Feasibility of a Nonoperative Management Strategy for Uncomplicated Acute Appendicitis in Children

Peter C Minneci, MD, MHSc, FACS, Jason P Sulkowski, MD, Kristine M Nacion, MPH, Justin B Mahida, MD, Jennifer N Cooper, PhD, MS, R Lawrence Moss, MD, FACS, Katherine J Deans, MD, MHSc, FACS

BACKGROUND: For decades, urgent operation has been considered the only appropriate management of acute appendicitis in children. The purpose of this study was to investigate the feasibility of nonoperative management of uncomplicated acute appendicitis in children.

STUDY DESIGN: A prospective nonrandomized clinical trial of children with uncomplicated acute appendicitis comparing nonoperative management with urgent appendectomy was performed. The primary result was 30-day success rate of nonoperative management. Secondary outcomes included comparisons of disability days, missed school days, hospital length of stay, and measures of quality of life and health care satisfaction.

RESULTS: Seventy-seven patients were enrolled during October 2012 to October 2013; 30 chose nonoperative management and 47 chose surgery. There were no significant differences in demographic or clinical characteristics. The immediate and 30-day success rates of nonoperative management were 93% (28 of 30) and 90% (27 of 30). There was no evidence of progression of appendicitis to rupture at the time of surgery in the 3 patients for whom nonoperative management failed. Compared with the surgery group, the nonoperative group had fewer disability days (3 vs 17 days; \( p < 0.0001 \)), returned to school more quickly (3 vs 5 days; \( p = 0.008 \)), and exhibited higher quality of life scores in both the child (93 vs 88; \( p = 0.01 \)) and the parent (96 vs 90; \( p = 0.03 \)), but incurred a longer length of stay (38 vs 20 hours; \( p < 0.0001 \)).

CONCLUSIONS: Nonoperative management of uncomplicated acute appendicitis in children is feasible, with a high 30-day success rate and short-term benefits that include quicker recovery and improved quality of life scores. Additional follow-up will allow for determination of longer-term success rate, safety, and cost effectiveness. (J Am Coll Surg 2014;219:272–279. © 2014 by the American College of Surgeons)
Several recent European randomized controlled trials suggest that therapy with antibiotics alone is a safe treatment option for appendicitis.\(^7\)\(^–\)\(^11\) However, these studies primarily enrolled adults. Data in pediatric appendicitis are promising but limited to 1 international retrospective study of just 16 patients, which reported an 81% 1-year success rate of nonoperative management in children with nonperforated appendicitis.\(^7\)

Although appendectomy is curative, it exposes children to the risks of anesthesia and surgery. In addition, it is associated with missed school, activity restriction, and alteration of daily life for the child and family. Given an option to avoid surgery, many families might choose nonoperative management. The objective of this study was to determine the feasibility of a nonoperative management strategy for uncomplicated acute appendicitis in children.

**METHODS**

**Study design**

This is an ongoing prospective nonrandomized clinical trial comparing nonoperative management with urgent appendectomy in children with acute appendicitis. Patients presenting to our hospital meeting the following criteria were eligible for enrollment: age 7 to 17 years; ≤48 hours of abdominal pain; white blood cell count <18,000 cells/μL; radiographic evidence based on final radiologic interpretation of nonruptured acute appendicitis on either ultrasound or CT with an appendiceal diameter ≤1.1 cm without phlegmon, abscess, or fecalith; and evaluation by a surgeon confirming clinical suspicion of acute appendicitis. Exclusion criteria include a positive pregnancy test, diffuse peritonitis on clinical examination, or a history of chronic intermittent abdominal pain. Families of eligible patients are counseled on each treatment option and then allowed to choose either nonoperative management (nonoperative group) or routine surgical management (surgery group). To minimize selection bias, all children meeting the inclusion criteria were evaluated by 1 of 3 trained physicians to establish eligibility and perform trial enrollment. This report presents our planned 30-day analysis to assess the feasibility of a nonoperative management strategy for uncomplicated appendicitis in children. A subsequent analysis to evaluate success rate, safety, and cost effectiveness at 1-year follow-up is planned.

**Treatment arms**

Nonoperative management consists of hospital admission with a minimum of 24 hours of IV antibiotics (ie, piperacillin-tazobactam or ciprofloxacin/metronidazole if penicillin allergic) and observation. Pain medicine is administered as needed. Diet is advanced after a minimum of 12 hours npo and only when clinical improvement (ie, decreased pain or tenderness) is recognized. Patients are switched to oral antibiotics (ie, amoxicillin-clavulanate or ciprofloxacin/metronidazole if penicillin allergic) when they are tolerating a regular diet. At least 1 dose of oral medication is administered in the hospital to ensure tolerance. Oral antibiotics are prescribed to complete a total course of 10 days (including the duration of IV antibiotics). Evidence of clinical worsening, such as increased pain or progressive systemic signs of sepsis or failure to demonstrate any clinical improvement (eg, decreased tenderness, resolution of fever, decreased pain, or resolution of nausea or emesis) within 24 hours of antibiotics, is deemed a failure of nonoperative management and prompts conversion to surgical therapy with laparoscopic appendectomy. Any patient managed nonoperatively that returns after discharge with abdominal pain and has a clinical evaluation consistent with appendicitis undergoes urgent laparoscopic appendectomy. Phone or in-person follow-up is conducted at 2 to 5 days, 10 to 14 days, and 30 days after discharge.

Surgical management consists of hospital admission with initiation of IV antibiotics and urgent laparoscopic appendectomy within 12 hours of admission. Postoperatively, antibiotics are discontinued, diet is advanced, and patients are usually discharged within 24 hours. Phone or in-person follow-up is conducted at 30 days.

**Outcomes**

The primary result is the success rate of nonoperative management, defined as the percent of patients treated nonoperatively who do not undergo an appendectomy. Two analyses of this result are planned. The first analysis is at 30 days to assess feasibility and initial safety, and the second is at 1 year to determine success rate, safety, and cost effectiveness. Secondary outcomes include hospital length of stay, disability days (reported as days to return to normal activity for the child and as days to return to normal schedule for the parent), missed school days, and quality of life measures at 30 days. Return to normal activity was defined as the child returning to all of their activities, including participation in physical education, recess, sports, and other afterschool activities. Return to normal schedule was defined as the parent resuming their normal full schedule at work and/or home. The Quality of Life measure examined in this study was the score on the PedsQL survey, developed by Dr James W Varni.\(^12\)\(^–\)\(^17\) The PedsQL Quality of Life Inventory: Child and Parent Report questionnaires were given to the subject and parent at the 30-day follow-up.\(^12\)\(^–\)\(^17\) In addition, the PedsQL Healthcare Satisfaction Generic Module: Parent Report was completed by the parent at 30 days.\(^18\)
Statistical analysis

Sample size was calculated on the success rate of nonoperative management at 30 days. Based on an expected success rate of 88% at 30 days, 28 patients treated nonoperatively are needed to have a 95% CI with a lower limit of 70%, based on the exact binomial distribution.19,20 This lower limit of 70% was chosen because it was considered a clinically acceptable success rate to offer nonoperative management to patients. To allow for dropout of a small number of patients, we planned to enroll 30 patients into the nonoperative treatment arm. Assuming 40% of eligible patients would choose nonoperative management, a total of 75 patients would need to be enrolled to obtain the needed number of patients choosing nonoperative management.

Continuous variables were described with means and standard deviations or medians and interquartile ranges and compared between treatment groups using t-tests or Mann-Whitney U tests. Categorical variables were described using frequencies and percentages and compared between treatment groups using chi-square tests or Fisher’s exact tests. Quality of life and health care satisfaction scores in the 30-day period after hospitalization were compared between treatment groups using the Mann-Whitney U test. All tests were 2-sided and p < 0.05 was considered statistically significant. SAS software (version 9.3, SAS Institute) was used for all statistical analyses.

This study was approved by our Institutional Review Board and was registered with ClinicalTrials.gov. All participants provided written informed consent.

RESULTS

Characteristic of study groups

Seventy-seven patients were enrolled; 30 patients chose nonoperative management and 47 chose surgery (Fig. 1). There were no significant differences in demographic characteristics, duration of pain, presenting symptoms, method of diagnosis, or white blood cell counts (Table 1). Within the surgery group, pathology demonstrated complicated appendicitis in 13% (n = 6 with 2 gangrenous and 4 perforated) and no appendicitis in 4% (n = 2 with 1 normal and 1 with granulomas).

Figure 1. Study flow diagram.
Primary outcomes: 30-day success rate of nonoperative management

The immediate and 30-day success rates of nonoperative management were 93% (28 of 30; 95% CI, 78–99) and 90% (27 of 30; 95% CI, 79–100). Of the 3 failures, 2 patients underwent laparoscopic appendectomy during the initial admission because of insufficient clinical improvement. Pathology revealed acute appendicitis in 1 patient and appendicitis secondary to a carcinoid tumor in the other. The third patient presented with recurrent abdominal pain 1 day after being discharged, had imaging consistent with early appendicitis, and underwent laparoscopic appendectomy; however, pathology showed a normal appendix with reactive lymph nodes. No patients in whom nonoperative management failed within 30 days exhibited progression of their appendicitis to rupture or gangrene at the time of appendectomy.

Secondary outcomes: comparison of 30-day outcomes between groups

Table 2 displays 30-day outcomes comparisons between the groups. Patients choosing nonoperative management had a considerably shorter time to return to normal activities and fewer missed school days. Compared with the surgery group, hospital length of stay was significantly longer in the nonoperative group (median 38 hours [interquartile range 31 to 42 hours] vs median 20 hours [interquartile range 16 to 34 hours]; p < 0.0001). Postoperative emergency department visits in the nonoperative group were for reports of abdominal pain; in the surgery group, emergency department visits were related to wound complications.

Quality of life and health care satisfaction scores at 30-day follow-up are shown in Table 3. Compared with patients in the surgery group, quality of life scores from both the child and parent were considerably higher in patients managed nonoperatively. Parental satisfaction with care was equally high in both groups at 30-day follow-up.

DISCUSSION

This study is the first prospective trial of a nonoperative management strategy for acute appendicitis in the United States and is the first in children internationally. Our results suggest that nonoperative management of acute appendicitis in children is feasible, with immediate and 30-day success rates of 93% and 90%, respectively. Patients managed nonoperatively had a more rapid return to normal activities, fewer missed school days, and higher quality of life scores at 30 days post hospitalization. In addition, in patients for whom nonoperative management failed, either initially or delayed, there was no progression to rupture at the time of appendectomy.

Nonoperative management of appendicitis has recently emerged as a viable treatment alternative to surgery and is being used increasingly in adults. There have been several randomized controlled studies comparing appendectomy with antibiotics in adult patients with...
Appendicitis. A meta-analysis of these studies demonstrated that nonoperative management had a pooled success rate of 63% at 1 year, with considerably lower risks of complications and no difference in the risk of developing complicated appendicitis. This meta-analysis concluded that nonoperative management of appendicitis is a safe initial treatment. Several hospitals in Europe have adopted it as their initial therapy with appendectomy reserved for medical failure. However, these results might not be generalizable to children because these studies did not include children and they had variable inclusion criteria. Many of these studies enrolled all patients with appendicitis regardless of length of symptoms, imaging findings, or suspicion of more advanced or complicated disease. Clinical factors associated with a higher likelihood of failure of nonoperative management include the presence of a fecalith or fluid collection on imaging and an appendiceal diameter >1.1 cm. Therefore, to minimize the risk of harm in our study, we excluded patients with these characteristics. Our 30-day success rate of 90% is higher than rates reported in most of the adult studies. However, it is similar to the 30-day success rate of 88% reported in the adult trial that specifically attempted to enroll patients with uncomplicated appendicitis. In addition, our 30-day results are consistent with the initial success rate of 94% reported by Abes and colleagues in their retrospective study of nonoperative management in children with nonperforated appendicitis.

Importantly, the recent adult trials of nonoperative management of appendicitis did not demonstrate an increased risk of perforated appendicitis developing in patients managed nonoperatively. Our early results are consistent with the results reported in the adult trials. Within the surgery group in our study, 6 patients had complicated appendicitis at the time of appendectomy, with 4 having perforated appendicitis. However, no patient in whom nonoperative management failed within 30 days had progression of appendicitis to complicated appendicitis at the time of appendectomy. In addition, in the patient with a carcinoid tumor, symptoms did not improve with antibiotics alone and the patient underwent appendectomy within 24 hours of admission. This rare case highlights the importance of in-hospital monitoring for clinical improvement as part of a nonoperative treatment strategy. During the initial hospitalization, the lack of improvement of this patient’s symptoms was promptly recognized and an appendectomy was performed without disease progression.

The effects of medical interventions on patient-centered outcomes, such as disability days, quality of life, and health care satisfaction, are being assessed more frequently in pediatric clinical trials. Incorporation of these measures as either primary or secondary outcomes contributes to the larger body of knowledge pertaining to the impact of medical interventions on childhood adjustment. In our study, patients managed nonoperatively had fewer disability days with fewer missed school days and a more rapid return to normal activities, including organized events and sports. In fact, most children managed nonoperatively returned to both school and extracurricular activities within 1 day.

### Table 2. Comparison of Outcomes at 30-Day Follow-Up

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Nonoperative management (n = 28)</th>
<th>Surgery (n = 38)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay, h, median (IQR)</td>
<td>38.0 (31.0–42.0)</td>
<td>20.0 (16.0–34.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Days to return to normal activities, median (IQR)</td>
<td>3.0 (2.5–6.5)</td>
<td>16.5 (9.0–21.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Days of school missed, median (IQR)</td>
<td>3.0 (2.0–5.0)</td>
<td>5.0 (3.0–6.0)</td>
<td>0.008</td>
</tr>
<tr>
<td>Days for guardian to return to normal schedule, median (IQR)</td>
<td>2.0 (1.0–3.0)</td>
<td>3.0 (1.0–5.0)</td>
<td>0.12</td>
</tr>
<tr>
<td>Fevers, n (%)</td>
<td>2 (7.1)</td>
<td>4 (10.5)</td>
<td>1.00</td>
</tr>
<tr>
<td>Abdominal pain, n (%)</td>
<td>6 (21.4)</td>
<td>12 (31.6)</td>
<td>0.36</td>
</tr>
<tr>
<td>Nausea, n (%)</td>
<td>1 (3.6)</td>
<td>3 (7.9)</td>
<td>0.63</td>
</tr>
<tr>
<td>Vomiting, n (%)</td>
<td>3 (10.7)</td>
<td>3 (7.9)</td>
<td>0.69</td>
</tr>
<tr>
<td>Patients with an ED visit at 30 d, n (%)</td>
<td>2 (7.14)</td>
<td>4 (10.5)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*Data are presented as medians and interquartile ranges. IQR, interquartile range.

### Table 3. Quality of Life and Health Care Satisfaction Between Nonoperative and Operative Groups

<table>
<thead>
<tr>
<th>30 Days after hospitalization</th>
<th>Nonoperative management (n = 28)</th>
<th>Surgery (n = 38)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child QOL questionnaire</td>
<td>93.0 (87.0–96.7)</td>
<td>87.5 (81.5–93.5)</td>
<td>0.011</td>
</tr>
<tr>
<td>Parent proxy for child QOL questionnaire</td>
<td>95.7 (90.8–98.9)</td>
<td>89.7 (82.6–95.7)</td>
<td>0.026</td>
</tr>
<tr>
<td>Parent healthcare satisfaction</td>
<td>99.0 (95.8–100.0)</td>
<td>99.0 (95.9–100.0)</td>
<td>0.721</td>
</tr>
</tbody>
</table>

*Data are presented as medians and interquartile ranges. QOL, quality of life.
after hospital discharge. Compared with appendectomy, nonoperative management of appendicitis was less disruptive to the lives of the patients and their families. The importance of this quicker resumption of normal activities to the patient and their families was reflected in the higher quality of life scores reported by both the children and parents 30 days after hospitalization. Based on studies of healthy children and children with acute and chronic health conditions, the minimal clinically important differences in PedsQL scores are 4.4 on the child report and 4.5 on the parent report. These minimal clinically important differences represent the smallest differences in scores that patients perceive to be beneficial and that would mandate a change in the patient’s management. In our study, patients who chose nonoperative management had higher PedsQL scores that were both statistically and clinically significant.

Several intra-abdominal infections, previously treated with urgent operations, are now successfully managed with initial antibiotic therapy alone. For example, diverticulitis has evolved into a medically managed disease, with surgery reserved for patients in whom medical therapy fails. In addition, similar transitions to primarily medical management have occurred with intra-abdominal abscesses from Crohn’s disease and acute supplicative salpingitis. During the last 20 years, appendicitis has also evolved to incorporate alternative treatment strategies based on severity of illness. Patients with perforated appendicitis with abscesses are now often managed nonoperatively with radiographic-guided catheter drainage of intra-abdominal abscesses and prolonged antibiotics. Investigators are now also reconsidering the need for an interval appendectomy in these severe cases. Our current study attempts to explore medical options in the management of appendicitis. Although appendectomy is curative, perioperative complications occur in 8.7% to 11.1% of patients, and recovery from an uncomplicated appendectomy might require children to miss up to a week of school and their caregiver to potentially miss equal amounts of work. A successful nonoperative treatment strategy for early appendicitis can markedly decrease the number of appendectomies performed, thereby limiting the number of children and families exposed to the risks and stress associated with surgery.

We chose to perform a nonrandomized prospective clinical trial based on patient choice because we believe that the success of each treatment option partially depends on which outcomes are most important to the patient and their family. For example, although initial nonoperative management of early appendicitis might be safe for most patients, appendectomy might be a better treatment option for patients who live in remote areas or for families who are so fearful of a recurrence that they are likely to return to the emergency department every time abdominal pain develops in their child. For these patients, the risk of postoperative complications might be perceived as minor compared with the benefit of a curative appendectomy. In contrast, for families who are averse to surgery, initial nonoperative therapy might be the least stressful and most appealing choice because it can eliminate the need for an operation and its inherent risks and expedite a quicker return to activities. For these reasons, we opted to allow eligible patients and their families to choose between surgery and nonoperative management rather than randomize patients to 1 of the 2 treatment groups.

One potential limitation of performing a patient-choice trial is the possibility for selection bias. In clinical practice, both the surgeon’s opinions and specific patient characteristics can affect which treatments are chosen. These represent 2 potential sources of bias in a patient-choice trial. With surgeon bias, the opinions of the consulting surgeon on each treatment can influence the patient and family to choose a particular treatment option. Although, it is not possible to entirely control for this bias outside of a randomized controlled trial design, we attempted to minimize selection bias introduced by the medical team by using a standardized scripted consenting process with only a few trained physicians performing trial enrollment. The second possibility for bias is that a specific patient characteristic (eg, sex) might affect the treatment choice. To assess for bias based on underlying patient characteristics, we compared the groups for differences in important demographic and clinical variables (Table 1) and did not identify any significant differences. It should also be noted that, compared with a randomized controlled trial, the patient-choice trial can allow for enrollment of a more diverse group of “research subjects” who more accurately reflect the overall patient population. One potential reason patients/families refuse to participate in a randomized controlled trial is because they cannot choose the treatment; by offering choice and not randomizing to a treatment, these families might be more inclined to participate in the study. This potential advantage of the patient-choice design is supported by the high percentage of eligible patients that agreed to enroll in our study.

CONCLUSIONS

This study of a nonoperative management strategy for uncomplicated acute appendicitis demonstrates a high early success rate and improved patient-centered outcomes in patients managed nonoperatively. These results support nonoperative management of appendicitis as a...
viable treatment option for children with acute appendicitis. Additional enrollment and follow-up will allow us to determine success rate, safety, and cost effectiveness at 1 year and throughout childhood.

Author Contributions
Study conception and design: Minneci, Sulkowski, Nacion, Cooper, Moss, Deans
Acquisition of data: Minneci, Sulkowski, Nacion, Mahida, Deans
Analysis and interpretation of data: Minneci, Sulkowski, Nacion, Mahida, Cooper, Moss, Deans
Drafting of manuscript: Sulkowski, Nacion, Cooper
Critical revision: Minneci, Moss, Deans

REFERENCES

33. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. Med Care 2001;39:800–812.