Antibiotic Treatment and Appendectomy for Uncomplicated Acute Appendicitis in Adults and Children

A Systematic Review and Meta-analysis

Mauro Podda, MD, Chiara Gerardi, Pharm D,† Nicola Cillara, MD,‡ Nicola Fearnhead, MD, FRCS,§ Carlos Augusto Gomes, MD, PhD,¶ Arianna Birindelli, MD,|| Andrea Mulliri, MD,** Richard Justin Davies, M Chir, FRCS,§ and Salomone Di Saverio, MD, FRCS§*

Objective: The aim of this meta-analysis was to summarize the current available evidence on nonoperative management (NOM) with antibiotics for uncomplicated appendicitis, both in adults and children.

Summary Background Data: Although earlier meta-analyses demonstrated that NOM with antibiotics may be an acceptable treatment strategy for patients with uncomplicated appendicitis, evidence is limited by conflicting results.

Methods: Systematic literature search was performed using MEDLINE, the Cochrane Central Register of Controlled Trials, and EMBASE databases for randomized and nonrandomized studies comparing antibiotic therapy (AT) and surgical therapy-appendectomy (ST) for uncomplicated appendicitis. Literature search was completed in August 2018.

Results: Twenty studies comparing AT and ST qualified for inclusion in the quantitative synthesis. In total, 3618 patients were allocated to AT (n = 1743) or ST (n = 1875). Higher complication-free treatment success rate (82.3% vs 67.2%; $P < 0.00001$) and treatment efficacy based on 1-year follow-up rate (93.1% vs 72.6%; $P < 0.00001$) were reported for ST. Index admission antibiotic treatment failure and rate of recurrence at 1-year follow-up were reported in 8.5% and 19.2% of patients treated with antibiotics, respectively. Rates of complicated appendicitis with peritonitis identified at the time of surgical operation (AT: 21.7% vs ST: 12.8%; $P = 0.07$) and surgical complications (AT: 12.8% vs ST: 13.6%; $P = 0.66$) were equivalent.

Conclusions: Antibiotic therapy could represent a feasible treatment option for image-proven uncomplicated appendicitis, although complication-free treatment success rates are higher with ST. There is also evidence that NOM for uncomplicated appendicitis does not statistically increase the perforation rate in adult and pediatric patients receiving antibiotic treatment. NOM with antibiotics may fail during the primary hospitalization in about 8% of cases, and an additional 20% of patients might need a second hospitalization for recurrent appendicitis.

Keywords: acute appendicitis, antibiotic therapy, appendectomy, conservative treatment, meta-analysis, nonoperative management, uncomplicated appendicitis

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Acute appendicitis remains one of the most common causes of an acute abdomen and is the commonest surgical disease among adult and pediatric patients presenting to emergency departments, both in the United States and Europe.[1]

In North America, the incidence is 100 per 100,000 person-years, with a stable trend throughout the latest decades of the 20th century. Although the disease was relatively uncommon outside Western countries during the 20th century, a rising incidence is reported from the beginning of the 21st century within newly industrialized countries.[2]

Since the first successful appendectomy was performed by Claudius Amyand in 1735 at St. George's Hospital in London, surgery has been the mainstay of treatment for over 2 centuries. Current evidence suggests laparoscopic appendectomy as the gold standard for surgical treatment, with lower incidence of wound infections, postintervention morbidity, shorter hospital stay, and higher quality of life scores when compared with open appendectomy.[3]

Although conservative management with antibiotics has been well established for intra-abdominal infections of other sources (in

From the *Department of General, Emergency and Robotic Surgery, San Francesco Hospital, Nuoro, Italy; †Centro di Politiche Regolatorie del Farmaco, IRCCS – Istituto di Ricerche Farmacologiche "Mario Negri", Milano, Italy; ‡Department of Surgery, Santissima Trinità Hospital, Cagliari, Italy; §Cambridge Colorectal Unit, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK; ¶Department of Surgery, Hospital Universitario Terezinha de Jesus, Universidade Federal de Juiz de Fora, Juiz de Fora, Brazil; ||Trauma Surgery Unit, Maggiore Hospital Regional Emergency Surgery and Trauma Center, AUSL Bologna Local Health District Bologna, Bologna, Italy; and **Department of Digestive Surgery, University Hospital of Caen, Caen cedex, France.

Contributions of authors: M.P.: Study conception and design, literature search, acquisition, interpretation and analysis of data; drafting and critically revising the article for important intellectual content; and final approval of the version to be published. C.G.: Study conception and design, literature search, acquisition, interpretation and analysis of data; drafting and critically revising the article for important intellectual content; and final approval of the version to be published. N.C.: Interpretation and analysis of data; drafting and critically revising the article for important intellectual content; and final approval of the version to be published. N.F.: Interpretation and analysis of data; critically revising the article for important intellectual content; and final approval of the version to be published. C.A.G.: Interpretation and analysis of data; critically revising the article for important intellectual content; and final approval of the version to be published. A.B.: Interpretation and analysis of data; critically revising the article for important intellectual content; and final approval of the version to be published. A.M.: Interpretation and analysis of data; critically revising the article for important intellectual content; and final approval of the version to be published. R.J.D.: Interpretation and analysis of data; drafting and critically revising the article for important intellectual content; editing and revising the English for the final version to be published; and final approval of the version to be published. S.D.S.: Study conception and design, literature search, acquisition, interpretation and analysis of data; drafting and critically revising the article for important intellectual content; Editing and revising the English for the final version to be published; and final approval of the version to be published.

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Reprints: Dr. Mauro Podda, MD, Department of Surgery: General, Emergency and Robotic Surgical Unit, San Francesco Hospital, ASSL Nuoro, ATS Sardegna, Via Mannironi, 1, 08100 Nuoro, Italy. E-mail: mauropodda@ymail.com.

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particular, for uncomplicated acute sigmoid diverticulitis), nonoperative management (NOM) of uncomplicated appendicitis is still limited by conflicting results coming from recent studies with high risk of bias.[4,5]

To date, many randomized controlled trials and nonrandomized studies have promoted antibiotic therapy as a safe approach to appendectomy for adult patients with uncomplicated appendicitis, suggesting success rates as high as 90% at 30 days and 75% within 1 year of treatment.[6–9] More recently, results of NOM with antibiotics in children have confirmed that the conservative strategy is a safe and effective alternative to surgery, with 64% to 86% success rates, lower incidence of complications, and no differences in the rate of complicated appendicitis compared to appendectomy.[10,11]

However, the recently published Jerusalem Guidelines and separately the European Association of Endoscopic Surgery (EAES) guidelines, note inadequate evidence to recommend routine NOM, and so generally appendectomy remains the treatment of choice recommended in Europe and the United States.[3,12]

Despite earlier meta-analyses demonstrating that NOM with antibiotics may be an acceptable treatment strategy for patients with uncomplicated appendicitis, there is still a lack of evidence regarding effectiveness and safety, potential complications, duration of pain, costs, lengths of hospital stay and time to return to normal daily life activity following NOM.[5,13–16]

The aim of this systematic review and meta-analysis was to summarize and systematically review the current available evidence on the antibiotic approach to uncomplicated appendicitis both in adults and children.

METHODS

This systematic review and meta-analysis was conducted according to the recommendations of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines,[17] the meta-analysis of observational studies in epidemiology checklist for observational studies (MOOSE),[18] and was specified in a registered protocol (PROSPERO: CRD42018104806). All stages of study identification, selection, quality assessment and data abstraction were carried out independently by 2 reviewers (M.P. and S.D.S.). Any discrepancies were resolved by consulting a third reviewer (C.G.).

Study Identification

MEDLINE (via PubMed), the Cochrane Central Register of Controlled Trials, and EMBASE were systematically searched for relevant studies. Reference lists of relevant studies were searched manually and the ''related articles'' function in PubMed was used. The search strategy combined text words and MeSH terms related to antibiotic therapy (AT) versus appendectomy/surgical therapy (ST) of uncomplicated appendicitis in adults and children: [appendicitis, antibiotic, nonoperative treatment, conservative management, nonoperative management] and [appendicitis, appendectomy, appendicectomy, laparoscopic appendectomy].

Corresponding search strategies were used for the Cochrane Central Register of Controlled Trials and EMBASE. No language restrictions were applied. Literature search was completed in August 2018.

The detailed search strategy is freely accessible in the protocol (PROSPERO: CRD42018104806).

Study Selection

For sensitivity reasons, not only randomized controlled trials (RCTs) but also prospective cohort studies (PCSs) and retrospective cohort studies (RCSs) comparing AT and ST as primary treatment for uncomplicated appendicitis in adults and children were included in the systematic review and meta-analysis. All studies eligible for inclusion had to report a clear definition of the diagnosis ''uncomplicated acute appendicitis.'' Only studies that reported at least one of the primary outcome or secondary outcomes were included.

The exclusion criteria were: studies not reporting data on the selected outcomes of interest, or articles in which the outcomes of interest could not be calculated; studies not specifying the patients selection criteria; studies reporting on complicated appendicitis (gangrenous, perforated appendicitis with abscess or generalized peritonitis); studies not reporting the specific antibiotic treatment regimens used for the AT; non-human studies; studies that reported only percentages instead of absolute numbers or odds ratios; review articles; editorials; comments; letters and case reports. The 2 reviewers independently screened all studies retrieved from the search, and full text articles were obtained if inclusion criteria were fulfilled. Where there was overlap in patient cohorts of 2 studies, the most recent and largest study was included in the systematic review and meta-analysis.

Risk of Bias Assessment

The risk of bias for the studies enrolled in the systematic review and meta-analysis was assessed according to the Cochrane handbook for systematic reviews of interventions,[19] using the Cochrane risk of bias tool for RCTs, and the risk of bias in nonrandomized studies tool (ROBINS-I) for PCSs and RCSs.[20]

Quality of Evidence Assessment

The grading of recommendations assessment, development and evaluation (GRADE) methodology was applied for assessing quality of evidence, and reported in the results.[21]

Outcomes Measures

- Primary outcome measures were evaluated to assess effectiveness and safety of AT and ST for uncomplicated appendicitis. The following outcomes were reviewed:
  1. Complication-free treatment success: success of the initial treatment (AT or ST) with an uncomplicated course (no postoperative complications, adverse events, or treatment failure occurring);
  2. Treatment efficacy based on 1-year follow-up (intention-to-treat analysis): efficacy for AT was defined as achieving a definitive improvement without requiring surgery within a median follow-up of 1 year. Lack of efficacy in the AT group included both persistence of acute appendicitis during the hospitalization (index admission AT failure: nonresolving appendicitis with persistent or worsening symptoms during the primary hospitalization) and recurrent acute appendicitis. On the other hand, efficacy for the ST was defined as uncomplicated appendicitis confirmed at the time of the surgical operation or histological verification of appendicitis, and resolution of symptoms after surgical treatment.
  3. Complicated appendicitis with peritonitis identified at the time of surgical operation: in the AT group the analysis was carried out within the cohort of patients who underwent appendectomy after the failure of the AT.
  4. Postintervention complications (intention-to-treat analysis): the number and rates of postoperative abscesses, surgical site infections, incisional hernias, obstructive symptoms, and other general complications, including adverse reaction to antibiotics, anesthesiology complications, cardiovascular and pulmonary adverse events were analyzed on an intention-to-treat basis.

5. Surgical complications: the number and rates of surgical complications only were analyzed both for patients who underwent ST as primary treatment and for those who underwent surgery as second line approach, after failure of AT treatment during the hospitalization, or for recurrent appendicitis.

- Secondary outcome measures were evaluated to assess other potential benefits and drawbacks of AT and ST in terms of:
  1. Number and rates of patients treated with a laparoscopic approach in both groups.
  2. Total costs: total medical and surgical costs for the primary hospital stay (primary costs), including materials, medications, radiology and surgical resources, pathology, laboratory tests). Costs were also analyzed for all appendicitis-related care (conservative treatment success or failure vs surgery without complications or surgery with complications). Currency conversion from original value to USD (United States Dollar) was made on August 15, 2018.
  3. Length of primary hospital stay: number of days of primary inpatient admission.
  4. Total length of stay per patient: number of days of hospitalization for readmissions added to the number of days of primary inpatient admission.
  5. Duration of pain (in days) following AT and ST.
  6. Length of sick leave (in days) following AT and ST.
  7. Length of time off work (in days) following AT and ST.
  8. Quality of life following AT and ST.

Data Extraction

The 2 reviewers independently reviewed each included article. A predefined paper-based sheet was used for data extraction.

Data collected for each article comprised the following predefined items: 1) Study identifier (first author, year of publication); 2) Essential study data (study period, study location, study population); 3) Study design (RCT, q-RCT, PCS, RCS); 4) Treatment arms and number of enrolled subjects; 5) Baseline characteristics of study subjects (mean age, sex, WBC count, body temperature, CRP concentration, Alvarado/AIR/PAS score on admission); 6) General characteristics of eligible studies (inclusion and exclusion criteria, sample size calculation, preintervention imaging techniques, treatment modalities, definition of the investigated primary and secondary outcomes); 7) Treatment outcomes, as described above.

Statistical Analysis

The meta-analysis was conducted by searching for a numerical estimate of the outcome of interest.

Variables for pooled analysis were considered if they were previously evaluated by at least 2 studies. All statistical analyses were carried out using Reviewer Manager software (Review Manager—RevMan—version 5.3.5, 2014, The Nordic Cochrane Centre, Cochrane Collaboration, www.cochrane-handbook.org). Data entries in the columns of forest plots were double-checked individually by 2 reviewers to avoid errors. The odds ratio (OR) with 95% confidence interval (95% CI) was calculated for dichotomous variables, and the standardized mean difference (SMD) with 95% CI for continuous variables. When continuous data were presented as medians and range, the method by Hozo et al to estimate respective means and standard deviations was applied.[22] The point estimate of the OR value was considered statistically significant at *P* level of less than 0.05 if the 95% CI did not cross the value 1. The point estimate of the SMD value was considered statistically significant at *P* level of less than 0.05 if the 95% CI did not cross the value 0.

Heterogeneity of the results across studies was assessed using the Higgins' I^2 and chi-square tests. A *P* value of chi-square test less than 0.10 with an I^2 value of greater than 50% was considered indicative of substantial heterogeneity. Fixed-effects model (Mantel–Haenszel) was implemented if statistically significant heterogeneity was absent. Otherwise, a random-effects model was used for meta-analysis if statistically significant heterogeneity was found, according to the method of DerSimonian and Laird.[23]

Given that substantial differences in methodology and clinical settings were found among individual studies, subgroup analyses were planned with the aim of exploring interstudy heterogeneity (adults vs children and RCTs vs non-RCTs). Funnel plots were created to evaluate the risk of publication bias.

RESULTS

A total of 8120 references were identified through database searching. Two more references were identified by searching lists of retrieved studies (Fig. 1).

Fifty-three full text publications were finally assessed for eligibility, of which 20 comparing AT and ST were included for quantitative synthesis. Seven of the included studies were randomized controlled trials (RCTs),[6–10,24,25] 8 were prospective cohort studies (PCSs),[11,26–32] 4 were retrospective cohort studies (RCSs),[33–36] and 1 was a quasirandomized study (q-RCT).[37] Ten studies were conducted in adults,[6–9,24–26,31,36,37] and 10 in children.[10,11,27–30,32–35] In total, 3618 patients were allocated to AT (n = 1743) or ST (n = 1875). General characteristics of patients as reported in the studies are shown in Table 1.

Study Characteristics

Large heterogeneity was found among the included studies with regard to diagnostic criteria for uncomplicated appendicitis. Marked heterogeneity was also demonstrated in type of antibiotics administered, duration of administration, and different outcomes evaluated.

A single pediatric patient was enrolled in the otherwise adult population pilot study by Talan et al.[9] For this reason, running a minimal risk of selection bias, the trial was included among adult studies.

Hansson et al implemented quasi-randomization by date of birth. Patients, once randomized to a specific treatment, were allowed to cross-over and receive the alternative treatment based on their preference or medical judgment, resulting in cross-over (47.5% of patients in the AT group underwent surgery, and 7.8% in the ST group were finally treated conservatively with antibiotics).[37]

Mahida et al[29] assessed the feasibility of NOM with antibiotics only in children with an appendicolith identified on preintervention imaging. Poillucci et al[36] included 14 patients (8.7%) with a radiological diagnosis of complicated disease (phlegmon or abscess). The randomized pilot trial by Talan et al[9] evaluated safety and feasibility of a protocol allowing outpatient antibiotic management. This study was therefore excluded from the pooled analysis of length of hospitalization (Supp. Digit. Content. Tab. 1, http://links.lww.com/SLA/B582).

Risk of Bias and Quality of Evidence Assessment

Three of the 8 RCTs were judged at a low risk of bias,[6,9,10] 2 at high risk,[25,37] and 3 at unclear risk.[7,8,24] All but 3 trials[24,25,37] generated random sequence adequately and reported allocation concealment, resulting in a low risk of selection bias. None of the trials reported attempts at blinding patients, personnel, outcome assessors, or data analysts. None of the trials were considered at high risk of selective reporting and incomplete outcome data, as

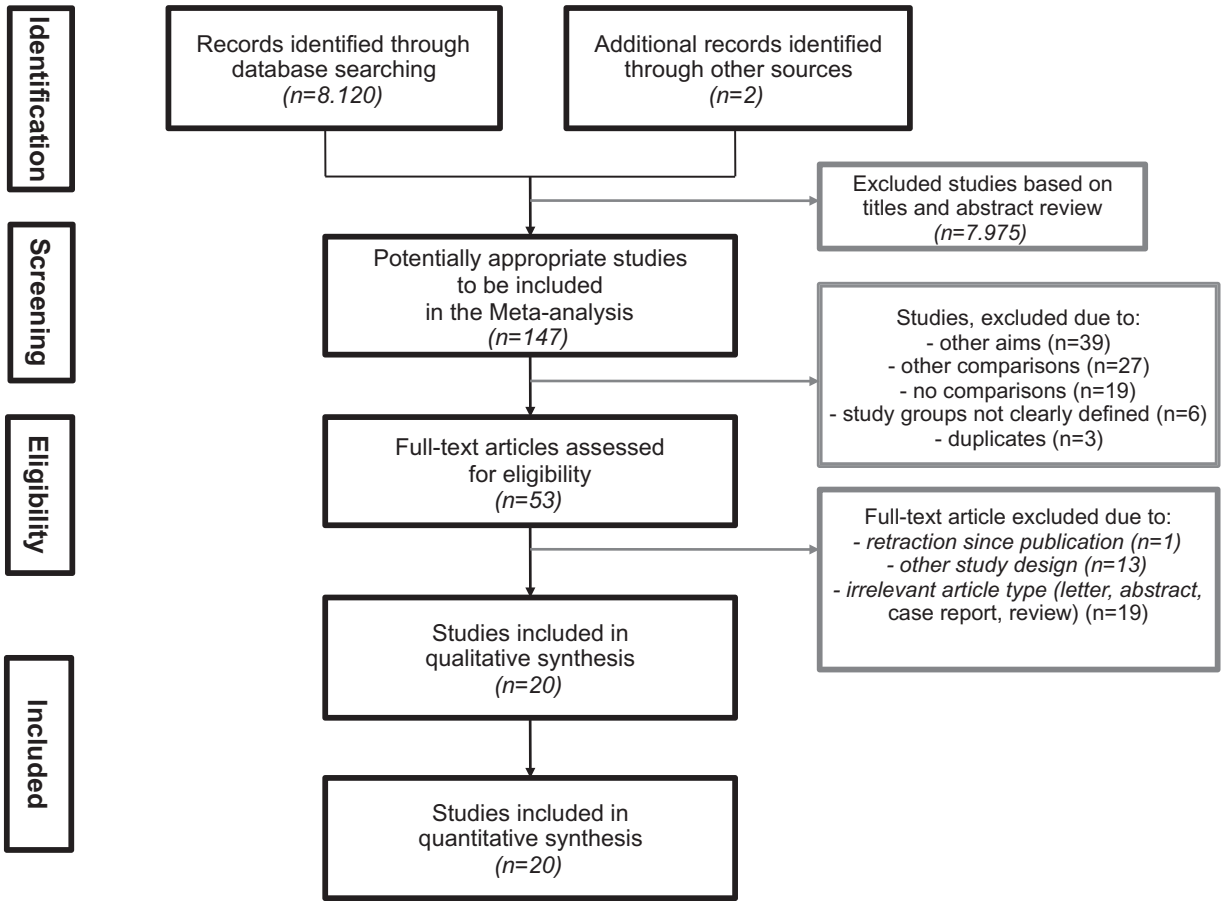


FIGURE 1. The PRISMA flow diagram for search and selection of articles included in the systematic review and meta-analysis.

primary endpoints were clearly defined and reported in each study (Supp. Digit. Content. Tab. 2, http://links.lww.com/SLA/B582). Four of the 10 non-RCTs were considered at serious risk of bias according to the ROBINS-I tool,[11,29,33,34] whereas the remaining 6 were judged at low or moderate risk (Supp. Digit. Content. Tab. 2, http://links.lww.com/SLA/B582). Graphically, potential publication bias was present for the following outcomes of interest: complication-free treatment success, treatment efficacy based on 1-year follow-up, postintervention complications, surgical complications, complicated appendicitis with peritonitis identified at the time of surgical operation, and length of primary hospital stay. Funnel plots have been provided as supplemental digital content (Supp. Digit. Content. Fig. 1, http://links.lww.com/SLA/B582). Overall quality of evidence, according to the GRADE criteria, was moderate for complication-free treatment success, treatment efficacy based on 1-year follow-up, postintervention complications, length of sick leave, and length of time off work. Surgical complications, length of primary hospital stay, duration of pain, and total costs had a low quality of evidence, whereas outcome results for intraoperative finding of complicated appendicitis with peritonitis were judged as very low (Table 2).

Complication-free Treatment Success

Overall, 20 studies reported the rate of complication-free treatment success (Table 3). The study by Koike et al[34] did not report the results in the ST group, and so, the pooled analysis included 19 studies. Taking into account any type of postinterventional complications (including treatment failure), a significantly higher success rate was reported for ST: 82.3% for ST versus 67.2% for AT (sample size: 3374; OR 0.30; 95% CI 0.20–0.47; $P < 0.00001$; $I^2 = 77\%$). Subgroup analyses of the outcome revealed no significant difference between adults (sample size: 2767; AT: 68.7% vs ST: 80.9%; OR 0.37; 95% CI 0.22–0.63; $P = 0.0003$; $I^2 = 84\%$) and children (sample size: 607; AT: 60.3% vs ST: 88.9%; OR 0.21; 95% CI 0.10–0.44; $P < 0.0001$; $I^2 = 51\%$; test for subgroup differences: $P = 0.21$; $I^2 = 35.5\%$) and between RCTs (sample size: 1800; AT: 65.7% vs ST: 79.6%; OR 0.30; 95% CI 0.15–0.58; $P = 0.0004$; $I^2 = 82\%$) and n-RCTs (sample size: 1574; AT: 68.7% vs ST: 86.1%; OR 0.30; 95% CI 0.16–0.56; $P < 0.0001$; $I^2 = 77\%$; test for subgroup differences: $P = 0.96$; $I^2 = 0\%$) (Fig. 2).

Treatment Efficacy Based on 1-year Follow-up

Data from 19 studies were included in the pooled analysis investigating the treatment efficacy based on 1-year follow-up (Table 3).

A significantly higher success rate was reported for ST: 93.1% versus 72.6% for AT (sample size: 3374; OR 0.12; 95% CI 0.06–0.24; $P < 0.00001$; $I^2 = 81\%$). Subgroup analyses of the outcome revealed no significant difference between adults (sample size: 2767; AT: 73.6% vs ST: 91.9%; OR 0.18; 95% CI 0.08–0.41; $P < 0.0001$; $I^2 = 88\%$) and children (sample size: 607; AT: 68.1% vs ST: 98.1%; OR 0.08; 95% CI 0.04–0.16; $P < 0.00001$; $I^2 = 0\%$; test for

TABLE 1. General Characteristics of Patients as Reported in the Studies Included for the Systematic Review and Meta-analysis

Study	Study Type	Study Period	Study Location	Study Population	Patients N.		Sex (M:F)		Age—Years: Mean ± SD		WBC Count ($\times 10^9$/L): Mean ± SD— Admission		Body Temperature: Mean ± SD —Admission		CRP Concentration (mg/L): Mean ± SD—Admission		Alvarado or AIR or PAS Score: Mean ± SD—Admission	
					A	S	A	S	A	S	A	S	A	S	A	S	A	S
Eriksson S 1995	RCT	1992–1994	Sweden	Adults	20	20	14:6	13:7	27.8 ± 10.1	35 ± 16.1	13.8 ± 4.4	13.9 ± 4.1	37.2 ± 0.7	37.1 ± 0.7	41 ± 30	40 ± 38	NR	NR
Styrud J 2006	RCT	1996–1999	Sweden	Adults	128	124	128:0	124:0	NR	NR	12.5 ± 3.8	12.4 ± 3.5	37.5 ± 0.7	37.4 ± 0.8	55 ± 44	54 ± 49	NR	NR
Hansson J 2009	q-RCT*	2006–2007	Sweden	Adults	119	250	62:57	138:112	40 ± 2	37 ± 1	12.2 ± 0.4	13.5 ± 0.3	37.2 ± 0.1	37.5 ± 0.1	51 ± 5	56 ± 3	NR	NR
Turhan AN 2009	RCT	2005–2006	Turkey	Adults	107	183	65:42	125:58	30.9 ± 1.3	26.2 ± 0.7	NR	NR	NR	NR	NR	NR	6.5 ± 0.1	6.4 ± 0.1
Vons C 2011	RCT	2004–2007	France	Adults	119	120	73:47	70:49	31 ± 9	34 ± 12	13.6 ± 3.6	13.1 ± 3.4	NR	NR	NR	NR	NR	NR
Armstrong J 2014	RCS	2012–2013	Canada	Children	12	12	4:8	6:6	12.2 ± 4.2	12 ± 3.2	16.1 ± 4.4	14.0 ± 4.2	NR	NR	13.6 ± 26.8	54 ± 23.4	NR	NR
Koike Y 2014	RCS	2004–2010	Japan	Children	130	114	66:59	NR	7.0 ± 4.0	NR	12.5 ± 4.0	NR	NR	NR	26.6 ± 0.8	NR	8.2 ± 0.2	NR
Park HC 2014	PCS	2010–2011	Korea	Adults	119	159	57:62	86:73	36.7 ± 14.1	38.4 ± 13.8	11.5 ± 3.8	12.1 ± 4.1	37.5 ± 1	37.8 ± 1.1	41.2 ± 48.3	46.3 ± 49.5	6.9 ± 1	7.0 ± 1
Minneci PC 2015	PCS	2012–2013	USA	Children	37	65	24:13	45:20	11 ± 1.1	12 ± 1.1	12.9 ± 1.6	12.9 ± 1.3	NR	NR	NR	NR	NR	NR
Salminen P 2015	RCT	2009–2012	Finland	Adults	257	273	155:102	174:99	33 ± 6.1	35 ± 5.4	11.7 ± 3.9	12 ± 4	NR	NR	29 ± 15	36 ± 13.5	NR	NR
Svensson JF 2015	RCT	2012–2012	Sweden	Children	24	26	14:10	12:14	12.2 ± 2.6	11.1 ± 2.4	14.0 ± 4.0	14.5 ± 6.4	37.3 ± 0.7	37.5 ± 0.6	30.5 ± 53.1	27.0 ± 50.2	NR	NR
Hartwich J 2016	PCS	2012–2014	USA	Children	24	50	14:11	30:19	12.6 ± 0.6	12.1 ± 0.5	15.2 ± 0.9	15.3 ± 0.5	NR	NR	NR	NR	NR	NR
Mahida JB 2016	PCS†	2014–2015	USA	Children	5	9	1:4	5:4	14 ± 0.1	11 ± 1.7	13.8 ± 1.8	14.3 ± 0.3	NR	NR	NR	NR	NR	NR
Tanaka Y 2016	PCS	2007–2013	Japan	Children	78	86	52:26	61:25	10.1 ± 2.0	10.4 ± 2.3	14.7 ± 3.7	15.3 ± 3.8	NR	NR	47 ± 48	61 ± 57	NR	NR
Allievi N 2017	PCS	2011–2015	Italy	Adults	284	109	135:149	59:50	36.8 ± 16.6	39.6 ± 15.9	13.0 ± 4.0	13.8 ± 4.2	NR	NR	52.9 ± 4.2	65.2 ± 5.0	6.2 ± 1.6	6.8 ± 1.8
Gorter RR 2017	PCS	2012–2014	Netherlands	Children	25	19	15:10	14:5	14 ± 2.0	14 ± 2.8	12.0 ± 3.7	12.0 ± 4.9	NR	NR	35 ± 32	30 ± 54.2	NR	NR
Lee SL 2017	PCS	2015–2016	USA	Children	51	32	30:21	17:15	10 ± 1.7	11 ± 2.0	13 ± 1.4	14 ± 2.0	37.5 ± 0.3	37.2 ± 0.3	NR	NR	7 ± 0.8	7 ± 0.6
Mudri M 2017	RCS	2012–2015	UK	Children	26	26	7:19	18:8	12	11	NR	NR	NR	NR	NR	NR	NR	NR
Poillucci G 2017	RCS	2014–2016	Italy	Adults	162	184	63:99	86:98	33.6 ± 16.5	35.8 ± 17.2	NR	NR	NR	NR	NR	NR	6.1 ± 1.3	6.9 ± 1.9
Talan DA 2017	RCT	2015–2015	USA	Adults	16	14	9:7	9:5	31 ± 18.4	36 ± 11.8	14.2 ± 3.7	15.3 ± 4.3	36.8 ± 0.3	36.9 ± 0.5	25.9 ± 57.4	64.8 ± 71.6	8 ± 1.7	8 ± 1.7
Total					1.743	1.875	988:752	1.092:667	21.8 ± 11.6	23.4 ± 12.4	13.3 ± 1.2	13.6 ± 1.1	37.2 ± 0.2	37.3 ± 0.2	37.3 ± 12.8	48.5 ± 13.6	NA	NA

A indicates antibiotic group; AIR, appendicitis inflammatory response; NA, not applicable; NR, not reported; PAS, pediatric appendicitis score; PCS, prospective cohort study; q-RCT, quasi-randomized controlled trial; RCS, retrospective cohort study; RCT, randomized controlled trial; S, surgery group; SD, standard deviation.

*Per-protocol analysis.

†Uncomplicated acute appendicitis with appendicolith.

TABLE 2. Level of Evidence According to the GRADE Criteria

Outcome	No. of Studies	No. of Patients	Quality Assessment						Overall Quality of Evidence*
			Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	
Complication-free treatment success	8	1800	7 RCTs, 1 q-RCT	Serious	Serious	Not serious	Not serious	Serious	Moderate
Treatment efficacy based on 1-yr follow-up	8	1800	7 RCTs, 1 q-RCT	Not serious	Serious	Not serious	Not serious	Serious	Moderate
Intraoperative finding of complicated appendicitis with peritonitis	7	1192	6 RCTs, 1 q-RCT	Serious	Serious	Serious	Serious	Serious	Very low
Postintervention complications	7	1750	6 RCTs, 1 q-RCT	Serious	Serious	Not serious	Not serious	Serious	Moderate
Surgical complications	7	1149	6 RCTs, 1 q-RCT	Serious	Serious	Serious	Not serious	Serious	Low
Length of primary hospital stay	7	1770	6 RCTs, 1 q-RCT	Serious	Serious	Serious	Not serious	Not serious	Low
Duration of pain	2	608	1 RCT, 1 q-RCT	Serious	Serious	Not serious	Not serious	Serious	Low
Length of sick leave	3	1151	2 RCTs, 1 q-RCT	Serious	Serious	Not serious	Not serious	Not serious	Moderate
Length of time off work	2	491	2 RCTs	Serious	Not serious	Not serious	Not serious	Not serious	Moderate
Total costs (successful treatment)	3	449	2 RCTs, 1 q-RCT	Serious	Serious	Serious	Not serious	Not serious	Low

Meta-analysis of RCTs comparing conservative management with antibiotics and appendectomy for: complication-free treatment success, treatment efficacy based on 1-yr follow-up, intraoperative finding of complicated appendicitis with peritonitis, postintervention complications, surgical complications, length of primary hospital stay, duration of pain, length of sick leave, length of time off work, and total costs.

*Summary estimate based on the quality assessment items.

Q-RCT indicates quasi-randomized controlled trial; RCT, randomized controlled trial.

subgroup differences: $P = 0.13$; $I^2 = 57.0\%$) and between RCTs (sample size: 1800; AT: 73.8% vs ST: 94.7%; OR 0.12; 95% CI 0.05–0.26; $P < 0.00001$; $I^2 = 67\%$) and n-RCTs (sample size: 1574; AT: 71.6% vs ST: 90.8%; OR 0.12; 95% CI 0.04–0.35; $P < 0.0001$; $I^2 = 85\%$; Test for subgroup differences: $P = 0.95$; $I^2 = 0\%$) (Fig. 3). All the studies but that by Park et al[26] reported the rate of index admission antibiotic treatment failure. This was 8.5%. Overall, the rate of recurrence at 1-year follow-up was 19.2%. Laparoscopic appendectomy rates were reported by 8 authors in the AT group[8,10,27,32,33,35,36] and by 14 authors in the ST group[7–10,25,27,30–33,35,36] (Supp. Digit. Content. Tab. 3, http://links.lww.com/SLA/B582). However, only 2 studies were eligible for the quantitative analysis.[8,36] Results indicated that no significant difference in the rate of laparoscopic appendectomy was present between the group of patients submitted to surgery as first-line treatment and those who underwent surgery after failure of NOM with antibiotics (sample size: 624; AT: 54.2% vs ST: 77.4%; OR 0.31; 95% CI 0.06–1.55; $P = 0.16$; $I^2 = 87\%$).

Intraoperative Finding of Complicated Appendicitis With Peritonitis

Three studies did not report data on this outcome,[28,31,34] and 3 studies did not report any such event.[9,33,35] The meta-analysis was conducted on 14 studies.[6–8,11,24–27,29,30,32,36] All studies, except Turhan et al[25] (based on intraoperative observation alone) reported the incidence of complicated appendicitis by histologic examination. Overall, it was 21.7% for AT versus 12.8% for ST (sample size: 1868; OR 2.01; 95% CI 0.93–4.34; $P = 0.07$; $I^2 = 71\%$). The odds ratio for complicated appendicitis was doubled for patients in the AT group undergoing surgery following failure of NOM. However, the difference was not statistically significant. Subgroup analyses revealed no significant differences between adults (sample size: 1583; AT: 21.8% vs ST: 12.7%; OR 2.63; 95% CI 0.98–7.09; $P < 0.00001$; $I^2 = 81\%$) and children (sample size: 285; AT: 20.1% vs ST: 13.9%; OR 1.17; 95% CI 0.35–3.88; $P = 0.80$; $I^2 = 30\%$; Test for subgroup differences: $P = 0.31$; $I^2 = 4.7\%$) and between RCTs (sample size: 1192; AT: 22.9% vs ST: 11.6%; OR 2.96; 95% CI 0.91–9.60; $P = 0.0002$; $I^2 = 77\%$) and n-RCTs (sample size: 676; AT: 19.6% vs ST: 14.9%; OR 1.30; 95% CI 0.52–3.21; $P = 0.58$; $I^2 = 49\%$; Test for subgroup differences: $P = 0.28$; $I^2 = 15.9\%$) (Table 3) (Supp. Digit. Content. Fig. 2, http://links.lww.com/SLA/B582).

Postintervention Complications

All studies except Koike et al[34] reported the rate of postintervention complications. Three studies[10,28,29] did not observe any such adverse events, whereas Allievi et al[31] reported the postintervention complications rate only for patients in the ST group. The meta-analysis was conducted on the remaining 15 studies. Overall, the rate of complications of AT was significantly lower compared to ST (sample size: 2843; AT: 7.1% vs ST: 14.5%; OR 0.41; 95% CI 0.22–0.77; $P = 0.006$; $I^2 = 68\%$). Subgroup analyses revealed that the postintervention complications rate was statistically higher in the ST group limited to the adult population (sample size: 2374; AT: 6.6% vs ST: 14.5%; OR 0.39; 95% CI 0.16–0.94; $P = 0.04$; $I^2 = 80\%$), but not in children (sample size: 469; AT: 9.6% vs ST: 12.5%; OR 0.57; 95% CI 0.28–1.16; $P = 0.12$; $I^2 = 0\%$), although no significant differences were found between the two subgroups (test for subgroup differences: $P = 0.53$; $I^2 = 0\%$).

AT was associated with a significantly lower rate of complications in non-RCT studies (sample size: 1750; AT: 5.3% vs ST: 12.1%; OR 0.31; 95% CI 0.15–0.65; $P = 0.002$; $I^2 = 28\%$) but not in RCTs (sample size: 1093; AT: 8.2% vs ST: 15.9%; OR 0.55; 95% CI 0.21–0.45; $P = 0.22$; $I^2 = 81\%$). The test for subgroup difference indicated that the design of the study did not modify the effect of

TABLE 3. Summary of Primary Outcomes (Complication-free Treatment Success, Treatment Efficacy Based on 1-yr Follow-up, Intraoperative Finding of Complicated Appendicitis With Peritonitis, Postintervention Complications, Surgical Complications)

	Complication-free Treatment Success. N (%)*		Treatment Efficacy Based on 1-yr Follow-up (ITT). N (%)†		Intraoperative Finding of Complicated Appendicitis With Peritonitis. N (%)‡		Postintervention Complications (ITT). N (%)		Surgical Complications. N (%)‡	
Study	**A**	**S**	**A**	**S**	**A**	**S**	**A**	**S**	**A**	**S**
Eriksson S 1995	13 (65)	18 (90)	13 (65)	20 (100)	1 (14.3)	1 (5)	–	2 (10)	–	2 (10)
Styrud J 2006	93 (72.6)	107 (86.3)	97 (75.8)	120 (96.8)	12 (38.7)	6 (5)	4 (3.1)	17 (13.7)	4 (12.9)	17 (13.7)
Hansson J 2009	57 (47.9)	143 (57.2)	93 (78.2)	223 (89.2)	6 (26)	50 (20)	36 (30.2)	80 (32)	6 (26)	74 (29.6)
Turhan AN 2009	82 (76.6)	175 (95.6)	87 (81.3)	183 (100)	–	31 (16.9)	5 (4.7)	8 (4.4)	5 (26.3)	8 (4.4)
Vons C 2011	63 (52.9)	114 (95)	75 (63)	117 (97.5)	12 (27.2)	21 (18)	12 (10.1)	3 (2.5)	12 (27.3)	3 (2.5)
Armstrong J 2014	7 (58.3)	10 (83.3)	8 (66.7)	12 (100)	–	–	1 (8.3)	2 (16.7)	1 (25)	2 (16.7)
Koike Y 2014	105 (78.3)	NR	105 (78.3)	NR	NR	NR	NR	NR	NR	NR
Park HC 2014	95 (79.8)	136 (85.5)	96 (80.6)	152 (95.5)	4 (20)	11 (6.9%)	1 (0.8)	16 (10)	1 (5)	16 (10)
Minneci PC 2015	28 (75.7)	56 (86.2)	28 (75.7)	61 (93.8)	1 (11.1)	8 (12.3)	–	5 (7.7)	–	5 (7.7)
Salminen P 2015	180 (70)	209 (76.5)	186 (72.4)	254 (93)	14 (16.5)	2 (0.7)	6 (2.3)	45 (16.5)	6 (8.6)	45 (16.5)
Svensson JF 2015	18 (75)	26 (100)	18 (75)*	26 (100)*	–	5 (19.2)	–	–	–	–
Hartwich J 2016	17 (70.8)	50 (100)	17 (70.8)	50 (100)	NR	NR	–	–	–	–
Mahida JB 2016	2 (40)	9 (100)	2 (40)	9 (100)	–	6 (66.7)	–	–	–	–
Tanaka Y 2016	55 (70.5)	84 (97.7)	55 (70.5)	86 (100)	1 (7.1)	–	–	2 (2.3)	–	2 (2.3)
Allievi N 2017	232 (81.7)	89 (81.6)	232 (81.7)§	78 (71.5)§	NR	NR	NR	20 (18.3)	NR	20 (18.3)
Gorter RR 2017	9 (36)	8 (42.1)	21 (84)	19 (100)	–	4 (21)	12 (48)	11 (57.9)	–	2 (10.5)
Lee SL 2017	17 (33.3)	25 (78.1)	26 (50.9)	31 (96.8)	8 (50)	10 (31.2)	9 (18)	6 (19)	3 (12.5)	6 (19)
Mudri M 2017	17 (65.4)	21 (80.7)	17 (65.4)	25 (96.1)	–	–	–	4 (15.4)	–	4 (15.4)
Poillucci G 2017	87 (53.7)	159 (86.4)	87 (53.7)*	159 (86.4)*	10 (29.4)	44 (23.8)	4 (2.5)	25 (13.6)	4 (7.1)	25 (13.6)
Talan DA 2017	13 (81.2)	12 (85.7)	14 (87.5)	14 (100)	–	–	1 (6.2)	2 (14.3)	–	2 (14.3)
Total	1.190 (67.2)	1.451 (82.3)	1.277 (72.6)	1.639 (93.1)	69 (21.7)	199 (12.8)	91 (7.1)	248 (14.5)	42 (12.8)	233 (13.6)

*Success of the initial treatment with uncomplicated course (no postoperative complications, adverse events, or treatment failure occurring).

†If not otherwise specified, efficacy means clinical recovery without need for surgical treatment at 1-year follow-up in the antibiotic group, and positive diagnosis of acute appendicitis during operation and resolution of symptoms after surgical treatment in the surgery group.

‡In the antibiotic group, after failure of the primary treatment and subsequent surgery.

§In the antibiotic group the failure rate was intended as the necessity of appendectomy during index admission (acute failure) or a new episode of suspected appendicitis requiring surgical treatment within 1 year from discharge (delayed failure).

A indicates antibiotic group; CT, computed tomography; ITT, intention-to-treat analysis; NR, not reported; NA, not applicable; S, surgery group; US, ultrasound scan.

interventions ($P = 0.37$; $I^2 = 0\%$) (Table 3) (Supp. Digit. Content. Fig. 3, http://links.lww.com/SLA/B582).

Surgical Complications

Nineteen of 20 studies reported data on surgical complications. Allievi et al[31] reported the surgical complications rate only for patients in the ST group. Koike et al did not provide results for this outcome of interest.[34] Three studies[10,28,29] did not observe any adverse events. The pooled analysis involved 15 studies. Overall, the rates of surgical complications after AT and ST were equivalent (sample size: 1894; AT: 12.8% vs ST: 13.6%; OR 1.16; 95% CI 0.59–2.28; $P = 0.66$; $I^2 = 57\%$). Subgroup analyses of the outcome revealed no significant difference between adults (sample size: 1598; AT: 14.0% vs ST: 14.5%; OR 1.32; 95% CI 0.53–3.28; $P = 0.55$; $I^2 = 74\%$) and children (sample size: 296; AT: 7.1% vs ST: 8.7%; OR 0.86; 95% CI 0.31–2.36; $P = 0.77$; $I^2 = 0\%$; Test for subgroup differences: $P = 0.54$; $I^2 = 0\%$). In the same way, subgroup analysis of the outcome revealed no significant difference between RCTs (Sample size: 1179; AT: 16.9% vs ST: 15.3%; OR 1.77; 95% CI 0.58–5.35; $P = 0.32$; $I^2 = 78\%$) and non-RCT studies (sample size: 715; AT: 6.8% vs ST: 10.6%; OR 0.64; 95% CI 0.32–1.29; $P = 0.21$; $I^2 = 0\%$; test for subgroup differences: $P = 0.13$; $I^2 = 56.6\%$) (Table 3) (Supp. Digit. Content. Fig. 4, http://links.lww.com/SLA/B582).

Overall, the rate of wound infections (sample size: 1492; AT: 4.2% vs ST: 6.9%; OR 0.90; 95% CI 0.24–3.41; $P = 0.87$; $I^2 = 68\%$), bowel obstruction (sample size: 1107; AT: 3.2% vs ST: 3.9%; OR 0.90; 95% CI 0.41–2.01; $P = 0.80$; $I^2 = 0\%$), incisional hernia (sample size: 616; AT: 0% vs ST: 0.6; OR 1.33; 95% CI 0.15–11.81; $P = 0.49$; $I^2 = 0\%$) and abscess formation (sample size: 1351; AT: 0.9% vs ST: 1.9; OR 1.08; 95% CI 0.41–2.80; $P = 0.88$; $I^2 = 0\%$) were similar between the 2 groups (Supp. Digit. Content. Tab. 4, http://links.lww.com/SLA/B582), (Supp. Digit. Content. Fig. 5, http://links.lww.com/SLA/B582).

Total Costs

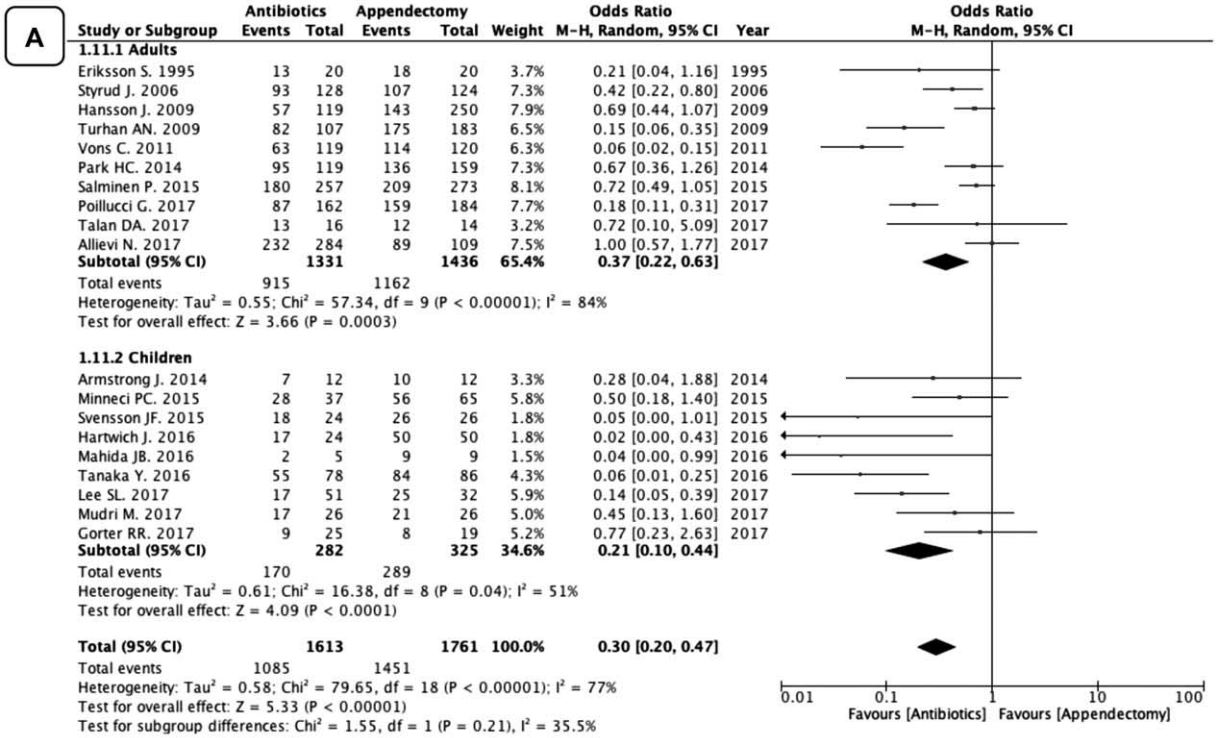
The pooled analysis of primary costs included 7 studies.[9,10,26–28,34,37]

Overall, AT resulted in significantly lower costs when compared to ST (sample size: 1147; \$ 2509.14 ± 1621.5 vs \$ 4898.57 ± 3641.5; SMD −3.65; 95% CI −5.36–1.93; $P < 0.00001$, $I^2 = 98\%$). Two studies were included in the meta-analysis of all appendicitis-related care costs.[10,27] Results demonstrated significantly lower costs in the AT group (sample size: 152; AT: \$ 4074.50 ± 204.3 vs ST: \$ 5117 ± 124.4; SMD −0.69; 95% CI −1.02–0.35; $P < 0.0001$, $I^2 = 43\%$) (Supp. Digit. Content. Tab. 3, http://links.lww.com/SLA/B582), (Supp. Digit. Content. Fig. 6, http://links.lww.com/SLA/B582).

Length of Primary Hospital Stay

The pooled analysis of length of primary hospital stay included 13 studies.[6–8,10,24–27,30,31,33,36,37]

Overall, AT and ST showed an equivalent length of primary hospital stay (sample size: 3077; Days 2.9 ± 1.3 vs Days 3.3 ± 1.7; SMD −0.55; 95% CI −1.49–0.39; $P = 0.25$; $I^2 = 99\%$). Subgroup analyses of the outcome revealed no significant difference between



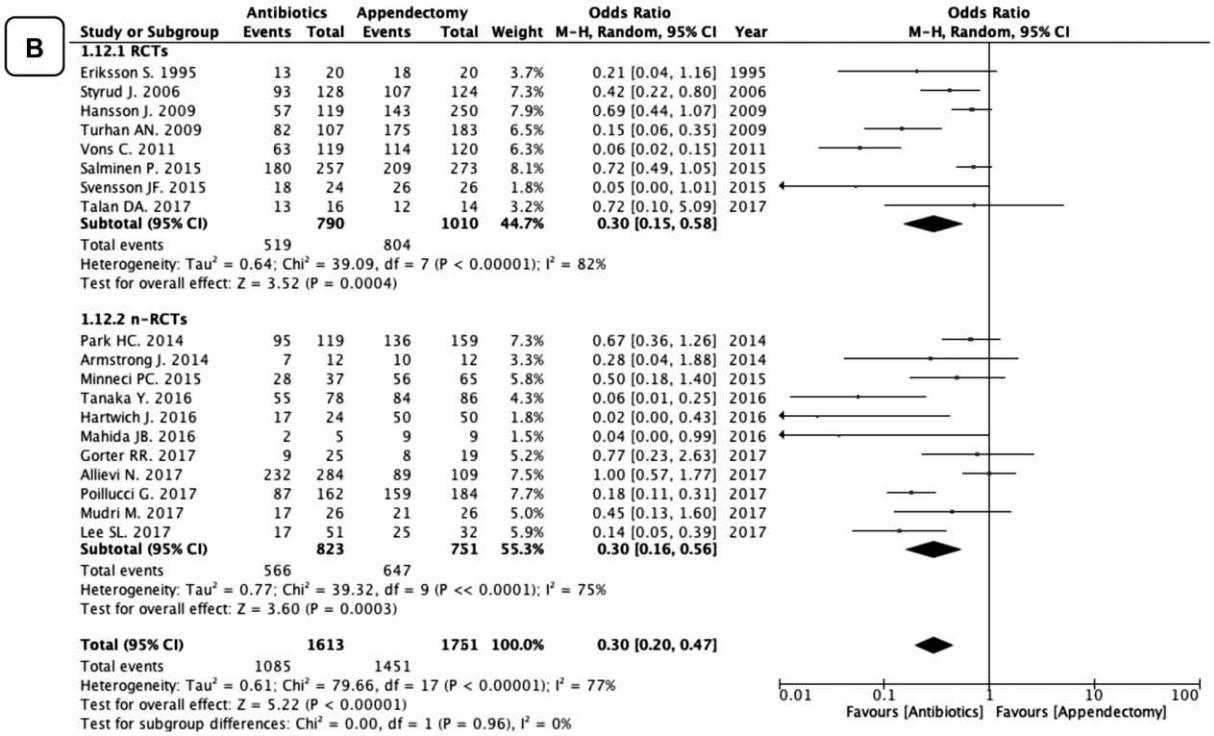


FIGURE 2. Meta-analysis of complication-free treatment success. Subgroup analyses: adults versus children [A], and RCTs versus n-RCTS [B].

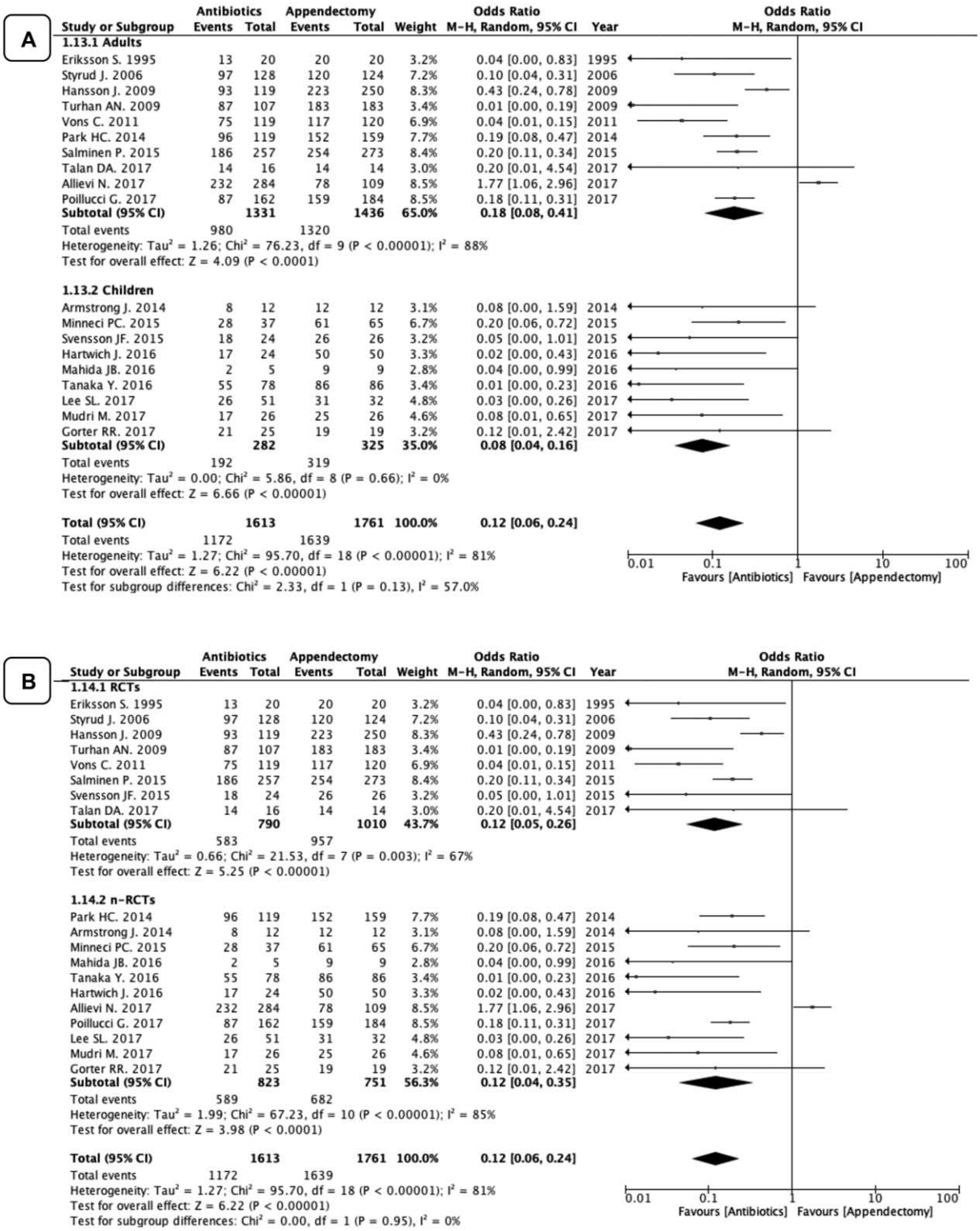


FIGURE 3. Meta-analysis of treatment efficacy based on 1-year follow-up. Subgroup analyses: adults versus children [A], and RCTs versus n-RCTS [B].

adults (sample size: 2737; SMD −0.20; 95% CI −1.34–0.93; $P = 0.73$; $I^2 = 99\%$) and children (sample size: 340; SMD −1.40; 95% CI −3.71–0.92; $P = 0.24$; $I^2 = 98\%$; test for subgroup differences: $P = 0.36$; $I^2 = 0\%$).

In non-RCT studies (sample size: 1770; SMD −1.52; 95% CI −2.42–0.63; $P = 0.0009$; $I^2 = 98\%$) AT resulted in a significantly shorter length of stay, whereas in RCTs (sample size: 1307; SMD 0.35; 95% CI −1.30–2.00; $P = 0.68$; $I^2 = 99\%$) the difference was not statistically significant. Test for subgroup differences ($P = 0.05$; $I^2 = 73.7\%$) indicated that there was no statistically significant subgroup effect, suggesting that the study design did not modify the effect of AT in comparison with ST (Supp. Digit. Content. Tab. 4, http://links.lww.com/SLA/B582), (Supp. Digit. Content. Fig. 7, http://links.lww.com/SLA/B582).

Total length of stay per patient, duration of pain, length of sick leave, length of time off work, the total length of stay per patient were documented in 4 studies.[31–34] It did not differ significantly between AT and ST (sample size: 744; Days 2.9 ± 1.2 vs Days 3.8 ± 1.3; SMD −0.32; 95% CI −0.74–0.09; $P = 0.12$; $I^2 = 81\%$).

Duration of pain was evaluated in 3 studies.[8,32,37] Results of the pooled analysis did not demonstrate any statistically significant difference between AT and ST (sample size: 691; Days 3.2 ± 1.7 vs Days 4.9 ± 3.1; SMD −1.62; 95% CI −3.61–0.38; $P = 0.11$; $I^2 = 99\%$).

The length of sick leave was reported by 5 authors.[6,7,27,32,37] Overall, results of the pooled analysis did not differ significantly between AT and ST (sample size: 1336; Days 8.4 ± 6 vs Days 10 ± 6; SMD −0.57; 95% CI −4.24–3.10; $P = 0.76$; $I^2 = 100\%$). In the same way, subgroup analyses of the outcome revealed no significant difference between adults (Sample size: 1151; SMD −0.61; 95% CI −5.10–6.31; $P = 0.83$; $I^2 = 100\%$) and children (sample size: 185; SMD −2.33; 95% CI −5.76–1.09; $P = 0.18$; $I^2 = 99\%$; Test for subgroup differences: $P = 0.39$; $I^2 = 0\%$).

The length of time off work, documented in 3 studies,[7,8,31] did not show any statistically significant difference between AT and ST (sample size: 884; Days 7.9 ± 1.9 vs Days 11.7 ± 2.5; SMD −0.52; 95% CI −1.24–0.20; $P = 0.15$; $I^2 = 96\%$) (Supp. Digit. Content. Tab. 4, http://links.lww.com/SLA/B582), (Supp. Digit. Content. Fig. 8, http://links.lww.com/SLA/B582).

Quality of Life

Three studies provided data regarding quality of life.[9,27,32] However, due to the different scales used to assess the outcome, it was not possible to perform a pooled analysis. In the study by Talan et al, AT patients had higher physical SF-12v2 Health Survey scores than ST patients both at 2-weeks (median 54 vs 44) and at 1-month follow-up (median 56 vs 47).[9]

On the other hand, results of the mental SF-12v2 component showed higher values for patients who underwent ST both at 2 weeks (median 58 vs 55) and at 1 month follow-up (median 56 vs 55). In children, Minneci et al (95.7 vs 91.3) and Lee et al (100 vs 100) reported similar Pediatric Quality of Life scores between AT and ST groups at 1-year and at 1-month, respectively.[27,32]

DISCUSSION

This comprehensive systematic review and meta-analysis of 20 studies including over 3600 patients has demonstrated that antibiotic therapy as a primary nonoperative management strategy for uncomplicated appendicitis in both adults and children is associated with a treatment failure rate of 27.7% at 1 year follow-up, a lower complication-free treatment success rate compared to appendectomy (67.2% vs 82.3%, $P < 0.0006$) and a tendency toward a doubled (although not statistically significant) incidence of complicated appendicitis at delayed surgery in the overall population (21.7% vs 12.8%, $P = 0.07$), especially in adults (21.8% vs 12.7%, $P = 0.06$). Nevertheless, there are some advantages to antibiotic therapy over appendectomy with lower rate of postintervention complications (7.1% vs 14.5%, $P = 0.006$) and reduced healthcare costs. All other outcomes that impact the patient experience, including complications following surgery, length of hospitalization, duration of pain, length of sick leave, and length of time off work, did not show any statistically significant difference between the 2 different treatment modalities.

Our results are in line with those reported by Sallinen et al in their recent meta-analysis. These authors found a similar incidence of recurrent appendicitis at 1 year (22.6%) compared with our results (19.2%) and concluded that the tradeoff between AT and ST (3% fewer major complications, 7% fewer minor complications, a mean of 4 days' shorter sick leave, and 92% fewer appendectomies in the first month) must be balanced against a 23% recurrence rate within 1 year of follow-up and slightly longer hospital stay.[14]

In accordance with the Affordable Care Act (ACA), patients need to be informed of the most recent clinical evidence regarding management of appendicitis, and engaged in sharing decision-making processes.[38] Despite this established principle, little is known about patients' attitudes and expectations when a diagnosis of appendicitis is made. In 2018, an anonymous Internet-based survey conducted by Hanson et al, asked survey respondents to choose a treatment between laparoscopic appendectomy, open appendectomy, and NOM with antibiotics in the eventuality they had uncomplicated appendicitis. Of the 1738 respondents, 85.8% chose laparoscopic appendectomy, 4.9% open appendectomy, and 9.4% antibiotics alone. This study provides a robust evidence base to support creation of decision aids that may help patients with uncomplicated appendicitis be better involved in decisions about their care.[39]

Unfortunately, we were not able to perform any type of meta-analysis for quality of life following NOM with antibiotics and appendectomy. Although in children equivalent Pediatric Quality of Life scores have been reported, it is interesting to note that results of the mental SF-12v2 component score demonstrated higher values for adult patients who underwent surgery than for those treated with NOM in the study by Talan et al. This finding adds to the debate on the current perceptions of the antibiotic-first strategy for uncomplicated appendicitis, possibly demonstrating anxiety about future episodes of abdominal pain in patients who did not receive definitive surgical treatment, and introducing an element of decisional regret.[9]

Few studies have focused on how to distinguish patients who might respond well to NOM with antibiotics from those who require appendectomy. Hansson et al, in their report on 581 patients published in 2014, found that patients with assumed uncomplicated appendicitis who fulfilled all criteria with CRP <60 g/L, WBC $<12 \times 10^9$/L and age <60 years had an 89% chance of recovery with antibiotics.[40] In another recent study, patients with a longer duration of symptoms prior to admission (> 24 h) were more likely to have successful NOM, probably because the lack of progression to complicated disease is associated with an indolent clinical evolution. Other independent predictors of success included lower temperature, imaging-confirmed uncomplicated appendicitis with lower modified Alvarado score (< 4), and smaller diameter of the appendix.[41]

The prospective trial by Mahida et al reported that the failure rate of NOM in children affected by uncomplicated appendicitis with appendicolith was high (60%) at a median follow-up of less than 5 months.[29] The presence of an appendicolith has been associated with high failure rates in the reports published by Tanaka et al (failure rate: 47%), Svensson et al (failure rate: 60%), and Lee et al, concluding that patients with evidence of appendicolith on imaging had an initial

failure rate of NOM more than twice that of patients without an appendicolith.[10,30,32]

The theory hypothesizing that perforated appendicitis might be a different disease entity from uncomplicated appendicitis, rather than being the natural evolution of the disease, has some support in a recent meta-analysis demonstrating that delaying appendectomy for up to 24 hours after admission does not appear to be a risk factor for complicated appendicitis, postoperative morbidity, or surgical-site infection.[42]

In our meta-analysis, although the odds ratio for complicated appendicitis was doubled in adult patients undergoing surgery following failure of NOM with antibiotics, the difference did not reach statistical significance. In the subgroup analysis of pediatric patients, where all the participants underwent preliminary ultrasound or CT scan, the odds ratio was 1.17, demonstrating comparable risk of complicated appendicitis between AT and ST. With the caveat that some of the studies included in this met-analysis are derived from low quality scientific evidence, our pooled results indicate that a trial of antibiotic therapy does not lead to a statistically significant increased risk of developing diffuse peritonitis.

When analyzing patients who underwent surgery after failure of AT, similar rates of surgical complications were reported in the AT and ST groups (12.8% vs 13.6%), suggesting that the decision to delay appendectomy can be safely made without excess risk of developing postoperative complications as a result. In the same way, the systematic review by Gorter et al concluded that children with uncomplicated appendicitis who needed a delayed appendectomy for early failure, recurrent appendicitis, or interval appendectomy following NOM did not experience more surgical complications than those who underwent immediate appendectomy.[43]

The incidence of intraoperative finding of complicated appendicitis, however, may not be considered a reliable outcome of safety in the evaluation of NOM. Complicated appendicitis might already have been present in a percentage of patients at the time of randomization, and so, the question arises as to whether this could be related to a lack of accuracy in the diagnostic process, rather than a real progression of uncomplicated appendicitis on to perforation. Within RCTs that used CT scan to reach a precise diagnosis of uncomplicated appendicitis, the rate of perforated appendicitis varied from 18% in the surgery group in the study by Vons et al [*Vons*] to 1% in the trial by Salminen et al.[6] This suggests that even CT scan is not able to distinguish with absolute certainty uncomplicated from perforated forms of appendicitis, especially in the absence of clear findings of extraluminal air, increased wall thickness > 3 mm, and intraluminal fecalith.[44]

Based on the study published by Wu et al, NOM without interval appendectomy is the least costly and most effective treatment strategy for adult patients with uncomplicated appendicitis. Health economic modeling suggests that surgery would become the preferred strategy only if combined NOM failure during first hospitalization and recurrence rates exceeded 56%.[45] NOM was also the most cost-effective strategy in children, even when considering combined rates of rescue appendectomy for antibiotic-first failure and interval appendectomy set at 41% (which is significantly higher than the 18.3%–35.7% rate reported by recent RCTs). According to the same models, NOM would remain cost-effective up to a 1-year recurrence rate of 32.3%.[46]

Successful antibiotic therapy resulted in an approximate 50% reduction in costs in our meta-analysis ($ 2509 vs $ 4898). Surprisingly, even when all appendicitis-related care costs (ie, including antibiotic treatment failure and subsequent surgery, and costs due to management of surgical complications in both groups) were analyzed, AT represented the most cost-saving option ($ 4074 vs $ 5117).

Our meta-analysis demonstrated that AT and ST had an equivalent length of primary hospital stay. In non-RCT studies, AT resulted in a significantly shorter length of stay, whereas in RCTs it did not. A possible explanation for these results is that, in the context of experimental trials, patients randomized to NOM with antibiotics have a predetermined length of hospitalization. Indeed, in European trials, patients randomized to antibiotic-first therapy were required to be hospitalized for 3 days, whereas the general trend in the USA is toward shorter hospitalization.[27] Even when analyzing the outcome for patients who required further hospitalizations for treating surgical complications or recurrent episodes of acute appendicitis, the total length of stay did not differ between the 2 groups.

The implementation of treatment and follow-up protocols based on outpatient antibiotic management, and new evidence indicating safety and feasibility of same-day laparoscopic appendectomy for uncomplicated appendicitis may result in optimization of the resource used by reducing inpatient admissions and hospital costs for both nonoperative and surgical treatment in the future.[9,47]

In recent years, there has been a worldwide increase in infections caused by multidrug resistant organisms, as a result of widespread antibiotic use and excessive antimicrobial prescribing practice. In particular, antibiotic regimens that involve the use of ampicillin/sulbactam are no longer recommended because of the increasing rate of β-lactamase producing *Escherichia coli*, resulting in a reduction in antibiotic susceptibility.[48] Piperacillin-Tazobactam, as well as Penem antibiotics, have been used as first-line antibiotic therapy for patients with uncomplicated appendicitis to address the increasing rate of *E coli* resistant to third-generation cephalosporins, ampicillin, and amoxicillin.[6,10,27,28] The use of Ertapenem or Meropenem to ensure that most of the bacteria associated with appendicitis-related infection are adequately covered could lead to increased carbapenem resistance, with a major problem in controlling severe infections when they occur, especially in patients with neutropenic sepsis and complicated intra-abdominal infections.

Recently, the results of the study entitled "Randomized clinical trial of antibiotic therapy for uncomplicated appendicitis" by Park et al challenged the need for even antibiotic therapy in uncomplicated appendicitis and reported promising results regarding possible spontaneous resolution in some patients. Analysis of the primary outcome measure indicated that treatment failure rates in patients presenting with CT-confirmed uncomplicated appendicitis were similar among those receiving supportive care with either a no-antibiotic regimen or a 4-day course of antibiotics, with no difference in the rates of perforated appendicitis between the 2 groups was reported.[49] Whether recovery from nonperforated appendicitis is the result of antibiotic therapy or natural clinical remission, and so whether antibiotics are superior to simple supportive care for uncomplicated appendicitis remains to be established. If future research demonstrates that antibiotics do not provide any advantage over observation alone in uncomplicated appendicitis, this could have a major impact in reducing the use of antimicrobial agents, especially in this era of increasing antimicrobial resistance worldwide.

This systematic review and meta-analysis is the largest published analysis to date on this topic, with outcomes analyzed for both adult and pediatric populations. In addition, the GRADE methodology has been used to evaluate the quality of the evidence as part of our study. A limitation of our study derives from the difficulty of establishing appropriate endpoints in order to compare such different types of treatment for uncomplicated appendicitis, with mortality being such a rare event and for example, the need for further interventions always going to be lower in the ST group.

In our meta-analysis, even taking account of the 14.5% of ST group patients suffering postintervention complications, and the 27.4% of AT group patients experiencing a failure of NOM with antibiotics, both treatment effectiveness and complication-free treatment success rates were better in the ST group, with the obvious advantage that, once the inflamed appendix has been removed, the objective of the complete and long-term avoidance of further appendicitis has been achieved. Nevertheless, NOM with antibiotics might spare a surgical procedure, and thus its potentially related complications, in more than 70% of cases. Little evidence on quality of life or patient experience may also represent relevant limitations.

Another important limitation of the present systematic review with meta-analysis is the small number of well-designed RCTs that have reported on this subject to date, especially regarding pediatric patients. Overall quality of evidence for each of the outcome measures was very low to moderate, and statistical heterogeneity was high for the main outcomes. As diagnostic workup and treatment of uncomplicated appendicitis varies widely across different countries and hospitals, drawing up definitive and universal recommendations on NOM remains elusive. For example, the study by Van Rossem et al showed that preoperative imaging was conducted in 32.8% of UK patients with suspected acute appendicitis, in contrast to 99.5% of patients in the Netherlands.

This led to a large difference in the normal appendectomy rate (20.6% in the UK vs 3.2% in the Netherlands). As NOM for uncomplicated appendicitis requires preoperative imaging, adoption of this approach will require re-evaluation of management algorithms to include imaging in some healthcare systems.[50]

Once considered one of the most significant limitations to the widespread adoption of NOM for uncomplicated appendicitis, the lack of investigation on the long-term clinical efficacy of antibiotics has been addressed in 2018, when Salminen et al published the 5-year follow-up results of the APPAC randomized clinical trial. The authors demonstrated that, among patients who were initially treated with antibiotics for uncomplicated appendicitis, the likelihood of late recurrence within 5 years was 39.1%, with only 2.3% of patients submitted to surgery for recurrent appendicitis diagnosed with complicated forms of the disease, and overall complication rate significantly reduced in the antibiotic group compared to the appendectomy group (6.5% vs 24.4%, $P < 0.001$). This long-term follow-up supported the feasibility of NOM with antibiotics as an alternative to surgery for uncomplicated appendicitis.[51]

As the superiority of one therapy over the other cannot be established due to the fundamental difference of such treatment strategies in the management of uncomplicated appendicitis, further scientific efforts should be focused on the attempt to provide surgeons with clinical, laboratory, and radiological scores which allow the early identification of those patients who might respond well to NOM with antibiotics.

In the meantime, the results of the present meta-analysis may well have the potential to guide and change practice patterns toward more rational and stratified diagnostic and therapeutic pathways, based on current evidence, and avoiding simplistic ''one size fits all'' approaches.

CONCLUSIONS

This study provides evidence required for clinicians to provide evidence-based advice to patients with radiologically confirmed uncomplicated appendicitis regarding both antibiotic therapy and surgical appendectomy as primary treatment options. Patients should be advised that, although limited by a lower efficacy rate compared to surgery, NOM with antibiotics is a safe option for patients keen to avoid appendectomy, and that this approach is successful in the majority of cases. However, patients must also be informed that NOM may fail within 24 to 48 hours in about 8% of cases, and an additional 20% might need a second hospitalization for recurrent AA. NOM for uncomplicated appendicitis does not statistically increase the perforation rate in adult and pediatric patients receiving antibiotic treatment, and the decision to delay appendectomy does not result in increased risk of postoperative complications.

While this systematic review and meta-analysis presents evidence to suggest that NOM with antibiotic is safe and, in most cases, effective, properly powered and well-constructed studies are still required to establish the optimal management strategy for treating uncomplicated appendicitis.

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