



Long-term results of nonoperative treatment for uncomplicated acute appendicitis

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ABSTRACT

Background/Aims: This study aimed to assess the long-term (>12 months) efficacy of nonoperative treatment (antibiotic administration) in the management of uncomplicated acute appendicitis (AA).

Materials and Methods: We surveyed uncomplicated AA patients who elected to undergo nonoperative treatment between 2010 and 2012. A binary logistic regression analysis was performed to identify the critical predictors of recurrence. Age, gender, presence of appendicolith, and white blood cell count on admission were analyzed as possible predictors of recurrence.

Results: The median follow-up period of the study was 23 months. Twelve of 118 patients (10.2%) were diagnosed with recurrent appendicitis. Seven were retreated with the same antibiotic protocol and did not show further recurrence. The binary logistic regression analysis revealed statistical significance only for the presence of appendicolith [$P=0.001$, Exp (B)=0.058, B=-2.845]. Recurrence rate was lower in the presence of appendicolith.

Conclusion: Nonoperative treatment of uncomplicated AA is an effective option. Recurrence is rare and it can be addressed efficiently with the administration of a second course of antibiotics. The presence of appendicolith should not discourage physicians from prescribing nonoperative treatment for patients with uncomplicated AA.

Keywords: Appendicitis, nonoperative treatment, recurrence

INTRODUCTION

The lifelong incidence of acute appendicitis (AA) ranges between 5%-25%, with appendectomy being the most frequently performed emergency abdominal surgery worldwide. In the United States alone, 250,000 appendectomies are performed annually, using one million hospital days and costing three billion dollars per year (1-4). Consequently, management of AA requires consideration of the patient's welfare as well as the economic impact to society.

Acute appendicitis presents in two forms: uncomplicated and complicated. Traditionally, uncomplicated AA has been treated by appendectomy, whereas the first treatment response to complicated AA is nonoperative intervention (e.g., intravenous antibiotic delivery). Much of the research completed to date draws comparisons between the divergent management plans for AA (5-9).

The flaw with this approach, however, is that the two treatment options should be viewed as complements rather than competitors. At the most basic level, the majority of appendectomized patients receive antibiotics during hospitalization as a form of prophylaxis or therapy; hence, to consider these treatment methods as mutually incompatible is counterproductive. For this reason, the current study did not seek to compare and contrast treatment methods, but looked to address the relationship between uncomplicated and complicated AA and the synergies of nonoperative and operative protocols for their treatment.

In the case of uncomplicated AA, surgical intervention is considered necessary for early resolution to contain the disease; this approach minimizes the opportunity for internal perforation and other secondary infectious

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complications, and it rules out appendiceal malignancy. In addition, appendectomy holds the advantages of single hospital admission and recurrence prevention (10). Despite the many substantiated benefits of surgical intervention, nonoperative treatment is preferred for complicated AA. Nonoperative treatment eliminates irreversible loss of organ functionality. In addition, the costs are lower and the risks associated with invasive surgery are excluded.

Considering the shortcomings of appendectomy, there is a growing body of research assessing the potential for nonoperative therapy to be extended to uncomplicated AA. Such research promotes the alignment of treatment methods for both uncomplicated and complicated AA (5-9). Although research advocating the replacement of appendectomy with nonoperative therapy for cases of uncomplicated AA has garnered strong momentum, many of these studies have been limited to a 12-month follow-up period (5-9). The aim of the present study was to assess the efficacy of nonsurgical treatment of AA over an extended period of follow-up (>12 months). More specifically, this study sought to confirm that nonoperative treatment for uncomplicated AA does not increase the risk of long-term recurrence or adversely impact the future health management of the patient.

MATERIALS AND METHODS

After obtaining institutional ethical board approval, the medical records of 162 patients (all of whom gave written informed consent) treated via nonoperative methods for uncomplicated AA were examined. All patients were confirmed cases of uncomplicated AA; diagnosis was verified using a combination of computer tomography (CT) and ultrasound (US). After diagnosis, patients were educated on the advantages and disadvantages of appendectomy vis-à-vis nonoperative treatment according to their ages and individual medical status.

Nonoperative treatment is an intravenous antibiotic regime with the following protocol: 1 g ceftriaxone twice daily and 500 mg metronidazole three times daily, followed by an oral course of ampicillin/sulbactam (750 mg twice daily) and metronidazole (500 mg three times daily) for 10 days. All patients underwent the same treatment course, with the exception of one patient who was found to be allergic to penicillin. Penicillin allergy precludes the use of ceftriaxone and ampicillin (both drugs contain the beta-lactam ring); therefore, ciprofloxacin (200 mg twice daily) was applied as an alternative antibiotic treatment, and the patient was not excluded from study.

Subsequent to antibiotic delivery, if symptoms did not improve within 48 h, appendectomy was performed. Two patients (1.2%) did not achieve symptomatic relief within 48 h. After 2 months, a barium enema or colonoscopy was performed on all patients identified with an increased risk of colorectal malignancy (e.g., aged ≥ 50 years).

Individual patients were administered a questionnaire for assessing pain management, need for hospital readmission, and general treatment after discharge. Of the 162 case files obtained under ethical board approval, 42 patients were excluded from study as they did not participate in the questionnaire survey. The questionnaire sample totaled 118 respondents.

Statistical analysis

A binary logistic regression analysis was performed to aggregate patient data and ascertain useful predictors of recurrence. Age, gender, white blood cell (WBC) count, and the presence of an appendicolith on admission were investigated as critical predictors of recurrence. Age and WBC count at admission were subdivided into two categories: age <30 years or ≥ 30 years; WBC count <12,000 cells/ μL $\geq 12,000$ cells/ μL . Statistical analyses were performed using SPSS software version 16.0 (SPSS Inc.; Chicago, Illinois, USA). A *P* value of <0.05 was considered statistically significant.

RESULTS

Female to male ratio was 36 to 84 and median age was 31 years (range, 18–92 years). An appendicolith was detected in 17 patients, and the median WBC count at admission was 12,800 cells/ μL (range, 11,000–17,800). Two patients (1.2%) did not achieve symptomatic relief within 48 h. Surgical investigation of these patients revealed gangrenous appendicitis and local findings of peritonitis. None had appendicolith or postoperative complications. Median hospitalization time was 2 days (range, 1–7 days; mean hospitalization time $\pm$ SD was 2.8 ± 1.8 days).

Two months after successful medical therapy, 19 patients underwent a colonic examination to exclude colorectal malignancy. No malignancies were detected; however, the colonoscopy of one patient revealed that the orifice of the appendix was edematous. Upon histopathological examination, edema and signs of mild chronic inflammation were observed (Figure 1).

The median follow-up period for the study was 23 months (range, 12–36 months). Sixteen of 118 patients (13.6%) experienced pain symptoms indicative of ongoing AA complications. Fifteen of these were readmitted to hospital and 12 (10.2%) were diagnosed with recurrent appendicitis. Presentation of recurrence spanned a range of 1–22 months; however, two-thirds of recurrence cases were observed within the first year of follow-up.

For 10 of the 12 patients affected by recurrent AA, records were obtained for further evaluation. In all cases, diagnosis of recurrence and assessment of appendicolith formation were confirmed by CT. Two of the 10 patients investigated had appendicolith presentation at first treatment; however, no appendicolith was detected on readmission.

Seven of the 10 patients investigated elected to continue with nonoperative treatment and undertook a second course of

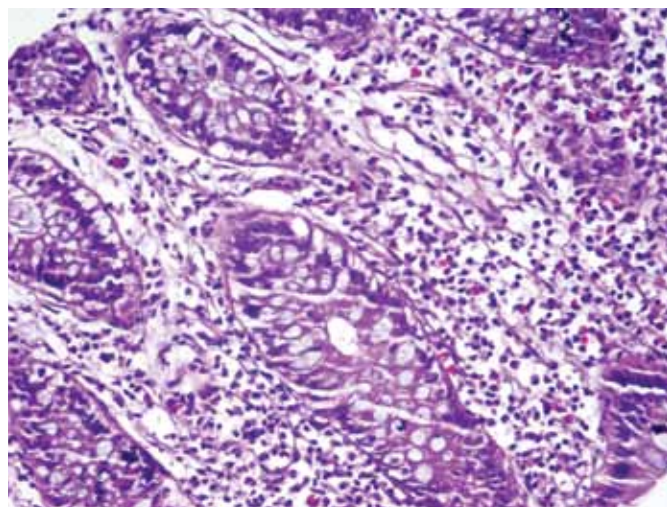


Figure 1. A Chronic inflammatory reaction accompanied by eosinophilia in the appendiceal orifice (HEX400).

intravenous antibiotics. The results were favorable with none of the patients exhibiting any further symptoms of recurrence. The remaining three patients underwent appendectomy.

Table 1 summarizes the results of the binary logistic regression analysis. The data indicate statistical significance only for the presence of appendicolith [$P=0.001$, Exp (B)=0.058, B=-2.845]. The Exp (B) value 0.058 implied that the presence of appendicolith measurably decreased the risk of recurrent appendicitis.

DISCUSSION

Nonoperative treatment is a safe and effective response to complicated AA (11,12); however, this concept is a contentious point among medical professionals because of the potential need for interval appendectomy (IA). IA is the surgical removal of the appendix 6-8 weeks following nonoperative treatment for complicated AA. To state simply, nonoperative treatment is not accepted unanimously as the leading treatment for complicated AA owing to the likelihood of recurrence and subsequent surgical intervention. However, the rate of recurrent appendicitis is low (6%-20%), and the complication rate of IA (9%-19%) does not differ markedly from emergency appendectomy (13-15). Furthermore, routine IA following initial nonoperative treatment for complicated AA is not a cost-effective intervention (16).

Today, treatment of uncomplicated AA remains a controversial topic. The classical dogma of "the treatment of AA is surgery" is widely advocated by most surgeons. This traditional theory was adopted as a response to resource limitations (restricted access to physicians and absence of antibiotic treatment). In today's medical environment, however, antibiotics are routinely used, and contact time with physicians has expanded. As a result, there is an increasing body of evidence suggesting that nonoperative treatment is a viable option for the management of uncomplicated AA.

Table 1. Results of binary logistic regression analysis

Characteristics	Recurrent (n=12)	Nonrecurrent (n=106)	Exp (B) value	p value
Age			0.352	0.143
18-29	8	46		
≥30	4	60		
Gender			0.183	0.070
Male	9	73		
Female	3	33		
White blood cell counts, cells/ μ L			0.417	0.216
≤12,000	4	94		
>12,000	8	12		
The presence of appendicolith			0.058	0.001
Yes	6	11		
No	6	95		

Although nonoperative treatment eliminates risks associated with abdominal surgery and general anesthesia (17), there are still valid concerns attributed to its practice. Specifically, nonoperative treatment may result in failed antibiotic response, risk of progression to complicated AA, and recurrence. Another concern is the possibility of malignancy in appendix as a cause of AA (18). The results of this study confirm that nonoperative therapy does not achieve 100% efficacy; however, data reveal that in those cases where nonoperative treatment fails impact on the patient is minimal.

Failed antibiotic response is defined as a lack of improvement or clinical progression within 48 h after initial treatment. Liu and Fogg (19) reported failure rates ranging between 0% and 11.8%. The results of the current study show a failure rate of 1.2%. None of these values are significant. Furthermore, as has already been noted, antibiotics are a common element of both nonoperative and operative management plans; hence, a failed antibiotic response alone is not a sufficient argument to exclude nonoperative therapy as a treatment protocol for uncomplicated AA.

Regarding the risk of progression to complicated appendicitis, Teixeira et al. (20) noted the following points: even though appendectomy delay is not associated with higher perforation rates, it may result in an increased risk of surgical-site infection (SSI) in patients with nonperforated appendicitis. Yardeni et al. (21) also investigated the impact of delayed appendectomy in a pediatric population with acute (presumed) nonperforated appendicitis. The study found that morbidity rates were most notably controlled where antibiotics were delivered as an initial treatment protocol. Specifically, antibiotics were found to positively influence morbidity rates-even where surgical intervention was delayed up to 24 h. Likewise, in a recent meta-analysis of randomized controlled trials for the treatment of uncom-

plicated AA, Varadhan et al. (22) demonstrated that antibiotic treatment (as a response to delayed appendectomy) was associated with a decreased risk of both perforation and surgical complications.

The patients of the current study who failed to respond to non-operative treatment and elected to undergo appendectomy did not present with SSI. It is assumed that SSI was successfully avoided because of the antibiotic response generated by initial nonoperative intervention. The results of the current study support the theory that antibiotic delivery assists with minimizing the risk of progression to complicated AA. In addition, our observations indicate that prevention of SSI may be attributed to antibiotic delivery offered at least 48 h prior to appendectomy.

With reference to recurrence as a drawback in the practice of nonoperative treatment for uncomplicated AA, prior studies by Varadhan et al. have reported a recurrence rate of 20% (68 out of 345 patients) (22). In another study, Liu and Fogg (19) documented a mean recurrence rate of $14.2\% \pm 10.6\%$. Kaminski et al. (23) reported that 39 of 864 patients (5%) had developed a recurrence in a retrospective study (13 of the 39 were treated nonoperatively; no further recurrence episodes were observed in these patients). In the present study, recurrence rate was 10.2%. The time frames for monitoring recurrence differentiate these studies. Varadhan et al. did not investigate patterns of recurrence for any period >12 months. Conversely, the present study operated on a median follow-up period of 23 months, with two-thirds of recurrences observed within the first year and no recurrences observed beyond 22 months. In addition, seven recurrences were treated with another course of antibiotics. Thus, the current study not only reinforces the data from prior studies but also indicates that nonoperative treatment for uncomplicated AA does not increase the risk of long-term recurrence or adversely affect the patient's future health management.

Although it is generally accepted that recurrence is one of the most common side effects of nonoperative treatment of uncomplicated AA, the characteristics that increase a patient's propensity toward recurrence are less understood. Factors allegedly associated with a high risk of recurrent appendicitis include retained fecal stones, increased C-reactive protein levels (>4 mg/dL), elevated differential count of banded neutrophils, and partial small bowel obstruction on admission (24-31). However, all of these are risk factors associated with complicated AA. The most important factor for the recurrence of uncomplicated AA is the presence of an appendicolith. Research on this topic, however, is not conclusive. Kaminski et al. (23) reported that age, Charlson comorbidity index, type of appendicitis, or percutaneous abscess drainage had no influence on the recurrence of AA treated nonoperatively. This study did not reference the association between recurrence and presence of appendicolith. On the other hand, Lien et al. (32) investigated

the appendicolith as a predictive factor for recurrence (along with age, gender, comorbidities, presenting symptoms, laboratory data, appendicitis type, duration of antibiotic treatment), but reported no significant association between appendicolith and recurrence. According to Lien et al. (32), male gender is the only significant factor associated with recurrence (hazards ratio 3.45; 95% confidence interval, 1.15-10.39). Tsai et al. (33) investigated the CT findings between patients with and without recurrent appendicitis in a retrospective study. They found that presence of calcified appendicolith was associated with recurrence. It should be noted, however, that Tsai et al. focused only on CT findings; the study did not investigate other potential risk factors or include a logistic regression analysis. The current study observed that recurrence was negatively affected by the presence of appendicolith. Moreover, CT found no appendicolith on the second hospitalization of two patients with recurrent appendicitis who had an appendicolith on previous admission. These results exhibit an undocumented pattern for the relationship between appendicolith presentation and recurrence. The data indicate a decreased risk of recurrent appendicitis when an appendicolith is diagnosed; however, further research is required to confirm these findings.

Tumors are one of the etiological factors of AA. Although this relationship directly counteracts the argument promoting nonoperative treatment for uncomplicated AA, malignancy risk is very low in appendectomy specimens. Hansson et al. (6) reported two (of 369) AA patients with malignancies of appendix or colon, both of which were discovered only at the time of appendectomy. Consequently, risk of malignancy is not a deterrent in the selection of nonoperative treatment for cases of uncomplicated AA. Although the current study intended to focus solely on uncomplicated cases of AA, colonoscopy and barium enema were performed in accordance with colorectal cancer screening recommendations. No appendiceal or colorectal malignancy was revealed by these procedures; however, findings of mild chronic inflammation were incidentally found in the appendiceal orifice of one patient. Such inflammation may be representative of chronic appendicitis, but limited data and analysis in this area prevent further assumptions or conclusions.

Our results indicate that nonoperative intervention for uncomplicated AA is an effective treatment option. According to the results of the present and previous studies, intravenous antibiotic regime as a robust and successful treatment program in nearly 90% of all patients with uncomplicated AA. Although recurrence is a plausible event following treatment of uncomplicated AA via nonoperative techniques, it typically presents within a short time and does not pose ongoing risks to the patient's future health management. In addition, recurrence can be addressed efficiently with the administration of a second course of antibiotics. Despite the prevalence of contrary belief, the presence of appendicolith should not discourage physicians from prescribing nonoperative treatment for patients with uncomplicated AA. Indeed, nonoperative treatment

should be considered as a first line therapy not only for complicated AA but also for uncomplicated AA.

Ethics Committee Approval: Ethics committee approval was received for this study from Non-invasive Research Ethics Committee of Firat University.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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