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Five-Year Follow-up of Antibiotic Therapy for Uncomplicated Acute Appendicitis in the APPAC Randomized Clinical Trial

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IMPORTANCE Short-term results support antibiotics as an alternative to surgery for treating uncomplicated acute appendicitis, but long-term outcomes are not known.

OBJECTIVE To determine the late recurrence rate of appendicitis after antibiotic therapy for the treatment of uncomplicated acute appendicitis.

DESIGN, SETTING, AND PARTICIPANTS Five-year observational follow-up of patients in the Appendicitis Acuta (APPAC) multicenter randomized clinical trial comparing appendectomy with antibiotic therapy, in which 530 patients aged 18 to 60 years with computed tomography–confirmed uncomplicated acute appendicitis were randomized to undergo an appendectomy (n = 273) or receive antibiotic therapy (n = 257). The initial trial was conducted from November 2009 to June 2012 in Finland; last follow-up was September 6, 2017. This current analysis focused on assessing the 5-year outcomes for the group of patients treated with antibiotics alone.

INTERVENTIONS Open appendectomy vs antibiotic therapy with intravenous ertapenem for 3 days followed by 7 days of oral levofloxacin and metronidazole.

MAIN OUTCOMES AND MEASURES In this analysis, prespecified secondary end points reported at 5-year follow-up included late (after 1 year) appendicitis recurrence after antibiotic treatment, complications, length of hospital stay, and sick leave.

RESULTS Of the 530 patients (201 women; 329 men) enrolled in the trial, 273 patients (median age, 35 years [IQR, 27-46]) were randomized to undergo appendectomy, and 257 (median age, 33 years, [IQR, 26-47]) were randomized to receive antibiotic therapy. In addition to 70 patients who initially received antibiotics but underwent appendectomy within the first year (27.3% [95% CI, 22.0%-33.2%]; 70/256), 30 additional antibiotic-treated patients (16.1% [95% CI, 11.2%-22.2%]; 30/186) underwent appendectomy between 1 and 5 years. The cumulative incidence of appendicitis recurrence was 34.0% (95% CI, 28.2%-40.1%; 87/256) at 2 years, 35.2% (95% CI, 29.3%-41.4%; 90/256) at 3 years, 37.1% (95% CI, 31.2%-43.3%; 95/256) at 4 years, and 39.1% (95% CI, 33.1%-45.3%; 100/256) at 5 years. Of the 85 patients in the antibiotic group who subsequently underwent appendectomy for recurrent appendicitis, 76 had uncomplicated appendicitis, 2 had complicated appendicitis, and 7 did not have appendicitis. At 5 years, the overall complication rate (surgical site infections, incisional hernias, abdominal pain, and obstructive symptoms) was 24.4% (95% CI, 19.2%-30.3%) (n = 60/246) in the appendectomy group and 6.5% (95% CI, 3.8%-10.4%) (n = 16/246) in antibiotic group ($P < .001$), which calculates to 17.9 percentage points (95% CI, 11.7-24.1) higher after surgery. There was no difference between groups for length of hospital stay, but there was a significant difference in sick leave (11 days more for the appendectomy group).

CONCLUSIONS AND RELEVANCE Among patients who were initially treated with antibiotics for uncomplicated acute appendicitis, the likelihood of late recurrence within 5 years was 39.1%. This long-term follow-up supports the feasibility of antibiotic treatment alone as an alternative to surgery for uncomplicated acute appendicitis.

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In order to avoid the complications of perforation and pelvic sepsis, appendectomy has been the standard treatment for all cases of acute appendicitis for over a century.[1] More recently, improvements in diagnostic imaging and antibiotics have facilitated a more selective approach. Abdominal computed tomography (CT) imaging very reliably establishes a diagnosis of appendicitis and can determine if the disease is complicated or uncomplicated. Better preoperative diagnostic capabilities enabled trials of antibiotics to treat appendicitis without surgery. Several recent randomized clinical trials have demonstrated the feasibility of antibiotic-only treatment for appendicitis.[2-4] All these trials had relatively short and, for some, incomplete follow-up of the patients receiving antibiotic treatment.

We conducted a randomized clinical trial comparing antibiotic treatment with appendectomy for patients with CT-confirmed acute uncomplicated appendicitis with 1-year follow up.[3] With nearly complete follow-up of all patients enrolled in the trial, we found that 73% of all patients with appendicitis treated with antibiotics alone did not require surgery at 1 year. However, appendicitis could have recurred in those patients, so the important unanswered question is what were the long-term outcomes for these patients? This study reports the 5-year outcomes for all the patients enrolled in the original Appendicitis Acuta (APPAC) trial.

Key Points

Question What is the long-term recurrence rate in patients with uncomplicated acute appendicitis treated with antibiotics?

Findings In this 5-year observational follow-up of 257 patients initially treated with antibiotics for uncomplicated acute appendicitis, the cumulative incidence of recurrent appendicitis at 1, 2, 3, 4, and 5 years was 27.3% at 1 year, 34.0% at 2, 35.2% at 3, 37.1% at 4, and 39.1% at 5 years.

Meaning Long-term follow up of patients with uncomplicated acute appendicitis suggests that initial treatment with antibiotics rather than surgery may be a feasible alternative.

Methods

Trial Design, Participants, and Interventions

The study design, rationale, and methods for the initial APPAC trial have been previously reported (Supplement 1).[3,5] The complete study protocol[5] was approved by the ethics committees of the 6 participating hospitals (Turku, Oulu, and Tampere university hospitals and Jyväskylä, Mikkeli, and Seinäjoki central hospitals), and all patients gave written informed consent to participate in the study.

Briefly, the initial APPAC trial was a multicenter, open-label, randomized clinical noninferiority trial conducted from November 2009 to June 2012 in Finland involving 530 patients aged 18 to 60 years with CT-confirmed uncomplicated acute appendicitis. Following CT confirmation for the presence of uncomplicated acute appendicitis, patients were randomized to receive either appendectomy or antibiotic treatment with intravenous ertapenem sodium (1 g/d) for 3 days, followed by 7 days of oral levofloxacin (500 mg once daily) and metronidazole (500 mg 3 times/d). CT criteria for acute appendicitis included appendiceal diameter exceeding 6 mm with wall thickening accompanied with at least one of the following features: abnormal contrast enhancement of the appendiceal wall, inflammatory edema, or fluid collections around the appendix. Exclusion criteria included complicated acute appendicitis (defined as the presence of an appendicolith, perforation, abscess, or suspicion of a tumor on the CT scan), age younger than 18 years or older than 60 years, contraindications for CT, peritonitis, inability to adhere with treatment and provide informed consent, and the presence of serious systemic illness. Following the initial randomization, patients in the antibiotic group were followed up by surgeons who could use their clinical judgement to pursue appendectomy if considered necessary. Most of the treating surgeons were not part of the core study team and provided care as they would in their normal clinical practice. If the surgeons on call suspected progressive infection, perforated appendicitis, or peritonitis in a patient in the antibiotic group, the decision to perform appendectomy was left to their discretion with no prespecified criteria established to guide that decision. The last follow-up date for the current 5-year report was September 6, 2017.

Objective

The objective for the long-term follow-up study was to determine the late recurrence rate of appendicitis after initial treatment with antibiotic therapy. Late complications occurring in both study groups were also assessed.

Randomization

Patients were randomized by a closed envelope method either to undergo appendectomy or receive antibiotic therapy. The randomization was performed with 1:1 equal allocation ratio.

Long-term Follow-up

After the initial 1-year follow-up, patient outcomes were assessed by telephone interviews conducted 3 to 5 years after the intervention. Patients were asked about recurrent appendicitis after antibiotic therapy or postoperative complications if tanahey underwent appendectomy. Upon study enrollment, patients were instructed to contact the research hospital if they experienced any problems. For patients who could not be reached for follow-up by telephone or clinic visit, a search of electronic hospital records in each research hospital district was performed to retrieve information about possible appendectomy in the antibiotic group or other additional intervention-associated visits to the hospital or hospitalizations in both study groups.

Outcome Measures

The primary end point of the original APPAC study was treatment success predefined to be assessed at 1-year follow-up.[3,5] Success for the appendectomy group was defined as a patient successfully undergoing an appendectomy. In the antibiotic group, treatment efficacy was defined as 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.

The predefined secondary end points at 3, 5 and 10 years included late recurrence (after 1 year) of acute appendicitis after antibiotic treatment, overall postintervention complications (surgical site infections, incisional hernias, abdominal or incisional pain, or obstructive symptoms), length of hospital stay (both primary hospitalization and all additional hospital stays), the amount of sick leave (both primary recovery period and all additional appendicitis treatment-associated sick leave days), postintervention pain scores (visual analog scale [VAS] score range, 0-10 [0 indicates no pain; 10 indicates the worst possible pain]), and treatment costs.[5] Cost data are not reported in this article. Recurrent appendicitis was diagnosed on a clinical basis as determined by the treating surgeon without any protocol-required repeat imaging or predefined clinical criteria for making the decision to proceed with appendectomy. Patients initially treated with antibiotics who subsequently underwent appendectomy had the preoperative diagnosis of appendicitis evaluated by surgical and histopathological examination of the resected specimen. Complications included all adverse events that occurred during the entire 5-year follow-up period. Postintervention complications included adverse events such as incisional hernias, possible adhesion-related problems, persistent abdominal or incisional pain, or wound infection (surgical site infection <30 days).

Statistical Analysis

Sample size calculations for APPAC were reported previously.[3] Categorical variables were described using frequencies and percentages with 95% CIs, continuous variables as means with 95% CIs or if the data were skewed, as medians with 95% CIs and interquartile ranges (IQRs). Statistical significance for categorical data was tested using the Pearson χ^2 test. Difference between groups in length of hospital stay and sick leave was tested using Mann-Whitney *U* test. An additional Kaplan-Meier analysis was performed to evaluate the time of recurrence of all patients in the antibiotic group who underwent appendectomy for suspected appendicitis recurrence. A log-rank test was used to test the differences between the VAS pain score categories at 2 months. Additional post hoc analyses using Cox proportional hazards regression models were performed to evaluate possible prognostic factors for recurrence of appendicitis in antibiotic group. Bivariable analyses were performed for age, sex, C-reactive protein, leukocytes, and VAS pain scores, and because there was only 1 statistically significant predictor, no further multivariable analyses were conducted. Proportional hazards assumptions were evaluated using the Schoenfeld residuals and assumption was valid in all of the analyses. The main analyses were based on the intention-to-treat principle. Two-sided *P* values of less than 0.05 were considered statistically significant. Missing data were excluded from the analyses. Statistical analyses were performed using SAS System for Windows (Version 9.4, SAS Institute Inc) (see the original statistical analysis plan in Supplement 1).

Results

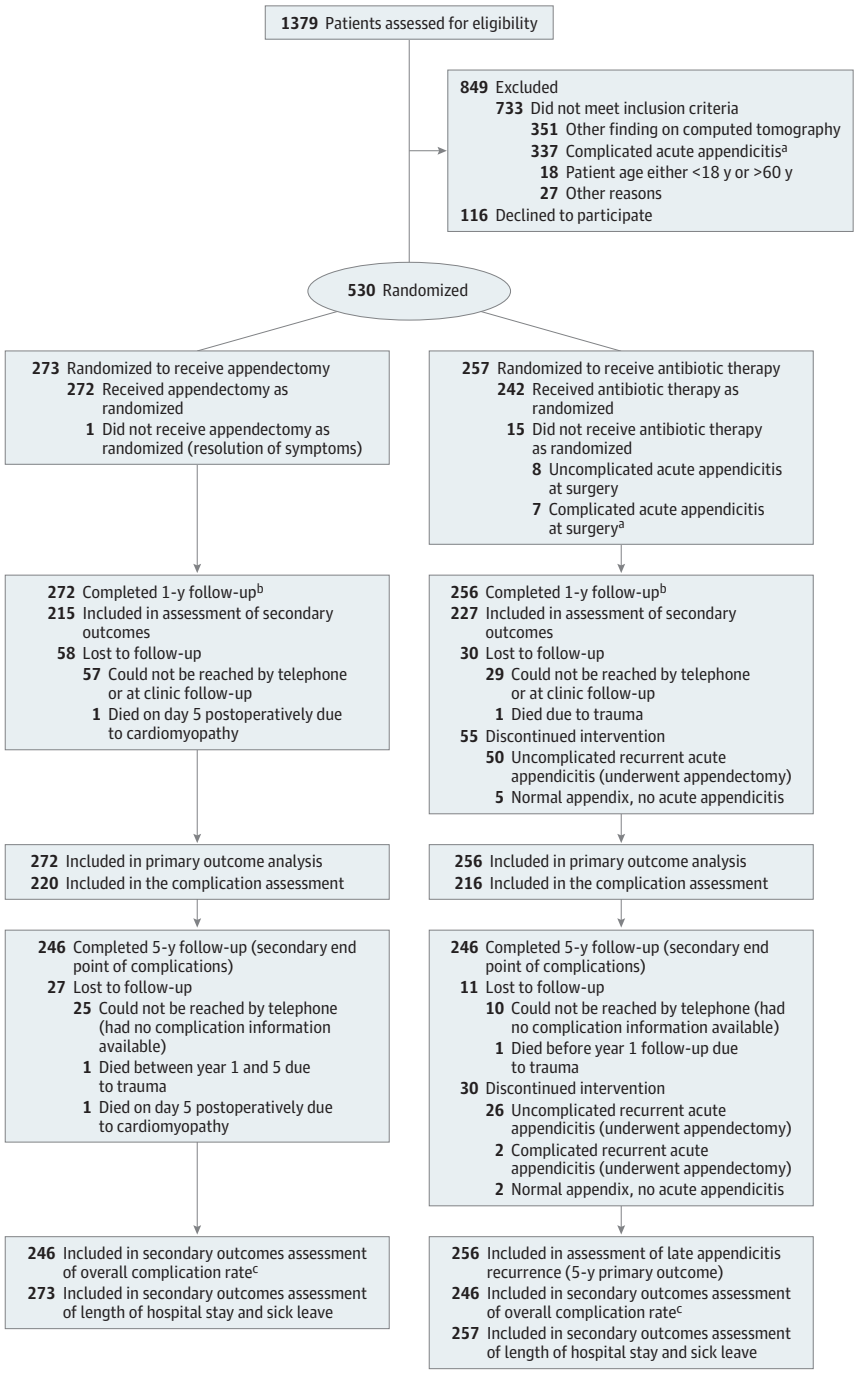
Figure 1 shows the trial profile. The baseline characteristics of the trial patients were shown in the report of main findings for this trial.[3] Baseline demographic characteristics between the study groups were similar. Of the 530 patients (201 women; 329 men) enrolled in the trial, 273 patients (median age, 35 years [IQR, 27-46]) were randomized to undergo appendectomy, and 257 (median age, 33 years, [IQR, 26-47]) were randomized to receive antibiotic therapy. There were 3 deaths unrelated to intervention, of which 2 were in the appendectomy group. The 3 patients who died were included in the primary outcome analysis because they underwent the allocated intervention, leaving 272 patients in the surgery group and 256 patients in the antibiotic group available for the primary outcome analysis at 5-year follow-up. **Figure 2** shows the cumulative incidence of acute appendicitis recurrence in the antibiotic group. At 1-year follow-up, the cumulative incidence of recurrence was 27.3% (95% CI, 22.0%-33.2%; 70/256).[3] The cumulative incidence of recurrence at 2, 3, 4, and 5 years was 34.0% (95% CI, 28.2%-40.1%; 87/256) at 2 years, 35.2% (95% CI, 29.3%-41.4%; 90/256) at 3 years, 37.1% (95% CI, 31.2%-43.3%; 95/256) at 4 years, and 39.1% (95% CI, 33.1%-45.3%; 100/256) at 5 years (Figure 2).

In the first year following randomization, 70 patients in the antibiotic group underwent appendectomy. In all subsequent years, 30 more patients in the antibiotic group (16.1%; 95% CI, 11.2%-22.2%; 30/186) had an appendectomy. Of the 100 patients in the antibiotic group who underwent appendectomy during the entire course of this study, 15 were operated on during the initial hospitalization.[3] Of the 85 antibiotic group patients who underwent appendectomy after discharge from the study admission, 76 (50 ≤ 1 year and 26 > 1 year) were found to have had uncomplicated appendicitis when the specimen was examined pathologically. Complicated appendicitis was not found in any patient operated on during the first year of the study but was found in 2 patients in years 2 through 5 following the index admission for this study. No appendicitis was found in 7 patients, 5 of these during the first year of the study and 2 during the longer follow-up period, resulting in true recurrence rate of 32.4% (78 true recurrences after initial hospitalization out of 241 patients in the antibiotic group with initial successful treatment). Among patients in the antibiotic group, 1 was operated on during the long-term follow-up period outside of the country and did not have histopathology available. This patient was assumed to have uncomplicated appendicitis because the patient reported having an uneventful recovery following the operation.

There were no appendiceal tumors in the 30 patients in the antibiotic group who underwent appendectomy between years 1 and 5; at the 1-year follow-up,[3] 4 patients (1.5%, 95% CI, 0.4%-3.7%; 4/272) in the surgical group were found to have an appendiceal tumor (1 polyp and 3 neuroendocrine tumors). The only statistically significant prognostic factor for acute appendicitis recurrence was VAS pain score at 2 months (hazard ratio for pain vs no pain, 3.2 [95% CI, 1.6-6.5]; *P* = .001). The VAS pain score at 2 months (pain vs no pain) association to appendicitis recurrence is also presented using a Kaplan-Meier curve (**Figure 3**).

At 5 years, the overall complication rate of 24.4% (95% CI, 19.2%-30.3%; n = 60/246) in the appendectomy group was significantly higher than the overall complication rate of 6.5% (95% CI, 3.8%-10.4%; n = 16/246) in antibiotic group (difference, 17.9 percentage points [95% CI, 11.7-24.1]; *P* < .001; **Table**).

Figure 1. Patient Flow in the Appendicitia Acuta (APPAC) Trial at 5-Year Follow-up



[a] Includes appendicolith, perforation, abscess, or suspicion of tumor.

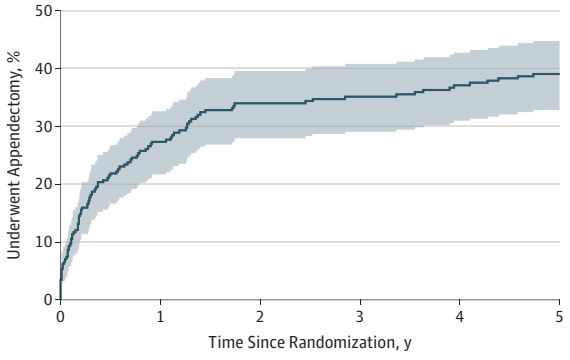
[b] See Salminen et al.[3]

[c] Includes all adverse events during the entire follow-up period (variable yes/no for complications), ie, patients with a possible complication at previous follow-up are included in the 5-year analysis even if they were not reached by phone (1 patient in the appendectomy group and 10 patients in the antibiotic group).

There were only 2 patients in the appendectomy group with a severe complication requiring a reoperation under general anesthesia (1 hernioplasty and 1 laparoscopic adhesiolysis); all other patients in both study groups had less-severe complications (58/246 in the appendectomy group and 16/246 in the antibiotic group). Laparoscopic appendectomy was performed on 28 (7.5% [95% CI, 5.1%-10.7%]; 28/372) patients in the study (15 [4.3%]; 15/342 patients during the first year and additional 13 [43.3%]; 13/30 patients between years 1 and 5.

When comparing the overall complication rate of patients undergoing appendectomy in both study groups, there was no statistically significant difference between surgically treated patients in the antibiotic group patients vs those who were randomized to the appendectomy group (overall appendectomy complication rate, 17.8% [95% CI, 10.5%-27.3%]; n = 16/90) (difference, 6.6 percentage points [95% CI, −2.9-16.2]; P = .20). The median length of hospital stay was 3 days (95% CI, 3-3) in the appendectomy group and 3 days (95% CI, 3-3) in the

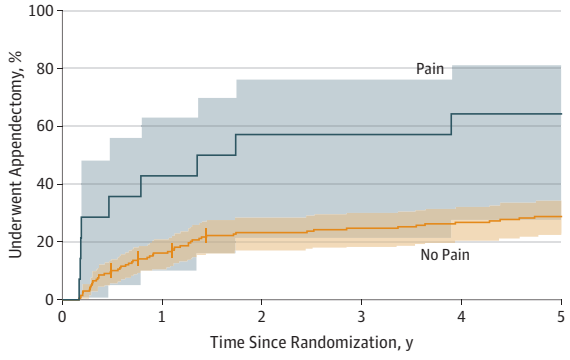
Figure 2. Kaplan-Meier Graph for Time to Recurrence After Antibiotic Therapy at 5-Year Follow-up



No. at risk 256 186 169 166 161 156

There were 256 antibiotic group patients available (one death excluded) for assessment of appendicitis recurrence. Of these, 15 underwent appendectomy during the primary hospitalization (ie, nonresponders to antibiotic therapy: 7/15 had complicated acute appendicitis, and 8/15 had uncomplicated acute appendicitis at surgery and histopathology). Of the 85 patients who underwent appendectomy for suspected appendicitis recurrence, 78 had a true recurrence (76 with uncomplicated and 2 with complicated acute appendicitis) and 7 patients did not have appendicitis at histopathology.

Figure 3. Kaplan-Meier Graph for Time to Recurrence Associated With Visual Analog Scale (VAS) Pain Score at 5-Year Follow-up



No. at risk

No pain	198	166	152	149	145	141
Pain	14	8	6	6	5	5

The red ticks represent the patients with false-positive surgery after 2-month follow-up (n = 4) (ie, no appendicitis at surgery or histology). Shading around lines indicates 95% CI; n = 212 at 0 months. There were 226 patients in the antibiotic group who had not undergone appendectomy, and VAS at 2 months was available for 212 of these patients (log-rank $P < .001$).

antibiotic group (there was no difference, 0 days). The median time used for sick leave was 22 days (95% CI, 19-23) after appendectomy and 11 days (95% CI, 11-12) after antibiotic therapy ($P < .001$; difference, 11 days).

Discussion

In this study of nonoperative treatment of appendicitis, 100 of the 256 patients in the antibiotic group (39.1%) ultimately underwent appendectomy after 5 years of follow-up. Most of these patients (70/100, 70%) had their episode of recurrent appendicitis within 1 year of initial presentation. No patient initially treated with antibiotics, who ultimately developed recurrent appendicitis, had any complications related to the delay in surgery. These findings demonstrate the feasibility of treating appendicitis with antibiotics and without surgery. Nearly 2/3 of all patients who initially presented with uncomplicated appendicitis were successfully treated with antibiotics alone and those who ultimately developed recurrent disease did not experience any adverse outcomes related to the delay in appendectomy.

Of the 100 patients who underwent appendectomy, 7 did not actually have appendicitis. If surgery could have been avoided in these patients, the success rate for antibiotic treatment of appendicitis would have been 163/256 (63.7%). At the time the study was initiated, antibiotic treatment for appendicitis was not considered an acceptable treatment for the disease. In order to conduct this study, the surgeons providing care for the study patients had the discretion to treat them using their clinical judgment rather than follow any protocol for deciding when to perform an appendectomy for patients in the antibiotic treatment group. This led to some patients undergoing appendectomy who did not have appendicitis or who might have been successfully treated with antibiotics or another course of antibiotics. Future studies should investigate protocols for further imaging or antibiotic treatment for patients who develop recurrent appendicitis after they were initially treated with antibiotics.

Previous studies of antibiotic treatment of appendicitis had varying approaches to establishing the diagnosis, differences in study eligibility, and the treatments administered. Some of the trials established a diagnosis by clinical means only.[6,7] Results from these trials may differ from the APPAC trial because of the better diagnostic accuracy available by CT scan as was performed in APPAC. Vons et al,[4] randomly assigned 119 patients to surgery and 122 to receive amoxicillin and clavulanic acid after the diagnosis of appendicitis was made by CT scan. This study differed from APPAC by including patients with complicated appendicitis and those having appendicoliths. Also, the antibiotic used in the Vons study[4] was suboptimal for the treatment of serious intraabdominal infection. Thus, APPAC is not directly comparable to prior studies of antibiotic treatment of appendicitis,[2,4,8-11] but is more reflective of contemporary approaches to the diagnosis and treatment of appendicitis.

Prior studies of antibiotic treatment of appendicitis have found an association between appendicolith and appendicitis recurrence.[4,12] Because of this association, patients assessed for eligibility in the APPAC trial were excluded if CT imaging showed an appendicolith. Prior studies regarding appendicolith were not powered to definitively establish the relationship between appendicoliths and appendicitis recurrence when appendicitis is treated with antibiotics. This warrants further study.

Appendectomy has a reasonably low complication rate. APPAC was not powered to study complications of either appendectomy or antibiotic treatment. There was a higher complication rate for appendectomy, mostly from infection. These complications could be reduced by adopting a laparoscopic approach. Laparoscopic appendectomy has a very low complication rate and is associated with rapid return to normal

Table. Complications in the Operative and Antibiotic Therapy Treatment Groups at 1 Year and 5 Years

	Time of Outcome Assessment, y	Surgical Group		Antibiotic Group		Difference		*P* Value[a]
		No.	% (95% CI)	No.	% (95% CI)	No.	% (95% CI)	
Overall complication rate	1	45[b]	20.5 (15.3-26.4)	6[b]	2.8 (1.0-6.0)	39	17.7 (11.9-23.4)	<.001
	5	60[b,c]	24.4 (19.2-30.3)	16[b,c]	6.5 (3.8-10.4)	44	17.9 (11.7-24.1)	<.001
Surgical site infections	1 and 5	24		1		23		<.001
Organ space	1 and 5	1		0		1		
Deep incisional	1 and 5	4		0		4		
Superficial	1 and 5	19		1		18		
Incisional hernias	1	2[d]		0		2		.16
	5	2		3[e]		−1		>.99
Abdominal or incisional pain or obstructive symptoms[g]	1	23[f]		4		19		<.001
	5	38		13		25		<.001

[a] Calculated using Pearson χ^2 test.

[b] Denominators for the surgical group were 220 at year 1 and 246 at year 5, and for the antibiotic group, 216 at year 1 and 246 at year 5.

[c] Complications accounted in the overall complication rate at 5 y included all adverse events during the whole follow-up period (variable yes/no for complications), ie, possible complications at previous follow-up are included in the 5-y analysis.

[d] One patient required hernioplasty within 1-y follow-up, and the other patient had not required hernia repair up to the 5-y follow-up (both underwent appendectomies).

[e] Patients underwent appendectomy between 1 and 5 y, none of the patients required hernia repair up to the 5-y follow-up (2 underwent an open appendectomy; 1 underwent a laparoscopic appendectomy).

[f] One patient underwent laparoscopic adhesiolysis within 1-y follow-up.

[g] Category includes complaints of possible adhesion-related problems manifesting as difficulties in bowel function and abdominal or incisional pain interfering with daily life.

function.[13] Although commonly performed in the United States, laparoscopic surgery requires substantial investment in equipment and supplies that are not available in much of the world. Thus, the complication rates we observed for open appendectomy may be similar to those expected for regions where open appendectomy might be the standard approach. Given the lower complication rate in the antibiotic group, it might be considered a preferable approach for the initial treatment of appendicitis in resource-limited settings.

The success of antibiotic treatment for appendicitis calls into question prior beliefs that appendicitis inevitably results in serious intraabdominal infection if appendectomy is not performed. In fact, when appendicitis was first described, its existence was supported, in part, by observation in autopsy studies that appendicitis could spontaneously resolve.[1,14] That appendicitis can resolve with no treatment was recently shown in a randomized trial by Park et al,[15] in which 121 patients with acute CT-confirmed uncomplicated appendicitis received a 4-day course of antibiotic treatment with cefmetazole and metronidazole compared with a group of 124 patients who were observed with no antibiotics or surgery. After a median follow-up time of 19 months, 25/121 (20.7%) of the antibiotic-treated and 29/124 (23.4%) of the observation-only patients required subsequent appendectomy.[15] These data show that uncomplicated appendicitis can resolve with no specific treatment, further calling into question the need for appendectomy when uncomplicated CT-diagnosed appendicitis first presents. These results showing spontaneous resolution of uncomplicated acute appendicitis should be verified by a double-blinded placebo-controlled randomized trial, but only supportive care may also be a valid future treatment option.

The strengths of this study include enrollment of a large number of patients at several different medical centers; many different surgeons providing care as they would irrespective of the study; and long-term, 5-year, nearly complete follow-up. These characteristics enhance the likelihood that the study results are generalizable to routine surgical practice. In addition, by effectively excluding the patients with complicated acute appendicitis (assessed using CT), this study population consisted of true uncomplicated acute appendicitis patients as only 1.5% (4/273) of patients in the appendectomy group and 2.8% (7/253) of patients in the antibiotic group presented with a complicated acute appendicitis at initial trial intervention.

Limitations

This study has several limitations. First, we did not have a protocol guiding decision making regarding performance of an appendectomy following randomization. The decision for surgery was left to the discretion of the treating surgeon. Conceivably, this resulted in more appendectomies than were absolutely necessary since some of the surgeons were not convinced that antibiotics were adequate treatment for appendicitis (ie, during the primary hospitalization, 8 of the 15 patients evaluated to be nonresponders to antibiotics had an operative finding of uncomplicated acute appendicitis). In addition, 7 of the 85 appendectomies performed for a clinical diagnosis of recurrent appendicitis proved not to be appendicitis, suggesting an overly aggressive approach to surgery based on trial protocol of appendectomy for suspected recurrence.

The second limitation was the use of open rather than laparoscopic appendectomy. Laparoscopic appendectomy is associated with shorter hospital stay, faster return to normal activity, and fewer wound infections as compared with the open operation.[13] However, at the time this study was conducted, open operation was the standard approach, and in the Finnish health care system, laparoscopic appendectomy was only starting to gain popularity. Results of this study are still pertinent to resource-limited environments where laparoscopic surgery is not affordable. Also, the operative technique does

not influence the major finding that appendicitis can be successfully treated with antibiotics for most patients.

The third limitation is the median hospital stay of 3 days for the antibiotic group. When this protocol was designed, there was little information available to guide the application of antibiotic treatment for appendicitis. We took a very conservative approach, using very broad-spectrum antibiotics while observing patients in the hospital for 3 days. Our findings show that antibiotic treatment of appendicitis is feasible. Future studies should examine different antibiotic regimens and fewer days of hospital observation.[15] These factors can markedly reduce the hospital stay and shorter hospital stays have been reported in the NOTA study (Non Operative Treatment for Acute Appendicitis; Di Saverio et al[16]), with a 0.4 days mean length of stay, and in a US pilot study by Talan et al,[17] which demonstrated successful outpatient antibiotic management with total hospital time of 16 hours.

Conclusions

Among patients who were initially treated with antibiotics for uncomplicated acute appendicitis, the likelihood of late recurrence within 5 years was 39.1%. This long-term follow-up supports the feasibility of antibiotic treatment alone as an alternative to surgery for uncomplicated acute appendicitis.

ARTICLE INFORMATION

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REFERENCES

1. Livingston E, Vons C. Treating appendicitis without surgery. *JAMA*. 2015;313(23):2327-2328.

2. Huang L, Yin Y, Yang L, Wang C, Li Y, Zhou Z. Comparison of antibiotic therapy and appendectomy for acute uncomplicated appendicitis in children. *JAMA Pediatr*. 2017;171(5):426-434.

3. Salminen P, Paajanen H, Rautio T, et al. Antibiotic therapy vs appendectomy for treatment of uncomplicated acute appendicitis. *JAMA*. 2015;313(23):2340-2348.

4. Vons C, Barry C, Maitre S, et al. Amoxicillin plus clavulanic acid versus appendicectomy for treatment of acute uncomplicated appendicitis. *Lancet*. 2011;377(9777):1573-1579.

5. Paajanen H, Grönroos JM, Rautio T, et al. A prospective randomized controlled multicenter trial comparing antibiotic therapy with appendectomy in the treatment of uncomplicated acute appendicitis (APPAC trial). *BMC Surg*. 2013;13:3.

6. Hansson J, Körner U, Khorram-Manesh A, Solberg A, Lundholm K. Randomized clinical trial of antibiotic therapy versus appendicectomy as primary treatment of acute appendicitis in unselected patients. *Br J Surg*. 2009;96(5):473-481.

7. Styrud J, Eriksson S, Nilsson I, et al. Appendectomy versus antibiotic treatment in acute appendicitis. a prospective multicenter randomized controlled trial. *World J Surg*. 2006;30(6):1033-1037.

8. Harnoss JC, Zelienka I, Probst P, et al. Antibiotics versus surgical therapy for uncomplicated appendicitis. *Ann Surg*. 2017;265(5):889-900.

9. Rollins KE, Varadhan KK, Neal KR, Lobo DN. Antibiotics versus appendicectomy for the treatment of uncomplicated acute appendicitis. *World J Surg*. 2016;40(10):2305-2318.

10. Sallinen V, Akl EA, You JJ, et al. Meta-analysis of antibiotics versus appendicectomy for non-perforated acute appendicitis. *Br J Surg*. 2016;103(6):656-667.

11. Tanaka Y, Uchida H, Kawashima H, et al. Long-term outcomes of operative versus nonoperative treatment for uncomplicated appendicitis. *J Pediatr Surg*. 2015;50(11):1893-1897.

12. Shindoh J, Niwa H, Kawai K, et al. Predictive factors for negative outcomes in initial non-operative management of suspected appendicitis. *J Gastrointest Surg*. 2010;14(2):309-314.

13. Sauerland S, Jaschinski T, Neugebauer EA. Laparoscopic versus open surgery for suspected appendicitis. *Cochrane Database Syst Rev*. 2010;(10):CD001546.

14. Fitz R. Perforating inflammation of the vermiform appendix. *Am J Med Sci*. 1886;92:321-346.

15. Park HC, Kim MJ, Lee BH. Randomized clinical trial of antibiotic therapy for uncomplicated appendicitis. *Br J Surg*. 2017;104(13):1785-1790.

16. Di Saverio S, Sibilio A, Giorgini E, et al. The NOTA study (Non Operative Treatment for Acute Appendicitis): prospective study on the efficacy and safety of antibiotics (amoxicillin and clavulanic acid) for treating patients with right lower quadrant abdominal pain and long-term follow-up of conservatively treated suspected appendicitis. *Ann Surg*. 2014;260(1):109-117.

17. Talan DA, Saltzman DJ, Mower WR et al. Antibiotics-first versus surgery for appendicitis: a US pilot randomized controlled trial allowing outpatient antibiotic management. *Ann Emerg Med*. 2017;70(1):1-11.e19.