CHAPTER 7

Initial antibiotic treatment for acute simple appendicitis in children is safe: Short-term results from a multicentre prospective cohort study

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Surgery 2015;157:916-923

Abstract

Background

Initial antibiotic treatment for acute appendicitis has been shown to be safe in adults; so far not much is known about the safety and efficacy of this treatment in children. The aims of this study were to investigate the feasibility of an RCT evaluating initial antibiotic treatment for acute appendectomy in children with acute simple appendicitis and to evaluate the safety of this approach.

Methods

In a multicentre prospective cohort study patients aged 7-17 years with a radiologically confirmed simple appendicitis were eligible. Intravenous (IV) antibiotics (amoxicillin/clavulanic acid 25/2,5 mg/kg 4 times daily; maximum 6000/600mg per day and gentamicin 7 mg/kg once daily) were administered for 48 to 72 hours. Clinical reevaluation at every six hours, daily blood samples and ultrasound follow up after 48 hours was performed. In case of improvement after 48 hours, oral antibiotics were given for in total 7 days. At anytime in case of clinical deterioration or nonimprovement after 72 hours, an appendectomy could be performed. Follow-up until 8 weeks after discharge. Adverse event were defined as major complications of antibiotic treatment, e.g. allergic reactions, perforated appendicitis and recurrent appendicitis.

Results

Of 44 eligible patients, 25 participated (inclusion rate 57% [95%CI: 42-70%]). Delayed appendectomy was performed in two, while the other 23 were without symptoms at the 8 weeks follow-up. Minor complications occurred in three patients. None of the patients suffered from an adverse event, or a recurrent appendicitis.

Conclusions

Our study shows that an RCT comparing initial antibiotic treatment strategy with urgent appendectomy is feasible in children; the intervention appears safe.

Introduction

Acute appendicitis is a common gastrointestinal disease in children, generally considered to require surgical intervention. In the Netherlands more than 15,000 appendectomies are performed annually of which more than 5,500 (37%) in patients below the age of 20.[1,2] This ancient strategy is based upon the entrenched idea that appendicitis is an irreversibly progressive disease, starting with an uncomplicated stage and leading to a complicated stage with gangrene, perforation and peritonitis. Surgeons, therefore, have advocated an aggressive surgical treatment ever since Fitz's report in 1886.[3] Removal of a healthy appendix was never seen as an undesirable, let alone adverse, event.

Recently, this paradigm has shifted. Based upon epidemiologic, radiologic and pathologic studies several authors no longer consider appendicitis as an invariably irreversible progressive disease.[4-8] Rather, they envisage two types of appendicitis: simple (or uncomplicated or nonperforated) appendicitis with no tendency to progress, and complex (or complicated or perforated) appendicitis.[4,5,7] In this view, the latter group represents a spectrum of disease severity and includes not only perforated appendicitis, but also gangrenous appendicitis, periappendicular abscess, periappendicular contained mass and generalised purulent peritonitis.[4,5,7,9,10]

Subsequently, the effectiveness of initial antibiotic treatment for acute appendicitis in adults was investigated. Five randomised controlled trials (RCTs) showed that antibiotic treatment alone was effective in 41-85% of the patients with a follow-up period of one year.[11-15] Several meta-analyses on this topic summarised the results of these studies inconsistently, with some favouring antibiotic treatment over primary appendectomy, while others either favoured appendectomy or were inconclusive.[16-21] Most authors conclude that antibiotic treatment alone is less effective than an appendectomy and therefore promote appendectomy.[16-20] However, the methodological quality of the included studies was low to moderate, there was considerable statistical heterogeneity (I^2: 43-70%), and these inferences continue to be questioned.[16-18]In addition, potential long-term disadvantages of surgery in children has not been evaluated adequately.

In children, no prospective studies have been conducted yet. A recent review aiming to determine the role of conservative treatment for acute appendicitis in children stated that there are no reliable data, although there are some studies suggesting it to be safe.[21] One retrospective study of 16 children between the ages of 5 and 13 reported initial antibiotic treatment as safe and effective, with a recurrence rate of 13% (2/16) within one year after discharge.[22] Another recent retrospective study (n=12) concluded that antibiotic treatment for early acute appendicitis in selected children "can be successful". They found that 75%

of the patients (less than 18 years old) did not require an appendectomy, avoiding surgery related complications.[23] Another case series, reporting on 5 children who were not operated due to haematological malignancy and coexisting chemotherapy induced neutropenia, reported antibiotic treatment to be curative in four of them (follow-up range: 0.53 years).[24] Initial antibiotic treatment for acute appendicitis in children may therefore be considered safe. Still this controversial idea encounters resistance both in the general public as well as in the medical sector.

We conducted a pilot study with two goals: 1) to investigate the feasibility of an RCT comparing initial antibiotic treatment for acute appendectomy for children with acute simple appendicitis, 2) to investigate the safety of initial antibiotic treatment alone in terms of failures and complications of antibiotic treatment.

Patients and Methods

Design, setting This multicentre prospective cohort study was performed in four hospitals in the Netherlands, including two academic (tertiary referral) centres and two large peripheral hospitals. The study started in September (VU University Medical Centre, Amsterdam), November (Academic Medical Centre, Amsterdam), December 2012 (Red Cross Hospital, Beverwijk) and February 2014 (Flevoziekenhuis, Almere). Inclusion lasted until the 7th of June 2014. The medical ethics committee of the VU University medical centre approved the study protocol.

Study population All children 7 - 17 years with a simple appendicitis, confirmed by imaging studies, were eligible for inclusion. Imaging studies had to confirm the diagnosis within 8 hours after presentation at the emergency department otherwise patients were excluded. Both radiologists and trainees did the imaging studies, although the latter were supervised. If ultrasound was inconclusive, additional imaging studies such as MRI or CT could be performed according to the preference of the surgeon, radiologist and in accordance with the local protocol for the diagnostic work-up of appendicitis in children. Simple appendicitis was defined based upon both clinical and radiological variables.

Clinical criteria included:

- Unwell, but not generally ill
- Localised tenderness in the right iliac fossa region
- Normal/Hyperactive bowel sounds
- No mass palpable
- No diffuse guarding.

Ultrasonography criteria included:

- Incompressible appendix with an outer diameter of >6mm
- Hyperaemia within the appendiceal wall
- Infiltration of the surrounding fat
- No signs of perforation/abscess/mass/phlegmon/disseminated peritoneal fluid/extra-luminal gas

Patients younger than 7 years old, those who presented with severe general illness (generalised peritonitis, severe sepsis or septic shock and signs of complex appendicitis) and those with a faecalith present on ultrasound were excluded. In addition, patients with severe associated conditions or malformations and those with documented type 1 allergy to the antibiotics used were excluded.

The responsible physician informed eligible patients and their parents about this study and, if they agreed to participate, written informed consent was obtained before the start of the antibiotic administration.

Intervention Study participants were admitted to the paediatric (surgical) ward and received intravenous (IV) antibiotics (amoxicillin/clavulanic acid 25/2.5 mg/kg 4 times daily; maximum 6000/600mg per day and gentamicin 7 mg/kg once daily) for at least 48 hours. During the first 24 hours no oral intake was permitted and IV fluids were given. Every 6 hours clinical re-evaluation was performed systematically to identify signs of clinical deterioration at an early stage. If the clinical condition was improved (i.e. no fever, normal heart rate, normal daily activity, less pain) after 24 hours, normal diet was started. After 48 hours the ultrasonography was repeated. If the patient met the criteria for improvement described below, treatment was switched to oral antibiotics (amoxicillin/clavulanic acid 500/125 mg 3 times daily). The patient was kept in the hospital for another 24 hours to ensure adequate oral intake of the antibiotics and to observe the clinical status. If the clinical course was favourable, the patient was discharged after 72 hours since admission with oral antibiotics for another 4 days.

The following criteria of improvement were used:

- Body temperature < 38 degrees Celsius
- Visual analogue scale (VAS)/comfort scale <4
- Adequate oral intake
- Able to mobilise
- Lower level of C-reactive protein (CRP) and amount of leukocytes than at admission
- No signs of complex appendicitis on repeat ultrasound

If after 48 hours the patient did not meet these criteria for improvement, IV administration was continued for another 24 hours with reevaluation. In case of either not meeting the criteria of improvement after 72 hours or signs of clinical deterioration during the antibiotic course, appendectomy was performed with its approach (open or laparoscopic) according to the surgeon's preference.

Data collection, follow-up, outcome measures A standardised case record form was used to record all pre-, per - and posttreatment data. Follow up was conducted after 2 and 8 weeks in the outpatient clinic. The proportion of eligible patients willing to participate was used as primary endpoint for feasibility. This was defined as the number of patients who consented to participate divided by the total number of eligible patients, who had been informed and asked to participate in this study. An RCT was considered feasible if the lower boundary of the 95% CI of the proportion was greater than 33%.

The safety of initial antibiotic treatment alone was investigated in terms of the proportion of patients in whom antibiotic treatment failed, i.e. who needed appendectomy due to lack of response, and the occurrence of major complications of antibiotic treatment, e.g. allergic reactions, perforated appendicitis, need for readmission and recurrent appendicitis. If patients had to undergo appendectomy, the following outcomes were considered as safety issues as well: negative appendectomy, abscess formation, wound infection, wound rupture, wound herniation, readmission, reoperation, anaesthesia related, prolonged ileus requiring total parenteral nutrition, secondary bowel obstruction and pneumonia.

Statistical analysis Descriptive statistics were performed using SPSS version 20 (SPSS, Chicago, IL, USA). Percentages and 95% CIs were calculated using the software CIA.[25]

Results

Feasibility of the initial antibiotic strategy During the study period, 117 children with acute appendicitis were examined at the Emergency Departments of the participating hospitals. Seventy-three of them did not fulfil the inclusion criteria. The main exclusion criterion was the complexity of appendicitis. In 23 patients, the appendix could not be visualised on the ultrasound and it was decided not to obtain additional imaging studies, but to admit these patients for observation or to perform a diagnostic laparoscopy.

Of the 44 patients who were eligible, 25 patients were willing to participate, yielding an inclusion rate of 57% [95% CI: 42-70%], as is indicated in Figure 1. Reasons for nonparticipation were

mostly lack of parental confidence in this unorthodox treatment. General characteristics of our study group are displayed in table 1. In 24 patients the appendix could be visualised on ultrasound. In the remaining patient this was not the case but an additional CT was performed which confirmed the diagnosis of simple appendicitis. Therefore all included patients had a radiological confirmed appendicitis.

Table 1. Clinical characteristics.

Clinical variable	(N=25)
Age (years)*	13 (10-16)
Sex (M/F)	15/10
Duration of pain (days)*	2 (1-4)
Nausea	19 (76%)
Vomiting	11 (44%)
Diarrhoea	3 (12%)
Fever	4 (16%)
Anorexia	17 (68%)
Physical examination	
Temperature (degrees Celsius)*	37.3 (36.0-38.3)
Heart rate (beats/minute)*	85 (61-122)
Weight (kg)*	50 (26.5-95.0)
Localised RLQ pain	25 (100%)
Laboratory results	
CRP (mg/L)*	29.0 (1.0-112.0)
Leukocytes (x10^9/L)*	12.7 (5.7-19.2)
Ultrasound findings	
Appendix visible	24 (96%)
Noncompressible	24 (96%)
Tenderness	24 (96%)
Diameter (in mm)*	9.0 (6.0-15.0)
Faecalith	0 (0%)
Free fluid	12 (48%)
Infiltrate	0 (0%)
Abscess	0 (0%)
Lymphadenopathy	9 (36%)
Mesenteric fat infiltration	22 (88%)
Complex signs	0
Additional imaging study	1 (4%): CT-scan (case in which the appendix could not be visualised by US)

Results are displayed as number of patients (percentage), unless noted otherwise
* Results are displayed as median and (range)

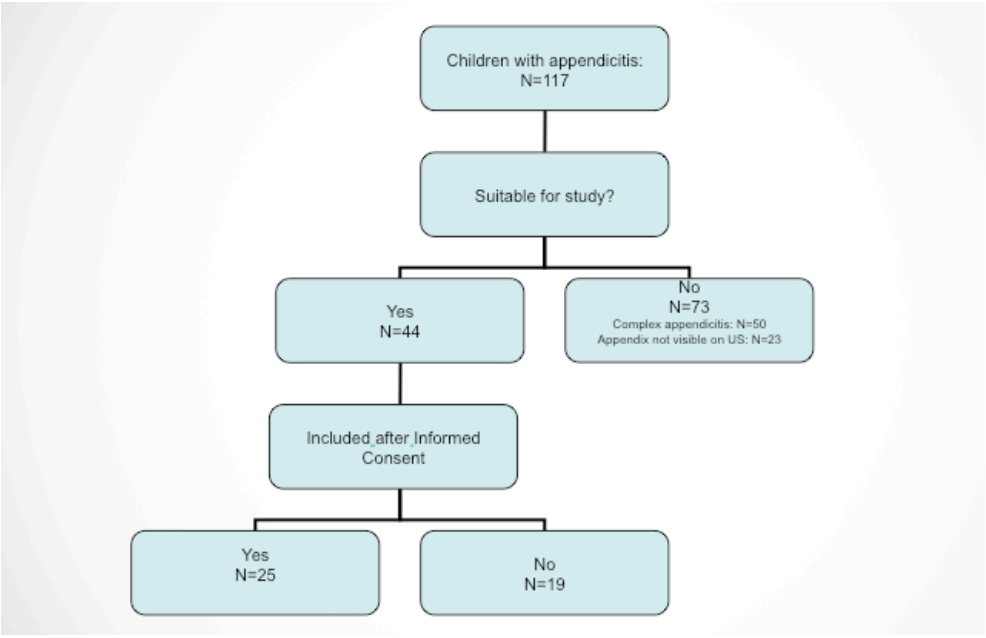

Figure 1. Flow diagram of patients with acute appendicitis

Safety of the initial antibiotic strategy All 25 patients were discharged with oral antibiotics. Twenty-three patients, 92% [95%CI: 75 - 98%] were still without symptoms after this treatment at the 8 weeks follow-up. Two patients eventually underwent appendectomy, one of them within one week after the start of antibiotic treatment because of persistent complaints with a faecalith visible on the second ultrasound. Due to the significant improvement of his clinical condition, it was decided to change to oral antibiotic treatment after 48 hours and an extra follow-up check was made. However, at this follow-up he had persistent complaints and it was decided to perform an appendectomy. The other patient underwent an appendectomy after 6 weeks because of suspected recurrent appendicitis. Both patients underwent laparoscopic appendectomy without complications. Histopathological examination of the first appendix revealed chronic fibrosis with little inflammation response, while the other appendix only showed fibrosis and no inflammation. The short-term complications associated with initial antibiotic treatment strategy are summarised in table 2. All patients recovered uneventfully after their complication. None of the included patients eventually suffered from complex appendicitis.

Table 2. Overview of the initial antibiotic treatment; appendectomy and complications.

	Number of patients	Comment
Delayed appendectomy	2/25	
Postappendectomy complications	0/2	
Complication	3/25	Clinical phase: Overdose antibiotics, no consequence (1) Eight week follow-up: • Cystitis (additional antibiotic treatment) (1) • Assumed allergic reaction to oral antibiotics. (1)
Unscheduled extra emergency department visits	3/25	Reason: Abdominal pain in all three
Recurrent appendicitis	0/25	
Complex appendicitis	0/25	

Figure 2 shows the flow diagram of the 25 patients treated with initial antibiotic treatment. During the clinical phase of the study, all patients responded well to intravenous antibiotics. As demonstrated in the figure, 22 out of 25 patients received intravenous antibiotics for 48 hours. The reasons for prolonged intravenous administration of antibiotics (72 hours) were a VAS score above three in one patient and an increasing CRP level in the remaining two patients. All patients did fulfil the criteria for improvement after 72 hours.

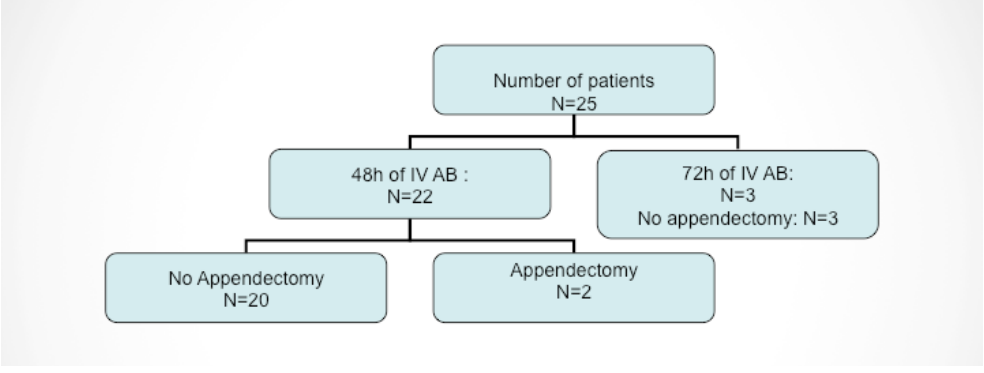

Figure 2. Flow diagram of the APAC study patients

Discussion

This multi-centre prospective cohort study shows that a subsequent RCT comparing initial antibiotic treatment with acute appendectomy for acute simple appendicitis in children is feasible and safe. The initial antibiotic strategy (with an appendectomy in case of failure) was effective in all cases. In our study almost all patients on initial antibiotic treatment did not need appendectomy within 8 weeks after initial antibiotic treatment. The two patients in whom eventually an appendectomy was performed, did not have any complications. We conclude that this strategy is safe for children with simple appendicitis.

To our knowledge this is the first prospective study investigating the short-term results of initial antibiotic treatment of appendicitis in children. As initial antibiotic treatment has conquered the field of other previously strictly surgical diseases such as diverticulitis, the investigation of this strategy in simple appendicitis in adults was a logical next step, with promising results.[11-15] Urgent appendectomy for simple appendicitis, although effective, has been associated with complications such as surgical site infection (SSI), small bowel obstruction (SBO), intra-abdominal abscess and appendectomy of an appendix sana.[11-15] Its associated mortality rate is low at 0.07-0.7%.[26,27]The major advantage of initial antibiotic treatment is the avoidance of surgery and its above mentioned related (early, but especially late) complications. In children with simple appendicitis the frequency of postappendectomy complications depends on the surgical approach, but ranges from 3-11% at one year follow-up.[11-15,23,28,29]

Not much is yet known about initial antibiotic treatment strategy in children. Outcomes reported in the scarce available literature and our study have been summarised in table 3.[22-24] In total 58 patients have been treated with the initial antibiotic treatment strategy. In the majority of patients (n=49), surgery could be avoided (84% [95% CI: 73-95%]). The remaining nine patients underwent an appendectomy for the following reason: failure of the initial antibiotic treatment (n=5), recurrent appendicitis (n=3) and suspicion of recurrent appendicitis, although the diagnosis could not be confirmed (n=1). Other complications associated with initial antibiotic strategy were noted in three of the 58 patients. The question is whether these complications would imply an important argument against the strategy of antibiotics only, as in our study most of the complications were not severe and did not require invasive procedures. In comparison to the known literature of postappendectomy complications (up to 11%), this strategy potentially reduces the incidence of complications. This is in line with results from meta-analyses demonstrating that in adults initial antibiotic treatment reduced the risk of complications with 43-46%.[16,18,21,23,28]

Table 3. Overview of outcomes of the treatment strategy of antibiotics only in the literature[22-24]

First author, n	Initial Antibiotic Treatment				Delayed appendectomy after initial antibiotic strategy (Reason)	
	No complications	**Failure of initial AB strategy**	**Complications**	**Recurrence at follow-up**	**No complications**	Complications
Abes[22] N=16	13	1	0	2	3 (2=recurrence 1= failure)	0
Wiegering[24] N=5	4	1	0	0	1 (Failure)	0
Armstrong[23] N=12	9	2	0	1	2 (1= failure, 1=recurrent)	1 (failure) (IAA)
Gorter (Current study) N=25**	21	1	3	0	2 (1= failure 1= suspicion recurrent appendicitis)	0
Overall N=58	47 (81%) 69-89%*	5 (9%) 4-18%*	3 (5%) 2-14%*	3 (5%) 2-14%*	8 (14%) 7-25%*	1 (2%) 0-9%*

Results are displayed as number of patients (percentage), unless noted otherwise

- * Results are displayed as 95% Confidence interval of the above mentioned percentage.
- ** Current study

To reduce the frequent adverse effects of appendectomy in patients who may benefit from antibiotics alone, this should be considered the first step in a treatment algorithm for acute simple appendicitis, reserving an appendectomy only for those not responding to initial antibiotic treatment.[16,21] This strategy might be up to 100% effective in treating acute simple appendicitis. Meta-analyses on this subject should therefore focus on effectiveness and complications associated with the complete strategy – up to a year after the acute episode - rather than comparing the efficacy of antibiotics alone to appendectomy.

A major criticism to previous studies in adults was the lack of radiological confirmation. All children in our study had ultrasound proven appendicitis and would traditionally have been scheduled for surgery. The strength of our protocol is the strict selection of children and adolescents who might benefit from initial antibiotic treatment. Although there are several scoring systems for the differentiation of simple from complex appendicitis, we were unable to use them, as they are not compatible with our national guideline for the work-up of acute appendicitis.[30-34] In our study, CT was only performed in a 16-year-old boy, weighing 95 kg. Although CT is valuable in detecting both simple and complex appendicitis in adults, it should preferably be avoided in children because of the radiation associated.[30-34] Ultrasound has a good sensitivity (99%), specificity (95%) and positive predictive value (97%) in diagnosing appendicitis in children, although its value might be reduced especially in the obese children.[35-37] With ultrasound simple appendicitis can be differentiated from complex appendicitis. [35,36-40] However, since ultrasound is operator dependent the reported sensitivity and specificity might have a limited generalisability. The stringency of our inclusion criteria may explain the relatively large proportion of patients treated successfully with antibiotics alone. Selection of those patients who might benefit from initial antibiotic treatment is crucial. Therefore a tailor-made approach for acute appendicitis is necessary.

Opponents of initial antibiotic treatment raise several concerns, such as the relatively high therapeutic failure rate of antibiotic treatment alone (up to 59%).[16-21] In our opinion, however, the initial antibiotic strategy should be part of an algorithm, starting with antibiotic treatment and including appendectomy for those not responding. Effectiveness of this strategy is therefore comparable with acute appendectomy as a first step i.e. 100%. The gain can be shown in reduction of medical and financial costs of the primary appendectomy. In our study, the costs of our strategy were assumed to be relatively high due to increased length of hospital stay, additional ultrasounds and blood draws, procedures which were included in our study protocol for safety issues. As results of our study now seem to be favourable regarding the safety, we plan to reduce the number of blood samples per patient to 2 and to reduce the minimum length of hospital stay to 48 hours instead of 72 hours. This will further reduce the costs associated with our strategy.

Another potential disadvantage is the fact that due to not removing an inflamed appendix, parents will be concerned about (recurrent) appendicitis every time a child develops abdominal pain in the future. In our study, three of the 25 children visited the ER after the intervention due to recurrent abdominal pain. This rate might even increase over time. However, we think that when sufficient information is given to the parents regarding so called alarm symptoms, and when the conservative treatment becomes less unusual, the rate will be comparable to that after an initial appendectomy.

Some authors are concerned about the higher incidence of perforated appendicitis, complications associated with delayed appendectomy and recurrent appendicitis. None of the patients in our study had a perforated appendicitis. In the literature only one patient was reported to suffer from a perforated appendicitis, while being treated with antibiotics (table 3).[24] Regarding postoperative complications, none were noted in our study group. In only one of the nine patients undergoing a delayed appendectomy described in the literature (Table 3), a complication was noted; an intra-abdominal abscess requiring readmission but no invasive procedure.[23] Meta-analyses of adult RCTs did not show a higher incidence of surgical site infections after delayed appendectomy.[16-21] In addition the assumed incidence of recurrent appendicitis in adults varies from 14-35%. The latter rate is questionable, as important information such as how the diagnosis was made and if pathologic examination confirmed recurrent appendicitis is lacking.[11-21] However, when looking at the available literature in children, recurrent appendicitis ranges from 0-13%, with an average of 5% (table 3). In our study group, no recurrences are yet reported. Nevertheless, the occurrence of perforated appendicitis was not higher among adult patients with recurrent appendicitis and some specialists suggest that antibiotics could be given for a second time, as is sometimes done in patients with diverticulitis.[16] Another concern is the possibility of missing an underlying cause for the acute appendicitis, in particular malignancy, the prevalence of which ranges from 0.5% in children to 1.6% in adults with a first episode of appendicitis.[41-44] It is questionable if this justifies primary appendectomy in all cases, the more because these patients will probably not respond to antibiotics and therefore require subsequent further action anyway.

Our study has some limitations. One of the main concerns to our study might be the antibiotics used. Based upon our standard postoperative protocol for patients with perforated appendicitis, we have chosen to administer amoxicillin/clavulanic acid combined with gentamicin, as *Escheria coli* is increasingly resistant in Europe.[45] Secondly, only 25 patients were included. The relatively low number is explained by both the stringency of our inclusion and exclusion criteria, the initial scepticism of both medical personnel as well as parents against this new treatment strategy, but also by the fact that two tertiary referral centres participated in this study. The proportion of patients with complex appendicitis in these centres is much higher than in

large peripheral centres. Furthermore, we decided to exclude patients younger than 7 years old as the incidence of complex appendicitis in this specific age group is higher. Surprisingly, in most patients with inconclusive results from ultrasound, it was decided not to obtain additional imaging studies but to admit and observe the patients or to perform a diagnostic laparoscopy. This has also attributed to the relatively small number of patients included. Thirdly, the follow -up period of 8 weeks can be considered insufficient. For now we can conclude that the short-term results of the pharmaceutical treatment are favourable, avoiding surgery in the majority of the patients. However, long-term results need to confirm these conclusions. Fourthly, the hospitalisation time is longer than in case of an appendectomy. In the future, however, it will be possible to reduce the hospitalisation time in patients who have improved sufficiently after 48 hours of intravenous antibiotics. For safety reasons this was not done in the current study. Lastly, our study design is an uncontrolled cohort study. This study was designed as a pilot study to investigate the feasibility and safety of the treatment protocol starting with antibiotics. Eventually a subsequent RCT will be set up comparing both strategies.

In conclusion, our study confirms that an RCT comparing initial antibiotic treatment strategy with urgent appendectomy is feasible in children; the intervention appears safe.

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