Critical Review Form

Therapy

Nonoperative Treatment With Antibiotics Versus Surgery for Acute Nonperforated Appendicitis in Children: A Pilot Randomized Controlled Trial. Ann Surg. 2014 Jul.

Objectives: **"(i) to evaluate the feasibility of recruiting children with acute appendicitis to an RCT comparing non-operative treatment with appendectomy; (ii) to evaluate the safety of non-operative treatment with antibiotics of acute nonperforated appendicitis in children; and (iii) to generate pilot data to inform our future planned efficacy study." (p. 1)**

Methods: **This nonblinded, randomized controlled pilot trial enrolled children from Astrid Lindgren Children's Hospital in Stockholm Sweden between February 7 and October 25, 2012. Children between the ages of 5 and 15 with a clinical diagnosis of appendicitis that would typically require appendectomy were eligible for enrollment. Exclusion criteria included suspicion of perforation, appendiceal mass, or previous non-operative treatment of acute appendicitis.**

Children were randomized to either appendectomy or non-operative management. Patients undergoing appendectomy were given a preoperative dose of metronidazole. Following surgery, patients with simple or phlegmonous appendicitis received no additional antibiotics; those with gangrenous appendicitis received 24 hours of trimethroprim/sulfamethoxazole and metronidazole; those with perforated appendicitis were given at least 3 days of trimethroprim/sulfamethoxazole and metronidazole, depending on clinical course. Patients receiving non-operative management were given intravenous meropenem and metronidazole for at least 48 hours. Once the child was improved and tolerating PO intake, the regimen was changed to oral ciprofloxacin and metronidazole for 8 more days. Patients in both groups were eligible for discharge when they were afebrile for 24 hours, had adequate analgesia on oral pain meds, were tolerating a liquid diet, and were mobile.

The primary outcome was resolution of symptoms without "significant complications," which were defined as any of the following:

1) **Length of stay (LOS) > 7 days**
2) **Abscess formation**
3) **Need for surgery within 48 hours in the non-operative group**
4) **Recurrence of appendicitis within 3 months**
5) **Negative appendectomy.**

Secondary outcomes included time to discharge, complications (wound infection, dehiscence, diarrhea, etc.), and recurrent appendicitis within 1 year. Follow-up in clinic occurred at 4-6 weeks after discharge for all subjects; one-year follow-up occurred either in the clinic or by telephone interview with one of the parents.

During the trial period, 225 children were identified with appendicitis requiring surgical intervention; 51 of these were enrolled, though one subject withdrew consent after randomization, leaving 24 subjects in the non-operative group and 26 subjects in the operative group. The overall mean age was 11.2 years, 52% were male, and 86% had symptoms for < 48 hours. All subjects in the operative group had a laparoscopic appendectomy, and all cases were confirmed as appendicitis by histology.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	
1.	Were patients randomized?	Yes. "Allocation to groups (1:1 ratio) was made via weighted minimization at the time of enrollment in the study using the following criteria: 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." (p. 2)
2.	Was randomization concealed (blinded)?	Yes. "Randomization was performed using a computer-based randomization program…which allowed complete concealment of randomization sequence." (p. 2)
3.	Were patients analyzed in the groups to which they were randomized?	Yes. All patients randomized to surgical intervention underwent laparoscopic appendectomy and were analyzed as such. Of the 24 subjects randomized to non-operative treatment, one child underwent appendectomy on day 2 and a second child underwent appendectomy on day 9. These subjects were still analyzed in the non-operative group. Therefore an intention to treat analysis was used.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. The authors used weighted minimization to help ensure that group allocation was similar with respect to certain known prognostic factors (age, sex, duration of symptoms). Patients in the two groups were similar with respect to these factors, as well as CRP level at admission, WBC at admission, and temperature at admission.
B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	

1.	Were patients aware of group allocation?	Yes. Given ethical concerns, this was an open-label trial. Given the nature of the study and involvement of children, it seems unlikely that performance bias on the part of the patients would affect the outcomes.
2.	Were clinicians aware of group allocation?	Yes. It is possible as a result that some form of performance bias on the part of the clinicians could influence the outcomes (i.e. earlier discharge).
3.	Were outcome assessors aware of group allocation?	Yes. The long-term outcomes were fairly objective (need for appendectomy), and hence it seems unlikely that **observer bias** would affect the results.
4.	Was follow-up complete?	Yes. In-hospital data was available for all patients, and all patients presented for outpatient clinic follow-up 4 to 6 weeks after discharge. Due to difficulties with follow-up at one year after discharge, telephone interview with one of the parents at one year was considered acceptable. The purpose of this one-year follow-up was to assess for episodes of recurrent appendicitis or need for appendectomy.
II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect?	• With regards to the primary outcome, no significant complications were observed in the operative group; in the non-operative group one child required surgery within 48 hours while another had recurrent appendicitis on day 9 and was readmitted and underwent appendectomy. The child requiring surgery within 48 hours had a histologically normal appendix and was diagnosed with mesenteric lymphadenitis. Therefore the primary outcome occurred less frequently in the operative group (0% vs. 8.3%) but this was not statistically significant (ARR 8.3%, 95% CI -2.7 to 19.4; p = 0.23). • In the operative group, there were no minor complications at one-year follow-up. In the non-operative group, 7 patients underwent appendectomy: one for appendicitis at 9 months, which was positive; one at parental request in an asymptomatic child, which was negative; and 5 for "mild" abdominal pain, all revealing fibrosis of the appendix without inflammation. • The median time to discharge was shorter in the surgical group (median 34.5 hours vs. 51.5 hours, p = 0.0004).

		• The cost of the initial inpatient stay was lower in the non-operative group (median 30732 vs. 63863 SEK, p < 0.0001). • Including the cost of appendectomy in the follow-up period, the total cost of treatment was similar between operative and non-operative groups (45805 vs. 34587 SEK, p = 0.11).
2.	How precise was the estimate of the treatment effect?	See above. This was a very small pilot study and was not powered to detect potentially clinically significant differences in the primary outcomes.
III.	**How can I apply the results to patient care (answer the questions posed below)?**	
1.	Were the study patients similar to my patient?	Yes. These were children between the ages of 5 and 15 with acute, nonperforated appendicitis, diagnosed on either ultrasound or CT scan. Despite differences in nationality and ethnic background, there is no clear biological reason for outcomes to be different between our patients and those in Stockholm, Sweden. While the proportion of children with obesity would likely be higher in our patient population, it is unclear if this would affect the efficacy of non-operative management in appendicitis.
2.	Were all clinically important outcomes considered?	No. The primary outcome was a composite of "significant complications," but many other patient-centered outcomes were not addressed. These include time to return to normal activities, time off work for parents, time out of school for children, and patient satisfaction.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. This was a small, open-label, randomized study and could potentially have been subject to selection performance bias and observer bias. The results do suggest that selective non-operative management of acute, uncomplicated, pediatric appendicitis is safe and may prevent a significant number of children from requiring surgical intervention. The authors did not address several patient-centered outcomes, including time to return to normal activities, time off work for parents, time out of school for children, and patient satisfaction. Larger randomized trials will need to be performed to confirm the potential benefits of non-operative management on these outcomes. Additionally, long-term outcomes such as the need for appendectomy later in life, recurrent pain, or small bowel obstruction are difficult to assess in such studies.

Limitations:

1. **This was a very small study enrolling only 50 patients. The resulting confidence intervals for the outcomes are wide.**

2. **This was understandably an open-label trial, but as such is subject to performance bias and observer bias.**

3. **There were 37 eligible subjects who were not asked to participate in the study for unclear reason; an additional 77 subjects were asked, but parental consent was not given. This is potentially a source of selection bias.**

4. **Subjects in the non-operative group were required to receive 48 hours of antibiotics, inflating the length of stay in this group. Conversely, there was a wide range in the time between randomization and surgery in the operative group (0.8 to 26.2 hours), inflating the length of stay in this group.**

5. **The authors failed to address several patient-centered outcomes, including time to return to normal activities, time off work for parents, time out of school for children, and patient satisfaction.**

Bottom Line:

In this small, randomized trial, there was an absolute reduction in the primary outcome of 8.3% for those receiving appendectomy. However, at one year, 15 of 24 children (62%) in the non-operative group were able to avoid surgery. There were no serious complications in either group. These results suggest that initial non-operative management is safe and effective in pediatric appendicitis. Further studies will be needed to confirm these results in a larger sample size, and should consider other patient-centered outcomes related to time off work/school, time to return to normal activities, and patient/parent satisfaction.