Journal of Pediatric Surgery 51 (2016) 111–116

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jpedsurg

Nonoperative treatment of acute appendicitis in children: A feasibility study☆,☆☆

Joseph Hartwich, Francois I. Luks *, Debra Watson-Smith, Arlet G. Kurkchubasche, Christopher S. Muratore, Hale E. Wills, Thomas F. Tracy Jr.

Division of Pediatric Surgery Hasbro Children's Hospital and Alpert Medical School of Brown University, Providence, RI

ARTICLE INFO

Article history:
Received 29 September 2015
Accepted 7 October 2015

Key words:
Appendicitis
Nonoperative treatment
Appendectomy
Antibiotics
Cost-utility analysis

ABSTRACT

Purpose: Nonoperative treatment of acute appendicitis appears to be feasible in adults. It is unclear whether the same is true for children.

Methods: Children 5–18 years with <48 h symptoms of acute appendicitis were offered nonoperative treatment: 2 doses of piperacillin IV, then ampicillin/clavulanate ×1 week. Treatment failure (worsening on therapy) and recurrence (after completion of therapy) were noted. Patients who declined enrollment were asked to participate as controls. Cost–utility analysis was performed using Pediatric Quality of Life Scale (PedsQL®) to calculate quality-adjusted life month (QALM) for study and control patients.

Results: Twenty-four patients agreed to undergo nonoperative management, and 50 acted as controls. At a mean follow-up of 14 months, three of the 24 failed on therapy, and 2/21 returned with recurrent appendicitis at 43 and 52 days, respectively. Two patients elected to undergo an interval appendectomy despite absence of symptoms. Appendectomy-free rate at one year was therefore 71% (C.I. 50–87%). No patient developed perforation or other complications. Cost–utility analysis shows a 0.007–0.03 QALM increase and a $1359 savings from $4130 to $2771 per nonoperatively treated patient.

Conclusion: Despite occasional late recurrences, antibiotic-only treatment of early appendicitis in children is feasible, safe, cost-effective and is experienced more favorably by patients and parents.

For over one hundred years surgical therapy has been the mainstay for treatment of acute appendicitis. This therapy has transformed a potentially fatal condition to a commonplace illness with a mortality rate close to zero. Most recent reports suggest that morbidity rates in children are approximately 2.7% in nonperforated and 16% in perforated appendicitis [1–4].

Nonoperative management of acute appendicitis is well described in adults [3,5–8]. This treatment is based on the premise that nonperforated and perforated appendicitis are physiologically different entities, rather than progression of disease. Using this rationale, it becomes reasonable to treat uncomplicated (nonperforated) appendicitis in a similar fashion to uncomplicated diverticulitis [7,9,10]. Furthermore, advances in imaging and diagnostic risk stratification have greatly improved the accuracy of the diagnosis of acute appendicitis without perforation [11–15]. Reported success rates of nonoperative management in adults have approached 90% in the short term and 75% overall, with no long term sequelae and minimal risk of perforation [6,8].

Initial nonoperative treatment of *perforated* appendicitis has been well reported in children, and has demonstrated equivalence in efficacy (if not always in cost). Nonsurgical treatment of early, uncomplicated appendicitis, however, had not been considered until very recently. Within the last 24 months, three small studies have attempted to emulate the adult experience with antibiotic-only treatment of acute appendicitis. Initial success ranged from 75% to 90%, but long-term data are lacking. In addition, these studies largely failed to find a statistically significant difference in overall cost when compared with operative management. This is likely owing to a combination of study design, variable duration of hospitalization and prolonged courses of intravenous antibiotics.

We report a single institution clinical trial in children aged 5–18 for nonoperative management of acute appendicitis. Inpatient intravenous antibiotic administration was limited to two doses of piperacillin-tazobactam (Zosyn®), followed by seven days of outpatient oral ampicillin-clavulanate (Augmentin®). Primary outcomes were progression to operative therapy and recurrence. Secondary outcomes included a cost–utility analysis and comparison with comparable patients with acute appendicitis who underwent conventional operative therapy.

☆ Level of evidence: II.

☆☆ Roles:
Concept of the study: JH, FIL, TFT.
Patient enrollment, study performance: JH, FIL, DWS, AGK, CSM, HEW, TFT.
Analysis of results: JH, DWS, FIL.
Manuscript preparation: JH, FIL.
Manuscript review and approval: JH, FIL, DWS, AGK, CSM, HEW, TFT.

* Corresponding author at: Division of Pediatric Surgery, Hasbro Children's Hospital, 2, Dudley Street, Suite 190, Providence, RI 02905. Tel.: +1 401 228 0556.
E-mail address: Francois_Luks@brown.edu (F.I. Luks).

http://dx.doi.org/10.1016/j.jpedsurg.2015.10.024
0022-3468/

1. Methods

The study was approved by the Institutional Review Board (IRB) of Hasbro Children's and Rhode Island Hospital. All children aged 5–18 years who presented to the Hasbro Children's Hospital Emergency Department with a clinical diagnosis of acute uncomplicated appendicitis were eligible for enrollment. Exclusion criteria included symptoms greater than 48 h, presence or suspicion of abscess on imaging, clinical suspicion of perforated appendicitis, significant comorbidities, inability (or unwillingness) to complete seven days of oral antibiotics, allergy to penicillin, and inability to return to the hospital in a timely fashion if symptoms recurred or persisted.

Patients who met inclusion criteria were offered to enroll in the study (nonoperative treatment of appendicitis). Patients and families who refused to undergo nonoperative treatment were asked to participate as controls (standard appendectomy, analysis of records and completion of a postdischarge questionnaire, see below).

Power analysis: The primary goal of the study was to determine the feasibility of nonoperative treatment in children, and to compare it with published rates in adults. A failure rate of nonoperative treatment >50% was considered undesirable; given an overall 75% success rate in adult studies (>300 patients), a success rate <50% represents a moderate-to-large effect size ($w = 0.4$); with uneven group sizes (study:control 1:2 ratio), this required 24–30 patients in the pediatric pilot group to detect a significant difference with 80% power (β).

Study patients were immediately given a dose of intravenous piperacillin-tazobactam (Zosyn®, Pfizer, New York, NY) at a dose of 100 mg/kg and admitted to the surgical ward for observation. Intravenous pain medication (morphine sulfate) was given as needed and diet was advanced *ad libitum*. Patients were given an additional dose of Zosyn® at 6–8 hours. If, at this time, patients were objectively better (afebrile, diminished abdominal pain, tolerating a diet), they were discharged to home with a one-week course of ampicillin-clavulanate (Augmentin®) at a dose of 50 mg/kg/d in three divided doses. Patients received a phone call 48 hours after discharge by a research nurse inquiring about overall clinical condition.

All patients who had clinical worsening or lack of improvement of symptoms within the first 8 hours, and those who had a recurrence of symptoms while taking oral antibiotics, were considered early failures and underwent appendectomy without additional imaging. Those who had a return of symptoms after the one-week antibiotic treatment period were considered recurrences and underwent imaging based on clinical symptoms and the judgment of the treating surgeon. If clinically and/or radiologically confirmed, they underwent appendectomy for appendicitis.

Patients who were successfully treated with antibiotics alone were seen in the office one month after discharge and all were offered an interval appendectomy approximately 2 months after initial appendicitis. Patients who underwent an appendectomy during the initial admission (controls, and patients who failed antibiotic therapy alone) were seen a month later as well. Patients and their parents were given a utility questionnaire at that time (see below). Patients who underwent delayed appendectomy (recurrence or interval appendectomy by choice) were seen in the office one month later and were given a second questionnaire. All patients were tracked for additional appendicitis-related hospital admissions or emergency room visits for a mean follow-up time of 14 months.

Cost–utility analysis was performed according to the decision tree in Fig. 1. The decision tree consists of mutually exclusive events and their observed incidence. In the control group (upfront appendectomy), the only possible nodes were "no complications" or "complications" following appendectomy. In the antibiotics group, the nodes included initial success/failure of the treatment (failure representing persistent or recurrent signs and symptoms while on antibiotics), recurrence (after completion of antibiotic treatment) and interval appendectomy (patient preference). Terminal nodes for all appendectomies were "no complications" or "complications."

Utility was derived from PedsQL® 4.0 Generic Core Scales questionnaires given to patients and their parents [16]. The PedsQL® questionnaire was licensed from the MAPI Research Trust, which holds the copyright. It consists of 23 items grouped into four domains: physical functioning (PF), emotional functioning (EF), social functioning (SF) and school functioning (SchF). Various age-appropriate versions of the questionnaire exist. For this study, patients older than 7 years were asked to complete the questionnaire (Child Report for children 8–12 years, Teen Report for children older than 12 years) within a

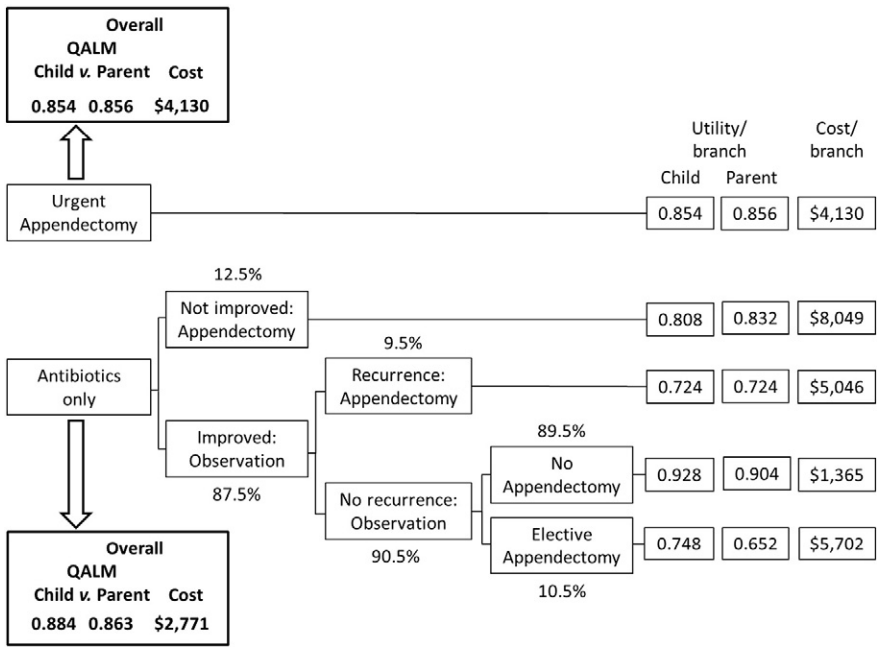

Fig. 1. Cost–utility analysis of treating acute appendicitis with antibiotics only or by urgent appendectomy (control group). Percentages above boxes reflect incidences found in this study. Utility and cost for each branch (possible outcome) from Tables 1 and 2, respectively. Overall utility and cost for both treatment options (bold boxes, left) are the product of the incidences of each node and their respective utility/branch and cost/branch (see text for details).