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High failure rate of nonoperative management of acute appendicitis with an appendicolith in children

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ABSTRACT

Background: The purpose of this study was to investigate the feasibility of nonoperative management of acute appendicitis in children with an appendicolith identified on preoperative imaging.
Study design: We performed a prospective nonrandomized trial of nonoperative management of uncomplicated acute appendicitis with an appendicolith in children aged 7 to 17 years. The primary outcome was the failure rate of nonoperative management, defined as having undergone an appendectomy. Early termination was set to occur if the lower limit of the 95% confidence interval of the failure rate was greater than 20% at 30 days or 30% at 1 year.
Results: Recruitment for this study was halted after enrollment of 14 patients (N = 5 nonoperative; N = 9 surgery). The failure rate of nonoperative management was 60% (3/5) at a median follow-up of 4.7 months (IQR 1.0–7.6) with a 95% CI of 23%–88%. None of the three patients that failed nonoperative management had complicated appendicitis at the time of appendectomy, while six out of nine patients who chose surgery had complicated appendicitis (0/3 vs. 6/9, p = 0.18). The trial was stopped for concerns over patient safety.
Conclusions: Nonoperative management of acute appendicitis with an appendicolith in children resulted in an unacceptably high failure rate.

Appendectomy for uncomplicated acute appendicitis is an invasive procedure requiring general anesthesia with associated perioperative risks and postoperative pain and disability. In comparison, previous studies demonstrate that nonoperative management of appendicitis in children may be associated with fewer days of disability following treatment, fewer posttreatment complications, and lower cost of care [1,2]. However, in selecting nonoperative treatment, the patient and family accept a risk of treatment failure, which is associated with a higher cost of care and more days of disability.

Among studies comparing patients undergoing nonoperative management versus surgery, nonoperative management fails in 19%–40% of patients [1–6]. Studies which used more conservative inclusion criteria, such as lower white blood cell count thresholds, shorter duration of pain prior to presentation, and absence of phlegmon or abscess on imaging, report lower failure rates of nonoperative management [1–4]. Identifying factors associated with failure of nonoperative management is important to allow for better patient selection to minimize potential harm.

It has been suggested that the presence of an appendicolith (a stone-like piece of stool, also commonly referred to as a fecalith) increases the risk of nonoperative treatment failure in patients with suspected uncomplicated acute appendicitis. The objective of this study was to assess the feasibility of nonoperative management of acute uncomplicated appendicitis in children with an appendicolith identified on preoperative imaging.

1. Methods

1.1. Study design

This was a prospective nonrandomized clinical trial comparing nonoperative management to urgent appendectomy in children with acute appendicitis with an appendicolith. Patients presenting with appendicitis were screened for enrollment from July 2014 through March 2015. The inclusion criteria were: patients aged 7 to 17 years, abdominal pain for less than or equal to 48 h, leukocyte count less than 18,000 cells/μL, clinical history and examination consistent with acute appendicitis as determined by a surgeon, and radiographic evidence of nonruptured acute appendicitis on ultrasound (US) or computed tomography (CT) with a maximum appendiceal diameter less than or equal to 1.1 cm with an appendicolith but without phlegmon

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or abscess as determined by the radiologist's reading. The age range was limited to patients ≥7 years of age to ensure adequate communication skills to relay changes in clinical symptoms and to <18 years of age to restrict this study to pediatric patients. Exclusion criteria were findings of diffuse peritonitis, positive urine pregnancy test, history of chronic intermittent abdominal pain, or C-reactive protein (CRP) greater than 4 mg/dL (if obtained).

Patients meeting these eligibility criteria were approached for enrollment. Prior to offering enrollment, patients were evaluated by one of two trained physicians to confirm eligibility from the standpoint of history and examination. This confirmation was performed to minimize selection bias. Enrolled patients and families were educated on both nonoperative management (nonoperative group) and urgent appendectomy (surgery group). Patients and families then elected one of the two treatment options. Study data were maintained using the Research Electronic Data Capture (REDCap) tool [7].

1.2. Treatment Arms

Nonoperative management consisted of admission to the surgical ward and administration of intravenous piperacillin-tazobactam (ciprofloxacin and metronidazole if penicillin allergic) for a minimum of 24 h, paired with serial abdominal examinations. Patients were kept nil per os (NPO) for a minimum of 12 h. Patients showing improvement (defined as decreased pain and tenderness) were advanced on their diet. Patients who continued to show improvement and were tolerating a regular diet at 24 h after initiation of IV antibiotics were given a trial of amoxicillin–clavulanate (oral ciprofloxacin and metronidazole, if penicillin allergic) while in the hospital. Patients who tolerated the trial of oral antibiotics were then discharged to complete a 7 day course of antibiotics (including the IV therapy). Conversely, patients who worsened clinically (increasing pain or tenderness, or showing new or persistent signs of systemic inflammatory response, or persistent nausea or emesis) were deemed to have experienced failure of nonoperative management. All patients who had failure of nonoperative management underwent urgent appendectomy. Patients previously treated nonoperatively who returned to the hospital with recurrent appendicitis underwent urgent appendectomy. The planned follow-up periods were at 2–5 days, 10–14 days, 30 days, 6 months and 1 year after discharge.

Patients and families choosing primary surgical management were admitted to the surgical ward, given intravenous piperacillin–tazobactam (or ciprofloxacin and metronidazole, if penicillin allergic) and underwent urgent appendectomy. The planned follow-up periods for this cohort were at 30 days, 6 months and 1 year after discharge.

1.3. Outcomes

The primary outcome was the percent of patients who were successfully managed nonoperatively with success defined as not undergoing appendectomy by one year after discharge. Secondary outcomes included the percent of patients found to have complicated appendicitis (gangrenous or perforated) on pathologic examination.

1.4. Statistical analysis

Sample size was calculated on the anticipated success of nonoperative management at 30 days. Assuming a 30-day success rate of nonoperative management of 80% [1,8], 40 patients were needed in the nonoperative arm to have a lower limit of the 95% confidence interval of 65% based on the exact binomial distribution [9]. Investigators established this to be the lowest clinically acceptable success rate to warrant offering nonoperative management to patients. As an additional safety measure, the 30-day and 1-year success rates were calculated after every 5 patients who selected nonoperative management reached the respective time point. It was decided a priori that study enrollment would be stopped if the lower 95% confidence limit of the failure rate exceeded 20% at 30 days or 30% at 1 year.

Continuous variables were described with medians and interquartile ranges (IQRs) and compared between groups using Mann–Whitney U tests. Categorical variables were described using frequencies and percentages and compared between groups using Fisher exact tests or chi-square tests. Confidence intervals for estimated proportions were calculated using the adjusted Wald method [10]. All tests were 2-sided and a cutoff of $p < 0.05$ was used to determine statistical significance. All statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC). This study was approved by our Institutional Review Board. The legal guardians of each participant provided written informed consent and children of at least 9 years of age provided written informed assent. Patients and guardians did not receive any remuneration for participation in the study, but the legal guardian did receive a $20 gift card for completing follow-up surveys at the 30 day, 6 month, and 1 year time points. This trial is registered with clinicaltrials.gov (NCT02189668).

2. Results

Over the study period, 14 patients met inclusion criteria and were enrolled; 5 chose nonoperative management and 9 chose surgery. There were no significant differences in demographic characteristics, duration of pain, presenting symptoms, method of diagnosis, or white blood cell counts (Table 1).

Recruitment for this study was halted after the enrollment of 14 patients, as the failure rate of nonoperative management was 60% (N = 3, 95% CI 23%–88%) at a median follow-up of 4.7 months (IQR 1.0–7.6). Two of the patients who elected nonoperative management experienced failure of the treatment prior to hospital discharge. Both patients developed increased abdominal pain and tenderness and per protocol were considered failures of nonoperative management and underwent appendectomy. Both patients were found to have acute appendicitis on pathology. The third patient who experienced failure of nonoperative management had a recurrence of appendicitis 8 months after enrollment and was found to have acute appendicitis on pathology. In addition, the rate of complicated appendicitis in the surgery group

Table 1
Baseline demographic and clinical characteristics for all enrolled patients by treatment decision (N = 14).

Characteristic	Nonoperative group (N = 5) Median (IQR) or N (%)	Surgery group (N = 9) Median (IQR) or N (%)	P-value
Age, years	14 (13–14)	11 (9–15)	0.36
Male	1 (20)	5 (56)	0.30
White	2 (40)	8 (89)	0.09
Hispanic	0 (0)	2 (22)	0.51
Transferred from another institution	2 (40)	3 (33)	1.00
More than one language spoken in the home	0 (0)	2 (22)	0.51
Insurance status			0.44
Private	4 (80)	4 (44)	
Medicaid	1 (20)	3 (33)	
No insurance	0 (0)	2 (22)	
Complaints on initial presentation			
Duration of abdominal pain, h	18 (10–24)	13 (12–24)	1.00
Fever	2 (40)	4 (44.4)	1.00
Vomiting	4 (80)	7 (78)	1.00
Diarrhea	2 (40)	0 (0)	0.11
Ultrasound	4 (80)	6 (67)	1.00
CT scan	1 (20)	3 (33)	1.00
White blood cell count, 1000 cells/μL	13.8 (9.4–16.0)	14.3 (13.8–14.9)	0.69

Reported as frequency (percent) for categorical variables and median (interquartile range) for continuous variables. CT: Computed tomography.