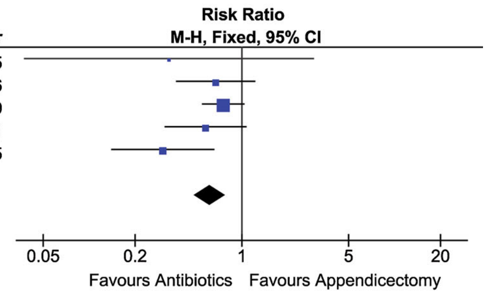


Fig. 2 Treatment outcome: antibiotics (*top*) and appendicectomy (*bottom*)

Study or Subgroup	Antibiotic treatment Events	Total	Appendicectomy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Eriksson	1	20	3	20	2.1%	0.33 [0.04, 2.94]	1995
Styrud	16	128	23	124	16.6%	0.67 [0.37, 1.21]	2006
Hansson	53	202	58	167	45.0%	0.76 [0.55, 1.03]	2009
Vons	14	120	24	119	17.1%	0.58 [0.31, 1.06]	2011
Salminen	8	257	28	273	19.2%	0.30 [0.14, 0.65]	2015
Total (95% CI)		**727**		**703**	**100.0%**	**0.62 [0.49, 0.78]**	
Total events	92		136				

Heterogeneity: Chi² = 5.36, df = 4 (P = 0.25); I² = 25%
Test for overall effect: Z = 4.00 (P < 0.0001)



Study or Subgroup	Antibiotic treatment Events	Total	Appendicectomy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Eriksson	1	20	3	20	3.9%	0.33 [0.04, 2.94]	1995
Styrud	16	128	23	124	30.1%	0.67 [0.37, 1.21]	2006
Vons	14	120	24	119	31.0%	0.58 [0.31, 1.06]	2011
Salminen	8	257	28	273	35.0%	0.30 [0.14, 0.65]	2015
Total (95% CI)		**525**		**536**	**100.0%**	**0.50 [0.35, 0.72]**	
Total events	39		78				

Heterogeneity: Chi² = 2.96, df = 3 (P = 0.40); I² = 0%
Test for overall effect: Z = 3.73 (P = 0.0002)

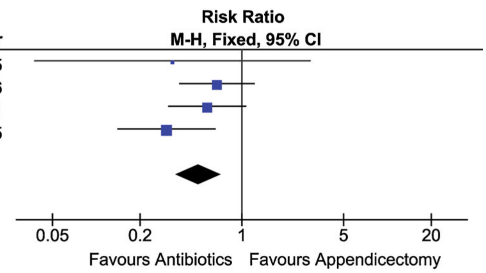
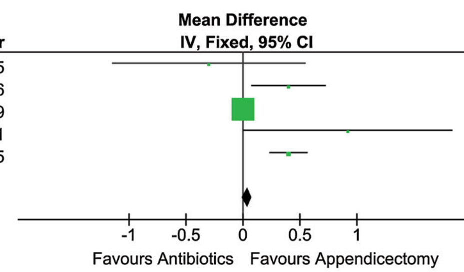


Fig. 3 Forest plot comparing complication rates for patients receiving antibiotic therapy versus appendicectomy for acute uncomplicated appendicitis: (*top*) all studies and (*bottom*) studies with no cross-over of patients. A Mantel–Haenszel random-effects model was used to perform the meta-analysis and risk ratios are quoted including 95 % confidence intervals

Study or Subgroup	Antibiotic Treatment Mean	SD	Total	Appendicectomy Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Eriksson	3.1	0.3	20	3.4	1.9	20	0.3%	-0.30 [-1.14, 0.54]	1995
Styrud	3	1.4	128	2.6	1.2	124	2.0%	0.40 [0.08, 0.72]	2006
Hansson	3	0.1	202	3	0.3	167	89.8%	0.00 [-0.05, 0.05]	2009
Vons	3.96	4.87	120	3.04	1.5	119	0.2%	0.92 [0.01, 1.83]	2011
Salminen	3.2	0.9	257	2.8	1	273	7.8%	0.40 [0.24, 0.56]	2015
Total (95% CI)			**727**			**703**	**100.0%**	**0.04 [-0.00, 0.09]**	

Heterogeneity: Chi² = 30.75, df = 4 (P < 0.00001); I² = 87%
Test for overall effect: Z = 1.75 (P = 0.08)



Study or Subgroup	Antibiotic Treatment Mean	SD	Total	Appendicectomy Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Eriksson	3.1	0.3	20	3.4	1.9	20	2.8%	-0.30 [-1.14, 0.54]	1995
Styrud	3	1.4	128	2.6	1.2	124	19.2%	0.40 [0.08, 0.72]	2006
Vons	3.96	4.87	120	3.04	1.5	119	2.4%	0.92 [0.01, 1.83]	2011
Salminen	3.2	0.9	257	2.8	1	273	75.7%	0.40 [0.24, 0.56]	2015
Total (95% CI)			**525**			**536**	**100.0%**	**0.39 [0.25, 0.53]**	

Heterogeneity: Chi² = 3.89, df = 3 (P = 0.27); I² = 23%
Test for overall effect: Z = 5.47 (P < 0.00001)

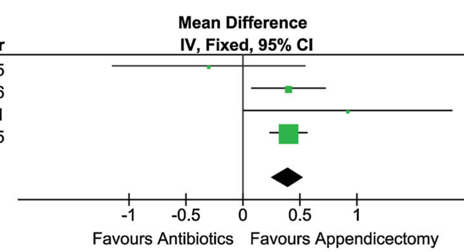


Fig. 4 Forest plot comparing overall primary hospital length of stay for patients receiving antibiotic therapy versus appendicectomy for acute uncomplicated appendicitis: (*top*) all studies and (*bottom*) studies with no cross-over of patients. An inverse-variance random effects model was used to perform the meta-analysis and mean differences are quoted including 95 % confidence intervals

of the literature evidence in order for patients to gain sufficient benefits from avoiding surgery. Of the 695 patients who underwent antibiotic therapy, 587 (84 %) were treated successfully during the index hospital admission, but 21 % ($n = 123$) of these patients were readmitted with symptoms of recurrent appendicitis within the 1-year follow-up period. Appendicectomy was performed in 98 % of those with recurrent appendicitis, but only 10.8 % of these patients had complicated appendicitis, and 7.5 % of patients had a normal appendix.

Strengths of study

When compared with previous meta-analyses [15, 18], the present meta-analysis includes one additional trial [25] which contains the largest number of patients ($n = 530$) and addresses some of the major weaknesses of previous trials. Prior to this, the largest study was on 369 patients [19], and there were high cross-over rates between treatment modalities. The most recent study [25] also only recruited patients with CT-proven uncomplicated appendicitis, in comparison to several of the previous studies which included those with clinical suspicion of appendicitis [19, 21] and may have resulted in several false positive cases of appendicitis. CT scanning is known to have high sensitivity and specificity for the diagnosis of appendicitis [33], yet only Salminen et al. [25] and Vons et al. [20] adopted this for the diagnosis of appendicitis in their studies. One of the criteria for the definition of complicated appendicitis in this study was the presence of an appendicolith on CT imaging. This criterion would only be discernible on CT imaging rather than clinical suspicion of acute appendicitis and is predictive of failure of non-operative management [20, 34]. It should however be considered that imaging modalities, including CT, ultrasound and MRI, are poorly predictive in the differentiation of simple and perforated appendicitis, which may bias the potential success of primary treatment with antibiotics [35]. However, as many patients with suspected appendicitis are young, routine CT scanning of all patients with right iliac pain may increase the risks associated with exposure to radiation. In addition, the hospital LOS in the antibiotic group was dictated by the study protocol which determined the patient must remain in hospital for 72 h prior to discharge for safety reasons. Without this protocol, it may be that antibiotic therapy exerts a more powerful reduction in overall hospital length of stay when compared to appendicectomy. In keeping with the previous meta-analysis conducted by our group [18], the outcome measures are considered as a composite of relevant factors pertinent to each treatment modality, making this a more reflective outcome of all possible complications rather than just those seen in the immediate postoperative period.

Limitations of study

The studies included in this meta-analysis span a 20-year period, during which time multiple advances have been made which may affect the results of this analysis including a greater array of broad-spectrum antibiotic therapy, increasing use of CT imaging to diagnose complicated and uncomplicated appendicitis, increasing use of laparoscopic appendicectomy and greater emphasis on decreasing overall LOS. In addition, several of the studies required a protracted recruitment period, with low overall recruitment rates to the study, making it likely that selection bias may have influenced the results significantly, making the results less generalisable to the overall population. The route, type and timing of antibiotic administration were variable between the studies. Four studies [19, 21, 22, 25] administered antibiotics for a variable period following commencement of the intervention (between 24 and 72 h), whereas one study [20] administered oral antibiotics as the first line treatment, with the intravenous route only used in patients with nausea and vomiting. This may have implications on the likelihood of success of antibiotic therapy. The type of antibiotic was also variable, with three studies using a combination of β lactam and nitroimidazole antibiotics [19, 21, 22], one using a combination of β lactam antibiotics [20] and one using a carbapenem antibiotic [25]. Only a small number of patients underwent laparoscopic rather than open appendicectomy, even in the most recent studies, with Salminen et al. [25] using this in just 5.5 % of cases. Given the reduction this is thought to have upon LOS, morbidity and postoperative recovery, this may have had an impact upon the results. The method for diagnosis of appendicitis was also variable between the studies, with all studies considering history and clinical findings consistent with appendicitis, but only some studies including radiological confirmation [20, 22, 25]. Time to discharge from hospital and resultant hospital LOS tended to be shorter in the appendicectomy group, with some studies imposing a standard duration for intravenous antibiotics which exceeded the normal LOS. This was most evident in the most recent study [25] in which patients in the antibiotic group were given 72 h of intravenous antibiotics by protocol, irrespective of their clinical status, from a safety standpoint, which probably resulted in a falsely prolonged LOS in this cohort. It should also be considered that those patients undergoing appendicectomy who had complicated appendicitis diagnosed intraoperatively typically underwent a course of intravenous antibiotics which could have resulted in a reduced rate of complications.

It is known that acute uncomplicated appendicitis may resolve spontaneously without intervention, with studies suggesting this to be not uncommon [36, 37]. It is not clear what proportion of patients treated with primary antibiotic therapy were successfully treated due to the presence of resolving appendicitis rather than the efficacy of the antibiotic therapy.

From a histopathological standpoint, the documentation of evidence for the histological diagnosis of appendicitis was variable, and generally poor, in the studies. In the most recently conducted study [25], appendicitis was confirmed if there was transmural neutrophil invasion involving the appendiceal muscularis layer which more accurately reflects a positive diagnosis of acute appendicitis. However, one study [20] included 'mucosal inflammation', although it has been established that this can be seen in asymptomatic patients with no evidence of appendicitis [38]. Three studies [19, 21, 22] document that resected appendices were sent for histological examination; however, the histopathological features required for a diagnosis of appendicitis were not detailed. In addition, these studies do not consider the pathological entity of neuroimmune appendicitis which is considered to be a distinct condition [39]. As a consequence, there may be a higher incidence of chronic abdominal pain in those patients treated with antibiotics which may not be detected in the studies to date.

The level of heterogeneity was generally high, although this was improved by excluding the single study in which cross-over between treatment modalities was commonplace [19]. There was no heterogeneity when this analysis was performed for overall complication rate, with moderate heterogeneity when the study was included. LOS was highly heterogeneous when all studies were considered ($I^2 = 87$ %); however, there was low heterogeneity when the study by Hansson et al. [19] was excluded. Both analyses were highly heterogeneous when the incidence of complicated appendicitis was considered. This was further emphasised by the GRADE analysis which found the quality of evidence to be between low and moderate for all outcomes, and as such, the quality of evidence from this meta-analysis is similar to that of the previous meta-analysis conducted by our group [18].

Comparison with other studies

The results of this meta-analysis are similar to a previous meta-analysis conducted [18] examining four RCTs. The current study employed the same methodology and similarly found a significant reduction in the rate of postoperative complication in favour of the antibiotic group; however, no significant difference in LOS or the risk of developing complicated appendicitis. The strength of the significance was higher in the current study, possibly related to the large increase in patient numbers associated with including the results of the large new study [25].

Conclusions

This meta-analysis of five randomised controlled trials further reinforces evidence that antibiotic therapy represents a safe, efficacious and viable treatment option for the treatment of uncomplicated acute appendicitis. Given that a significant percentage of operations show a normal appendix, it is somewhat surprising that antibiotics are not employed early and see if improvements occur prior to surgery. Of all the patients included in this meta-analysis, 66 % were treated successfully with primary antibiotic therapy with no symptom recurrence at 1 year. The studies included report a treatment efficacy of antibiotics of 41.1–78.5 % versus 85–100 % for appendicectomy. These results should however be interpreted in light of high levels of heterogeneity and low to moderate levels of evidence.

However, despite the evidence reinforcing the safety and efficacy of primary antibiotic therapy for patients with uncomplicated appendicitis, this treatment has not yet gained widespread acceptance [26]. Reasons for this are varied and include lack of equipoise on the part of surgeons and patients, the impracticality of obtaining CT scans to diagnose uncomplicated appendicitis in all patients with right iliac fossa pain, and the fear of litigation should patients develop complications after antibiotic therapy. A number of centres have adopted a more pragmatic approach of treating patients with antibiotics for 24–48 h after admission, continuing them if patients improve or performing an appendicectomy if they do not.

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Compliance with ethical standards

Conflict of Interests None of the authors has a conflict of interest to declare.

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