Appendicectomy versus antibiotics for acute uncomplicated appendicitis in children: an open-label, international, multicentre, randomised, non-inferiority trial

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Summary

Background Support for the treatment of uncomplicated appendicitis with non-operative management rather than surgery has been increasing in the literature. We aimed to investigate whether treatment of uncomplicated appendicitis with antibiotics in children is inferior to appendicectomy by comparing failure rates for the two treatments.

Methods In this pragmatic, multicentre, parallel-group, unmasked, randomised, non-inferiority trial, children aged 5–16 years with suspected non-perforated appendicitis (based on clinical diagnosis with or without radiological diagnosis) were recruited from 11 children's hospitals in Canada, the USA, Finland, Sweden, and Singapore. Patients were randomly assigned (1:1) to the antibiotic or the appendicectomy group with an online stratified randomisation tool, with stratification by sex, institution, and duration of symptoms (≥48 h *vs* <48 h). The primary outcome was treatment failure within 1 year of random assignment. In the antibiotic group, failure was defined as removal of the appendix, and in the appendicectomy group, failure was defined as a normal appendix based on pathology. In both groups, failure was also defined as additional procedures related to appendicitis requiring general anaesthesia. Interim analysis was done to determine whether inferiority was to be declared at the halfway point. We used a non-inferiority design with a margin of 20%. All outcomes were assessed in participants with 12-month follow-up data. The trial was registered at ClinicalTrials.gov (NCT02687464).

Findings Between Jan 20, 2016, and Dec 3, 2021, 936 patients were enrolled and randomly assigned to appendicectomy (n=459) or antibiotics (n=477). At 12-month follow-up, primary outcome data were available for 846 (90%) patients. Treatment failure occurred in 153 (34%) of 452 patients in the antibiotic group, compared with 28 (7%) of 394 in the appendicectomy group (difference 26·7%, 90% CI 22·4–30·9). All but one patient meeting the definition for treatment failure with appendicectomy were those with negative appendicectomies. Of those who underwent appendicectomy in the antibiotic group, 13 (8%) had normal pathology. There were no deaths or serious adverse events in either group. The relative risk of having a mild-to-moderate adverse event in the antibiotic group compared with the appendicectomy group was 4·3 (95% CI 2·1–8·7; p<0·0001).

Interpretation Based on cumulative failure rates and a 20% non-inferiority margin, antibiotic management of non-perforated appendicitis was inferior to appendicectomy.

Funding None.

Lancet 2025; 405: 233–40

This online publication has been corrected. The corrected version first appeared at thelancet.com on February 6, 2025

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Introduction

Appendicitis is the most common surgical emergency in children, with a lifetime risk of 7–8% and a peak incidence in the teenage years.[1] The standard of care has been appendicectomy since the operation was first described in 1886.[2] Although there have long been examples of treating appendicitis with antibiotics alone instead of surgery,[3] this strategy has only recently begun to be formally compared in trials with appendicectomy in adults and children. Laparoscopic appendicectomy for non-perforated appendicitis has a low risk of complications; however, because it is an abdominal operation requiring general anaesthesia, it inevitably exposes the child to a risk of complications. Even with current imaging methods, about 5% of patients undergoing appendicectomy are expected to be found to have a normal appendix and, thus, to have had an unnecessary operation.[4]

Several studies have documented that antibiotic therapy alone is highly successful as an initial treatment for appendicitis and is associated with more rapid return to normal activity than surgery.[5–9] The Midwest Pediatric Surgery Consortium conducted a non-randomised patient preference trial in 1068 children, showing that about two-thirds of patients treated with antibiotics avoided an operation at 1 year and those patients had

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Research in context

Evidence before this study

Appendicitis is the most common surgical emergency in children, with a lifetime risk of 7–8%. Studies in adults and children have documented that antibiotic therapy alone can be successful for the initial treatment of appendicitis and is associated with a more rapid return to normal activity than surgery. A non-randomised patient preference study in 1068 children in the USA, conducted by the Midwest Pediatric Surgery Consortium, showed that about two-thirds of patients treated with antibiotics avoided an operation at 1 year, and these patients had fewer disability days than those treated with primary laparoscopic appendicectomy. A multicentre, randomised trial conducted by the Comparison of Outcomes of antibiotic Drugs and Appendectomy collaborative in 1552 adult patients, with 30-day EQ-5D score as primary outcome, concluded that antibiotics were non-inferior to appendicectomy, but the failure rate with antibiotics was almost 30%. Two previous prospective randomised controlled trials in children have both been small pilot studies. To date, there has been no large, randomised study in children comparing antibiotics and surgery to treat appendicitis.

Added value of this study

This study is the first large, pragmatic, randomised trial to compare antibiotics and appendicectomy for the treatment of uncomplicated appendicitis in children. For antibiotics, treatment failure was defined as the need for appendicectomy within 1 year, and for appendicectomy, failure was defined as a negative appendicectomy. Based on these definitions, antibiotics were inferior to appendicectomy. Analysis of secondary outcomes showed that patients in the antibiotic group spent more time in hospital, in line with previous studies, but had an early return to school and normal activities; these patients required almost no pain medication.

Implications of all the available evidence

Our study shows that antibiotics are inferior to appendicectomy as the initial treatment of uncomplicated appendicitis in children. This trial, combined with the other large studies, shows that conducting further direct comparative studies is not likely to create much change in future direction in terms of management of acute uncomplicated appendicitis. Nonetheless, in the future, we could add to the secondary analyses thus far performed in the other studies to characterise the patients most likely to be treated successfully with antibiotics alone.

fewer disability days compared with those treated with primary laparoscopic appendicectomy.[9]

Large, multicentre, randomised trials have been done in adults, such as the study conducted by the Comparison of Outcomes of antibiotic Drugs and Appendectomy (CODA) Collaborative.[10] In the CODA trial, 1552 patients were randomly assigned to antibiotics or appendicectomy to compare the primary outcome of 30-day European Quality of Life five dimensions score. The authors concluded that antibiotics were non-inferior according to this metric. However, the failure rate with antibiotics was nearly 30%. Two prospective randomised controlled trials have been done in children, but these were small pilot studies;[7,11] thus, there has been no large-scale, randomised study in children that would allow an unbiased comparison of outcomes between these two very different treatment strategies. Therefore, we designed and conducted the APPY trial—a multicentre, randomised trial comparing laparoscopic appendicectomy with antibiotics alone in children with uncomplicated appendicitis.

Methods

Study design

We conducted an open-label, pragmatic, non-blinded, parallel, multicentre, randomised, non-inferiority trial at 11 children's hospitals in Canada, the USA, Finland, Sweden, and Singapore. The protocol was developed in accordance with the SPIRIT guidelines[12] and has been published previously.[13] No important changes were made to the originally implemented protocol across the study period. Approval was obtained from the local institutional ethics board for each enrolling site. Patients were enrolled after informed consent was obtained from their legal guardian.

Participants

The study population consisted of children between the ages of 5 years and 16 years diagnosed with simple appendicitis. Families were offered enrolment into the trial or to proceed with appendicectomy according to the local centre's standard of care. The enrolment process occurred after the diagnosis of appendicitis was made. Inclusion criteria were diagnosis of non-perforated appendicitis, written informed parental permission, and written informed child assent in accordance with local institutional policy. Exclusion criteria were suspicion of perforated appendicitis on clinical or radiological grounds, appendix mass or phlegmon, previous antibiotic treatment to at least a second dose, positive pregnancy test, previous episode of appendicitis or appendix mass or phlegmon treated non-operatively, and current treatment for malignancy or presence of a comorbid condition that would alter length of stay.

Randomisation and masking

Patients were randomly assigned to the antibiotic group or the appendicectomy group with an online stratified randomisation tool provided by randomize.net (Interrand, Ottawa, ON, Canada). Parameters were set to provide study group assignments for the proposed sample size based on a 1:1 ratio with concealment of allocation and stratification by sex, duration of symptoms (≥48 h *vs* <48 h), and trial site. Masking of patients and medical staff enrolling patients, conducting follow-up, or analysing data was not implemented.

Procedures

Patients randomly assigned to the antibiotic group were started on intravenous fluids, antibiotics, and analgesia and admitted to hospital for observation. The choice of antibiotics was dependent on the standards for treating appendicitis at the local centre. Patients were allowed a clear liquid diet. If liquids were tolerated and they were progressing as expected, then regular diet was allowed. Patients were discharged after a minimum of 12 h of intravenous antibiotic therapy if they were tolerating a regular diet with good pain control and vital signs within normal limits. If the patient was not improving enough to advance and prepare for discharge on the day after admission, they were allowed either another day of antibiotics or were scheduled for next available appendicectomy. This decision was made jointly by the patient, their family, and the care team. If the patient's clinical condition had deteriorated on the first day, they were taken for appendicectomy. If the patient was not improving by the second day after admission, they were scheduled for appendicectomy. On discharge, patients were prescribed 10 days of oral amoxicillin–clavulanic acid or ciprofloxacin and metronidazole. Patients taking these medications for at least 7 days were classified as completing the course. Following discharge, children were not offered elective appendicectomy. Families were counselled that recurrence of appendicitis within 12 months would be treated with appendicectomy without another attempt at antibiotic treatment.

In the appendicectomy group, patients were also started on intravenous fluids and antibiotics but scheduled for laparoscopic appendicectomy in the next available slot in the operating room, depending on the typical operating standards within each centre. If no perforation of the appendix was identified, no further antibiotics were given after the operation and patients were discharged when able, including on the same day. Children with perforated appendicitis were treated according to local protocol. The type of antibiotics used was centre-dependent and the same as those used in the antibiotic group.

In both groups, patients were given a diary to document their medication schedule and time to return to activity, school, and sporting level of activity. They were seen in early follow-up within 6 weeks or contacted by telephone. Patients who had not reached a failure endpoint were called at a minimum of 12 months from enrolment to verify that they had not developed a failure endpoint and to ascertain their satisfaction with the assigned treatment (via a questionnaire).

Outcomes

The primary outcome was treatment failure. In the antibiotic group, treatment failure was defined as the need for appendicectomy within 1 year. In the appendicectomy group, treatment failure was defined as either a negative appendicectomy or a complication related to appendicitis requiring a general anaesthetic within 1 year. Primary outcomes were recorded up to 1 year following random assignment or until an endpoint was met.

In addition to each component of the primary outcome, secondary outcomes were selected as being important measures of treatment efficacy that fulfil important core areas of relevance to clinicians and patients. These secondary outcomes were defined a priori as complications (adverse events related either to non-operative treatment of appendicitis or to appendicectomy that require additional interventions without general anaesthesia), and total duration of hospital stays (measured in days as a continuous variable) related to appendicitis, appendicectomy, or associated complications.

Statistical analysis

Assumptions underlying the sample size calculation have been reported previously,[13] with contributing data from a pilot study conducted by some members of the current investigator team[11] and existing literature (up to 2015) before the start of this trial.[8,14–16,17–21] We assumed a failure rate in the appendicectomy group of 7%, with a 5% negative appendicectomy rate and 2% additional intervention requiring general anaesthesia. In the antibiotic group, we assumed a total failure rate of 20%.

The sample size was calculated to test the null hypothesis that antibiotic treatment alone is inferior to appendicectomy by more than 20 percentage points, implying that surgeons and patients would be content with failure being within 20%. The non-inferiority margin was determined by trial investigators as a compromise between a margin that would be acceptable to patients and their families (who might find a margin wider than 20% acceptable) and one that might be acceptable to surgeons treating children (who would probably prefer a narrow margin) and is consistent with opinion within the literature.[22] With a one-sided α level of 5% and 90% power to show the alternative that antibiotic treatment alone is inferior to appendicectomy by 13 percentage points or less, a sample of 880 children with two equal groups of 440 was calculated to be required. Assuming a combined 10% dropout and loss to follow-up, we aimed to recruit 978 patients.

All participants in the two study groups were summarised descriptively. The primary outcome was analysed by comparing the difference in proportion of failures in each treatment group. The 90% CI for the difference between the two treatment groups was constructed such that if the upper bound of the confidence interval was less than 0·2 (ie, the 20% non-inferiority margin), the null hypothesis would be rejected and the antibiotic group declared non-inferior. All outcomes (primary and secondary) were assessed in participants with 12-month follow-up data, and missing data are described in the Results.

Length of hospital stay was compared between treatment groups by means of the Mann–Whitney *U* test, to account for right skewing from most patients spending a short time in hospital, with few and widely variable protracted stays. Total duration of hospital admissions in the first year following random assignment was also compared between treatment groups using the Mann-Whitney U-test. A zero-inflated Poisson regression was completed to assess differences in the number of emergency visits between study groups. Comparison of patient satisfaction ratings in the two study groups was done with a test of proportions. Data were collected at each local site and shared with the primary site (Children's Mercy, Kansas City, MO, USA). All statistical analysis was conducted using SAS (version 9.4).

See Online for appendix

An independent trial steering committee (TSC) and data monitoring committee (DMC) were established to oversee the trial. Members had no direct investment or participation in the study. Terms of reference and a DMC charter were developed based on the Data Monitoring Committees: Lessons, Ethics, Statistics (DAMOCLES) Study Group.[23] A planned interim analysis testing for inferiority was done once half of the planned sample size had been recruited. The interim analysis was based on a modified primary outcome with a 3-month follow-up period without bias adjustments, to reduce the number of patients affected if stopping the study were to be recommended. A stopping rule was set such that if a modified primary outcome (failure at 3-month follow-up) in the antibiotic group exceeded that in the appendicectomy group by more than 33%, the DMC would recommend to the TSC that recruitment be terminated. At this timepoint, the DMC also reviewed adverse events in each treatment group. Only serious adverse events (ie, death and lasting morbidity) were categorised separately.

The study was registered with ClinicalTrials.gov, NCT02687464.

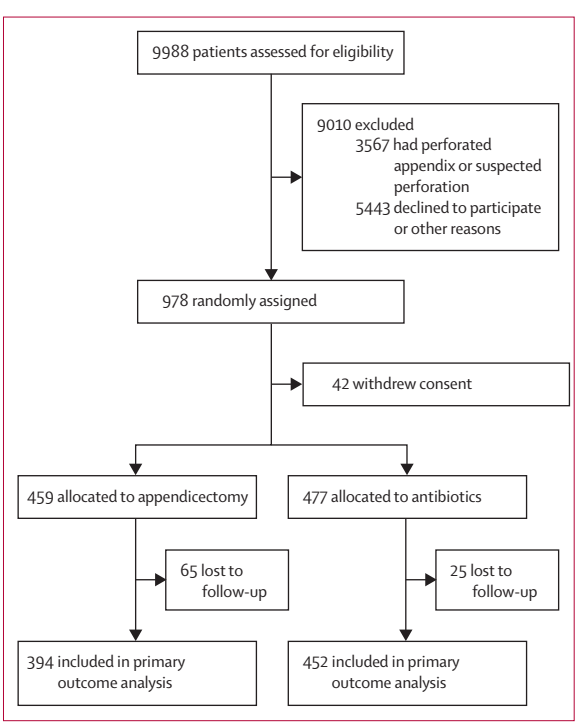

Figure: **Trial profile**

Role of the funding source

There was no funding source for this study.

Results

Between Jan 20, 2016, and Dec 3, 2021, we screened 9988 patients for eligibility and enrolled 978 patients across 11 centres (figure). During the course of screening and recruitment, an interim analysis was done (in June, 2019; appendix pp 4–9), and the TSC recommended that recruitment continue to achieve the full sample size. 42 patients withdrew consent after random assignment and did not have their data retained. Overall, 459 (49%) patients were randomly assigned to the appendicectomy group and 477 (51%) to the antibiotic group. Table 1 shows patient demographics and baseline clinical and radiological characteristics, including the presence of a fecalith on imaging, at initial presentation.

At the 12-month follow-up, data were available for 846 (90%) of 978 patients, of whom 394 were in the appendicectomy group and 452 in the antibiotic group (the remainder could not be contacted to ascertain their treatment failure status; figure). Primary outcome was assessed in those with 12-month follow-up (table 2). Treatment failure occurred in 28 (7%) of 394 patients in the appendicectomy group and in 153 (34%) of 452 patients in the antibiotic group. The difference in proportion of treatment failures between study groups (antibiotics *vs* appendicectomy) was 26·7% (90% CI 22·4–30·9). Because the upper bound of the confidence interval (30·9%) was greater than the inferiority margin (20%), the null hypothesis of antibiotic treatment alone being inferior to appendicectomy could not be rejected. In the antibiotic group, 72 instances of primary outcomes meeting the definition for treatment failure occurred during the index admission, and 81 occurred after discharge. In the appendicectomy group, most cases (27 of 28) that met the definition for treatment failure were negative appendectomies, and one patient

returned to the operating room for a related procedure under general anaesthesia. Primary outcome by stratification factors for both groups and time to failure in the antibiotic group are in the appendix (p 2).

As we did not have complete follow-up data, we considered the effect of missing data. The proportion of missing data was higher in the appendicectomy group (14%) than in the antibiotic group (5%). If we assume the incidence of treatment failure to be the same in patients with complete data and those with missing data, the overall trial results remain similar—ie, a 32% failure rate in the antibiotic group, 6% failure rate in the appendicectomy group, and difference of 26·1% (90% CI 22·2–30·1) between treatment groups. We believe this assumption is justified because of those patients we were able to contact, none had undergone appendicectomy or had a further, related procedure under general anaesthesia elsewhere.

Of the 459 patients who were randomly assigned to appendicectomy, 28 (6%) had pathology reported as perforated. Of the 72 patients randomly assigned to antibiotics for whom antibiotics failed early, 25 (35%) were classified as having a perforation. Of those in whom symptoms recurred and who returned for appendicectomy, four (5%) of 81 were considered as having a perforated appendix. Of those who underwent appendicectomy in the antibiotic group, 13 (8%) of 153 had normal pathology.

There were no deaths or serious adverse events in either group. The relative risk of having an adverse event related to treatment in the antibiotic group compared with the appendicectomy group was 4·3 (95% CI 2·1–8·7; p<0·0001; appendix p 3). In the antibiotic group, adverse effects were recorded in 40 (8%) of 477 patients (appendix p 3; these adverse events were mostly gastrointestinal distress). Only four of these patients required re-admission (one with *Clostridium* infection, one with haematemesis, one with an allergic reaction, and one with gastroenteritis). Two patients in the antibiotic group who underwent appendicectomy within 1 year developed a surgical-site infection. In the appendicectomy group, adverse events were recorded in nine (2%) of 459 patients. One of these patients was included in the primary outcome data because they required reoperation under general anaesthetic; this reoperation was also counted as an adverse event as it was not an anticipated potential outcome of appendicectomy. The other eight (2%) patients had a surgical-site infection; three of the eight patients with infection developed an abscess, of whom two had perforated appendicitis.

During the initial hospitalisation, the median length of stay for the appendicectomy group was 1·0 day (IQR 0·76–1·68), compared with 1·25 days (0·92–2·09) for the antibiotic group (p<0·0001). Patients in the antibiotic group also spent more total time in hospital during the 12-month follow-up period, at a median of

	Randomly assigned (n=936)		12-month primary endpoint recorded (n=846)	
	Antibiotic group (n=477)	Appendicectomy group (n=459)	Antibiotic group (n=452)	Appendicectomy group (n=394)
Study site				
Kansas City (MO, USA)	107 (22%)	107 (23%)	99 (22%)	74 (19%)
Helsinki (Finland)	91 (19%)	86 (19%)	87 (19%)	81 (21%)
Stockholm (Sweden)	73 (15%)	61 (13%)	69 (15%)	57 (15%)
Montreal (QC, Canada)	47 (10%)	49 (11%)	45 (10%)	47 (12%)
Calgary (AB, Canada)	41 (9%)	40 (9%)	41 (9%)	38 (10%)
Winnipeg (MB, Canada)	31 (7%)	26 (6%)	31 (7%)	21 (5%)
Uppsala (Sweden)	25 (5%)	27 (6%)	25 (6%)	27 (7%)
Memphis (TN, USA)	21 (4%)	20 (4%)	20 (4%)	15 (4%)
London (ON, Canada)	16 (3%)	20 (4%)	13 (3%)	13 (3%)
Vancouver (BC, Canada	16 (3%)	16 (4%)	14 (3%)	14 (4%)
Singapore	9 (2%)	7 (2%)	8 (2%)	7 (2%)
Age at admission, years	10·6 (8·7–12·9)	10·9 (8·7–13·5)	10·7 (8·7–12·9)	10·8 (8·7–13·2)
Weight, kg	38·0 (28·5–51·0)	38·0 (28·8–53·0)	38·0 (28·7–51·0)	37·3 (28·6–51·5)
BMI, kg/m²	19·0 (16·4–22·3)	18·0 (15·2–22·7)	19 (16·5–22·3)	17·7 (15·0–21·8)
Sex				
Male	300 (62·9%)	295 (64·3%)	288 (63·6%)	256 (65·0%)
Female	177 (37·1%)	164 (35·7%)	165 (36·4%)	138 (35·0%)
Duration of symptoms, days	1 (1–2)	1 (0–2)	1 (1–2)	1 (0–2)
Temperature at admission, °C	37·0 (36·7–37·5)	37·1 (36·8–37·6)	37·0 (36·7–37·6)	37·1 (36·8–37·6)
White blood cells (1000 per mL)	13·4 (9·9–16·9)	13·4 (10·2–17·0)	13·5 (9·8–16·9)	13·3 (10·2–16·8)
Symptoms ≥48 h	135 (28·3%)	129 (28·2%)	127 (15·3%)	106 (12·8%)
Fecalith on Imaging	62 (13·0%)	52 (11·3%)	58 (12·8%)	48 (12·2%)

Data are median (IQR) for continuous variables and n (%) for categorical variables.

Table 1: **Enrolment, patient demographics, and presenting signs and symptoms by study group**

	Treatment failure, n (%)
Appendicectomy group (n=394)	
Normal pathology	27 (7%)
Complication requiring general anaesthetic within 1 year*	1 (<1%)
Antibiotic group (n=452)	
Failure of initial antibiotic treatment†	72 (16%)
Recurrence and subsequent appendicectomy	81 (18%)

Data are from the population with 12-month follow-up data. *Patient returned to hospital for laparoscopic evacuation of haematoma. †Appendicectomy was done if patient's clinical condition deteriorated on first day of treatment or did not improve enough after 2 days of antibiotic treatment.

Table 2: **Breakdown of primary outcomes**

1·6 days (IQR 1·0–2·6), compared with 1·0 day (0·75–1·7) in the appendicectomy group (p<0·0001).

In the antibiotic group, 52 (46%) of 112 visits to the emergency department occurred within the first 6 weeks following initial discharge after random assignment. According to the zero-inflated Poisson regression model, the number of return visits to the emergency department relating to appendicitis during the study period was not significantly different between the two study groups (β=0·38; 95% CI −0·01 to 0·77; p=0·057). However, the odds of a patient having one or more emergency department visits were higher in the antibiotic group than in the appendicectomy group (odds ratio 1·58, 95% CI 1·05 to 2·42; p=0·031).

Regarding convalescence, 154 (34%) of 459 participants in the appendicectomy group and 179 (38%) of 477 in the antibiotic group had at least one day's entry in their 14-day diary. 300 (90%) of these 333 individuals completed all 14 days of the diary. Fewer days were taken to return to normal activity and to school in the antibiotic group than in the appendicectomy group (p<0·0001; table 3). Furthermore, the median duration of pain medication use in the appendicectomy group was 3 days (IQR 1–5), whereas patients in the antibiotic group generally did not require pain medications (p<0·0001; table 3). 148 (83%) patients in the antibiotic group took a full course of antibiotics (9 or 10 days).

During the final follow-up at 12 months, families of patients who had not had treatment failure were asked if they were satisfied with their treatment allocation and to explain the reason for their answer. In the antibiotic group, 214 (73%) of 293 respondents were satisfied, the most common reason being that they wanted to avoid surgery (147 [67%] of 214). Of the 79 (27%) who were unsatisfied, the most common reason was that they were concerned about recurrence (41 [52%] of 79). In the appendicectomy group, 213 (73%) of 291 respondents were satisfied, a satisfaction level that was not significantly different to that in the antibiotic group (95% CI 0·68–0·78; p=0·96). The most common reasons were the effectiveness of surgery (102 [48%] of 213) and that they were happy to avoid the risk of recurrence (61 [27]%). Of the 78 (27%) of 291 in the appendicectomy group who were not satisfied, most had wanted to avoid surgery (64 [82%]).

	Antibiotic group (n=179)	Appendicectomy group (n=154)	p value
Days until back to normal activity	1 (1–3)	4 (2–5)	<0·0001
Days until back at school	2 (2–4)	3 (2–5)	<0·0001
Days taking pain medicine	0 (0–1)	3 (1–5)	<0·0001
Days taking antibiotics	9 (8–10)	NA	NA
Individuals taking full course of antibiotics	148 (83%)	NA	NA

Data are median (IQR) for continuous variables and n (%) for categorical variables. Data are from participants with 12-month follow-up data who filled out their 14-day diary. NA=not applicable.

Table 3: **Patient-reported diary summary**

Discussion

Given the increasing interest in treating children with uncomplicated appendicitis without surgery, considering the comparative outcomes of these two very different treatment approaches is important to guide treatment decisions. Although previous studies have described populations of children treated with either surgery or antibiotics, there has not been a large, randomised study with the benefit of removing the possibility of selection or other bias. Our key motivation for conducting the APPY trial was to generate this unbiased dataset. Our study was designed as a non-inferiority trial because we recognised that although there was no realistic possibility of antibiotics being superior to appendicectomy, there could be benefits to non-operative treatment that patients and surgeons might be willing to accept if surgery could be avoided. At the trial design stage, we set the non-inferiority margin at 20%. Within this framework, our study showed that antibiotic management is inferior to appendicectomy.

The threshold for this declaration might be debated among clinicians and researchers. The implication of the 20% non-inferiority margin in this trial is an underlying assumption that to realise the potential benefits of avoiding surgery, patients or surgeons would be willing to accept a failure rate with antibiotics that is 20% higher than that with surgery. At the time of trial development, nearly 10 years previously, an adult non-inferiority trial was criticised for using a margin of 10%, which was considered too narrow.[24,25] At the time, a Cochrane review proposed a non-inferiority margin of 20% to maintain the balance between antibiotics being less effective but also less invasive.[22] Following discussion among our investigator group, we chose to use a 20% margin but recognised that patients and parents might be willing to accept a margin wider than 20%, whereas many clinicians would only be willing to accept a narrower margin. Ultimately, the difference in failure rate between treatment groups was larger than 20%, and inferiority was declared because the entirety of the 95% CI of the difference was greater than 20%. Despite this result, we suspect that this difference will continue to be interpreted from opposite viewpoints. Those most interested in avoiding an operation will see these data as providing hope, whereas those most interested in avoiding initial treatment failure or recurrence will see the failure rate as unacceptably high. Either way, we believe that the data we have generated advance knowledge of the comparative outcomes of these two different treatment modalities and will inform future shared decision making.

We found a raw failure rate for antibiotics of 34% at 1 year, which gave us a 26% difference, compared with the 20% expected difference. This overall failure rate is nearly identical to the rate found in the Midwest Pediatric Surgery Consortium patient choice study.[9] This finding is important because the Consortium study used restrictive inclusion criteria, whereas our study was overtly pragmatic. Patients in the Consortium study were only included with imaging-confirmed uncomplicated appendicitis as assessed by ultrasound, CT, or MRI; an appendix diameter of 1·1 cm or less; no abscess, fecalith, or phlegmon; white blood cell count of 5000–18 000 per µL; and abdominal pain for less than 48 h before the start of antibiotics. We only excluded those with suspected perforated appendicitis, and did not specify the modalities used to diagnose appendicitis and clarify the population to approach for the study. These liberal inclusion criteria probably account for the 7% incidence of perforation found at the time of appendicectomy in the appendicectomy group. This rate is a surrogate for the overall perforation rate at presentation in the antibiotics group, as we will never know of those who recovered and did not have an appendicectomy. Although the high rate of perforation seen in those whose treatment failed early suggests our pragmatic trial design probably contributed to the failures in the antibiotic group, the overall failure rate was the same as more conservative designs. One benefit of our pragmatic design is that it improves the generalisability of our findings.

Patients in the appendicectomy group had a significantly shorter length of hospital stay than those in the antibiotic group because many of the patients treated with appendicectomy could be discharged immediately after the operation, whereas those treated with antibiotics had a period of observation in hospital. In addition, the total length of hospital stay was increased in the antibiotic group as a result of the 81 (17%) patients who subsequently returned to the hospital for an appendicectomy. Most comparative trials have found a similar difference. Two recent meta-analyses of adult trials reported a longer hospital stay with antibiotics, documenting a mean increase of 0·53 days, compared with surgery.[26,27] This finding was the same magnitude of difference that we found in this trial—ie, a 0·6 day difference between medians in favour of appendicectomy. However, moving forward without a strict protocol, patients could be treated much more aggressively up to discharge from the emergency department. The subsequent step of progression could be patients diagnosed in the paediatrician's office or in urgent care being sent home on oral antibiotics with instructions to return with worsening pain.

Once patients were discharged from the hospital, those in the antibiotic group were left with the risk of recurrence. However, these patients had an earlier return to activity, school, and sports, compared with patients in the appendicectomy group. This result was also expected because in patients treated with antibiotics, pain begins to improve rapidly with antibiotics, and these patients have no somatic injury from which to recover. Effectively, by the second day, comparing the treatment groups is akin to comparing patients who have had an umbilical repair (appendicectomy group) with patients who are recovering from a minor gastrointestinal illness (antibiotic group) 2 days previously. This more rapid return to normalcy with antibiotic treatment has also been documented in all comparative studies with this focus.[5–9] Notably, the need for appendicectomy in the antibiotics group occurred early, with the majority of treatment failures occurring within the first 100 days, similar to findings from the CODA trial.[10]

In the CODA trial, adult patients expressed greater regret and dissatisfaction when allocated to the antibiotic group than when allocated to the appendicectomy group,[28] which seems intuitive given the potential anxiety regarding recurrence in patients treated with antibiotics. However, in our study, 1-year satisfaction with treatment allocation was the same in both groups. The most rational explanation for this finding might be that most people who consented to the study did so in the hope of avoiding an operation. As the default treatment was appendicectomy in those not participating in the trial, the study was the only opportunity for patients to be treated with antibiotics alone.

Limitations of this study include our inability to precisely track the declined consents and reasons for refusal. Although we initially intended to do so, with the ultimate lack of funding, the consenting process fell on the resident teams across all sites, and reasons for non-enrolment became impossible to capture at scale. Other datapoints were also unfeasible to track, such as total health-care visits and subsequent tests. Another limitation is our 10% missing data, with a higher proportion of missing data in the appendicectomy group. In the final analysis of the primary outcome, we only included patients whom we had been able to contact at 12 months to confirm their treatment failure status (specifically, that they had not had a complication related to appendicitis that had been treated at a different institution). Because most centres in the study are the dominant paediatric centres in their regions, patients with complications would have been unlikely to have presented elsewhere. Notably, of all the families we contacted in both groups, we did not uncover a single patient who had reached an endpoint at an outside hospital that we had not already captured (ie, none of the contacted patients had had an appendicectomy at another hospital). Our sensitivity analysis indicates that if we assume that event rates in the cases with missing data are identical to those with complete data, the trial conclusion remains unchanged. Given that we did not capture ethnicity or include countries with greater resource constraints, the results do not give us insight into those populations.

In conclusion, in the context of a permitted 20% non-inferiority margin, antibiotic treatment for uncomplicated appendicitis in children was inferior to appendicectomy in this trial. Duration of hospitalisation was shorter with appendicectomy, but antibiotic treatment led to a shorter period of convalescence and more rapid return to normal function.

Contributors

SDSP: study design, study oversight, analysis, and manuscript creation. JRN-M: data analysis and manuscript creation. NJH: study design and manuscript creation. SE: study design, oversight of randomisation, and manuscript review. JSS, TW, MBe, and JFS: study design, site co-principal investigator, and manuscript review. MA: study design and site co-principal investigator. EPM: data collection and organisation of trial conduct. NP, MBr, AM, ES, YT-L, and SN: site co-principal investigator and manuscript review. RK: study design, site principal investigator, and manuscript review. HEL, TJ, and AB: site principal investigator and manuscript review. A-MK and JD: data collection, site co-principal investigator, and manuscript review. ARW and AP: study design and manuscript review.

Declaration of interests

We declare no competing interests.

Data sharing

De-identified individual participant data collected during the APPY trial will be available beginning at 1 year and ending at 3 years following Article publication. Proposals should be directed to the corresponding author to gain access. Proposals will need to be reviewed by all authors and centres. If approved, the requestor or requestors will need to sign a data use agreement and agree on reasonable environments to make data available.

Acknowledgments

No external funding was received for the overall running of the trial. In Sweden, grant funding secured from the Swedish Research Council and Stiftelsen Frimurare Barnhuset in Stockholm was used to pay for research nurses in both Stockholm and Uppsala. At the London (ON, Canada) site, grant funding was obtained from the Academic Medical Organisation of Southwestern Ontario to partly fund a research coordinator. AP was the initial primary investigator of the study with the working group named on the published protocol first authored by NJH. We would like to acknowledge those who contributed to the study but were not able to be named as authors. These include but are not limited to Gabrielle Derraugh, Elin Ost, Chen Yong, Candy Choo Suet Cheng, Lauren Camp, Kathy Johnson, and Risto Rintala. We also thank all of the surgeons, research coordinators, research fellows, and consenters who facilitated the completion of this trial.

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