Antibiotics-First Versus Surgery for Appendicitis: A US Pilot Randomized Controlled Trial Allowing Outpatient Antibiotic Management

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Study objective: Randomized trials suggest that nonoperative treatment of uncomplicated appendicitis with antibiotics-first is safe. No trial has evaluated outpatient treatment and no US randomized trial has been conducted, to our knowledge. This pilot study assessed feasibility of a multicenter US study comparing antibiotics-first, including outpatient management, with appendectomy.

Methods: Patients aged 5 years or older with uncomplicated appendicitis at 1 US hospital were randomized to appendectomy or intravenous ertapenem greater than or equal to 48 hours and oral cefdinir and metronidazole. Stable antibiotics-first-treated participants older than 13 years could be discharged after greater than or equal to 6-hour emergency department (ED) observation with next-day follow-up. Outcomes included 1-month major complication rate (primary) and hospital duration, pain, disability, quality of life, and hospital charges, and antibiotics-first appendectomy rate.

Results: Of 48 eligible patients, 30 (62.5%) consented, of whom 16 (53.3%) were randomized to antibiotics-first and 14 (46.7%) to appendectomy. Median age was 33 years (range 9 to 73 years), median WBC count was 15,000/μL (range 6,200 to 23,100/μL), and median computed tomography appendiceal diameter was 10 mm (range 7 to 18 mm). Of 15 antibiotic-treated adults, 14 (93.3%) were discharged from the ED and all had symptom resolution. At 1 month, major complications occurred in 2 appendectomy participants (14.3%; 95% confidence interval [CI] 1.8% to 42.8%) and 1 antibiotics-first participant (6.3%; 95% CI 0.2% to 30.2%). Antibiotics-first participants had less total hospital time than appendectomy participants, 16.2 versus 42.1 hours, respectively. Antibiotics-first-treated participants had less pain and disability. During median 12-month follow-up, 2 of 15 antibiotics-first-treated participants (13.3%; 95% CI 3.7% to 37.9%) developed appendicitis and 1 was treated successfully with antibiotics; 1 had appendectomy. No more major complications occurred in either group.

Conclusion: A multicenter US trial comparing antibiotics-first to appendectomy, including outpatient management, is feasible to evaluate efficacy and safety. [Ann Emerg Med. 2017;70:1-11.]

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INTRODUCTION

Background

Standard management of acute uncomplicated appendicitis has been appendectomy, but 7 randomized controlled trials,[1-7] nonrandomized pediatric trials,[8-12] and case series[13-16] suggest that an antibiotics-first approach is safe, with no increased risk of subsequent perforation and sepsis, and no reported deaths. In the largest randomized trial, the 1-year appendectomy rate among 257 adults with imaging-confirmed acute uncomplicated appendicitis treated with antibiotics-first was 27%.[6] A meta-analysis found that antibiotic treatment was associated with fewer complications and less pain and disability than appendectomy.[17]

Patients undergoing appendectomy are typically hospitalized and discharged when they can tolerate fluids and achieve pain control. In the US, the trend is toward shorter hospital stays and, for appendicitis, length of postoperative hospitalization has decreased because more appendectomies are performed

Editor's Capsule Summary

What is already known on this topic
There is limited evidence suggesting that uncomplicated appendicitis can be treated with antibiotics instead of surgery.

What question this study addressed
Is an outpatient strategy of antibiotics as safe and effective as hospitalization and appendectomy?

What this study adds to our knowledge
In this randomized controlled trial of computed tomography–proven appendicitis, the 15 evaluable patients receiving antibiotics all recovered. Two, however, had recurrence; one treated with appendectomy and one that resolved with further antibiotics.

How this is relevant to clinical practice
This pilot study cannot establish safety or efficacy but does suggest feasibility for a large-scale trial of nonoperative management.

laparoscopically.[18] All previous trials have required patients randomized to antibiotics to be hospitalized, and most appendectomies in these trials were performed by open technique. Primary antibiotic therapy may offer the opportunity to avoid hospitalization with discharge from the emergency department (ED) after treatment initiation, observation, and symptom control. This is the current management for acute uncomplicated diverticulitis,[19] but it has yet to be studied in patients with uncomplicated appendicitis.

Importance

Approximately 300,000 people undergo appendectomy, resulting in nearly $2 billion in health care costs annually in the US.[20] After appendectomy, patients miss a median of 10 to 14 days from work and resume normal activity in 7 to 21 days.[21] Despite the results of European randomized controlled trials supporting the efficacy of antibiotics-first management, the actual application and effectiveness of nonoperative treatment have been questioned because of evidence gaps,[22] and this approach has been infrequently used in the US according to the National Inpatient Sample database.[23] To our knowledge, no US randomized trial comparing an antibiotics-first approach to urgent appendectomy among patients with uncomplicated appendicitis has been reported.

Goals of This Investigation

We present the methodology and results of a pilot randomized trial comparing antibiotics-first to appendectomy among patients receiving a diagnosis of uncomplicated appendicitis designed to determine the feasibility of conducting a large multicenter US trial. To adapt an antibiotics-first treatment strategy to US treatment patterns, we evaluated a protocol allowing outpatient antibiotic management. As opposed to previous trials that focused on the possible futility of antibiotic management and had a primary outcome of appendectomy rate in the antibiotics-first group,[1-3,6,7] we evaluated a primary outcome that was independent of treatment strategy, the 1-month major complication rate. We evaluated patient-centered outcomes secondarily. Additionally, we report the frequency with which antibiotic-treated participants reached clinical stability in the ED, allowing successful outpatient management, and outcomes after 1-year follow-up.

MATERIALS AND METHODS
Study Design and Setting

We conducted a pilot randomized trial comparing antibiotics-first to urgent appendectomy among patients with acute uncomplicated appendicitis. We enrolled patients from March to September 2015 at Olive View–UCLA Medical Center, a County of Los Angeles UCLA-affiliated hospital. The Olive View–UCLA institutional review board approved the study and protocol amendments. (All members of the Olive View–UCLA Appendicitis Study Group are listed in Appendix E1, available online at http://www.annemergmed.com.)

Selection of Participants

We included ED patients who had the presumptive diagnosis of acute appendicitis by the ED attending physician and who met the following criteria: (1) age 5 years or older; (2) radiographic diagnosis of uncomplicated appendicitis by computed tomography (CT) and/or ultrasonography as read by an attending radiologist and performed within 24 hours of consent; (3) clinical diagnosis of uncomplicated appendicitis by a surgical teaching service supervised by an attending surgeon; and (4) ability to provide written informed consent in English or Spanish (for participants ages 5 to 17 years, consent from parent/ guardian and assent, when appropriate). Study coordinators screened ED patients between 7 AM and 9 PM, including those who presented overnight and were in the ED at 7 AM.

We excluded patients with the following: (1) inability to return or be contacted for follow-up visits; (2) evidence of severe sepsis or septic shock; (3) high-risk diabetes (eg, insulin dependent, diabetic ketoacidosis, hyperosmolar

coma); (4) immunodeficiency (eg, absolute neutrophil count <500/μL, immunosuppressive drugs, chemotherapy, known AIDS [CD4 count <200/μL or AIDS-defining illness within the last year]) by patient history; (5) suspicion of acute coronary syndrome, congestive heart failure, or active chronic liver disease; (6) chronic renal insufficiency (serum creatinine level >2 mg/dL); (7) hepatic cirrhosis or failure; (8) acute inflammatory bowel disease or malignancy; (9) pregnant, nursing, or expectation of becoming pregnant within 10 days; (10) concurrent illness that would mandate hospitalization; (11) imaging findings suggesting a mass or mucocele; (12) severe allergy or reaction to study drugs or drugs similar to them; (13) receiving warfarin; (14) another infection requiring antibiotic treatment; (15) incarceration or police custody; (16) abdominal or pelvic surgery within the last month; (17) current long-term-care resident; (18) expected use of an investigational treatment; (19) intravenous drug use in the preceding month; (20) expected concurrent hemodialysis, peritoneal dialysis or indwelling peritoneal catheters or shunts, plasmapheresis, or hemoperfusion; (21) received parenteral antibiotics greater than or equal to 6 and less than or equal to 48 hours before screening; (22) received ertapenem within 24 hours before screening; or (23) previous study enrollment. Radiographic identification of appendicolith was initially an exclusion criterion but was later allowed (after 11 of 30 participants were enrolled) because of lack of consistent evidence for this being an antibiotic failure risk factor.

Methods of Measurement

On participant enrollment, we recorded demographics, history, pain severity, and physical examination findings. We obtained complete blood count, comprehensive metabolic panel, venous lactate level, and C-reactive protein tests. We assessed quality of life before appendicitis symptoms among adults by using the SF-12v2 Health Survey (acute version).[24] All patients with suspected appendicitis had abdominal imaging, CT with intravenous contrast in adults and ultrasonography in persons younger than 18 years, followed by CT if indicated. An attending radiologist initially reviewed imaging studies during ED evaluation. The radiographic diagnosis of uncomplicated appendicitis was pragmatic and based on the radiologist's global impression, as is done in routine practice. Subsequently, findings were recorded with standardized methods (radiology methods [Appendix E2, available online at http://www.annemergmed.com]). Treatment of pain was at the discretion of the treating clinician for participants in both groups.
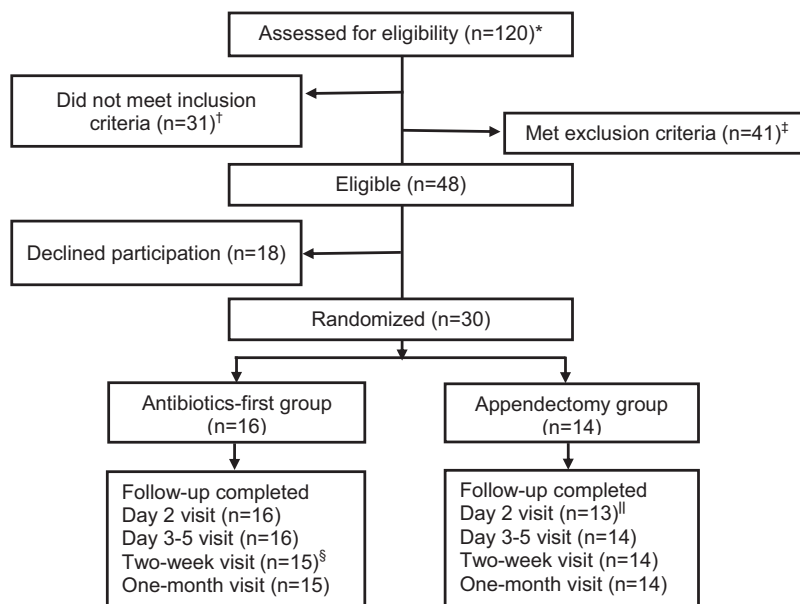
We conducted follow-up assessments on day 2 in person, days 3 to 5 by telephone (in person if the participant was

hospitalized), and at 2 weeks (days 10 to 18) and 1 month (days 25 to 35) in person. We report results through approximately 1 year; however, participants will be followed for 2 years. All participants had a physical examination on day 2 and days 3 to 5 (the examination was conducted if the participant was hospitalized), at 2 weeks, and at 1 month. Antibiotics-first participants had complete blood count, comprehensive metabolic panel, serum lactate level, and C-reactive protein evaluated on day 2. We provided participants 24-hour, 7-day-a-week telephone access to a study coordinator and ED attending physician if they had questions or required reevaluation.

Interventions

After obtaining written informed consent, a study coordinator opened an opaque envelope with the preassigned treatment, either appendectomy with perioperative antibiotics or antibiotics alone (with subsequent appendectomy, if necessary). An author (W.R.M.) generated the randomization sequence. Using an exact 1:1 treatment distribution, we initially created 50 random assignments. We then used the first 30 assignments to create a nearly equal 1:1 distribution to both treatment strategies, thus making it impossible for clinicians to predict treatment for the last enrolled participants according to anticipation of equal treatment group distribution.

We administered a once-a-day intravenous antibiotic, ertapenem 1 g, to participants older than 13 years. After patients underwent ED triage and a minimum 6 hours of observation, the treating clinician had the option to discharge a participant older than 13 years if the following criteria were met: (1) systolic blood pressure greater than 90 mm Hg, pulse rate less than 100 beats/min, and temperature less than 38.5°C (101.3°F); (2) pain controlled with oral analgesics according to physician judgment; (3) participant tolerated oral fluids and medication; (4) participant able to return for further evaluation; (5) treating physician comfortable with participant going home; and (6) participant comfortable going home. We required all discharged participants to return to the ED for reevaluation the following day. If on reevaluation the participant demonstrated no worsening and his or her pain was controlled, then a second ertapenem dose was administered. The participant was then discharged with an 8-day supply of an oral antibiotic regimen of cefdinir (off-label) and metronidazole in prelabeled blister packs. The dose of cefdinir was as follows: for adults and children older than 13 years, 300-mg capsules twice daily; and for children aged 5 to 12 years, 7 mg/kg twice daily, maximum 300 mg/ dose. The dose of metronidazole was as follows: for adults and children older than 13 years, 500-mg tablets 3 times

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                          Assessed for eligibility (n=120)*

Did not meet inclusion
    criteria (n=31)†                          Met exclusion criteria (n=41)‡

                               Eligible (n=48)

Declined participation (n=18)

                              Randomized (n=30)

   Antibiotics-first group                      Appendectomy group
         (n=16)                                     (n=14)

Follow-up completed                        Follow-up completed
Day 2 visit (n=16)                         Day 2 visit (n=13)ǁ
Day 3-5 visit (n=16)                       Day 3-5 visit (n=14)
Two-week visit (n=15)§                      Two-week visit (n=14)
One-month visit (n=15)                      One-month visit (n=14)
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* All patients with a presumptive emergency department diagnosis of appendicitis by an emergency medicine attending physician.

† Of the 31 patients who did not meet inclusion criteria, 11 had imaging that was interpreted as equivocal for appendicitis, 5 had imaging that was interpreted as equivocal for distinguishing complicated from uncomplicated appendicitis, 10 had imaging that was interpreted as complicated appendicitis, 4 had imaging suggesting acute uncomplicated appendicitis but did not have clinical confirmation by a surgeon, and 1 did not speak English or Spanish.

‡ Of the 41 patients who met exclusion criteria, 23 had an appendicolith, 11 had intravenous antibiotics >6 hours prior to enrollment, 2 were prisoners, 2 had ulcerative colitis, 1 had high-risk diabetes, 1 was immunocompromised, and 1 had another infection that required antibiotic treatment. Radiographic identification of an appendicolith was initially an exclusion criterion but was later allowed (after 11 of 30 participants were enrolled) because of lack of consistent evidence of this being a risk factor for antibiotic failure.

§ One antibiotics-first participant was lost to follow-up at the day 10-18 visit.

ǁ One appendectomy participant was intubated at the day 2 visit, so the visit was not completed.

Figure 1. Screening, randomization, and follow-up of patients with the ED diagnosis of appendicitis.

daily; and for children aged 5 to 12 years, 10 mg/kg 3 times daily, maximum 500 mg/dose. We dispensed oral antibiotics in a blister pack labeled with the specific date and time of dosing. Hospitalized participants in the antibiotics-first group who were older than 13 years received ertapenem 1 g intravenously every 24 hours, for a minimum of 2 doses, and children younger than 13 years received ertapenem intravenously every 12 hours (15 mg/kg per dose, maximum 1 g/day), for a minimum of 4 doses. We hospitalized participants younger than 13 years because ertapenem dosing for this age group is every 12 hours. The treating clinician could discharge a hospitalized participant older than 13 years and treated after 2 ertapenem doses with oral antibiotics by using the same criteria described above.

Criteria for transitioning an antibiotics-first participant to appendectomy were assessed by the surgeon site investigator (D.J.S.), in consultation with the participant's attending surgeon, and included (1) diffuse abdominal tenderness consistent with peritonitis; (2) severe sepsis or septic shock; or (3) no improvement in abdominal pain, temperature greater than or equal to $38.5°C$ ($101.3°F$), or WBC count less than 4,000 or greater than $15,000/\mu L$ after 48 hours of antibiotic treatment; and (4) participant consent.

We hospitalized all participants randomized to appendectomy. Urgent appendectomy was performed by an open or laparoscopic approach according to the surgeon's preference. Participants received 1 dose of ertapenem intravenously; additional preoperative antibiotic treatment was at the discretion of the treating clinicians. Treating clinicians discharged appendectomy participants by using the same criteria as above.

Outcome Measures

The primary outcome was the one-month major complication rate in a participant based on American

Table 1. Baseline characteristics of 30 participants with the diagnosis of acute uncomplicated appendicitis by treatment group.

Characteristic	Appendectomy, n=14	Antibiotics-First, n=16
Age, median (IQR; range), y	36 (33–46; 24–65)	31 (25–40; 9–73)
Male sex, No. (%)	9 (64.3)	9 (56.3)
Race, No. (%)		
White	12 (85.7)	13 (81.3)
Other	2 (14.3)	3 (18.8)
Hispanic ethnicity, No. (%)	12 (85.7)	14 (87.5)
Diabetes, No. (%)	0	1 (6.3)
Body mass index, median (IQR; range), kg/m^2	28.0 (24.6–29.8; 21.0–31.8)	27.3 (25.1–33.0; 22.3–43.3)
Previous abdominal/pelvic surgery, No. (%)	3 (21.4)	3 (18.8)
Symptoms		
Subjective fever, No. (%)	4 (28.6)	2 (12.5)
Nausea, No. (%)	13 (92.9)	12 (75.0)
Right lower quadrant pain, No. (%)	13 (92.9)	14 (87.5)
Duration of pain, median (IQR; range), days	1.0 (0.5–3.0; 0.5–5.0)	1.0 (1.0–2.5; 0.5–5.0)
Maximal pain before 24 h, median (IQR; range)*	10 (8–10; 5–10)	8 (8–10; 4–10)
Signs		
Localized rebound tenderness, No. (%)	10 (71.4)	8 (50.0)
Localized guarding, No. (%)	6 (42.9)	6 (37.5)
Triage temperature, median (IQR; range), °C	36.9 (36.6–36.7; 36.5–38.1)	36.8 (36.7–37.2; 36.4–37.3)
CT findings[†]		
Appendicolith, No. (%)[‡]	3 (21.4)	2 (13.3)
Appendiceal diameter, median (IQR; range), mm	9 (9–12; 7–8)	10 (9–12; 7–14)
Periappendiceal stranding, No. (%)	14 (100.0)	13 (86.7)
Periappendiceal fluid, No. (%)	3 (21.4)	2 (13.3)
Laboratory results		
WBC count, median (IQR; range), ×10^3/µL	15.3 (11.0–18.4; 8.1–23.1)	14.2 (11.3–17.0; 6.2–19.2)
Lactate, median (IQR; range), mmol/L[§]	1.0 (0.9–1.4; 0.6–1.6)	1.1 (0.9–1.5; 0.7–2.3)
CRP, median (IQR; range), mg/L[§]	64.8 (42.6–101.6; 8.2–256.4)	25.9 (10.8–64.8; 3.8–202.6)
Alvarado score, median (IQR; range)[‖]	8 (7–9; 4–10)	8 (7–9; 4–10)
Appendix pathology findings, No. (%)		
Normal	1 (7.1)	
Acute uncomplicated	9 (64.3)	NA
Suppurative or gangrenous	4 (28.6)	
Quality-of-life measures		
SF-12v2 Physical Component Score, median (IQR; range)[¶]	52.0 (47.4–57.0; 25.4–61.4)	55.9 (54.4–57.1; 41.7–64.1)
SF-12v2 Mental Component Score, median (IQR; range)[¶]	57.0 (41.9–61.2; 31.6–68.4)	49.4 (38.8–61.1; 35.5–62.1)

IQR, Interquartile range; *CRP*, C-reactive protein; *NA*, not applicable.

*Pain was rated on a scale of 0 to 10.

[†]One pediatric participant randomized to antibiotics-first did not receive a CT scan, so results are presented only for the 15 adult participants who did.

[‡]Radiographic identification of an appendicolith was initially an exclusion criterion but was later allowed (after 11 of 30 participants were enrolled) because of lack of consistent evidence of this being a risk factor for antibiotic failure.

[§]Two participants in the appendectomy group were missing results for lactate and CRP.

[‖]The Alvarado score[28] consists of the following components (points): right lower quadrant tenderness (0/2), elevated temperature (≥37.3°C [99.1°F]) (0/1), rebound tenderness (0/1), migration of pain to the right lower quadrant (0/1), anorexia (0/1), nausea or vomiting (0/1), leukocytosis greater than 10,000 cells/µL (0/2), and polymorphonuclear cells greater than 75% (0/1).

[¶]SF-12v2 Health Survey Acute version[24] (1-week recall) was used for adult (14 appendectomy and 15 antibiotic-first) participants to assess baseline quality of life before their appendicitis symptoms.

College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) criteria[25,26] modified to include major antibiotic-related complications. Major complications were defined as (1) organ/space infection, including peritonitis (not including uncomplicated appendicitis or complicated appendicitis found only at surgery); (2) wound dehiscence; (3) pneumonia; (4) unplanned intubation; (5) pulmonary embolism; (6) mechanical ventilation for more than 48 hours; (7) progressive renal insufficiency; (8) major urinary tract infection (eg, pyelonephritis); (9) malignant hyperthermia; (10) stroke/cerebral vascular accident; (11) coma for more than 24 hours; (12) cardiac arrest; (13) myocardial infarction; (14) bleeding requiring transfusion; (15) severe sepsis and septic shock; (16) deep venous thrombosis; (17) unexpected re-operation related to appendicitis; (18) dehydration requiring hospitalization; (19) unplanned hospitalization related to a complication of appendicitis or its treatment after initial hospitalization (not including suspicion of appendicitis or appendectomy in the antibiotics-first group); and (20) antibiotic-related adverse event, including colitis, requiring hospitalization.

Secondary outcomes included (1) appendectomy rate in the antibiotics-first group; (2) quality of life, measured by the SF-12v2 Health Survey[24] (baseline) and the PedsQL Survey,[27] both at 2 weeks and 1 month; (3) days unable to perform normal activities and work or school; (4) days of analgesic use; (5) pain scores at and 24 hours before each visit; (6) total hours in the ED and hospital at the initial visit from triage until ED or hospital discharge; (7) total hours in the hospital (including the ED) through 1 month; (8) Alvarado scores[28] on day 1 for both groups and day 2 for antibiotics-first participants; and (9) hospital charges. We assessed medication adherence by inspecting blister packs for retained pills or, if lost, by reviewing a memory aid and participant interview. Adverse events were graded according to standard definitions.[29] We collected baseline and outcome data on qualifying patients who declined participation by chart review.

Analysis

We managed study data using REDCap (Vanderbilt, Nashville, TN).[30] We determined a sample size of 30 participants for this pilot investigation (4.5% of the projected sample; sample size calculation [Appendix E3, available online at http://www.annemergmed.com]) evaluating the feasibility of a large multicenter trial testing noninferiority of the antibiotics-first approach for major complication rate. Because this was a pilot study, we did not conduct formal hypothesis testing and present results as descriptive statistics in the intention-to-treat population.

RESULTS
Characteristics of Study Participants

Of 48 eligible patients, 30 (62.5%) agreed to participate, of whom 16 (53.3%) were randomized to antibiotics-first and 14 (46.7%) to appendectomy (Figure 1). At follow-up, all participants completed therapy in their assigned group and all except one (96.7%) were seen or contacted at each specified follow-up visit. One participant in the antibiotics-first group had a follow-up telephone call at day four and reported complete recovery but did not return subsequently.

Baseline characteristics were similar between treatment groups (Table 1 and Table E1 [available online at http://www.annemergmed.com]), and between qualifying enrolled and nonenrolled patients (Table E2, available online at http://www.annemergmed.com). For all participants, median age was 33 years (range 9 to 73 years old), 60.0% were male, 83.3% were white, and 86.7% were Hispanic. Right lower-quadrant pain was the most frequent symptom (27 participants [90%]). Participants had a median of 1 day of pain (range 0.5 to 5.0 days) with a median maximal pain level of 9 of 10 (range 4 to 10). Median triage temperature was 36.9°C (98.4°F) (range 36.4°C to 38.1°C [97.5°F to 100.6°F]). Median WBC count was 15,000/mL (range 6,200 to 23,100/mL). Each group's median Alvarado scores was 8 (range 4 to 10), including those who declined participation. All participants had CT imaging with intravenous contrast, except 1 child, who had ultrasonography and 1 adult who had an elevated creatinine level. Median appendiceal diameter was 10 mm (range 7 to 18 mm). An appendicolith was detected in 5 participants (17.2%).

Among 15 antibiotics-first participants with complete follow-up, 14 (93.3%) completed 100% of oral antibiotic doses; 1 participant lost 1 tablet. Among 14 appendectomy participants, median time to operation was 8.0 hours (range 2.7 to 38.0 hours; 2 outliers >24 hours due to emergency surgeries interrupting scheduling). Appendectomy was performed laparoscopically in 9 (64.3%) participants and by open technique in 5 (35.7%) participants.

Main Results

Rates of hospitalization and ED discharge and time in hospital are summarized in Table 2. Of 15 adults treated with antibiotics-first, 14 (93.3%) met discharge criteria after a period of ED observation and were sent home with ED follow-up on day 2. One adult treated with antibiotics-first was hospitalized overnight on day 2 for observation and pain control after initial ED discharge. Per protocol, the one pediatric participant in the antibiotics-first group was hospitalized for twice-daily dosing of ertapenem. All appendectomy participants were

Table 2. Disposition, appendectomy rate, and hospital duration through 1 month for 30 participants with the diagnosis of acute uncomplicated appendicitis by treatment group.

Characteristic	Appendectomy, n=14	Antibiotics-First, n=16
Hospital admission at initial visit, No. (%)	14 (100)	2 (12.5)*
Received appendectomy, No. (%)	14 (100)	0
Time in hospital for initial visit, median (IQR; range), h	42.1 (28.8–51.0; 28.0–109.2)	12.3 (10.4–14.8; 7.7–80.3)
Total time in hospital, median (IQR; range), h[†]	42.1 (28.8–65.0; 28.0–128.8)	16.2 (14.2–34.3; 10.9–106.6)

*Fourteen participants were discharged from the ED.
[†]Total time in the hospital includes ED time and day 2 antibiotics-first group's evaluation and second intravenous dose of ertapenem and any subsequent hospital stay in both groups through the 1-month follow-up visit.

Table 3. Pain, analgesic use, activity, and quality-of-life outcomes of 30 participants with the diagnosis of acute uncomplicated appendicitis by treatment group.

Characteristic	Appendectomy, n =14	Antibiotics-First, n=16
Number of participants pain free, No. (%)		
At day 2*	0	5 (31.3)
Days 3–5	1 (7.1)	10 (62.5)
2 wk	2 (14.3)	12 (75.0)
1 mo	9 (64.3)	14 (87.5)
Total days receiving analgesics, median (IQR; range)		
Through day 2	1.0 (0.0–1.0; 0.0–1.0)	0.5 (0.0–1.0; 0.0–1.0)
Days 3–5	2.0 (1.0–2.0; 0.0–3.0)	1.0 (0.0–1.0; 0.0–3.0)
2 wk	4.0 (2.0–6.0; 1.0–10.0)	1.0 (0.0–1.0; 0.0–12)
1 mo	4.5 (3.0–8.0; 1.0–24.0)	1.0 (0.0–1.5; 0.0–12)
Unable to perform normal activities, No. (%)		
At day 2	14/14 (100.0)	10/16 (62.5)
Day 2 to 3–5	12/14 (85.7)	7/16 (43.8)
Days 3–5 to 2 wk	6/14 (42.9)	1/15 (6.7)
2 wk–1 mo	2/13 (15.4)	0/15
Quality-of-life measures		
SF-12v2 Physical Component score, median (IQR; range)[†]		
2 wk	44 (36–51; 31–56)	54 (52–58; 38–63)
1 mo	47 (40–53; 32–55)	56 (47–57; 33–62)
SF-12v2 Mental Component score, median (IQR; range)[†]		
2 wk	58 (48–61; 17–68)	55 (53–59; 38–61)
1 mo	56 (43–58; 37–68)	55 (49–57; 36–63)

*Follow-up visits occurred at day 2, days 3 to 5, 2 weeks (days 10 to 18), and 1 month (days 25 to 35) after enrollment (day 1).
[†]SF-12v2 Health Survey Acute version[24] (1-week recall) was used for adult (14 appendectomy and 15 antibiotic-first) participants at 2 weeks and the 4-week recall version at 1 month.

admitted to the hospital. Median total hospital time (including ED time) during 1 month was 16.2 hours (range 10.9 to 106.6 hours) in the antibiotics-first group compared with 42.1 hours (range 28.0 to 128.8 hours) in the appendectomy group. Median hospital charges were $5,145 (range $3,885 to $38,337) in the antibiotics-first group and $12,447 (range $7,430 to $41,832) in the appendectomy group.

At 1 month, major complications occurred in 2 appendectomy participants (14.3%; 95% confidence interval [CI] 1.8% to 42.5%) and 1 antibiotics-first participant (6.3%; 95% CI 0.2% to 33.9%). Among appendectomy participants, 1 sustained a trochar-related retroperitoneal hemorrhage, and 1, who was found to have cecal inflammation and a normal appendix at appendectomy, developed a postoperative intra-abdominal abscess on day 5. All antibiotic-treated participants had symptom resolution. One antibiotic-treated participant (without appendicolith) had recurrent appendicitis complicated by a phlegmon seen on CT scan on day 18 that was successfully treated with antibiotics (all major complications are described in Figure E1, available online at http://www.annemergmed.com). During median 12-month follow-up (range 9 to 18 months), 2 of 15 antibiotics-first participants (13.3%; 95% CI 3.7% to 37.8%) developed recurrent appendicitis; 1 had appendectomy for pathology-confirmed uncomplicated appendicitis at 9 months. No more major complications

occurred in the 15 antibiotics-first and 14 surgery participants who followed-up during this period.

Table 3 and Table E3 (available online at http://www.annemergmed.com) show pain levels, analgesic use, activity, and quality-of-life outcomes by visit. Antibiotics-first participants were pain free and returned to normal activities sooner and had higher physical SF-12v2 Health Survey® scores than appendectomy participants. Figure 2 depicts extent of improvement of antibiotics-first participants over the first day based on serial Alvarado scores; most improved
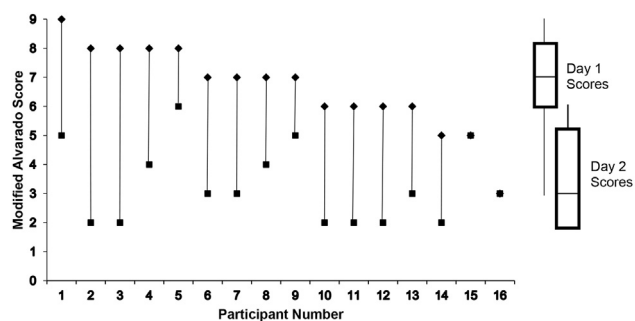
*The modified Alvarado score[25] consists of the following components (points): right lower quadrant tenderness (0/2); elevated temperature (≥37.3°C [99.1°F]) (0/1); rebound tenderness (0/1); anorexia (0/1); nausea or vomiting (0/1); leukocytosis >10,000 cells/mL (0/2); polymorphonuclear cells >75% (0/1). The modified score does not include migration of pain to the right lower quadrant since this variable would not be applicable for comparison of serial scores among a cohort of patients with imaging-confirmed appendicitis. The maximum modified Alvarado score is 9 instead of 10 for the original score.
There was no change between day 1 and day 2 scores for participant numbers 15 and 16.

Figure 2. Modified Alvarado scores* at day 1 (♦) and day 2 (■) for 16 participants with the diagnosis of acute uncomplicated appendicitis randomized to antibiotics-first treatment.

substantially and none worsened. Antibiotic-treated participants experienced more, mostly mild, adverse events, including diarrhea, headache, and nausea (Table E4, available online at http://www.annemergmed.com). We observed no wound infections.

LIMITATIONS

This study has a number of limitations. First, because a sham surgery would be unethical, these investigations are unblinded and management of participants and outcome assessments could be biased. Second, the small number of participants, and only 1 child, preclude full assessment of comparative effectiveness and could account for no case of initial antibiotic failure and the low recurrence rate. Third, this was a single-center study of mostly Hispanic patients treated at 1 Los Angeles–area public teaching hospital and the findings may not be generalizable. Notable, however, among this frequently non-English-speaking population, medication adherence and follow-up were sufficient to allow 14 of 15 adults to be managed successfully as outpatients after ED discharge. As opposed to past studies in which crossover from the assigned to alternate treatment strategy occurred in up to 53%,[4] we had none, which may be due to providing adequate education, pain control, and access to follow-up care. Finally, clinical examination and imaging misclassify some cases as uncomplicated appendicitis that are actually nonappendicitis or complicated disease. We had 1 appendectomy case (7.2%) in which appendicitis was not found on pathologic review; we did not categorize this as a major complication of surgery. Similarly, we did not categorize the day 2 overnight hospitalization of one antibiotic-treated participant for observation and pain control as a major complication because it was part of the treatment strategy. Complicated appendicitis can be missed preoperatively and only discovered at surgery, as we observed in 4 participants (28.6%).[5-7,31,32] Because finding complicated appendicitis only at surgery, and not according to clinical examination and imaging, would be more common among patients undergoing routine as opposed to rescue surgery, we did not include it as a major complication in general or consider it as a major complication only in the antibiotics-first group, which has been a criticism of one trial that concluded that the antibiotics-first approach was not noninferior to appendectomy.[5,33] Consequently, we may have missed cases of complicated disease that developed between randomization and operation. However, this is unlikely, given the generally short time to surgery and evidence that surgery delays for patients receiving antibiotics do not appear to be associated with an increased perforation rate.[34]

DISCUSSION

In this pilot randomized trial comparing antibiotics-first and appendectomy, we describe a novel, safe, and effective strategy that allows outpatient antibiotic management of imaging-confirmed uncomplicated appendicitis. All but 1 of the 15 adult patients randomized to antibiotics-first were successfully managed as outpatients after a minimum 6-hour ED observation period after triage. Of 15 antibiotics-first participants followed over approximately 1 year, only 2 (13.3%) had recurrence of appendicitis; 1 underwent appendectomy and the other was successfully treated medically. Unlike in past trials, in which approximately one quarter of patients had appendectomy during 1 year of follow-up, only 1 (6.7%) participant in this pilot did. The ability to manage appendicitis with antibiotics and without hospitalization could significantly reduce costs and could be an important consideration for a patient choosing between surgical and medical management. To our knowledge, this pilot study is also the first randomized trial comparing antibiotics-first and appendectomy to be conducted in the US. Although concerns have been raised that patients would refuse to participate in randomized trials of appendicitis if they could not choose their treatment,[8] approximately two thirds of eligible patients provided consent, no participants crossed over to the alternate treatment strategy, and nearly universal follow-up was achieved. These trial performance measures and excellent outcomes support the feasibility of a large multicenter US randomized trial.

We included patients similar to those enrolled in most published trials (ie, patients with clinical- and CT-confirmed uncomplicated appendicitis). We excluded patients with severe sepsis, immunocompromise, or with acute comorbidities, but not the elderly and those with most stable comorbidities. Initially, we excluded patients with appendicolith because the results of some[9,14] but not all studies[4,5,7,10-12,15] found an association with antibiotic failure. Given our early success with antibiotic therapy, we later elected to include patients with appendicolith to explore the feasibility of including this large subset in future trials.

The hospital stays we report are shorter than those reported from previous randomized trials, likely due in part to differences between European and US health care practices. Among the 7 European trials comparing an antibiotics-first approach to urgent appendectomy, duration of hospitalization has been similar between treatment groups, approximately 3 days.[1-7] In these trials, patients randomized to antibiotics-first were required to be hospitalized up to 3 days, and most appendectomies were performed by open

technique. The general trend in US healthcare is toward shorter hospital stays. The US Nationwide Inpatient Sample of adults who underwent appendectomy from 2003 to 2011 revealed that mean stay decreased from 3.2 to 2.6 days while laparoscopically performed procedures increased from 40.7% to 80.1%.[18] Same-day laparoscopic appendectomy, using discharge criteria similar to ours, has been described, although it is not widely practiced.[35]

Unlike past randomized trials, we applied symmetrical discharge criteria for participants in each group, ie, clinical stability, tolerating fluids, and pain control with oral medications. Participants older than 13 years randomized to antibiotics-first were evaluated, treated, and observed in the ED and were discharged if these criteria were met. Participants then returned for a next-day ED follow-up evaluation. To ensure effective antibiotic coverage, we administered a Food and Drug Administration–approved once-a-day parenteral antibiotic recommended for intra-abdominal infections, ertapenem,[36] at enrollment and the next day, followed by oral antibiotics to complete a 10-day course. Our rationale for using a long-acting parenteral agent was that, early in appendicitis, nausea and vomiting could interfere with full adherence with an oral antibiotic regimen. All appendectomy participants were hospitalized as opposed to most adult antibiotics-first-treated participants, who were discharged from the ED. Consequently, antibiotics-first participants had substantially reduced total hospital time, including ED time (median 16.2 hours compared with 42.1 hours through 1 month). Other off-label once-daily parenteral antibiotic strategies could be used, also allowing similar management in young children.

Previous randomized trials had various criteria for antibiotic failure and reported that about 10% of antibiotics-first-treated participants required appendectomy during their initial hospitalization.[2,4-7] One trial found that the presence of an appendicolith was a significant risk factor for initial antibiotic failure.[14] None of our antibiotic-first participants had initial treatment failure, including 2 with appendicolith. Because almost all of our antibiotics-first-treated participants were discharged from the ED, lack of initial antibiotic failure may be due to fewer opportunities for surgeons to observe variations in pain control and suggest operative intervention and patient inertia to continue outpatient care once home. Knowledge of the association of appendicolith and complicated disease may also decrease a provider's threshold to consider a case a treatment failure. The appendicitis recurrence rate after antibiotics may be as low as 15% over the first year following the initial attack of appendicitis with a more extended antibiotic trial. One of the 2 antibiotic-treated participants who had recurrence chose retreatment with antibiotics, an option that would further decrease subsequent appendectomy rate.

As opposed to previous trials in which the primary outcome was appendectomy rate in the antibiotic group,[1-3,6,7] we chose an outcome independent of treatment strategy, ie, major complications defined by ACS NSQIP criteria modified to include serious antibiotic-related adverse events.[25,26] Before conducting this trial, we surveyed persons with and without previous appendectomy and found they prioritized clinical outcomes over quality-of-life and pain outcomes.[37] Clinical outcomes are also likely more important to physicians whom patients trust for direction of their care. We observed the rate of major complications (all of which occurred in the first month) among participants in the antibiotics-first and appendectomy groups to be 6.3% and 14.3%, respectively. The high rate in the appendectomy group likely represents a sampling error. Rates of major complications after appendectomy at our hospital have historically been consistent with reported rates of less than or equal to 5%,[25,26,38] and no qualifying but nonenrolled patient receiving appendectomy experienced a major complication.

Secondary outcomes, which included pain scores, analgesic use, disability time, and quality-of-life measures, favored the antibiotics-first group. Remarkably, approximately one third of antibiotic-treated participants were pain free and resumed their normal activities after approximately 24 hours. Few data exist describing the rate and variability of early response to antibiotics.[1] Although the Alvarado score[28] was developed as a clinical tool to diagnose appendicitis, it contains components that clinicians might use to follow the progress of an antibiotic-treated patient, eg, fever, tenderness, nausea, leukocytosis. In most antibiotics-first participants, as reflected by serial scores, these findings substantially improved during only 1 day. A few participants had lower scores that stayed constant, but ultimately their symptoms resolved, suggesting that, even with persistent symptoms at 24 hours, it is reasonable to continue antibiotics. Next-day contact by telephone may be sufficient for most patients. Participants treated with antibiotics-first experienced more mild adverse events, such as diarrhea, nausea, and headache, likely related to greater antibiotic exposure. However, these symptoms did not interfere with good antibiotic adherence.

Antibiotic management of uncomplicated appendicitis remains an uncommon practice in the US.[23,39] We believe that clinical and patient-centered outcomes require comparison in a large US-based multicenter randomized trial among a diverse population in which

imaging is routinely used, most appendectomies are performed laparoscopically, early discharge is promoted, including from the ED for antibiotics-first patients, and patients are offered antibiotic retreatment and are followed for at least 2 years. In accordance with our successful experience with this pilot study, we believe that such a trial is necessary and feasible.

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***Annals'* Impact Factor rose to an all-time high this year, to 5.008.**

APPENDIX E1

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APPENDIX E2

Radiology Methods

Imaging studies were first interpreted by an on-call attending radiologist, which was the interpretation used to decide patient eligibility. Subsequently, imaging was reviewed by a full-time radiologist who recorded findings on a standardized form.

Computed tomography (CT) was performed on a multi-detector row CT scanner (Somatom Definition Flash 64 [Siemens Healthcare, Forcheim, Germany]), using a standard imaging protocol: 120 kVp, 24 x 1.2-mm collimation, pitch of 1, 90-second delay after intravenous contrast administration at 3 mL/sec (Omnipaque 350 mgl/mL [GE Healthcare, Little Chalfont, UK]). Tube current modulation (CARE kv) was used on each case with a quality reference mAs setting of 250, which corresponds to a default $CTDI_{vol}$ of 16 mGy. Pediatric CT protocols were utilized for patients less than 18 years of age. Intravenous contrast agent was administered unless contraindicated by decreased glomerular filtration rate less than 30 ml/min or history of severe allergic reaction to iodinated contrast. Enteric contrast material was not administered according to our standard protocol for abdominal CT studies performed in the emergency department. Images were reconstructed in the axial plane at 5-mm and in the coronal plane at 2-mm section thickness, and interpreted on a picture archiving and communication system (PACS) station by a staff radiologist. CT imaging findings were described/dictated using standardized definitions (see below). Ultrasound was performed by using the graded compression technique with a curved 3.5 to 5.0-MHz array and linear 10-MHz array transducers.

We used 4 methods to decrease the radiation dose. We decreased the radiation dose by: (1) Performing a CT abdomen and pelvis with IV contrast only and eliminated the non-contrast CT liver part of the study, which accounts for 40% to 60% of the total radiation dose of a CT of the abdomen and pelvis with and without contrast; (2) Using tube current (mAs) modulation software

Siemens CARE Dose4D in acquisition of CT studies, which adjusts the tube current (mAs) based on the size and shape of the patient; (3) Using tube voltage (kV) modulation software Siemens CARE kV, which adjusts the tube voltage based on the patient's topogram and the selected examination protocol; and (4) Providing CT coronal reformations obtained at 2-mm intervals for all studies, which has been shown to improve confidence in visualization of the appendix and in diagnosis or exclusion of appendicitis, avoiding potential interpretations of equivocal for appendicitis, which may lead to repeat imaging and increased radiation dose.[1]

CT studies were reviewed for the following: appendiceal diameter (maximum wall-to-wall); hyperemia (increased appendiceal wall enhancement relative to adjacent bowel wall); periappendiceal fluid, non-physiologic; periappendiceal stranding, presence, and degree (mild [perceptible haziness or increased attenuation in the mesoappendix or retroperitoneal fat], moderate [significantly increased attenuation and/or stranding of the mesenteric fat at the right side of the pelvis], and severe [extensively increased attenuation and/or stranding of the mesenteric fat at the right side of the pelvis and/or lower part of the abdomen]); phlegmon (diffuse and substantial inflammation of the peri-appendiceal fat with ill-defined fluid, with or without air collections); abscess (discrete fluid, with or without an air collection, with well-defined wall); appendicolith; extraluminal (free air); and mucocele (dilated appendix >15 mm without signs of appendicitis, ie, hyperemia, fat stranding, free fluid, free air, peri-appendiceal phlegmon, or abscess).

Ultrasound studies were interpreted for the following: visualization of the appendix, appendiceal diameter, compressibility of the appendix, peri-appendiceal or right lower quadrant fluid collection, and appendicolith. Appendiceal diameter was measured from serosal to serosal surface while imaging the appendix in the transverse plane. Compressibility was defined as measurable change in the caliber of the lumen of the appendix. A fluid collection had a definable wall and mass effect. Appendicolith was defined as an echogenic, well-defined focus within the appendix with posterior acoustic shadowing.

In addition to recording diagnostic characteristics for each case, each reviewer provided an impression of one of the following: normal appendix, acute uncomplicated appendicitis, acute complicated appendicitis, and equivocal for appendicitis. For CT interpretation, an additional diagnostic option was equivocal for uncomplicated versus complicated appendicitis. The imaging criteria for the final

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diagnosis were derived from a review of literature and included those features previously reported to have diagnostic value.[2-9]

APPENDIX E3

Sample Size Calculation

The current operative approach to appendicitis is associated with serious adverse complications in approximately 3% of patients,[1,2] resulting in recovery without serious complications in 97% of cases. Existing trials demonstrate similar rates of recovery among patients treated with primary antibiotic therapy.[3] The rate of uneventful recovery among a relatively healthy population eligible for inclusion in this study is likely to be higher than that observed in the general population. Thus, assuming recovery rates without serious complications in 97% of cases for both treatment arms, and assuming a 5% limit of indifference, a noninferiority trial with a power of 95% and statistical significance of 5% could be completed with 662 patients (331 patients assigned to each arm). Assuming that 10% of patients are unable to complete the study (due to lack of follow-up, protocol violations, and other unforeseen events), the study may need to enroll as many as 736 patients. It has been suggested that pilot studies should include 30 patients or 3% of the sample size for the actual trial, whichever is greater.[4] Under this principle, our estimated sample size for the pilot study is 30 patients (4.5% of the projected sample).

Our limit of indifference of 5% comes from the following analysis. The potential for cost savings drives the use of antibiotics to treat acute uncomplicated appendicitis. Surgical treatment, including emergency department evaluation, physician fees, laboratory and imaging fees, and operating and hospital costs, currently approaches $8,000 per patient.[1,5,6] Primary treatment with antibiotics eliminates many hospital admissions and operation expenses, and reduces costs by 50% to $4,000 per case.[7] However, because primary treatment with antibiotics is associated with failure in up to 30% of cases,[3] the costs for treating patients who require surgical rescue is actually $500 greater than the cost of primary surgery.[7] This effect raises the overall costs of antibiotic treatment with surgical rescue to an average of $5,350 per patient, which still represents cost savings of $2,650 per case.

It is possible that initial cost-savings from the use of primary antibiotic treatment could be eroded through increased cost required to treat patients who experience major complications as a result of this treatment. The average cost of treating patients who experience a major complication following appendectomy is $38,000.[2] This is equivalent to the cost-savings that might be recognized through treating 14 patients with primary antibiotic therapy, and corresponds to a 7% increase in the rate of major complications. Consequently, primary treatment with antibiotic therapy with surgical rescue will present cost advantages provided the associated rate of major complications with this treatment does not exceed the major complication rate of primary surgical treatment by more than 7%.

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Table E1. Baseline characteristics of 30 participants with the diagnosis of acute uncomplicated appendicitis by treatment group.*

Characteristic	Appendectomy (n = 14)	Antibiotics-First (n = 16)
Age, median years (IQR, range)	36 (33-46; 24-65)	31 (25-40; 9-73)
Male sex	9 (64.3)	9 (56.3)
Race		
White	12 (85.7)	13 (81.3)
Black	0 (0.0)	0 (0.0)
Asian	0 (0.0)	0 (0.0)
Hawaiian/Pacific Islander	0 (0.0)	1 (6.3)
American Indian/Alaska Native	0 (0.0)	0 (0.0)
Other	1 (7.1)	2 (12.5)
Unknown	1 (7.1)	0 (0.0)
Hispanic ethnicity	12 (85.7)	14 (87.5)
Comorbidities		
Diabetes	0 (0.0)	1 (6.3)
HIV	0 (0.0)	0 (0.0)
COPD	0 (0.0)	0 (0.0)
CHF	0 (0.0)	0 (0.0)
Cancer	0 (0.0)	0 (0.0)
Body mass index, median kg/m^2 (IQR; range)	28.0 (24.6-29.8; 21.0-31.8)	27.3 (25.1-33.0; 22.3-43.3)
Prior abdominal/pelvic surgery	3 (21.4)	3 (18.8)
Cholecystectomy	0 (0.0)	1 (6.3)
Colectomy	0 (0.0)	0 (0.0)
Hysterectomy	1 (7.1)	0 (0.0)
Exploratory laparotomy	0 (0.0)	0 (0.0)
Other	3 (21.4)	2 (12.5)
Symptoms		
Subjective fever	4 (28.6)	2 (12.5)
Measured fever	1 (7.1)	0 (0.0)
Anorexia	10 (71.4)	11 (68.8)
Nausea	13 (92.9)	12 (75.0)
Vomiting	11 (78.6)	8 (50.0)
Right lower quadrant pain	13 (92.9)	14 (87.5)
Duration of pain, median days (IQR; range)	1.0 (0.5- 3.0; 0.5-5.0)	1.0 (1.0-2.5; 0.5-5.0)
Severity of pain		
Mild	1 (7.1)	3 (19.8)
Moderate	6 (42.9)	11 (68.8)
Severe	7 (50.0)	2 (12.5)
Maximal pain prior 24 hours[†], median (IQR; range)	10 (8-10; 5-10)	8 (8-10; 4-10)
Signs		
Localized rebound tenderness	10 (71.4)	8 (50.0)
Localized guarding	6 (42.9)	6 (37.5)
Triage pulse, median beats/min (IQR; range)	75 (70-82; 62-124)	78 (68-95; 56-107)
Triage SBP, median mm Hg (IQR; range)	112 (107-125; 87-135)	121 (107-131; 99-154)
Triage DBP, median mm Hg (IQR; range)	65 (62-72; 53-78)	68 (58-77; 48-91)
Triage respirations, median beats/min (IQR; range)	17 (17-18; 16-20)	18 (17-18; 16-20)
Triage temperature, median °C (IQR; range)	36.9 (36.6-36.7; 36.5-38.1)	36.8 (36.7-37.2; 36.4-37.3)
Computed tomographic findings[‡]		
Appendicolith[§]	3 (21.4)	2 (12.5)
Appendiceal diameter, median mm (IQR; range)	9 (9-12; 7-8)	10 (9-12; 7-14)
Periappendiceal stranding		
None	0 (0.0)	2 (12.5)
Mild	7 (50.0)	11 (68.8)
Moderate	6 (42.9)	1 (6.3)
Severe	1 (7.1)	0 (0.0)
NA	0 (0.0)	1 (6.3)
Hyperemia		
Yes	14 (100.0)	11 (68.8)
No	0 (0.0)	4 (25.0)
NA	0 (0.0)	1 (6.3)

Table E1. Continued.

Characteristic	Appendectomy (n = 14)	Antibiotics-First (n = 16)
Periappendiceal fluid		
Yes	3 (21.4)	2 (12.5)
No	11 (78.6)	13 (81.3)
NA	0 (0.0)	1 (6.3)
Laboratory results		
WBC count, x10^3/μL, median (IQR; range)	15.3 (11.0-18.4; 8.1-23.1)	14.2 (11.3-17.0; 6.2-19.2)
Neutrophils, median % (IQR; range)	83.8 (81.7-89.2; 60.2-94.4)	82.7 (79.8-90.9; 49.8-92.9)
Lactate, median mmol/L (IQR; range)[‖]	1.0 (0.9-1.4; 0.6-1.6)	1.1 (0.9-1.5; 0.7-2.3)
CRP, median mg/L (IQR; range)[‖]	64.8 (42.6-101.6; 8.2-256.4)	25.9 (10.8-64.8; 3.8-202.6)
Alvarado score[¶], median (IQR; range)	8 (7-9; 4-10)	8 (7-9; 4-10)
Received first parenteral antibiotic dose <6 hours prior to enrollment	4 (28.6)	5 (31.3)
Appendix pathology findings		
Normal	1 (7.1)	
Acute uncomplicated	9 (64.3)	
Suppurative and/or gangrenous	4 (28.6)	
Quality-of-life measures		
SF-12v2 Physical Component Score[#], median (IQR; range)	52.0 (47.4-57.0; 25.4-61.4)	55.9 (54.4-57.1; 41.7-64.1)
SF-12v2 Mental Component Score[#], median (IQR; range)	57.0 (41.9-61.2; 31.6-68.4)	49.4 (38.8-61.1; 35.5-62.1)

COPD, chronic obstructive pulmonary disease; *CHF*, congestive heart failure; *NA*, not available; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure.

*Data are presented as No. (%) unless otherwise indicated.

[†]Pain was rated on a scale of 0 to 10.

[‡]One pediatric participant randomized to antibiotics-first did not receive a CT scan, so results are only presented for the 15 adult participants who did.

[§]Radiographic identification of an appendicolith was initially an exclusion criterion but was later allowed (after 11 of 30 participants were enrolled) because of lack of consistent evidence of this being a risk factor for antibiotic failure.

[‖]Two participants in the appendectomy group were missing results for lactate and CRP.

[¶]The Alvarado score[28] consists of the following components (points): right lower quadrant tenderness (0/2); elevated temperature (≥37.3°C or 99.1°F) (0/1); rebound tenderness (0/1); migration of pain to the right lower quadrant (0/1); anorexia (0/1); nausea or vomiting (0/1); leukocytosis >10,000 cells/μL (0/2); polymorphonuclear cells >75% (0/1).

[#]SF-12v2® Health Survey Acute version[24] (1-week recall) was utilized for adult (14 appendectomy and 15 antibiotic-first) participants to assess baseline quality of life prior to their appendicitis symptoms.

Table E2. Baseline characteristics of qualifying enrolled and nonenrolled patients with the diagnosis of acute uncomplicated appendicitis.*

Characteristic	Enrolled n=30	Non-Enrolled n=18
Median age, years (IQR, range)	33 (29-45; 9-73)	29 (21-35; 12-55)
Male sex	16 (60.0)	13 (72.2)
Race		
White	25 (83.3)	18 (100.0)
Black	0 (0.0)	0 (0.0)
Asian	0 (0.0)	0 (0.0)
Hawaiian/Pacific Islander	1 (3.3)	0 (0.0)
American Indian/Alaska Native	0 (0.0)	0 (0.0)
Other	3 (10.0)	0 (0.0)
Unknown	1 (3.3)	0 (0.0)
Hispanic ethnicity	26 (86.7)	17 (94.4)
Symptoms		
Subjective fever	6 (20.0)	3 (16.7)
Anorexia	21 (68.8)	7 (38.9)
Nausea	25 (75.0)	14 (77.8)
Vomiting	19 (50.0)	8 (44.4)
Right lower quadrant pain	27 (87.5)	17 (94.4)
Duration of pain, median days (IQR; range)	1.0 (1.0-3.0; 0.5-5.0)	1.0 (1.0-1.5; 0.5-4.0)
Severity of pain		
Mild	4 (19.8)	2 (11.1)
Moderate	17 (68.8)	13 (72.2)
Severe	9 (12.5)	3 (16.7)
Signs		
Triage temperature, median °C (IQR; range)	36.9 (36.7-37.2; 36.4-38.1)	36.9 (36.7-37.3; 36.6-38.2)
Computed tomographic findings[†]		
Appendicolith[‡]	5/29 (17.2)	1/17 (5.9)
Appendiceal diameter, median mm (IQR; range)	10 (9-12; 7-18)	11 (10-14; 7-20)
Periappendiceal stranding		
None	2 (6.9)	0 (0.0)
Mild	18 (62.1)	12 (70.6)
Moderate	7 (24.1)	4 (23.5)
Severe	1 (3.4)	1 (5.9)
NA	1 (3.4)	0 (0.0)
Hyperemia		
Yes	24 (82.8)	16 (94.1)
No	4 (13.8)	1 (5.9)
NA	1 (3.4)	0 (0.0)
Periappendiceal fluid		
Yes	5 (12.5)	4 (23.5)
No	24 (82.8)	13 (76.5)
NA	1 (3.4)	0 (0.0)
Laboratory results		
WBC count, median $\times 10^3/\mu L$ (IQR; range)	15.0 (11.3-17.0; 6.2-23.1)	15.1 (11.9-17.2; 9.4-19.1)
Neutrophils, median % (IQR; range)	83.9 (81.1-89.7; 49.8-94.4)	81.8 (72.1-85.9; 57.8-94.8)
Alvarado score[§], median (IQR; range)	8 (7-9; 4-10)	8 (6-8; 3-9)
Appendix pathology findings		
Normal	1/14 (7.1)	0 (0.0)
Acute uncomplicated	9/14 (64.3)	12 (70.6)
Suppurative and/or gangrenous	4/14 (28.6)	5 (29.4)
Perforated	0/14 (0.0)	1 (5.9)
Received appendectomy	14/14 (100)	17 (94.4)
Open	5 (35.7)	6/17 (35.2)
Laparoscopic	9 (64.3)	11/17 (64.7)
Major complications	3 (10.0)	0 (0.0)

*Data are presented as No. (%) unless otherwise indicated.

[†]One patient of pediatric age in each group did not get a computed tomography scan.

[‡]Radiographic identification of an appendicolith was initially an exclusion criterion but was later allowed (after 11 of 30 participants were enrolled) because of lack of consistent evidence of this being a risk factor for antibiotic failure.

[§]The Alvarado score[24] consists of the following components (points): right lower quadrant tenderness (0/2); elevated temperature (≥37.3°C or 99.1°F) (0/1); rebound tenderness (0/1); migration of pain to the right lower quadrant (0/1); anorexia (0/1); nausea or vomiting (0/1); leukocytosis >10,000 cells/μL (0/2); polymorphonuclear cells >75% (0/1).

Randomized to Surgery

Complication - Unplanned intubation due to retroperitoneal trocar-related injury with ICU admission on day 1

A 34-year old male with no major co-morbidities or past surgeries presented with a half-day history of severe abdominal pain with anorexia, nausea, and vomiting, and examination findings of localized right lower quadrant abdominal tenderness without rebound or guarding. His WBC count was 17.0 x10^3/μL and his computed tomography (CT) scan revealed a 9-mm diameter appendix and mild stranding with hyperemia. He underwent laparoscopic appendectomy, which demonstrated appendicitis with no purulent fluid, gangrene, perforation, or abscess. Intraoperatively, a retroperitoneal hematoma was observed. Intubation was maintained, the participant was admitted for one day to the ICU for observation, and recovered without need for blood transfusion.

Complications - Organ space infection (pelvic abscess diagnosed 2 days after discharge) and unplanned hospitalization on day 5

A 59-year-old female with no major co-morbidities and prior Caesarian section presented with a 5-day history of severe abdominal pain with anorexia and nausea, and examination findings of right lower quadrant abdominal rebound tenderness and guarding. Her WBC count was 8.1 x 10^3/μL and her CT scan revealed a 7-mm diameter appendix with an appendicolith and moderate stranding and hyperemia,

and no periappendiceal fluid. She underwent open appendectomy and inflammation of the cecum was observed, but the appendix appeared normal and was normal on pathology review. The participant returned on day 5 (2 days after being discharged from the hospital) complaining of suprapubic pain and a CT scan revealed a 5-cm fluid collection with an enhancing wall in the pelvis consistent with an abscess. The participant received percutaneous drainage and antibiotics and recovered.

Randomized to Antibiotics-First

Complication - Organ space infection and unplanned hospitalization due to recurrent perforated appendicitis on day 18

A 37-year-old female with no other major co-morbidities or past surgeries presented with a 4-day history of moderate abdominal pain with chills and anorexia, and examination findings of right lower quadrant abdominal rebound tenderness without guarding. Her WBC count was 11.9 x 10^3/μL and her CT scan revealed a 9-mm diameter appendix and moderate stranding and hyperemia and no appendicolith. The participant gradually improved, and on day 11 reported no pain and had no abdominal tenderness. On day 18, the participant returned with right lower quadrant pain and a CT revealed a 10-mm appendix with an associated phlegmon and 1.3-cm fluid collection. The participant wished to avoid surgery. She was treated with antibiotics and recovered. She was offered and declined interval appendectomy.

Figure E1. Summary of major complications.

Table E3. Pain, analgesic use, activity, and quality-of-life outcomes of 30 participants with the diagnosis of acute uncomplicated appendicitis by treatment group.*

Characteristic	Appendectomy (n=14)	Antibiotics-First (n=16)
Number of participants pain-free		
At day 2[†]	0 (0.0)	5 (31.3)
Day 3-5	1 (7.1)	10 (62.5)
Two weeks	2 (14.3)	12 (75.0)
One month	9 (64.3)	14 (87.5)
Total days on analgesics, median (IQR; range)		
Through day 2	1.0 (0.0-1.0; 0.0-1.0)	0.5 (0.0 -1.0; 0.0-1.0)
Day 3-5	2.0 (1.0-2.0; 0.0-3.0)	1.0 (0.0-1.0; 0.0-3.0)
Two weeks	4.0 (2.0-6.0; 1.0-10.0)	1.0 (0.0-1.0; 0.0-12)
One month	4.5 (3.0-8.0; 1.0-24.0)	1.0 (0.0-1.5; 0.0-12)
Maximal pain score[‡] prior 24 hours, median (IQR; range)		
Day 2	9.0 (7.0-9.0; 4.0-10.0)	4.5 (3.0-6.5; 1.0-9.0)
Day 3-5	4.5 (4.0-6.0; 2.0-8.0)	2.0 (0.5-5.5; 0.0-7.0)
Two weeks	3.5 (1.0-4.0; 0.0-8.0)	0.0 (0.0-2.0; 0.0-7.0)
One month	1.0 (0.0-4.0; 0.0-8.0)	0.0 (0.0-2.0; 0.0-6.0)
Total days missed normal activities, median (IQR; range)		
Through day 2	1.0 (1.0-1.0; 0-1.0)	1.0 (0.0-1.0; 0.0-1.0)
Day 3-5	2.0 (2.0-3.0; 1.0-4.0)	1.0 (0.5-2.5; 0.0-4.0)
Two weeks	2.5 (2.0-9.0; 1.0-13)	1.0 (0.5-2.5; 0.0-6.0)
One month	4.0 (2.0-9.0; 1.0-28)	1.0 (0.5-2.5; 0.0-6.0)
Unable to perform normal activities		
At day 2	14/14 (100.0)	10/16 (62.5)
Day 2 to 3-5	12/14 (85.7)	7/16 (43.8)
Day 3-5 to two weeks	6/14 (42.9)	1/15 (6.7)
Two weeks to one month	2/13 (15.4)	0/15 (0.0)
Total days missed work or school, median (IQR; range)	n=8[§]	n=13[§]
Through day 2	1.0 (0.5-1.0; 0.0-1.0)	1.0 (1.0-1.0; 0.0-1.0)
Day 3-5	2.5 (1.5-3.0; 0.0-4.0)	1.0 (1.0-3.0; 0.0-3.0)
Two weeks	3.5 (2.0-10; 1.0-13)	2.0 (1.0-3.0; 0.0-7.0)
One month	3.5 (2.5-22; 2.0-28)	2.0 (1.0-3.0; 0.0-7.0)
Missed any work or school		
At day 2	8/8 (100)	10/13 (76.9)
Day 2 to 3-5	6/8 (75.0)	7/13 (53.8)
Day 3-5 to two weeks	5/8 (62.5)	4/12 (33.3)
Two weeks to one month	4/8 (50.0)	0/12 (0.0)
Quality-of-life meaures		
SF-12v2 Physical Component Score[‖], median (IQR; range)		
At two weeks	44 (36-51; 31-56)	54 (52-58; 38-63)
One month	47 (40-53; 32-55)	56 (47-57; 33-62)
SF-12v2 Mental Component Score[‖], median (IQR; range)		
At two weeks	58 (48-61; 17-68)	55 (53-59; 38-61)
One month	56 (43-58; 37-68)	55 (49-57; 36-63)
PEDsQL Physical Health Score[¶]		
At two weeks		97
One month		97
PEDsQL Psychosocial Health Score[¶]		
At two weeks		95
One month		95

*Data are presented as No. (%) unless otherwise indicated.
[†]Follow-up visits occurred at day 2, day 3-5, two weeks (day 10-18) and one month (day 25-35) after enrollment (day 1).
[‡]Pain was rated on a scale of 0-10, 10 being the most pain.
[§]Not all participants worked or went to school, so were omitted from these descriptions. Denominators are indicated.
[‖]SF-12v2® Health Survey Acute version[24] (1-week recall) was utilized for adult (14 appendectomy and 15 antibiotic-first) participants at two weeks and the 4-week recall version at one month.
[¶]The PEDsQL™ Survey Acute version[27] child report for ages 8-12 years (1-week recall) was utilized for the pediatric participant (randomized to antibiotics-first) at two weeks and the 4-week recall version at one month.

Table E4. Number of adverse events by severity* and treatment group through 1 month for 30 participants with the diagnosis of acute uncomplicated appendicitis.

Adverse Event	All	Appendectomy			Antibiotics-First	
		Mild	Moderate	Life- Threatening	Mild	Moderate
Diarrhea	14	1	1	0	11	1
Back pain	14	9	0	0	5	0
Subjective fever/chills	11	5	0	0	6	0
Nausea	9	2	0	0	7	0
Headache	9	1	0	0	6	2
Anorexia	7	2	0	0	5	0
Constipation	6	1	1	0	4	0
Abdominal pain (new)	4	1	0	0	1	2
Rash	4	2	0	0	2	0
Dizziness	3	1	0	0	2	0
All other[†]	22	4	3	1	13	1
Total events	**103**	**29**	**5**	**1**	**62**	**6**
Number per participant, median (IQR; range)	3 (1-4; 0-9)	2 (1-3; 0-6)			4 (1-7; 1-9)	

*All adverse events were graded for severity as follows: mild (Grade 1), events that required minimal or no treatment and did not interfere with the participant's daily activities; moderate (Grade 2), events that resulted in a low level of inconvenience or concern with the therapeutic measures, and may have caused some interference with functioning; severe (Grade 3), events that interrupted a participant's usual daily activity and may have required systemic drug therapy or other treatment, and were incapacitating; and life-threatening (Grade 4), any adverse drug experience that placed the participant at immediate risk of death, not including a reaction that had it occurred in a more severe form, might have caused death.[29]

[†]Other adverse events graded as mild in the antibiotics-first group were fatigue (1), metallic smelling mouth (1), gastritis (2), bloating (1), yeast infection (1), chest pressure (1), right leg and testicular numbness (1), vaginal itchiness (1), irritation with bowel movements (1), itching (1), inability to pass gas/bloating (1), and burning on urination (1). The adverse event graded as moderate in the antibiotics-first group was a phlegmon. Adverse events graded as mild in the appendectomy group were abdominal cramping (1), chest pain (1), testicular pain (1), and double vision (1), and adverse events graded as moderate were intraabdominal abscess (1), sore throat (1), and numbness in abdomen (1). The adverse event graded as life-threatening in the appendectomy group was a trochar-related injury causing a retroperitoneal hematoma that required prolonged intubation and ICU admission for observation but no blood transfusions.