Operation versus antibiotics—The "appendicitis conundrum" continues: A meta-analysis

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BACKGROUND: Acute appendicitis continues to constitute a diagnostic and therapeutic challenge. The aim of this study was to synthesize evidence from randomized controlled trials (RCTs) comparing nonoperative versus surgical management of uncomplicated acute appendicitis in adult patients.

METHODS: A systematic literature search of the PubMed, Cochrane, and Scopus databases was performed with respect to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement (end-of-search date: January 29, 2017). Data on the study design, interventions, participants, and outcomes were extracted by two independent reviewers. The random-effects model (DerSimonian-Laird) was used to calculate pooled effect estimates when substantial heterogeneity was encountered; otherwise, the fixed-effects (Mantel-Haenszel) model was implemented. Quality assessment of included RCTs was performed using the modified Jadad scale.

RESULTS: Five RCTs were included in this review. Overall, 1,430 adult patients with uncomplicated acute appendicitis underwent either nonoperative (n = 727) or operative management (n = 703). Treatment efficacy at 1-year follow-up was significantly lower (63.8%) for antibiotics compared with the surgery group (93%) (risk ratio [RR], 0.68; 95% confidence interval [CI], 0.60–0.77; $p < 0.001$). Overall complications were significantly higher in the surgery group (166/703 [23.6%]) compared with the antibiotics group (56/727 [7.7%]) (RR, 0.32; 95% CI, 0.24–0.43; $p < 0.001$). No difference was found between the two treatment modalities in terms of perforated appendicitis rates (RR, 0.52; 95% CI, 0.14–1.92), length of hospital stay (weighted mean difference [WMD], 0.20; 95% CI, −0.16 to 0.56), duration of pain (WMD, 0.22; 95% CI, −5.30 to −5.73), and sick leave (WMD, −2; 95% CI, −5.2 to 1.1).

CONCLUSIONS: Conservative management of uncomplicated appendicitis in adults warrants further study. Addressing patients' expectations via a shared decision-making process is a crucial step in optimizing nonoperative outcomes. (*J Trauma Acute Care Surg.* 2017;82: 1129–1137. Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Systematic review, level II.

KEY WORDS: Antibiotics; appendicitis; meta-analysis; nonoperative management; surgery.

Appendicitis has plagued physicians and patients alike, long before Dr Fitz's descriptive article in 1886,[1] many times proving to be a fatal disease. In the last three centuries, despite the fact that appendectomy is the most common emergency general surgery procedure in the world,[2] the choice of perioperative antibiotics, the surgical approach, and the length of postoperative stay have great variability in the surgical community. Despite its commonplace occurrence, acute uncomplicated appendicitis continues to present a diagnostic and therapeutic challenge to surgical and emergency practitioners.[3–9] In addition, operative management of appendicitis continues to have certain drawbacks including morbidity due to general anesthesia, as well as postoperative complications such as surgical site infections, incisional hernias, and small bowel obstruction.[10]

The aim of the current meta-analysis was to systematically review all available evidence and analyze key outcome measures associated with nonoperative versus operative management of acute uncomplicated appendicitis in adult patients.

METHODS

Search Strategy and Eligibility of Studies

The systematic review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines and in line with the protocol agreed by all authors.[11] Eligible articles were identified through research of the PubMed, Scopus, and Cochrane bibliographical databases (last search date was January 29, 2017) by two independent reviewers (K.S.M., K.P.E.). The following MeSH terms were utilized: "appendicitis," "appendectomy," "appendicectomy," "surgery," "antibiotics," "drug therapy," "randomized controlled trial," in combination with Boolean operators *AND*, *OR*, *NOT.* Reference lists were searched for relevant articles utilizing systematic "snowball" procedure guidelines.[12]

Eligible studies were (*a*) published in English, (*b*) reported evidence in humans, (*c*) designed as randomized controlled trials (RCTs), (*d*) compared adult patients (>18 years old) who received a diagnosis of uncomplicated appendicitis and were treated primarily with either surgery or antibiotics. Excluded studies met at least one of the following criteria: (*a*) not published in English, (*b*) experimental studies in animals, (*c*) nonrandomized prospective studies, (*d*) retrospective studies, (*e*) studies involving pediatric patients (<18 years old) with appendicitis, (*f*) articles reporting on complicated appendicitis (gangrenous or perforated appendicitis with appendicular mass, abscess or generalized peritonitis), (*g*) reviews and meta-analyses, (*h*) editorials, perspectives and letters to the editor, and (i) articles irrelevant to appendicitis.

Outcome Measures

All outcomes were documented with regard to intention-to-treat analysis when possible. The primary end point of our study was treatment efficacy. Particularly, for the antibiotics

Submitted: October 29, 2016, Revised: February 4, 2017, Accepted: February 27, 2017, Published online: March 23, 2017.
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DOI: 10.1097/TA.0000000000001450

group, treatment efficacy was defined as complete symptom resolution without requiring surgery within 1 year of follow-up from initial presentation and treatment with antibiotics. For the surgery group, treatment efficacy was defined as histological verification of appendicitis, confirming appendectomy was the appropriate treatment modality. In addition, we documented the presence of an antibiotics failure subgroup (AFS), composed of patients who failed to improve or deteriorated clinically with initial nonoperative treatment and required appendectomy during their initial hospitalization.

The following continuous variables were assessed: (*a*) length of hospital stay, (*b*) duration of pain, (*c*) sick leave, and (*d*) time off work. Postoperative complications and perforated appendicitis rates in the surgery group were compared both with the entire antibiotics cohort and with the AFS as categorical outcomes. Nonetheless, we included only pertinent complications that were reported by all studies, namely, perforations, wound infections, abscesses, incisional hernias, and obstructive symptoms. Finally, we analyzed overall complications defined as the sum of perforations, wound infections, abscesses, incisional hernias, and obstructive symptoms.

Data Extraction and Effect Estimates

Two reviewers, blind to each other (K.S.M. and K.P.E.) independently reviewed the full articles of eligible studies and performed the data extraction and tabulation. All disagreements were resolved with discussion, and final decision was reached by consensus. Particularly, the following data were extracted: first author, year of publication, country of enrollment, study interval, number of patients who received surgery or antibiotics, patient demographics (age, gender), clinical and laboratory findings at initial presentation (duration of pain, temperature, white blood cell count, C-reactive protein), postoperative complications, length of hospital stay, length of sick leave, length of time

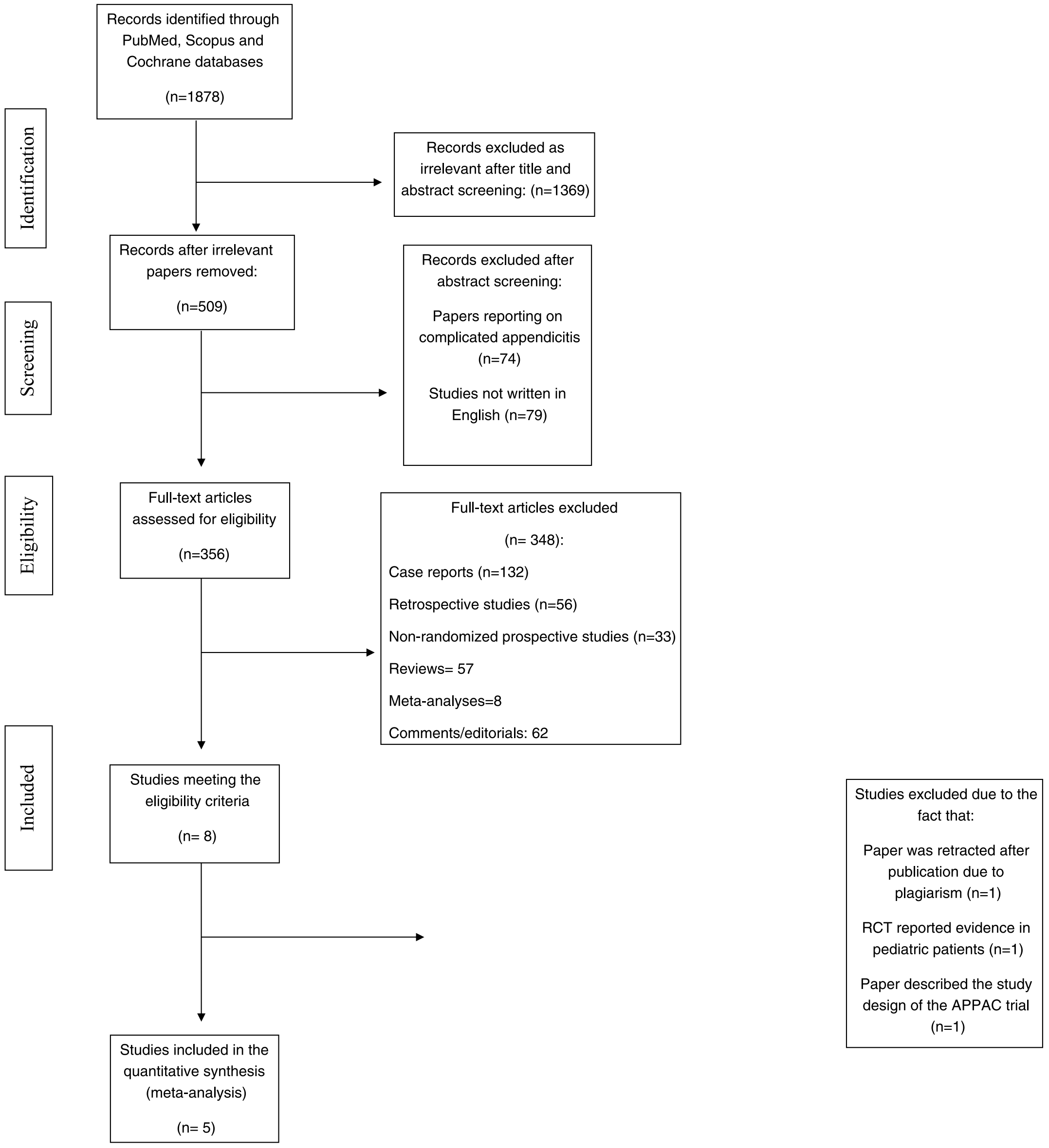

Figure 1. PRISMA search flow diagram.

off work, and number of patients lost at follow-up. Regarding categorical outcomes, data pertaining to the underlying 2 × 2 tables were extracted (namely, numbers of patients presenting with the outcome and those free of the outcome, separately for the surgery and antibiotics groups); regarding continuous outcomes, the mean, SD, and number of patients were extracted separately for the surgery and antibiotics arms.

Meta-analysis and Sensitivity Analyses

Based on extracted data, risk ratios (RRs) and 95% confidence intervals (CIs) were calculated by means of 2 × 2 tables for each categorical outcome; RR greater than 1 denoted the outcome was more frequently present in the antibiotics group. Moreover, weighted mean difference (WMD) with its 95% CI was calculated for each continuous outcome; WMD of greater than 0 corresponded to larger values in the antibiotics group. When continuous data were presented as medians and range, we applied the method of Hozo et al.[13] to estimate the respective means and SDs. Continuity correction of 0.5 in studies with zero cell frequencies was adopted. Between-study heterogeneity was assessed through Cochran Q statistic and by estimating I^2.[14] High heterogeneity was confirmed with a significance level of $p < 0.10$ and I^2 value of 50% or greater. The random-effects model (DerSimonian-Laird) was used to calculate pooled effect estimates when high heterogeneity was encountered; otherwise, the fixed-effects (Mantel-Haenszel) model was implemented. Sensitivity analyses were performed by exclusion of studies for the outcomes that this was deemed clinically important with the aim of providing the readership with a more robust and clinically useful evidence synthesis. Also, a separate sensitivity analysis of postoperative complications was undertaken in order to evaluate whether different antibiotic regimens influenced the clinical outcome. The level of statistical significance was set at 0.05.

Assessment of Study Quality and Publication Bias

The modified Jadad scale was used to assess the risk of bias of included RCTs. Randomization, blinding, withdrawals/dropouts, inclusion/exclusion criteria, adverse effects, and statistical analysis were included in the modified Jadad scale.[15] The score ranges from 0 to 8, with a score of 4 to 8 denoting high quality and 0 to 3 denoting low quality.

Two reviewers (K.S.M. and K.P.E.) working independently rated the studies, and final decision was reached by consensus with a third reviewer (J.V.S.). Although our initial purpose was to evaluate the existence of publication bias using the Egger formal statistical test,[16] statistical evaluation was performed only when the number of included studies was adequate (≥10), given that the power of the test is otherwise substantially compromised.[14] For the interpretation of Egger test, statistical significance was defined as $p < 0.1$.[16] Statistical analysis was performed in R statistical software, using the libraries "meta" and "rmeta."[17]

RESULTS

Primary Outcomes

Literature Sources

The initial literature search yielded 1,878 potentially relevant records. After screening titles and abstracts, 509 reports

TABLE 1. Characteristics of Eligible RCTs

Study ID	Study Period	Country	Type of Study	No. of Patients Screened	No. of Patients Randomized		Age Mean (SD), y		Males: Females		Overall Complications,* n, f %		Patients Lost at Follow-up	
					Abs	Sur	Abs	Sur	Abs	Sur	Abs	Sur	Abs	Sur
Eriksson and Granstrom,[19] 1995	May 1992 to March 1994	Sweden	RCT	45	20	20	27.8 (10.1)	35 (16.2)	14:6	13:7	1 (5%)	2 (10%)	1	0
Styrud et al.,[20] 2006	March 1996 to June 1999	Sweden	RCT	N/R	128	124	N/R	N/R	128:0	124:0	11 (8.5%)	23 (18.5%)	N/R	N/R
Hansson et al.,[22] 2009	May 2006 to September 2007	Sweden	RCT	369	202	167	38 (14.2)	38 (12.9)	103:99	92:75	22 (10.9%)	68 (33.6%)	27	46
Vons et al.,[21] 2011	March 2004 to January 2007	France	RCT	243	120	119	31 (9)	34 (12)	73:47	70:49	12 (10%)	22 (18.3%)	9	15
Salminen et al.,[23] 2015	November 2009 to June 2012	Finland	RCT	1,379	257	273	33** *(26–47)*	35** *(27–46)*	155:102	174:99	10 (3.9%)	51 (18.6%)	30	58

Data in italics are 25th–75th percentile.
*Overall complications included perforations, wound infections, abscesses, incisional hernias, obstructive symptoms.
**Median value.
Abs indicates antibiotics group; Sur: surgery group; n, absolute frequency; f, relative rate; N/R: not reported.

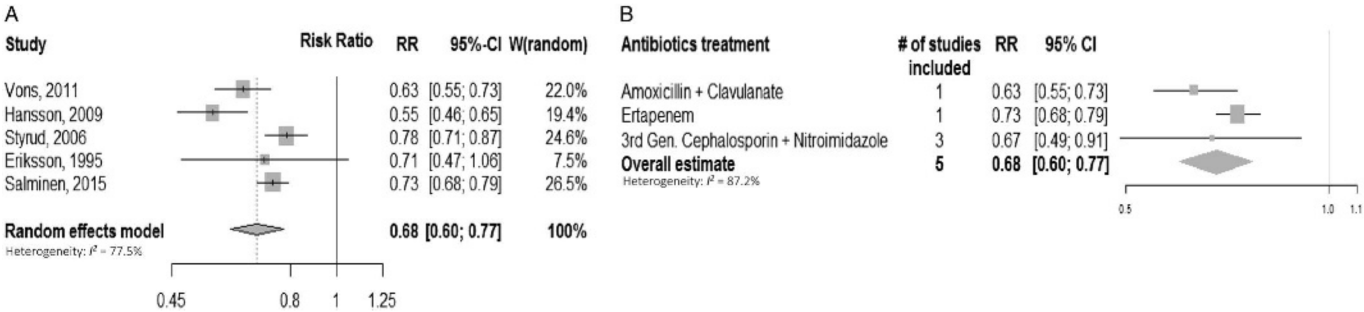

Figure 2. Antibiotics versus surgery for uncomplicated acute appendicitis: (*A*) forest plot for treatment efficacy, (*B*) forest plot for treatment efficacy stratified by the reported antibiotic combination. RR of greater than 1 denotes outcome more frequently present in the antibiotics group.

were retrieved for full-text evaluation. The study by Malik and Bari[18] was excluded from our analysis since it was retracted because of plagiarism. Ultimately, five randomized controlled studies satisfied predetermined search criteria and were included in the pooled analysis[19–23] (Fig. 1).

During the period May 1992 to June 2012, 1,430 adult patients with uncomplicated acute appendicitis were randomized to receive either nonoperative (n = 727) or operative treatment (n = 703). Four studies were multi-institutional,[20–23] whereas Eriksson and Granstrom[19] conducted a single-center study. Randomization methods were reported as computer generated,[21] external randomization,[20] and by date of birth.[22] The randomization method was not adequately described in two studies.[19,23] Allocation concealment was reported in three RCTs as utilization of sealed envelopes,[19,21,23] whereas it was not described in the other two studies.[20,22] Hansson et al.[22] reported protocol violation after randomization due to crossover of patients between treatment groups and ultimately presented their findings as both intention to treat and per protocol. Vons et al.,[21] as well as Salminen et al.,[23] conducted open-label, noninferiority RCTs.[21,23] Given the nature of the interventions that were being compared, none of the studies were blinded. General description of study characteristics is provided in Table 1 and Supplemental Table 1 (http://links.lww.com/TA/A910).[19–23] Quality assessment of the included RCTs using the modified Jadad scale[15] can be reviewed in Supplemental Table 2 (http://links.lww.com/TA/A910). Finally, funnel plots to assess publication bias are presented in Supplemental Figures 1A and 1B (http://links.lww.com/TA/A911).

Treatment Efficacy

The primary outcome variable for the current analysis was treatment efficacy, as determined by complete resolution of symptoms following primary therapeutic approach (surgery vs. antibiotics) without any subsequent intervention required. Particularly, overall treatment efficacy in the antibiotic group at 1-year follow-up was 63.8% (n = 464/727) versus 93% (n = 654/703) in the surgery group. Nonoperative management 1-year success rates varied between eligible studies (Eriksson and Granstrom,[19] 60%; Styrud et al.,[20] 75.8%; Vons et al.,[21] 63.3%; Hansson et al.,[22] 45.5%; Salminen et al.,[23] 72.8%). Complete resolution of symptoms was less likely with the nonoperative approach (RR, 0.68; 95% CI, 0.60–0.77; $p < 0.001$). Results of the current analysis are shown in Figure 2A. All reported antimicrobial regimens resulted in similar efficacy (Fig. 2B). Notably, treatment for all antibiotic groups favored the operative approach.

Overall Complications

All five studies provided data regarding this outcome.[19–23] Overall complications were significantly higher in the surgery group (166/703 [23.6%]) compared with the antibiotics group (56/727 [7.7%]) (RR, 0.32; 95% CI, 0.24–0.43; $p < 0.001$) (Fig. 3A). Stratification of complication rates according to different antibiotic regimens used can be reviewed in Figure 3B.

Perforated Appendicitis Rates

Another important clinical outcome variable was the occurrence of perforated appendicitis. All five studies reported on this end point.[19–23] The incidence of perforated appendicitis was significantly greater for the antibiotic failure subgroup (n = 27/52 [52%]) compared with the surgery group (n = 82/776 [10.5%]) (RR, 6.72; 95% CI, 2.56–17.66; $p < 0.001$) (Fig. 4A). Of note, Hansson et al.[22] provided perforated appendicitis rates only per protocol. When examining the effect of specific

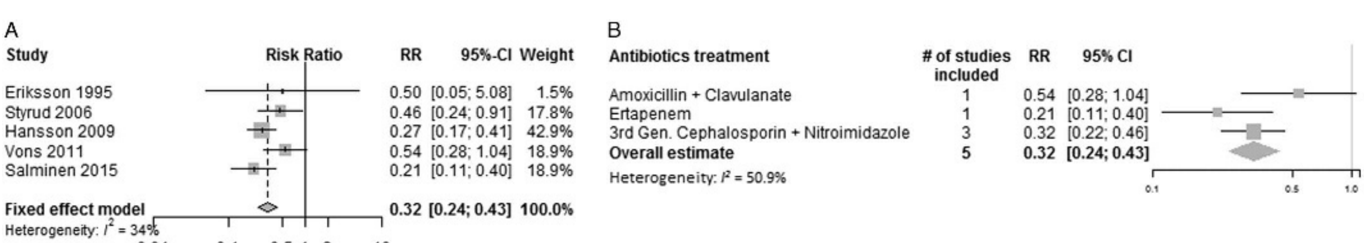

Figure 3. Antibiotics versus surgery for uncomplicated acute appendicitis: forest plot for overall complications. RR of greater than 1 denotes outcome more frequently present in the antibiotics group.

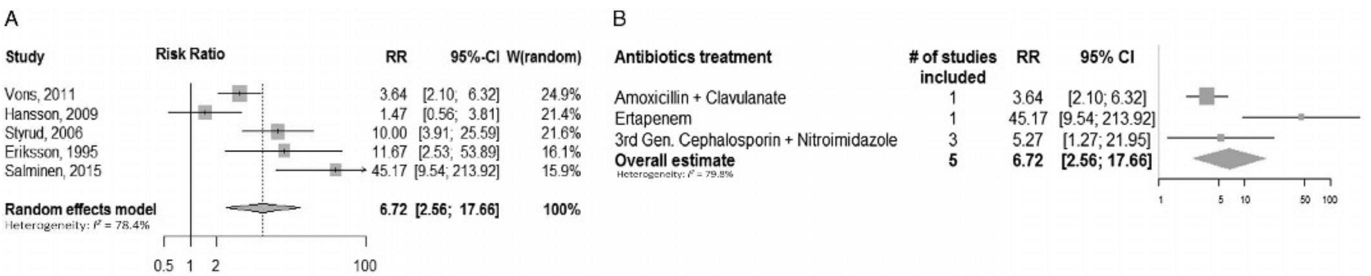

Figure 4. Antibiotics failure subgroup versus surgery for uncomplicated acute appendicitis: (*A*) forest plot for perforated appendicitis rates, (*B*) forest plot for perforated appendicitis rates stratified by the reported antibiotic combination. RR of greater than 1 denotes outcome more frequently present in the antibiotics group.

antibiotic regimens, we found that ertapenem monotherapy resulted in the highest risk of subsequent perforation, probably for reasons unrelated to the antibiotic itself (RR, 45.17; 95% CI, 9.54–213.92; Fig. 4B). In addition, we repeated the analysis of perforated appendicitis rates and compared the entire antibiotics cohort to the appendectomy group. No difference was observed between the two treatment modalities (RR, 0.52; 95% CI, 0.14–1.92; p = 0.32) (Fig. 5A). Also, no differences were identified between different antibiotic regimens (Fig. 5B).

Hospital Length of Stay

Four studies were included in the analysis of hospital length of stay (Fig. 6A).[19–22] Overall, we noted no significant differences between the two general approaches with regard to the length of hospital stay (WMD, 0.20 days; 95% CI, −0.16 to 0.56; p = 0.285). When examining hospital length of stay from the perspective of antibiotic therapy used, there were no differences noted between different regimens (Fig. 6B).

Secondary Outcomes

Duration of Pain, Sick Leave, and Time Off Work

We found no significant difference between the two groups (antibiotics versus appendectomy) in terms of overall duration of pain (WMD, 0.22 days; 95% CI, −5.30 to −5.73; p = 0.938) (see Supplemental Figure 2A, http://links.lww.com/TA/A911). However, only two studies reported sufficient information to perform this particular analysis.[19,21]

There was no significant difference between the two groups in terms of amount of sick leave, expressed in days (WMD, −2 days; 95% CI, −5.2 to 1.1; p = 0.199) (see Supplemental Figure 2B, http://links.lww.com/TA/A911). However, these results are severely limited because of only two studies reporting data in this particular comparison.[20,22]

Regarding total time off work, only two studies reported data with sufficient granularity for inclusion in the statistical analysis.[20,21] Based on pooled data, surgery was associated with longer posttreatment time off work than antibiotic therapy alone (see Supplemental Figure 2C, http://links.lww.com/TA/A911; WMD, −1.52 days; 95% CI, −3.02 to −0.02 days; p = 0.046).

Wound Infection

Four studies reported on this clinical end point.[19,21–23] The current analysis compared surgical patients with those who failed antibiotics and subsequently underwent surgery. The relative risk of wound infection was nearly three times greater in the antibiotics group compared with the appendectomy group (RR, 2.83; 95% CI, 1.41–5.68; p = 0.003; see Supplemental Figure 3A, http://links.lww.com/TA/A911). Except for ertapenem, all antibiotic regimens were associated with significantly elevated relative risk of wound infection following surgery after failed primary antimicrobial therapy (see Supplemental Figure 3B, http://links.lww.com/TA/A911).

Presence of Obstructive Symptoms

Three studies reported on this clinical outcome.[21–23] The current analysis demonstrated lack of association between the treatment modality and the subsequent development of "bowel obstruction" symptoms (RR, 2.47; 95% CI, 0.244–25.02; p = 0.444).

Incisional Hernia

We found no difference between primary surgical therapy and secondary operative approach following failed antibiotic with regard to the incidence of incisional hernia (RR, 1.28; 95% CI, 0.20–7.97; p = 0.79). Of note, only two studies reported on this outcome.[22,23]

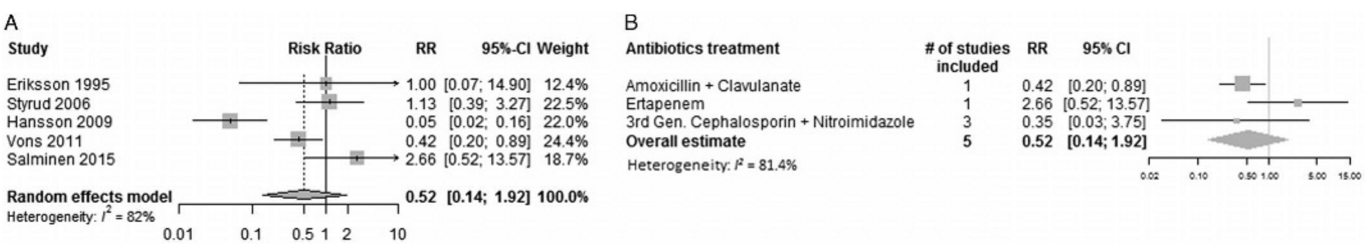

Figure 5. Antibiotics versus surgery for uncomplicated acute appendicitis: forest plot for perforated appendicitis rates. RR of greater than denotes outcome more frequently present in the antibiotics group.

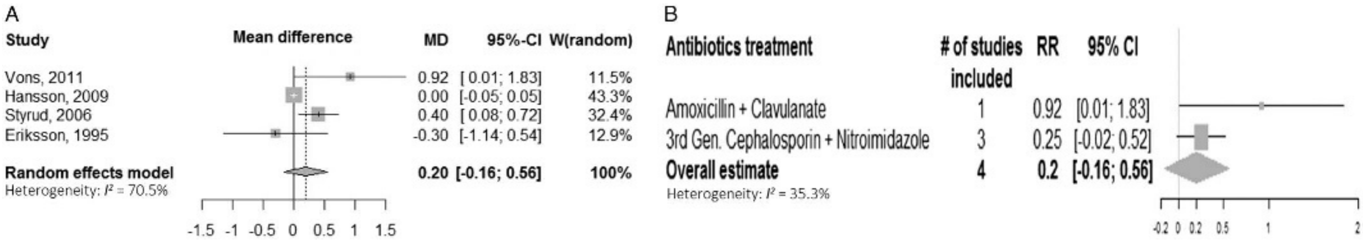

Figure 6. Antibiotics versus surgery for uncomplicated acute appendicitis: (*A*) forest plot for hospital length of stay, (*B*) forest plot for hospital length of stay stratified by the reported antibiotic combination. WMD of greater than 0 and RR of greater than 1 denote outcome more frequently present in the antibiotics group.

Abscess Formation

Because of a very limited number of reported events in the source studies (e.g., three studies reported zero events), meta-analysis was not suitable using the current data set.

Sensitivity Analysis

Hansson et al.[22] reported substantial protocol violation after randomization, with more than 50% crossover of patients between treatment arms. Sensitivity analyses were performed by exclusion of this study for all outcomes with the aim of providing the readership with a more robust and clinically useful evidence synthesis. After sensitivity analysis, wound infection rates did not differ significantly between the antibiotics and surgery groups (RR, 3.52; 95% CI, 0.48–25.64; $p = 0.214$) (see Supplemental Figure 3C, http://links.lww.com/TA/A911). No other outcomes were altered after excluding the RCT by Hansson et al.[22] (see Supplemental Figures 4A, 5A, 6A, 7A and 8A, http://links.lww.com/TA/A911). We also performed sensitivity analyses after excluding older studies (Eriksson and Granstrom[19] and Styrud et al.[20]), but no differences occurred in any of the outcomes (see Supplemental Figure 3D, 4B, 5B, 6B, 7.B and 8B, http://links.lww.com/TA/A911).[19,20]

Readmissions

In the entire cohort managed nonoperatively, 122 (20.8%) of 586 patients presented with symptoms alarming for recurrence of appendicitis after discharge. After surgical intervention, nine patients (1.3%) had a normal appendix excised. On the other hand, 113 specimens revealed acute appendiceal inflammation with 99 (81%) of 122 consistent with no perforation.

DISCUSSION

Arguably, the "best practice" for appendicitis remains debatable. The present meta-analysis of five RCTs involving 1,430 adult patients evaluated the impact that the APPAC trial[23] exerted on known outcomes of nonoperative management of uncomplicated acute appendicitis.[19–22,24] The study highlights a number of substantial findings, many of which are critical to the maintenance of a competitive surgical practice in the era of value-based health care and global realignment toward pay-for-performance reimbursement paradigms.[25,26]

Our study's primary end point of treatment efficacy demonstrated a favorable outcome in the surgical group (RR, 0.6805; 95% CI, 0.5988–0.7734; $p < 0.001$). Nevertheless, 586 (80.6%) of 727 patients treated nonoperatively experienced complete symptom resolution during their initial hospitalization. However, 122 (20.8%) of the remaining 586 patients did develop a recurrence of appendicitis within 1 year of follow-up. Thus, surgeons can cite a nearly 80% success rate of antibiotic treatment during their initial presentation of appendicitis. On the other hand, these patients should be counseled that their risk of recurrence is 20% within the ensuing 12 months.

Interestingly, prior studies have demonstrated a 20% spontaneous resolution to appendicitis, without the need for any medical or surgical intervention.[27] Considering also the approximately 5% negative appendectomy rate,[28,29] nearly 25% of patients with a diagnosis of uncomplicated appendicitis require neither medical treatment nor surgical intervention. In addition, it is important to note that a majority of the current data for "histologically verified appendicitis" do not confirm the presence of true "transmural inflammation" seen on microscopic examination.[23] Therefore, the real negative appendectomy rate is probably higher than previously appreciated. Notably, "neuroproliferation" in the appendix, in association with an increase in neurotransmitters substance P and vasoactive intestinal peptide, may be involved in the pathophysiology of acute right abdominal pain in the absence of an acute inflammation of the appendix.[30] Overall, considering the above data, approximately 75% of patients presenting with acute uncomplicated appendicitis will require medical or surgical intervention.

Even though no difference was detected in terms of length of hospital stay, the vast majority of patients in the studies that were analyzed underwent an open appendectomy, and mean admissions were more than 1 day.[19–23] Yet in the last few decades and particularly in the United States, the introduction of advanced laparoscopic techniques in conjunction with improved perioperative management has led to many patients with acute appendicitis being discharged directly from the recovery room, essentially making this an outpatient procedure.[31] Therefore, in the world of laparoscopy, the data on hospital length of stay may already be outdated.

The current analysis also found significantly higher overall complications in the surgery group (23.6%) compared with the antibiotics group (7.7%) ($p < 0.001$). Nevertheless, morbidity related to the use of antibiotics was widely underreported in all studies included in the present meta-analysis. Indeed, an aspect of antibiotic use that should not go unmentioned is the growing body of literature on antibiotic-resistant bacteria or the so-called superbugs that are infesting our intensive care units and hospitals. In a statement from the World Health Organization on antimicrobial resistance, they mention that it "…is an increasingly serious threat to global public health that requires action…." Bacteria such as carbapenem-resistant Enterobacteriaceae, methicillin-resistant *Staphylococcus aureus*, and vancomycin-resistant *Enterococcus* are just a few of these superbugs that are affecting patient care and are the result of antibiotic overexposure, not to mention the opportunistic *Clostridium difficile*, responsible for the most nosocomial bacterial infections, causing half a million infections in the United Sates in 2011.[32] As stewards of the health care system, we must be cognizant of the long-term impacts that our management choices have on our patients and communities. The Centers for Disease Control and Prevention stated in its recent press report on superbugs that clinician should "improve antibiotic use through stewardship."[37] We believe this should also be part of the discussion that the surgeon should have with the patient in making an educated decision on choosing an operative versus nonoperative treatment for uncomplicated acute appendicitis.

Furthermore, although the antibiotic failure subgroup appeared to have an increased risk of appendicular perforation ($p < 0.001$), no difference was observed when the entire antibiotics cohort was compared with the appendectomy group ($p = 0.32$). Of note, only Salminen et al.[23] and Vons et al.[21] used computed tomography scans to evaluate the likelihood of appendicitis, despite the high level of diagnostic accuracy that this imaging modality has.[33] Nonetheless, radiological techniques cannot safely differentiate between uncomplicated and perforated appendicitis, which may jeopardize the efficacy of nonoperative management.

On the same note, despite the fact that several surgeons feel a medicolegal responsibility to operate on a computed tomography diagnosis of appendicitis,[33] a low Alvarado score could also justify the nonoperative management with antibiotics alone.[34] Furthermore, understanding the safety of nonoperative management for uncomplicated appendicitis, the surgical community is encouraged to include this discussion with the patient as part of the informed consent.[35]

Our methodological approach differs significantly from other recently published meta-analyses.[6,24,36] First, we adopted definitions of treatment efficacy that do not involve complications, whereas previous meta-analyses pooled early treatment failures and recurrences with complications and analyzed them as a combined outcome representing "treatment efficacy."[24,36] Nevertheless, such studies could be criticized as being a priori skewed toward favoring nonoperative management in terms of efficacy as morbidity related to the use of antibiotic is widely underreported.[6,19–23] Second, to the best of our knowledge, this is the first meta-analysis to stratify outcomes by the reported antibiotic combination. In addition, Sallinen et al.[6] included data from an RCT reporting evidence in children,[32] which was not a focus in our study. Reviewing outcomes only in adults provided a more homogenous study population in terms of age distribution, while also facilitating the likelihood of generalizability of our findings. Lastly, Sallinen et al.[6] compared only the "surgery group" with the entire "antibiotic group." In our study, we analyzed postoperative outcomes comparing the "surgery group" to both the AFS and to the entire antibiotics cohort. Hence, we present the results in both ways and provide a more accurate view of the underlying effects and associations between the two patient groups. We believe that surgeons are interested in knowing both aspects of the management options to empower their patients in making the proper decision.

Limitations

The limitations of this meta-analysis reflect largely the limitations of the included studies, which can be summarized as follows: (1) the existence of only five RCTs with (2) a moderate patient specimen size (n = 1,748) and (3) inadequate follow-up to draw safe conclusions regarding the true place of antibiotics in treatment of uncomplicated appendicitis. (4) Also, we could not rule out the likelihood of treatment bias that is probably inherent in the studies reviewed. (5) Moreover, it is important to note that statistical heterogeneity for the risk of perforation and wound infection is high ($I^2 = 78.4\%$ and 89.1%, respectively), whereas for the risk of obstructive findings comparing the subgroup to surgery, heterogeneity was much lower ($I^2 = 29.4\%$). (6) Interestingly, based on the modified Jadad scale, all included RCTs were methodologically sound. Nevertheless, it is not uncommon for well-designed studies to fail to provide high-level of evidence regarding outcomes of interest, and we thus believe that this should be taken into account when assessing antibiotics as a tenable alternative to appendectomy. (7) Lastly, the lack of uniform reporting across all source studies and (8) the paucity of events in certain critical categories (e.g., abscess) precluded us from deducing safe conclusions for these outcomes.

CONCLUSIONS

Despite the extensive research and thorough publications on appendicitis, there still appears to be a lack of consensus and standardization on its management. The present meta-analysis synthesizes evidence from five RCTs comparing nonoperative versus surgical management of uncomplicated acute appendicitis in adult patients. Treatment efficacy at 1-year follow-up was significantly lower (63.8%) for antibiotics compared with the surgery group. Overall complications were significantly higher in the surgery group compared with the antibiotics cohort. No differences were found in terms of perforated appendicitis rates, length of hospital stay, duration of pain, sick leave, time off work, incisional hernias, and small bowel obstruction between the two treatment modalities. Although surgery remains the time-proven definitive management for appendicitis, and similar to other "surgical diseases" where nonoperative management may be used, safe options that satisfy individual circumstances must be considered and discussed with the patients of the 21st century.

AUTHORSHIP

J.V.S., K.S.M., and K.P.E. formed study concept and design. K.S.M. and K.P.E. performed acquisition of data. J.V.S., K.S.M., A.G., S.P.S., C.J.B., M.M.M., and K.P.E. performed analysis and interpretation of data. J.V.S., K.S.M., A.G., S.P.S., C.J.B., M.M.M., and K.P.E. drafted the manuscript. J.V.S., K.S.M., A.G., S.P.S., C.J.B., M.M.M., and K.P.E. performed critical revision of the manuscript for important intellectual content. A.G., K.S.M., and K.P.E. performed statistical analysis. K.S.M. provided administrative, technical, or material support. K.P.E. performed supervision.

ACKNOWLEDGMENTS

The authors thank David S. Morris, MD, for his important intellectual contribution to this work.

DISCLOSURE

The authors declare no conflicts of interest.

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