# NON-OPERATIVE TREATMENT VERSUS APPENDECTOMY FOR ACUTE NONPERFORATED APPENDICITIS IN CHILDREN: FIVE -YEAR FOLLOW UP OF A RANDOMIZED CONTROLLED PILOT TRIAL

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**Running title:** Non-operative treatment of appendicitis

## INTRODUCTION

Acute appendicitis is one of the most common surgical emergencies worldwide. In Western countries, 8-10% of the population will have acute appendicitis at some point in their life(1) and 1-8% of children presenting with acute abdominal pain to the emergency room are diagnosed with acute appendicitis(2). Despite the increasing knowledge regarding non-operative treatment of appendicitis, an early surgical intervention is still the standard treatment.

A recent meta-analysis of non-operative versus surgical treatment of acute uncomplicated appendicitis in adults suggested that antibiotic treatment without surgery is an effective alternative in this group of patients(3). A recently published five-year follow-up of RCT comparing non-operative treatment with surgery for acute uncomplicated appendicitis in adults supports this strategy (4). A systematic review and meta-analysis of the same topic in children with acute uncomplicated appendicitis showed conflicting data, although, in the conclusion, the surgical treatment was favoured (5). However, this meta-analysis included only one single randomized controlled study, which was our pilot trial, while the rest of the studies were small, uncontrolled studies based on prospective patient-choice cohorts or retrospective physician-choice cohort (5). The period of follow-up in the included studies varied from one to four years.

We have previously reported the feasibility of non-operative treatment in children in a prospective randomized controlled pilot trial with a short-term follow-up of one year (6). But, for non-operative treatment to be a relevant alternative to surgical treatment, the long-term outcome needs to be further evaluated and be acceptable.

The aim of this study was to present five-year follow-up data of the previous randomized controlled pilot trial. The study was designed to assess the hypothesis that non-operative

treatment of acute nonperforated appendicitis in children is safe and feasible in the intermediate term follow-up.

# METHODS

## Trial design

This was a single-centre five-year follow-up study of a previous RCT comparing non-operative treatment with antibiotics and appendectomy for acute nonperforated appendicitis in children.

## Participants

In the RCT, children between five and 15 years of age with clinical diagnosis of acute nonperforated appendicitis, who prior to the trial would have undergone surgery, were invited to participate. A prior history of non-operative treatment of acute appendicitis was an exclusion criterion for the RCT. The clinical diagnosis of acute nonperforated appendicitis was based on clinical examination, laboratory tests and radiological imaging.

## Study settings

The RCT took place at the Astrid Lindgren's Children's Hospital, Karolinska University Hospital, Stockholm, Sweden, between February and October 2012. This is a tertiary pediatric surgical centre covering the greater Stockholm area with a population of approximately 2.5 million inhabitants in 2012. At the time of the trial, all patients younger than 15 years of age with acute appendicitis in the Stockholm area were treated at this hospital.

## Interventions

After providing written informed consent, the children were randomly allocated to either appendectomy or non-operative treatment with antibiotics. Patients randomized to surgery were subjected to a standard appendectomy. This included fluid resuscitation and pre-operative antibiotic prophylaxis with 20 mg/kg of metronidazole. All patients underwent a

laparoscopic operation, even if the surgical modality was not specified in the study protocol. The further post-surgical treatment with antibiotics was depending on the intra-operative findings. The patients with a phlegmonous appendicitis did not received any further treatment. Those with gangrenous appendicitis received 24 hours of intravenous(iv.) trimethoprim/sulfametoxazol and metronidazole. In the cases of perforated appendicitis, they received at least three days of iv. trimethoprim/sulfametoxazol and metronidazole, depending on clinical improvement.

The children randomized to non-operative treatment were given iv. meropenem (10 mg/kg x 3 per 24 hours) and metronidazole (20 mg/kg x 1 per 24 hours) for at least two days. As soon as the children were tolerating oral intake, they were given oral ciprofloxacin (20 mg/kg x2 per 24 hours) and metronidazole (20 mg/kg x 1 per 24 hours) for a total of ten days treatment.

For this five-year follow-up, we performed a review of the computerised notes to assess for failures, completed with a telephone contact with all patients and/or parents. This was done to find any interventions happening outside the reach of our computerised notes system and also to complete a short questionnaire.

## OUTCOMES

The primary endpoint was treatment failure, defined as a need for secondary intervention under general anaesthesia, related to the previous diagnosis of acute nonperforated appendicitis. This endpoint measure was designed to be applicable to both treatment groups despite a diverging panorama of complications. Appendectomy (for recurrent appendicitis or surgeon/patient/parent decision), surgery for or drainage of a deep abscess, surgery for malignancy of the appendix or caecum or surgery for mechanical bowel obstruction were the suggested reasons for treatment failure.

The secondary endpoints were hospital readmission, length of hospital stay at readmission, accident and emergency (A&E) admission related to failure or complication of initial treatment, and total cost.

Acute appendicitis was confirmed by histopathology according to Carr(7).

## Sample size

The initial RCT was designed as a pilot trial to assess the feasibility of a multi-centre RCT. Therefore, a power calculation was not performed. Fifty patients were included in the study based on the historic admission figures, an estimated recruitment rate of 30% and the ambition to conclude the enrolment within a six-month period. For this follow-up, no patients were added to or excluded from the original cohort.

## Randomization

Allocation to groups (1:1 ratio) was made via weighted minimisation at the time of enrolment in the study (6). The following criteria were used: age (5-10 years or 11-15 years), sex (male or female), and duration of symptoms (<48 or ≥48 hours). All factors were weighted equally. A computer-based randomisation program (Simin v 6.0; Institute of Children Health, London) was used for randomisation. After acceptance of enrolment, the attending pediatric surgeon used the computer-based randomisation program to put in the relevant minimization criteria and received the random treatment allocation at the same time.

## Blinding

For the RCT, it was not possible to blind patients, parents or surgeons due to the nature of the treatment modalities. Blinding was not performed during the five-year follow-up.

## Statistical methods

Data are presented as the proportion of patients or median (range). Data were compared using the Mann-Whitney U-test, Fisher's exact test or with a Kaplan-Meier survival analysis, using IBM SPSS Statistics version 22.

This trial is reported in accordance with the CONSORT-guidelines(8).

## Ethical approval

The study was approved by the regional Ethics Review Board in Stockholm, Sweden, ref 2011/1234-31/4.

# RESULTS

A total of 225 children with a clinical diagnosis of acute appendicitis were screened for eligibility during the study period, and 168 met the eligibility criteria. The total number of patients excluded due to various reasons is shown in Figure 1.

We randomized 51 patients. One patient withdrew consent after randomization but before initiation of treatment, leaving 26 randomized to surgery and 24 to non-operative treatment. At inclusion, all 50 patients had a radiological evaluation. 46 patients had only an abdominal ultrasound, four patients had both an abdominal ultrasound and CT scan. All patients were diagnosed with acute appendicitis; 12 patients had appendicitis with appendicolith. There was one patient, who had both an ultrasound and CT scan, randomized to non-operative treatment, who underwent an appendectomy because of ongoing abdominal pain, where the initial diagnosis was acute appendicitis, but after appendectomy the senior radiologist changed the diagnosis to mesenteric lymphadenitis. The one-year follow up was finished in October 2013. The results after one year of follow-up have previously been reported (6).

The five-year follow-up of all the 50 participants enrolled in the study was performed between September 26 and November 15, 2017. Each patient had been followed up for at least five years (5.3 years (5.0-5.6)) after enrolment. During the follow-up, there were nine patients who had a radiological examination in the non-operative group, seven patients had only an ultrasound, one patient had both an ultrasound and CT-scan; and one patient had only CT-scan. The results were: six patients were diagnosed with acute appendicitis, among them

one patient was diagnosed with suspicion of perforation; one patient had normal appendix; and one patient had an appendix with a diameter exceeding 6mm, but there were no signs of inflammation.

Baseline demographic and admission characteristics were similar between patients randomized and those who declined to participate. However, symptom duration was shorter in the randomized children compared to children not invited to participate (Table 1). There were no differences between the patients randomized to non-operative treatment compared to those randomized to surgery (Table 2).

## Outcomes

In the appendectomy group, there were no complications after the initial treatment (0/26). All patients underwent laparoscopic appendectomy without perioperative complications. Histological examination confirmed acute appendicitis in all cases. In total in the surgical group, there were 20 patients with histopathological diagnosis of phlegmonous appendicitis, four patients had gangrenous appendicitis, and two patients had perforated gangrenous appendicitis. One patient reported cosmetic dissatisfaction with the infraumbilical scar at one-year follow-up, but at five-year follow-up the patient was satisfied. There were no complications registered at five-year follow-up. No patients were readmitted related to the previous appendectomy during the five-year follow-up period.

In the non-operative group, there were 11 failures which resulted in appendectomy at the five-year follow-up (11/24). Nine of the 11 failures occurred during the first year after the inclusion, in two of these patients acute appendicitis was verified histologically, as previously reported. Another two patients had undergone appendectomy between one and five years of follow up. In both these cases of late failure, acute appendicitis was confirmed by histopathology. All patients with failure in the non-operative group underwent uncomplicated appendectomies, ten laparoscopic and one open procedure. The indication for appendectomy,

histopathological appearance of the appendix and resolution of symptoms of these patients are shown in table 3.

The rate of appendectomy over time in the non-operative group is presented in Figure 2, both for all appendectomies and for appendectomy with histopathologically confirmed appendicitis. In the non-operative group, there were 11 appendectomies. Overall, there was no surgery or drainage of deep abscess, no surgery for malignancy of appendix or caecum, or surgery for mechanical bowel obstruction.

Secondary outcome (readmission to a hospital and length of hospital stay during readmission 35.5 (17 – 196) hours, A&E admission).

During five-year follow up, there were no visits to the A&E department registered in the surgical group. In total, there were 12 patients in the non-operative group who visited the emergency department at least once. One patient visited the emergency department three times prior to the admission for appendectomy. The non-operative treatment group can be divided into two subgroups. The first group are the patients who underwent appendectomy. In this group one patient had complaints of abdominal pain both before study inclusion and after the appendectomy. In the subgroup of the patients who still had not undergone appendectomy at the five-year follow up, there were five patients who had abdominal pain problems. Of these patients, one did not visit the emergency department, one had a phone contact with our hospital, and three patients visited the emergency department two times. At the end of the follow-up period they had no problem with abdominal pain related to the previous diagnosis of acute appendicitis.

The total cost of treatment after five-year follow up was similar in the both groups (non-operative treatment 40,547 (34,467 – 112,936) SEK vs surgery 42,099 (38,107 – 81,067) SEK.) (P=0.36, Figure 3).

## DISCUSSION

This is the first study assessing five-year outcome of non-operative treatment of acute nonperforated appendicitis in children. Most recent studies of non-operative treatment of acute appendicitis have focused on the success of treatment or recurrence of symptoms necessitating appendectomy within the first year. Of the 24 children randomized to non-operative treatment, 13/24 (54%) have not had an appendectomy within five years, and only 4/24 (17%) have had an appendectomy for histologically confirmed recurrent acute appendicitis. Of the 15 children not having an appendectomy within the first year, two (13%) had an appendectomy within the following four years. During five-year follow-up interviews, all parents expressed satisfaction with their choice to participate in the study, also in cases where their children underwent appendectomy during the study period.

Importantly, none of the children with recurrence presented with perforated appendicitis, and all had an uncomplicated course, suggesting that initial non-operative treatment is safe in the medium-term, although the number of patients is limited.

Two patients randomized to surgery (2/26; 8%) had a finding of perforated appendicitis. They did not have any clinical or radiological signs of perforation during initial evaluation of eligibility for the study. It is not possible to identify when perforation occurred and we do not know this was due to radiologically missed perforated appendicitis, or to perforation occurring between recruitment and surgery.

**Limitations**

There are a few limitations of this study. First, the study was designed as a pilot RCT with relatively small sample size not powered to detect differences in treatment efficacy. The purpose was to determine whether treatment with antibiotics is feasible and safe. However, the outcome data can be used to design and perform future prospective multicentre studies. The second limitation is that we did not have a protocol how to deal with patients in the non-operative treated group presenting with recurrent abdominal symptoms. As this was the first randomized controlled study of non-operative treatment of acute nonperforated appendicitis in children and we did not want to risk any missed neoplasm, we were liberal with appendectomy. In most cases the indication for surgery was mild abdominal pain and a decision made by an attending surgeon and parents. There is a possibility that parents of the children in the non-operative treatment group were concerned about abdominal pain as a potential symptom of recurrent appendicitis and, therefore, wanted their child to undergo an appendectomy. However, the surgical treatment was successful and without any perioperative complications.

**Generalisability**

The study includes a representative spectrum of pediatric patients with acute nonperforated appendicitis. All patients who, prior to the study, would have undergone a surgery and had no clinical or radiological suspicion of perforated appendicitis, could have participated in the study. We did not use any clinical scoring system as we feel that the available scoring systems are most useful in situations where abdominal ultrasound and CT are not routinely available. In our centre, we have a negative appendectomy rate of 3.8% (9). However, there were 37 (22 %) patients who had never been asked to participate in the study for unknown reasons. One possible motive explaining this could be surgical bias, in cases where children had longer

duration (more than 48 hours) of symptoms, the urge of the surgeon to do an appendectomy. We did not exclude patients with appendicolith on radiological imagining.

**Interpretation**

We demonstrated that non-operative treatment of acute nonperforated appendicitis can be reliably and effectively delivered in children.

To date there have been a few studies with various study designs comparing non-operative treatment of acute nonperforated appendicitis in children but no fully powered randomized controlled trials (2, 3, 5). Minneci and co-workers published a prospective patient-choice cohort study with patient and parents' choice between appendectomy and non-operative management. In the study they included 102 patients (age 7-17) with acute uncomplicated appendicitis, where 65 patients chose appendectomy, and 37 chose non-operative management. The success rate of the non-operative management was 89% at 30 days follow-up, and 75% at one year follow-up. There were nine patients who underwent an appendectomy during one-year follow-up. Even though they tried to minimize bias by evaluating the eligible patients by four trained surgeons, there still is the selection and preference bias which cannot be ignored. Due to the lack of randomization, there is a likelihood of bias towards the less severely ill patients in preference toward non-operative treatment. One may assume that the groups differed in severity of illness and/or pain (not published in baseline clinical characteristics). The fewer disability days in the non-operative group might also suggest that they were not particularly unwell. Only a true RCT will minimise the probability of these differences influencing trial results.

As this is the first RCT in children, we are not able to compare our findings directly with other study results in children. Many studies, for diseases occurring both in adults and children, are usually initially performed in adults, followed by studies in children. Salminen and co-workers have recently published a five-year follow-up of antibiotics therapy for acute

uncomplicated appendicitis in the "APPAC"-trial in adults. There was 39% (100 of the 256 patients) recurrence after 5-year follow-up. Most of these patients (70/100, 70%) had their recurrent appendicitis within one year from the initial presentation. 15 patients underwent surgery during the initial hospitalisation. 76 out of 85 patients had an uncomplicated appendicitis confirmed histopathologically. There were seven patients without acute appendicitis on histopathology. Complicated appendicitis was found in two patients who underwent appendectomy in second to fifth year. In this study, the researchers excluded patients with appendicolith because of the concern of not definitive relationship between appendicolith and recurrence of AA.

In our findings, there were only four children with acute appendicitis on histopathology in the non-operative group. The most of the histopathological findings were an appendix without inflammation, but with fibrotic changes. It is difficult to say if these changes occurred post-inflammatory, or it could have been fibrous obliteration from the beginning, or chronic fibrosis, or neurogenic appendicopathy (10). The clinical symptoms of these patients are not distinguishable from patients with AA (10). We have no way of knowing how many patients in the non-operative group had no acute appendicitis as we did not operate on them. We are aware that there can be some patients who did not have an acute appendicitis at the time of randomisation. We only know that the two groups of patients were very similar at the time of randomisation. It is difficult to know the exact treatment effect of antibiotics. There is the possibility of spontaneous resolution of symptoms. However, these are two entities that need to be addressed in future. It is not possible to separate these two effects in our study.

In addition, there is a concern about missing a neoplasm in the appendix, or leaving a chronical infection which could lead to increased incidence of bowel cancer in these patients. Enblad and co-workers have recently published a population-based study from the Swedish National Inpatient Register, showing that patients with non-surgical treatment of appendicitis

have an increased short and long-term incidence of bowel cancer(11). They state that patients with non-operative treatment of acute appendicitis had an elevated risk of right-sided colon cancer up to five years after appendicitis. However, there was only 1% of patients with bowel cancer in the age group ten to 19. There is not more specific description of which type of cancer, or how advanced the disease they had was in this age group, no information about how they were diagnosed or treated. We do not know the causation between non-operative treatment of acute appendicitis and cancer. Underlying malignancy can present for the first time with the symptoms of acute appendicitis, and it is important to be aware of it. However, we cannot be certain how they got diagnosed with acute appendicitis, and how they were treated, if not surgically. We do not currently support routine use of non-operative treatment with antibiotics outside the scope of randomized controlled trials or other prospective studies.

**Registration and funding**

The trial is registered at ClinicalTrials.gov, number NCT01572558. This trial was supported by HRH Crown Princess Lovisa Foundation, Sällskapet Barnavård, the Swedish Order of Freemasons, the Centre for Clinical Research Västerås and the Swedish Research Council. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. SE receives support from the National Institute of Health Research Great Ormond Street Hospital Biomedical Research Centre (UK).

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**Figure 1.** Study flowchart

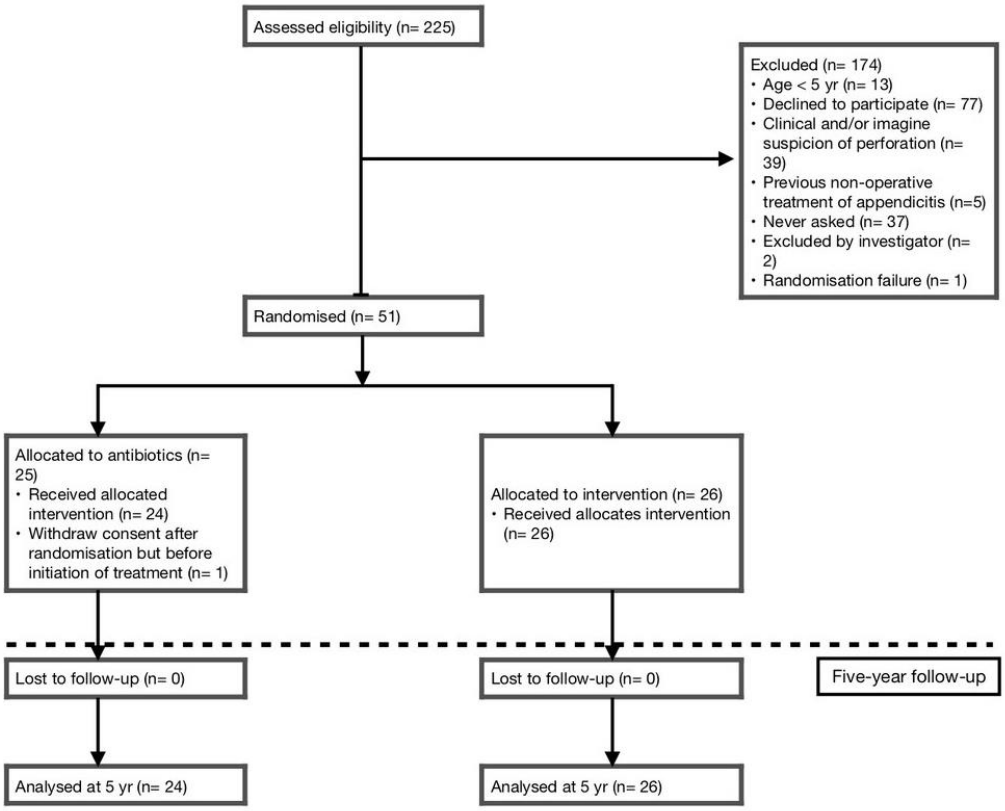


**Figure 2.** Proportion of patients not having had an appendectomy, all cases (red) and histologically confirmed appendicitis (black).

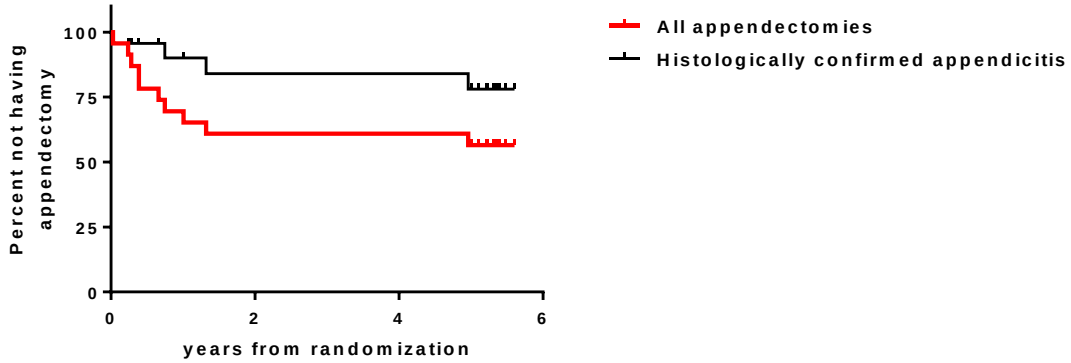

**Figure 3.** Total cost of treatment in individual patients. Horizontal line is median cost.

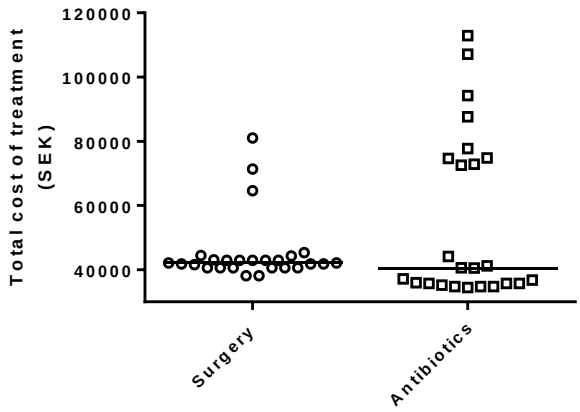

**TABLE 1.** Comparison between enrolled, randomized, children, children who declined to participate and children who were not invited to participate.

| | **Randomized children (n=50)** | **Declined to participate (n=77)** | **P*** | **Not invited to participate(n=37)** | **P**** |
|---|---|---|---|---|---|
| Age (years) | 11.2 (5.9-15.0) | 11.0 (5.8-14.9) | 0.369 | 10.8 (5.3-14.9) | 0.268 |
| Male gender, n (%) | 26 (52) | 42 (55) | 0.779 | 23 (62) | 0.345 |
| Duration of symptoms <48 hrs, n (%) | 43 (86) | 61 (79) | 0.332 | 25 (68) | 0.040 |
| CRP (mg/l) at admission | 28 (1-185) | 19 (1-152) | 0.414 | 17.5 (1.0-150.0) | 0.909 |
| WBC ($x10^9$/l) at admission | 14.3 (4.5-26.9) | 15.0 (5.2-27.2) | 0.086 | 15.0 (6.1-33.5) | 0.297 |
| Neutrophils ($x10^9$/l) at admission | 11.5 (2.5-23.5) | 12.5 (1.5-24.0) | 0.155 | 3.6 (12.5-30.1) | 0.295 |
| Temperature at admission (˚C) | 37.4 (36.3-39.0) | 37.3 (35.9-37.3) | 0.177 | 37.1 (35.7-39.3) | 0.392 |

Data presented as median (range) unless specificed.

*Comparison between randomized children and those who decline to participate.

**Comparison between randomized children and those who were not invited to participate.

CRP indicates C-reactive protein; WBC, white blood cells.

**Table 2.** Comparison of participants randomized to nonoperative treatment and appendectomy.

| | Randomized children | | |
|---|---|---|---|
| | **Surgery (n=26)** | **Non-operative treatment (n=24)** | **p** |
| Age (years) | 11.1 (6.2-14.8) | 12.2 (5.9-15.0) | 0.130 |
| Male gender n (%) | 12 (46) | 14 (58) | 0.389 |
| Duration of symptoms <48 hrs, n (%) | 23 (88) | 20 (83) | 0.602 |
| CRP (mg/l) at admission | 27.0 (1.0-175.0) | 30.5 (1.0-185.0) | 0.892 |
| WBC ($x10^9$/l) at admission | 14.5 (4.5-26.9) | 14.0 (4.8-19.0) | 0.918 |
| Neutrophils ($x10^9$/l) at admission | 11.6 (2.9-23.5) | 11.5 (2.5-16.8) | 1.000 |
| Temperature (˚C) at admission | 37.5 (36.5-38.5) | 37.3 (36.6-39.0) | 0.199 |

Data presented as median (range) unless specified.
CRP indicates C-reactive protein; WBC, white blood cells.

**Table 3.** All patients with failure of non-operative treatment

| Patient number | Time to failure* (in months) | Indication for surgery | Histopathology** | Resolution of symptoms |
|---|---|---|---|---|
| **1.** | 60 | Abdominal pain & back pain | Phlegmonous appendicitis | Yes |
| **2.** | 12 | Abdominal pain | Incipient appendicitis | No |
| **3.** | 8 | Parental request | No inflammation, mild fibrosis | Yes |
| **4.** | 0 | No resolution of symptoms | No inflammation | Yes |
| **5.** | 3 | Abdominal pain | No inflammation, appendicolith | Yes |
| **6.** | 0 | No resolution of symptoms | Perforated appendicitis | Yes |
| **7.** | 9 | Abdominal pain | Phlegmonous appendicitis | Yes |
| **8.** | 5 | Abdominal pain | No inflammation, fibrosis | Yes |
| **9.** | 5 | Abdominal pain | Acute eosinophilic appendicitis | Yes |
| **10.** | 3 | Abdominal pain | No inflammation | Yes |
| **11.** | 16 | Abdominal pain | Phlegmonous appendicitis | Yes |

*Time from initial discharge to secondary intervention.

**Histopathology according to Carr.