Antibiotics Versus Surgical Therapy for Uncomplicated Appendicitis: Systematic Review and Meta-analysis of Controlled Trials (PROSPERO 2015:CRD42015016882)

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Objective: The aim was to investigate available evidence regarding effectiveness and safety of surgical versus conservative treatment of acute appendicitis.

Summary of Background Data: There is ongoing debate on the merits of surgical and conservative treatment for acute appendicitis.

Methods: A systematic literature search (Cochrane Library, Medline, Embase) and hand search of retrieved reference lists up to January 2016 was conducted to identify randomized and nonrandomized studies. After critical appraisal, data were analyzed using a random-effects model in a Mantel-Haenszel test or inverse variance to calculate risk ratio (RR) or mean difference (MD) with 95% confidence intervals (CIs).

Results: Four trials and four cohort studies (2551 patients) were included. We found that 26.5% of patients in the conservative group needed appendectomy within 1 year, resulting in treatment effectiveness of 72.6%, significantly lower than the 99.4% in the surgical group, (RR 0.75; 95% CI 0.7–0.79; $P = 0.00001$; $I^2 = 62\%$). Overall postoperative complications were comparable (RR 0.95; 95% CI 0.35–2.58; $P = 0.91$; $I^2 = 0\%$), whereas the rate of adverse events (RR 3.18; 95% CI 1.63–6.21; $P = 0.0007$; $I^2 = 1\%$) and the incidence of complicated appendicitis (RR 2.52; 95% CI 1.17–5.43; $P = 0.02$; $I^2 = 0\%$) were significantly higher in the antibiotic treatment group. Randomized trials showed significantly longer hospital stay in the antibiotic treatment group (RR 0.3 days; 95% CI 0.07–0.53; $P = 0.009$; $I^2 = 49\%$).

Conclusions: Although antibiotics may prevent some patients from appendectomies, surgery represents the definitive, one-time only treatment with a well-known risk profile, whereas the long-term impact of antibiotic treatment on patient quality of life and health care costs is unknown. This systematic review and meta-analysis helps physicians and patients in choosing between treatment options depending on whether they are risk averse or risk takers.

Keywords: antibiotic, appendectomy, appendicitis, conservative, surgery, treatment

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The lifetime risk for acute appendicitis is 6.7% to 8.6%.[1] It is the most frequent cause of acute abdomen in emergency care units in Europe and North America.[1] The therapeutic gold standard is appendectomy, which was first described by McBurney[2] in 1894 and is still one of the most frequently performed nonelective operations worldwide.[1,3,4] Nevertheless, due to the variety of symptoms and differential diagnoses, the diagnosis can be difficult,[5] delayed, or even wrong.[6–8] The main criteria are the history and the findings of physical examination and ultrasound, which are summarized in scores to facilitate the diagnosis.[9] In the case of uncertainty, computed tomography with the highest available sensitivity and specificity[10–12] or diagnostic laparoscopy may be indicated.[13]

Laparoscopic surgery has become the preferred method for appendectomy in Canada and Germany.[14,15] Due to the evidence indicating reduced incidence of both wound infections and postoperative morbidity, shorter hospital stay and higher postoperative quality of life with the laparoscopic approach, the European Association for Endoscopic Surgery (EAES) and the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) recommend laparoscopic surgery as the gold standard.[16,17]

Early operation in order to avoid increased morbidity, such as abscess and perforation or mortality due to complicated appendicitis, is the standard.[6,8] The therapeutic strategy also embraces the effort to decrease the number of negative appendectomies. Some authors have stated that thanks to improved diagnostic tools, the number of negative appendectomies can be decreased without influencing the perforation rate, provided intensive surveillance is performed in the case of diagnostic uncertainty.[5,18,19] Despite the diagnostic possibilities, however, the frequency of appendectomy is still much higher than the incidence of appendicitis.[1,20] Owing to the varying quality of surgery depending upon optimization of the negative appendectomy rate, efforts to propagate antibiotic (AT) treatment as a noninvasive alternative have intensified. Nevertheless, trials of varying quality addressing this question have come to ambivalent conclusions.[21–28]

Despite decades of experience of surgery to treat the widespread disease of uncomplicated appendicitis, there is still a lack of evidence regarding not only effectiveness and safety but also lengths of hospital stay and costs, hampering the decision between AT and operative treatment (OT).[29] The aim of this systematic review and meta-analysis was to compare these parameters for AT and OT.

METHODS

This systematic review was conducted according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[30] (see Figure, Supplemental Digital Content 1, PRISMA checklist, http://links.lww.com/SLA/B126) and as outlined in a predefined protocol (PROSPERO 2015:CRD42015016882). All stages of study selection, data abstraction, and quality assessment were carried out independently by 2

reviewers (I.Z. and P.P.). Any disagreements were resolved by consulting a third reviewer (J.C.H.).

Literature Search

MEDLINE (via PubMed), the Cochrane Library, and EMBASE were systematically searched for relevant studies. No language restrictions were applied. Reference lists of relevant studies were searched manually and the ''related articles'' function in Pub Med was used. The search strategy combined text words and MeSH terms related to AT versus OT of uncomplicated appendicitis: ((((((''Appendicitis''[Mesh] OR appendicitis[tiab]) AND (''anti-bacterial agents''[MeSH Terms] OR (''anti-bacterial''[All Fields] AND ''agents''[All Fields]) OR ''anti-bacterial agents''[All Fields] OR ''antibiotics''[All Fields])) AND (''surgical procedures, operative''[MeSH Terms] OR (''surgical''[All Fields] AND ''procedures''[All Fields] AND ''operative''[All Fields]) OR ''operative surgical procedures''[All Fields] OR ''operation''[All Fields]))) NOT child*)). Corresponding search strategies were used for the Cochrane Library and EMBASE. The search was started by initiation of each database until January 12, 2015. The detailed search strategy is freely accessible in the protocol (PROSPERO 2015:CRD42015016882).

Study Selection

For sensitivity reasons following the ''best evidence approach'', we included not only all available randomized controlled trials (RCTs) but also nonrandomized clinical cohort studies (non-RCTs) assessing conservative versus surgical treatment for uncomplicated acute appendicitis in adult patients were included. For inclusion, all studies had to contain a clear definition of the diagnosis ''uncomplicated appendicitis.'' All studies related to complicated appendicitis or treatments in children were excluded.

Only studies that reported at least the primary outcome or one of the secondary outcomes were included. Titles and abstracts were screened independently by 2 reviewers and full text articles were obtained if inclusion criteria were fulfilled or if clarification was required. In the event that 2 or more publications reported on the same population of patients, the study with the most comprehensive data was used.

Outcome Measures

The definitions of outcome parameters are summarized in Table 1 (Definitions of investigated outcomes).

The outcome measures were as follows:

(1) Effectiveness (treatment effectiveness, complication-free treatment success);
(2) Safety (postoperative complications, adverse events of AT treatment, complicated progress of disease);
(3) Length of hospital stay and costs.

Data Extraction

A standardized paper-based sheet was used for data extraction (see Figure, Supplemental Digital Content 2, Data extraction sheet, http://links.lww.com/SLA/B127). The data extraction sheet comprised the following predefined items: (i) study identifier (first author and year of publication); (ii) essential study data (country of study conduct, study design [case-control study, case series, retrospective or prospective cohort study, etc.], mono-/multicenter, recruitment and follow-up period, treatment arms, number of subjects); (iii) baseline characteristics of study subjects (mean age, sex, type of disease, etc.); (iv) quality features. Finally, the outcome parameters described above were extracted for individual treatment groups as far as reported. Baseline comparability of the different treatment groups was evaluated.

Assessment of Risk of Bias

The risk of bias was assessed using the Cochrane risk of bias tool.[31] The assessment was based on the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias.

Statistical Analysis

The software RevMan (Version 5.3; Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Germany) was used for statistical analysis. Data entries in the columns of forest plots were double-checked individually by the 2 reviewers to avoid data entry errors. The risk ratio (RR) with 95% confidence interval (95% CI) was calculated for dichotomous variables and the mean difference (MD) with 95% CI for continuous variables.

All findings of clinical and statistical heterogeneity caused by differences in the study population, definition of outcome parameters, or perioperative management were investigated. Statistical heterogeneity was investigated by inspecting the forest plot and *I*-squared statistic. An $I^2 < 25\%$ was considered to indicate low heterogeneity and an $I^2 > 75\%$ to indicate high heterogeneity. Where heterogeneity remained unexplained, the random-effects model was applied.[32] Heterogeneity among the studies, as denoted by the χ^2 and I^2 values, was generally high and is displayed with every meta-analysis. Subgroup analyses were planned to allow for interstudy heterogeneity (RCTs vs non-RCTs), operative approach

TABLE 1. Definitions of Investigated Outcomes

Effectiveness	Treatment effectiveness	Success of the initial treatment
	Complication-free treatment success	Success of the initial treatment with uncomplicated course (no postoperative complications, adverse events, or treatment failure occurring)
Safety	Postoperative complications	Incidence of surgical site infections, abscess/fluid collections, and peritonitis
	Adverse events of antibiotic treatment	Diarrhea, fungal infections, and exanthema
	Complicated progress of disease	Finding of a complicated appendicitis in patients undergoing surgery
Length of hospital stay	Number of days of primary inpatient admission	
Costs	Total medical costs for the primary hospital stay, including materials, medical drugs, radiology and surgery resources, postoperative surveillance, laboratory tests and pathology	

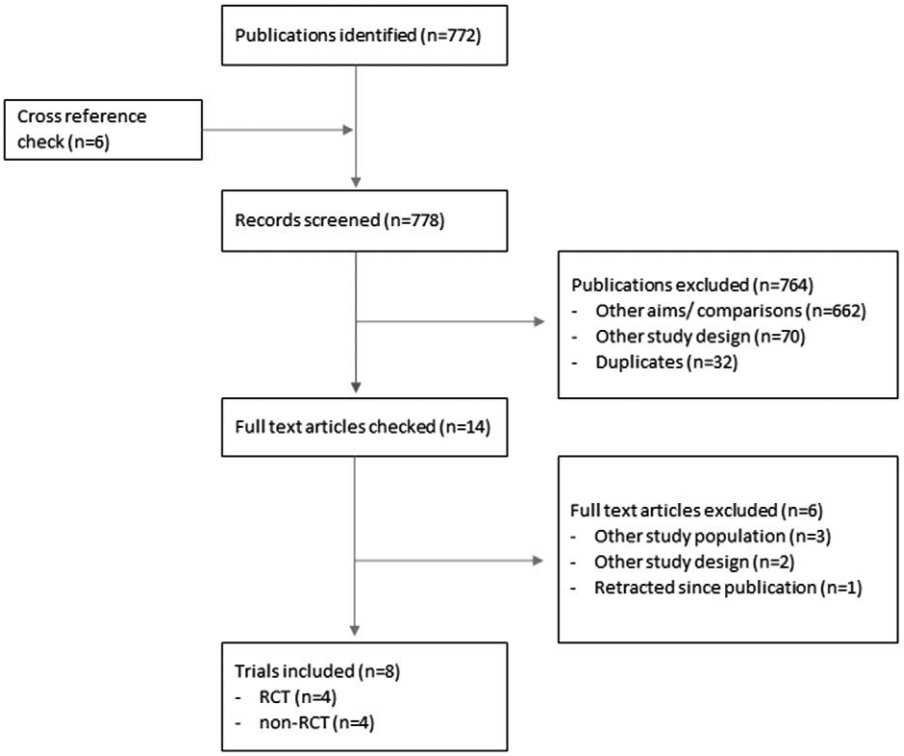

FIGURE 1. PRISMA flow diagram.

(laparoscopic vs open appendectomy), and complicated disease progress. In the case of substantial differences in methodological quality among individual studies or substantial clinical variability, sensitivity analyses were performed. Data that were difficult to categorize or presented in different forms across studies were treated as binary data. Funnel plots were created to evaluate the risk of publication bias. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 772 references were identified through database searching (Fig. 1: PRISMA flow diagram). Six more references were identified by searching lists of retrieved studies. Fourteen full-text publications were finally assessed for eligibility, of which 8 were included for quantitative synthesis.[21–28]

Study Characteristics

All 14 studies included patients with uncomplicated acute appendicitis. One study was excluded after retraction by the journal.[33] After careful reading of the full texts, 5 more studies did not meet the inclusion criteria due to features of their study design or the population analyzed[34–38] (Fig. 1): each 2 studies included patients with complicated appendicitis or did not compare with a control group and 1 had a retrospective study design. Four of the included studies were RCTs[21,25,26,28] and 4 were non-RCTs[22–24,27] (see Table 2: Summary of included studies). Hansson et al[22] implemented quasi-randomization by date of birth. Patients and surgeons were allowed to change the treatment regime, resulting in cross-over (47.5% of patients in the AT group underwent surgery and 7.8% in the operative group were finally treated conservatively with ATs). Due to this corruption of the randomization principle, this trial was evaluated as a nonrandomized cohort study.[22]

In total, 2551 patients were allocated to AT (n = 1312) or OT (n = 1239). There was no significant difference between the 2 groups regarding age or sex, except that Styrud et al[26] included only male patients. The patients' age ranged from 13 to 75 years (mean 33.08 years). The diagnosis of acute appendicitis was made after history taking, physical examination, laboratory results, ultrasound, and or computer tomography. Appendectomy in the OT group was laparoscopic (281/852; 33.0%) or open (571/852; 67.0%) as reported by 5 groups of authors.[24–28] The sample size ranged from n = 40 to n = 558 patients. With the exception of Eriksson et al[21] (30 days), the duration of follow-up was at least 1 year.

Critical Appraisal of Included Studies

Three of the 4 RCTs reported random sequence generation and allocation concealment,[25,26,28] resulting in a low risk of selection bias. In 1 RCT,[21] the risk of selection bias remained unclear, and for the 4 non-RCTs,[22–24,27] the risk of selection bias was considered high. None of the studies reported attempts at blinding. Although it is clear that masking of patients and treating physicians may be difficult, blinding of outcome assessors would have been feasible, and therefore, the distortion of the measured effect by detection and performance bias remains unclear in all of the studies. One study was considered to have a high risk of attrition bias[22] because the numbers reported in tables and in the text were inconsistent and drop-out at 1 year follow-up was unexplained. Three studies[21,26,27] were considered at a high risk of selective reporting because of a lack of predefined endpoints, and 1 study[22] changed the primary endpoint for publication of results. Two studies were at a high risk of bias[23,27] owing to differences in diagnostic procedures between the conservative and the surgical group. An overview of risk of bias is shown in Fig. 2. Graphically, no potential publication bias was present. Funnel plots are provided as supplemental material (see Figure,

TABLE 2. Summary of Included Studies

Study	Study Design	Diagnosis		Interventions			Outcomes		Follow-up
Eriksson et al,[21] Sweden	RCT, single center, 40 patients	History, physical examination, laboratory results, ultrasound	AT group	OT group			AT group n/20 (%)	OT group n/20 (%)	6, 10, and 30 days AD
		Antibiotic agent	Cefotaxime + tinidazole (hospital stay), ofloxacin + tinidazole (AD)	Not as standard†	Effectiveness	Treatment effectiveness	12/20 (60%)	20/20 (100%)	
		Duration of antibiotic treatment (days AD)	10	—		Complication-free treatment success	12/20 (60%)	19/20 (95%)	
		Operative approach	n.a.	n.a.	Safety	Postoperative complications	0/8 (0%)	1/20 (5%)	
						Adverse events of antibiotic treatment	n.a.	n.a.	
						Complicated progress of disease	1/8 (12.5%)	1/20 (5%)	
					Length of hospital stay	(mean ± SD)	3.1 ± 0.3	3.4 ± 1.9	
Styrud et al,[26] Sweden	RCT, multicenter (6 centers), 252 patients	History, physical examination, laboratory results, ultrasound	AT group	OT group			AT group n/128 (%)	OT group n/124 (%)	1 week, 6 weeks, and 1 year AD
		Antibiotic agent	Cefotaxime + tinidazole (hospital stay), ofloxacin + tinidazole (AD)	Not as standard†	Effectiveness	Treatment effectiveness	97/128 (75.8%)	124/124 (100%)	
		Duration of antibiotic treatment (days AD)	10	—		Complication-free treatment success	93/128 (72.7%)	107/124 (86.3%)	
		Operative approach	n.a.	LA: 93.5%, OA: 6.5%	Safety	Postoperative complications	4/31 (12.9%)	17/124 (13.7%)	
						Adverse events of antibiotic treatment	n.a	n.a.	
						Complicated progress of disease	12/31 (38.7%)	7/124 (5.6%)	
					Length of hospital stay	(mean ± SD)	3.0 ± 1.4	2.6 ± 1.2	
Turhan et al,[27] Turkey	Quasi non-RCT*, single center, 290 patients	History, physical examination, and laboratory results; ultrasound and CT if required	AT group	OT group			AT group n/107 (%)	OT group n/183 (%)	10 days, 2 months, 6 months, and 1 year AD
		Antibiotic agent	Ampicillin + gentamicin + metronidazole	Not as standard†	Effectiveness	Treatment effectiveness	87/107 (81.3%)	183/183 (100%)	
		Duration of antibiotic treatment (days AD)	10	—		Complication-free treatment success	82/107 (76.6%)	176/183 (96.2%)	

TABLE 2. (*Continued*)

Study	Study Design	Diagnosis			Interventions			Outcomes		Follow-up
			Operative approach	n.a.	LA: 18%, OA: 82%	Safety	Postoperative complications	5/19 (26.3%)	7/183 (3.8%)	
							Adverse events of antibiotic treatment	n.a	n.a	
							Complicated progress of disease	0/19 (0%)	34/183 (18.6%)	
						Length of hospital stay	(mean ± SD)	3.14 ± 0.1	2.4 ± 0.14	
Hansson et al,[22] Sweden	Quasi non-RCT*, multicenter (3 centers), 369 patients	History, physical examination, and laboratory results; ultrasound and CT if required		AT group	OT group			AT group n/119 (%)	OT group n/250 (%)	1 month and 1 year AD
			Antibiotic agent	Cefotaxime + metronidazole (hospital stay), ciprofloxacin + metronidazole (AD)	Not as standard†	Effectiveness	Treatment effectiveness	93/119 (78.2%)	245/250 (98%)	
			Duration of antibiotic treatment (days AD)	10	—		Complication-free treatment success	74/119 (62.2%)	208/250 (83.2%)	
			Operative approach	n.a.	LA and OA	Safety	Postoperative complications	1/23 (4.3%)	28/250 (11.2%)	
							Adverse events of antibiotic treatment	18/119 (15.1%)	10/250 (4.0%)	
							Complicated progress of disease	10/23 (43.5%)	92/250 (36.8%)	
						Length of hospital stay	(mean ± SD)	2.0 ± 0.1	3.0 ± 0.2	
Vons et al,[28] France	RCT, multicenter (6 centers), 239 patients	CT		AT group	OT group			AT group n/120 (%)	OT group n/119 (%)	15, 30, 90, 180, and 360 days AD
			Antibiotic agent	Amoxicillin + clavulanic acid	Not as standard†	Effectiveness	Treatment effectiveness	76/120 (63.3%)	119/119 (100%)	
			Duration of antibiotic treatment (days AD)	8	—		Complication-free treatment success	72/120 (60.0%)	116/119 (97.5%)	
			Operative approach	LA: 65.9%, OA: 34.1%	LA: 65.5%, OA: 34.5%	Safety	Postoperative complications	4/44 (9.1%)	3/119 (2.5%)	
							Adverse events of antibiotic treatment	0/120 (0%)	0/119 (0%)	
							Complicated progress of disease	12/44 (27.3%)	21/119 (17.6%)	
						Length of hospital stay	(mean ± SD)	n.a.	n.a	

TABLE 2. (*Continued*)

Study	Study Design	Diagnosis		Interventions				Outcomes		Follow-up
Hansson et al,[23] Sweden	Non-RCT, multicenter (2 centers), 553 patients	History, physical examination and laboratory results; ultrasound and CT if required		AT group	OT group			AT group n/442 (%)	OT group n/111 (%)	6 months and 1 year AD
			Antibiotic agent	Piperacillin + tazobactam (hospital stay), ciprofloxacin + metronidazole (AD)	Not as standard†	Effectiveness	Treatment effectiveness	304/442 (68.8%)	109/111 (98.2%)	
			Duration of antibiotic treatment (days AD)	9	—		Complication-free treatment success	283/442 (64.0%)	91/111 (82.0%)	
			Operative approach	n.a.	n.a.	Safety	Postoperative complications	8/133 (6.0%)	18/111 (16.2%)	
							Adverse events of antibiotic treatment	13/442 (2.9%)	2/111 (1.8%)	
							Complicated progress of disease	55/133 (41.4%)	45/111 (40.5%)	
						Length of hospital stay	(mean ± SD)	2.3 ± 0.1	2.9 ± 0.3	
Park et al,[24] Korea	Non-RCT, single center, 278 patients	History, physical examination, laboratory results, ultrasound, and/or CT		AT group	OT group		AT group n/119 (%)	OT group n/159 (%)		7 and 30 days AD, then median 14 months
			Antibiotic agent	Second-generation cephalosporin + metronidazole	Not as standard†	Effectiveness	Treatment effectiveness	96/119 (80.7%)	159/159 (100%)	
			Duration of antibiotic treatment (days AD)	2	—		Complication-free treatment success	95/119 (79.8%)	148/159 (93.1%)	
			Operative approach	‡	LA: 96.3%, OA: 3.7%	Safety	Postoperative complications	1/20 (5.0%)	11/159 (6.9%)	
							Adverse events of antibiotic treatment	n.a.	n.a.	
							Complicated progress of disease	4/20 (20%)	11/159 (6.9%)	
						Length of hospital stay	(mean ± SD)	3.4 ± 1.3	6.4 ± 1.7	
Salminen et al,[25] Finland	RCT, multicenter (6 centers), 530 patients	CT		AT group	OT group			AT group n/257 (%)	OT group n/273 (%)	1 week, 2 months, and 1 year after intervention
			Antibiotic agent	Ertapenem (first 3 days) and levofloxacin (day 3–10)	Not as standard†	Effectiveness	Treatment effectiveness	187/257 (72.8%)	272/273 (99.6%)	
			Duration of antibiotic treatment (days AD)	n.a.	—		Complication-free treatment success	186/257 (72.4%)	248/273 (90.8%)	

TABLE 2. (*Continued*)

Study	Study Design	Diagnosis	Interventions		Outcomes		Follow-up
		Operative approach§	LA: 5.5%, OA: 94.5%	Safety	Postoperative complications	1/70 (1.4%)	24/273 (8.8%)
					Adverse events of antibiotic treatment	0/257 (0%)	0/273 (0%)
					Complicated progress of disease	7/70 (10%)	4/273 (1.5%)
					Length of hospital stay (mean ± SD)	3.2 ± 0.9	2.8 ± 1.0

AD indicates after discharge; AT, antibiotic treatment; CT, computed tomography; LA, laparoscopic approach; n.a., not applicable; OA, open approach; OT, operative treatment; RCT, randomized controlled trial; SD, standard deviation.

*Due to lack of description of randomization or major cross-over.

†Except perioperative antibiotic prophylaxis/single-shot.

‡Most appendectomies were performed via laparoscopic procedure.

§Most appendectomies were performed via open surgical approach.

Supplemental Digital Content 3, funnel plots showing no potential publication bias, http://links.lww.com/SLA/B128).

Parameters of Effectiveness and Safety

The study by Styrud et al[26] had to be excluded from quantitative analysis because detailed complication rates were not reported.

Effectiveness

Treatment Effectiveness

All studies reported the rate of recurrence of symptoms within 1 year: Overall, it was 27.4% for AT versus 0% for OT. The majority of these patients with treatment failure (96.7%) eventually underwent surgery. Thus, within the first year, 26.5% of the patients in the AT group underwent appendectomy due to persistent, worsening, or recurrent symptoms. The rate of surgery within 30 days was 13.4%. As reported by all except 3 studies,[24,27,28] overall 53.6% (142/265) of operations in the AT group were performed during the primary hospital stay. Subgroup analyses revealed no significant differences between RCTs and cohort studies (RR 0.72; 95% CI 0.25–2.08; $P = 0.54$; $I^2 = 68.6\%$). Despite a reoperation rate of 0.6%, 1-year treatment success was significantly superior in the OT group (AT 72.6%, OT 99.4%) (RR 0.75; 95% CI 0.70–0.79; $P = 0.00001$; $I^2 = 62\%$) (Fig. 3: Forest plot of effectiveness – treatment effectiveness).

Complication-free Treatment Success

Taking into account any kind of postinterventional complication (postoperative complications, adverse events, and treatment failure), the complication-free treatment success of AT (68.4%) was significantly inferior to that of OT (89.8%) (RR 0.78; 95% CI 0.72–0.83; $P < 0.00001$; $I^2 = 16.2\%$) (Fig. 4: Forest plot of effectiveness – complication-free treatment success). The rate of false-negative appendectomies, reported in all except 2 studies,[27,28] was 6% (56/939).

Safety

Postoperative Complications

Regarding postoperative complications, no significant difference was found in postoperative complications between immediate appendectomy and surgery after failure of AT treatment (*see* Figure, Supplemental Digital Content 4, which demonstrates nonsignificant difference in postoperative complications, http://links.lww.com/SLA/B129). Overall, 6.9% (24/348) of surgically treated AT patients and 8.8% (109/1239) of OT patients had postoperative complications (RR 0.95; 95% CI 0.35–2.58; $P = 0.91$; $I^2 = 0\%$). The incidence of surgical site infection was 3.7% (13/317) in the AT group and 1.5% (70/1115) in the OT group (RR 0.84; 95% CI 0.48–1.49; $P = 0.56$; $I^2 = 43.3\%$). Postoperative abscesses and fluid collections were reported in only 4 studies.[22–24,27] There was no significant difference in the incidence of abscess or fluid collections between AT (1.5%; 4/273) and OT (1.8%; 18/996) (RR 0.7; 95% CI 0.24–2.02; $P = 0.51$; $I^2 = 0\%$). Postoperative peritonitis was reported by 3 authors[21,24,28]; the rate did not differ significantly between AT (4.1%; 2/48) and OT (0.7%; 2/298) (RR 3.97; 95% CI 0.58–27.02; $P = 0.16$). Subgroup analyses of the postoperative complications, overall and individually, revealed no significant differences between RCTs and non-RCTs (Supplemental Digital Content 4, http://links.lww.com/SLA/B129).

Adverse Events of Antibiotic Treatment

Four groups of authors[22,23,25,28] investigated adverse events of AT, but 2 of them[25,28] did not observe any such events in 773 patients. Overall, 3.3% (31/938) of the AT group and 1.6% (12/753) of the OT

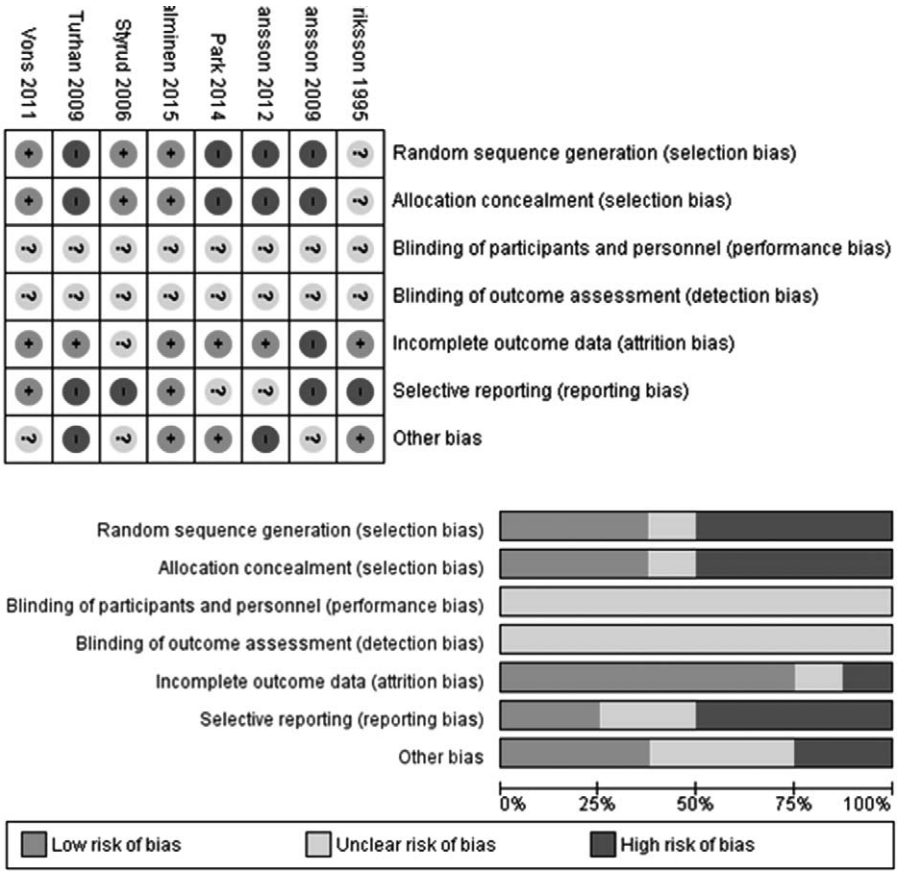

FIGURE 2. Risk of bias analysis.

group patients suffered adverse events; the difference was significant (RR 3.18; 95% CI 1.63–6.21; $P = 0.0007$; $I^2 = 1\%$) (see Figure, Supplemental Digital Content 5, which demonstrates significant difference in adverse events of AT treatment, http://links.lww.com/SLA/B130).

Complicated Progress of Disease

All studies reported the incidence of complicated appendicitis in patients undergoing surgery, documented by histopathologic examinations, except Turhan et al[27] (intraoperative observations): Overall, it was 29.0% (101/348) for AT versus 17.4% (215/1239) for OT. In RCTs and overall, the relative risk for complicated appendicitis is at least doubled and thus significantly increased in patients of the AT group undergoing surgery (RR 2.00; 95% CI 1.11–3.58; $P = 0.02$; $I^2 = 76.3\%$) (Fig. 5: Forest plot of safety – complicated progress of disease).

As reported by all except 3 studies,[24,27,28] the overall incidence of complicated appendicitis differed significantly between AT group patients undergoing surgery at primary stay (48.6%) and at readmission (13.0%) (RR 2.52; 95% CI 1.17–5.43; $P = 0.02$; $I^2 = 0\%$). Subgroup analyses revealed no significant difference in RCTs (see figure, Supplemental Digital Content 6, which demonstrates

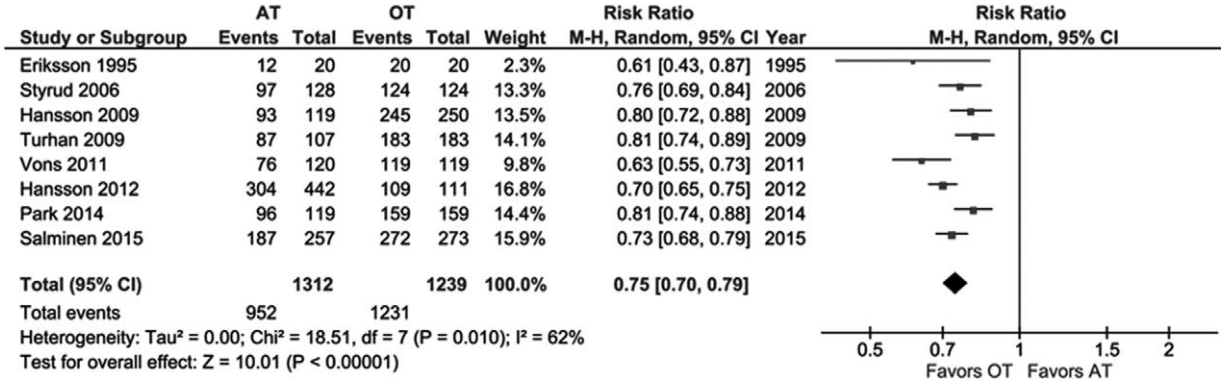

FIGURE 3. Forest plot of effectiveness – treatment effectiveness.

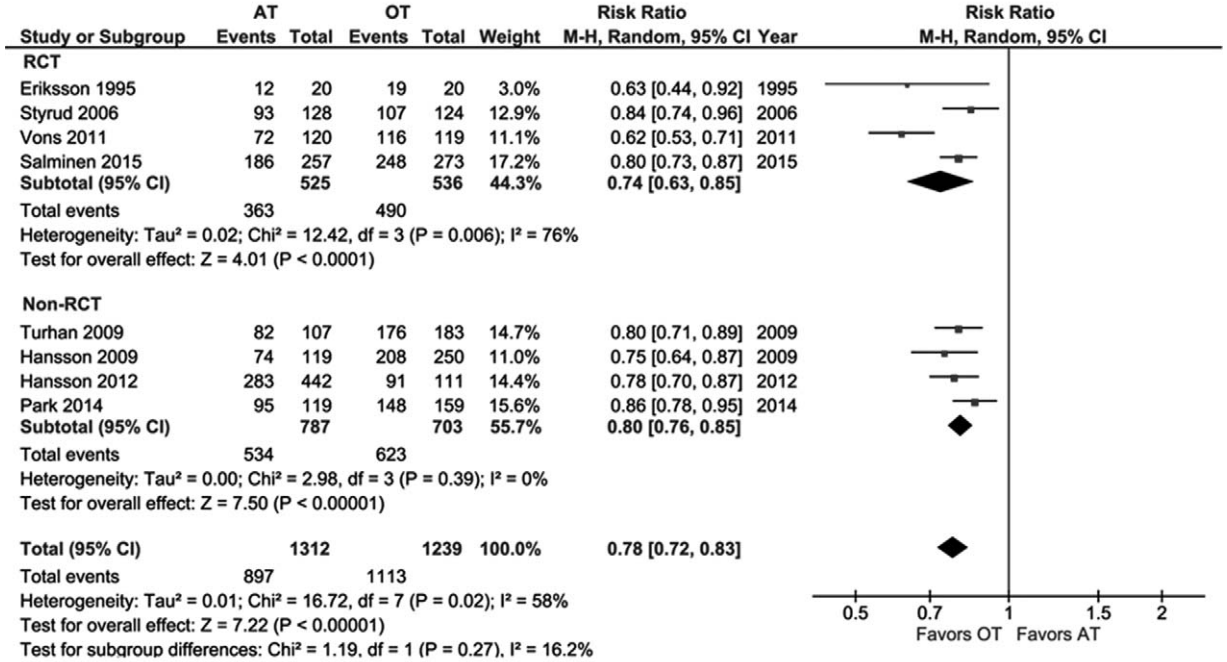

FIGURE 4. Forest plot of effectiveness – complication-free treatment success.

significant higher incidence of complicated appendicitis of AT group patients undergoing surgery at primary stay, http://links.lww.com/SLA/B131).

Length of Hospital Stay and Costs

The length of primary hospital stay, documented in all studies except 1,[28] was significantly shorter for the OT group in RCTs (RR 0.3 days; 95% CI 0.07–0.53; $P = 0.009$; $I^2 = 49\%$). Overall, however, the duration of hospital stay did not differ significantly between AT and OT (RR -0.73; 95% CI -2.69 to 1.23; $P = 0.47$; $I^2 = 0\%$) (see Figure, Supplemental Digital Content 7, which demonstrates significant difference in length of hospital stay among RCTs, http://links.lww.com/SLA/B131). The overall hospital stay (including readmissions up to 1 year) was reported only by Vons et al.[28] Only Park et al[24] reported complete data of treatment costs (AT $\$1140 \pm 226$ vs OT $\$2207 \pm 357$; $P < 0.001$).

Sensitivity and Subgroup Analyses

To detect possible differences resulting from study design, sensitivity and subgroup analyses were conducted. For each outcome, RCTs and non-RCTs were compared. Only for complicated progress of disease, length of hospital stay, and incidence of complicated appendicitis at primary stay versus readmission, significant differences were found between the subgroups (Fig. 5, Supplemental Digital Content 6, http://links.lww.com/SLA/B131, Supplemental Digital Content 7, http://links.lww.com/SLA/B131). In addition, laparoscopic and open appendectomies were compared with regard to safety of the intervention: no significant difference in postoperative complications was found (RR 1.06; 95% CI 0.2–5.65; $P = 0.95$; $I^2 = 0\%$) (see Figure, Supplemental Digital Content 8, which demonstrates nonsignificant difference in postoperative complications comparing laparoscopic vs open appendectomy, http://links.lww.com/SLA/B131).

DISCUSSION

Since the first description by McBurney,[2] appendectomy has been the gold standard of treatment for acute appendicitis. A conservative approach with ATs was first described by Coldrey in 1959.[39] Since then, the safety and effectiveness of these 2 treatment options has been debated. This systematic review and meta-analysis is the first to evaluate the data of RCTs and non-RCTs in this regard. The 8 studies analyzed included more than 2500 patients.

Regarding effectiveness outcomes, both treatment effectiveness and complication-free treatment success were better in the surgical group. The obvious advantage of surgery is the complete and long-term avoidance of further appendicitis. Self-evidently, recurrent appendicitis is impossible after surgery. Unfortunately, there are still no follow-up data extending beyond 1 year after conservative treatment. Also, it should be considered that the general lifetime risk of 6.7% to 8.6% for appendicitis persists in AT group patients.[1] In this systematic review, a failure of initial treatment was counted as a complication of the postinterventional course (Fig. 4). Even taking account of the 0.4% to 1.0% of OT group patients suffering from adhesions in the further postoperative course[40] (and without counting the same risk for the surgically treated AT group patients), the complication-free treatment success was still significantly in favor of OT (68.4% vs 88.8% to 89.4%). Moreover, the low rate of false-negative appendectomies clearly shows that unnecessary surgery is rare in these times of improved diagnostic tools.

In view of the fact that mainly the primary hospital stay but not the overall length of hospital stay was reported, the high rate of 1-year symptom recurrence in the AT group (27.4% vs 0%) clearly indicates even more significantly reduced hospital stay and costs in the OT group. Therefore, complications were clearly less severe and less frequent in the surgical group.[41]

Furthermore, 2 factors relevant to AT for acute appendicitis have to be discussed. First, in at least 1% of appendectomies, there is

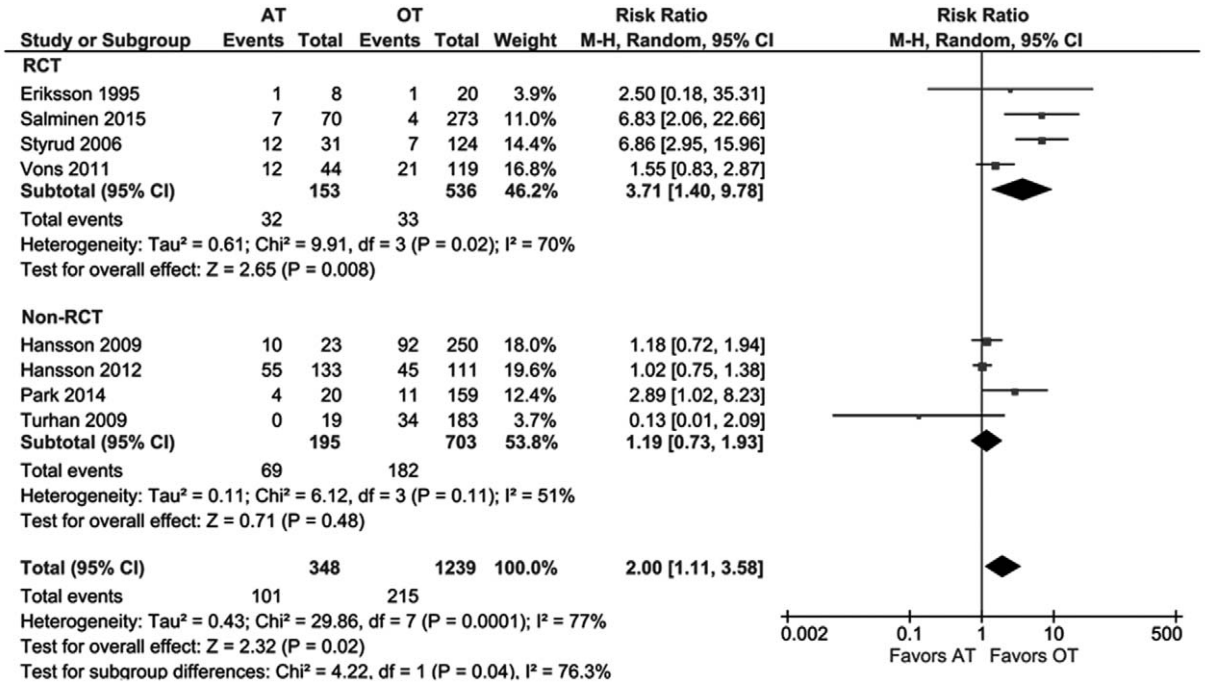

FIGURE 5. Forest plot of safety – complicated progress of disease.

histologic demonstration of carcinoma.[42,43] If these patients were given ATs, the malignancy causing the appendicitis would remain untreated, with potentially fatal consequences. Other malignancies and diseases such as neuroendocrine carcinomas, cases of Crohn disease, or sigmoid diverticulitis at elongated sigmoid colon should also be taken into consideration. Second, unnecessary use of ATs should be avoided. The duration of AT treatment varied from 24 to 72 hours of intravenous followed by 2 to 10 days of oral administration. Vons et al[28] used amoxicillin with clavulanic acid, and most of the other studies treated conservatively with cefotaxime and metronidazole or tinidazole.[21,22,24,26] The rate of *Escherichia coli* resistant to third-generation cephalosporins rose from 9.7% in 2011 to 12.7% in 2013.[44] Salminen et al[25] administered ertapenem and levofloxacin, which cannot be considered a first-line AT therapy. AT treatment-associated adverse events occurred in 5% to 25% of cases[45]; nevertheless, only 4 studies[22,23,25,28] investigated them and 2 of these, including n = 773 patients, reported no case of diarrhea, fungal infection, or exanthema, suggesting potential under-investigation or under-reporting.[25,28]

Two meta-analyses were published by Varadhan et al[46] in 2010 and 2012, including 462 and 900 patients, respectively. In the article that appeared in a surgical journal, appendectomy was suggested as gold standard.[46] In a medical journal, by contrast, ATs were considered effective and safe as primary treatment.[41] These 2 analyses are now outdated and had much lower sample sizes than our study. Moreover, neither AT side effects nor initial treatment failure rates were evaluated.

A recently published systematic review without meta-analysis by Ehlers et al[47] focused on filling the remaining gaps in the evidence regarding AT versus OT of acute, uncomplicated appendicitis. Only 6 studies[21,22,25–28] were included. Two recently published non-RCTs with a total of 800 patients were neglected,[23,24] and despite massive cross-over and lack of description of randomization, 2 studies[22,27] were analyzed as RCTs. Finally, Ehlers et al[47] did not provide new guidance to physicians who might consider conservative treatment as a part of their practice.

Our study is limited by the different tools used for the diagnosis of appendicitis, the varying type and duration of AT treatment, and insufficient reporting of postinterventional complications: All studies based the diagnosis on medical history and physical examination as well as laboratory findings, but not all used further tools such as ultrasound and/or computer tomography. Although the current standard is laparoscopy,[14,15] in the investigated studies, appendectomy was mostly performed via an open approach. However, the open approach had no influence on the safety of intervention in this meta-analysis.

Despite the heterogeneity of the study designs, sensitivity and subgroup analyses of each outcome revealed no significant differences between RCTs and non-RCTs (except for complicated progress of disease, incidence of complicated appendicitis at primary stay vs readmission, and length of hospital stay).

Although cephalosporins with imidazole compounds or gyrase inhibitors are mostly used for conservative treatment based on the evidence presented here, the best choice of first-line AT treatment for uncomplicated appendicitis remains unclear. The use of second-line or rescue ATs is strongly discouraged.

Trials comparing all aspects of conservative and OTs are needed. It would be beneficial to compare AT therapy with laparoscopic appendectomy. Long-term surveillance, especially in the conservative treatment group, is required to establish the long-term recurrence rates of appendicitis. For operated patients, a validated classification of postoperative complications is necessary.[48] In terms of further safety evaluation, it would be worthwhile to quantify a potential increase of the severity of complications after operation during first hospital stay versus after readmission in the AT group patients. And these numbers, again, have to be compared with immediate surgery in the OT group.

For patients with AT therapy, adverse events must be rigorously monitored. Lengths of hospital stay and costs have to be calculated for the complete burden of the disease, that is, taking all recurrences into account. Most importantly, data on how the AT and surgical therapies affect quality of life must be generated to properly address the impact of both treatments and patients' preferences should be gathered.

In conclusion, despite the heterogeneity of study designs and the above-mentioned limitations, this systematic review and meta-analysis of more than 2500 patients reveals that surgery is an effective and safe treatment of acute uncomplicated appendicitis even if patients need to be operated after an unsuccessful AT therapy. However, ATs may prevent some patients from appendectomies. To truly permeate the topic of conservative versus invasive treatment of appendicitis, an important factor is missing: How is the patient's well-being under therapy, that is, peri-interventional quality of life? At comparable rates of postoperative complications and adverse events, everyone would prefer a therapy with a 99.4% success rate and no long-term recurrence before a therapy with a 72.6% success rate and an unknown long-term effect. However, if we know that the first therapy is invasive and the second is conservative, we hesitate because we anticipate that the invasive treatment has a negative impact on quality of life. However, exactly this factor is not investigated in any of the trials. It is possible that at a well-known and calculable risk, operated patients suffer less pain and are mobilized earlier in trade for an hour of sleep. As long as this factor is unknown, no definitive answer on superiority of any treatment can be given! Moreover, at the chance to avoid surgery, AT treatment increases the probability of prolonged burden of disease by longer hospital stay and readmissions. The present data should be used to discuss these tradeoffs with the patients. Depending on whether patients are risk averse or risk takers and on their own values, some patients would prefer AT treatment and others surgery. Therefore, the present data help physicians to assist patients in deciding for a treatment preference. Notwithstanding ongoing debates, the available evidence does not justify routine AT treatment for acute, uncomplicated appendicitis.

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