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Appendectomy versus Antibiotic Treatment in Acute Appendicitis. A Prospective Multicenter Randomized Controlled Trial

Johan Styrud MD, PhD,[1] Staffan Eriksson MD, PhD,[1]* Ingemar Nilsson MD, PhD,[2] Gunnar Ahlberg MD, PhD,[2] Staffan Haapaniemi MD, PhD,[3] Gunnar Neovius MD,[4] Lars Rex MD,[5] Ibrahim Badume MD,[6] Lars Granström MD, PhD[1]

[1]*Department of Surgery, Karolinska Institutet at Danderyd Hospital, S-182 88 Stockholm, Sweden*
[2]*Department of Surgery, St Göran Hospital, Karolinska Institutet, S-171 77 Stockholm, Sweden*
[3]*Department of Surgery, Norrköping Hospital, S-60182 Norrköping, Sweden*
[4]*Department of Surgery, Kristianstad Central Hospital, S-29185 Kristianstad, Sweden*
[5]*Department of Surgery, Borås Hospital, S-50182 Borås, Sweden*
[6]*Department of Surgery, Katrineholm Hospital, S-64122 Katrineholm, Sweden*

Abstract

Background: Appendectomy has been the treatment for acute appendicitis for over 120 years. Antibiotic treatment has occasionally been used in small uncontrolled studies, instead of operation, but this alternative has never before been tried in a multicenter randomized trial.

Patients and Methods: Male patients, 18–50 years of age, admitted to six different hospitals in Sweden between 1996 and 1999 were enrolled in the study. No women were enrolled by decision of the local ethics committee. If appendectomy was planned, patients were asked to participate, and those who agreed were randomized either to surgery or to antibiotic therapy. Patients randomized to surgery were operated on with open surgery or laparoscopically. Those randomized to antibiotic therapy were treated intravenously for 2 days, followed by oral treatment for 10 days. If symptoms did not resolve within 24 hours, an appendectomy was performed. Participants were monitored at the end of 1 week, 6 weeks, and 1 year.

Results: During the study period 252 men participated, 124 in the surgery group and 128 in the antibiotic group. The frequency of appendicitis was 97% in the surgery group and 5% had a perforated appendix. The complication rate was 14% in the surgery group. In the antibiotic group 86% improved without surgery; 18 patients were operated on within 24 hours, and the diagnosis of acute appendicitis was confirmed in all but one patient, and he was suffering from terminal ileitis. There were seven patients (5%) with a perforated appendix in this group. The rate of recurrence of symptoms of appendicitis among the 111 patients treated with antibiotics was 14% during the 1-year follow-up.

Conclusions: Acute nonperforated appendicitis can be treated successfully with antibiotics. However, there is a risk of recurrence in cases of acute appendicitis, and this risk should be compared with the risk of complications after appendectomy.

*Present address: Department of Surgery, Västerås Hospital, S-721 89 Västerås, Sweden
Correspondence to: Johan Styrud, MD, PhD, Department of Surgery, Karolinska Institutet at Danderyd Hospital, S-182 88 Stockholm, Sweden, e-mail: johan.styrud@ds.se

More than 120 years have passed since A. Grooves performed the first appendectomy in 1883.[1] Early appendectomy has been advocated, especially since R. Fitz in 1886 published a classic paper on 247 patients with perforated appendicitis.[2]

There have been occasional reports of conservative treatment with antibiotics in acute appendicitis. In 1959, Coldrey reported 471 patients who underwent treatment with antibiotics alone,[3] and a report from China in 1977 described 425 patients who were treated without surgery, but with antibiotics or traditional Chinese medicine.[4] At follow-up 7% had recurrence. Antibiotic treatment has also been described in nine U.S, submariners.[5]

In patients with an appendiceal mass the recommended treatment today is conservatively with antibiotics, and interval appendectomy is under debate.[6,7]

We have previously shown in a pilot study of 40 patients, that 19/20 (95%) were successfully treated with antibiotics.[8] Treatment with antibiotics resulted in significantly less pain compared to open appendectomy. However, with a recurrence rate of 7/19 (37%), it was suggested that the treatment should be used when surgery presented a high risk of complications. The pilot study led to a larger study to determine whether antibiotic treatment in acute non-perforated appendicitis could be recommended.

The aim of the present study was to compare antibiotic treatment with surgery in acute appendicitis in a large series of patients.

PATIENTS AND METHODS

Participants

Six hospitals in Sweden took part in the randomized study. They were Danderyd Hospital, St Göran Hospital, Norrköping Hospital, Kristianstad Hospital, Borås Hospital, and Katrineholm Hospital.

A series of 252 men 18–50 years of age were randomized to the study between March 1996 and June 1999. No women were enrolled in this multicenter study by decision of the local ethics committee. All patient data are presented in Table 1. Excluded were patients with suspicion of perforation of the appendix, those unwilling to participate, patients with a C-reactive protein (CRP) level <10 mg/l, and any who had had an allergic reaction to the antibiotics to be used in the treatment protocol.

Study Design

All patients admitted for suspected acute appendicitis with a CRP level >10 mg/l in whom perforation was not suspected were asked to participate in the study.[8–11] Each patient was randomized to surgery or antibiotic therapy at the time the decision was taken that surgery was needed. Randomization of each participant was performed by a telephone call to Danderyd Hospital where a sealed envelope was opened and revealed the assignment of surgery or antibiotic therapy. Patients randomized to surgery were operated open or laparoscopically, at the surgeon's discretion. All removed appendices were sent for histopathological examination. Patients who underwent appendectomy were discharged when their condition was deemed satisfactory. The level of pain and sickness as well as the time off work were recorded.

Table 1.
Patient data in the different groups

	Antibiotics	Surgery
No of patients	128	124
C-reactive protein	55 + 44	54 + 49
Total white cell count	12.5 + 3.8	12.4 + 3.5
Body temperature	37.5 + 0.7	37.4 + 0.8

Note: Values are mean + S.D.

Patients who received antibiotic treatment were given the same antibiotics used in the earlier pilot study, but oral treatment was given for 10 days.[8] Treatment was begun with 2 days of i.v. cefotaxime (Claforan; Aventis Pharma, Stockholm, Sweden), 2 g 12 hourly, and tinidazole (Fasigyn; Pfizer, Täby, Sweden), 0.8 g daily. Patients received intravenous fluids during the first 24 hours and were allowed to eat during the second hospital day. If their symptoms did not improve within the first 24 hours, an appendectomy was performed. Participants who received antibiotics alone, were discharged after the 2 days of i.v therapy and received oral treatment with ofloxacin (Tarivid; Aventis Pharma, Stockholm; Sweden), 200 mg twice daily, and tinidazole (Fasigyn; Pfizer, Täby, Sweden), 500 mg twice daily for 10 days.

Participants were evaluated at follow-up after 1 week, 6 weeks, and 1 year. The number of days of sick leave from work, the level of pain, and the complications, if any, were recorded. All conservatively treated patients with a suspected recurrence of appendicitis underwent surgery.

Statistical Methods and Data Management

To evaluate hypotheses of variables in contingency tables, the chi-square test was used or, in the case of small expected frequencies, Fisher's exact test was performed. Statistical comparisons to test differences between the two groups were made with Student's *t*-test for uncorrelated means. The within-group analysis was

Table 2.
Hospital stay, sick leave, and time off work in the different groups treated for acute appendicitis

	Antibiotics	Surgery
Hospital stay (days)	3.0 + 1.4	2.6 + 1.2
Sick leave (days)	5.3 + 4.1	6.0 + 4.4
Time off work (days)	8.0 + 8.0	10.1 + 7.6

Values are mean + S.D.

made by use of the pairwise Student's *t*-test for correlated means. In addition, descriptive statistics and graphical methods were used to characterize the data. All analyses were carried out by use of the SAS system, version 8.08 (SAS Institute, Cary; NC, USA), and the 5% level of significance was considered. In the case of a statistically significant result the probability value (*P* value) has been given.

The trial was approved by the local ethical committees, as well as the Swedish Federal Drug Administration (läkemedelsverket). All participants were informed orally and by written information.

RESULTS

Acute appendicitis was found in 97% of the 124 patients randomized to surgery. Eight patients (6%) underwent laparoscopic procedures. At operation and normal histopathological examination of the appendix, three patients had mesenteric adenitis and one patient had no evidence of pathology. All appendices were sent for histopathological examination, except in one patient with gangrenous appendicitis. Six (5%) patients had perforated appendices. The complication rate among this surgery group was 14% (17/124), mainly wound infections. The time in hospital, sick leave taken and time lost from work are shown in Table 2.

Of the 128 patients enrolled in the antibiotic group, 15 patients (12%) were operated within the first 24 hours due to lack of improvement in symptoms and apparent local peritonitis. The operation showed that seven patients (5%) had perforation. One patient did not have acute appendicitis; instead terminal ileitis was found. A total of 113 patients were successfully treated with antibiotics and were sent home for oral antibiotic therapy for 10 days. The length of the hospital stay and duration of sick leave were comparable to the surgery group (Table 2).

To learn whether the patients enrolled in this multicenter study differ from those who were unwilling to participate, we examined the medical records of all men in the 18–50-year age range that underwent appendectomy at Danderyd Hospital between 1996 and 1997. A total of 196 men were operated on, and 67 were excluded from the study for the following reasons: suspicion of perforation (41 patients, 61%), CRP <10 mg/l (25 patients, 37%), and allergy to the antibiotics selected for the study (1 patient, 2%). Another 79 patients were unwilling to participate or were not informed about the study. Of the 50 patients that were enrolled, 25 were randomized to surgery. There were no significant differences in histopathological findings between those who participated and those who did not (Table 3).

Table 3.
The histopathological diagnosis in 79 men unwilling to be enrolled in the study compared with 25 men that enrolled and were included in the surgery group ad Danderyd Hospital 1996–1997

	Percentage (n)	
Diagnosis	Unwilling	Surgery enrolled
Appendicitis		
Phlegmonous	51 (40)	48 (12)
Gangrenous	39 (31)	36 (9)
Perforated	1 (1)	12 (3)
Normal	4 (3)	4 (1)
Other diagnosis	4 (3)	0

During the 1-year follow-up period there were 17 (14%) complications in the surgery group, most of them wound infections. Four patients had complications after surgery in the antibiotic-treated group. The recurrence rate within 1 year was 15% (16 patients) in the group treated with antibiotics. After an average time of 4 months, those patients underwent operation according to the study protocol (range: 1–10 months after antibiotic treatment). In five of these patients a perforated appendix was found at operation.

DISCUSSION

The diagnosis of acute appendicitis is often difficult to make. We have previously shown that with an increasing interest in acute appendicitis, and by measuring CRP repeatedly, we have been able to increase diagnostic accuracy in patients with acute appendicitis.[12] A high diagnostic accuracy was important when patients were enrolled in our study, because a high probability of acute appendicitis was mandatory. In the group treated with antibiotics it can be presumed that 97% had appendicitis. It is obvious from Table 3 that patients enrolled in the study didn't differ significantly from the total group of patients at one of the participating hospitals (Danderyd Hospital) during the study period.

Although our intention was to exclude patients with perforations, 5% of the patients in our series had a perforated appendix, fewer than in most studies of patients with appendicitis.[12–14] The seven patients with perforated appendix in the antibiotic group did not have a longer hospital stay than the six patients with perforation in the operated group. Nor did their period of sick leave or time lost from work vary. According to the protocol, patients with a high suspicion of perforation were operated on immediately. A perforation rate of 15%–25% is often seen in large groups of patients with acute appendicitis.[12,15] This indicates that most patients with suspected acute appendicitis presenting at the emergency department do not need an emergency operation. Instead, they can be treated with antibiotics, and if symptoms progress within the first 24 hours, they can undergo appendectomy.

Women were excluded from our study by a decision of the ethics committee, but it is reasonable to believe that the results we found in men would be relevant for women.

This study shows that antibiotic treatment alone is sufficient in most patients with acute appendicitis; only 17 patients (12%) from the antiobiotic treatment group went on to operation within 24 hours. The recurrence rate of symptoms within 1 year was 15% (16 patients), and many of those patients ask to be treated conservatively a second time! The incidence of perforation was not higher among patients with recurrence, and it may be that antibiotic treatment could have been used a second time. If a fecal stone is lodged in the appendix, there might be a higher incidence of recurrence.[16]

There are several different types of antibiotics, and combinations of antibiotics, that can be used in the treatment of appendicitis. We used the same combination we had used in a pilot study with good results.[8]

There are some potential advantages of antibiotic treatment versus surgery, one of which is medical cost. The length of hospital stay could also be shorter with antibiotic treatment, because parenteral administration of antibiotics is probably necessary for only 24 hours. Such patients can be discharged with oral antibiotics for 10 days and follow-up examination scheduled after the first week.

Another advantage is that risks associated with surgery and anesthesia are eliminated in patients with acute appendicitis who receive conservative antibiotic treatment. Although operative risk is small, complications do exist. There is also a small morbidity risk at appendectomy, and that risk is of course increases with age and concomitant diseases. The rate of intestinal obstruction is known to be highest after appendectomy of a healthy appendix,[17] but any abdominal operation can result in adhesions, which may cause intestinal obstruction later in life.

A potential disadvantage of antibiotic treatment is allergy to the drugs employed. As mentioned above, several different types, and combinations, of antibiotics could be used. Allergy would not be a problem if the surgeon is aware of the possibility of allergy and prescribes antibiotics suitable for each patient.

Acute appendicitis is a common disease,[14] and if antibiotic treatment proves successful in treating the majority of patients, there will be a large increase in antibiotic use in the population. That will enhance the risk that patients will develop susceptibility to bacteria strains that are resistant to an increasing number of antibiotics, especially if the criteria for treatment are not correct. Because there is already a large problem with multiresistant bacteria, this is a major disadvantage of routine antibiotic treatment of acute appendicitis. Therefore it might not be logical to recommend antibiotic treatment to such a large group of patients.

It is crucial to use antibiotic treatment with the same high diagnostic accuracy required before considering surgery; *i.e.,* no patients should be treated with antibiotics without history and clinical signs indicating appendicitis. The diagnosis should be confirmed with CT scan and/or ultrasonography, and no patient without an elevated CRP level should be treated for suspected appendicitis.[13,18]

Antibiotic treatment can be recommended in patients with a high surgical risk, *i.e.,* elderly patients with poor heart and lung function, and severely obese patients.

In conclusion, this study shows that acute appendicitis can be treated successfully with antibiotics with a short hospital stay, minimal sick leave, and limited duration of pain. There is a risk of recurrence, which should be compared with the rate of complications after appendectomy.

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REFERENCES

1. Harris CW. The first elective appendectomy? Can J Surg 1961;4:405–410.
2. Fitz RH. Perforating inflammation of the vermiform appendix. Am J Med Sci 1886;92:321–346.
3. Coldrey E. Five years of conservative treatment of acute appendicitis. J Int Coll Surg 1959;32:255–261.

4. Anonymous. Combined traditional Chinese and Western medicine for acute appendicitis. Chinese Med J 1977;3: 266–269.
5. Adams ML. The medical management of acute appendicitis in a nonsurgical environment: a retrospective case review. Milit Med 1990;155:345–347.
6. Nitecki S, Assalia A, Schein M. Contemporary management of appendeceal mass. Br J Surg 1993;80:8–20.
7. Eriksson S, Styrud J. Interval appendicectomy: a retrospective study. Eur J Surg 1998;164:771–774.
8. Eriksson S, Granström L. Randomized controlled trial of appendicectomy versus antibiotic treatment therapy for acute appendicitis. Br J Surg 1995;82:166–169.
9. Eriksson S, Granström L, Bark S. Laboratory tests in patients with suspected acute appendicitis. Acta Chir Scand 1989;155:117–120.
10. Eriksson S, Granström L, Carlström A. The diagnostic value of repetitive preoperative analysis of C-reactive protein and total leukocyte count in patients with suspected acute appendicitis. Scand J Gastroenterol 1994;29:1145–1149.
11. Hallan S, Åsberg A. The accuracy of C-reactive protein in the diagnosing acute appendicitis—a meta analysis. Scand J Clin Lab Invest 1997;57:373–380.
12. Styrud J, Eriksson S, Segelman J, *et al.* Diagnostic accuracy in 2351 patients undergoing appendicectomy for suspected acute appendicitis. Dig Surg 1999;16:39–44.
13. Styrud J, Josephson T, Eriksson S. Reducing negative appendectomy evaluation of ultrasonography and computer tomography in acute appendicitis. Int J Qual Health Care 2000;12:65–68.
14. Andersson RE, Hugander A, Thulin AJG. Diagnostic accuracy and perforation rate in appendicitis: association with age and sex of the patient and with appendectomy rate. Eur J Surg 1992;158:37–41.
15. Andersson R, Hugander A, Thulin A, *et al.* Indications for operation in suspected appendicitis and incidence of perforation. Br Med J 1994;308:107–110.
16. Eriksson S, Tisell Å, Granström L. Ultrasonographic findings after conservative treatment of acute appendicitis and open appendicectomy. Acta Radiol 1995;36:173–177.
17. Arnbjörnsson E. Small intestinal obstruction after appendectomy: an avoidable complication. 1984;41:354–357.
18. Andersson R, Hugander A, Ghazi S, *et al.* Why does the clinical diagnosis fail in suspected appendicitis. Eur J Surg 2000;166:796–802.