## Appendectomy versus antibiotics for acute uncomplicated appendicitis in children: An open label, international, multicenter, non-inferiority, randomized trial.

Shawn D St. Peter, MD1\*, Janelle R. Noel-MacDonnell,PhD2, Nigel J Hall, MD, PhD3\*, Simon Eaton, PhD4\*, Janne S. Suominen MD5, Tomas Wester, MD, PhD6\*, Jan F. Svensson, MD, PhD6\*, Markus Almström MD,PhD6, E. Pete Muenks MSc1, Marianne Beaudin, MD7\*, Nelson Piché, MD7\*, Mary Brindle, MD, MPH8\*, Ali MacRobie8, Richard Keijzer, MD, PhD9\*, Helene Engstrand Lilja, MD, PhD10\*, Ann-Marie Kassa RN, PhD10 Tim Jancelewicz MD11\*, Andreana Butter MD12\*, Jacob Davidson MSc12, Erik Skarsgard MD13\*, Yap Te Lu MD14, Shireen Nah MD15, Andrew R Willan, PhD16\*, Agostino Pierro, MD, PhD17\*

1 Department of Surgery, Children’s Mercy, Kansas City, MO, USA

2Department of Health Services and Outcomes Research, Children’s Mercy, Kansas City, MO, USA

3University Surgery Unit, Faculty of Medicine, University of Southampton, Southampton, UK.

4Department of Pediatric Surgery, Great Ormond Street Hospital, London, United Kingdom

5Department of Pediatric Surgery, Helsinki University Hospital, University of Helsinki, Helsinki, Finland

6Department of Pediatric Surgery, Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm, Sweden

7Division of Pediatric Surgery, Centre Hospitalier Universitaire Ste-Justine, Université de Montréal, Montréal, Québec, Canada.

8Department of Surgery, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

9Departments of Surgery, Division of Pediatric Surgery, Pediatrics & Child Health, University of Manitoba, Winnipeg, Manitoba, Canada

10 Division of Pediatric Surgery, Uppsala University

11 Le Bonheur Children’s Hospital, University of Tennessee Health Science Center, Memphis, TN, USA

12 Division of Pediatric Surgery, Children’s Hospital, LHSC, London, Ontario, Canada

13Department of Surgery, British Columbia Children's Hospital, Vancouver, British Columbia, Canada

14Division of Pediatric Surgery, KK Women’s and Children’s Hospital, Singapore.

15Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia.

16Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada

17Division of General and Thoracic Surgery, Hospital for Sick Children, Toronto, Ontario, Canada

Full Professor - \*

**Corresponding Author**

Shawn D. St. Peter, M.D.

Surgeon-in-Chief/Senior Vice President

Children’s Mercy Hospital

2401 Gillham Road

Kansas City, MO 64108

Tel: 816-234-3575

Fax: 816-983-6885

Email: sspeter@cmh.edu

**Disclosure:**

None of the authors have any disclosures.

**Running head:**

**APPY Trial: -Antibiotics versus appendectomy for pediatric appendicitis**

**Abstract**

**Background:**

The support for treatment of uncomplicated appendicitis with non-operative management as opposed to surgery has been building in the literature. We conducted a randomized trial to compare failure rates.

**Methods:**

We conducted a pragmatic multicenter, parallel-group, unmasked, non-inferiority, randomized trial completed at 11 children’s hospitals across the globe. We used a non-inferiority design with a margin of 20%, and randomized in a 1:1 allocation while stratifying by sex, institution and duration of symptoms (≥ 48 hours verses <48 hours). Patients were 5-16 years of age with suspected non-perforated appendicitis. The primary outcome was treatment failure up to one year following randomization. Failure in the antibiotic arm was removal of the appendix, and failure in the appendectomy arm was a normal appendix based on pathology. In both arms, a failure was counted for an additional procedure related to appendicitis requiring general anesthesia. Interim analysis was performed to determine if inferiority was to be declared at the half-way point. The trial was registered at ClinicalTrials.gov (NCT02687464).

**Findings:**

Between January, 2016 and December, 2021, 936 patients were randomized (459 in appendectomy arm and 477 in antibiotic arm). At 12-month follow-up, primary outcome data were available for 846 (90·3%). The failure rate in the antibiotic arm was 33·8% compared to 7·1% in the appendectomy arm. The difference is 26·7% (90% CI: 0·22, 0·31).

Of the 459 patients who were randomized to appendectomy, 28 (6·5%) had pathology reported as perforated. Of the 72 randomized to antibiotics who failed antibiotics early, 25 (34·7%) were classified as perforation. All but 1 patient that met the definition for treatment failure with appendectomy were negative appendectomies. Of those who underwent appendectomy in the antibiotic group, 13 (9·2%) had normal pathology.

**Interpretation:**

Based on a 20% non-inferiority margin, antibiotic management of non-perforated appendicitis is inferior to appendectomy based on cumulative failure rates.

**Funding:** The overall execution of the trial received no external funding. However, at the Swedish sites, grant funding was secured from the Swedish Research Council and Stiftelsen Frimurare Barnhuset in Stockholm 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 (AMOSO) to partially fund a research coordinator.

**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 appendectomy since the operation was first described in 1886 (2). Although there have long been examples of treating appendicitis without surgery but with antibiotics alone (3), this strategy has only recently begun to be formally compared to appendectomy in adults and children. Laparoscopic appendectomy for non-perforated appendicitis has a low risk of complications; however, it is an abdominal operation requiring general anesthesia and hence exposes the child inevitably to a risk of complications of these. Even with current imaging methods, it can be expected that around five percent of patients undergoing appendectomy will be found to have a normal appendix, and thus they underwent an unnecessary operation (4).

Several studies have documented antibiotic therapy alone is highly successful as initial treatment of appendicitis and is associated with more rapid return to normal activity than surgery (5-9). The Midwest Pediatric Surgery Consortium performed a non-randomized patient preference trial in 1,068 children demonstrating about two-thirds of patients treated with antibiotics avoided an operation at one year and those patients had fewer disability days compared to primary laparoscopic appendectomy (9).

Large, multicenter randomized trials have been performed in adults, such as that by the CODA collaborative (Comparison of Outcomes of antibiotic Drugs and Appendectomy) (10). In the CODA trial, 1,552 patients were randomized to compare the primary outcome of 30-day European Quality of Life – five dimensions score. They concluded that antibiotics were non-inferior according to this metric. However, the failure rate with antibiotics was near 30%. Although there have been two prospective randomized controlled trials in children, both have been small pilot/feasibility studies(7,11), so there has been no large-scale randomized study in children allowing an unbiased comparison of outcomes between these two very different treatment strategies. We therefore designed and conducted the APPY trial - a multicenter, randomized trial comparing laparoscopic appendectomy to antibiotics alone in children with uncomplicated appendicitis.

**METHODS**

***Study design***

We conducted an open label, pragmatic, non-inferiority, non-blinded, parallel, multicenter randomized trial. The protocol was developed in accordance with the SPIRIT guidelines (12) and has been previously published (13). There were no important changes 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 obtaining informed consent from the patient’s legal guardian.

***Participants***

The study population consisted of children between the ages of 5 and 16 years diagnosed with simple appendicitis. Families were offered enrollment into the trial or to proceed with appendectomy per local center standard of care. The enrollment process occurred after the diagnosis of appendicitis was made.

Inclusion criteria

* Diagnosis of non-perforated appendicitis
* Written informed parental permission
* Written informed child assent in accordance with local institutional policy

Exclusion criteria

* Suspicion of perforated appendicitis based on clinical or radiological grounds
* Appendix mass or phlegmon
* Prior antibiotic treatment to at least a second dose
* Positive pregnancy test
* Previous episode of appendicitis or appendix mass/ phlegmon treated non-operatively
* Current treatment for malignancy or presence of co-morbid condition that would alter length of stay

***Randomization***

After signed informed consent/assent, patients enrolled in the study were randomized using an online stratified randomization tool provided by randomize.net (Interrand Inc., Ottawa, Ontario). Parameters were set to provide study arm assignments for the proposed sample size based on a 1:1 ratio with concealment of allocation and stratified by sex, duration of symptoms (> 48 hours versus < 48 hours) and trial site.

***Interventions***

Antibiotic group: All patients randomized to this study arm were defined as the ‘antibiotic group’. Patients were started on intravenous fluids, antibiotics, analgesia, and admitted to the hospital for observation. The choice of antibiotics was dependent on the standards for treating appendicitis at the local center. 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 hours intravenous antibiotic therapy if 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, then they were allowed another day of antibiotics or scheduled for next available appendectomy. This was a joint decision between the patient/family and care team. If the clinical condition had deteriorated on the first day, then they were taken for appendectomy. If the patient was not improving by the second day after admission, they were scheduled for appendectomy. Upon discharge, patients were prescribed 10 days of oral amoxicillin/clavulanic acid or ciprofloxacin and metronidazole. Patients taking at least seven days were classified as completing the course. Following discharge, children were not offered elective appendectomy. Families were counselled that recurrence of appendicitis within 12 months would be treated with appendectomy without another attempt at antibiotic treatment.

Appendectomy group: All patients randomized to this study arm were defined as the ‘appendectomy group’. Patients were also started on intravenous fluids and antibiotics but scheduled for laparoscopic appendectomy in the next available slot in the operating room depending on the typical operating standards within each center. If no perforation of the appendix was identified, then no further antibiotics were given after the operation and patients were discharged when able, including the same day. Children with perforated appendicitis were treated according to local protocol. The type of antibiotics utilized was center-dependent and the same as those used in the antibiotic group.

***Outcomes***

The primary outcome was treatment failure. In the antibiotic group, this was the need for appendectomy within one year. In the appendectomy group, this was defined either a negative appendectomy or a complication related to appendicitis requiring a general anesthetic within one year.

In addition to each component of the primary outcome, further secondary outcomes were selected as being important measures of treatment efficacy that fulfil important core areas of relevance to clinicians and patients including pathophysiological manifestations, life impact, resource use, and death. These were recorded up to one year following randomization or until an endpoint was met. These were defined a priori as:

- complications: adverse events related to either nonoperative treatment of appendicitis or appendectomy which require additional interventions without general anesthesia.

- time to discharge home after randomization

- duration of hospital admissions related to appendicitis, appendectomy, or their complications.

***Follow-up***

This was a triple unblinded study. 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 reached by phone. Patients who hadn’t reached a failure endpoint were called at a minimum of 12 months from enrolment to be sure they hadn’t developed a failure endpoint, and to ascertain their satisfaction with their assigned treatment.

***Sample size calculation***

Assumptions underlying the sample size calculation have been previously reported (13) with contributing data arising from a pilot study conducted by some members of the current investigator team (11), and the existing literature up to 2015 prior to the start of this trial (14-22). We assumed a failure rate in the appendectomy group of 7% with a 5% negative appendectomy 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 appendectomy by more than 20 percentage points implying 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 which may be acceptable to patients and their families (who may find a wider margin acceptable) and that which may be acceptable to surgeons treating children (who would likely tolerate a lower margin) and is consistent with opinion within the literature (26). Using a one-sided test at 5% level of significance and 90% power for the alternative that antibiotic treatment alone is inferior to appendectomy by 13 percentage points or less, required a sample of 880 children with two equal groups of 440. Assuming a combined 10% drop out and loss to follow-up, we aimed to recruit 978 patients.

***Analysis***

 All participants in the two study arms were descriptively summarized. The primary outcome was analysed by comparing the difference in proportion of failures in each treatment group. To facilitate this, the 90% confidence interval for the difference (antibiotics – appendectomy) was constructed, so that if the upper-bound of the confidence interval was less than 0·2 (i.e. the 20% non-inferiority margin), the null hypothesis would be rejected, and the antibiotic arm declared non-inferior.

Time to discharge was compared between treatment arms using a Mann-Whitney U-test to account for right skewing from most patients spending a short time in the hospital with few and widely variable protracted stays. Total duration of hospital admissions in the first year following randomization was compared between treatment arms also using a Mann-Whitney U-test. A zero-inflated Poisson regression was completed to assess differences in the number of emergency visits between study arms. All outcomes were analysed on an intention-to-treat basis and missing data are described in the results. Data were collected at each local site and shared with the primary site. All statistical analysis was conducted using SAS Version 9·4 (SAS Institute, Cary, NC, USA).

**Oversight**

 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 was developed, based on the DAMOCLES (DAta Monitoring Committees: Lessons, Ethics, Statistics) Study Group (24). A planned interim analysis testing for inferiority was undertaken once half of the planned sample size had been recruited. The interim analysis was based on a modified primary outcome with a three-month follow-up period without bias adjustments. In this way, if stopping the study was recommended, we wouldn’t have many that were already enrolled and in the active follow-up period. A stopping rule was set such that if a modified primary outcome (failure at three months follow-up) in the antibiotic arm exceeded that in the appendectomy arm by over 33%, the DMC would recommend to the TSC that recruitment be terminated. The DMC also at this time point reviewed adverse events in each trial arm. The study was registered with ClinicalTrials.gov on January 13, 2016 (NCT02687464) and is reported in accordance with CONSORT guidelines.

***Role of Funding Source***

The overall execution of the trial received no external funding. In Sweden, grant funding was secured from the Swedish Research Council and Stiftelsen Frimurare Barnhuset in Stockholm. The grants were 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 (AMOSO) to partially fund a research coordinator.

**RESULTS**

***Study Population***

Recruitment began on January 20, 2016 and continued to December 3, 2021, at which point the total of 978 patients were enrolled across 11 centres (Table 1). There were 42 patients who withdrew consent and did not have their data retained. An interim analysis was performed in June, 2019, and the TSC recommended that recruitment continue to achieve the full sample size. Overall, 459 (49%) were randomized to the appendectomy group and 477 (51%) to the antibiotic group. At the 12-month follow up, data were available for 846 (90.3%) of whom 394 were in the appendectomy group and 452 in the antibiotic group. The remainder of cases could not be contacted to ascertain their treatment failure status. See CONSORT flow diagram for details (Figure 1).

At initial presentation, patient demographics including age at admission, weight, body mass index, and sex were similar in both groups (Table 1). In addition, baseline clinical and radiological characteristics including the presence of a fecalith on imaging were similar (Table 1).

***Primary Outcome***

Primary outcome was assessed in those with 12-month follow-up. Treatment failure occurred in 7·1% (28/394) of those in the appendectomy group and in 33·8% (153/452) of those in the antibiotic group (Table 2). The difference in proportion of treatment failures between trial arms (antibiotics – appendectomy) was 26·7% (90% CI: 22·4%, 30·9%). Since the upper bound of the confidence interval (30·9) was greater than the inferiority margin (20), inferiority cannot be rejected. Of those who met the definition for treatment failure in the antibiotic group, 72 occurred during the index admission and 81 occurred after discharge. In the appendectomy group the majority of cases (27/28) that met the definition for treatment failure were negative appendectomies and there was one patient who returned to the operating room for a related procedure under general anaesthesia. Primary outcome by stratification factors is demonstrated in Supplemental Figure 1. Time to failure in the antibiotic group is demonstrated in Supplemental Figure 2.

Since we did not have complete follow-up, we considered the impact of missing data. The proportion of missing data was higher in the appendectomy group (14·1%) than the antibiotic group (5·2%). If we assume that the incidence of treatment failure in cases with complete data and cases with missing data is the same then the overall trial results remain similar: 32·2% failure rate in the antibiotic group and 6·1% failure rate in the appendectomy group, and difference between trial arms of 26·1% (90% CI: 22·2%, 30·1%). We believe this assumption is justified since of those who we were able to contact, there were no patients who had undergone appendectomy or had a further related procedure under general anaesthesia elsewhere.

***Secondary outcomes***

Pathology

Of the 459 patients who were randomized to appendectomy, 28 (6·5%) had pathology reported as perforated. Of the 72 randomized to antibiotics who failed antibiotics early, 25 (34·7%) were classified as perforation. Of those who recurred and returned for appendectomy, 4/81 (4·9%) were considered perforated. Of those who underwent appendectomy in the antibiotic group, 13 (9·2%) had normal pathology.

Adverse Events

There were no deaths in either group. The relative risk of having an adverse event in the antibiotic group compared to the appendectomy group was 4·3 (95% CI: 2·1, 8·7; P<0·0001) (Supplemental Table 1). In the antibiotic group, adverse effects were recorded in 40 patients (8·4%). These were mostly gastrointestinal distress, however, only four required re-admission. One with Clostridium infection, one with hematemesis, one allergic reaction, and one for gastroenteritis. There were two patients in the antibiotic group who underwent appendectomy and developed a surgical site infection. In the appendectomy group, adverse events were recorded in nine patients (2·0%). One was discussed in the primary outcome with re-operation and the other eight patients had a surgical site infection (1·7%). Of those, three patients developed an abscess, of which two had perforated appendicitis.

Length of Hospital Stay

During the initial hospitalization, median length of stay for the appendectomy group was 1·0 days (IQR: 0·76, 1·68), compared to 1·25 days (IQR: 0·92, 2·09) for the antibiotic group (P<0·001). Patients in the antibiotic group also spent more total time in the hospital during the 12 month follow-up period at a median of 1·6 days (IQR: 1, 2·6) compared to one day (IQR: 0·75, 1·7) in the appendectomy group (P < 0·001).

Emergency Return Visits

In the antibiotic group, approximately 46% (52/112) of visits occurred within the first six weeks following initial discharge after randomization. The number of return visits to the emergency department relating to appendicitis during the study period were no different when comparing study arms (β=0·38; 95% CI: -0·01, 0·77; P=0·057) in the zero-inflated Poisson regression model. However, the odds of a patient in the antibiotic group having one or more emergency department visits increased by 58% (odds ratio (OR) =1·58; 95% CI: 1·05, 2·42; P=0·031).

Convalescence

Approximately, one-third of participants had at least one day’s entry in their 14-day diary (33·6% in the appendectomy arm and 37·7% in the antibiotic arm). Approximately 90% of these individuals completed all 14 days of the diary. Days taken to return to normal activity and to school were fewer in the antibiotic group compared to the appendectomy group (both P<0·0001;( Table 3)). Furthermore, the median duration of pain medication use in the appendectomy group was three days, while patients in the antibiotic group generally did not require pain medications (P<0·0001; Table 3). Eighty-two percent of patients in the antibiotics group took a full course of antibiotics with most taking nine or ten days of antibiotics.

 Patient Satisfaction

During the final follow-up, families were asked if they were satisfied with their treatment allocation and to explain why. In the antibiotic group, 214 (214/293=73·0%; 95% CI: 0·68, 0·78) were satisfied. The most common reason was they wanted to avoid surgery (147/214=67·1%). Of the 79 (27·0%) unsatisfied, the common reason was they were concerned about recurrence (41/79=51·9%). In the appendectomy group, 213 (213/291=73·2%; 95% CI: 0·68, 0·78) were satisfied, which was not different from the antibiotic group (P = 0·96). The most common reasons were the effectiveness of surgery/satisfied with outcome (102/213=47·9%) and they were happy to avoid the risk of recurrence (61/213=28·6%). Of the 78 (26·8%) in the appendectomy group who were not satisfied, most had wanted to avoid surgery (64/78=82·0%).

**DISCUSSION**

With a building interest in treating children with uncomplicated appendicitis without surgery, it is important to consider the comparative outcomes of these two very different treatment approaches to guide treatment decisions. While previous studies have described populations of children treated with either surgery or antibiotics, there has not been a large, randomized study with the benefit of removing the possibility of selection or other bias. Our key motivation to performing the APPY trial was to generate this unbiased dataset. Our study was designed as a non-inferiority trial since we recognized that there was no realistic possibility of antibiotics being superior to appendectomy but equally recognized that there was an acceptance that there may be benefits to non-operative treatment that patients and surgeons may be willing to accept if surgery could be avoided. At the trial design stage, we set a non-inferiority margin at 20%. Within this framework, our study demonstrates that antibiotic management is inferior to appendectomy.

The threshold for this declaration may serve as fodder for debate amongst clinicians and researchers. The implication of the 20% non-inferiority margin in this trial is an underlying assumption that patients or surgeons would be willing to accept a failure rate with antibiotics that is 20% higher than that with surgery to realize the potential benefits of avoiding surgery. At the time of trial development nearly ten years previously, there was an adult non-inferiority trial criticized for using a too narrow margin of 10%. (23,25) A Cochrane review at the time proposed a non-inferiority margin of 20% holding the balance between antibiotics being less effective but also less invasive (26). Following discussion amongst our investigator group, we elected to use a 20% margin but recognized that patients and parents may be willing to accept a wider margin whereas many clinicians may only be willing to accept a narrower margin. Ultimately the difference in failure rate between treatment arms was larger than 20% and inferiority declared since the entirety of the 95% CI of the difference is greater than 20%. Despite this, we suspect this difference will continue to be interpreted from opposite viewpoints. Those most interested in avoiding an operation will see these data as providing hope while those most interested in avoiding initial treatment failure or recurrence will see the failure rate as unacceptably high. Either way, we believe the data we have generated advance our 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 approximately one-third at one year, which gave us a 26% difference compared to the 20% expected difference. This overall failure rate is nearly identical to the failure rate found in the Midwest Pediatric Surgery Consortium patient choice study [9]. This is an important finding because the Consortium study used restrictive inclusion criteria while our study was overtly pragmatic. Patients in the Consortium study needed to have imaging-confirmed uncomplicated appendicitis by ultrasound, computed tomography (CT), or magnetic resonance imaging of an appendix with a diameter of 1·1 cm or less and no abscess, fecalith, or phlegmon. In addition, they needed a white blood cell count between 5,000/μL and 18,000/μL, and abdominal pain for less than 48 hours prior to the start of antibiotics. We only excluded those with suspected perforated appendicitis. We also didn’t specify the modalities employed to diagnose appendicitis and clarify the population to approach for the study. These liberal inclusion criteria likely account for the 7% incidence of perforation found at the time of appendectomy in the appendectomy arm. This number is a surrogate for the overall perforation rate at presentation in the antibiotics arm, since we will never know of those who recovered and did not get an appendectomy. Although the high rate of perforation seen in those who failed early suggests our pragmatic trial design likely contributed to the antibiotic failures, the overall failure rate was the same as more conservative designs. One benefit of our pragmatic design is that it improves the generalizability of our findings.

The appendectomy group had a significantly shorter length of stay. This was due to the period of observation in hospital for those treated with antibiotics while many appendectomy patients could be discharged after the operation. In addition, the total length of stay was increased in the antibiotic group from the 17% who returned to the hospital for an appendectomy later. Most comparative trials have found the same difference as two recent meta-analyses of adult trials concluded a longer stay with antibiotics, documenting an average increase of 0·53 days with antibiotics (27,28). This was the same magnitude of difference we documented in this trial, which was found to be a 0·6 day difference between medians in favor of appendectomy. However, moving forward without a strict protocol, patients could be treated much more aggressively up to discharge from the emergency department. The following step of progression could be patients diagnosed in the pediatrician’s office or urgent care are 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, patients in the antibiotic group enjoyed earlier return to activity, school, and sports. This was also expected since their pain begins to improve rapidly with antibiotics, and they have no somatic injury from which to recover. Effectively by the second day, it is akin to comparing patients who’ve had an umbilical repair (appendectomy group) to those who are recovering from a minor gastrointestinal illness (antibiotic group) two days prior. This more rapid return to normalcy with antibiotic treatment has also been documented in all comparative studies with this focus (5-9). It is also noteworthy, that the need for appendectomy in the antibiotics arm occurred early with the majority of failures occurring within the first 100 days (Figure 2). This is also similar to the CODA trial (10).

In the CODA trial, adult patients expressed greater regret and dissatisfaction when allocated to the antibiotic arm (29). This seems intuitive with the potential stress of recurrence as opposed to the appendectomy group. However, in our study, the one-year satisfaction with allotment was the same between groups. The most rational explanation elevating the satisfaction with antibiotics and decreasing the satisfaction with appendectomy might lie in the fact that most people who consented to the study did so in hopes of avoiding the operation. Since our default was to perform appendectomy in those not participating in the trial, the study was the only opportunity for antibiotics alone.

Limitations 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-enrollment became impossible to capture at scale. There were other datapoints that were also unfeasible to track such as total healthcare visits and subsequent tests. Another limitation is our 10% missing data with higher proportion of missing data in the appendectomy arm. In the final analysis we only included patients who we had been able to contact at 12-months to confirm their failure status, specifically that they hadn’t had a complication related to appendicitis treated at a different institution. For most centers, it would be unlikely that patients would have had complications present elsewhere as most are the dominant pediatric center in the region. It is noteworthy that 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 hadn’t already captured. Our sensitivity analysis indicates that if we assume identical event rates in the cases with missing data to those with complete data then 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.

**CONCLUSIONS**

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

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 Table 1. Enrollment by Study Site and Study Arm

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**Table 1.** **Enrollment, Patient Demographics and Presenting Signs and Symptoms by Study Arm**

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|  | **Randomized****(n=936)** | **12-Month Follow-Up or Endpoint Recorded****(N=846)** |
| **Antibiotics Group****(n=477)** | **Appendectomy Group****(n=459)** | **Antibiotics Group****(n=452)** | **Appendectomy Group****(n=394)** |
| Study Site Kansas City (USA) Helsinki (Finland) Stockholm (Sweden) Montreal (Canada) Calgary (Canada) Winnipeg (Canada) Uppsala (Sweden) Memphis (USA) London, Ontario (Canada) Vancouver (Canada) Singapore | 107 (22·4%)91 (19·1%)73 (15·3)47 (9·9%)41 (8·6%)31 (6·5%)25 (5·2%)21 (4·4%)16 (3·4%)16 (3·4%)9 (1·8%) | 107 (23·3%)86 (18·7%)61 (13·3%)49 (10·7%)40 (8·7%)26 (5·7%)27 (5·9%)20 (4·3%)20 (4·3%)16 (3·6%)7 (1·5%) | 99 (21·9%)87 (19·3%)69 (15·3%)45 (9·9%)41 (9·1%)31 (6·9%)25 (5·5%)20 (4·4%)13 (2·8%)14 (3·1%)8 (1·8%) | 74 (18·8%)81 (20·6%)57 (14·5%)47 (11·9%)38 (9·6%)21 (5·3%)27 (6·9%)15 (3·8%)13 (3·3%)14 (3·6%)7 (1·7%) |
| 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 (kilogram) | 38·0 (28·5, 51·0) | 38·0 (28·8, 53·0) | 38·0 (28·7, 51·0) | 37·3 (28·6, 51·5) |
| Body Mass Index Percentile | 19·0 (16·4, 22·3) | 18·0 (15·2, 22·7) | 19 (16·5, 22·3) | 17·7 (15·0, 21·8) |
| Gender (Male), n (%) | 300 (62·9%) | 295 (64·4%) | 288 (63·6%) | 256 (65·0%) |
| Duration of Symptoms (days) | 1 (1, 2) | 1 (0, 2) | 1 (1, 2) | 1 (0, 2) |
| Temperature at Admission (℃) | 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 (K/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 hours, n (%) | 135 (28·3%) | 129 (28·2%) | 127 (15·3%) | 106 (12·8%) |
| Fecalith on Imaging, n (%) | 62 (13·0%) | 52 (11·3%) | 58 (12·8%) | 48 (12·2%) |

Continuous variables are expressed as median (interquartile range), and categorical variables are expressed as frequencies (n) and percentages (%). Both the randomized sample and the 12-month follow-up pertain to the intent-to-treat population.

**Table 2. Trial Outcomes**

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| **12-Month Endpoint (n=847)**  |
| **Study Arm**  | **Failure N (%)**  | **Failure Breakdown**  |
| Appendectomy GroupN=394  | 28 (7.1%) | 27 (6.9%) – Normal pathology 1 (0.2%) - Returned for laparoscopic evacuation of hematoma |
| Antibiotics GroupN=452  | 153 (33.8%) | 72 (15.9%) – Failed initial antibiotic treatment 81 (17.9%) – Recurred, underwent appendectomy  |

  Data are reported as frequencies and percentages using the intent-to-treat population.

**Table 3. Patient Reported Diary Summary**

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|  | **Antibiotics Arm****(n=179)** | **Appendectomy Arm****(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 |
| Did Individual Take Full Course of Antibiotic | 82.6% | NA | NA |

Continuous variables are expressed as median (interquartile range), and categorical variables are expressed as frequencies (n) and percentages (%). Data are from the intent-to-treat population that filled out their 14-day diary.

***Supplemental Figure 1:* Primary outcome by stratification factors from randomization by study arm.** Odds ratios are presented along with their 95% confidence intervals. Kansas City (USA) was used as the reference group for all other participating sites.

***Supplemental Figure 2:*** **Time to appendectomy in the antibiotics arm.** Percent incidence of appendectomy with 95% confidence intervals at 7, 14, and 100 days post-randomization.

Data Sharing: De-identified individual participant data collected during the APPY trial will be available beginning 1 year and ending 3 years following the article publication. Proposals should be directed to the corresponding author to gain access. Proposal will need to be reviewed by all authors/centers. If approved, requestor(s) will need to sign a data use agreement and decide on reasonable environments to make data available