JAMA | Original Investigation

Association of Nonoperative Management Using Antibiotic Therapy vs Laparoscopic Appendectomy With Treatment Success and Disability Days in Children With Uncomplicated Appendicitis

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IMPORTANCE Nonoperative management with antibiotics alone has the potential to treat uncomplicated pediatric appendicitis with fewer disability days than surgery.

OBJECTIVE To determine the success rate of nonoperative management and compare differences in treatment-related disability, satisfaction, health-related quality of life, and complications between nonoperative management and surgery in children with uncomplicated appendicitis.

DESIGN, SETTING, AND PARTICIPANTS Multi-institutional nonrandomized controlled intervention study of 1068 children aged 7 through 17 years with uncomplicated appendicitis treated at 10 tertiary children's hospitals across 7 US states between May 2015 and October 2018 with 1-year follow-up through October 2019. Of the 1209 eligible patients approached, 1068 enrolled in the study.

INTERVENTIONS Patient and family selection of nonoperative management with antibiotics alone (nonoperative group, n = 370) or urgent (≤12 hours of admission) laparoscopic appendectomy (surgery group, n = 698).

MAIN OUTCOMES AND MEASURES The 2 primary outcomes assessed at 1 year were disability days, defined as the total number of days the child was not able to participate in all of his/her normal activities secondary to appendicitis-related care (expected difference, 5 days), and success rate of nonoperative management, defined as the proportion of patients initially managed nonoperatively who did not undergo appendectomy by 1 year (lowest acceptable success rate, ≥70%). Inverse probability of treatment weighting (IPTW) was used to adjust for differences between treatment groups for all outcome assessments.

RESULTS Among 1068 patients who were enrolled (median age, 12.4 years; 38% girls), 370 (35%) chose nonoperative management and 698 (65%) chose surgery. A total of 806 (75%) had complete follow-up: 284 (77%) in the nonoperative group; 522 (75%) in the surgery group. Patients in the nonoperative group were more often younger (median age, 12.3 years vs 12.5 years), Black (9.6% vs 4.9%) or other race (14.6% vs 8.7%), had caregivers with a bachelor's degree (29.8% vs 23.5%), and underwent diagnostic ultrasound (79.7% vs 74.5%). After IPTW, the success rate of nonoperative management at 1 year was 67.1% (96% CI, 61.5%-72.31%; $P = .86$). Nonoperative management was associated with significantly fewer patient disability days at 1 year than did surgery (adjusted mean, 6.6 vs 10.9 days; mean difference, −4.3 days (99% CI, −6.17 to −2.43; $P < .001$). Of 16 other prespecified secondary end points, 10 showed no significant difference.

CONCLUSION AND RELEVANCE Among children with uncomplicated appendicitis, an initial nonoperative management strategy with antibiotics alone had a success rate of 67.1% and, compared with urgent surgery, was associated with statistically significantly fewer disability days at 1 year. However, there was substantial loss to follow-up, the comparison with the prespecified threshold for an acceptable success rate of nonoperative management was not statistically significant, and the hypothesized difference in disability days was not met.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02271932

JAMA. doi:10.1001/jama.2020.10888
Published online July 27, 2020.

Editor's Note
Supplemental content

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Appendicitis is the most common indication for emergency abdominal surgery in both adults and children.[1] In the United States, more than 180 000 adults and 70 000 children undergo appendectomy annually.[2,3] Although curative, appendectomy is a major intra-abdominal procedure requiring general anesthesia with associated perioperative risks and postoperative pain and disability. Rates of perioperative complications after appendectomy for uncomplicated appendicitis range between 5% and 15%, with serious complications occurring in 1% to 7% of patients.[4-7] Recovery from an uncomplicated appendectomy is associated with a period of disability for both the patient and caregiver.[6,7]

Nonoperative management has been shown to be safe and efficacious in several clinical trials comparing appendectomy to antibiotics alone in adults.[7,8] In children, an increasing body of literature including prospective studies and meta-analyses also supports the safety and efficacy of nonoperative management of uncomplicated appendicitis.[3,6,9,10] The success rate of nonoperative management has been reported to be between 65% and 75% at 1 year with associated decreases in disability days, improved health-related quality of life (QOL), and high parental health care satisfaction.[6]

Currently, most children and adolescents with appendicitis are treated with an appendectomy. However, nonoperative management with antibiotics alone may be preferred by patients and families given its potential to treat the disease effectively with fewer negative effects on the child and family. The objective of this study was to determine the success rate of nonoperative management and compare differences in disability days, health-related QOL, medical/surgical complications, and satisfaction between nonoperative management and surgery across 10 midwestern children's hospitals in the United States.

Key Points

Question Among children with uncomplicated appendicitis, what is the success rate of an initial nonoperative management strategy with antibiotic therapy alone and is this approach associated with fewer disability days compared with an initial strategy of urgent laparoscopic surgery?

Findings In this nonrandomized controlled intervention study that used propensity score weighting and included 1068 children, 67.1% of the children who received initial nonoperative management with antibiotics alone did not require appendectomy by 1 year. Compared with a strategy of urgent surgery (≤12 hours of admission), initial management with antibiotics alone was significantly associated with fewer patient disability days at 1 year (6.6 days vs 10.9 days).

Meaning Among children with uncomplicated appendicitis, an initial nonoperative management strategy with antibiotics was successful for most children and, compared with urgent surgery, was associated with significantly fewer disability days at 1 year. However, the prespecified thresholds for success rate of nonoperative management and disability days were not met, and there were substantial missing data.

Methods

Study Overview

This was a prospective, nonrandomized, controlled, multiinstitutional study investigating a nonoperative management strategy for children with uncomplicated appendicitis across 10 children's hospitals participating in the Midwest Pediatric Surgery Consortium (MWPSC; http://www.mwpsc.org). All participating institutions are teaching hospitals. Patients and their families chose between nonoperative management with antibiotics alone (nonoperative group) or urgent laparoscopic appendectomy (surgery group).[11] The hypothesis was that nonoperative management would have a success rate of more than 75% and would be associated with fewer disability days and complications. Additionally, it was hypothesized that health-related QOL and health care satisfaction scores would not be significantly different between groups at 1 year follow-up. A more detailed description of the study design and methods has been previously published.[11] The study protocol and changes to the protocol are included in the online supplement (eTable 1 in Supplement 1). Institutional review board approval was obtained at each participating site, and written consent or assent (children ≥9 years of age) was obtained from all participants.

Multidisciplinary Group Involvement

As part of this Patient-Centered Outcomes Research Institute (PCORI)-funded project, a 44-member multidisciplinary team, including patients, families, pediatric surgeons, community pediatricians, emergency medicine physicians, nurses, patient educators, and payors, served as an integral part of the research team. The team members consistently asserted that families would have strong preferences for either nonoperative management or surgery, which would preclude their acceptance of randomization; therefore, a multi-institutional study with child-family choice of therapy was performed. The team members also identified treatment-associated disability, the success rate of nonoperative management, the risk of complicated appendicitis, and health-related QOL as the most important outcomes to assess in order to generate the information necessary to allow patients and families to make informed treatment decisions in clinical practice. As part of the study design process, the team members' opinions on acceptable thresholds for the success rate of nonoperative management and differences in disability days were collected during individual interviews. Subsequently, these were tallied, presented, and discussed during a group meeting to achieve consensus. Contributions of the individuals who participated in this group process are detailed in eTable 2 in Supplement 2.

Participants

Children aged 7 through 17 years diagnosed with uncomplicated appendicitis were screened for eligibility. Each site had a standardized algorithm for evaluating patients with suspected appendicitis, which included initial evaluation with an ultrasound unless the patient had an imaging study performed at an outside facility prior to presenting to the

emergency department. Inclusion criteria included all the following: (1) imaging-confirmed uncomplicated appendicitis by ultrasound, computed tomography (CT), or magnetic resonance imaging of an appendix with a diameter of 1.1 cm or less and no abscess, fecalith, or phlegmon; (2) a white blood cell count between 5000/μL and 18 000/μL; and (3) abdominal pain for less than 48 hours prior to the start of antibiotics. Exclusion criteria included any of the following: (1) a history of chronic intermittent abdominal pain, (2) diffuse peritonitis on physical examination, (3) a positive urine pregnancy test, or (4) communication difficulties (eg, severe developmental delay).[11] Race and ethnicity, as specified by the caregiver using fixed categories (**Table 1**), were collected to assess their association with treatment choice and outcomes.

Study Groups

After confirming eligibility and obtaining consent or assent, a physician-member of the research team used a standardized script and a 1-page decision aid (see eAppendix of the study protocol in Supplement 1) to present information on the 2 treatment options. After having their questions answered, the patient and family members chose either surgery or nonoperative management (**Figure**).

Surgery Group

Surgical management consisted of hospital admission with initiation of intravenous (IV) antibiotics (piperacillin-tazobactam or ciprofloxacin and metronidazole if penicillin allergic) and urgent laparoscopic appendectomy within 12 hours of admission. Postoperatively, antibiotics were discontinued, diet was advanced, and patients were discharged home when tolerating a regular diet. At discharge, all patients received standardized instructions related to resumption of activities.

Nonoperative Group

Nonoperative management consisted of hospital admission with a minimum of 24 hours of IV antibiotics (piperacillin-tazobactam, 2 g/0.25 g: if <40 kg, 300 mg piperacillin component/kg/d divided every 8 hours; if >40 kg, 3.375 g piperacillin-tazobactam every 6 hours; or if penicillin allergic, ciprofloxacin, 30 mg/kg/d divided every 8 hours up to 1200 mg/d and metronidazole, 30 mg/kg/d divided every 6 hours up to 500 mg per dose). Diet was advanced after a minimum of 12 hours and only when clinical improvement (decreased pain or tenderness) was recognized. Patients were switched to oral antibiotics (amoxicillin-clavulanate [45 mg/kg/d every 12 hours for those <14 years and 875 mg every 12 hours for those ≥14 years] or ciprofloxacin [30 mg/kg/d divided every 12 hours, maximum dose 1.5 g/d] and metronidazole [30 mg/kg/d divided every 6 hours], maximum dose, 500 mg, if penicillin allergic) when tolerating a regular diet (defined as consuming >50% of a meal similar to what they would eat at home). At least 1 dose was administered in the hospital to ensure tolerance. Patients were discharged home with a prescription for oral antibiotics to complete a total course of 7 days (inclusive of the IV antibiotics). Standardized discharge instructions allowed for resumption of activities as tolerated.

Failure of nonoperative management and crossover to appendectomy could occur in 2 situations during the initial admission: (1) did not improve after 24 hours of IV antibiotics: no clinical improvement (decreased tenderness, improvement in fever curve) or no symptomatic relief (decreased pain, resolution of nausea or vomiting, advancement of diet); or (2) clinical deterioration: worsening symptoms (increased abdominal pain) or evolving objective evidence of systemic signs of infection (increasing tachycardia, hypotension, persistent fever, or decreased mental status). In addition, any who returned after discharge with abdominal pain and had a clinical evaluation consistent with appendicitis, underwent urgent appendectomy.

Study Outcomes

There were 2 primary outcomes: disability days of the child at 1 year and success rate of nonoperative management at 1 year. Disability days were defined as the total number of days the child was not able to participate in all of his/her normal activities secondary to appendicitis-related care. Disability days and other patient-reported outcomes could only be evaluated for patients or caregivers who were successfully contacted and had completed the follow-up surveys at the specified time point (Figure). Success rate of nonoperative management was defined as the percent of patients treated nonoperatively who did not undergo an appendectomy within 1 year of enrollment. This outcome was evaluated for all children treated nonoperatively with information collected from follow-up visits and surveys, medical record review, or primary care provider follow-up calls where possible.

Secondary medical outcomes included the success rate of nonoperative management during the initial hospitalization; length of stay; rates of complicated appendicitis; and rates of treatment-related complications including in-hospital antibiotic adverse effects, unplanned emergency department visits, hospital readmission, and additional surgical or interventional procedures.[11] Secondary patient-reported outcomes included disability days of the child at 30 days and of the caregiver at 30 days and 1 year; health-related QOL at 30 days and 1 year (Pediatric Quality of Life [PedsQL Inventory] scale range, 0-100; higher scores indicate better QOL; minimal clinically important difference, ≥4)[12,13]; health care satisfaction at 30 days measured using the PedsQL 3.0 Healthcare Satisfaction Generic Module-Parent Report (scale range, 0-100; higher scores indicate greater satisfaction)[12-17]; satisfaction with the initial treatment decision at 30 days and 1 year were assessed using the Satisfaction with Decision Scale (scale range, 0-30; higher scores indicative of greater satisfaction).[18,19] Prespecified cost-effectiveness analyses were not performed as part of this PCORI-funded study.

Post hoc analyses performed included assessing associations between caregiver election to convert to surgery and the success rate of nonoperative management, and the negative appendectomy rate (based on histopathology demonstrating an appendix without abnormality) and the difference in treatment failure rates considering a negative appendectomy as a failure for surgery and undergoing appendectomy as a failure for nonoperative management.

Table 1. Patient and Clinical Characteristics

	Treatment group, No./total (%)		Absolute standardized difference[a]
	Nonoperative (n = 370)	Surgery (n = 698)	
Patient characteristics			
Age, y			
Mean (SD)	12.3 (2.8)	12.6 (2.8)	11.2
Median (IQR)	12.3 (10.0-14.6)	12.5 (10.5-14.9)	0.2
Sex			
Boys	229 (61.9)	436 (62.5)	1.2
Girls	141 (38.1)	262 (37.5)	1.2
Body mass index for age percentile, No.	263	444	
Mean (SD)	61.9 (31.7)	65.1 (31.2)	10.3
Median (IQR)	70.6 (34.5-91.4)	73.7 (39.8-93.1)	3.1
Race[b]			
White	276/364 (75.8)	599/693 (86.4)	27.3
Black	35/364 (9.6)	34/693 (4.9)	18.2
Other	53/364 (14.6)	60/693 (8.7)	18.5
Not reported or not documented	6	5	
Ethnicity[b]			
Not Hispanic or Latino	243/364 (66.4)	455/691 (65.9)	1.2
Other	86/364 (23.5)	163/691 (23.6)	0.3
Hispanic or Latino	37/364 (10.1)	73/691 (10.6)	1.5
Not reported or not documented	4	7	
Insurance			
Private	249/368 (67.7)	478/694 (68.8)	2.6
Medicaid	109/368 (29.6)	189/694 (27.2)	5.3
Other or no insurance	10/368 (2.7)	27/694 (3.9)	6.5
Not reported or not documented	2	4	
Clinical characteristics			
White blood cell count (×1000 cells), No.	369	696	
Mean (SD)	12.3 (3.2)	12.5 (3.1)	6.2
Median (IQR)	12.5 (10.3-14.9)	12.7 (10.3-15.0)	0.2
Presentation to ED			
6-11:59 AM	77/368 (20.9)	130/687 (18.9)	5.0
12-4:59 PM	91/368 (24.7)	160/687 (23.3)	3.3
5-10:59 PM	119/368 (32.3)	223/687 (32.5)	0.3
11 PM-5:59 AM	81/368 (22.0)	174/687 (25.3)	7.8
Not reported or not documented	2	11	
Duration of pain at ED presentation, h, No.	365	693	
Mean (SD)	18.6 (11.2)	18.4 (10.8)	2.6
Median (IQR)	16 (10-24)	18 (10-24)	2
Pain score (0-10 scale), No.	336	627	
Mean (SD)	5.0 (2.8)	5.0 (3.0)	2.4
Median (IQR)	5 (3-7)	6 (2-7)	1[a]
Symptoms at presentation			
Nausea	228 (61.6)	408 (58.5)	6.5
Emesis	158 (42.7)	317 (45.4)	5.5
Anorexia	168 (45.4)	302 (43.3)	4.3
Diarrhea	39 (10.5)	91 (13.0)	7.7
Fever	71 (19.2)	147 (21.1)	4.7
Imaging performed[c]			
Ultrasound	295 (79.7)	520 (74.5)	12.5
CT scan	102 (27.6)	226 (32.4)	10.5
CT and ultrasound performed	27 (7.3)	48 (6.9)	2.7

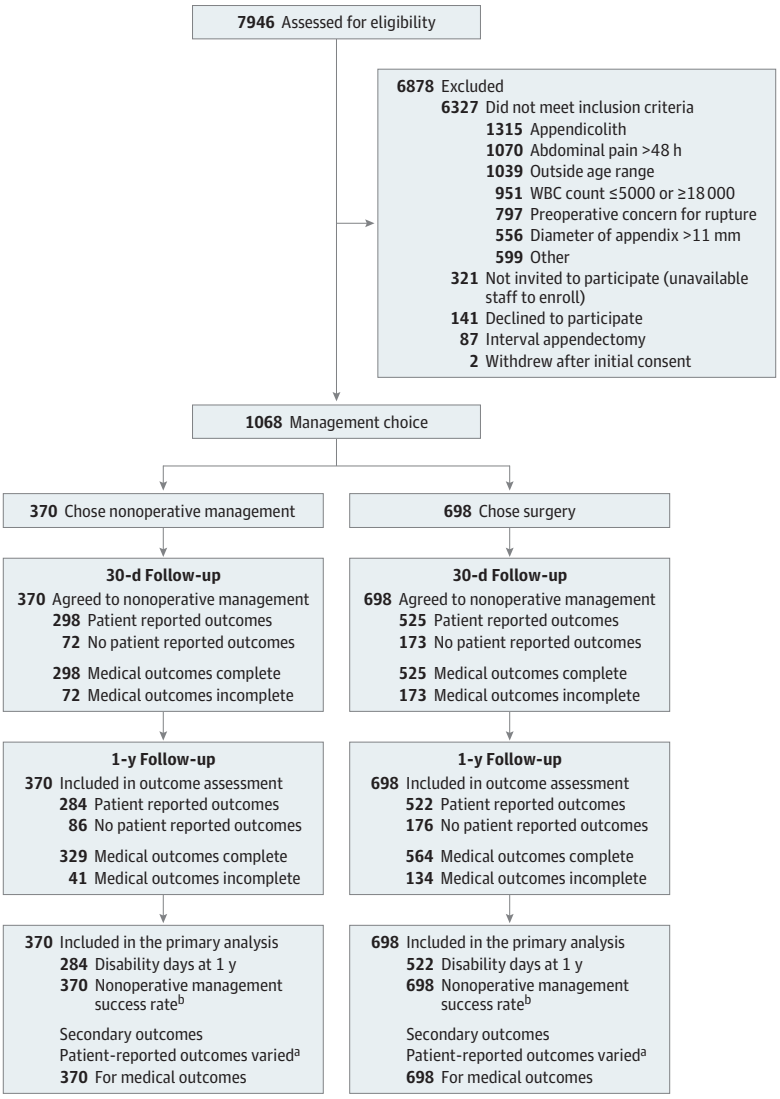
Abbreviations: CT, computed tomography; ED, emergency department; IQR, interquartile range.

[a] Absolute standardized difference is calculated as the absolute value of the difference in the means, medians, or difference in proportions between intervention groups in pooled standard deviations.

[b] Race/ethnicity were self-reported by the caregiver using surveys with the predefined categories listed in the table. Other includes Asian, American Indian, Alaskan Native, and biracial patients.

[c] Imaging performed includes studies performed at an outside facility prior to transfer in to 1 of the participating institutions and studies performed at one of the participating institutions.

Figure. Study Flow of Nonoperative Management and Surgery for Uncomplicated Appendicitis



[a] Sample sizes for secondary patient-reported outcomes vary based on availability of completed surveys for each measure.

[b] Although nonoperative management success rate can only be assessed in the nonoperative management group, the data from all 698 surgery group patients were used to perform the inverse probability of treatment weighting analysis for nonoperative management success rate.

Sample Size and Power Calculations

The overall study sample size was based on 2 primary outcomes, with the intervention considered a success by either end point. The sample size needed to assess the primary outcome of the 1-year success rate of nonoperative management was based on an expected success rate of greater than 75% derived from preliminary data, compared with the lowest desirable success rate of 70% based on subjective surgeon input.[6] The threshold success rate was set at 70% to accommodate the opinions of the surgeons at each site and to obtain complete surgical group participation from each site at the beginning of the study. In contrast, the team members (patients and their families, primary care physicians, nurses, emergency department physicians, and payors) favored a threshold success rate of 50%. For the outcome of disability days at 1 year, children enrolled in nonoperative management were expected to have 5 fewer disability days in the year following treatment (assuming a mean of 10 disability days [SD, 9.8 days]) than children who had initial surgery (assuming a mean of 15 disability days [SD, 7.7 days]) based on available preliminary data.[6] The threshold clinically important difference according to the group input was 3 days. The 2-sided type I error rate for the multiple primary end points was set to 5% at the design stage. The sample size was driven by the need to have adequate power (≥80%) for the success rate of nonoperative management; therefore, we allowed more of the overall type I error to be allocated to this outcome. More specifically, 4% 2-sided type I error (2% as a 1-sided test) was allocated to evaluate if the success rate of nonoperative management at 1 year was greater than 70% and 1% 2-sided type I error to test that there was an improvement of at least 5 days in disability days in the nonoperative group compared with the surgical group. Each primary outcome was evaluated relative to these levels. Under a group sequential design, with 1 interim analysis (for futility) and 1 final analysis and overall type I error (2 sided) of 5% (adjusted as described) and

approximately 10% loss to follow-up, a minimum of 364 nonoperatively treated patients were needed to achieve at least 80% power for each primary end point. With the proposed sample sizes (364 nonoperative and 544 surgery patients based on an expected choice rate for nonoperative management of 40%), more than 90% power was expected to detect the mean difference of 5 disability days.[11] During the first 18 months of enrollment, the choice rate for nonoperative management was 35%. Consequently, the overall study sample size was increased to allow for enrollment of the needed 364 patients for the nonoperative group.

An interim analysis was performed after 25% (n = 92) of the total of nonoperative patients who completed 1-year follow-up. Using the initial 246 participants enrolled, an initial set of inverse probability of treatment weights (IPTWs) was developed and used to perform an adjusted assessment for futility of both primary end points using the Lan-Demets[20] spending function approach with O'Brien-Fleming boundary for each primary end point. The interim analyses were reviewed by the data and safety monitoring board. No safety concerns were identified and criteria for futility for either primary outcome (*P* value boundary of 0.73 for success rate and *P* value boundary of >.99 for disability days) were not met; therefore, the study was allowed to enroll to completion.

Statistical Methods

Comparisons between pretreatment characteristics by treatment group, as initially chosen, were measured through the absolute standardized difference (ASD). Data for children and parents who were lost to follow-up or who withdrew from follow-up were included through the follow-up periods when available.

Summary statistics for outcomes, unadjusted for pretreatment covariates, are reported for comparison to adjusted estimates. Evaluation of study outcomes, primary and secondary, is made through regression model estimation, weighted by IPTW because treatment allocation was not randomized.[11,21-23] Stabilized inverse probability weights were used to mitigate the influence of very small estimated probabilities from the propensity score model.[24] The probability of treatment selection was modeled via logistic regression considering the variables listed in eTable 3 in Supplement 2 (including enrolling site) and using multiple imputation for missing covariate data (eTable 3 and supplemental text description of eMethods in Supplement 2).[25-28] Treatment was considered the method chosen at the time of study consent. Regression models were used to make final inference, which allowed for adjustment for any covariate that remained unbalanced after IPTW. Regression models considered the estimated IPTW and inference used robust sandwich-type standard errors, and the risk difference or mean difference was estimated through marginal standardization.[29,30]

Medical outcomes (including success rate of nonoperative management) were assessed using medical record review for all patients enrolled because of the high likelihood that these patients would be referred back to the treating hospital if additional appendicitis-related care were needed. As an additional analysis, medical outcomes for only the subset of participants who had complete follow-up (completed follow-up survey, successful review of PCP records, or known failure of nonoperative management prior to 1 year) are reported herein. For patient-reported outcomes (including disability days), measures were only available for those who completed follow-up surveys. For each outcome, the number of responses for each group is specified throughout. For secondary outcomes, *P* values and 95% CIs are presented at the nominal level (2-sided). Because of the potential for inflation of type I error due to multiple comparisons, findings for secondary end points should be considered exploratory.

Missing data were multiply imputed, by chained equations, for use in estimating the propensity score and subsequent IPTW analyses, rather than include a missing category for each covariate with missing data in models used to estimate the IPTW (eTable 3 and supplemental description in the eMethods section in Supplement 2). The majority of the missing data from the baseline characteristics were due to the personal preference of the patient-family to not answer questions.

Data management and analyses were performed using SAS software, version 9.4 (SAS Institute Inc), and analyses and imputation (through *mi impute chained*) was performed in Stata version 15.1 (StataCorp LLC). .

Results

Enrollment and Follow-up

Between May 1, 2015, and October 31, 2018, 1068 patients enrolled with 370 (35%) choosing nonoperative management and 698 (65%) choosing surgery (Figure). Overall, 19.3% of patients presenting with appendicitis met eligibility criteria, of which 79% (1209 of 1530) were approached to enroll in the study. The enrollment rate of eligible patients approached was 88% (1068 of 1209). The number of patients enrolled varied by site with a range of 15 to 260 patients enrolled. Overall, 126 surgeons performed appendectomies during the study across the 10 sites with median surgeon case volume of 4 (interquartile range [IQR], 2.8) for the duration of the study. The 30-day lost to follow-up rates in the surgery group for patient-reported outcomes was 25% (173 of 698) and for medical outcomes, 25% (173 of 698). At 1 year, they were 25% (176 of 698) and 19% (134 of 698) (Figure). Incomplete follow-up rates in the nonoperative management group for patient-reported and medical outcomes were both 19% (72 of 370) at 30 days. At 1 year, the loss to follow-up for patient-reported outcomes were 23% (86 of 370) and the medical outcomes, 11% (41 of 370) (Figure). For the primary outcomes, disability days at 1 year were analyzed in 75% (522 of 698) of the surgery group and 77% (284 of 370) of the nonoperative management group. The success rate of nonoperative management at 1 year was analyzed in all patients in the nonoperative group (Figure). eTable 4 in Supplement 2 shows a comparison of patients with complete and incomplete follow-up.

Demographics and Clinical Characteristics

The baseline demographics and clinical characteristics by treatment choice are shown in Table 1 along with the ASD

Table 2. Household and Hospital Characteristics

	Treatment group, No./total (%)		Absolute standardized difference[a]
	Nonoperative (n = 370)	Surgery (n = 698)	
Household characteristics			
Education of primary caregiver			
<High school	15/339 (4.4)	19/595 (3.2)	6.4
High school or GED	52/339 (15.3)	103/595 (17.3)	5.3
Some college	41/339 (12.1)	122/595 (20.5)	22.9
Associate's	41/339 (12.1)	86/595 (14.5)	7.0
Bachelor's	101/339 (29.8)	140/595 (23.5)	14.2
Master's	56/339 (16.5)	88/595 (14.8)	4.8
Doctorate	14/339 (4.1)	14/595 (2.4)	10.0
Professional degree	19/339 (5.6)	23/595 (3.9)	8.2
Not reported or not documented	31	103	
Total household income, $			
<25 000	41/326 (12.6)	69/575 (12.0)	1.8
25 000- 49 999	68/326 (20.9)	124/575 (21.6)	1.7
50 000-99 999	91/326 (27.9)	175/575 (30.4)	5.5
≥100 000	126/326 (38.7)	207/575 (36.0)	5.5
Not reported/not documented	44	123	
Household income earner(s)			
Single	161/339 (48.9)	273/583 (46.8)	4.2
Double	168/339 (51.1)	310/583 (53.2)	4.2
Not reported or not documented	41	115	
Primary language spoken at home			
English	284/353 (80.5)	569/653 (87.1)	18.2
Spanish	29/353 (8.2)	51/653 (7.8)	1.5
Other primary	40/353 (11.3)	33/653 (5.1)	23.0
Not reported or not documented	17	45	
Hospital characteristics			
Transferred in from another ED or hospital	159 (43)	313 (44.9)	3.8
Sites (No. enrolled)			
1 (No. = 260)	92 (24.9)	168 (24.1)	1.9
2 (No. = 217)	79 (21.4)	138 (19.8)	3.9
3 (No. = 135)	52 (14.1)	83 (11.9)	6.4
4 (No. = 109)	35 (9.5)	74 (10.6)	3.8
5 (No. = 101)	35 (9.5)	66 (9.5)	0.01
6 (No. = 84)	19 (5.1)	65 (9.3)	16.2
7 (No. = 61)	18 (4.9)	43 (6.2)	5.7
8 (No. = 45)	21 (5.7)	24 (3.4)	10.7
9 (No. = 41)	10 (2.7)	31 (4.4)	9.4
10 (No. = 15)	9 (2.4)	6 (0.9)	12.4

Abbreviations: ED, emergency department; GED, General Educational Development; IQR, interquartile range.

[a] Absolute standardized difference is calculated as the absolute value of the difference in the means, medians, or difference in proportions between intervention groups in pooled standard deviations.

between groups. Household and hospital characteristics with ASDs between groups are shown in **Table 2**. The groups were similar in most measured variables, with an ASD less than 20%. However, patients choosing nonoperative management were more often younger (median age, 12.3 years [IQR, 10.0-14.6 years] vs 12.5 years [IQR, 10.5-14.9 years]), Black (9.5% vs 4.9%) or other race (14.3% vs 8.6%), had caregivers with a bachelor's degree (27.3% vs 20.1%), more likely to have undergone an ultrasound (79.7% vs 74.5%), and less likely to have undergone a CT scan (27.6% vs 32.4%).[25-28] After IPTW by the stabilized weight, all pretreatment covariates were well-balanced, with all ASD less than 20%, and the vast majority less than 10% (eTable 5 in Supplement 2). The stabilized IPTW had a mean value 0.995 (range, 0.405-5.244).

Primary Outcomes

Adjusted and unadjusted results for primary outcomes are shown in **Table 3**. The success rate of nonoperative management at 1 year was 67.1% (96% CI, 61.5% to 72.3%; P = .86) (Table 3). Disability days at 1 year were significantly fewer in the nonoperative management group than the surgery group (adjusted, 6.6 vs 10.9 days; mean difference, −4.3 days (99% CI, −6.17 to −2.43; P < .001).

Table 3. Patient Primary Outcomes

Primary outcomes at 1 y	Unadjusted			Adjusted[a]			
	Nonoperative	Surgery	Absolute difference (99% CI)	Nonoperative, %	Surgery, %	Difference (99% CI)[b]	*P* value[c]
Success rate, No. /total (%)	245/370 (66.2)			67.1 (96% CI, 61.5 to 72.3)[b]			.86
Disability days[d]							
Mean (99% CI)	6.5 (5.24 to 7.75)	10.9 (9.97 to 12.19)	−4.44 (2.66 to 6.22)	6.6 (5.21 to 7.94)	10.9 (9.60 to 12.15)	−4.30 (−6.17 to −2.43)	<.001
Median (IQR)	4.0 (1.0-9.0)	7.0 (4.0-14.0)					

Abbreviation: IQR, interquartile range.

[a] Inverse probability of treatment weighting analysis, adjusted for age, sex, site, race, ethnicity, insurance payor, patient transferred to recruiting institution, highest education level of primary caregiver, total household income, household income source from single or double income, primary language spoken at home, white blood cell count, ultrasound performed, CT scan performed, pain duration at presentation to the emergency department, nausea at presentation, emesis at presentation, diarrhea at presentation, fever at presentation, anorexia at presentation, time of day of presentation to the emergency department, and BMI percentile.

[b] Per the study design, the 5% α was split so that the primary outcomes were tested at a 4% level (2-sided, 2% 1-sided) for the success rate of nonoperative management and a 1% level (2-sided) for disability days. The reported 99% and 96% confidence intervals reflect this.

[c] *P* value for success-rate outcomes are 1-sided against the null of 70%.

[d] Defined as the total number of days patient or caregiver were not able to participate in normal activities secondary to appendicitis-related care (n = 284 nonoperative; n = 522 surgery).

Secondary Outcomes—Medical

Adjusted and unadjusted results for secondary outcomes are shown in **Table 4**. The success rate of nonoperative management during the initial hospitalization was 85.4% (95% CI, 81.0% to 88.9%; *P* < .001) (Table 4). Of the 53 patients for whom nonoperative management failed and who had undergone appendectomy during the initial admission, 16 were due to caregiver election to convert to surgery. Of the 37 remaining, 16 had clinical worsening; 16 did not improve, 6 did not meet discharge criteria within 48 hours (2 of whom also had clinical worsening and 1 of whom did not improve), and 2 were not documented. The success rate of nonoperative management at 1 year for the 329 patients with complete follow-up was 62.8% (95% CI, 57.1% to 68.3%; *P* = .99). Rates of complicated appendicitis were not significantly different between nonoperative management and surgery (3.3% vs 3.6%; mean difference, −0.3% (−2.6% to 2.1%; *P* = .82).

Treatment-associated complications including rates of in-hospital antibiotic adverse effects, postoperative infections, readmissions, surgery during readmissions, and emergency department visits after discharge for the nonoperative management and surgery groups are shown in **Table 5**.

Secondary Outcomes—Patient Reported

Nonoperative management was associated with significantly fewer disability days among patients at 30 days (adjusted, 3.3 vs 6.5 days, mean difference, −3.22 [95% CI, −4.02 to −2.41; *P* <.001) (Table 4). Nonoperative management was associated with significantly fewer disability days among the caregivers at 30 days (adjusted, 2.4 vs 3.1 days; mean difference, −0.75 [95% CI, −1.36 to −0.15]; *P* = .02) and at 1 year (adjusted, 3.3 vs 4.1 days; mean difference, −0.81 [95% CI, −1.54 to −0.08]; *P* = .03). Health care satisfaction scores at 30 days were not significantly different between nonoperative management and surgery (adjusted, 93.5 vs 94.2; mean difference, −0.73 [95% CI, −2.41 to 0.94]; *P* = .40). Satisfaction with decision scores were significantly lower in the nonoperative group at 30 days (27.6 vs 28.7; mean difference, −0.97 [95% CI, −1.52 to −0.43]; *P* < .001) and at 1 year (27.7 vs 28.5; mean difference, −0.79 [95% CI, −1.36 to −0.23]; *P* = .006).

The adjusted health-related QOL scores reported by patients and caregivers were significantly higher in the nonoperative group at 30 days than in the surgery group (patient-report, 89.0 vs 86.3; mean difference, 2.73 [95% CI, 1.00 to 4.46]; *P* = .002; parent-proxy report, 89.5 vs 86.3; mean difference, 3.2 [95% CI, 1.60 to −4.81]; *P* < .001). The adjusted health-related QOL scores reported by patients and caregivers at 1 year were not significantly different (patient-report, 90.8 vs 92.3; mean difference, −1.46 [95% CI, −2.92 to 0.04]; *P* = .05; parent-proxy report, 91.6 vs 92.5; mean difference, −0.90 [95% CI, −2.29 to 0.49]; *P* = .20).

Post Hoc Analyses

When the 16 patients (4.3%) who converted to operative management due to family decision were excluded, the adjusted success rate of nonoperative management during the initial hospitalization was 89.3% (95% CI, 85.1%-92.4%) and at 1 year was 70.2% (95% CI, 64.8%-75.1%) (Table 4). The unadjusted negative appendectomy rate was 7.5% (52 of 698) in the surgical group. Among patients for whom nonoperative management failed, the overall unadjusted negative appendectomy rate was 4.8% (6 of 125) with a rate of 9.4% (5 of 53) for treatment failure during the initial hospitalization and 1.4% (1 of 72) for those with recurrence after discharge. The adjusted negative appendectomy rate in the surgical group was 7.5% (95% CI, 5.4%-9.5%) and the adjusted mean difference between groups in the treatment failure rate accounting for negative appendectomies was 25.4% (95% CI, 19.9%-30.9%) (Table 4).

Discussion

In this study involving 1068 children with uncomplicated appendicitis, an initial nonoperative management strategy with antibiotics alone had a success rate of 67.1% for those

Table 4. Patient Secondary Outcomes

	Unadjusted			Adjusted[a]			
	Nonoperative	Surgery	Absolute difference (95% CI)	Nonoperative, %	Surgery, %	CI or difference; nonoperative-surgery (95% CI)[b]	*P* value[c]
Medical							
Success rate							
At hospitalization, No./total (%)	317/370 (85.7)			85.4		81.0 to 88.9	<.001
1 y for completers	204/329 (62.0)			62.8		57.1 to 68.3	.99
Length of stay, index hospitalization, No.[d]	370	698					<.001
Mean (95% CI), d	1.5 (1.31 to 1.61)	1.0 (0.92 to 1.15)	0.43 (0.24 to 0.61)	1.5 (1.26 to 1.68)	1.0 (0.92 to 1.13)	0.45 (0.21 to 0.68)	
Median (IQR). d	1.0 (1.0 to 2.0)	1.0 (1.0 to 1.0)					
Complicated appendicitis, No./total (%)[e]	13/370 (3.5)	25/698 (3.6)		3.3	3.6	−0.3 (−2.6 to 2.1)	.82
Patient reported							
Patient disability days at 30 d, No.[f]	299	521					
Mean (95% CI)	3.3 (2.77 to 3.89)	6.4 (5.91 to 6.97)	−3.11 (−3.88 to −2.34)	3.3 (2.76 to 3.88)	6.5 (5.96 to 7.12)	−3.22 (−4.02 to −2.41)	<.001
Median (IQR)	2.0 (0 to 4.0)	5.0 (2.0 to 10.0)					
Caregiver disability days at 30 d, No.	246	463					
Mean (95% CI)	2.5 (1.99 to 3.02)	3.1 (2.74 to 3.40)	−0.56 (−1.18 to 0.05)	2.4 (1.92 to 2.81)	3.1 (2.71 to 3.52)	−0.75 (−1.36 to −0.15)	.02
Median (IQR)	1.0 (0.0 to 3.0)	2.0 (0.0 to 4.0)					
Caregiver disability days at 1 y, No.	277	511					
Mean (95% CI)	3.5 (2.94 to 4.14)	4.1 (3.57 to 4.57)	−0.53 (−1.31 to 0.25)	3.3 (2.75 to 3.83)	4.1 (3.60 to 4.59)	−0.81 (−1.54 to −0.08)	.03
Median (IQR)	2.0 (0.0 to 4.0)	3.0 (1.0 to 5.0)					
Health care satisfaction at 30 days, No.[g]	295	519					
Mean (95% CI)	92.8 (91.26 to 94.29)	94.2 (93.20 to 95.16)	−1.40 (−3.21 to 0.40)	93.5 (92.16 to 94.90)	94.2 (93.30 to 95.22)	−0.73 (−2.41 to 0.94)	.40
Median (IQR)	97.9 (92.4 to 100.0)	99.0 (93.8 to 100)					
Satisfaction with decision score[h]							
30 Days							
No. of patients	296	523					
Mean (95% CI)	27.6 (27.18 to 28.09)	28.7 (28.45 to 28.95)	−1.06 (−1.58 to −0.55)	27.7 (27.21 to 28.16)	28.7 (28.39 to 28.93)	−0.97 (−1.52 to −0.43)	<.001
Median (IQR)	30.0 (25.5 to 30.0)	30.0 (29.0 to 30.0)					
1 Year							
No. of patients	280	522					
Mean (95% CI)	27.7 (27.26 to 28.16)	28.5 (28.14 to 28.78)	−0.75 (−1.30 to −0.20)	27.7 (27.21 to 28.14)	28.5 (28.15 to 28.79)	−0.79 (−1.36 to −0.23)	.006
Median (IQR)	30.0 (26.0 to 30.0)	30.0 (29.0 to 30.0)					
Quality of life score[i]							
30 Days							
Patient reported, No.	274	488					
Mean (95% CI)	88.9 (87.66 to 90.13)	86.1 (85.11 to 87.14)	2.77 (1.17 to 4.36)	89.0 (87.68 to 90.36)	86.3 (85.19 to 87.38)	2.73 (1.00 to 4.46)	.002
Median (IQR)	91.3 (82.6 to 97.8)	89.1 (78.8 to 95.7)					
Parent reported, No.	292	517					
Mean (95% CI)	89.1 (87.88 to 90.32)	86.0 (85.03 to 87.02)	3.08 (1.50 to 4.65)	89.5 (88.21 to 90.71)	86.3 (85.25 to 87.27)	3.2 (1.60 to 4.81)	<.001
Median (IQR)	91.3 (81.5 to 98.9)	89.1 (79.3 to 95.7)					

(continued)

Table 4. Patient Secondary Outcomes (continued)

	Unadjusted			Adjusted[a]			
	Nonoperative	Surgery	Absolute difference (95% CI)	Nonoperative, %	Surgery, %	CI or difference; nonoperative-surgery (95% CI)[b]	*P* value[c]
1 Year							
Patient reported, No.	271	496					
Mean (95% CI)	90.6 (89.43 to 91.69)	92.2 (91.38 to 93.01)	−1.64 (−3.03 to −0.24)	90.8 (89.58 to 92.01)	92.3 (91.44 to 93.07)	−1.46 (−2.92 to 0.04)	.05
Median (IQR)	93.5 (84.8 to 98.9)	95.7 (88.0 to 100.0)					
Parent reported, No.	280	520					
Mean (95% CI)	91.3 (90.20 to 92.36)	92.6 (91.82 to 93.41)	−1.34 (−2.68 to 0.001)	91.6 (90.46 to 92.69)	92.5 (91.66 to 93.30)	−0.90 (−2.29 to 0.49)	.20
Median (IQR)	93.5 (87.0 to 98.9)	95.7 (89.1 to 100.0)					
Post hoc outcomes, No./total (%)							
Caregiver election to convert to surgery	16/370 (4.3)			4.4		2.6 to 7.2	
Success rate							
Initial hospitalization excluding elective conversion to surgery (n = 354)	317/354 (89.5)			89.3		85.1 to 92.4	
1-y excluding elective conversion to surgery (n = 354)	245/354 (69.2)			70.2		64.8 to 75.1	
Treatment failure rate accounting for negative appendectomy	125/370 (33.8%)	52/698 (7.5%)		32.9	7.5	25.4 (19.9 to 30.9)	

Abbreviations: BMI, body mass index; ED, emergency department; IQR, interquartile range; QOL, quality of life.

[a] See Table 3 footnotes for analysis and adjusted variables..

[b] See Table 3 footnotes for definitions of statistical tests.

[c] *P* value for success rate outcomes are 1-sided against the null of 70%.

[d] Length of stay did not include time in the emergency department.

[e] Defined as visualization of a hole in the appendix, extramural appendicolith, or frank pus in the abdomen during appendectomy or pathologic findings of transmural inflammation with perforation through the wall of the appendix.

[f] See Table 3 footnotes for definition.

[g] Satisfaction at 30-day was measured using the Pediatric Quality of Life Inventory (PedsQL) 3.0 Healthcare Satisfaction Generic Module-Parent Report (range, 0-100; higher scores indicate greater satisfaction).

[h] The 30-day and 1-year scores were assessed with the Satisfaction with Decision Scale (range, 0-30; higher scores indicate greater satisfaction).

[i] Health-related quality of life at 30-day and 1-year was assessed through the PedsQL scales (range, 0-100; higher scores indicate better QOL); the minimal clinically important difference is 4 or more.

Table 5. Treatment Associated Complications

	No./total (%)	
	Nonoperative	Surgery
In-hospital antibiotic side effect[a]	9/370 (2.4)	4/698 (0.6)
Postoperative infection[b]	1/370 (0.3)	8/698 (1.1)
Readmissions[c]	85/370 (23.0)	20/698 (2.9)
Surgery during readmission[d]	80/370 (21.6)	4/698 (0.6)
Any emergency department visit after discharge[e]	92/370 (24.9)	48/698 (6.9)

[a] Includes skin rash, wheezing, nausea, or emesis.

[b] One nonoperative and 8 surgery superficial wound infections; 1 surgery intra-abdominal deep-space infection.

[c] When readmissions for recurrent appendicitis are excluded, the nonoperative readmission rate is 1.6%.

[d] When recurrent appendicitis is excluded, the nonoperative surgery during readmission rate was 0.3%.

[e] When recurrent appendicitis is excluded, the nonoperative emergency department visit rate was 3.5%.

patients who completed the study follow-up. Compared with urgent laparoscopic appendectomy (within 12 hours of admission), nonoperative management was associated with significantly fewer disability days for both the child and caregivers at 30 days and at 1 year. The rates of complicated appendicitis and health care satisfaction scores were not significantly different between groups. Satisfaction with decision scores were very high in both groups but were significantly lower in the nonoperative group.

Several randomized clinical trials and cohort studies have consistently demonstrated the safety and efficacy of nonoperative management of uncomplicated appendicitis in adults and children.[6,7,9,10] These studies report 1-year success rates of nonoperative management between 65% and 80% with no increase in the rate of complicated appendicitis associated with nonoperative management and similar or lower overall rates of complications with nonoperative management compared with surgery. This study demonstrated that nonoperative management was associated with a success rate of 67% at 1 year, and there was no significant difference in the rate of complicated appendicitis compared with surgery. Potential benefits associated with nonoperative management in this study include significantly fewer disability days for both the patient and caregiver and the possible avoidance of unnecessary negative appendectomies that occurred in 7.5% of patients in the surgical group. This study also provides generalizable estimates of the expected postoperative outcomes associated with laparoscopic appendectomy for uncomplicated appendicitis including a 6.9% rate of

emergency department visits, 2.9% rate of readmissions, 1.1% rate of postoperative infections, and 0.6% rate of reoperation. The results from this study can be used to further characterize the different risks and benefits associated with surgery and nonoperative management for the treatment of uncomplicated pediatric appendicitis.

In conjunction with input from the multidisciplinary team involved in this project, this study was designed to compare nonoperative management and surgery in a more pragmatic study that mimicked clinical practice. During the study, each site enrolled patients using a decision aid that explained the risks and benefits of each treatment. All subsequent clinical care decisions after enrollment were made by the clinical team using standardized clinical protocols for each treatment with minimal involvement of the research team. Furthermore, the clinical information needed to assess eligibility criteria for nonoperative management is routinely collected as part of clinical care. The results from this study should be readily implementable as the decision aid and treatment protocols can be easily translated into pediatric clinical practice.

The individuals involved in this multidisciplinary team represented the perspectives of patients, families, primary care physicians, emergency department physicians, nurses, and payors. During the design of this study, the consensus for acceptable thresholds for both the success rate of nonoperative management and differences in disability days among the team were both lower than those of the surgeons involved in the study. This difference is important because the major trials of nonsurgical treatment of appendicitis have been driven by surgeon expectations and therefore may have been biased against medical management.[6,7] The higher statistical thresholds mandated by surgeons in studies investigating nonoperative management may have set levels to consider nonoperative management successful higher than what patients, families, and other medical specialists would consider acceptable. This can lead to negative studies of nonoperative management and limit its acceptance into clinical practice. In the current study, the 67.1% success rate fell below the acceptable success rate of 70% based on surgeon consensus. However, if the acceptable threshold level of 50% had been used, then this study would have been considered a success. Furthermore, if negative appendectomies are considered failures of surgical management, then the difference in failure rates between the 2 treatments is 25.4%, which is less than the 30% prespecified acceptable failure rate for nonoperative management. Taken together, these results support offering nonoperative management as a treatment option for uncomplicated pediatric appendicitis.

Families have strong treatment preferences with most not willing to allow their child to participate in a trial in which treatment would be determined by randomization.[9,10] In a recent survey, 89 caregivers (79% of 113) of children admitted for suspected appendicitis reported that they were not willing to let their child's appendicitis treatment be determined by randomization.[31] The most commonly cited reason against randomization was wanting to have the ability to make an autonomous decision after weighing the risks and benefits of each treatment. The patient choice design used in this nonrandomized, controlled, intervention study facilitated broad enrollment, and therefore improved the generalizability of the results. In this study, 88% of eligible patients who were approached agreed to enroll. Furthermore, a previous clinical trial demonstrated that caregivers making the choice between surgery and nonoperative management for their child's appendicitis reported high scores for decisional self-efficacy, health care satisfaction, preparation for decision-making, and satisfaction with their decision and reported low scores for decisional conflict and decisional regret.[32] These results suggest that caregivers of children with uncomplicated appendicitis can effectively make an informed treatment decision for their child's appendicitis.

When this study was initiated, most pediatric clinicians were uncomfortable with the concept of nonoperative management of uncomplicated appendicitis. Therefore, the nonoperative management treatment protocol and threshold success rate were developed to minimize risks and achieve consensus from surgeons across the participating institutions. The protocol used was based on a previous pediatric study[6] and included hospital admission with a minimum of 24 hours of IV antibiotics and a minimum of 12 hours of observation prior to allowing any oral intake. Furthermore, the threshold success rate was set at the surgeon-preferred level of 70% rather than the multidisciplinary group's preferred level of 50%. With additional reports demonstrating the safety and efficacy of nonoperative management, the threshold for an acceptable success rate has decreased and the treatment algorithms have changed to minimize length of stay and diet limitations.[9,33-37] One way to increase the potential benefits of nonoperative management would be to decrease or eliminate the hospital stay by performing outpatient management with a long acting antibiotic and short period of observation in the emergency department. This has been successfully reported and is being actively studied among adult patients, but there are limited data for children.[33,34] With increasing experience with nonoperative management within pediatric surgery, outpatient nonoperative management protocols may be able to be initiated and studied in the near future.

Limitations

This study has several limitations. First, the results of this study are only applicable to a limited percentage of children who present with acute appendicitis. Due to the inclusion-exclusion criteria, only 19.3% patients with appendicitis treated at the participating sites qualified for this study. These criteria were intentionally selected based on the available data in the literature related to the safety and efficacy of nonoperative management for children and to ensure consensus across the participating institutions. Also, all the participating sites are tertiary children's hospital whose patient population may include a lower proportion of children meeting eligibility criteria. Second, the nonrandomized treatment allocation potentially allows for treatment selection bias, where treatment may be affected by participant characteristics and those choosing nonoperative management differ, on average, from those choosing surgery. However, several steps

to minimize this were taken including the use of a standardized enrollment script and decision aid, specific inclusion and exclusion criteria, standardized treatment protocols and algorithms, and obtaining agreement to participate from all participating surgeons prior to beginning the study. Furthermore, treatment decision-making in clinical practice is affected by the biases of patients, families, and surgeons, suggesting that a patient choice treatment allocation may be more reflective of current practice. Moreover, robust inferential methods to aid in accounting for treatment confounding bias were used. Third, the generalizability of the results may be limited by the substantial rates of incomplete follow-up.

Conclusions

Among children with uncomplicated appendicitis, an initial nonoperative management strategy with antibiotics alone had a success rate of 67.1% and, compared with urgent surgery, was associated with statistically significantly fewer disability days at 1 year. However, there was substantial loss to follow-up, the comparison with the prespecified threshold for an acceptable success rate of nonoperative management was not statistically significant, and the hypothesized difference in disability days was not met.

ARTICLE INFORMATION

Accepted for Publication: June 3, 2020.

Published Online: July 27, 2020. doi:10.1001/jama.2020.10888

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Author Contributions: Dr Minneci had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Statistical analysis: Hade, Sebastião, Gadepalli, Cooper.
Obtained funding: Minneci, Deans.
Administrative, technical, or material support: Minneci, Hade, Lawrence, Sebastião, Hirschl, Gadepalli, Helmrath, Kohler, Sato, Lal, Kabre.
Supervision: Minneci, Hade, Hirschl, Helmrath, Sato, Lal, Landman, Kabre, Cooper, Deans.
Other - site principal investigator: Saito.

Conflict of Interest Disclosures: Dr Minneci reported grants from PCORI during the conduct of the study. Dr Hade reported grants from PCORI during the conduct of the study; grants from NIH, grants from Smart Columbus, and grants from PCORI/PCORnet outside the submitted work. Dr Saito reported grants from PCORI during the conduct of the study; grants from AHRQ outside the submitted work. Dr Mak reported grants from PCORI during the conduct of the study; grants from Thrasher outside the submitted work. Dr Gadepalli reported grants from PCORI during the conduct of the study. Dr Sato reported grants from PCORI during the conduct of the study. Dr Cooper reported grants from PCORI during the conduct of the study. Dr Deans reported grants from PCORI during the conduct of the study. No other disclosures were reported.

Funding/Support: This study is funded by award CER-1507-31325 from PCORI, an independent, nonprofit organization authorized by the US Congress in 2010. This project is also supported by grant UL1TR001070 from the National Center for Advancing Translational Sciences.

Role of the Funder/Sponsor: Funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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Disclaimer: The content of this work is solely the responsibility of the authors and does not necessarily represent the official views of PCORI, its Board of Governors or Methodology Committee, the National Center for Advancing Translational Sciences or the National Institutes of Health.

Data Sharing Statement: See Supplement 3.

Additional Contributions: We thank our multidisciplinary stakeholder members for all of their input and dedication to this study: *Patient or caregivers:* Alyssa Gilman, Amanda Forystek, Endia McHenry, Sonya Sigers, Kaleb Boyd, Liz Sullivan, Maxwell Blom, Melissa R. Blom, Lorelei Moulin, Darcy Moulin, Nicholas Hawke, Kimberly Hawke, William Hawke, Nicolas Valdes, Lisa Valdes, Maurilio Valdes, Nolan Chehak, LuAnne Farr, Joshua Montalvo, Illuminado Castellano, Rheya Wheeler, Cherie Caldwell, Robert Rohloff, Samantha Schlaeppi, Tanner Goodman, Lisa Shrader, William Blake Godwin, Diana Godwin, Trinity Patten, Rebeccah Abanukam, Aubrey K. Gibson, Aria K. Gibson, Jason Gibson, Christy L. McDonald, and Bobby J. McDonald Jr; *Nationwide Children's Hospital:* R. Lawrence Moss, MD, Courtney Porter, RN, Kathryn Nuss, MD, Paul Seese, RN; Sean Gleeson, MD, MBA; *University of Chicago Medicine*: Alisa McQueen, MD; *University of Louisville School of Medicine*: Stephan Baum, MD; *Ann & Robert Lurie Children's Hospital of Chicago*: Dana Aronson Schinasi, MD; *Washington University:* Gian Musarra, MD, *Medical College of Wisconsin:* Michael Levas, MD; and Darryl Robbins, DO, community physician, all of whom received a stipend for their participation. We also thank the following staff

members on this project: Beth Fischer, PhD, and Karen Leonhart, BS, Nationwide Children's Hospital; Jana Creps, University of Michigan–C.S. Mott Children's Hospital; Michelle Knezevich, MS, Children's Hospital of Milwaukee, who received no remuneration beyond their salaries.

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