Randomized clinical trial

Randomized clinical trial of antibiotic therapy *versus* appendicectomy as primary treatment of acute appendicitis in unselected patients

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Background: **A trial in selected men suggested that antibiotic therapy could be an alternative to appendicectomy in appendicitis. This study aimed to evaluate antibiotic therapy in unselected men and women with acute appendicitis.**

Methods: **Consecutive patients were allocated to study (antibiotics) or control (surgery) groups according to date of birth. Study patients received intravenous antibiotics for 24 h and continued at home with oral antibiotics for 10 days. Control patients had a standard appendicectomy. Follow-up at 1 and 12 months was carried out according to intention and per protocol.**

Results: **Study and control patients were comparable at inclusion; 106 (52·5 per cent) of 202 patients allocated to antibiotics completed the treatment and 154 (92·2 per cent) of 167 patients allocated to appendicectomy had surgery. Treatment efficacy was 90·8 per cent for antibiotic therapy and 89·2 per cent for surgery. Recurrent appendicitis occurred in 15 patients (13·9 per cent) after a median of 1 year. A third of recurrences appeared within 10 days and two-thirds between 3 and 16 months after hospital discharge. Minor complications were similar between the groups. Major complications were threefold higher in patients who had an appendicectomy ($P < 0·050$).**

Conclusion: **Antibiotic treatment appears to be a safe first-line therapy in unselected patients with acute appendicitis. Registration number: NCT00469430 (http://www.clinicaltrials.gov).**

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Introduction

Appendicectomy is a classic surgical procedure, which was introduced around 1880. Non-operative management had been used earlier for many patients, but morbidity and mortality were high for both conservatively treated and appendectomized patients. In 1959 Coldrey[1] studied 471 patients who received antibiotics as single treatment, although this did not receive much attention. Standard treatment for acute appendicitis remained early appendicectomy to avoid perforation, but population-based evaluations have indicated significant long-term risks following surgical exploration for appendicitis[2]: small bowel obstruction requiring operation has been shown to occur in 1·3 per cent by 30 years, and 30-day mortality to be 0·24 per cent with increased standard mortality ratio[3,4]. A negative appendicectomy is particularly hampered with problems[5]. Therefore in recent years there has been increased interest in antibiotic therapy as primary treatment[6], and several studies have indicated that perforated appendicitis in children can be treated with antibiotics[7–9]. In addition, retrospective studies in adults with perforated appendicitis treated conservatively suggested that late recurrences exhibited a mild clinical course[10,11].

One randomized trial that compared appendicectomy with antibiotic therapy in men (aged 18–50 years) found that 88 per cent improved without surgery, and 14 per cent had recurrent appendicitis within 1 year[12]. It is uncertain to what extent such promising results are representative of unselected patients. The present study was designed to investigate whether antibiotic therapy is a feasible first-line therapy in unselected men and women older than 18 years.

Methods

This prospective controlled trial was undertaken at Sahlgrenska University Hospital, Östra University Hospital and Kungälv Hospital, Sweden. All patients older than 18 years with assumed appendicitis were eligible for inclusion. Acute appendicitis was diagnosed according to established practice: the attending physician decided based on disease history, clinical status, laboratory tests and, in some cases, ultrasonography, computed tomography and gynaecological examination. Patients who had surgery at Östra University Hospital were used only as a reference cohort for comparison with study and control groups at the Sahlgrenska and Kungälv Hospitals. Patients allocated to antibiotics, surgery and reference groups were all included during the same period. The three hospitals recruited patients from the main population across a wide area of Gothenburg city (around $0{\cdot}9 \times 10^6$ inhabitants) with an incidence of appendicitis close to 0·1 per cent.

Patient allocation

A total of 369 consecutive patients were allocated to antibiotic treatment or surgery (*Fig. 1*): those with an uneven date of birth were allocated to antibiotics (study group), and those with an even date of birth to appendicectomy (control group). Informed consent was obtained after verbal and written information had been

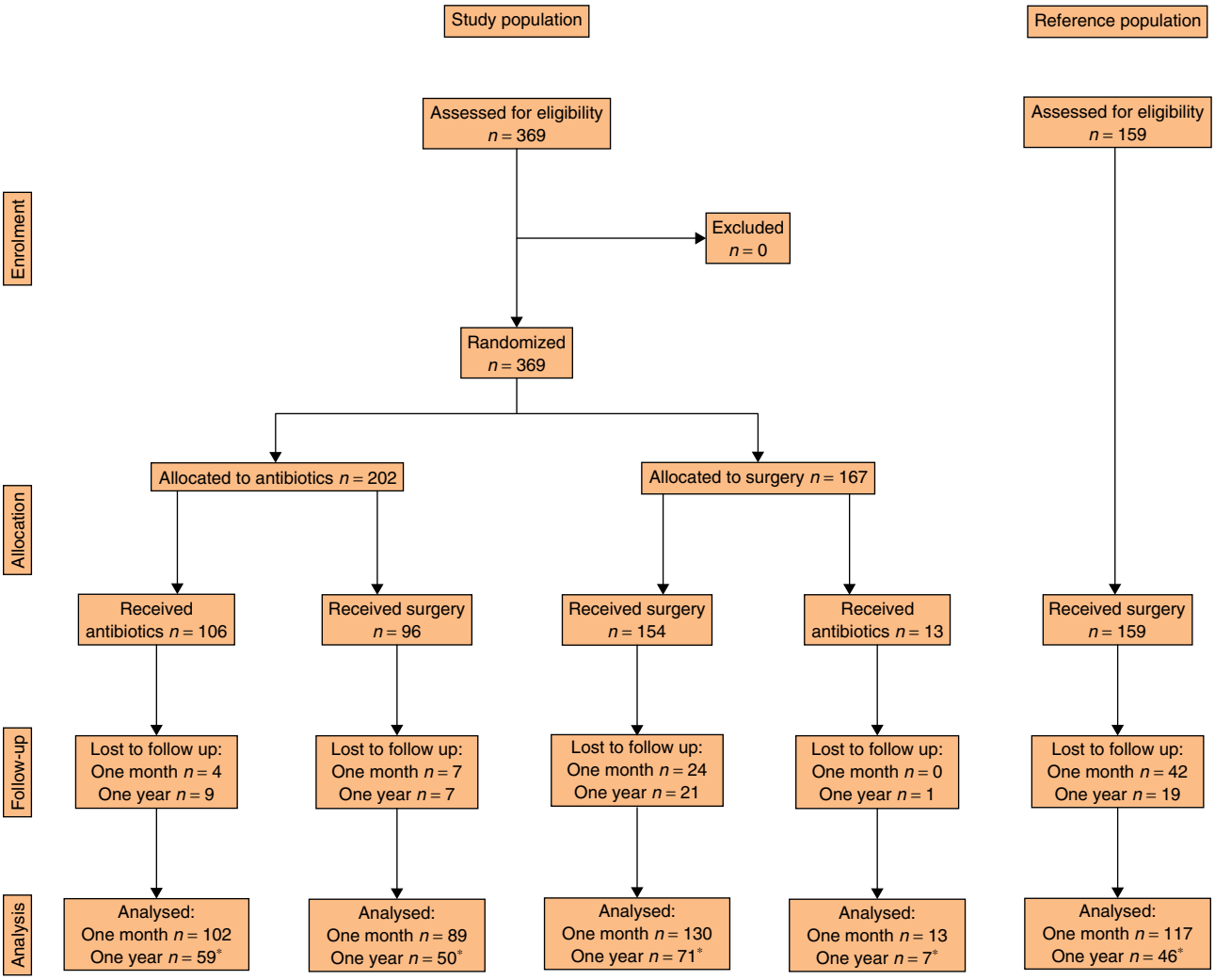

Fig. 1 CONSORT diagram. At one-year follow-up questionnaires were sent to 225 (60·9 per cent) patients from the study population and 65 (40·9 per cent) patients from the reference poplation who had reached one year at the time of analysis (remaining patients were followed up for less than one year). Questionnaires were returned from 187 (83·1 per cent) of the study population and 46 (70·8 per cent) of the reference population. The medical records of all patients were analysed at both one month and median one year

given. All included patients remained in their allocated groups during follow-up, even when intention to treat was abandoned owing to criteria defined in the protocol. Patients allocated to antibiotic treatment could have surgery without any predetermined specification if the surgeon in charge deemed it necessary or if the patient preferred initial operation. Similarly, patients allocated to surgery could choose antibiotic treatment as their first choice, as defined by the ethical permission.

Interventions

Study patients received intravenous antibiotics (cefotaxime 1 g twice and metronidazole 1·5 g once) for at least 24 h. During this time patients received intravenous fluids with no oral intake. Patients whose clinical status had improved the following morning were discharged to continue with oral antibiotics (ciprofloxacin 500 mg twice a day and metronidazole 400 mg three times a day) for a total of 10 days. In patients whose clinical condition had not improved, intravenous treatment was prolonged.

Appendicectomy was always performed according to the authors' usual practice: single-dose antibiotic prophylaxis, open or laparoscopic technique and postoperative antibiotic treatment when the appendix was gangrenous or perforated. The appendix was sent for histological examination and specimens for bacterial culture were taken from the base of the appendix at operation.

Data collection and follow-up

Pre-, per- and post-treatment data were recorded according to the protocol. A questionnaire was sent to all patients after 1 and 12 months. Telephone calls were made to all patients who did not respond. Complications, recurrences and reoperations were registered.

Outcome measures

Primary endpoints were treatment efficacy and major complications. Efficacy for antibiotic treatment was defined as definite improvement without the need for surgery within a median follow-up of 1 year. Efficacy for surgical treatment was confirmed appendicitis at operation or another appropriate surgical indication for operation. Major complications were reoperation, abscess formation, bowel obstruction, wound rupture or hernia, or serious anaesthesia-related or cardiac problems. Secondary endpoints were minor complications, length of antibiotic therapy, abdominal pain after discharge from hospital, length of hospital stay and sick leave. The total costs for the primary hospital stay (including materials, medical drugs, radiology and surgery resources, postoperative surveillance, laboratory tests and pathology) were analysed for each patient.

Statistical analysis

Prestudy estimates suggested that at least 200 allocated patients would be necessary to confirm a 10–15 per cent difference in treatment efficacy and complications between study and control patients at 80 per cent power with a 5 per cent significance level. The χ^2 test was used to check for differences between proportions. Student's t test or ANOVA was used for comparisons of continuous variables between groups. $P < 0{\cdot}050$ was considered significant in two-tailed tests. Analyses were primarily made by intention to treat and secondarily per protocol. SPSS® version 15·0 software (SPSS, Chicago, Illinois, USA) was used for the statistical calculations.

This study was approved by the Committee of Ethics at the University of Gothenburg (172-05).

Results

A total of 369 eligible consecutive patients were included between May 2006 and September 2007: 202 patients in the study group (antibiotics) and 167 patients in the control group (appendicectomy) (*Fig. 1*). Some 106 (52·5 per cent) in the study group completed the intended antibiotic treatment, and 154 (92·2 per cent) in the control group had appendicectomy. Reasons for non-fulfilment of scheduled treatment included patient preference for the other treatment (33 patients; 30·3 per cent), the surgeon deciding that surgery was necessary based on clinical evaluation (19 patients; 17·4 per cent) and surgery being deemed necessary without any further specification (45 patients; 41·3 per cent) (*Table 1*). The study included 99·2 per cent of all patients appearing with assumed acute appendicitis at the three hospitals.

Logistic analysis indicated that phlegmonous and gangrenous appendicitis were mathematically related to blood white cell count, and perforated appendicitis was related to C-reactive protein, white cell count and body temperature (*Table 2*). C-reactive protein, white cell count and temperature predicted abdominal status defined as local tenderness, local peritonitis or generalized peritonitis ($P < 0{\cdot}001$; $r = 0{\cdot}22$). Recurrent appendicitis was predicted only by body temperature (odds ratio 2·79 (95 per cent confidence interval 1·40 to 5·57); $P < 0{\cdot}004$).

Table 1 Reasons for patient transfers from allocated treatment group

	Antibiotics ($n = 202$)	Surgery ($n = 167$)
Patient wanted the other therapy	26	7
Patient withdrew from the study	4	
Patient 'too ill for operation'		1
Follow-up expected to be impossible	2	
Allocation fault		2
Surgeon judged an operation to be necessary		
Based on specified clinical judgement	19	
Based on unspecified clinical judgement	45	
Total	96	10

Table 2 Multivariable analysis of blood chemistry and body temperature as predictors of confirmed appendicitis

	Odds ratio	*P**
Phlegmonous		
C-reactive protein (mg/l)	1·00 (0·99, 1·00)	
White cell count ($\times 10^9$/l)	1·15 (1·06, 1·25)	0·001
Body temperature (°C)	0·83 (0·52, 1·34)	
Gangrenous		
C-reactive protein (mg/l)	1·01 (1·00, 1·01)	
White cell count ($\times 10^9$/l)	1·21 (1·10, 1·33)	0·001
Body temperature (°C)	1·16 (0·68, 1·99)	
Perforated		
C-reactive protein (mg/l)	1·01 (1·00, 1·02)	0·005
White cell count ($\times 10^9$/l)	1·22 (1·11, 1·35)	0·001
Body temperature (°C)	2·03 (1·19, 3·45)	0·009

Values in parentheses are 95 per cent confidence intervals. *Logistic regression analysis.

Patient characteristics

All patient groups were well matched for subject, clinical and diagnostic variables at inclusion (*Table 3*). Two significant differences were found between study and control patients when analysed by intention to treat: a higher white cell count and a higher proportion of local peritonitis in the surgery group. Patients evaluated per protocol showed a similar distribution. There were differences in age, white cell count, and the proportion of radiological and gynaecological examinations between reference patients and pooled study and control patients (*Table 3*).

Of the 202 patients primarily allocated to antibiotic treatment, 106 received the intended antibiotic therapy and 96 had an appendicectomy. The only significant difference in patient characteristics between these two subgroups was slightly higher body temperature in patients transferred for appendicectomy (*Table 4*).

Primary endpoints

Treatment efficacy

Efficacy in the study group according to intention to treat was 48·0 per cent (97 of 202) (*Table 5*). Eleven (9·2 per cent) of 119 patients who primarily received antibiotics had an appendicectomy owing to clinical progression within 24–36 h. These patients had similar preoperative characteristics to those who fulfilled the antibiotic treatment. Of 250 surgically explored patients, 223 (89·2 per cent) had appendicitis or another surgically curable diagnosis. Thus primary treatment efficacy was 90·8 per cent for antibiotic therapy compared with

Table 3 Patient characteristics at inclusion

	Intention to treat		Per protocol		
	Antibiotics ($n = 202$)	Surgery ($n = 167$)	Antibiotics ($n = 119$)	Surgery ($n = 250$)	Reference group ($n = 159$)
Sex ratio (M : F)	103 : 99	92 : 75	62 : 57	138 : 112	92 : 67
Age (years)*	38(1)	38(1)	40(2)	37(1)	34(1)§
Previous abdominal surgery†	20 (9·9)	27 (16·2)	14 (11·8)	33 (13·2)	14 (8·8)
Suspicion of previous appendicitis†	18 (8·9)	10 (6·0)	6 (5·0)	23 (9·2)	10 (6·3)
Clinical variables					
C-reactive protein (mg/l)*	55(4)	54(4)	51(5)	56(3)	54(5)
White cell count ($\times 10^9$/l)*	12·7(0·3)‡	13·6(0·3)	12·2(0·4)‡	13·5(0·3)	14·2(0·3)§
Body temperature (°C)*	37·3(0·1)	37·5(0·1)	37·2(0·1)‡	37·5(0·1)	37·5(0·1)
Local peritonitis†	34 (16·8)‡	43 (25·7)	20 (16·8)	60 (24·0)	27 (17·0)
General peritonitis†	9 (4·5)	4 (2·4)	3 (2·5)	10 (4·0)	6 (3·8)
Diagnostic variables†					
Radiological imaging (CT/US)	57 (28·2)	42 (25·1)	37 (31·1)	60 (24·0)	25 (15·7)§
Gynaecological examination	139 (68·8)	102 (61·1)	77 (64·7)	165 (66·0)	75 (47·2)§

*Values are mean(s.e.m.); †values in parentheses are percentages. CT, computed tomography; US, ultrasonography. ‡$P < 0·050$ *versus* the surgery group; §$P < 0·050$ *versus* the pooled antibiotics and surgery groups; χ^2 test, ANOVA.

Table 4 Patient characteristics at inclusion of patients randomized to antibiotics

	Antibiotics ($n = 106$)	Surgery ($n = 96$)
Sex ratio (M : F)	52 : 54	51 : 45
Age (years)*	40(2)	35(2)
Previous abdominal surgery†	12 (11·3)	9 (9)
Suspicion of previous appendicitis†	6 (5·7)	12 (13)
Clinical variables		
C-reactive protein (mg/l)*	51(6)	59(6)
White cell count ($\times 10^9$/l)*	12·4(0·4)	12·9(0·4)
Temperature (°C)*	37·2(0·1)‡	37·5(0·1)
Local peritonitis†	16 (15·1)	19 (20)
General peritonitis†	3 (2·8)	6 (6)
Diagnostic variables†		
Radiological imaging (CT/US)	33 (31·1)	23 (24)
Gynaecological examination	70 (66·0)	68 (71)

*Values are mean(s.e.m.); †values in parentheses are percentages. CT, computed tomography; US, ultrasonography. ‡$P < 0·010$ *versus* the surgery group; χ^2 test, ANOVA.

89·2 per cent for surgical exploration analysed per protocol. The diagnoses at operation within groups are shown in *Table 6*. At 1 year, antibiotic treatment efficacy decreased to 78·2 per cent because of recurrences, significantly lower than the surgery group ($P < 0·050$) (*Table 5*).

Recurrences

Of 108 patients who initially improved without surgery, 15 (13·9 per cent) had recurrent appendicitis at a median of 1 year (*Table 5*). One-third of recurrences appeared within 10 days of hospital discharge and two-thirds between 3 and 16 months from discharge. Relapsing patients were both men and women aged between 35 and 83 years. Twelve of these 15 patients had surgery, and three had a second round of antibiotic treatment with success during the later follow-up. Four relapsing patients had gangrenous or perforated appendicitis, and others had less severe inflammation. One patient had ileocaecal resection because of pronounced inflammatory changes.

Major complications

Major complications were three times higher in patients who had an appendicectomy ($P < 0·050$) (*Table 7*). However, this risk was not related to patients who were considered to need surgery. One patient (0·8 per cent) initially receiving antibiotics had an abdominal operation (not an appendicectomy) related to the initial condition at 1 year. Five patients (2·0 per cent) who initially had appendicectomies had abdominal reoperations. Two patients had hemicolectomies owing to malignancies of the appendix or colon discovered at appendicectomy;

Table 5 Treatment efficacy and recurrences at a median of 1 year

	Intention to treat		Per protocol		
	Antibiotics ($n = 202$)	Surgery ($n = 167$)	Antibiotics ($n = 119$)	Surgery ($n = 250$)	Reference group ($n = 159$)
Treatment efficacy					
Primary hospital stay	97 (48·0)*	142 (85·0)	108 (90·8)†	223 (89·2)	142 (89·3)
At 1 year	83 (41·1)*	142 (85·0)	93 (78·2)*	223 (89·2)	142 (89·3)
Recurrences	14*	1	15*	0	0
Appendicectomy	11	1	12		
Second antibiotic treatment	3		3		

Values in parentheses are percentages. *$P < 0·050$ *versus* the surgery group; †not significant *versus* the surgery group; χ^2 test.

Table 6 Number of patients with a diagnosis at operation (evaluated per protocol)

	Antibiotics ($n = 119$)			
	Lack of improvement ($n = 11$)	Recurrences ($n = 12$)	Surgery ($n = 250$)	Reference group ($n = 159$)
Appendicitis	9	12	220	141
Phlegmonous	3	8	128	80
Gangrenous	3	1	42	35
Perforated	3	3	50	26
Other diagnosis	2		30	18
Normal	1		13	11
Surgically non-treatable			14	6
Surgically treatable	1		3	1

Table 7 Major complications within a median of 1 year

	Intention to treat		Per protocol		
	Antibiotics ($n = 202$)	Surgery ($n = 167$)	Antibiotics ($n = 119$)	Surgery ($n = 250$)	Reference group ($n = 159$)
Reoperation	1*	5†	1*	5†	1‡
Abscesses	5	5	1	9	3
Small bowel obstruction		4		4	2
Wound rupture	1	2		3	1
Wound hernia		1		1	1
Pulmonary embolism		1		1	
Postoperative cardiac problems§	2	1		3	
Aspiration at extubation					1
Ileocaecal resection	2	2	1	3	1
Caval vein thrombosis					1
Total	11 (5·4)¶	18 (10·8)	3 (2·5)¶	25 (10·0)	11 (6·9)

Values in parentheses are percentages. *Diagnostic laparoscopy; †small bowel obstruction (in three), hemicolectomy, and peritonitis or abscess; ‡hemicolectomy; §requiring admission to cardiac unit. ¶$P < 0{\cdot}050$ *versus* the surgery group.

Table 8 Minor complications within a median of 1 year

	Intention to treat		Per protocol		
	Antibiotics ($n = 202$)	Surgery ($n = 167$)	Antibiotics ($n = 119$)	Surgery ($n = 250$)	Reference group ($n = 159$)
Prolonged postoperative course*	9	4		13	3
Bladder dysfunction†	5	1	1	5	1
Anaesthesia related‡		2		2	1
Diarrhoea§	5	19	14	10	3
Clostridium infection	1	1	1	1	
Fungal infection¶	4		4		2
Wound infection#	13	7	1	19	7
Other**	4	3	1	6	2
Total	40 (19·8)††	37 (22·2)	33 (27·7)††	55 (22·0)	19 (11·9)

Values in parentheses are percentages. *With paralysis or vomiting; †requiring urinary catheter at discharge from hospital; ‡tooth injury and stomach tube in airways; §more than a few days; ¶vaginal or anal; #requiring nurse visits after discharge; **thrombophlebitis, rectus muscle haematoma, sensoric loss in leg, urticaria and scrotal oedema. ††Not significant *versus* the surgery group.

one in the control group and one in the reference group.

Post-treatment abscesses were found in both groups. In one patient who had initially received antibiotics, the abscess was drained percutaneously without complications. Nine patients who initially had surgery had abscesses, and four of these required drainage (rectal or vaginal) under general anaesthesia. Four patients had ileocaecal resection instead of simple appendicectomy because of technical difficulties at operation with pronounced inflammatory changes: one patient after antibiotic therapy with recurrent appendicitis and three with the primary operation. Major complications were not significantly related to open or laparoscopic surgery, in agreement with earlier conclusions from meta-analyses[13,14].

Secondary endpoints

Minor complications

Proportions of minor complications were similar among all patient groups (*Table 8*). The most frequent minor complication in the study group was diarrhoea, compared with wound infection in the control group evaluated per protocol.

Patient experience

The number of days with abdominal pain after leaving hospital was significantly fewer in study than control patients (*Table 9*). The proportion of patients still experiencing some kind of symptom after 1 month did not differ between study and control patients, based on information from 334(90·5 per cent) of the patients who

Table 9 Patient experience reported at 1 and 12 months

	Intention to treat		Per protocol		
	Antibiotics ($n = 202$)	Surgery ($n = 167$)	Antibiotics ($n = 119$)	Surgery ($n = 250$)	Reference group ($n = 159$)
Duration of postoperative abdominal pain (days)*	6(1)†	9(1)	5(1)†	8(1)	8(1)
Reduced satisfaction 1 month after treatment	31 (15·8)	26 (18·0)	17 (15·1)	40 (18·0)	22 (18·9)
Subjective abdominal pain during 1 year	39 (34·2)	30 (31·7)	28 (42·0)†	40 (28·0)	22 (23·9)

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.e.m.). †$P < 0·050$ *versus* the surgery group.

answered the questionnaire at 1 month. The proportion of patients who had some kind of abdominal pain during their first post-treatment year was significantly higher among patients on antibiotics analysed per protocol based on the answers of 187(3·18 per cent) of patients who were sent the questionnaire at 1 year.

Antibiotic therapy

Study and control patients received a similar amount of intravenous antibiotics, but oral intake was greater in study patients (*Table 10*).

Hospital stay, sick leave and total costs

Days in hospital, days of sick leave and total costs for primary hospital care are shown in *Table 11*. Study patients had significantly fewer days of sick leave. The total costs in Swedish krona (SEK) were 10 000 SEK (about £819 at time of going to press) lower in study patients evaluated as intention to treat and 19 000 SEK (£1555·59) lower analysed per protocol treatment than in control patients.

Table 10 Number of days on intravenous and oral antibiotic therapy (evaluated per protocol)

	Antibiotics ($n = 119$)	Surgery ($n = 250$)	Reference group ($n = 159$)
Intravenous	1·6(0·1)	1·6(0·2)	1·3(0·1)
Oral	8·4(0·2)*	3·0(0·3)	2·6(0·3)
Total	10(0·3)*	4·6(0·4)	3·9(0·3)

Values are mean(s.e.m.). *$P < 0·001$ *versus* the surgery group.

Discussion

This study comparing antibiotics and surgery to treat acute appendicitis found comparable treatment efficacy: 90·8 per cent for antibiotic therapy and 89·2 per cent for surgery. Fifteen patients (13·9 per cent) who received antibiotics had a recurrence after a median of 1 year. On the other hand, major complications were three times higher in those who had an appendicectomy.

Appendicectomy has been regarded standard treatment for acute appendicitis for more than a century, although occasional reports of conservative treatment with antibiotics have implied that there may be alternatives to surgery in selected patients. A prospective multicentre randomized trial recently reported that selected patients with acute appendicitis could be treated successfully with antibiotics with a short hospital stay, minimal sick leave and limited duration of pain[12], and the risk of recurrence should be compared with a significant rate of severe complications after appendicectomy[2–4]. The study by Styrud and colleagues[12] included only men (aged 18–50 years) admitted to six different university and regional hospitals in Sweden. These patients participated in a randomization procedure at the time of the clinical decision to perform standard appendicectomy. Patients randomized to antibiotic therapy were treated intravenously for 2 days followed by oral treatment for 10 days, and appendicectomy was performed if symptoms did not resolve within 24 h; 88 per cent improved without surgery. However, a subgroup analysis of patients who had surgery at Danderyd

Table 11 Duration of hospital stay and sick leave in relation to total costs for hospital treatment

	Intention to treat		Per protocol		
	Antibiotics ($n = 202$)	Surgery ($n = 167$)	Antibiotics ($n = 119$)	Surgery ($n = 250$)	Reference group ($n = 159$)
Primary hospital stay (days)	3(0·1)	3(0·3)	2(0·1)	3(0·2)	2(0·1)
Sick leave (days)	7(1)*	11(1)	5(1)*	10(1)	10(1)
Total cost for primary hospital admission (SEK)	26 300(1200)*	36 400(3300)	18 000(1100)*	36 900(2300)	

Values are mean(s.e.m.). SEK, Swedish krona. *$P < 0·010$ *versus* the surgery group.

Hospital in Stockholm between 1996 and 1997 indicated that 171 of 221 patients were excluded owing to inclusion criteria, were uninformed of the study or were unwilling to participate. Therefore the results from that important study are mainly relevant for selected men with a high probability of appendicitis recommended for appendicectomy.

The present study was designed to evaluate the effects of antibiotic treatment compared with surgery on unselected patients older than 18 years with a high probability of acute appendicitis, irrespective of any estimated risk of perforation. Diagnostic criteria for suspected appendicitis were conventional evaluation of clinical abdominal status, disease history and laboratory tests. There was a deliberate attempt not to make a consensus definition of appendicitis, leaving the physicians in charge to decide when patients were eligible for the study based on their own preferred diagnostic criteria. It was also a prerequisite that this study should not lead to increased costs from diagnostic procedures such as computed tomography or ultrasonography beyond the clinical need for appropriate treatment.

For the present study, it was decided not to randomize patients by conventional means. Preliminary evaluation indicated that patient inclusion would be highly dependent on how patients were invited by the physicians, and most surgeons are reluctant not to operate on patients with probable acute appendicitis. The evaluation suggested that few patients would be included in a study based on conventional blinded envelope procedures, which was also evident in the earlier randomized study[12]. Therefore the ethics committee allowed the use of a modified randomization procedure, with all patients with suspected appendicitis being included in the study and offered a systematic treatment according to uneven (antibiotic) or even (operation) date of birth, but with any surgeon or patient being able to change the allocation based on medical judgement or personal preference. It may therefore be questionable whether the allocation procedure used in this study represented valid randomization. However, this is of little importance with respect to evaluating treatment efficacy, compliance and complications, as inclusion covered all patients presenting with appendicitis in the city of Gothenburg. The entire study cohort was primarily evaluated by intention to treat and then per protocol. In addition, the study included a complete cohort of patients with acute appendicitis from the neighbouring university hospital during the same period (reference patients) in order to demonstrate whether patient allocation and treatment algorithm created any skew in patient distribution. All patients in the study (antibiotic), control (surgery) and reference (surgery) groups were thus recruited from Gothenburg on the west coast of Sweden, which was assumed to harbour an evenly distributed population with respect to the possibility of developing acute appendicitis.

The results showed that patient characteristics at inclusion and evaluated both by intention to treat and per protocol were highly comparable and did not differ principally among study, control and reference patients in any clinically important aspect. Moreover, patient characteristics were also similar to those of patients at inclusion in the study by Styrud and colleagues[12]. Therefore it is clear that allocating patients to different treatments created homogeneous distributions of patients among groups, probably not different from chance selection.

Ninety-six patients initially allocated to antibiotic therapy transferred to appendicectomy (*Table 1*). Patient characteristics of these patients at the time of inclusion did not differ significantly in any important aspect from those of patients who completed antibiotic therapy according to allocation. This suggests that indications for switching patients from the intended antibiotic treatment to surgery were dependent on individual judgements or preferences relating more to the surgeons than to clinical status. In line with this observation, for 45 of these patients, surgeons could not provide a reason for their conversion to surgery except that an operation was warranted (*Table 1*).

Minor complications occurred in around 20 per cent of all groups evaluated by intention to treat or per protocol, numerically higher than reported in trials of laparoscopic *versus* open surgical procedures[15]. However, the per-protocol analysis showed that major complications were three times higher in patients who had surgery for appendicitis than those who received antibiotics. This difference was not related to patients who were thought to require surgery at inclusion. Patients reported significantly shorter abdominal pain with antibiotic treatment, although long-term abdominal discomfort may have been more frequent. There was no difference in primary hospital stay, but patients on antibiotic therapy had significantly less sick leave. The costs for primary hospital admission and treatment were 50 per cent less in patients treated with antibiotics according to the per-protocol analysis and around 25 per cent less according to the intention-to-treat analysis.

The present study has confirmed previous findings on selected men with acute appendicitis, and has demonstrated that antibiotic treatment seems to be an appropriate alternative to conventional appendicectomy in unselected

patients with probable acute appendicitis diagnosed by conventional means and applied according to best individual practice. Multivariable analysis of patient characteristics failed to demonstrate any logistic model for inclusion or rejection of patients for the specified treatments. Furthermore, it confirmed that C-reactive protein is not a significant predictor in the assessment of the phlegmonous and gangrenous appendix, unlike total blood leucocyte count. Therefore most patients older than 18 years without obvious signs of intra-abdominal perforation can be offered antibiotic treatment as first-line therapy. Clinical progression and surgical judgement may then decide whether there is a real need for surgical exploration in an expected subgroup of 5–10 per cent of all patients appearing with suspected or established appendicitis. The benefit would be a significantly reduced frequency of major complications related to surgery. The possible drawbacks to treating acute appendicitis with antibiotics do not appear relevant, despite the well recognized risk of increased environmental burden and antibiotic resistance; major complications following unnecessary surgery seem a more pertinent risk to patients.

The authors will now challenge the results of this study with a stricter introduction of antibiotic treatment as first-line therapy to patients with acute appendicitis for further scientific evaluation.

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