

# Randomized controlled trial of appendicectomy versus antibiotic therapy for acute appendicitis

S. ERIKSSON and L. GRANSTRÖM

Department of Surgery, Karolinska Institute, Danderyd Hospital, S-182 88 Danderyd, Sweden  
Correspondence to: Dr S. Eriksson

In a prospective controlled study the effect of antibiotics as the only treatment in acute appendicitis was evaluated. Of 40 patients admitted with a duration of abdominal pain of less than 72 h, 20 received antibiotics intravenously for 2 days followed by oral treatment for 8 days and 20 considered as controls were randomized to surgery. All patients treated conservatively were discharged within 2 days, except one who required surgery after 12 h because of peritonitis secondary to perforated appendicitis. Seven

patients were readmitted within 1 year as a result of recurrent appendicitis and underwent surgery, when appendicitis was confirmed. The diagnostic accuracy within the operated group was 85 per cent. One patient had perforated appendicitis at operation. Antibiotic treatment in patients with acute appendicitis was as effective as surgery. The patients had less pain and required less analgesia, but the recurrence rate was high.

Over 100 years have passed since McBurney<sup>1</sup> reported his study of eight patients with acute appendicitis with special reference to early appendicectomy.

The idea of conservative treatment with antibiotics is not novel and Coldrey<sup>2</sup> in 1959 treated 471 unselected patients conservatively, with low mortality and morbidity rates. His idea was as controversial then as it is today. Of 500 patients with suspected acute appendicitis 425 were treated conservatively, with use of traditional Chinese medicines and antibiotics in some<sup>3</sup>. Only seven of 100 patients at follow-up had recurrent appendicitis. In both studies patients were assessed by history and clinical examination, the treatment differed without standardization and there was no consecutive follow-up. A recent study<sup>4</sup> of 695 children has demonstrated that the administration of preoperative antibiotic treatment can be used as a means of delaying appendicectomy, particularly during twilight hours. The incidence of perforation, complications and hospitalization in children operated on within 6 h was the same as that of those undergoing operation between 6 and 18 h after admission<sup>4</sup>.

The appendiceal mass can be treated successfully by conservative management<sup>5-10</sup>, but some recommend interval appendicectomy<sup>5,9</sup> in case there is a caecal neoplasm or recurrent appendicitis supervenes.

Conservative treatment of acute appendicitis has been described in American submariners<sup>11</sup> (nine patients) and on board Soviet ships at sea (247)<sup>12</sup>. There has been no prospective randomized trial.

The present pilot prospective randomized study compared the results of conservative treatment with antibiotics and surgery in patients with acute appendicitis.

## Patients and methods

### Patients

The trial was approved by the local ethical committee. Some 45 adults were admitted with a history and clinical signs of acute appendicitis. The time of onset of abdominal pain was ascertained and patients were examined by the same surgeon before inclusion in the study. Five patients did not agree to be randomized and under-

went surgery; they had acute appendicitis. Forty patients (27 men and 13 women aged 18-75 years) were randomized between May 1992 and March 1994. Some patient data are available in Table 1.

Investigations included ultrasonography and laboratory tests, namely, estimation of total white blood cell count (WBC) and C-reactive protein (CRP) level, as diagnostic tools to identify patients with a high probability for acute appendicitis<sup>13-16</sup>.

Inclusion criteria included typical history and clinical signs, positive findings at ultrasonography and either increased WBC and CRP values, or high CRP or WBC levels on two occasions within a 4-h interval.

### Conservative treatment

Cefotaxime (Claforan; Hoechst, Stockholm, Sweden) 2 g 12 hourly and tinidazole (Fasigyn; Pfizer, Täby, Sweden) 800 mg daily were given for 2 days. Patients received only intravenous fluids during this period. Pain was registered every 6 h using a visual analogue scale and oral temperature was measured twice daily. Patients were excluded from the study in the event of increased abdominal pain and generalized peritonitis, and subjected to surgery (only one patient was affected and subsequent data were discounted). Patients

Table 1 Patient data

	Antibiotics	Surgery
No. of patients	20	20
Mean (range) age (years)	27.8 (18-53)	35.0 (19-75)
Sex ratio (M:F)	14:6	13:7
Duration of pain (h)	21.0(14.7)	18.4(11.8)
Total white blood cell count on admission ( $\times 10^9/l$ )	13.8(4.4)	13.9(4.1)
C-reactive protein concentration on admission (mg/l)	41(30)	40(38)
Temperature on admission ( $^{\circ}C$ )	37.2(0.7)	37.1(0.7)
Morphine dose (mg)	0.9(2.5)	17.8(15.3)*
No. treated with antibiotics	20	5
Hospital stay (days)	3.1(0.3)	3.4(1.9)
Wound infection		1
Recurrent appendicitis	7	—
Follow-up (months)	17.2(8.0)	17.0(6.3)

Values are mean(s.d.). \* $P < 0.001$  (Student's *t* test)

were discharged after 2 days and received oral treatment with ofloxacin (Tarivid; Hoechst) 200 mg twice daily and tinidazole 500 mg twice daily for 8 days.

**Surgery**

Patients who underwent surgery were treated with antibiotics only in the event of perforation or for 24 h in cases of abdominal spillage. Operated patients were discharged when conditions were satisfactory and they wished to return home. Visual analogue scale scores were registered every 6 h and oral temperature was measured twice daily. All excised appendices were sent for histological examination.

**Follow-up**

All patients were seen at 6, 10 and 30 days after admission and blood was taken for determination of WBC and CRP levels, pain registered as visual analogue scale scores and oral temperature measured. Abdominal and rectal examinations were carried out on days 6 and 10. Stools were examined for *Clostridium difficile* toxin at day 30 to exclude pseudomembranous colitis. Ultrasonography was performed on days 10 and 30; results have been presented elsewhere<sup>17</sup>. All conservatively treated patients with suspected recurrent appendicitis underwent surgery.

**Methods**

Ultrasonography was applied by using the compressive technique described by Puylaert<sup>18</sup>. Positive findings for acute appendicitis included a diameter greater than 6 mm and a non-compressible appendix. An invisible appendix was considered as negative.

CRP levels were quantified by a turbidimetric assay on a Paramax instrument (Baxter, Irvine, CA, USA) using antibodies (Dako, Copenhagen, Denmark). The upper limits of the reference intervals used were  $9.0 \times 10^9/l$  for WBC and 10 mg/l for CRP.

Pain was registered by patients using a visual analogue scale every 6 h during hospital stay<sup>19</sup>. Pain was also checked daily by the same surgeon (S.E.) with a visual analogue scale score and at follow-up. The score ranged from no pain (0 mm) to unbearable pain (100 mm). Pain was treated with morphine delivered intramuscularly or intravenously during hospitalization, which was noted. Patients wanting analgesia at home were prescribed paracetamol (Alvedon, Astra, Södertälje, Sweden) and dextropropoxyphene (Doloxene; Lilly, Stockholm, Sweden).

**Statistical analysis**

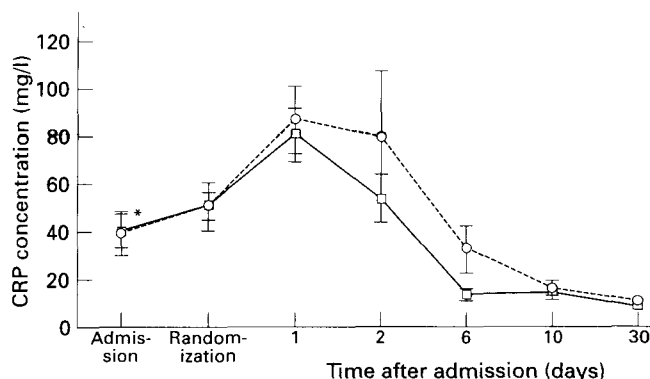
Statistical comparisons between groups were made using Student's *t* test for uncorrelated means and within groups by use of the pairwise Student's *t* test for correlated means. Descriptive statistics and graphical methods were employed to characterize the data. All analyses were carried out using the Statistical Analysis System (SAS Institute, Cary, North Carolina, USA)<sup>20-22</sup>.  $P < 0.05$  was considered significant.

**Results**

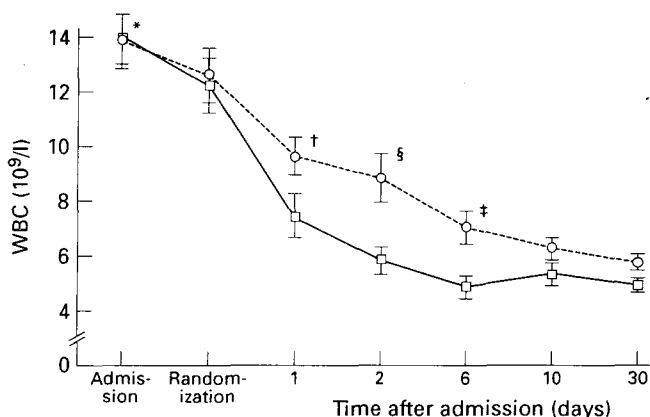
In all patients there was a significant increase in CRP levels from admission to randomization (Fig. 1), and a significant decrease in WBC (Fig. 2).

**Conservative treatment**

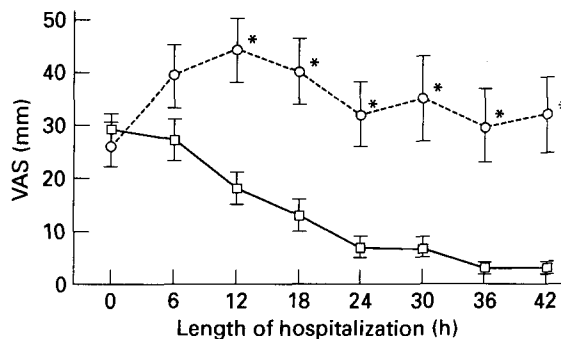
There was a significant decrease in morphine consumption in patients managed with antibiotics ( $P < 0.001$ ) (Table 1) and significantly less pain was recorded after 12 h conservative treatment ( $P < 0.001$ ) (Fig. 3). Significantly lower pain scores were also noted by the surgeon (Fig. 4). The WBC declined significantly faster in patients treated with antibiotics (Fig. 2) and mean temperature was significantly lower on days 1 and 2 ( $P < 0.05$ ), with not more than



**Fig. 1** Mean(s.e.m.) concentration of C-reactive protein (CRP) in patients with acute appendicitis treated with antibiotics (□) or surgery (○) during hospitalization and at 30 days of follow-up. \* $P < 0.001$  (admission versus randomization, Student's *t* test)

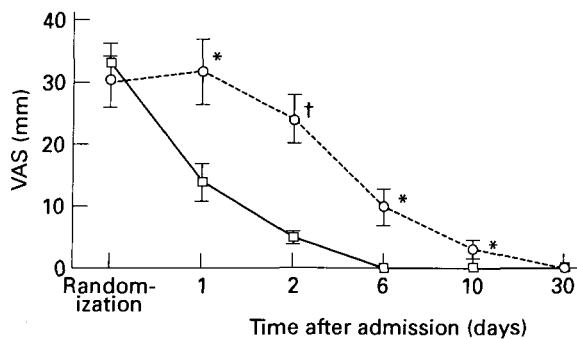


**Fig. 2** Mean(s.e.m.) total white blood cell count (WBC) in patients with acute appendicitis treated with antibiotics (□) or surgery (○) during hospitalization and at 30 days of follow-up. \* $P < 0.001$  (admission versus randomization); † $P < 0.05$ , ‡ $P < 0.01$ , § $P < 0.001$  (surgery versus antibiotics, Student's *t* test)



No. of patients	0	6	12	18	24	30	36	42
Antibiotics	20	20	18	19	19	19	18	18
Surgery	20	16	16	20	13	12	11	10

**Fig. 3** Pain recorded using a visual analogue scale (VAS) by patients with acute appendicitis treated with antibiotics (□) or surgery (○). Number of patients lower than 20 indicates that the patient was asleep or had been discharged. Values are mean(s.e.m.). \* $P < 0.001$  (surgery versus antibiotics, Student's *t* test)



No. of patients	Randomization	1	2	6	10	30
Antibiotics	20	20	19	19	19	19
Surgery	20	20	10	20	20	20

Fig. 4 Pain recorded using a visual analogue scale (VAS) by surgeon (S.E.) in patients with acute appendicitis treated with antibiotics (□) or surgery (○) during hospitalization and at 30 days of follow-up. Number of patients lower than 20 indicates that the patient was asleep or had been discharged. Values are mean (s.e.m.). \* $P < 0.01$ , † $P < 0.001$  (surgery versus antibiotics, Student's *t* test)

Table 2 Histopathological diagnosis in patients who underwent surgery

Diagnosis	No. of patients
Appendicitis	
Phlegmonous	8
Gangrenous	8
Perforation	1
Total	17
Normal appendix	
Mesenteric adenitis	2
Enteritis <i>Campylobacter</i>	1
Total	3

0.5°C difference. The pattern of CRP levels in both groups was the same (Fig. 1).

#### Surgery

Of patients who underwent surgery 17 had proven appendicitis at histological examination (Table 2). Three patients were treated with antibiotics during or directly after operation.

#### Follow-up

There was a significant decrease in pain on days 6 and 10 in patients treated with antibiotics ( $P < 0.01$ ) (Fig. 4). The WBC also continued to decrease in this group on day 6 (Fig. 2). There were no differences in CRP levels and mean temperature between the two groups at these visits (Fig. 1). One patient with campylobacterial enteritis who underwent surgery returned at day 4 with diarrhoea and was treated with erythromycin for 1 week. One patient with phlegmonous appendicitis was readmitted on day 6 after appendicectomy because of a wound infection without abscess formation and treated with antibiotics for 4 days (cefotaxime and tinidazole intravenously) (Table 1). No postoperative infection was noted in the three surgical patients treated with antibiotics before surgery. None of the 39 patients having stools checked for *C. difficile* toxin had positive findings (one surgical patient was not analysed).

Seven patients given antibiotic treatment were readmitted with recurrent appendicitis: six had phlegmonous appendicitis and one a perforated appendicitis after 15 h of pain before hospitalization. Surgery occurred after a mean of 7 (range 3–12) months after conservative management. No chronic findings were noted at histopathological examination.

#### Discussion

High diagnostic accuracy is required in patients with suspected acute appendicitis as negative appendicectomy carries significant morbidity from wound sepsis, intestinal obstruction, pneumonia and infertility from fimbrial damage<sup>23,24</sup>. There is a greater risk for abdominal adhesions after laparotomy for healthy appendices compared with that for acute appendicitis<sup>25,26</sup>. The appendix can be a useful conduit for reconstructive surgery (e.g. hepaticoportopappendicostomy<sup>27</sup> or ureteroplasty<sup>28</sup>).

Measurement of WBC and CRP levels<sup>13–15</sup>, and ultrasonography<sup>16,29</sup>, may help achieve a more accurate diagnosis. The WBC was significantly decreased in both groups between the level found on admission and at randomization as previously reported<sup>14</sup>. During this period the level of CRP significantly increased, emphasizing the importance of repetitive analyses in patients with suspected acute appendicitis<sup>14,15</sup>.

Clinical follow-up at day 30 after antibiotic treatment is probably sufficient. The present study demonstrates that 10-day antibiotic treatment is sufficient in patients treated conservatively. This is a shorter period than that described by others<sup>11</sup>. Conservative treatment started within 6 h of abdominal pain was not less effective as reported by others<sup>12</sup>.

All patients were followed after conservative treatment until normal findings were found at ultrasonography or surgery, and results, have been reported elsewhere<sup>17</sup>. A mucocoele can be recognized by ultrasonography<sup>16,30</sup>. Carcinoid, the most common tumour of the appendix<sup>31,32</sup>, might not have normal findings at ultrasonographic follow-up, as it is a firm solid lesion most often located in the tip of the appendix<sup>31</sup>. The incidence of carcinoid is three to seven in every 1000 appendicectomies<sup>31,32</sup>; the tumour occurs more frequently in women (2–4:1) and is often asymptomatic<sup>32</sup>.

Recurrence in the present study was high (seven patients at 17.2 months) and could increase with time. This value was higher than that reported in earlier studies of patients with appendicitis treated with antibiotics<sup>2,3</sup> and in those with appendicular abscesses<sup>5–7</sup>, but inclusion criteria were more liberal and follow-up periods short. Recurrence of appendiceal abscess after 3 months is rare<sup>6,7</sup>. Larger studies are needed to establish the superiority of antibiotic treatment over surgery in a larger population.

The study indicates patients' interest in conservative treatment as 40 of 45 agreed to participate in the study despite being informed about the risk for recurrence.

#### Acknowledgements

The authors thank Dr Gunnar Granström, Department of Infectious Diseases, Karolinska Institute, Danderyd Hospital, for help in designing the antibiotic treatment and Dr Anders Moberg, Department of Pathology, Danderyd Hospital, for pathological evaluation. This work was supported by the Danderyd Hospital, the funds of the Karolinska Institute, Swedish Hoechst AB, Pfizer AB and the Mutual Group Life Insurance Company 'Förenade Liv', Stockholm, Sweden.

## References

- 1 McBurney C. Experiences with early operative interference in cases of disease of the vermiform appendix. *New York Medical Journal* 1889; **50**: 676-84.
- 2 Coldrey E. Five years of conservative treatment of acute appendicitis. *Journal of the International College of Surgeons* 1959; **32**: 255-61.
- 3 Anonymous. Combined traditional Chinese and western medicine in acute appendicitis. *Chinese Med J* 1977; **3**: 266-9.
- 4 Surana R, Quinn F, Puri P. Is it necessary to perform appendectomy in the middle of the night in children? *BMJ* 1993; **306**: 1168.
- 5 Arnbjörnsson E. Management of appendiceal abscess. *Curr Surg* 1984; **41**: 4-9.
- 6 Bagi P, Dueholm S. Nonoperative management of the ultrasonically evaluated appendiceal mass. *Surgery* 1987; **101**: 602-5.
- 7 Engkvist O. Appendectomy à froid: a superfluous routine operation? *Acta Chirurgica Scandinavica* 1971; **137**: 797-800.
- 8 McPherson AG, Kinmonth JB. Acute appendicitis and the appendix mass. *Br J Surg* 1945; **32**: 365-70.
- 9 Thomas DR. Conservative management of the appendix mass. *Surgery* 1973; **73**: 677-80.
- 10 Mosegaard A, Nielsen OS. Interval appendectomy. A retrospective study. *Acta Chirurgica Scandinavica* 1979; **145**: 109-11.
- 11 Adams ML. The medical management of acute appendicitis in a nonsurgical environment: a retrospective case review. *Milit Med* 1990; **155**: 345-7.
- 12 Gurin NN, Slobodchuk IuS, Gavrilov IuF. The efficacy of the conservative treatment of patients with acute appendicitis on board ships at sea. *Vestn Khir* 1992; **148**: 144-50.
- 13 Eriksson S, Granström L, Bark S. Laboratory tests in patients with suspected acute appendicitis. *Acta Chirurgica Scandinavica* 1989; **155**: 117-20.
- 14 Eriksson S, Granström L, Carlström A. The diagnostic value of repetitive preoperative analyses of C-reactive protein and total leucocyte count in patients with suspected acute appendicitis. *Scand J Gastroenterol* 1994 (in press).
- 15 Eriksson S, Granström L, Olander B, Wretling B. Sensitivity of interleukin-6 and C-reactive protein concentrations in the diagnosis of acute appendicitis. *Eur J Surg* 1994 (in press).
- 16 Granström L, Eriksson S, Tisell Å. Ultrasonography as a tool in the diagnosis of acute appendicitis. A prospective study. *Surgical Research Communications* 1992; **11**: 309-14.
- 17 Eriksson S, Tisell Å, Granström L. Ultrasonographic findings after conservative treatment of acute appendicitis and open appendectomy. *Acta Radiol* 1994 (in press).
- 18 Puylaert JBCM. Acute appendicitis: US evaluation using graded compression. *Radiology* 1986; **158**: 355-60.
- 19 Huskisson EC. Measurement of pain. *Lancet* 1974; **ii**: 1127-31.
- 20 SAS\* *Language: Reference, Version 6*. 1st ed. Cary, North Carolina: SAS Institute, 1990.
- 21 SAS\* *Language and Procedures: Usage, Version 6*. 1st ed. Cary, North Carolina: SAS Institute, 1989.
- 22 SAS/STAT\* *User's Guide, Version 6*. 4th ed. Volumes 1 and 2. Cary, North Carolina: SAS Institute, 1990.
- 23 Deutsch AA, Shani N, Reiss R. Are some appendicectomies unnecessary? An analysis of 319 white appendices. *J R Coll Surg Edinb* 1983; **28**: 35-40.
- 24 Pieper R, Kager L, Näsman P. Acute appendicitis: a clinical study of 1018 cases of emergency appendectomy. *Acta Chirurgica Scandinavica* 1982; **148**: 51-62.
- 25 Arnbjörnsson E. Small intestinal obstruction after appendectomy: an avoidable complication? *Curr Surg* 1984; **41**: 354-7.
- 26 Räf LE. Causes of abdominal adhesions in cases of intestinal obstruction. *Acta Chirurgica Scandinavica* 1969; **135**: 73-6.
- 27 Grosfeld JL, Weinberger M, Clatworthy HW Jr. Vascularized appendical transplants in biliary and urinary tract replacement. *J Pediatr Surg* 1971; **6**: 630-8.
- 28 Weinberg RW. Appendix ureteroplasty. *Br J Urol* 1976; **48**: 234.
- 29 Eriksson S, Granström L, Tisell Å. Ultrasonography in suspected acute appendicitis. Is it difficult to learn? *Br J Surg* 1993; **80**(Suppl): 4.
- 30 Athey PA, Hacken JB, Estrada R. Sonographic appearance of mucocele of the appendix. *J Clin Ultrasound* 1984; **12**: 333-7.
- 31 Rosai J. Surgical pathology. In: *Gastrointestinal Tract, Appendix*. Washington, DC: CV Mosby, 1989: 566-7.
- 32 Roggo A, Wood WC, Ottinger LW. Carcinoid tumors of the appendix. *Ann Surg* 1993; **217**: 385-90.