Randomized clinical trial

Randomized clinical trial of antibiotics in acute uncomplicated diverticulitis

A. Chabok[1], L. Påhlman[2], F. Hjern[3], S. Haapaniemi[4] and K. Smedh[1], for the AVOD Study Group

[1]Colorectal Unit, Department of Surgery, and Centre for Clinical Research Uppsala University, Västmanlands Hospital, Västerås, [2]Colorectal Unit, Department of Surgical Sciences, Uppsala University, Uppsala, [3]Division of Surgery, Department of Clinical Sciences, Danderyd Hospital, Karolinska Institute, Stockholm, and [4]Department of Surgery, Vrinnevi Hospital, Norrköping, Sweden

Correspondence to: Dr K. Smedh, Department of Surgery, Central Hospital, SE-72189 Västerås, Sweden (e-mail: kenneth.smedh@ltv.se)

Background: **The standard of care for acute uncomplicated diverticulitis today is antibiotic treatment, although there are no controlled studies supporting this management. The aim was to investigate the need for antibiotic treatment in acute uncomplicated diverticulitis, with the endpoint of recovery without complications after 12 months of follow-up.**

Methods: **This multicentre randomized trial involving ten surgical departments in Sweden and one in Iceland recruited 623 patients with computed tomography-verified acute uncomplicated left-sided diverticulitis. Patients were randomized to treatment with (314 patients) or without (309 patients) antibiotics.**

Results: **Age, sex, body mass index, co-morbidities, body temperature, white blood cell count and C-reactive protein level on admission were similar in the two groups. Complications such as perforation or abscess formation were found in six patients (1·9 per cent) who received no antibiotics and in three (1·0 per cent) who were treated with antibiotics ($P = 0·302$). The median hospital stay was 3 days in both groups. Recurrent diverticulitis necessitating readmission to hospital at the 1-year follow-up was similar in the two groups (16 per cent, $P = 0·881$).**

Conclusion: **Antibiotic treatment for acute uncomplicated diverticulitis neither accelerates recovery nor prevents complications or recurrence. It should be reserved for the treatment of complicated diverticulitis. Registration number: NCT01008488 (http://www.clinicaltrials.gov).**

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Introduction

Diverticulosis of the colon is an increasingly common, benign disorder in Western countries. It occurs in about one-third of the population older than 45 years and in up to two-thirds of the population aged above 85 years[1]. Diverticulitis is defined as inflammation or infection in a diverticula-bearing colonic segment.

Although a majority of individuals with diverticulosis remain asymptomatic, 10–25 per cent will develop diverticulitis during their lifetime[2]. Uncomplicated diverticulitis presents most frequently with abdominal pain, fever and raised inflammatory parameters, and more than 70 per cent of patients are treated conservatively[3,4]. Uncomplicated diverticulitis is a costly disease with an increasing incidence and a decreasing age at acute admission[4–6].

Antibiotics have been used in the treatment of uncomplicated diverticulitis since their introduction, as the condition has been suggested to be caused by bacterial infection. Despite the lack of controlled studies and previously demonstrated disease resolution without antibiotic treatment[7,8], treatment with antibiotics has become the standard of care for uncomplicated diverticulitis. Some authors, however, have suggested that diverticulitis could be a form of inflammatory bowel disease and not the result of microperforation[9,10], questioning the rationale behind prescribing antibiotics for the treatment of uncomplicated diverticulitis.

It is widely believed that the unnecessary use of antimicrobials is a major cause of the widespread emergence of resistant organisms, which is beginning to threaten the continued effectiveness of antibiotics. Although resistance to antibiotics is a natural phenomenon, it has been aggravated by their overuse[11].

The aim of the present study was to evaluate whether antibiotic treatment for acute uncomplicated left-sided diverticulitis is necessary for recovery without complications after a 12-month follow-up interval.

Methods

Study design

The AVOD (Antibiotika Vid Okomplicerad Divertikulit – Swedish for 'antibiotics in uncomplicated diverticulitis') study was conducted as an open multicentre randomized controlled trial that ran between October 2003 and January 2010 with the participation of ten surgical departments in Sweden and one in Iceland. Patients aged over 18 years with acute uncomplicated left-sided diverticulitis were eligible. Inclusion and exclusion criteria are shown in *Table 1*. Uncomplicated diverticulitis was defined as an episode with a short history and with clinical signs of diverticulitis, without sepsis, with an increased body temperature and inflammatory parameters, verified by computed tomography (CT), and without any sign of complications such as abscess, free air or fistula.

Patients with clinical signs of acute diverticulitis and a body temperature of 38°C or more either at or within 12 h before admission were evaluated by clinical examination, blood tests, and CT of the abdomen and pelvis. CT scans were assessed by the radiologist on duty at each centre. An immediate preliminary report was given and later checked by a senior staff radiologist. After confirmation of the diagnosis of uncomplicated diverticulitis by CT[12] and screening for eligibility, informed consent was obtained. Randomization in blocks of four and stratified by centre was performed by opening a sealed envelope, distributed by the Centre for Clinical Research in Västerås. The sizes of the blocks were unknown to the participating units. At each centre, a local investigator was responsible for recruiting patients to the trial and controlling the randomization process. A case record form (CRF) was completed for each patient, including demographic data, medical history, previous symptoms of diverticulitis, physical examination and laboratory results, and abnormalities seen on CT. Pain was recorded on a visual analogue scale (VAS, 0–10 cm) and abdominal tenderness at palpation on a scale of 0–4 (*Table 2*).

To clarify the selection of the cohort, all eligible patients who were not included in the study were to be registered, stating the reasons for not participating according to the Consolidated Standards for Reporting Trials (CONSORT) statement[13].

The study was commenced at two centres (Västerås and Uppsala) in October 2003 and at the other nine centres between 2004 and 2006. According to the expected inclusion rate, the study was estimated to end in January 2009.

The study was approved by the ethics committee of the Faculty of Medicine, Uppsala University, and followed the Declaration of Helsinki guidelines.

Table 1 Study inclusion and exclusion criteria

Inclusion criteria
Adult patient aged over 18 years
Acute lower abdominal pain with tenderness
Body temperature ≥ 38°C at admission or during the last 12 h before admission
Raised WBC and C-reactive protein level, or at least increased WBC if short history
Signs of diverticulitis on CT
Informed consent
Exclusion criteria
Signs of complicated diverticulitis on CT with abscess, fistula or free air in abdomen or pelvis
Signs of other diagnosis on CT
Receiving immunosuppressive therapy
Pregnancy
Ongoing antibiotic therapy
High fever, affected general condition, peritonitis or sepsis

WBC, white blood cell count; CT, computed tomography.

Table 2 Demographic data and patient characteristics

	No antibiotics ($n = 309$)	Antibiotics ($n = 314$)	P¶
Age (years)	57·1(13·2)	57·4(12·8)	0·853
Sex ratio (M : F)	110 : 199	110 : 204	0·882#
Co-morbidity*‡	91 (29·4)	92 of 312 (29·5)	0·992#
Previous diverticulitis*	137 of 306 (44·8)	110 of 309 (35·6)	0·020#
Body mass index (kg/m^2)	28·2(4·4)	27·9(4·4)	0·437
WBC ($\times 10^9$ cells/l)	12·3(3·3)	12·6(3·1)	0·276
CRP (mg/l)	91(61)	100(62)	0·070
Body temperature (°C)	38·1(0·6)	38·1(0·6)	0·350
Abdominal pain†	6 (4–8)	6 (5–8)	0·503**
Tenderness score§	3 (2–3)	3 (2–3)	0·950**

Values are mean(s.d.) unless indicated otherwise; *values in parentheses are percentages. †Median (interquartile range, i.q.r.) visual analogue scale (VAS, 1–10) score; §median (i.q.r.) tenderness score: 0, none; 1, mild local tenderness; 2, moderate local tenderness; 3, severe local tenderness; 4, local peritonitis. ‡Includes cardiovascular disease, pulmonary disease, renal failure and diabetes mellitus. WBC, white blood cell count; CRP, C-reactive protein. ¶Student's t test, except #Pearson's χ^2 test and **Mann–Whitney U test.

Study procedure

Eligible patients were randomized to treatment with intravenous fluids only (no-antibiotics group) or in combination with antibiotic therapy (antibiotics group). Broad-spectrum antibiotics were used according to the participating centres' routines, covering Gram-negative and anaerobic bacteria. Treatment was initiated with an intravenous combination of a second- or third-generation cephalosporin (cefuroxime or cefotaxime) and metronidazole, or with carbapenem antibiotics (ertapenem, meropenem or imipenem) or piperacillin–tazobactam. Orally administrated antibiotics such as ciprofloxacin or cefadroxil combined with metronidazole were initiated subsequently on the ward or at discharge. The total duration of antibiotic therapy was at least 7 days.

The decision to discharge patients was made by the attending surgeon based on an improvement in clinical status as well as a reduction in the white blood cell count (WBC) and C-reactive protein (CRP) level, and the absence of fever. These signs were taken as surrogates for recovery and reflected the pragmatic design of the study. Complications during hospital stay were defined as bowel perforation with free air, abscess or fistula. Complications during follow-up were admission to hospital owing to recurrence and need for emergency or elective surgery.

Follow-up

At 6–8 weeks after discharge, patients had a colonic investigation by colonoscopy, barium enema or CT colonography if none of these had been done within 1 year before admission. The results of the investigations were registered and the extent of diverticular disease noted. After a minimum of 12 months, patients were contacted by telephone or letter to complete a questionnaire regarding abdominal pain, bowel symptoms or recurrence demanding readmission to hospital. If no answer was received after three reminders, the patient was registered as a dropout from follow-up.

Statistical analysis

Sample size was calculated from an estimated complication rate with antibiotic therapy of 1·5 per cent. An increase in the complication rate in the no-antibiotics group to a maximum of 6·5 per cent was regarded as acceptable. With $\alpha = 0{\cdot}05$ and a power of 80 per cent, each group should consist of 240 patients; with an estimated dropout rate of 20 per cent, the necessary sample size was calculated to be 600 patients.

The results were analysed on an intention-to-treat and per-protocol basis. Pearson's χ^2 test was used for discrete variables. The study arms were compared using an independent-samples t test for continuous variables with normal distribution. The Mann–Whitney U test was used for ordinal data or for data without normal distribution. A multivariable binary logistic model was performed to analyse relationships between the different variables and the occurrence of complications and recurrence.

In the primary analysis, short-term results regarding the occurrence of complications, need for surgery, hospital stay, abdominal pain, fever and abdominal tenderness were analysed. In the follow-up analysis, recurrence, need for surgery, changes in bowel habit, abdominal pain and results of colorectal examinations were analysed. Statistical significance was set at $P < 0{\cdot}050$, two-sided tests. All data analysis was performed using the SPSS® software package version 17.0 (SPSS, Chicago, Illinois, USA).

Results

In total, 669 patients were randomized, of whom 46 were excluded. Seven patients interrupted participation and one patient was excluded because of protocol violation. Thirty-eight patients did not meet the inclusion criteria: 13 had a diagnosis other than diverticulitis, eight were randomized despite previous inclusion in the study, seven had insufficient inclusion criteria (no fever, no inflammatory parameters), and five had other reasons for exclusion (linguistic problems, unclear CT reports and cardiac disease). Five patients were excluded on the day after randomization because of important changes between the preliminary and the definitive CT report, which showed complications of diverticulitis such as abscess formation or free air (*Fig. 1*). Some 623 patients (403 women) with CT-verified acute uncomplicated diverticulitis were enrolled in the study: 309 patients in the no-antibiotics and 314 in the antibiotics group (*Table 3*). The median age was 58 (range 23–88) years and median body mass index (BMI) 27·7 (range 18·4–44·1) kg/m^2.

Clinical characteristics

At the time of admission (all patients had a history of acute abdominal pain and fever), the groups presented with similar symptoms. Some 599 (96·6 per cent) of 620 patients had left lower abdominal pain. Fever (body temperature of 38°C or above) was noted in 557 (89·8 per cent) of 620 patients; 212 (34·2 per cent) of 619 patients reported a change in stool habit with constipation or loose stools; and 49 (7·9 per cent) of 619 had urinary tract symptoms such as

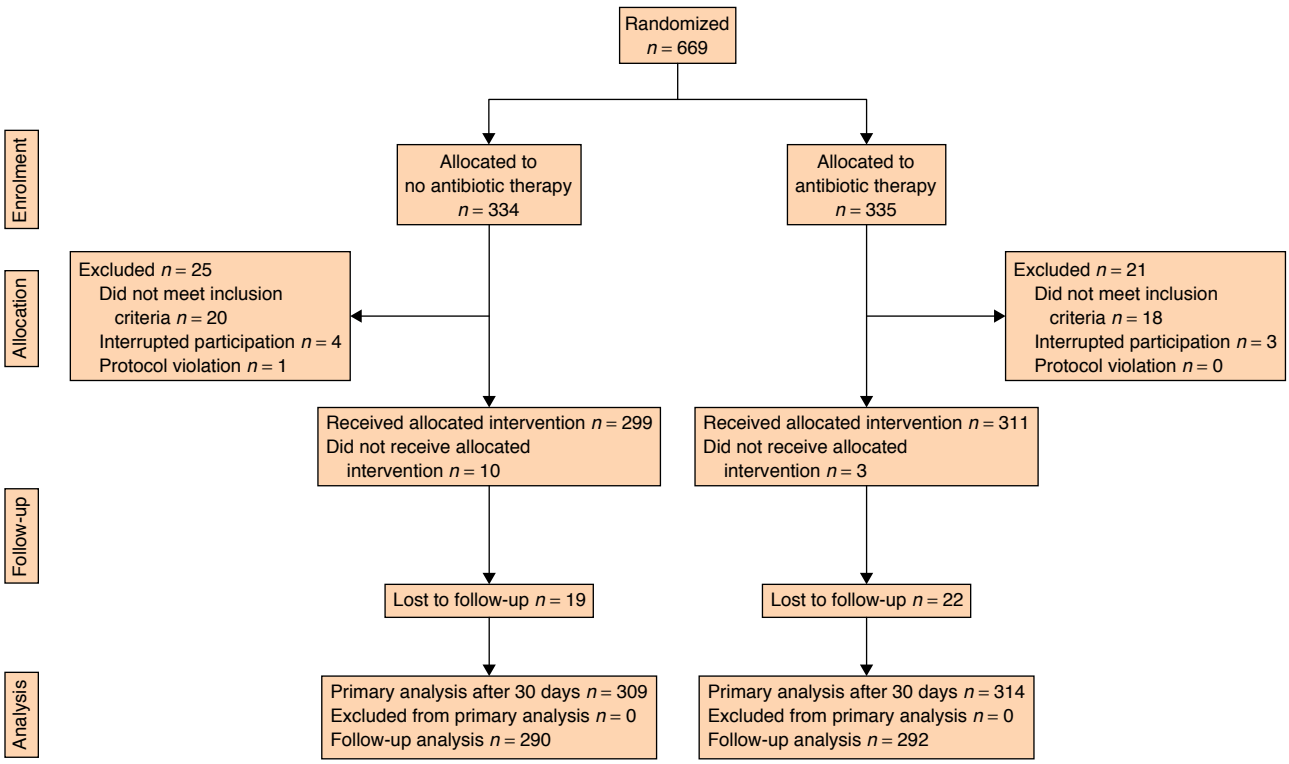

Fig. 1 CONSORT diagram for the trial

Table 3 Numbers of patients per hospital

Hospital	No antibiotics	Antibiotics	Total
Västerås	98 (31·7)	98 (31·2)	196 (31·4)
Danderyd	50 (16·2)	52 (16·6)	102 (16·4)
Norrköping	37 (12·0)	37 (11·8)	74 (11·9)
Uppsala	33 (10·7)	29 (9·2)	62 (10·0)
Reykjavik	22 (7·1)	21 (6·7)	43 (6·9)
Sunderby	17 (5·5)	24 (7·6)	41 (6·6)
Linköping	17 (5·5)	16 (5·1)	33 (5·3)
Hudiksvall	15 (4·9)	15 (4·8)	30 (4·8)
Mora	10 (3·2)	9 (2·9)	19 (3·0)
Gävle	5 (1·6)	7 (2·2)	12 (1·9)
Örebro	5 (1·6)	6 (1·9)	11 (1·8)
Total	309 (100)	314 (100)	623 (100)

Values in parentheses are percentages.

frequent micturition. There were no differences between the two groups with regard to these parameters.

Clinical details are listed in *Table 2*. The two groups were equally balanced regarding age, sex, BMI, co-morbidity and inflammatory parameters such as WBC, CRP level and body temperature. A history of previous diverticulitis was more frequent in the no-antibiotics group ($P = 0{\cdot}020$). Clinical bedside signs, such as pain measured by VAS and tenderness on abdominal palpation at admission, did not differ between the groups.

Abdominal pain, body temperature and abdominal tenderness on palpation decreased rapidly in both groups during the hospital stay (*Fig. 2*). Differences from baseline (the time of admission) for every patient were calculated for VAS, body temperature and tenderness score for each day in hospital. There were no differences between the groups for VAS ($P = 0{\cdot}253$–$0{\cdot}886$). Normalization of body temperature after 2 days was similar in the two groups ($P = 0{\cdot}343$). For the tenderness score, there was a statistically significant difference on the second day ($P = 0{\cdot}041$), with a mean difference from baseline of 0·8 for the no-antibiotics and 1·0 for the antibiotics group. The median hospital stay for both groups was 3 (range 0–25) days.

Primary analysis: complications and emergency surgery during hospital stay

Nine patients (1·4 per cent) suffered from complications, six with sigmoid perforation and three with abscess formation. In the no-antibiotics group, three had

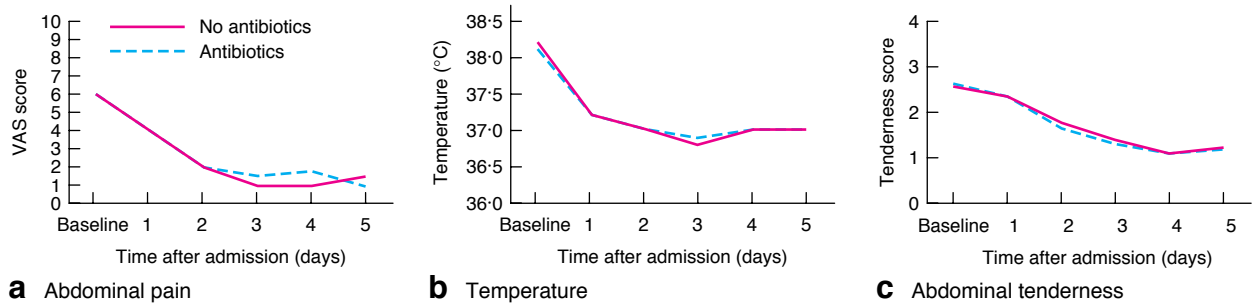

Fig. 2 Clinical bedside signs after admission for acute uncomplicated diverticulitis: **a** mean abdominal pain according to the visual analogue scale (VAS) score (0–10); **b** mean body temperature; **c** mean abdominal tenderness score at palpation (0–4)

perforations and three developed abscesses. In the antibiotics group, three patients had perforations. One patient with a perforation in the no-antibiotics group underwent emergency sigmoid resection but the other five patients with complications were treated without surgery, by means of antibiotics and percutaneous drainage when appropriate. In the antibiotic treatment group, all three patients with perforations underwent emergency sigmoid resection. There were no differences between the groups regarding complications or surgical procedures during the hospital stay (*Table 4*).

Ten patients (3·2 per cent) allocated to no antibiotics were started on antibiotic treatment because of increasing CRP level, fever or abdominal pain. No complications occurred during the hospital stay in these patients. In the antibiotics group, three patients (1·0 per cent) terminated antibiotic therapy because of allergic side-effects (*Fig. 1*). In a logistic regression model adjusting for age, sex, temperature, WBC, CRP, BMI, previous diverticulitis, number of previous episodes of diverticulitis, abdominal pain, abdominal tenderness score, co-morbidity and antibiotic treatment, there was no significant relationship with complications (data not shown).

Table 4 Complications, surgery, hospital stay and recurrent diverticulitis

	No antibiotics ($n = 309$)	Antibiotics ($n = 314$)	P†
Complications	6 (1·9)	3 (1·0)	0·302
Sigmoid perforation	3 (1·0)	3 (1·0)	0·985
Abscess	3 (1·0)	0 (0)	0·080
Sigmoid resections	7 (2·3)	5 (1·6)	0·541
During hospital stay	1 (0·3)	3 (1·0)	0·324
During follow-up	6 (1·9)	2 (0·6)	0·148
Hospital stay (days)*	2·9(1·6)	2·9(1·9)	0·717‡
Recurrent diverticulitis	47 of 290 (16·2)	46 of 292 (15·8)	0·881

Values in parentheses are percentages, unless indicated otherwise; *values are mean(s.d.). †Pearson's χ^2 test, except ‡Student's t test.

Follow-up analysis

In the no-antibiotics group, six patients were operated on during follow-up because of symptomatic diverticular disease, stricture, fistula, recurrent diverticulitis, recurrent diverticulitis with abscess formation, and colonic perforation that occurred during preparation for colonic examination (1 patient each). In the antibiotic treatment group, two patients had surgery for stricture during follow-up. There was no difference between the groups regarding surgery during follow-up (*Table 4*). Of the ten patients who crossed over from the no-antibiotics to the antibiotics arm, none had complications during follow-up although one patient was operated on for symptomatic diverticular disease.

Of the 623 patients, 41 were lost to follow-up. Recurrent diverticulitis occurred in 93 (16·0 per cent) of the remaining 582 patients during follow-up, with no significant difference between the two groups (*Table 4*). In a logistic regression model, adjusting for age, sex, temperature, WBC, CRP, BMI, previous diverticulitis, number of previous episodes of diverticulitis, abdominal pain, abdominal tenderness score, co-morbidity and antibiotic treatment, there was a significant relationship between previous diverticulitis and recurrence (odds ratio 2·78, 95 per cent confidence interval 1·76 to 4·41; $P = 0·009$). Previous diverticulitis explained 5·8 per cent of the variation in recurrence outcome (Nagelkerke R^2). No other variable was related to recurrence.

At the 1-year follow-up, symptoms of abdominal pain and changes in bowel habit did not differ between the groups (*Fig. 3a,b*). Colonic investigations were performed in 545 patients by colonoscopy, barium enema or CT colonography. There was no significant difference between the groups with respect to the findings or extent of diverticulosis (*Fig. 3c*). One patient in the antibiotics group died 9 months after discharge from metastatic gastric cancer. No patient had colorectal malignancy or Crohn's disease in the colon.

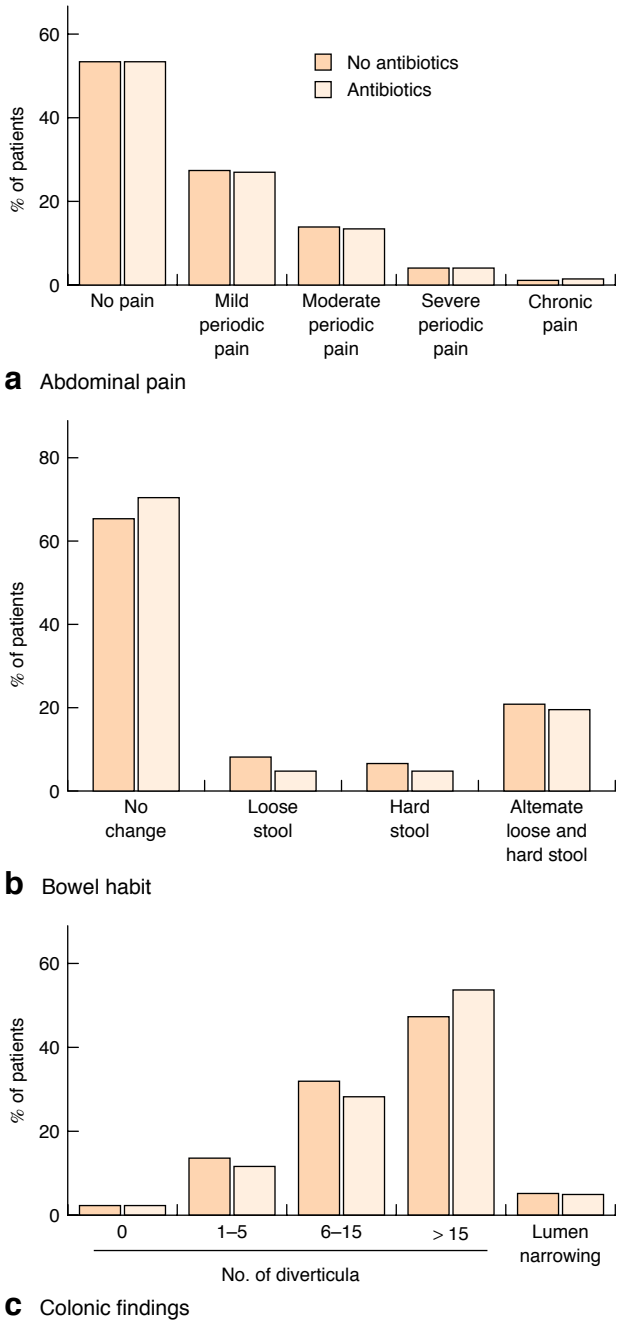

Fig. 3 **a** Abdominal pain at 1-year follow-up. **b** Change in bowel habit at 1-year follow-up. **c** Results of colonic investigations. **a** $P = 0{\cdot}959$, **b** $P = 0{\cdot}275$, **c** $P = 0{\cdot}247$ (Mann–Whitney U test)

Subgroup analysis

Per-protocol analysis, including the ten patients in the no-antibiotics group who received antibiotics, showed no differences between the groups regarding complications, operations, recurrences or hospital stay ($P = 0{\cdot}071$–$0{\cdot}982$).

In selected groups of patients with more severe symptoms and higher inflammatory parameters (CRP level greater than 150 mg/l, WBC 15×10^9 cells/l or above, temperature higher than 38·5°C, abdominal pain score of 8 or more, and tenderness score of 3 or above) there were no significant differences between the groups regarding complications or diverticulitis recurrence ($P = 0{\cdot}087$–$0{\cdot}978$).

When surgery during follow-up was added to the in-hospital complications, there was no significant difference between the two groups ($P = 0{\cdot}121$). When all events including recurrences were analysed, there was still no difference ($P = 0{\cdot}463$).

Discussion

This large multicentre randomized clinical trial of patients with CT-verified acute uncomplicated left-sided diverticulitis demonstrated a low overall complication rate with perforation and abscess formation (1·4 per cent), with no significant differences between patients treated, or not treated with antibiotics. Moreover, no differences were found between the groups with regard to frequency of surgery, length of hospital stay, recurrence of diverticulitis, abdominal pain, or changes in bowel habit after 12 months of follow-up. From these results it may be postulated that antibiotic treatment of acute uncomplicated diverticulitis does not prevent complications, accelerate recovery or prevent recurrence.

According to current guidelines, bowel rest or intake of oral fluids and a 7–10-day regimen of broad-spectrum antibiotics is recommended in patients with uncomplicated diverticulitis[14,15]. This treatment strategy has been reported to be successful in 85–100 per cent of patients[16,17]. The recommendations of antibiotic therapy are based on tradition and expert opinions, and not on evidence derived from controlled trials. There are some prospective studies regarding choice and duration of antibiotic therapy, but none challenging the use of antibiotics in this condition[8]. The only two studies evaluating the need for antibiotics in uncomplicated diverticulitis have been retrospective audits, with all the inherent limitations of such a design, that did not show any benefit of antibiotics[18,19].

There is an escalating problem with antibiotic resistance among bowel pathogens[20,21]. As antimicrobial use generally precedes the emergence of resistance, preventing the spread of resistant pathogens clearly requires optimal use of antibiotics. During the past decade, the prescription of antibiotics for children has been reduced by approximately 50 per cent in Sweden for certain diagnoses[22]. A similar

policy with strict indications for antibiotic use might be adopted for uncomplicated diverticulitis.

Apart from allergic reactions, we did not register any antibiotic side-effects such as antibiotic-associated abdominal pain, nausea, or diarrhoea with or without a *Clostridium difficile* infection. The possible development of such symptoms provides another important reason for reducing the frequent use of antibiotics in these patients.

Eleven departments participated in this study with different inclusion rates, which may raise the question of selection bias. However, both study groups were similar with regard to important clinical symptoms, fever, inflammatory parameters, grade of abdominal pain and tenderness score, co-morbidity, age, sex and BMI. The only variable that differed was previous episodes of diverticulitis, which were less frequent in the antibiotic treatment group. Some studies have reported that perforation is most frequent during the first attack[23–25], which would give patients in the no-antibiotics group a possible advantage in this respect. However, these patients would have been excluded by the CT findings. As the study was randomized, this difference can be regarded as a chance finding. Moreover, the results from logistic regression models adjusting for eventual episodes of previous diverticulitis did not detect any relationship with complications.

It could be argued that some centres included sicker patients than others, but owing to the block randomization and stratification by centre this should not have affected the results. In terms of symptoms and laboratory parameters, this cohort of patients was comparable to those of other studies that, in different ways, have evaluated antibiotic therapy in uncomplicated diverticulitis[17,26]. Moreover, there were no differences between the groups regarding complications or recurrence of diverticulitis in patients with more severe symptoms and higher values for inflammatory parameters.

An important limitation of the study was the failure to register all eligible patients at participating centres in order to clarify the cohort selection. The most significant reason for this was the large number of clinicians per centre involved in the study, where patients were enrolled in the emergency department or on the surgical ward after CT had been performed. Studies on patients with an emergency condition commonly encounter problems in registering all patients and completing the CRFs. A further criticism could be that the study was not blinded, although this might prove to be a strength owing to the lack of a placebo effect in patients in the no-antibiotics group.

The study was designed as a superiority study in order to evaluate the necessity for antibiotics for recovery without complications from acute uncomplicated diverticulitis. The results indicate that antibiotics do not prevent complications. However, the observed complication rate was 1 per cent in the antibiotics group, but almost 2 per cent in the no-antibiotics group. To show a possible significant difference between the groups with a power of 80 per cent, a trial would need to include at least 5500 patients. The logistics needed to include such a large number of patients might prove impossible, and perhaps be clinically irrelevant. A non-inferiority designed study with a lower significance level, however, would require many more patients.

An interesting finding in this study was the low frequency of elective surgery in patients who had an attack of uncomplicated diverticulitis. This situation reflects the Swedish policy of recommending surgery only for complicated diverticulitis.

The study indicates that patients with CT-proven uncomplicated diverticulitis have a very low risk (1·4 per cent) of developing severe complications such as perforations or abscesses. The question is whether or not hospital admission is necessary, and whether patients in that case could return home without antibiotics. The authors will investigate this in their next study.

This study evaluated the need for antibiotic treatment in acute uncomplicated diverticulitis. It showed that antibiotic therapy does not prevent surgical complications or recurrence, and does not shorten hospital stay. Antibiotics should be reserved mainly for patients with complicated diverticulitis.

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Collaborators

The AVOD study group consists of A. Chabok, K. Smedh, E. Strand (Västerås Central Hospital), L. Påhlman (Uppsala University Hospital), F. Hjern (Danderyd University Hospital), S. Haapaniemi (Vrinnevi Hospital Norrköping), T. Stefansson (National University Hospital,

Reykjavik, Iceland), M. Sundén (Sunderbys Hospital), P. Myrelid (Linköping University Hospital), U. Ersson (Huddiksvall Hospital), H. Laurell (Mora Hospital), G. Liljegren (University Hospital Örebro) and A. Faraj (Gävle Central Hospital).

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