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Evidence for an Antibiotics-First Strategy for Uncomplicated Appendicitis in Adults: A Systematic Review and Gap Analysis

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For more than 120 years, prompt appendectomy has been the standard approach for the treatment of acute appendicitis.[1-3] With >300,000 diagnoses of appendicitis annually, appendectomy is the most commonly performed urgent abdominal operation in the United States.[4,5] Despite the common occurrence of this condition and the relative ease with which appendectomy is performed, both clinicians and the general public question whether we should shift our approach toward nonoperative management of appendicitis.[6,7] Many clinicians in Europe have already adopted this approach; for example, survey data suggest that nearly one-quarter of surgeons in Ireland routinely treat patients with uncomplicated appendicitis nonoperatively.[8]

The idea that appendicitis can resolve without surgery is not new. In 1886, before the development of antibiotic therapy, Fitz[2] reported that many autopsy specimens showed evidence of previous appendicitis, indicating that some patients could resolve the disease without surgical intervention. In 1959, Coldrey[9] published his case series describing nonoperative treatment of acute appendicitis and concluded that many cases of appendicitis resolve without surgery. Despite this evidence, treatment in the United States has continued to be nearly entirely operative.[10] Evidence for antibiotics first has again surfaced with 6 small randomized controlled trials (RCTs) concluding that a majority of patients with acute, uncomplicated (nonperforated) appendicitis (AUA) can be treated safely with an antibiotics-first strategy, with rescue appendectomy if indicated.[11-16] Conclusions from meta-analyses of the RCTs support that an antibiotics-first strategy is safe and effective in a majority of patients,[3,17-20] but the most rigorous analysis[3] was unable to demonstrate noninferiority of an antibiotics-first approach, in part due to the power and low to moderate quality of the studies included. However, even this approach was limited in that the outcomes that were tested for noninferiority were not independent of the treatment strategy in all cases, making

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it difficult to reach meaningful conclusions about the comparative effectiveness of an antibiotics-first approach.

As clinicians in the United States consider incorporating the antibiotics-first strategy into their clinical practices,[6] it is important to recognize the limitations of earlier studies, how these limitations might prevent the clinical application of an antibiotics-first approach, and how the results of previous studies can be used to inform the treatment of patients with AUA. We aimed to identify remaining evidence gaps in the comparison of surgery and antibiotics-first for AUA, and to provide guidance to physicians who might consider adopting this strategy as part of their practice.

Methods

PubMed (Medline) and EMBASE were searched using defined search terms in June 2015 to identify RCTs that compared antibiotics with appendectomy for acute appendicitis, without time restrictions (Table 1). The search was restricted to English-language studies. Published reviews and meta-analyses were examined to identify additional studies that might not have been identified using our search strategy. After duplicates were removed, articles were screened for inclusion. Primary reasons for exclusion included study type (ie, non-RCT) and non-adult populations. Selected publications were reviewed by all authors and available results were extracted from the studies using a standard template. A review of common study limitations was conducted using iterative theme elicitation through in-person and teleconference reviews.

A summary of the main outcome measures for each RCT was compiled into a standard table. Outcomes of interest included length of follow-up, crossover rates during the initial hospitalization, proportion of patients treated with antibiotics first who underwent appendectomy (either during the initial hospital stay or during follow-up), proportion of patients with perforation, length of stay (LOS), days of pain, days missed from work or school, overall complication rates, and time period for follow-up. Our primary focus was to determine generalizability to the US population, inform patients and clinicians about the current state of the evidence, and identify gaps that need to be addressed in future studies. The focus of this work included study population and setting, inclusion and exclusion criteria, use of standardized health-literacy sensitive patient education and informed consent materials, analysis of eligible patients who declined participation in the study, use of adequate antibiotic regimen, rates of crossover after randomization, and use of validated patient-reported outcomes (PRO) assessment. We reviewed previously published meta-analyses to determine how their conclusions highlight the evidence gaps.

Results

A total of 7 studies[11-16,21] met the inclusion criteria, but one[21] was not included because it had been retracted for plagiarism.[22] All of the studies were conducted in Europe. In total, the 6 studies included 1,724 patients (proportion of women, 0% to 47%; mean or median age ranged from 26 to 38 years when reported). No study included individuals aged older than 75 years, and one study excluded women.[12] With the exception of one study that reported eventual appendectomy rates of 60% (primarily due to high crossover),[14] rates of appendectomy in the antibiotics-first group were between one-quarter and one-third of patients (24% to 35%) in the intention-to-treat analysis. Length of stay was similar between the 2 groups and was approximately 3 days (2.4 to 3.3 days for surgery and 3.0 to 3.96 days for antibiotics first). Length of stay evaluations were limited in this setting, given the fact that several studies had a prespecified minimum period of time that patients in the antibiotics-first cohort were required to stay in the hospital for ongoing observation,[11,13,14,16] rather than basing discharge criteria on physiologic or functional improvement. Days of pain and days away from work were lower in the group receiving antibiotics first. Across all studies, complications were higher in the surgical group (27%, range <1% to 33%) compared with the antibiotics-first group (9%, range 2.5% to 25%).

Results of clinical outcomes are summarized in Table 2.

Selection bias

A common theme across all studies was the possibility of considerable selection bias within the patients who participated in the trial. Three studies provided adequate information about the randomization technique.[14-16] No study provided detailed information about the informed consent materials that were used, and whether there was standardized health literacy-sensitive patient education material included with consent. Rates of crossover from antibiotics first to surgery during the index hospital stay varied widely (0% to 53%).

Beyond basic demographic information, such as age and sex, no study reported information about comorbid conditions that might influence a patient's clinical response to appendectomy vs antibiotics first. Additionally, no information was provided about socioeconomic status, ability to take time off of work or school, degree of social support, or necessity of travel in the future. All of these can affect a patient's willingness to participate in an RCT. Some potentially higher-risk patients were not included, which limits the generalizability of the study findings. We, therefore, do not know about the effectiveness of this approach in elderly populations, pregnant patients, or those with significant comorbid conditions. This raises concerns that perhaps study teams systematically excluded higher-risk populations who might respond differently to an antibiotics-first treatment strategy compared with average-risk patients.

Limited information was provided about patients who refused randomization. Only 2 studies included any description of patients who declined participation, limiting our ability to determine generalizability to a broad population.[12,16]

Diagnostic criteria

Most studies did not describe standardized diagnostic criteria that must be met for study eligibility. Examples of inclusion criteria include “suspected acute appendicitis”[12] or appendicitis “diagnosed according to established practice.”[14] Two studies used a range of clinical and radiographic modalities that were not standardized across patients.[11,13] Given this inconsistency, we do not know whether all of the patients had acute appendicitis or whether some patients with complicated appendicitis (such as those with peri-appendiceal abscess or fluid collection) were enrolled in the study. The lack of diagnostic consistency suggests that the study population described is not necessarily a population of patients with AUA. Inclusion of patients without appendicitis would appear to make antibiotics first seem more effective than it actually is, and inclusion of patients with complicated appendicitis would bias results in the opposite direction, and can impact crossover rates within the study.

Treatment strategy

Although each study had a unique treatment strategy consisting of either surgery or a prespecified antibiotic regimen, one study used only amoxicillin plus clavulanic acid in the antibiotics-first group,[15] an antibiotic that does not provide adequate coverage for typical causative agents in AUA, such as *Escherichia coli*,[23] and is not recommended for the treatment of appendicitis.[24] Most studies used open appendectomy as the primary surgical treatment. Rates of laparoscopy varied (range 5% to 66%), but in only one study were rates of laparoscopic surgery >50%.[15] This limits the generalizability of the findings to patients in the United States, where the vast majority of appendectomies are performed laparoscopically. This is especially challenging when evaluating postoperative complications, such as superficial surgical site infections (which can occur more frequently after open surgery) and deep-space infections (rates of which can be higher after laparoscopic surgery).[25]

Outcome selection

Many of the stated primary outcomes were vague or not clinically meaningful (eg, “treatment efficacy”[14] or improvement in WBC count[11]). The application of outcomes measures was not always independent of treatment assignment and was not applied consistently across groups. Only 2 studies had prespecified failure criteria for patients managed with antibiotics first.[15,16] Although most studies discussed general outcomes of pain or use of narcotic pain medication, no study used a validated PRO tool. This type of tool is important for measurement of quality of life (QoL), fear, and anxiety during the initial treatment period and follow-up. One study included an analysis that evaluated predictors of antibiotics-first failure, but did not find any characteristics that were associated with failure.[15] No studies identified biomarkers or included microbiology data.

The longest duration of follow-up in any study was 17 months.[11] All other studies had a follow-up period of 1 year, limiting information on long-term effectiveness of antibiotic treatment. Although this might be a reasonable period to measure treatment failure in the antibiotics-first group, or surgical complications in the surgery group, it might be too short an interval to detect occurrence of more-rare or time-dependent events, such as identification of appendiceal cancer or rates of recurrent appendicitis. There is minimal information on the success of treating recurrent episodes of appendicitis with antibiotics during the follow-up period.

A summary of all evidence gaps is presented in Table 3.

Meta-analyses

We reviewed 5 published meta-analyses on this topic,[3,17-20] all of which concluded that antibiotics first is probably a safe approach, but that definitive conclusions about its effectiveness compared with appendectomy cannot be made. All of the studies focused on analysis of the clinical outcomes (eg, complications, LOS, eventual rates of appendectomy), but only 2 examined patient-centered outcomes, such as pain control and days missed from work.[3,20] All noted that the quality of the RCTs was poor to moderate, making it difficult to make solid inferences going forward. Although acknowledging the difficulty of such an endeavor, Wilms and colleagues[3] concluded that a more high-quality RCT must be performed before making definitive conclusions about the comparative effectiveness of one approach over another.

Discussion

We sought to perform a systematic review of the evidence for an antibiotics-first strategy for AUA, focusing on evidence gaps that need to be addressed in future studies. We identified a total of 6 RCTs comparing appendectomy with antibiotics first for AUA. All studies had methodologic flaws, including inconsistent diagnostic criteria, high crossover rates, absence of PRO inclusion, and small homogenous study populations, all of which limit generalizability to a broad population. The US health care system is unique in terms of its delivery of care, focus on short hospital stays, limited sick leave provided to workers, and surgical techniques (which largely favor laparoscopy over open surgery for appendectomy). Future studies should address all of these items, but should also focus on QoL measures and PROs, such as overall burden of care to both the patient and the health care system. These types of outcomes can be measured using QoL instruments, such as the European Quality of Life-5 Dimensions, the Gastrointestinal Quality of Life Index, and the Patient Reported Outcomes Measurement Information System. Currently, the first US trial studying these issues, funded by an R21 from the NIH, is accruing patients and aims to address several of these limitations (ClinicalTrials.gov ID: NCT02447224), and a largerscale trial funded by the Patient Centered Outcomes Research Institute is planned.

Outside of RCTs, observational studies have contributed to the evidence base for an antibiotics-first strategy. A large retrospective study analyzing operative vs nonoperative treatment of appendicitis using a statewide administrative database found that rates of appendectomy in the nonoperative group were <10% during a mean follow-up period of >7 years. In a propensity score-matched cohort, mortality rates and charges related to patient care were not statistically different between the 2 groups. Although the LOS was longer in the nonoperative group by more than an entire day, they concluded that nonoperative management of appendicitis is safe. This study evaluated a large number of patients (>200,000), but was limited by the fact that it was using diagnostic codes to evaluate both incident and recurrent cases of appendicitis, which might have led to misclassification and bias.[10] Prospectively, Di Saverio and colleagues[26] evaluated outcomes of 159 patients undergoing nonoperative management for AUA and reported a failure rate of 12% at 7 days and with an overall efficacy of 83% during the follow-up period of 2 years. They concluded that a nonoperative treatment strategy for AUA is safe and effective. As this was an observational study, it again raises important questions about selection bias and confounding by indication. Neither of these studies evaluated potentially relevant and important PROs that can influence patient decision making, satisfaction with care, and QoL after treatment for appendicitis, such as gastrointestinal symptoms during the follow-up period and decisional regret surrounding the treatment choice.

Missing from many of these studies are data on the incidence of cancer in individuals who are treated nonoperatively. In general, <2% of appendectomy specimens are found to contain a neoplasm,[27] but these estimates are typically derived from population-level data and include all patients who undergo appendectomy regardless of whether they have complicated disease or not. Multiple case series describing patients undergoing interval appendectomy report higher rates of appendiceal cancer (12% to 29%).[27-29] These are retrospective reports and so the reason for interval appendectomy is not specified, but it is likely that these included many patients with complicated appendicitis who are excluded from RCTs studying this topic and presumed to be at higher risk for neoplasm than patients with AUA. Some studies have excluded patients with findings suggestive of potential tumor, but it remains to be determined whether AUA is an important precursor of appendiceal cancer in the general population.

This review is an assessment of the evidence gaps of the earlier studies and, as such, has several limitations. We restricted to English-language studies. We chose not to perform formal meta-analyses, given the existence of previously published reports of this nature. Although these studies quantitatively assess the collected body of evidence, we believe that a qualitative review such as ours best identifies the high-value targets for future research studies. We did not consider patient-level analyses but rather summarized the results using study-level information. Although the authors are all experts in clinical management of appendicitis, nonclinical methods experts were not included in this analysis.

Conclusions

The evidence base for antibiotics-first strategy has grown in the last 20 years, but several important questions remain about the comparative effectiveness of this approach. Future studies are necessary to inform patients and clinicians about the benefits of each approach for an individual patient. We recommend that clinicians interested in this approach consider enrolling patients in clinical trials or participate in a publicly available registry developed by emergency medicine physicians at the University of California, Los Angeles, CA, and surgeons at the University of Washington in Seattle, WA (www.becertain/appyregistry).

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Abbreviations and Acronyms

AUA	acute uncomplicated appendicitis
LOS	length of stay
PRO	patient-reported outcomes
QoL	quality of life
RCT	randomized controlled trial

Table 1

Search Terms Used in PubMed and Embase Searches

Database	Search terms
PubMed	“Appendectomy”[MAJR] AND “Appendicitis/drug therapy”[MAJR]
Embase	‘appendicitis’/exp OR appendicitis AND (‘antibiotics’/exp OR antibiotics) AND [adult]/lim AND (‘clinical trial’/de OR ‘comparative study’/de OR ‘controlled clinical trial’/de OR ‘controlled study’/de OR ‘multicenter study’/de OR ‘randomized controlled trial’/de) AND (‘acute appendicitis’/de OR ‘appendicitis’/de) AND (‘drug therapy’/lnk OR ‘surgery’/lnk) AND ([aged]/lim OR [middle aged]/lim OR [very elderly]/lim OR [young adult]/lim)

Table 2

Primary Outcomes Measures for the Randomized Controlled Trials Assessed in the Study Based on Intention-to-Treat Analysis

First author	Follow-up period	Crossover during index hospitalization*		Appendectomy rate†		Perforation rates, n (%)	Length of stay, d	Pain, d	Away from work/school, d	Complications, n (%)
		n	%	n	%					
Eriksson[11] (n = 40)	17 mo (average)	0/20	0	7/20	35	Surg: 1/20 (5)‡ Abx: 1/20 (5)§	Surg: 3.3 Abx: 3.1	Surg: >10 Abx: 6	NR	Surg: 1/20 (5) Abx: NR
Styrud[12] (n = 252)	1 y	15/128	12	31/128	24	Surg: 6/124 (5) Abx: 12/124 (10)	Surg: 2.6 Abx: 3.0	NR	Surg: 10.1 Abx: 8	Surg: 17/124 (14) Abx: 4/128 (3)
Turhan[13] (n = 290)	1 y	19/107	18	26/107	24	Surg: 34/183 (19) Abx: 0/107 (0)	Surg: 2.4 Abx: 3.14	NR	NR	Surg: 8/183 (4.4) Abx: 5/107 (4.7)
Hansson[14] (n = 369)	1 y	96/202	53	122/202	60	NR//	Surg: 3.0 Abx: 3.0	Surg: 9 Abx: 6	Surg: 11 Abx: 7	Surg: 55/167 (33)¶ Abx: 51/202 (25)
Vons[15] (n = 239)	1 y	NR		39/120	33	NR	Surg: 3.04 Abx: 3.96	Surg: 1.7 Abx: 1.63	Surg: 10.5 Abx: 9.8	Surg: 1/119 (<1) Abx: 3/120 (2.5)
Salminen[16] (n = 530)	1 y	15/257	6	70/257	27	Surg: 2/273 (<1) Abx: 5/257 (2)	Surg: 3.0 Abx: 3.0	NR#	Surg: 19 Abx: 7	Surg: 45/220 (20.5) Abx: 6/216 (2.8)

* Crossover from antibiotics first to appendectomy.

† Total rate of appendectomies from index hospitalization to follow-up period.

‡ Surgery-first group (intention to treat).

§ Antibiotics-first group.

// Reported rates per protocol rather than intention to treat.

¶ Includes both major and minor complications.

\# Visual Analogue Scale of pain recorded.

Abx, antibiotics; NR, not reported; Surg, surgery.

Table 3

Limitations of Previous Randomized Controlled Trials Evaluating Antibiotics First vs Appendectomy for Acute Appendicitis

	First author, year					
Study characteristic	**Eriksson, 1995[11]**	**Styrud, 2006[12]**	**Turhan, 2009[13]**	**Hansson, 2009[14]**	**Vons, 2011[15]**	**Salminen, 2015[16]**
Heterogeneous study population	–	–	–	–	–	–
AUA diagnosis by universal imaging	–	–	Yes	–	–	Yes
Standardized health literacy-sensitive patient education and informed consent	–	–	–	–	–	–
Adequacy of randomization technique	–	–	–	Yes	Yes	Yes
Analysis of characteristics of eligible patients refusing randomization	–	Yes	–	–	–	Yes
Adequate in vitro active antibiotics used	Yes	Yes	Yes	Yes	–	Yes
Limited post-randomization crossover to surgery unrelated to antibiotic failure	Yes	Yes	Yes	–	Yes	Yes
Primary outcome independent of treatment assignment and consistently applied between treatment groups	–	–	–	–	–	–
Validated secondary PRO measured	–	–	–	–	–	–
Major complications reported	–	–	Yes	Yes	Yes	Yes
Appendectomy criteria in antibiotic group	–	–	–	–	Yes	Yes
Adequate sample size	–	–	–	–	–	Yes
Hospital discharge/duration based on physiological and functional stability	–	–	–	–	–	–
Outcomes assessed to 2 y	–	–	–	–	–	–
Predictors of antibiotic response evaluated					Yes	
Biomarker predictor of antibiotic response evaluated	–	–	–	–	–	–

–, no or not reported; AUA, acute uncomplicated appendicitis; PRO, patient-related outcomes.