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Antibiotic Therapy for Uncomplicated Acute Appendicitis
Ten-Year Follow-Up of the APPAC Randomized Clinical Trial

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IMPORTANCE Antibiotic therapy is effective and safe for uncomplicated acute appendicitis in adults, but randomized clinical trial results exceeding 5 years are missing.

OBJECTIVE To determine the 10-year appendicitis recurrence and appendectomy rate in patients with uncomplicated appendicitis treated with antibiotics.

DESIGN, SETTING, AND PARTICIPANTS Ten-year observational follow-up of patients in the Appendicitis Acuta (APPAC) multicenter randomized clinical trial comparing appendectomy with antibiotics at 6 Finnish hospitals from November 2009 to June 2012, where 530 patients (aged 18-60 years) with uncomplicated acute appendicitis diagnosed by computed tomography were randomly assigned to appendectomy (n = 273) or antibiotics (n = 257). Last follow-up was April 29, 2024. This current analysis focused on assessing the 10-year appendicitis recurrence rate among patients assigned to antibiotics.

INTERVENTIONS Open appendectomy vs antibiotics 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).

MAIN OUTCOMES AND MEASURES Prespecified 10-year secondary end points included late (after 1 year) appendectomy and appendicitis recurrence rate after antibiotics and complications. Post hoc outcomes included the detection of possible appendiceal tumors among patients in the antibiotic group undergoing appendectomy or with an intact appendix using magnetic resonance imaging. Additional post hoc outcomes were quality of life and patient satisfaction.

RESULTS At 10-year follow-up, 253/257 patients (98.4%) randomized to receive antibiotics (median age, 33 years; 102 [40.3%] female) were assessed for appendicitis recurrence, with a true appendicitis recurrence rate (appendicitis at histopathology) of 37.8% (95% CI, 31.6%-44.1% [87/230]) and a cumulative appendectomy rate of 44.3% (95% CI, 38.2%-50.4% [112/253]). Overall, the 10-year cumulative complication rate in the group randomized to appendectomy was 27.4% (95% CI, 21.6%-33.3% [62/226]) and 8.5% (95% CI, 4.8%-12.1% [19/224]) in the group randomized to receive antibiotics ($P < .001$). There was no observed significant difference in quality of life between antibiotics and appendectomy (387/530; median health index value, 1.0 [95% CI, 1.0-1.0] for both groups; $P = .18$).

CONCLUSIONS AND RELEVANCE Among patients initially treated with antibiotics for uncomplicated acute appendicitis, the rate of recurrence and appendectomy at 10-year follow-up supports the use of antibiotics as an option for uncomplicated acute appendicitis in adult patients.

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Supplemental content

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Several randomized clinical trials (RCTs) show that antibiotics are a feasible and safe treatment alternative for computed tomography (CT)–confirmed uncomplicated acute appendicitis, both in the short term[1-5] and up to 3 years[6,7] or 5 years.[8] To our knowledge, there are no long-term follow-up results of RCTs comparing appendectomy and antibiotics, because the long-term follow-up (19-26 years) of the 2 early Swedish RCTs was conducted as a registry study of patients included in these RCTs.[9] In their registry follow-up, more than one-half of the patients treated nonoperatively did not experience recurrence and avoided surgery over approximately 2 decades.[9] The appendectomy rates in RCTs do not necessarily reflect the number of patients for whom surgical intervention after antibiotics was warranted, because the rationale for proceeding to surgery varied among studies,[4,10] and in some trials, laparoscopic appendectomy was mandated in the study protocol[3] for suspected appendicitis recurrence.

One concern with increasing nonoperative management for uncomplicated acute appendicitis is the remaining uncertainty of possible undetected appendiceal neoplasms, especially among older adults. However, the risk of appendiceal neoplasms is directly associated with appendicitis severity, underlining the importance of differentiating between uncomplicated and complicated acute appendicitis.[11] The reported appendiceal tumor risk associated with complicated acute appendicitis (2.4%[12]) has been reported to be higher compared with uncomplicated acute appendicitis (1.5%[12]),[13-16] with the highest prevalence of up to 14.3% in complicated acute appendicitis presenting with a periappendicular abscess in a recent large prospective cohort study.[12]

The Appendicitis Acuta (APPAC) trial compared antibiotic therapy with appendectomy for patients with CT-confirmed uncomplicated acute appendicitis and showed that 61% of all patients treated with antibiotics alone did not undergo surgery up to 5-year follow-up.[3,8] This predefined secondary analysis of the APPAC trial reports 10-year outcomes for all patients enrolled in the original RCT, focusing on late appendicitis recurrence and appendectomy rates.

Key Points

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

Findings In this 10-year observational follow-up of patients initially treated with antibiotics for uncomplicated acute appendicitis, the true appendicitis recurrence rate (appendicitis at histopathology) was 37.8% and the cumulative appendectomy rate was 44.3%.

Meaning Long-term follow-up of patients with uncomplicated acute appendicitis supports the use of antibiotics as an option for uncomplicated acute appendicitis in adult patients.

Methods

Trial Design, Participants, and Interventions

The study design, rationale, and methods for the trial have been previously reported.[3,8] The complete study protocol[3] was approved by the ethics committees of the 6 participating hospitals in Finland, and all patients provided written informed consent to participate in the study, including the long-term follow-up. Briefly, the initial APPAC trial was a multicenter, open-label, randomized, noninferiority clinical trial conducted from November 2009 to June 2012 involving 530 patients aged 18 to 60 years with CT-confirmed uncomplicated acute appendicitis. Patients were randomized with 1:1 allocation to 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). Following the initial randomization, in cases of clinically suspected appendicitis recurrence determined by the treating surgeon, the protocol-stated decision was to proceed with laparoscopic appendectomy. The last follow-up date for the current 10-year report was on April 29, 2024.

Objective and Predefined Outcomes

The primary end point of the initial APPAC study was treatment success at 1-year follow-up.[3] Success for the appendectomy group was defined as the patient successfully undergoing an appendectomy. In the antibiotic treatment group, treatment success was defined as resolution of acute appendicitis resulting in discharge from the hospital without the need for appendectomy and no recurrent appendicitis during a minimum follow-up of 1 year. The main aims of this 10-year secondary analysis were to assess the predefined late appendicitis recurrence and appendectomy rate after antibiotic treatment. The other predefined secondary end points at 10 years included overall postintervention complications. Complications included all adverse events that occurred during the entire 10-year follow-up period.

Post Hoc Outcomes

Post hoc outcomes included detection of possible appendiceal tumors in antibiotic patients with an intact appendix using magnetic resonance imaging (MRI), which was added as a protocol amendment with an additional written informed consent to assess possible appendiceal tumors at 10-year follow-up to ensure patient safety (Supplement 1). Additional post hoc secondary end points included quality of life (QOL) and patient satisfaction.

Long-Term Follow-Up

Long-term outcomes were assessed by telephone interviews at 10 years after study enrollment for all patients and for the patients in the antibiotic group with an intact appendix, also at the time of the MRI outpatient visit. Patients were asked about recurrent appendicitis after antibiotic treatment and postoperative complications if they underwent appendectomy. During 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 obtain information on possible appendectomy with histopathology

or other interventions associated with hospital visits or hospitalizations.

MRI Imaging in Patients With an Intact Appendix

MRI is the most accurate imaging modality for staging appendiceal malignancy, especially with diffusion-weighted imaging for pathological tissue cellularity assessment and intravenous contrast enhancement. The appendiceal diameter above 15 mm, or morphological cystic or soft-tissue mass changes, may achieve approximately 95% sensitivity in tumor detection.[17] All patients with an intact appendix were offered an abdominal MRI, which was evaluated by an experienced abdominal MRI radiologist (J.K.). The appendiceal MRI findings were categorized into 5 classes (ranging from normal appendix [class 1] to strong suspicion of an appendiceal tumor [class 5]), based on appendiceal diameter, morphology on contrast enhancement, and diffusion-weighted imaging (additional details available in eTable 3 in Supplement 2). Patients with a class of 4 or 5 (mild or strong tumor suspicion) were scheduled to undergo surgery, and the primary CT images were reevaluated by a radiologist (J.K.).

Quality-of-Life Assessment

Quality of life was assessed using the validated European QOL-5 Dimensions (EQ-5D-5L) questionnaire[18] complemented with questions on overall patient well-being and satisfaction with the received treatment, which were already used at the 7-year follow-up[19] during telephone interviews between February 2020 and March 2023. EQ-5D-5L descriptive questions cover 5 dimensions of everyday life: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, with health state scores (self-rated health visual analog scale) converted into a single index value[20] ranging between 0 (death) and 1 (full health). The EQ-5D-5L validation specific to Finland is not available, so we used the Denmark[21] validation, as the population closely resembles that of Finland. Patient satisfaction was assessed on a scale from 1 to 5: very satisfied, satisfied, indifferent, unsatisfied, and very unsatisfied. Patients were also asked if they would again choose the same treatment knowing the outcomes.

Statistical Analysis

Categorical variables were characterized using frequencies and percentages with 95% CIs, and continuous variables were described as medians with IQRs or 95% CIs. Statistical significance for categorical data was tested using Pearson χ^2 test or Fisher exact test in case of small frequencies. The difference between groups in continuous variables was tested using the nonparametric Kruskal-Wallis test. Kaplan-Meier analysis was performed to evaluate the time to a true appendicitis recurrence (histopathological confirmation, ie, transmural neutrophil invasion involving the appendiceal muscularis layer) in patients receiving antibiotics. The recurrence analysis excluded patients in the antibiotic group (n = 15) who underwent appendectomy during primary hospitalization. Patients (n = 2) who died during the follow-up with an intact appendix, patients (n = 2) not available for follow-up after moving abroad, and patients (n = 8) with no appendicitis at histopathology after appendectomy were censored at the time of loss to follow-up (time of death, moving, or operation).

Table 1. Baseline Characteristics of the Appendicitis Acuta (APPAC) Trial Patients at 10-Year Follow-Up

	Antibiotic therapy (n = 253)	Appendectomy (n = 219)
Sex, No. (%)		
Male	151 (59.7)	134 (61.2)
Female	102 (40.3)	85 (38.8)
Age, median (IQR), y	33.0 (26.0-47.0)	36.0 (28.0-48.0)
VAS score for pain (IQR)[a]	5.0 (4.0-7.0)	5.0 (4.0-7.0)
C-reactive protein (IQR), mg/L	29.4 (11.0-62.5)	37.0 (12.0-63.0)
Hemoglobin, mean (SD), g/L	141.0 (13.2)	142.6 (13.4)
Leukocyte count, mean (SD), $\times 10^9$/L	11.7 (3.9)	11.9 (3.9)
Creatinine, mean (SD), µmol/L	71.3 (13.7)	72.2 (14.4)
Duration of symptoms, h, No. (%)		
1-6	15/251 (6.0)	14/218 (6.4)
>6 and ≤18	37/251 (14.7)	23/218 (10.6)
>12 and ≤18	52/251 (20.7)	49/218 (22.5)
>18	147/251 (58.6)	132/218 (60.6)

Abbreviation: VAS, visual analog scale.

SI conversion factor: To convert creatinine values to mg/dL, divide by 88.4.

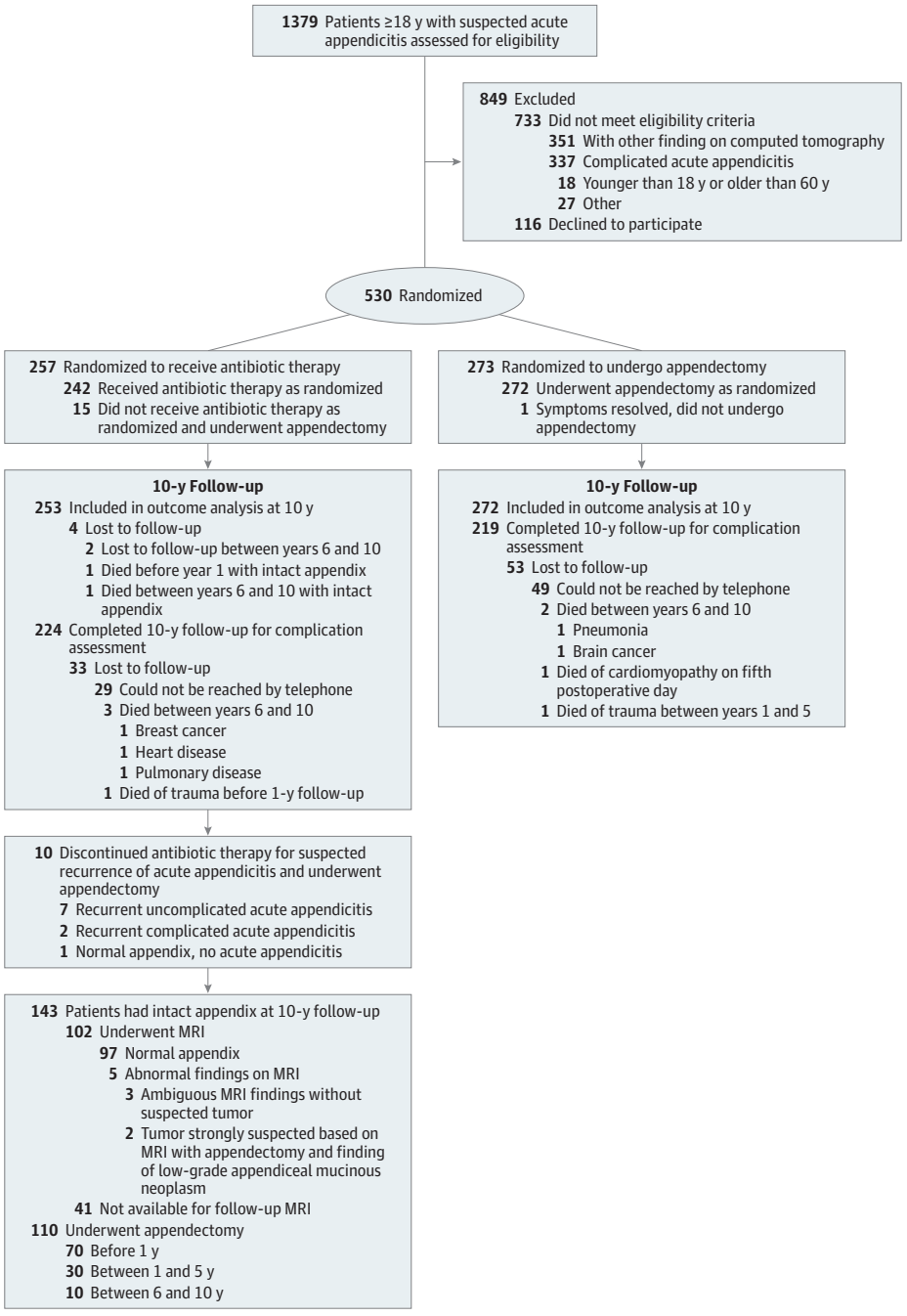
[a] Score range: 0-10; a score of 0 indicates no pain, and 10 indicates the worst possible pain.

The main analyses involved analysis of patients according to their randomized groups, with missing data handled as described above. Sensitivity analyses were performed for tumor prevalence, given the large proportion of patients not undergoing MRI, by assuming different tumor prevalences for patients with missing data. Additional subgroups, in which antibiotic group patients were divided into later appendectomy and no appendectomy groups, were described to assess patient satisfaction and treatment preferences. Two-sided *P* values less than .05 were considered statistically significant. Missing data were excluded from the analyses. Statistical analyses were performed using SAS version 9.4 for Windows (SAS Institute Inc).

Results

The baseline characteristics of all trial patients (eTable 1 in Supplement 2) were reported previously,[3] and the baseline characteristics of patients available for the 10-year follow-up are reported in **Table 1**. Of the 530 randomized patients (201 females; 329 males), 273 patients (median age, 35 years [IQR, 27-46]) were randomized to appendectomy and 257 (median age, 33 years [IQR 26-47]) to antibiotic therapy (**Figure 1**). At 10-year follow-up, 253 patients in the antibiotic treatment group were included in the primary analysis, including the 2 patients who died after they had undergone appendectomy. At 10 years, there were a total of 8 deaths, all unrelated to acute appendicitis. At 10 years, the true appendicitis recurrence rate was 37.8% (95% CI, 31.6%-44.1% [87/230]). The cumulative incidence of appendec-

Figure 1. Patient Flow in the Appendicitis Acuta (APPAC) Trial at 10-Year Follow-Up

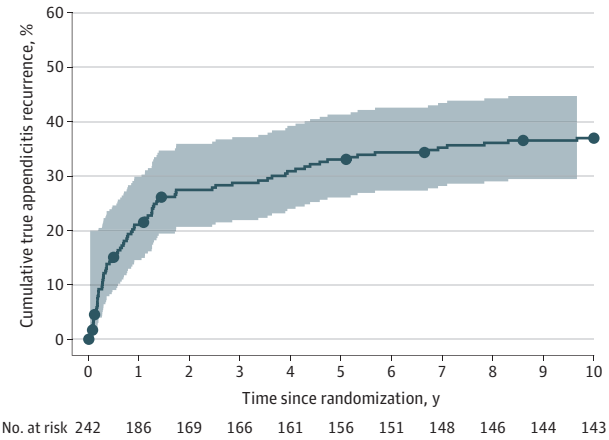


MRI indicates magnetic resonance imaging.

tomy was 27.3% at 1 year (95% CI, 22.0%-33.2% [70/256]),[3] 39.1% at 5-year follow-up (95% CI, 33.1%-45.3% [100/256]),[8] and 44.3% at 10 years (95% CI, 38.2%-50.4% [112/253]). The 10-year appendectomy rate includes the 2 patients operated on based on the follow-up MRI findings. **Figure 2** shows the cumulative incidence of true appendicitis recurrence rate at all points in the antibiotic group during the 10-year follow-up.

In the first year following randomization, 70 patients in the antibiotic group underwent appendectomy.[3] In the next 4 years, 30 additional patients in the antibiotic group underwent appendectomy.[8] During the subsequent years (beyond 5 years), 12 more patients treated with antibiotics underwent appendectomy. Of these 112 patients in the antibiotic group undergoing appendectomy during the entire course of this study, 15 (5.8%) were operated on during the initial hospitalization.[3] Of the 97 patients who underwent appendectomy after initial hospitalization and antibiotics, 83 (50 at 1 year, 26 between 1 and 5 years, and 7 between 6 and 10 years) were found to have uncomplicated acute appendicitis at histopathology. Compli-

Figure 2. Kaplan-Meier Graph for Time to True Recurrence (Appendicitis at Histology) After Antibiotic Therapy at 10-Year Follow-Up



Shaded regions indicate 95% CIs. The recurrence analysis excluded patients in the antibiotic group (n = 15) who underwent surgery during their primary hospitalization. Patients who died during the follow-up with an intact appendix (n = 2), patients not available for follow-up after moving abroad (n = 2), and patients with no appendicitis at histopathology after appendectomy (n = 8) were censored at the time of loss to follow-up (time of death, moved, or normal appendix at surgery). Dots on the curve indicate censoring. Observations were censored at 10 years; CIs are based on cumulative estimates and end prior to the final data collection at 10 years.

cated acute appendicitis was not found in any patients in the antibiotic group at 1 year; throughout the longer follow-up, 6 patients who had received antibiotics had complicated acute appendicitis at surgery (2 patients between 1 and 5 years and 4 between 6 and 10 years), including 2 patients with an appendiceal tumor detected on the 10-year follow-up MRI. At 10 years, there were altogether 8 patients who underwent appendectomy for suspected recurrence with no appendicitis at histopathology (5 at 1 year, 2 between 1 and 5 years, and 1 between 6 and 10 years).

The number of patients available for a 10-year telephone interview of the secondary end points was 224 of 253 (88.5%) for the antibiotic group and 219 of 269 (81.4%) for the appendectomy group. At 10 years, the overall cumulative complication rate in the appendectomy group was 27.4% (95% CI, 21.6%-33.3% [62/226]) and 8.5% (95% CI, 4.8%-12.1% [19/224]) in the antibiotic group ($P < .001$). The complications up to 5 years have been described in detail in the previous reports.[3,8] Between 6 and 10 years, 4 additional patients had complications: 2 in the appendectomy group (1 occasional adhesion-related pain, 1 numbness around scar) and 2 in the antibiotic treatment group, both having occasional adhesion-related pain after undergoing appendectomy during the follow-up.

Post Hoc Outcomes of Appendiceal Tumor Prevalence and QOL

At 10-year follow-up, of the 156 patients in the antibiotic group with an intact appendix at 5 years, 1 patient died with an intact appendix, 2 had missing data, and 10 underwent appendectomy, leaving 143 patients with an intact appendix available for MRI follow-up. Among these, 102 (71.3%) underwent MRI imaging. There were no differences in baseline characteristics between the 41 patients who did not undergo MRI and the 102 patients with follow-up MRI, and the tumor prevalence results were similar in the sensitivity analyses (eTable 2 in Supplement 2). MRI findings are reported in detail in **Table 2**. None of the patients who underwent MRI follow-up imaging had signs of appendiceal inflammation. There were 5 patients with an MRI class of 3 or higher, and detailed information on these patients is presented in eTable 3 in Supplement 2.

Two patients with suspected tumor (class 5) underwent appendectomy, presenting with a low-grade appendiceal mucinous neoplasm (LAMN) at histopathology. In retrospect, neither tumor was detectable in the primary CT. No other treatments in addition to appendectomy were needed. No other appendiceal tumors were detected in the 10 patients in the antibiotic group undergoing appendectomy between 6 and 10 years for suspected appendicitis recurrence. In the appendectomy group, there were 4 patients of 272 (1.5%) with an appendiceal tumor at 1 year (3 neuroendocrine tumors and 1 adenoma with low-grade dysplasia).[3] There was no statistically significant difference in tumor prevalence between the appendectomy group (1.5% [95% CI, 0%-2.9%]; 4/272) and the antibiotic group (0.9% [95% CI, 0%-2.2%]; 2/212; $P = .70$), and the overall tumor prevalence in uncomplicated acute appendicitis at 10 years was 1.2% (95% CI, 0.3%-2.2% [6/484]).

At the 10-year follow-up of the 530 patients enrolled in the APPAC trial, 387 (73.0%) participated in the QOL assessment (217 appendectomy group, 170 antibiotic group). Of the 170 patients in the antibiotic group, 89 (52.4%) had undergone appendectomy. The QOL (EQ-5D-5L) between treatment groups was similar (median health index value, 1.0 [95% CI, 1.0-1.0] in the group randomized to appendectomy and 1.0 [95% CI, 1.0-1.0] in the group randomized to receive antibiotics, $P = .18$). The patient median self-rated health visual analog scale value was higher in the group randomized to receive antibiotics than in the group randomized to appendectomy (85.0 [95% CI, 80.0-89.0] vs 80.0 [95% CI, 80.0-85.0], respectively; $P = .03$). Satisfaction with care and treatment preference results are reported in **Table 3**. Among patients randomly assigned to appendectomy or antibiotics, 78.0% (167/214) and 67.3% (111/165) would choose the same treatment again, respectively. After successful antibiotic treatment (no appendectomy), 90.9% (70/77) would again select antibiotics. Of the patients in the antibiotic group who underwent appendectomy during the 10-year follow-up, 46.6% (41/88) would again choose antibiotics.

Discussion

In this long-term follow-up of a large, randomized trial of operative vs nonoperative treatment of appendicitis, a true appendicitis recurrence rate following histopathological confirmation was 37.8% (87/230) among patients randomized to initial treatment with antibiotics, and 112 of the 253 patients in the antibiotic group (44.3%) underwent appendectomy after 10 years of follow-up. Most true recurrences (65/87 [74.7%])

Table 2. Magnetic Resonance Imaging (MRI) Findings in Patients With an Intact Appendix at 10 Years

	Patients with MRI (n = 102), No. (%)
Sex	
Male	63 (61.8)
Female	39 (38.2)
Appendix visualization	
Whole appendix	82 (80.4)
Part of the appendix	16 (15.7)
Appendix cannot be visualized	4 (3.9)
Appendiceal diameter (short axis), mm[a]	96/102 (94.1)
2	1
3	8
4	17
5	29
6	26
7	7
8	2
9	2
10	1
11	1
14	1
27	1
Appendiceal MRI class[b]	98/102 (96.1)
1: Normal benign features[c]	83/98 (84.7)
2: Benign features, mild dilation[d]	10/98 (10.2)
3: Abnormal, significant dilation[e] or ambiguous features[f]	3/98 (3.1)
4: Mild tumor suspicion[g]	0/98
5: Strong tumor suspicion[h]	2/98 (2.0)
Incidental findings	16/102 (15.7)
Uterine myoma	2/16 (12.5)
Ovarian cyst	2/16 (12.5)
Hepatic hemangioma	2/16 (12.5)
Crohn disease in terminal ileum	2/16 (12.5)
Hemorrhagic kidney cyst	1/16 (6.3)
Bosniak IIF kidney cyst	1/16 (6.3)
Ovarian prominence in PCO-like ovaries	1/16 (6.3)
Unspecific 4-6 mm periappendicular lymph nodes	1/16 (6.3)
A 5-mm cyst in the pancreatic head	1/16 (6.3)
Diffuse signal drop in the kidneys	1/16 (6.3)
Hepatic steatosis	1/16 (6.3)
Gallstones	1/16 (6.3)

Abbreviations: MRI, magnetic resonance imaging; PCO, polycystic ovary.

[a] The appendiceal diameter was missing in 6 patients; in 4 patients the appendix could not be visualized and in 2 patients, the diameter could not be reliably measured due to partial visualization.

[b] Class defined by short axis (maximum diameter of the appendix), absence or presence of morphological changes (mucous cyst [mucocele] or soft tissue mass with focal pathological enhancement), and absence or presence of diffusion-weighted imaging (DWI) pathology (focally restricted diffusion or segmentally restricted diffusion within thickened appendiceal wall, with reference to the adjacent normal ileum wall).

[c] Short axis 6 mm or less, morphological changes absent, DWI pathology absent.

[d] Short axis 7 to 10 mm, morphological changes absent, DWI pathology absent.

[e] Short axis 11 mm or greater, morphological changes absent, DWI pathology absent.

[f] Short axis 7 to 10 mm, morphological changes absent, DWI pathology unspecific.

[g] Short axis 10 mm or less, morphological changes present, and/or DWI pathology present.

[h] Short axis 11 mm or greater, morphological changes present, and/or DWI pathology present.

and appendectomies (87/112 [77.7%]) occurred within 2 years of initial presentation. At 10 years, there were 143 patients in the antibiotic group with an intact appendix available for follow-up MRI to detect possible appendiceal neoplasms, and 102 (71.3%) underwent MRI. There were 2 patients with a strong suspicion of an appendiceal tumor; they underwent appendectomy with a finding of LAMN at histology, and no additional treatments were needed. At 10 years, antibiotic therapy was durable, with the majority of patients not having additional recurrent disease. In addition, the risk of malignancy associated with uncomplicated acute appendicitis was very low—1.2% for all patients enrolled in the APPAC trial.

Antibiotic therapy for uncomplicated acute appendicitis without an appendicolith was already included in the World Society of Emergency Surgery 2020 guideline[22] (high-quality evidence; strong recommendation) and the American College of Surgeons (COVID-19 Guideline for Triage of Emergency General Surgery Patients)[23] as a safe alternative to surgery. The reported appendectomy rate in the RCTs must be distinguished from both primary nonresponsiveness to antibiotics and appendicitis recurrence. The criteria for nonresponsiveness to antibiotics and appendicitis recurrence have been subjective, and treatment decisions may have been primarily influenced by patient and surgeon bias[4,10,24] and the study protocols mandating appendectomy with suspected recurrence.[3] Besides successful initial treatment, the long-term risk of possible recurrent appendicitis is a key component of optimizing nonoperative management and patient

Table 3. Ten-Year Patient Satisfaction With the Treatment and Treatment Preference After Appendectomy, Antibiotics Alone, and Antibiotic Therapy With Later Appendectomy (Post Hoc Assessment)

	No./total (%) [95% CI]		
	Antibiotic therapy		
Questionnaire[a]	With no subsequent appendectomy	With later appendectomy	Appendectomy
Patient satisfaction			
No.	n = 79	n = 89	n = 217
Very satisfied	53/79 (67.1) [56.7-77.5]	21/89 (23.6) [14.7-32.5]	121/217 (55.8) [49.1-62.4]
Satisfied	23/79 (29.1) [19.1-39.2]	47/89 (52.8) [42.4-63.2]	89/217 (41.0) [34.4-47.6]
Indifferent	3/79 (3.8) [0.0-8.0]	3/89 (3.4) [0.0-7.1]	4/217 (1.8) [0.05-3.6]
Unsatisfied	0/79	11/89 (12.4) [5.5-19.2]	3/217 (1.4) [0.0-2.9]
Very unsatisfied	0/79	7/89 (7.9) [2.9-13.5]	0/217
Would opt for the same treatment again			
No.	n = 77	n = 88	n = 214
Yes	70/77 (90.9) [84.5-97.4]	41/88 (46.6) [36.1-57.1]	167/214 (78.0) [72.5-83.6]
No	2/77 (2.6) [0.0-6.2]	47/88 (53.4) [42.9-63.9]	45/214 (21.0) [15.5-26.5]
Uncertain	5/77 (6.5) [1.0-12.0]	0/88	2/214 (0.9) [0.0-2.2]

[a] The patient satisfaction and treatment preference questionnaires were administered during the standard follow-up phone calls or outpatient visits at 10 years.

satisfaction.[19] To our knowledge, this is the only RCT comparing antibiotics and appendectomy to report 10-year outcomes of antibiotic management for CT-confirmed uncomplicated acute appendicitis. The longest follow-up to date was the previous 5-year follow-up of this APPAC trial, showing an appendectomy rate of 39.1% at 5 years and an appendicitis recurrence rate of 32.4% (78/241)[8] corroborated by the 3-year follow-up of both the APPAC II (oral vs intravenous followed by oral antibiotics)[6] and APPAC III (double-blind placebo vs antibiotics)[7] RCTs on uncomplicated acute appendicitis.[7] The CODA (Comparison of Outcomes of Antibiotic Drugs and Appendectomy) trial long-term follow-up showed an appendectomy rate of 49% at 3 years, but the long-term outcomes were markedly limited by the very low follow-up rate of only 10% at 3 years.[1]

This secondary 10-year analysis confirms the feasibility and safety of antibiotics for uncomplicated acute appendicitis at long-term follow-up, because more than one-half of the patients treated nonoperatively avoided surgery. With the durability of the 5-year outcomes at 10 years, the currently available cost-utility data up to 5 years[25,26] can be applied to these long-term results, showing major cost savings associated with nonoperative treatment. The overall cost and resource savings will potentially be markedly further increased in the future by outpatient treatment.[27]

Based on the current study, this long-term safety also applies to the previous uncertainty of possible undetected appendiceal neoplasms. The appendiceal neoplasm rate of 0.9% in the antibiotic group was confirmed by histopathological assessment of all appendectomy specimens during the 10-year follow-up and by the high percentage (71.3%) of patients with an intact appendix undergoing MRI at 10 years. There were no appendiceal tumors in the 110 patients in the antibiotic group undergoing appendectomy during initial hospitalization or for suspected recurrence. The 2 antibiotic-treated patients diagnosed with LAMN underwent appendectomy based on the follow-up MRI. The overall prevalence of appendiceal neoplasms in patients with uncomplicated acute appendicitis treated with antibiotics was low (0.9%) and in concurrence with previous studies.[15,28] The risk of appendiceal tumor is markedly higher in patients with complicated acute appendicitis, similarly to complicated diverticulitis.[29,30] The risk is highest in patients with a periappendicular abscess, up to 14% to 20%,[12,13,15,28,31,32] underlining the different forms of disease severity within acute appendicitis.

According to current knowledge, evidence clearly supports phenotypic heterogeneity in acute appendicitis,[11,24,33] requiring differential diagnosis to rule out complicated acute appendicitis[34-36] but also enabling different treatment alternatives.[37] The degree to which uncomplicated and complicated acute appendicitis represent distinct vs progressive entities remains an area of active investigation, and there are still knowledge gaps regarding consistent criteria for distinguishing between the two. The presence of an appendicolith is associated with both an increased risk of primary nonresponsiveness to antibiotics[1,4,38,39] and a more complicated course of the disease.[4,40] The higher appendectomy rate in the CODA trial was related to the inclusion of patients with imaging evidence of an appendicolith.[1] In the recent individual patient data meta-analysis,[4] in patients with an appendicolith, initial antibiotic treatment increased the risk of complications compared with appendectomy, and approximately one-half of these patients underwent appendectomy during the first year. Other identified potential preintervention findings associated with primary nonresponsiveness to antibiotics include an appendiceal diameter greater than or equal to 15 mm, a body temperature exceeding 38 °C (100.4 °F),[41] or a contrast enhancement defect of the appendiceal wall.[42,43]

Limitations

This report has several limitations. First, the study protocol mandated laparoscopic appendectomy for all patients with clinically suspected appendicitis recurrence, which led to more appendectomies than were medically warranted. However, this

was done to ensure patient safety, also in light of the potential for missed appendiceal tumors. Together with MRI imaging of 71.3% of all antibiotic patients with an intact appendix, this resulted in a reliable appendiceal tumor rate assessment at 10-year follow-up, and the risk of missed appendiceal tumors related to antibiotic therapy is very low.

Second, the 41 patients assigned to the antibiotic group with an intact appendix who did not undergo follow-up MRI is a clear limitation of the trial. However, the majority of patients with an intact appendix underwent MRI, and we also aimed to mitigate this potential bias by performing a sensitivity analysis that showed similar results.

Third, due to the timing of the study, both the use of open rather than laparoscopic appendectomy and the 3-day hospital stay can be considered limitations, especially regarding surgical complications, treatment costs, and patient satisfaction. Future studies should examine the optimized nonoperative treatment in an outpatient setting, because uncomplicated acute appendicitis may even resolve by symptomatic treatment alone[7,44,45] and the majority of patients can be safely discharged from the emergency department.[2]

Fourth, the predefined cost-utility analysis is not presented with durability outcomes at 10 years; the already available 5-year cost analysis[25] was deemed sufficient, with results applicable to 10-year follow-up.

A fifth limitation is the use of a broad-spectrum antibiotic, because the major knowledge gap currently is the role of antibiotics in the treatment of uncomplicated acute appendicitis, which is currently being addressed by the ongoing APPAC IV randomized, double-blind clinical trial comparing oral moxifloxacin and placebo for uncomplicated acute appendicitis in an outpatient setting.[27]

The strengths of this multicenter RCT include the long-term, 10-year, nearly complete follow-up and the use of MRI to provide as objective an assessment as possible of the intact appendices.

Conclusions

This long-term RCT follow-up showed that among patients initially treated with antibiotics for uncomplicated acute appendicitis, the likelihood of appendicitis recurrence at 10 years was 37.8% and the appendectomy rate was 44.3%, supporting the use of antibiotics as an option for uncomplicated acute appendicitis in adult patients.

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