Management of acute appendicitis in adults: A practice management guideline from the Eastern Association for the Surgery of Trauma

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BACKGROUND: Acute appendicitis (AA) has been considered one of the most common acute surgical conditions in the world. Recent studies, however, have suggested that nonoperative management (NOM) with a course of antibiotics (ABX) may be as effective as surgery in treating appendicitis. As there are evolving perspectives regarding the optimal therapy for appendicitis, we sought to provide recommendations regarding the role of NOM with the administration of antibiotics (antibiotics-first approach) in uncomplicated AA as well as the need for routine interval appendectomy (RIA) in those presenting with appendiceal abscess or phlegmon (AAP) initially managed without appendectomy.

METHODS: A writing group from the Guidelines Committee of the Eastern Association for the Surgery of Trauma (EAST) performed a systematic review and meta-analysis of the current literature regarding appendicitis in adult populations. The Grading of Recommendations Assessment, Development and Evaluation methodology was applied and meta-analyses and evidence profiles generated.

RESULTS: When comparing antibiotics-first therapy to surgery for uncomplicated AA in adult populations, we found that perforation and recurrence of disease were the only outcomes consistently represented in the literature. For perforation, we were unable to make a definitive conclusion based on the degree of heterogeneity among the six randomized controlled trials reviewed. The risk of recurrence at 1 year with antibiotics-first treatment was 15.8% (95% confidence interval, 12.05–118.63). Critical outcomes could not be evaluated with the current literature. In NOM patients for AAP, the risk of recurrence was 24.3% if RIA was not performed (95% confidence interval, 2.74–73.11).

CONCLUSION: Based on the completed meta-analysis and Grading of Recommendations Assessment, Development and Evaluation profiles, we were unable to make a recommendation for or against the antibiotics-first approach as primary treatment for uncomplicated AA. For NOM with AAP, we conditionally recommend against RIA in an otherwise asymptomatic patient. This review reveals multiple limitations of the published literature, leaving ample opportunities for additional research on this topic. (*J Trauma Acute Care Surg.* 2019;87: 214–224. Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Systematic review, level II.

KEY WORDS: Appendicitis; appendiceal abscess; perforated appendicitis; antibiotic therapy; recurrent appendicitis.

Acute appendicitis (AA) is one of the most common acute surgical conditions. The overall incidence is approximately 86 per 100,000 patients per year with the highest prevalence of nonperforated appendicitis occurring among adolescents and young adult ages 13 years to 40 years. The incidence of perforated appendicitis is 19% with a bimodal distribution involving children and the elderly.[1]

In 2015, Salminen and colleagues published the Antibiotic Therapy versus Appendectomy for Treatment of Uncomplicated Acute Appendicitis (APPAC) trial comparing the effectiveness of antibiotics (ABX) to appendectomy. The APPAC trial revealed the antibiotics-first approach was noninferior to appendectomy when considering recurrence risk and potential risk of complications following delayed appendectomy.[2] This study, among others, sparked public interest in the treatment of appendicitis, and surgeons now find themselves engaging in more discussions about therapeutic options.

Perforated appendicitis often presents as either a phlegmon or an intraperitoneal abscess visualized on preoperative computed tomography (CT) scan, ultrasound, or magnetic resonance imaging (MRI). Although initial nonoperative management (NOM) of these patients is well accepted in the surgical community, the need for routine interval appendectomy (RIA) has been a subject for debate, particularly when it comes to the risk of recurrent appendicitis or the potential for missed malignancy. Andersson and Petzold[3] performed a systematic review and meta-analysis examining outcomes following initial NOM of perforated appendicitis. They concluded that the risk of occult malignancy at 1.2% did not necessarily justify the associated morbidity of RIA, which they reported to occur in approximately 11% of patients. Despite this study, some surgeons may be uncomfortable with foregoing RIA.

Members of EAST recently reviewed the current literature with goals of defining practice management guidelines for AA. To develop guidelines that considered patient values and preferences as well as the literature's empiric strength of evidence, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework was used.[4]

METHODS

The objective of developing a treatment guideline for AA was first to determine the role of the antibiotics-first approach as the primary treatment for uncomplicated AA and, second, to examine the need for RIA in patients with an appendiceal abscess or phlegmon (AAP) who initially undergo successful NOM.

The population (P), intervention (I), comparator (C), and outcome (O) questions were defined as the following:

Population, Intervention, Comparator, Outcome (PICO) 1: In adult patients with acute uncomplicated appendicitis (P), should antibiotics-first therapy (I) compared with appendectomy (C) be used to decrease the rates of perforation, abscess, and surgical wound infection, and to decrease hospital length of stay (LOS) and cost (O)?

PICO 2: In adult patients diagnosed with AAP initially managed NOM [P], should RIA [I] versus no appendectomy [C] be performed to decrease the risk of recurrent appendicitis and to lower the cost of treatment in an otherwise asymptomatic patient [O]?

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INCLUSION CRITERIA FOR THIS REVIEW

To devise an evidence-based recommendation for PICO 1, we limited the studies to randomized controlled trials (RCTs). Case reports, retrospective reviews, meta-analyses, review articles, and articles not available in English were omitted. When examining the literature for PICO 2, we included two retrospective studies for the sake of completing a meta-analysis as there was a paucity of available literature. Otherwise, there was only one RCT that compared RIA with ongoing expectant management following treatment for AAP.[5]

All adult nonpregnant patients older than 18 years were included for analysis. Following review of the literature, we included a RCT that involved patients older than 16 years.[6] This study was included for analysis of PICO 2 for two reasons: (1) it was one of only three studies that met the necessary criteria for review, and (2) the working group felt that including patients older than 16 years was pragmatic in nature because it is common for general surgeons to treat this age group as part of their adult practices. We did not find any other studies that featured an age cutoff of 16 years.

REVIEW METHODS

Identification of References

The EAST Guidelines Committee appointed a task force to define this guideline. No external funding was obtained. Task force leaders (A.R. and M.N.) performed a search of the US National Library of Medicine and National Institutes of Health PubMed databases for all entries in English involving human subjects from January 1, 1995, to September 30, 2017. This task was completed with the assistance of Lindsay Gil, BA, currently a fourth-year student at Loyola Medical School. The following MeSH terms were used: appendicitis, appendectomy, appendiceal, appendicectomy, nonoperative, antibiotics, antibacterials, medical treatment, antibiotic treatment, antibiotic therapy, interval appendectomy, delayed appendectomy, antibacterial treatment, antibacterial therapy, conservative management, medical management. Three medical databases were queried: PubMED, EMBASE, and Cochrane.

Over 4,300 articles were initially reviewed for relevancy. After omitting duplicates and irrelevant articles, 160 articles were dispersed for review. Please refer to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for further details (Fig. 1). Nine studies were selected for analysis.

Outcome Measures

Outcomes of importance to the PICO questions were achieved by consensus of task force members developing this guideline. Outcomes were ranked from 1 to 9 for each PICO question with the items ranked 7 to 9 of critical importance and those ranked 4 to 6 as important but not critical. For PICO 1, perforation, sepsis, and abscess were considered critical outcomes; while surgical wound infection, hospital length of stay (LOS) and cost were classified as important but not critical. Wound infections as an outcome, in patients who were treated initially with antibiotics only, was collected in cases where patients subsequently underwent appendectomy either because of failed antibiotics-first treatment or due to recurrent AA with postoperative wound infection. PICO question 2 ranked recurrent appendicitis, perforation, sepsis, and abscess

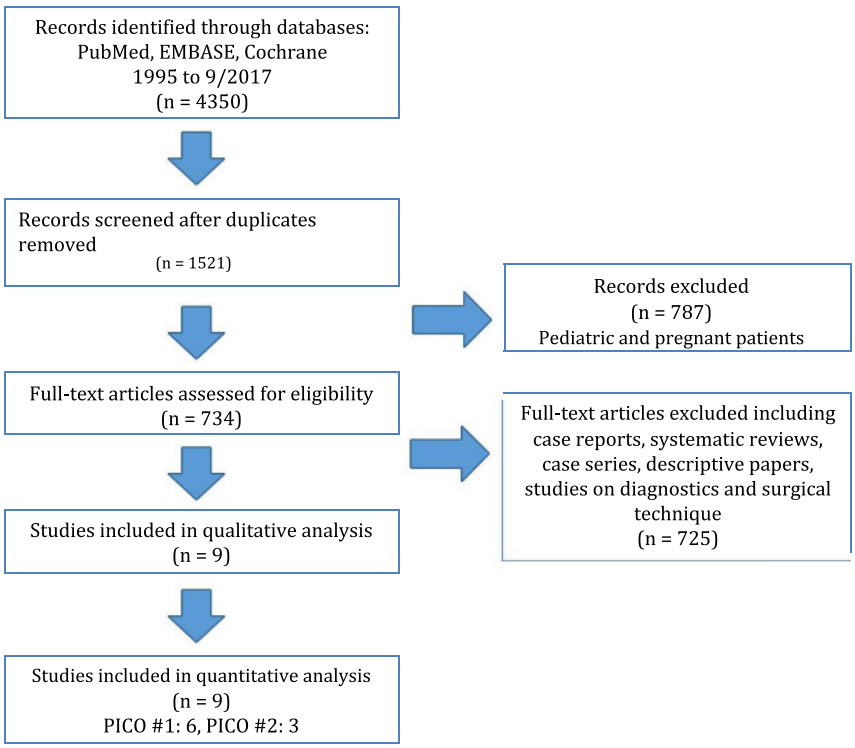


Figure 1. PRISMA flow diagram for systematic review.

as critical, and LOS, wound infection, malignancy and cost as important outcomes.

Data Extraction and Methodology

Studies were evaluated for level and quality of evidence per GRADE guidelines. In accordance with the guidelines for PRISMA, data extraction forms (Appendices 1 and 2 for PICO questions 1 and 2, respectively) were used to obtain data from each included study. Where it was possible, meta-analysis was performed using RevMan 5 (The Cochrane Collaboration, London, United Kingdom) with random-effects modeling. For cost and hospital LOS, differences in means were calculated, while for the remaining (dichotomous) outcomes, relative risks were determined for the experimental versus comparator groups. Evidence tables were developed using the GRADEpro Guideline Development Tool (Evidence Prime Inc., Hamilton, Ontario, Canada).

Methodological Quality Assessment

GRADE methodology was used to assess the quality of the selected articles ranked as high, moderate, low, or very low. To ensure that the evidence demonstrated a precise estimate of effect, the following principles were also considered: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Each principle was assessed and included in the evidence profile for each outcome. The quality of evidence was graded up or down based on the deficiencies of the described principles.

Recommendations were made based upon the known risk-benefit ratios and how they applied to accepted patient values and preferences. In turn, the group determined whether a specific guideline received a strong recommendation by prefacing the statement with "we recommend" whereas a weak recommendation would be introduced by the statement "we conditionally recommend."

Measurement of Heterogeneity

To assess whether or not study comparisons shared similar characteristics, the level of heterogeneity was evaluated to determine if patients were similar and received comparable care. Using RevMan software, the I^2 (%) statistic was calculated, with higher values illustrating greater heterogeneity between patient populations. The degree of heterogeneity was categorized as low (25–49%), medium (50–74%), and high (74–100%).[7] Additionally, the completed forest plots were examined to see the degree of overlap between confidence intervals (CIs) and the conclusions of the point estimates.

RESULTS

Results for Antibiotic-First Therapy for Uncomplicated Appendicitis (PICO 1)

In adult patients with acute uncomplicated appendicitis (P), should antibiotics-first therapy (I) compared to appendectomy (C) be employed to decrease the rates of perforation, abscess, and surgical wound infection, and to decrease hospital LOS and cost (O)?

Qualitative Analysis

There were six RCTs that compared ABX to surgery for the treatment of AA.[2,8–12] Overall, studies showed considerable clinical heterogeneity from a methodological perspective. Sample sizes varied in number of included subjects from 40 to 530. Randomization by closed envelopes was utilized in three studies.[2,8,9] One study randomized subjects by using even and uneven dates of birth.[10] The randomization processes in two other studies were not clearly described.[11,12]

All studies included adult patients (≥18 years old). However, there were upper limits of ages in two of the studies, 50 years and 60 years.[2,8] Styrud and colleagues[8] completed their study with male patients only as all female patients were excluded secondary to unexplained reasoning by the supervising ethics committee. Exclusion criteria ranged from patients with stated allergies to the studies' antibiotics or intravenous CT scan contrast to pregnancy and the presence of unrelated chronic illnesses, such as chronic kidney disease and undisclosed systemic illnesses.[2,8,9]

The preoperative diagnosis of AA was established exclusively by clinical examination in one study,[8] and in three other studies the clinical diagnosis was, in some instances, confirmed by ultrasound or CT.[10–12] In two other studies, CT was performed in all patients with suspected AA.[2,9] The CT signs of uncomplicated AA served as inclusion/exclusion criteria in these studies. Only patients with clearly defined preoperative, suspected uncomplicated AA were included in three studies.[2,8,9] Three other studies included patients with AA without differentiating whether they were complicated or uncomplicated.[10–12]

While the studies were successful in ensuring randomization, there was one major instance where patients in the antibiotic arm underwent appendectomy during the index hospitalization without clear reasoning. Hansson and colleagues reported that 96 (47.5%) of the 202 patients initially assigned to the antibiotic arm eventually underwent appendectomy following the initial diagnosis of appendicitis.[10] Reasons varied from recurrence to patient preference as well as the surgeon's discretion. Despite nearly 50% of patients initially randomized to ABX having underwent appendectomy, we proceeded with an intention-to-treat analysis to ensure a pragmatic approach to GRADE and to avoid overestimates of clinical effect following the study intervention—ABX.[13]

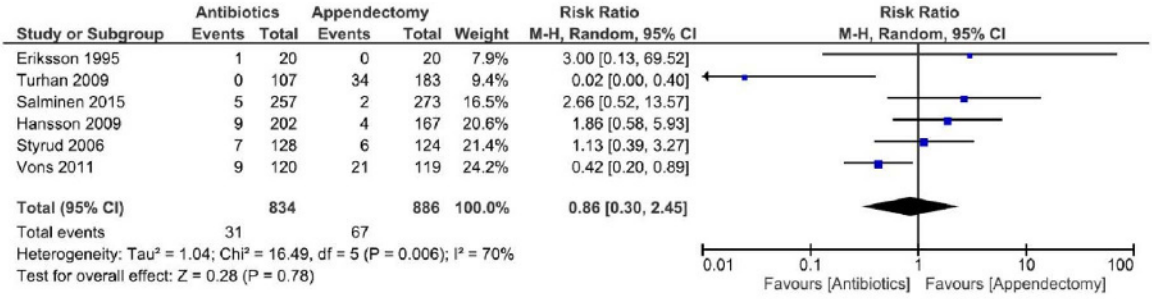
Broad-spectrum antibiotics from different pharmacological groups were used in the antibiotics arm. The course of ABX did not differ significantly among studies and consisted of 24 hours to 72 hours of parenteral followed by 7 days to 10 days of enteral therapy. The decision to operate on the antibiotic arm patients was based on the progression of acute appendicitis 24 hours to 72 hours after initiation of antibiotic treatment. The surgical approach, open vs. laparoscopic, was left to the discretion of the surgeon. Recurrent AA in the antibiotics-first arm was defined as return of symptoms within 1 month after the initial antibiotic treatment (Vons) and as a return of symptoms after the completion of ABX in the remaining five studies. All studies included a 1-year follow up.

Overall, the described inclusion and exclusion criteria and design of the studies precluded the ability to make complete generalizations that applied to the entire population.

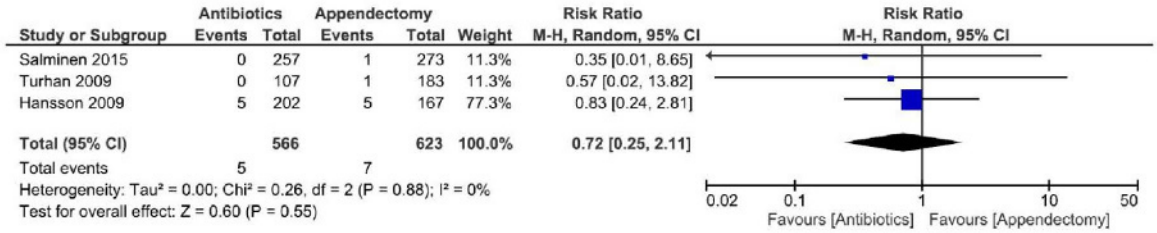
Quantitative Analysis

Six outcomes for PICO 1 were reported in the selected studies (Fig. 2). Two critical outcomes were reported. The risk of perforated acute appendicitis was found in six studies: the antibiotics-first arm contained 834 patients with a perforation risk of 3.7% versus 7.6% in 886 patients who underwent appendectomy. The relative risk (RR) was 0.86 with a 95% CI of 0.30

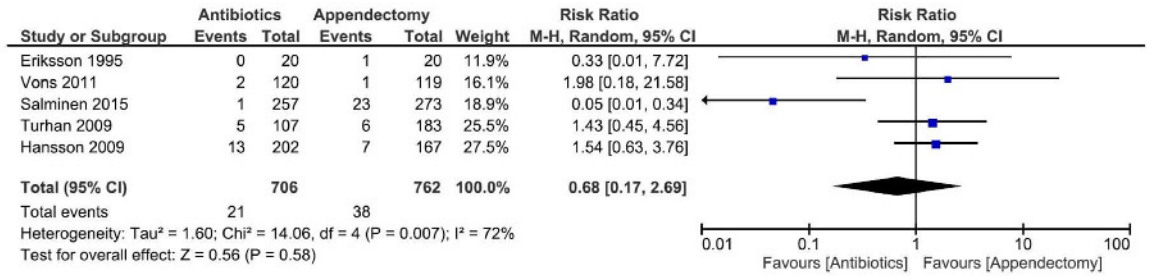
Perforation



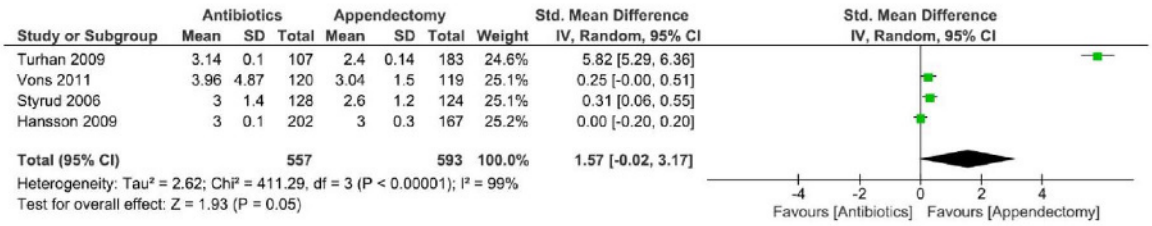
Abscess



Wound Infection



Hospital Length of Stay



Cost Effectiveness

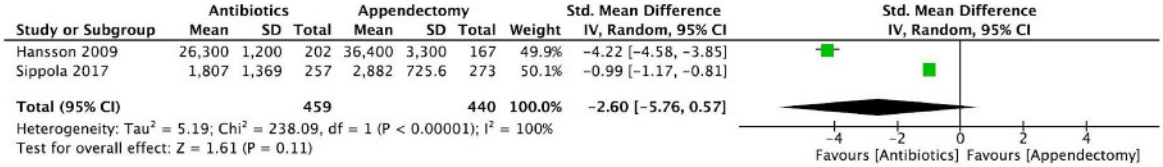


Figure 2. Forest plots illustrating outcomes for antibiotics-first therapy for uncomplicated appendicitis.

to 2.45. Three studies reported a risk of intraperitoneal abscess: the antibiotics-first arm was 0.9% compared to 1.1% in the appendectomy arm. The RR was 0.72 (95% CI, 0.25–2.11). The risk of surgical wound infection was 3% among 706 patients in the antibiotics-first group and 5% among 762 patients in the appendectomy group, with an RR of 0.68 (95% CI, 0.17–2.69).

Four studies contained data about LOS.[8,10–12] The mean difference in LOS showed 1.57 more days in the antibiotic arm (95% CI, −0.02 to 3.17). Cost of the treatment was extracted from the two studies that were performed in Sweden and Turkey and reported their results in local currencies as a mean. The cost was 28% to 37% higher in the surgically treated patients.[2,12,14] One noncritical outcome, recurrent acute appendicitis, was found in all six included studies. Recurrence was defined as the return of symptoms following completion of ABX. The antibiotics-first arm had a risk of recurrence of 15.8% (132 of 834 patients) with an RR of 37.8 (95% CI, 12.05–118.63).

Grading the Evidence

GRADE was also used to assess the quality of evidence (Table 1). Overall, the quality of evidence was low for all reported outcomes. No serious risk of publication bias was found in any of the included studies. The quality of the evidence was low for risks of perforated appendicitis, intraperitoneal abscess, and surgical wound infection. The low level of evidence was mainly related to inconsistency, indirectness, and imprecision of the data. The level of evidence for the cost, LOS, and recurrent appendicitis was found to be moderate.

Recommendation

After reviewing the GRADE profiles and considering the limitations of each study included in the analysis, the PMG group unanimously voted that a recommendation could not be made for or against antibiotics-first therapy versus surgery for acute uncomplicated appendicitis. Most outcomes of interest (perforation, abscess, wound infection, and LOS) did not particularly favor either treatment. Cost was inadequately studied, and not at all in the US population. The risk of recurrence ranges from 8.4% to 35%, which suggests that a proportion of patients may be adequately treated without appendectomy. Thus, discussion with patients should center on their preference or tolerance for uncertainty in regard to recurrence.

Review of Interval Appendectomy After Perforated Appendicitis (PICO 2)

In adult patients diagnosed with an AAP initially managed nonoperatively [P], should RIA [I] versus no appendectomy [C] be performed to decrease the risk of recurrent appendicitis and to lower the cost of treatment in an otherwise asymptomatic patient [O]?

Qualitative Analysis

There was one RCT and two retrospective studies that examined the desired patient population with appropriate clinical comparisons.[5,6,15] The RCT represented a single center's experience over a 3-year period with 40 of 60 patients included.[6] The two retrospective studies included documentation from 1,012 and 165 patients with median follow-up periods of approximately 4 years and 2.5 years, respectively.[5,15]

In the RCT, Kumar and colleagues compared three arms of adult patients all diagnosed with an AAP. Patients who underwent immediate surgery were omitted from this analysis leaving those who underwent RIA 6 weeks following their index hospitalization versus those who continued expectant management. The median follow-up period was 2.8 years.[6]

Appendiceal abscess or phlegmon was diagnosed clinically and via ultrasound or CT.[5,15] Kaminski and colleagues[5] did not include how patients were diagnosed as the data was obtained from a database of discharge information. As this particular study represented a cohort of patients in Southern California treated from 1992 to 2004, we assumed some ancillary imaging was used to confirm the diagnosis.

All studies described similar management strategies following diagnosis of perforated appendicitis including bowel rest and ABX. Percutaneous drainage was described in two studies[5,15] and selection for drainage was either at the surgeon's discretion[5] or if fever and abdominal pain failed to resolve after 3 days of NOM.[15] Hospital LOS for the index admission was documented in two studies and ranged from 6 days to 9.5 days.[5,15]

How the diagnosis of recurrent appendicitis was made is not elucidated by any of the studies; however, they do report on the mean time to recurrence. Kumar and colleagues reported that both instances of recurrent appendicitis occurred within 6 weeks of initial treatment while Lai noted that 20 of 24 patients who developed recurrent appendicitis did so within the first 6 months of their initial presentation. Kaminiski and colleagues reported a mean time to recurrence as 10 months with a standard deviation of 15 months. Kumar and Lai described reasons behind management of recurrence whereas Kaminski did not. Kumar and colleagues scheduled RIA as separate treatment arms whereas Lai and colleagues describe RIA in all but four patients. Lai and colleagues noted the following reasons for the four patients who continued NOM for recurrent appendicitis: advanced age, medical frailty, and patient preference. For RIA, the operative techniques were not well described. Kumar and colleagues described a "gridiron incision" as their open approach; other studies did not describe the operative approach other than Kaminski and colleagues noting that four patients required either an ileocecectomy or right hemicolectomy. Final pathology reports to confirm appendicitis were included in two of the three studies.[5,15]

Among patients who underwent surgical intervention, Lai and colleagues noted that 68% of patients who underwent RIA had appendicitis confirmed on pathology while 75% of patients who underwent appendectomy for clinical recurrence had appendicitis. Only Lai and colleagues reported malignancy findings: the incidence of colon cancer was 3.03% while the incidence of mucinous tumors of the appendix was 1.8%. Kumar and colleagues were less specific regarding surgical pathology only noting that the majority of patients who underwent appendectomy had either acute or chronic appendicitis on final pathology with one notable exception in the recurrence group whose pathology revealed infiltration of hookworms.

Finally, the description of surgical complications was variable. Kaminski and colleagues described the need for ileocecectomy in two patients as well as right hemicolectomy in two other patients. Wound infections, postoperative abscesses, or other complications were not mentioned. Lai and colleagues did not specifically mention any postoperative complications and Kumar and colleagues noted no complications in either patient arm. All papers, however, reported historical complication rates ranging from 9% to 23%, cumulatively.

TABLE 1. GRADE Evidence Profile for Antibiotics-First Therapy in Acute Uncomplicated Appendicitis

Evidence for PICO 1												
Certainty Assessment							No. Patients		Effect			
No. Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	In Adult Patients With Acute Uncomplicated Appendicitis Antibiotic Therapy	Surgery	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Perforated appendicitis												
6	Randomized trials	Not serious	Serious [a]	Not serious	Serious [b]	None	31/834 (3.7%)	67/886 (7.6%)	RR 0.86 (0.30–2.45)	11 fewer per 1,000 (from 53 fewer to 110 more)	Low	Critical
Abscess												
3	Randomized trials	Not serious	Not serious	Not serious	Serious [b]	None	5/566 (0.9%)	7/623 (1.1%)	RR 0.72 (0.25–2.11)	3 fewer per 1,000 (from 8 fewer to 12 more)	Moderate	Critical
Surgical wound infection												
5	Randomized trials	Not serious	Serious [a]	Not serious	Serious [b]	None	21/706 (3.0%)	38/762 (5.0%)	RR 0.68 (0.17–2.69)	16 fewer per 1,000 (from 41 fewer to 84 more)	Low	Important
Hospital LOS												
4	Randomized trials	Not serious	Serious [a]	Not serious	Not serious	None	557	593	—	SMD, 1.57 SD more (0.02 fewer to 3.17 more)	High	Important
Cost												
2	Randomized trials	Not serious	Not serious	Not serious	Not serious	None			—	SMD, 2.6 SD lower (5.76 lower to 0.57 higher)	High	Important

SMD, standardized mean difference. a = inconsistency due to wide variance of point estimates across studies; b = imprecision due to significant crossing over of the clinical decision threshold.

Quantitative Analysis

Recurrent AA was the only critical outcome delineated by the included studies (Fig. 3). Hospital LOS was also mentioned in each of the three studies and reported differently in each one. Based on the included studies, the risk of recurrent AA with ongoing NOM following initial treatment of AAP was 24.3% (238/978; RR, 14.16; 95% CI, 2.74–73.11).

When discussing hospital LOS, there were inconsistencies in reporting the data that precluded meta-analysis. For instance, Kaminski reported the difference in LOS between the patient cohorts, recurrent AA and RIA, as a median of 4 days versus 6 days, respectively. As for Lai and colleagues, the same outcome between these groups was reported as mean LOS: 6.75 ± 5.74 days for the recurrent AA group versus 4.43 ± 3.32 days for the RIA group. Kumar and colleagues reported a mean LOS of 14.7 days for the RIA group, however, did not comment on the LOS for two patients who developed recurrent AA and underwent appendectomy. Complications, such as sepsis, abscess, and wound infection, were not consistently discussed among the studies. Only one study reported on revised pathology and/or malignancy at the time of appendectomy. Seventeen (10.3%) of 164 patients had changes in diagnosis, five (3.03%) of these were cancer.[15]

Grading the Evidence

The quality of evidence evaluating recurrent appendicitis was low (Table 2). No serious risk of publication bias was noted. The risks of inconsistency, indirectness, and imprecision among the studies were not serious.

Recommendation

Based on the limited low-quality evidence available, the panel made a conditional recommendation against RIA following initial NOM of AAP. Overall, seven members of the working group voted against RIA, whereas two members voted for a conditional recommendation for IA, and one member voted that no recommendation could be made. Based on GRADE methodology, a conditional recommendation is offered when more than 50% of the group favors one intervention and no more than 20% of the group favors the alternative.[16] While the working group appreciates that the forest plot favors RIA for eliminating recurrent appendicitis, we believe that the majority of patients will not benefit from RIA should they remain asymptomatic. With this being said, there are certain situations where it should be strongly considered. The AAP can be the initial presentation of a malignancy. The overall risk of appendiceal malignancy is low; however, the risk progressively increases after the age of 40 years.[17,18] The use of CT, colonoscopy, and MRI have all been proposed for screening and surveillance, however, their individual sensitivity and specificity for detecting appendiceal malignancy is unknown. The decision to proceed with RIA versus surveillance testing or watchful waiting should be thoroughly discussed with the patient, keeping in mind the patient's age and potential for perioperative complications with RIA.

DISCUSSION

This systematic review and meta-analysis was unable to recommend for or against antibiotics-first treatment, compared with appendectomy, for AA. There are several reasons for this. Despite six RCTs, the quality of evidence examining operative intervention versus primary ABX for AA is lacking. This stems from the significant variability between the studies, the lack of standardized definitions differentiating treatment failures from recurrent disease, and patient inclusion criteria. When examining variability between studies, for example, one only needs to examine the differences in exclusion criteria alone to recognize that clinical pragmatism is lost. By excluding women in one study, patients greater than 50 years of age in two other studies, and patients with chronic comorbidities, there is immediate question as to the appropriateness of applying the reported results to daily clinical practice as those excluded comprise a significant proportion of the general population. Such observations make the need for future clinical trials paramount.

In addition, we found that the lack of standard clinical definitions describing appendicitis led to increased variability between the six studies and, furthermore, decreased the strength of the results. Only two of the included studies provided definitions of uncomplicated appendicitis versus complicated AA.[2,9] Acute uncomplicated appendicitis was based on the following CT findings: absence of extraluminal gas, periappendiceal fluid, disseminated intraperitoneal fluid,[9] while complicated AA was defined as presence of an appendicolith, perforation, abscess, or suspicion of a tumor on CT scan.[2] For the sake of clarity, we chose to concentrate on specific radiographic findings in PICO 2, appendiceal abscess and phlegmon, in lieu of the more vague term, complicated appendicitis. Treatment failure was not specified in

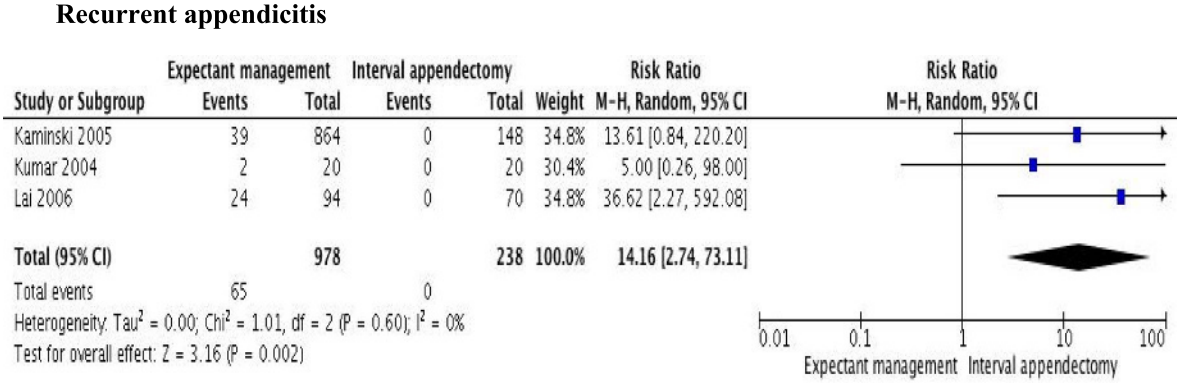


Figure 3. Forest plot describing recurrence following interval appendectomy for AAP.

TABLE 2. GRADE Evidence Profile for Interval Appendectomy Following Conservative Management of AAP

Evidence for PICO 2												
Quality Assessment							Summary of Findings					
							No. Patients		Effect			
No. Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Interval Appendectomy	Ongoing Expectant Management	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Recurrence												
3	Observational Studies	Not Serious	Not Serious	Not Serious	Not Serious	None	0/238 (0.0%)	65/978 (6.6%)	RR, 14.16 (2.74–73.11)	875 more per 1,000 (from 116 more to 1,000 more)	Low	Critical
									0.0%	0 fewer per 1,000 (from 0 fewer to 0 fewer)		

any of the included studies, but in all of them lack of clinical progression in the antibiotic arm in the first 24 hours to 48 hours led to the immediate appendectomy.[2,8–12] AA between 30 days to 1 year after initial ABX was defined as a recurrent AA in only one study.[9] As a group, we elected to define recurrence as the majority of the other studies had which is the return of symptoms following completion of ABX. After attempting to clarify ambiguous definitions, we found challenges with one study's methodology. Hansson and colleagues reported that almost half of the patients assigned to the antibiotic arm underwent appendectomy. It is difficult to claim that antibiotics are noninferior to surgery when a significant proportion of patients undergo appendectomy as a result of surgeon or patient preference.[10]

Recommendations against RIA in patients who have undergone successful conservative management for AAP have been recently endorsed. Such recommendations are based on the overall low incidence of malignancy as well as the known risks associated with RIA. When examining the risk of recurrent appendicitis alone, it is reported as similar to the risks associated with RIA suggesting little net benefit to date.[19,20] The idea that RIA is essential to detect and potentially treat underlying malignancy has recently been evaluated by Mällinen and colleagues.[21] They reported findings from their RCT involving 60 patients who were assigned to undergo RIA versus ongoing surveillance with MRI and colonoscopy. The study was terminated early upon discovering neoplasms in 12 (20%) of 60 patients. These findings are unusual, particularly given the small sample size in one country (Finland), and require further study on a larger scale to generalize the conclusion. Generally speaking, the findings of this solitary study do not outweigh the fact that, of all appendiceal specimens collected, neoplasms are recovered 0.9% to 1.4% of the time, and in spite of a recent report highlighting the relative increase in appendiceal cancer, the overall incidence remains 0.97 per 100,000 population.[22–24]

Similarly, the studies examining the rates of perforation in patients undergoing appendectomy or antibiotics-first treatment fail to appropriately evaluate both the increased diagnostic utility of surgery and the contribution of perforation to other morbidities. Patients with perforation diagnosed at the time of presentation via imaging are excluded from these studies, but there is likely a nonzero rate of perforation at presentation not visible on imaging. A patient managed with antibiotics-first therapy who clinically improves may never undergo interval imaging, while a patient undergoing appendectomy receives the most sensitive and specific test for perforated appendicitis: direct visualization. As such, the studies noting a significant decrease in perforation rate among patients treated nonoperatively (nearly half the patients in this meta-analysis) may be dramatically underdiagnosing perforation. Of course, if the patients with undiagnosed perforation require no further intervention, then the associated morbidity of perforation itself is called into question. The outcome is included here as part of the *a priori* defined PICO question, and it has classically been one of concern due to the understood natural history of appendicitis; perhaps, this should be reconsidered. The ongoing uncertainty of the outcomes studied in the reported RCTs remains a concern to surgeons and physicians. The greatest level of bias introduced in this meta-analysis is the result of significant heterogeneity between the populations included in the individual studies and in

the inconsistency of analysis. This is reflected in the above qualitative synthesis and in the grading of recommendations, and it cannot be overemphasized.

As for the studies delineating the potential of recurrence following successful nonoperative treatment of AAP, there are multiple limitations that prevent a strong recommendation of ongoing nonoperative treatment. The only randomized trial includes a mere 40 patients from a single center. All three studies are vague in defining the diagnosis of recurrent appendicitis, although one may assume that all diagnoses were clinical in origin. For example, the majority of patients in the Lai study who were selected for surgery had appendicitis confirmed on surgical pathology. We recognize that the overall incidence of occult malignancy was low at 4.8%; however, this was based on the findings of one study (Lai) and warrants further investigation.

As for describing complications, all three studies have very limited data. Four patients in the Kaminski article required partial colectomies; however, there is essentially no information regarding postoperative infections or healing complications. While hospital LOS may pose as a surrogate for complications, this is a large assumption and should not be inferred from the reported data.

Using These Guidelines in Clinical Practice

This guideline represents results of systematic review of available evidence regarding treatment of acute appendicitis with antibiotics-first therapy and the need for RIA in patients with a history of AAP treated nonoperatively on initial admission.

Based on the available evidence, a recommendation for or against the antibiotics-first therapy versus surgery for uncomplicated acute appendicitis could not be made. Traditionally, appendectomy has been the most common treatment option for uncomplicated AA; however, we reviewed a series of studies revealing success with ABX. As a group, we concluded that the serious degree of inconsistency and imprecision demonstrated by the majority of studies precludes making a formal recommendation. We unanimously agreed that clinical presentation, CT scan findings, and patient's preferences should be considered when advising patients on the treatment options for uncomplicated AA.

For patients treated conservatively for AAP, we conditionally recommend against RIA. While the recurrence rate of AA is relatively low, the main concern remains the potential malignant etiology of presumed perforated appendicitis. The clinician's suspicion for occult malignancy and the patient's risk factors for cancer—including age and family history—should be taken into consideration and a treatment plan devised based on individual circumstances. At present, there is not enough data to suggest that RIA is warranted for all patients.

Future Investigations

More studies are needed to assure that the antibiotics-first approach to an initial episode of acute appendicitis as well as long-term NOM of AAP is safe and carries minimal risk. A RCT that utilizes standard clinical definitions for "treatment failure" and "recurrence," includes patients that accurately depict the general population, and emphasizes the standard practice of laparoscopic appendectomy as the control may yield more meaningful outcomes.[25] As for the ongoing observation of patients previously treated NOM for AAP, future studies that examine the true cost and impact on quality of life are needed. Additionally, an established surveillance protocol for patients at risk of malignancy should be elucidated and evaluated for efficacy and safety.

CONCLUSION

In conclusion, our committee was able to make one recommendation based on the existing literature describing the management of appendicitis. When addressing AAP initially managed nonoperatively, we conditionally recommend against RIA. Based on adherence to GRADE methodology, the panel could not support RIA based on the low quality of literature and the known rarity of appendiceal malignancy. Patients should be followed on an interval basis and appropriately counseled on seeking medical treatment for signs and symptoms of recurrence. As for the initial management of acute uncomplicated appendicitis, we cannot offer a recommendation for or against appendectomy compared with the antibiotics-first approach. Future studies will help elucidate appropriate clinical decision making regarding the antibiotics first approach as the primary treatment for AA.

DISCLOSURE

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