

## Original Investigation

# Antibiotic Therapy vs Appendectomy for Treatment of Uncomplicated Acute Appendicitis

## The APPAC Randomized Clinical Trial

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**IMPORTANCE** An increasing amount of evidence supports the use of antibiotics instead of surgery for treating patients with uncomplicated acute appendicitis.

**OBJECTIVE** To compare antibiotic therapy with appendectomy in the treatment of uncomplicated acute appendicitis confirmed by computed tomography (CT).

**DESIGN, SETTING, AND PARTICIPANTS** The Appendicitis Acuta (APPAC) multicenter, open-label, noninferiority randomized clinical trial was conducted from November 2009 until June 2012 in Finland. The trial enrolled 530 patients aged 18 to 60 years with uncomplicated acute appendicitis confirmed by a CT scan. Patients were randomly assigned to early appendectomy or antibiotic treatment with a 1-year follow-up period.

**INTERVENTIONS** Patients randomized to antibiotic therapy received intravenous ertapenem (1 g/d) for 3 days followed by 7 days of oral levofloxacin (500 mg once daily) and metronidazole (500 mg 3 times per day). Patients randomized to the surgical treatment group were assigned to undergo standard open appendectomy.

**MAIN OUTCOMES AND MEASURES** The primary end point for the surgical intervention was the successful completion of an appendectomy. The primary end point for antibiotic-treated patients was discharge from the hospital without the need for surgery and no recurrent appendicitis during a 1-year follow-up period.

**RESULTS** There were 273 patients in the surgical group and 257 in the antibiotic group. Of 273 patients in the surgical group, all but 1 underwent successful appendectomy, resulting in a success rate of 99.6% (95% CI, 98.0% to 100.0%). In the antibiotic group, 70 patients (27.3%; 95% CI, 22.0% to 33.2%) underwent appendectomy within 1 year of initial presentation for appendicitis. Of the 256 patients available for follow-up in the antibiotic group, 186 (72.7%; 95% CI, 66.8% to 78.0%) did not require surgery. The intention-to-treat analysis yielded a difference in treatment efficacy between groups of -27.0% (95% CI, -31.6% to ∞) ( $P = .89$ ). Given the prespecified noninferiority margin of 24%, we were unable to demonstrate noninferiority of antibiotic treatment relative to surgery. Of the 70 patients randomized to antibiotic treatment who subsequently underwent appendectomy, 58 (82.9%; 95% CI, 72.0% to 90.8%) had uncomplicated appendicitis, 7 (10.0%; 95% CI, 4.1% to 19.5%) had complicated acute appendicitis, and 5 (7.1%; 95% CI, 2.4% to 15.9%) did not have appendicitis but received appendectomy for suspected recurrence. There were no intra-abdominal abscesses or other major complications associated with delayed appendectomy in patients randomized to antibiotic treatment.

**CONCLUSIONS AND RELEVANCE** Among patients with CT-proven, uncomplicated appendicitis, antibiotic treatment did not meet the prespecified criterion for noninferiority compared with appendectomy. Most patients randomized to antibiotic treatment for uncomplicated appendicitis did not require appendectomy during the 1-year follow-up period, and those who required appendectomy did not experience significant complications.

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**A**ppendectomy has been the standard treatment for acute appendicitis for over a century. More than 300 000 appendectomies are performed annually in the United States.<sup>1</sup> Although appendectomy is generally well tolerated, it is a major surgical intervention and can be associated with postoperative morbidity.<sup>2,3</sup>

Since the time Fitz described the relationship between the appendix and pelvic abscess and McBurney demonstrated reduced morbidity from pelvic infections attributable to appendectomy,<sup>4,5</sup> it has been thought that acute appendicitis invariably progresses to perforation. This line of thinking underlies the belief that emergency appendectomy is required when a diagnosis of appendicitis is made. Fitz's and McBurney's publications<sup>4,5</sup> predated the availability of antibiotics by 40 years. In the absence of antibiotics, appendectomy saved lives by reducing the risk of uncontrolled pelvic infection when appendicitis was present.

Even though appendectomy has been the mainstay treatment for appendicitis, relatively soon after antibiotics were available, Coldrey<sup>6</sup> reported treating 471 patients with acute appendicitis with antibiotic therapy in 1956. Mortality was low (0.2%) and recurrent appendicitis occurred in only 14.4% of patients. More recently, the notion of treating appendicitis with antibiotics was tested in 3 randomized clinical trials<sup>7-9</sup> (RCTs) (Table 1). The results from these 3 trials were summarized in a Cochrane analysis<sup>10</sup> and several meta-analyses.<sup>11-15</sup> Each of these trials had limitations, and appendectomy remains the standard approach for treating appendicitis.

To overcome the limitations of previous trials, we tested the hypothesis that appendicitis can be successfully treated with antibiotics by conducting a multicenter, open-label, non-inferiority RCT comparing antibiotic therapy with emergency appendectomy for treating uncomplicated acute appendicitis.

## Methods

### Trial Design

The Appendicitis Acuta (APPAC) trial was performed in 6 Finnish hospitals (Turku, Oulu, and Tampere university hospitals and Mikkeli, Seinajoki, and Jyväskylä central hospitals) from November 2009 until June 2012. All details of the trial design and methods were previously published.<sup>16</sup> The trial protocol was approved by the ethics committees of all the participating hospitals and appears in Supplement 1. All Finnish hospitals with sufficient patient volume agreeing to participate in the study were included. The study was conducted in accordance with the Declaration of Helsinki.<sup>17</sup> All patients gave written informed consent to participate in the study.

### Objective

The objective of the APPAC trial was to compare antibiotic therapy with emergency appendectomy in the treatment of uncomplicated acute appendicitis confirmed by a computed tomographic (CT) scan. We tested the hypothesis that antibiotic treatment of uncomplicated acute appendicitis was noninferior to appendectomy. Based on prior studies,<sup>13</sup> we as-

sumed that there would be a 24% difference in treatment efficacy between the surgical and antibiotic groups.

### Participants

Patients aged 18 to 60 years admitted to the emergency department with a clinical suspicion of uncomplicated acute appendicitis confirmed by a CT scan were enrolled in the study. Patients with complicated appendicitis, which was defined as the presence of an appendicolith, perforation, abscess, or suspicion of a tumor on the CT scan, were excluded. Other exclusion criteria were age younger than 18 years or older than 60 years, contraindications for CT (eg, pregnancy or lactating, allergy to contrast media or iodine, renal insufficiency with serum creatinine level >150 μmol/L, actively taking metformin), peritonitis, unable to cooperate and provide informed consent, and the presence of serious systemic illness.

### Abdominal CT

Acute appendicitis was considered present when the appendiceal diameter exceeded 6 mm with wall thickening and at least 1 of the following was present: abnormal contrast enhancement of the appendiceal wall, inflammatory edema, or fluid collections around the appendix.

### Randomization

Patients were randomized by a closed envelope method either to undergo open appendectomy or to receive antibiotic therapy with intravenous ertapenem. The randomization was performed with a 1:1 equal allocation ratio. There were 610 opaque, sealed, and sequentially numbered randomization envelopes. The envelopes were shuffled and then distributed to each participating hospital. To randomize a patient, the surgeon on duty in each participating hospital opened a consecutively numbered envelope that contained information regarding the randomization group assignment for the patient. Most of the treating surgeons were not part of the core study team and provided care as they did in their normal clinical practice.

### Interventions

#### Surgical Treatment

Open appendectomy was performed using a McBurney right-lower quadrant muscle-splitting incision technique. Some surgeons performed laparoscopic appendectomy. Prophylactic antibiotics (1.5 g of cefuroxime and 500 mg of metronidazole) were administered approximately 30 minutes before the incision was made. No further antibiotics were given to patients in the surgical group unless a wound infection was suspected postoperatively. Appendicitis was confirmed if there was histopathological evidence of transmural neutrophil invasion involving the appendiceal muscularis layer.

#### Antibiotic Therapy

Ertapenem was chosen as the antibiotic for this study because of its efficacy as a monotherapy for serious intra-abdominal infections,<sup>18</sup> requiring only a single, daily dose. Intravenous ertapenem sodium (1 g/d) was administered for

Table 1. Major Randomized Clinical Trials Comparing Antibiotic Therapy With Appendectomy in Patients With Acute Appendicitis

Source	Inclusion Criteria	Age Group, y	No. of Patients	Antibiotic Used for Nonsurgical Patients	Completeness of 1-Year Follow-up	Appendectomy in Patients Treated With Antibiotics <sup>a</sup>	Limitations
Styrud et al, <sup>8</sup> 2006	Clinical diagnosis and CRP >10 mg/L	18-50	Surgery: 124 Antibiotic: 128	IV: cefotaxime plus tinidazole Oral: ofloxacin plus tinidazole	Not stated	31/128 (24)	Female patients excluded, primary end point unclear
Hansson et al, <sup>7</sup> 2009	Clinical diagnosis	>18	Surgery: 167 Antibiotic: 202	IV: cefotaxime plus metronidazole Oral: ciprofloxacin plus metronidazole	Surgery: 47% Antibiotic: 54%	96/202 (48)	52.5% of patients in the antibiotic group crossed over to the surgery group
Vons et al, <sup>9</sup> 2011	CT imaging	>18	Surgery: 119 Antibiotic: 120	IV: amoxicillin plus clavulanic acid Oral: amoxicillin plus clavulanic acid	Surgery: 87% Antibiotic: 90%	44/120 (37)	Included patients with complicated acute appendicitis (appendicolith), suboptimal antibiotic for intra-abdominal infections

Abbreviations: CRP, C-reactive protein; CT, computed tomography; IV, intravenous.

<sup>a</sup> Data are expressed as No./total (%).

3 days to patients in the antibiotic group, with the first dose given in the emergency department. The clinical status of patients in the antibiotic group was reevaluated within 12 to 24 hours after admission by the surgeon on call. If the surgeon suspected progressive infection, perforated appendicitis, or peritonitis, the patient underwent appendectomy. Intravenous antibiotic treatment was followed by 7 days of oral levofloxacin (500 mg once daily) and metronidazole (500 mg 3 times per day).

### Follow-up

Patient outcomes were assessed during their hospital stay (days 0, 1, 2) and then by telephone interviews at 1 week, 2 months, and 1 year after the intervention. At both 1 week and 2 months following randomization, pain scores were obtained using a visual analog scale (VAS; Supplement 2), sick leave was registered, and the presence of wound infections and recurrent appendicitis was determined. Patients were instructed to contact the research hospital in the event they experienced any postintervention problems. They were asked about possible wound infections during the telephone interviews at 1 week and at 2 months following surgery. In cases of patient report of postoperative infection, hospital records were reviewed to verify that the wound infection was noted by the treating physicians.

For patients who could not be reached for follow-up by telephone or clinic visit, a search of hospital records in each research hospital district was conducted to retrieve information about appendectomy. It is likely that patients undergoing surgery during the course of the study would have their operation either in the research hospital or in a district hospital close to where they were randomized. It also is likely that if the patients required further hospital care during the course of the study, we would have found that information during our searches of the district medical records.

### Outcome Measures

The primary end point for patients in the antibiotic group was resolution of acute appendicitis, resulting in discharge from the hospital without the need for surgical intervention and no recurrent appendicitis during a minimum follow-up of 1 year

(treatment efficacy). Treatment success in the appendectomy group was defined as a patient successfully undergoing an appendectomy.

Secondary end points included overall postintervention complications, late recurrence (after 1 year) of acute appendicitis after conservative treatment, length of hospital stay and the amount of sick leave used by the patient, postintervention pain scores (VAS score range, 0-10; a score of 0 indicates no pain and 10 indicates the worst possible pain), and the use of pain medication. Postintervention complications included clinical wound infection (surgical site infection) occurring within 30 days after the operative procedure as diagnosed by a surgeon or with a positive bacterial culture,<sup>19</sup> other general postoperative complications (eg, pneumonia), adverse effects of the antibiotic treatment (eg, diarrhea), incisional hernia, possible adhesion-related problems (eg, bowel obstruction), and persistent abdominal or incisional pain.

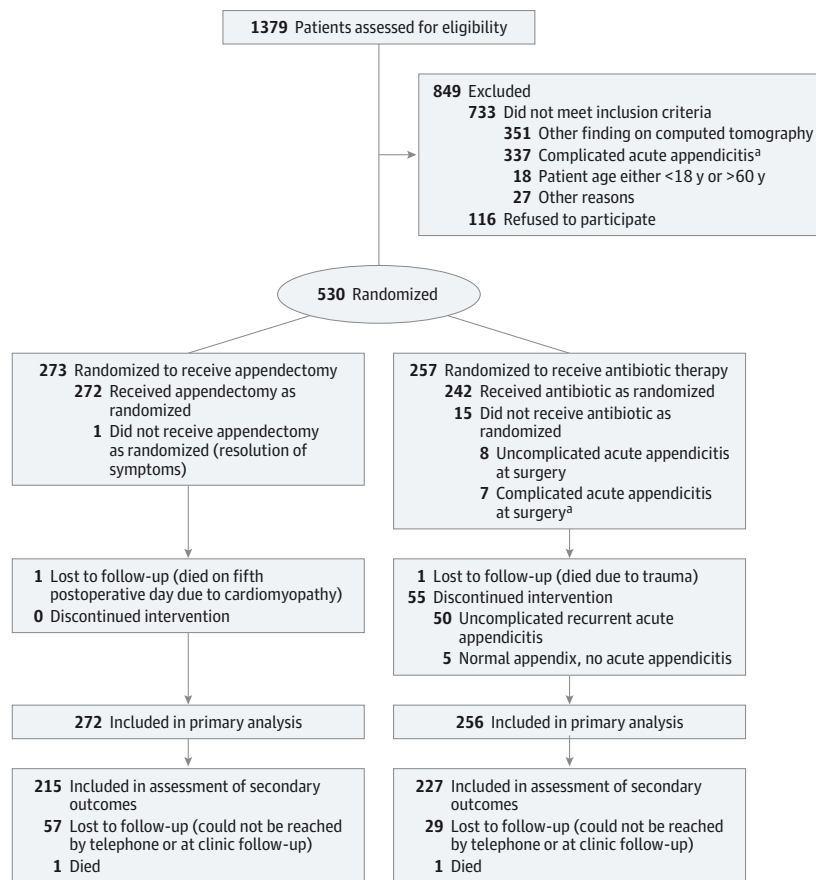
Recurrent acute appendicitis was diagnosed on a clinical basis. Patients treated with antibiotics who had a suspected recurrence of appendicitis always underwent appendectomy. The diagnosis of recurrent appendicitis was confirmed by surgical and histopathological examination of the resected specimen.

### Statistical Analysis

The sample size calculation for the trial assumed that all patients randomized to the surgical group would undergo appendectomy. For computational reasons, the success rate for surgery was assumed to be 99%. Prior similar studies found success rates for antibiotic treatment of approximately 70% to 80%.<sup>7,8</sup> Thus, we anticipated a 75% success rate in the antibiotic therapy group and a 24% (95% CI, 75%-99%) noninferiority margin was used for the sample size calculations.

We estimated that 275 patients per group would yield a power of 0.90 (1- $\beta$ ) to establish whether antibiotic treatment was noninferior to appendectomy using a 1-sided significance a level of .05 with Proc Power version 9.2 (SAS Institute Inc). We anticipated a 10% loss to follow-up, resulting in our plan to enroll 610 patients. Due to a slower than anticipated enrollment period, we recalculated the sample size when 530 patients were recruited. At that time, there was a

Figure. Path of Patients in the Appendicitis Acuta (APPAC) Trial



<sup>a</sup> Includes appendicolith, perforation, abscess, or suspicion of tumor.

power of 0.89 (1- $\beta$ ). With an assumed loss to follow-up rate of 10%, the calculation resulted in a power of 0.86, which we believed was adequate, allowing us to terminate enrollment.

Categorical variables were characterized using frequencies and percentages, continuous variables as means and standard deviations or, if the data were skewed, as medians with 25th and 75th percentiles. Statistical significance for categorical data was tested using the Pearson  $\chi^2$  test. Noninferiority for antibiotic therapy was tested using 1-sided Wald tests with an  $\alpha$  level of .05.

Differences between groups for normally distributed variables (hemoglobin level, leukocyte count, and creatinine level) were tested using the independent sample *t* test. The Mann-Whitney test was used for variables not normally distributed (ie, age, VAS pain scores, C-reactive protein level, length of hospital stay, and length of sick leave). The main analyses were based on the intention-to-treat principle. Statistical analyses were performed using SAS version 9.2 (SAS Institute Inc).

## Results

The **Figure** shows the trial profile. A total of 1379 patients were screened and 530 patients underwent randomization. There were 273 patients who were assigned to receive appendec-

tomy and 257 who were assigned to receive antibiotic therapy. One of the patients randomized to the antibiotic group died due to trauma within the year following randomization, leaving 256 patients available for follow-up.

There were 849 patients who did not meet the inclusion criteria and were excluded from the trial. Of these, 337 patients were found to have complicated acute appendicitis on a CT scan in the emergency department. In this cohort, 295 patients had an appendicolith, 51 patients had evidence of perforated appendicitis, and 40 patients had an intra-abdominal abscess; some patients may have had more than 1 finding (eg, perforated appendicitis with abscess). Baseline characteristics for patients who declined to participate were similar to those who underwent randomization with respect to age, sex, leukocyte count, and C-reactive protein level.

During the enrollment period, a total of 4380 appendectomies were performed at the 6 trial hospitals. Of these, 3667 patients had appendicitis; 3120 patients (85%) had uncomplicated acute appendicitis and 547 patients (15%) had complicated appendicitis presenting with perforation or an abscess. The negative appendectomy rate was 16% (713/4380).

## Primary Outcome

The baseline characteristics of the 2 groups were similar (**Table 2**). Of the 273 patients randomized to the surgical group,

Table 2. Baseline Characteristics of the Patients in the Appendicitis Acuta (APPAC) Trial<sup>a</sup>

	Surgical Group <sup>b</sup> (n = 273)	Antibiotic Group <sup>c</sup> (n = 257)
Sex		
Male	174 (63.7)	155 (60.3)
Female	99 (36.3)	102 (39.7)
Age, median (25th-75th percentile), y	35.0 (27-46)	33.0 (26-47)
VAS score for pain, median (25th-75th percentile) <sup>d</sup>	6.0 (4-7)	5.0 (4-7)
C-reactive protein, median (25th-75th percentile), mg/L	36.0 (14-61)	29.0 (11-63)
Hemoglobin, mean (SD), g/L	143.1 (13.5)	141.1 (13.2)
Leukocyte count, mean (SD), ×10 <sup>9</sup> /L	12.0 (4.0)	11.7 (3.9)
Creatinine, mean (SD), μmol/L	72.2 (14.3)	71.5 (13.8)
Duration of symptoms, h <sup>e</sup>		
1-6	16 (5.9)	15 (5.9)
>6 and ≤12	31 (11.4)	40 (15.7)
>12 and ≤18	64 (23.6)	52 (20.4)
>18	160 (59.0)	148 (58.0)

Abbreviation: VAS, visual analog scale.  
SI conversion factors: To convert C-reactive protein to nmol/L, multiply by 9.524; creatinine to mg/dL, divide by 88.4.

<sup>a</sup> Data are expressed as No. (%) unless otherwise indicated.

<sup>b</sup> Appendectomy was performed according to standard operative timing and treatment.

<sup>c</sup> The first intravenous dose was administered in the emergency department.

<sup>d</sup> Score range: 0-10; a score of 0 indicates no pain and 10 indicates the worst possible pain.

<sup>e</sup> For this characteristic, the denominator is 271 for the surgical group and 255 for the antibiotic group because 2 patients died in each group.

all but 1 underwent successful appendectomy, resulting in a success rate of 99.6% (95% CI, 98.0%-100.0%). The patient randomized to appendectomy who did not have an operation had resolution of symptoms before the operation could be performed. Fifteen patients (5.5%) underwent a laparoscopic appendectomy. Two patients (0.7%) in the surgical group did not have histopathological evidence of acute appendicitis in the resected specimens. One of these patients had inflammation in the lymphatic tissue and the other had mucosal inflammation but it did not extend to the muscularis of the appendix.

Four patients in the surgical group were found to have complicated appendicitis during their surgery. Of these 4 patients, 2 had a perforation and all had an appendicolith. The appendicolith was visible on a CT scan in all 4 patients and was also noted by the radiologist. These 4 patients were enrolled in the study and classified as protocol violations. Fifty-eight patients were lost to follow-up in the surgical group; specifically, there was 1 death and 57 patients could not be reached by telephone or at clinic follow-up. These 57 patients in the surgical group were included in the primary end point analysis because they had undergone appendectomy.

Of the 256 patients available for 1-year follow-up in the antibiotic group, 186 (72.7%; 95% CI, 66.8% to 78.0%) did not require appendectomy. Seventy patients (27.3%; 95% CI, 22.0% to 33.2%) in the antibiotic group underwent surgical intervention within 1 year of initial presentation for appendicitis. The intention-to-treat analysis yielded a difference between treatment groups of -27.0% (95% CI, -31.6% to ∞) ( $P = .89$ ). Because we established a 24% minimal clinically important difference, we did not demonstrate noninferiority of antibiotic treatment for appendicitis relative to surgical treatment.

In the primary outcome analysis of the antibiotic group, 30 patients could not be reached by telephone or at clinic follow-up. There was 1 death due to trauma during the 1-year follow-up, resulting in 256 patients for the analysis. District hospital medical record review provided information about possible appendectomy for the 29 patients in the antibiotic group who were not available for telephone or clinic follow-up.

Of 257 patients in the antibiotic group, 15 (5.8%; 95% CI, 3.3%-9.4%) underwent appendectomy during the initial hospitalization. Of these 15 patients, 7 (2.7%; 95% CI, 1.1%-5.5%) had complicated acute appendicitis at surgery and 8 (3.1%; 95% CI, 1.4%-6.0%) had uncomplicated appendicitis. Of the 7 patients with complicated acute appendicitis, there were 5 with perforated appendicitis. Of these 5 patients, 1 had an appendicolith not visible on a CT scan, 2 presented with severe gangrene of the inflamed appendix, and 1 underwent right hemicolectomy based on an intraoperative suspicion for a tumor with lymphadenopathy. However, histopathology of the resected specimen revealed only perforated appendicitis.

During the 1-year follow-up period, 55 patients in the antibiotic group were admitted to the hospital with a clinical suspicion of acute appendicitis and underwent appendectomy; 5 of the 55 had normal appendices when the resected appendix was assessed by histopathological examination. The remaining 50 patients had recurrent appendicitis both found during surgery and on histopathological examination of the resected appendix. The patients with recurrent appendicitis underwent appendectomy within a median of 102 days (95% CI, 68-134 days; 25th and 75th percentiles, 43 days and 204 days, respectively).

Of the 70 patients randomized to antibiotic treatment who subsequently underwent appendectomy, 58 (82.9%; 95% CI, 72.0%-90.8%) had uncomplicated acute appendicitis and 7 (10.0%; 95% CI, 4.1%-19.5%) had complicated acute appendicitis. A total of 5 patients (7.1%, 95% CI, 2.4%-15.9%) of the 70 patients in the antibiotic group undergoing appendectomy within the 1-year follow-up period did not actually require appendectomy because they were found to have normal appendices.

Despite having recurrent appendicitis and delayed operations, the surgical complication rate for the 57 patients in the antibiotic group who eventually underwent appendectomy was 7.0% (95% CI, 2.0%-17.0%; 4 patients with complications), which was lower than the rate of 20.5% (95% CI, 15.3%-26.4%; 45 patients with complications) for the 220 patients who underwent appendectomy in the surgical group. There was a

Table 3. Secondary Outcomes in the Appendicitis Acuta (APPAC) Trial

	Surgical Group (n = 273)	Antibiotic Group (n = 257)	P Value
Overall complication rate, % (95% CI)	20.5 (15.3-26.4) <sup>a</sup>	2.8 (1.0-6.0) <sup>b</sup>	<.001
Surgical site infections by type, No.	24	1	
Organ space	1	NA	
Deep incisional	4	NA	
Superficial	19	1	
Incisional hernias, No.	2	NA	
Abdominal, incisional pain, or obstructive symptoms, No.	23	4	
Length of primary hospital stay, median (25th-75th percentile), d	3.0 (2-3)	3.0 (3-3)	<.001
VAS score, median (25th-75th percentile) <sup>c</sup>			
At discharge from the hospital	3.0 (2-4)	2.0 (1-2)	<.001
At 1 wk	2.0 (1-3)	1.0 (1-1)	<.001
At 2 mo	1.0 (1-1)	1.0 (1-1)	.40
Length of sick leave, median (25th-75th percentile), d	19.0 (14-21)	7.0 (7-12)	<.001

Abbreviations: NA, not applicable; VAS, visual analog scale.

<sup>a</sup> Rate is based on complications in 45 patients of 220 total patients.

<sup>b</sup> Rate is based on complications in 6 patients of 216 total patients.

<sup>c</sup> Score range: 0-10; a score of 0 indicates no pain and 10 indicates the worst possible pain.

difference between groups of 13.4% (95% CI, 4.9%-21.9%) for the surgical complication rate ( $P = .02$ ). No patient in the antibiotic group developed an intra-abdominal abscess, including those who underwent delayed appendectomy.

### Secondary Outcomes

The 30-day mortality rate in the surgical group was 0.4%; 1 patient with cardiomyopathy died at home 5 days after surgery. There was 1 death in the antibiotic group unrelated to the randomized intervention. The secondary outcomes are summarized in Table 3.

The overall complication rate of 2.8% (95% CI, 1.0%-6.0%) was significantly lower in the antibiotic group (6/216 patients) than the overall rate of 20.5% (95% CI, 15.3%-26.4%) in the surgical group (45/220 patients). There was a difference between groups of 17.7% (95% CI, 11.9%-23.4%) for the overall complication rate ( $P < .001$ ).

There were 24 surgical site infections (1 organ space, 4 deep incisional, and 19 superficial). Four of the 5 patients in the surgical group with more severe infections had delayed healing of the incision and 1 patient had persistent incisional pain noted at the 2-month follow-up.

At the 1-year evaluation, there were 2 patients in the surgical group with incisional hernias and 1 of these patients required hernia repair. Twenty-three patients complained of possible adhesion-related problems manifested as difficulties with eating and bowel function and abdominal or incisional pain interfering with daily life as reported by the patients within 1 year of surgery. One patient in the surgical group underwent laparoscopic adhesiolysis. Outside the overall morbidity analysis, 16 patients in the surgical group reported concerns about poor cosmesis related to their incisional scar at 1-year follow-up.

The length of hospital stay (primary hospitalization) was statistically significantly shorter ( $P < .001$ ) in the surgical group (median, 3 days; 25th and 75th percentiles, 2 days and 3 days, respectively) than in the antibiotic-treated group (median, 3 days; 25th and 75th percentiles, 3 days and 3 days).

Four patients (1.5%) in the surgical group were found to have tumors; 3 were neuroendocrine tumors. These tumors were 0.1 mm in diameter (tip of the appendix), 0.7 mm in diameter (tip of the appendix), and 10 mm in diameter (base of the appendix). The patient with the 10-mm tumor subsequently underwent right hemicolectomy because of the tumor's size and location. One patient had a polyp with features of an adenoma with low-grade dysplasia at the tip of the appendix. One patient was evaluated for study enrollment despite the preintervention finding of an abscess on a CT scan. This patient was not enrolled in the study, underwent appendectomy with a histological finding of appendiceal adenocarcinoma, and later underwent right hemicolectomy.

### Discussion

To our knowledge, the APPAC trial is the largest multicenter, open-label, noninferiority RCT of antibiotic treatment for appendicitis conducted to date. When the trial was designed, we assumed that there would be sufficient benefits from avoiding surgery and that a 24% failure rate in the antibiotic group would be acceptable. Instead, we found a failure rate of 27.3% (95% CI, 22.0%-33.2%) and were not able to establish the noninferiority of antibiotic treatment for appendicitis.

Although we were not able to demonstrate the noninferiority of antibiotic treatment relative to appendectomy for appendicitis, we did find that 186 of 256 patients with uncomplicated acute appendicitis (72.7%; 95% CI, 66.8%-78.0%) were successfully treated with antibiotic therapy alone. This compares favorably with the results from previous randomized trials<sup>7-9</sup> and a recent population-based prospective study.<sup>20</sup> In our study, 70 of the 256 antibiotic-treated patients (27.3%) had an appendectomy. Following randomization, surgeons provided care based on their clinical experience and not by protocol.

Because 8 patients in the antibiotic group that underwent appendectomy did not have complicated appendicitis,

they might have been successfully treated with antibiotics again had the uncomplicated nature of their appendicitis been known. Five more patients in the antibiotic group underwent appendectomy for suspected recurrent acute appendicitis based on clinical examination but did not have appendicitis. Outcomes from these patients biased our results toward the null. No patient in the antibiotic group developed a serious infection resulting from delayed appendectomy, suggesting that the decision to delay appendectomy for uncomplicated acute appendicitis can be made with low likelihood of major complications resulting from delayed surgery.

Earlier trials<sup>7-9</sup> (Table 1) showing that acute appendicitis may be successfully treated with antibiotics have been limited by study design limitations such as reliance on clinical diagnosis of acute appendicitis, type and duration of antibiotic treatment, unclear determination of the primary end point, and highly restrictive patient selection.<sup>15,21</sup> Of the prior RCTs assessing antibiotic treatment for appendicitis, only Vons et al<sup>9</sup> used CT imaging confirmation to identify patients with uncomplicated acute appendicitis before randomization. In the other trials, appendicitis was diagnosed by clinical examination without confirmation by radiology. Because of its high sensitivity and specificity, CT has become the de facto standard for establishing the diagnosis of appendicitis in adults.<sup>22</sup> Use of CT reduces the negative appendectomy rate without resulting in increased cases of perforated appendicitis.<sup>23-27</sup> Routine use of CT in patients with suspected acute appendicitis can improve patient care by reducing unnecessary surgery, resulting in more efficient use of hospital resources.<sup>26</sup>

Similar to Vons et al,<sup>9</sup> we minimized the diagnostic uncertainty of appendicitis compared with when the diagnosis is made on clinical grounds by only enrolling patients into the trial who had a diagnosis of uncomplicated acute appendicitis confirmed by a CT scan. We excluded patients from enrollment if they had an appendicolith identified on a CT scan, whereas Vons et al<sup>9</sup> did not. Intraluminal appendicoliths can predict failed nonoperative management for appendicitis and the development of complicated acute appendicitis.<sup>28,29</sup>

Vons et al<sup>9</sup> noted that appendicoliths were significantly associated with a greater risk for complicated acute appendicitis. In their antibiotic-treated group, appendicoliths were associated with failed antibiotic treatment. If Vons et al<sup>9</sup> had excluded the patients with appendicoliths, no significant difference in posttreatment peritonitis would have been found between the antibiotic and appendectomy groups.

A limitation of prior antibiotic trials for treating appendicitis was the selection of the antibiotic. To succeed, the antibiotic must provide broad-spectrum coverage for all the pathogens that might cause appendicitis. This was a factor in the Vons et al<sup>9</sup> trial in which amoxicillin-clavulanic acid was used to treat appendicitis. This antibiotic is not optimal because it provides limited coverage for *Escherichia coli*, a major pathogen in the gastrointestinal tract. To avoid this limitation, we used ertapenem in our study because it provides broad-spectrum coverage and only requires a single, daily dose. Ertapenem effectively treats serious intra-abdominal infections.<sup>18</sup> A potential problem with using

broad-spectrum antibiotics like ertapenem is the risk for developing antibiotic resistance. Future studies of antibiotic treatment for appendicitis should seek efficacy while using antibiotics with a more restricted antibacterial spectrum.

The median length of hospital stay was longer in the antibiotic group; however, it was predefined in the protocol for the monitoring of patients in the antibiotic group to ensure patient safety in the trial. Because none of the patients initially treated with antibiotics and later having appendectomy had major complications, the length of hospital stay related to antibiotic therapy may possibly be shortened in practice. One drawback of antibiotic treatment for acute appendicitis is the possible bias due to spontaneously resolving appendicitis. A double-blind, placebo-controlled RCT is needed to differentiate these effects.

This study had several important limitations. Because appendectomy is considered the standard treatment for appendicitis, we had difficulty enrolling patients into the study. This caused us to reevaluate the necessary sample size for the study, potentially underpowering the study and resulting in indeterminate results. Even though we had difficulty in getting patients to enroll in the study, the study population closely resembled nonparticipants who underwent appendectomy during the same period at the study hospitals.

Another limitation is that the most of the appendectomies were performed using the open operative approach. Open appendectomy was chosen as the protocol operative intervention based on both (1) the standardization of the procedure regarding the large group of surgeons most familiar with the open technique and (2) the global generalization of the study results because the equipment for laparoscopic appendectomy and surgical experience are not available throughout the world. However, laparoscopic appendectomy is commonly performed and is associated with less pain, shortened hospital stay, faster return to normal activity, and fewer wound infections.<sup>30</sup> Given that the most common cause of morbidity in the surgical group of our study related to wound infection, the complication rate might have been less had the operations been performed laparoscopically.

Appendicitis may present in different ways. It can present as uncomplicated acute appendicitis as was the case for the patients enrolled in this study. Appendicitis also may present with complicated disease such as perforation, intra-abdominal abscess, or with appendicoliths. Consequently, acute appendicitis treatment should be individualized based on which form of the disease is present.<sup>31</sup> The most severe complications of appendicitis are diffuse peritonitis from a perforated appendicitis and intra-abdominal abscess. Of note, none of the antibiotic-treated patients experienced these complications, suggesting that not only is acute uncomplicated appendicitis documented by CT not a surgical emergency, but that delay in surgical treatment when preceded by a course of antibiotics has few consequences.

We did attempt to identify factors predictive of complicated appendicitis by analyzing the patients in the antibiotic group presenting with complicated acute appendicitis at surgery during the initial hospitalization. There were only 7 patients in the antibiotic group precluding identification of pre-

dictive factors for complicated acute appendicitis. There were 4 patients with tumors (1.5%) in our study and this percentage is in accordance with a recent large histopathological appendectomy study.<sup>32</sup> The clinical effect of incidental tumors of the appendix is unclear because the natural history of these lesions is not known. However, the use of CT imaging for diagnosing acute appendicitis may also enhance detection of these appendiceal tumors.

Another feature of our study was the low negative appendectomy rate attributable to CT imaging. Use of CT also enabled us to identify uncomplicated acute appendicitis that was successfully treated with antibiotics alone in the majority of patients enrolled in our study. Computed tomographic imaging can result in improved patient care and cost savings.<sup>26,33,34</sup> Concerns regarding radiation exposure may be minimized by use of low-dose CT for diagnosing acute appendicitis.<sup>22</sup>

Antibiotic treatment of patients with uncomplicated acute appendicitis was not shown to be noninferior to appendectomy for uncomplicated appendicitis within the first year of observation following initial presentation of appendicitis. Nevertheless, the majority (73%) of patients with uncomplicated

acute appendicitis were successfully treated with antibiotics. None of the patients treated initially with antibiotics and later with appendectomy had major complications. These results suggest that patients with CT-proven uncomplicated acute appendicitis should be able to make an informed decision between antibiotic treatment and appendectomy. Future studies should focus both on early identification of complicated acute appendicitis patients needing surgery and to prospectively evaluate the optimal use of antibiotic treatment in patients with uncomplicated acute appendicitis.

## Conclusions

Among patients with CT-proven, uncomplicated appendicitis, antibiotic treatment did not meet the prespecified criterion for noninferiority compared with appendectomy. Most patients randomized to antibiotic treatment for uncomplicated appendicitis did not require appendectomy during the 1-year follow-up period, and those who required appendectomy did not experience significant complications.

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