Randomized clinical trial

Randomized clinical trial of observational *versus* antibiotic treatment for a first episode of CT-proven uncomplicated acute diverticulitis

L. Daniels[1], Ç. Ünlü[1,4], N. de Korte[5], S. van Dieren[2], H. B. Stockmann[6], B. C. Vrouenraets[3], E. C. Consten[7], J. A. van der Hoeven[8], Q. A. Eijsbouts[5], I. F. Faneyte[9], W. A. Bemelman[1], M. G. Dijkgraaf[2] and M. A. Boermeester[1], for the Dutch Diverticular Disease (3D) Collaborative Study Group

[1]Department of Surgery and [2]Clinical Research Unit, Academic Medical Centre, University of Amsterdam, and [3]Department of Surgery, Onze Lieve Vrouwe Gasthuis West, Amsterdam, and Departments of Surgery, [4]Medical Centre Alkmaar, Alkmaar, [5]Spaarne Gasthuis Hospital, Hoofddorp, [6]Spaarne Gasthuis Hospital, Haarlem, [7]Meander Medical Centre, Amersfoort, [8]Albert Schweitzer Hospital, Dordrecht, and [9]Ziekenhuisgroep Twente Hospital, Almelo, The Netherlands

Correspondence to: Dr L. Daniels, Department of Surgery (G4), Academic Medical Centre, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands (e-mail: l.daniels@amc.uva.nl)

Background: **Antibiotics are advised in most guidelines on acute diverticulitis, despite a lack of evidence to support their routine use. This trial compared the effectiveness of a strategy with or without antibiotics for a first episode of uncomplicated acute diverticulitis.**

Methods: **Patients with CT-proven, primary, left-sided, uncomplicated, acute diverticulitis were included at 22 clinical sites in the Netherlands, and assigned randomly to an observational or antibiotic treatment strategy. The primary endpoint was time to recovery during 6 months of follow-up. Main secondary endpoints were readmission rate, complicated, ongoing and recurrent diverticulitis, sigmoid resection and mortality. Intention-to-treat and per-protocol analyses were done.**

Results: **A total of 528 patients were included. Median time to recovery was 14 (i.q.r. 6–35) days for the observational and 12 (7–30) days for the antibiotic treatment strategy, with a hazard ratio for recovery of 0·91 (lower limit of 1-sided 95 per cent c.i. 0·78; $P = 0·151$). No significant differences between the observation and antibiotic treatment groups were found for secondary endpoints: complicated diverticulitis (3·8 *versus* 2·6 per cent respectively; $P = 0·377$), ongoing diverticulitis (7·3 *versus* 4·1 per cent; $P = 0·183$), recurrent diverticulitis (3·4 *versus* 3·0 per cent; $P = 0·494$), sigmoid resection (3·8 *versus* 2·3 per cent; $P = 0·323$), readmission (17·6 *versus* 12·0 per cent; $P = 0·148$), adverse events (48·5 *versus* 54·5 per cent; $P = 0·221$) and mortality (1·1 *versus* 0·4 per cent; $P = 0·432$). Hospital stay was significantly shorter in the observation group (2 *versus* 3 days; $P = 0·006$). Per-protocol analyses were concordant with the intention-to-treat analyses.**

Conclusion: **Observational treatment without antibiotics did not prolong recovery and can be considered appropriate in patients with uncomplicated diverticulitis. Registration number: NCT01111253 (http://www.clinicaltrials.gov).**

Paper accepted 2 August 2016

Published online 30 September 2016 in Wiley Online Library (www.bjs.co.uk). **DOI:** 10.1002/bjs.10309

Introduction

The natural history of acute diverticulitis is mild and most patients are treated successfully by conservative measures[1–4]. It is uncertain, however, whether antibiotics are necessary in uncomplicated acute diverticulitis. Two retrospective comparative studies[5,6] and one randomized trial[7], which included about 40 per cent recurrent diverticulitis, have compared observational and antibiotic treatment in patients with uncomplicated acute diverticulitis. These studies have suggested that antibiotic treatment is not more successful than observational treatment. Most international guidelines remained unchanged and still recommend antibiotics[8–10]. Whether or not antibiotics are used varies between countries and disciplines[11–13]. In a recent review[14] it was stressed that further high-quality RCTs are required for the decision on antibiotics.

Importantly, antibiotic treatment is accompanied by several drawbacks. Besides costs, there are the risks of adverse effects and allergic reactions. Escalating antimicrobial resistance owing to antibiotic overuse is a global threat that is already being addressed in several fields in clinical medicine[15]. This pragmatic randomized trial tested the effectiveness of a strategy with or without antibiotics for a first episode of uncomplicated diverticulitis.

Methods

The DIABOLO (DIverticulitis: AntiBiotics Or cLose Observation?) trial was a multicentre (22 clinical sites), open-label, pragmatic, RCT of two strategies in patients with uncomplicated acute diverticulitis[16]. The study design reflects clinical practice in which the two studied approaches co-exist as standards of care.

This trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines (ClinicalTrials.gov NCT01111253; EudraCT number 2009-015004-26). The institutional review board (IRB) and Dutch Central Committee on Research Involving Human Subjects approved the study protocol[16]. An independent Data and Safety Monitoring Board (DSMB) evaluated the progress and safety of the trial at regular intervals. All serious adverse events were reported to the DSMB and IRB. An endpoint assessment committee adjudicated primary and main secondary endpoints.

Setting and participants

Patients were eligible if they had a first episode of left-sided, uncomplicated, acute diverticulitis, confirmed within 24 h by CT. Only modified Hinchey stages 1a–b (abscess size up to 5 cm) and Ambrosetti's 'mild' diverticulitis stage were included[17,18]. Main exclusion criteria were previous radiologically proven diverticulitis, higher modified Hinchey stages or Ambrosetti's 'severe' diverticulitis stage plus sepsis as defined by the American College of Chest Physicians/Society of Critical Care Medicine[19], and antibiotic use in the previous 4 weeks (*Table 1*). All participants provided written informed consent.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Only left-sided uncomplicated (mild) acute diverticulitis
	Clinical suspicion of acute diverticulitis. Ultrasound- or CT-proven diverticulitis at acute diagnostic evaluation. In the event of diverticulitis-negative ultrasound examination in patients with clinically suspected acute diverticulitis, intravenous contrast-enhanced CT mandatory for confirmation of diverticulitis or exclusion of other pathology. CT for Hinchey/Ambrosetti classification (a CT-based classification system) needed for all patients, but could be delayed by 1 day in those with ultrasound diagnosis. Stage of diverticultis defined according to the modified Hinchey/Ambrosetti classification; only stages 1a and 1b and 'mild' diverticulitis (1a, confined pericolic inflammation; 1b, confined small (< 5 cm) pericolic abscess) included
	Informed consent given by patient
Exclusion criteria	Previous ultrasound- and/or CT-proven episode of diverticulitis
	Ultrasonographic and/or CT suspicion of colonic cancer
	Inflammatory bowel disease
	Modified Hinchey stages 2, 3 and 4, or Ambrosetti's 'severe' diverticulitis stage, which require surgical or percutaneous treatment
	Other disease with expected survival < 6 months
	Contraindication to use of the study medication (e.g. advanced renal failure or allergy to all antibiotics used in this study)
	Pregnant, breastfeeding
	ASA fitness grade > III
	Immunocompromised
	Clinical suspicion of bacteraemia (sepsis[19])
	Inability to read/understand and fill in questionnaires
	Antibiotic use in the 4 weeks before inclusion

Randomization and interventions

Participants were assigned randomly to either an observational or antibiotic treatment strategy. Randomization was controlled centrally using a computerized system, with a random varying block size of two or four patients, stratified by Hinchey classification and centre. The procedure took place in the participating centres after all inclusion and exclusion criteria had been verified, and entered in the standardized secured web-based form. The outcome was generated automatically, thereby preserving concealment of the upcoming allocation sequence. Outcome assessors and investigators analysing data were masked to the allocation until analyses were finished.

Based on the practice guidelines of the Dutch Antibiotic Policy Committee and the American Society of Colon and Rectal Surgeons (ASCRS), amoxicillin–clavulanic acid was chosen as broad-spectrum antibiotic treatment[20,21]. The regimen consisted of a 10-day course, with intravenous administration of 1200 mg four times daily for at least 48 h, after which the route could be switched, if tolerated, to oral administration of 625 mg three times daily. In the event of allergy, a switch was made to the combination of ciprofloxacin and metronidazole.

With the antibiotic treatment strategy, the use of antibiotics led to admission of all patients on the premise that

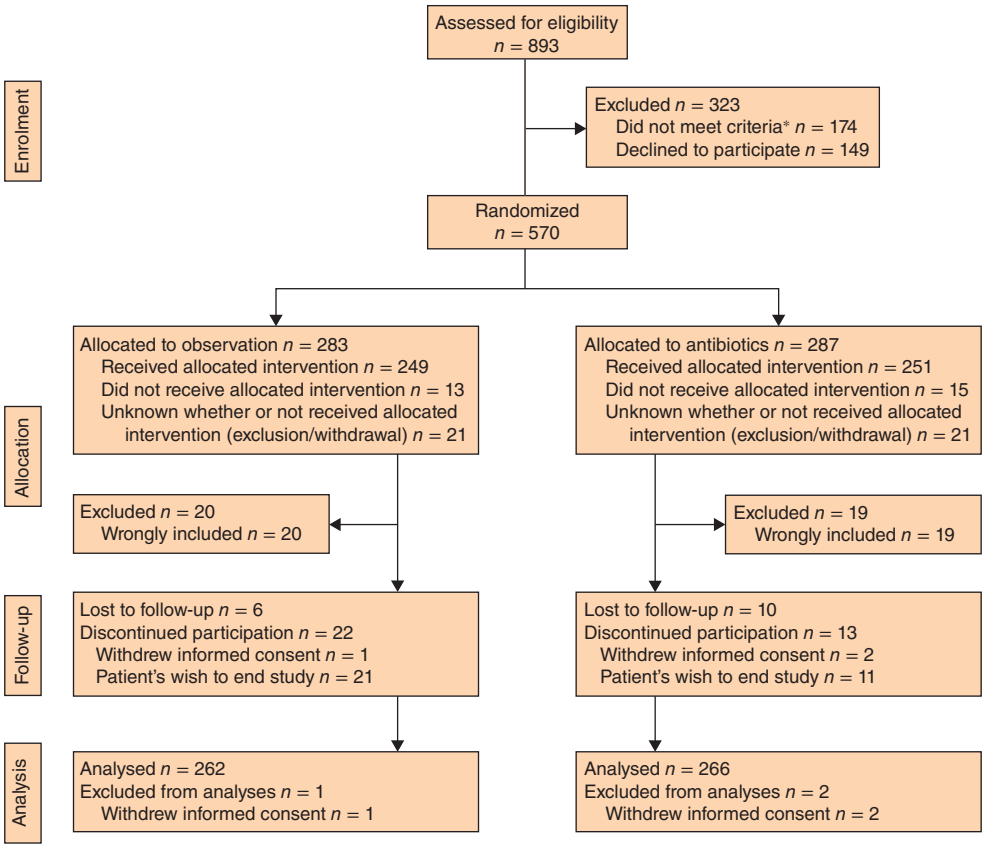

Fig. 1 CONSORT diagram for the trial. *Patients could have more than one reason for ineligibility for the study

treatment was started intravenously. Patients allocated to observational treatment could be treated directly in an outpatient setting when the following criteria were met: toleration of a normal diet (solid food and more than 1 litre oral fluids), temperature less than 38°C, pain score measured on a visual analogue scale (VAS) below 4 (with paracetamol at the most), capable of self-support at same level as before illness, and patient acceptance.

In both strategies, CT was repeated in the event of clinical deterioration. In the observation group, deterioration, proven subsequent complicated diverticulitis or another infectious focus dictated starting antibiotics. Start criteria were: temperature above 39°C, positive blood cultures and sepsis[19]. Patients were discharged if they fulfilled above-mentioned criteria.

Outcomes and follow-up

The primary outcome was time to recovery during 6 months of follow-up. Full recovery was defined by meeting the following criteria: discharge from hospital, normal diet, temperature less than 38°C, VAS pain score below 4 (with no use of daily pain medication), and resumption of preillness working activities as assessed by a daily patient diary.

Secondary outcomes were: days spent outside hospital in the 6-month period, readmission rate, occurrence of complicated diverticulitis (abscess, perforation, obstruction/stricture, diverticular bleeding or fistula), ongoing diverticulitis and acute diverticulitis recurrence, need for sigmoid resection or other (non-)surgical intervention within 6 and 12 months of follow-up, (serious) adverse events, side-effects of initial antibiotic treatment and all-cause mortality.

Details of the patients' adherence to the antibiotic regimen were obtained by telephone. At 2 and 6 months, the patient visited the outpatient clinic; follow-up at 12 and 24 months was by telephone. A standard case record form was used for collection of study variables. Oracle® Clinical, with internet-based remote data capture version 4.5.3 (Oracle, Redwood Shores, California, USA), was used for entering, managing and validating data.

Table 2 Baseline characteristics of patients according to study group

	Observation ($n = 262$)	Antibiotics ($n = 266$)
Age (years)*	57·4 (48·5–64·6)	56·3 (48·5–63·8)
Sex ratio (M : F)	135 : 127	132 : 134
Known antibiotic allergy	36 (13·7)	52 (19·5)
Penicillin allergy	5 (1·9)	14 (5·3)
Co-morbidity†	113 (43·1)	121 (45·5)
ASA fitness grade‡		
I	174 (66·4)	156 (58·6)
II	81 (30·9)	96 (36·1)
III	7 (2·7)	14 (5·3)
BMI (kg/m^2)*	26·4 (24·3–29·0) ($n = 242$)	27·2 (24·5–30·1) ($n = 250$)
Duration of gastrointestinal complaints (days)*	2 (1–4)	3 (1–5)
Body temperature (°C)*	37·3 (36·9–38·0)	37·3 (36·9–38·0)
Abdominal pain (VAS score, 1–10)*	6 (4–8) ($n = 223$)	6 (5–8) ($n = 219$)
Location of abdominal pain, left lower quadrant isolated	119 (45·4)	125 (47·0)
Vomiting	20 (7·6)	27 (10·2)
White blood cell count ($\times 10^9$ cells/l)*	12·5 (10·2–14·8)	12·0 (10·0–14·2)
C-reactive protein (mg/l)*	73·0 (44·5–125·5)	82·7 (42·0–128·3)
> 50 mg/l	188 of 261 (72·0)	191 (71·8)
Imaging diagnosis		
Ultrasonography	171 (65·3)	176 (66·2)
CT	258 (98·5)	259 (97·4)
Hinchey category 1a§	236 (90·1)	250 (94·0)

Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r.). †Includes cardiovascular disease and/or pulmonary disease and/or renal failure and/or diabetes mellitus. ‡Grade I, normal, healthy patient; grade II, patient with mild systemic disease; grade III, patient with severe systemic disease. §(Modified) Hinchey classification category 1a: colonic wall thickening and/or confined pericolic inflammation. VAS, visual analogue scale.

Statistical analysis

A *post hoc* power analysis was performed to detect a difference in time to recovery of more than 5 days between observational treatment and antibiotic treatment within a follow-up period of 180 days. This analysis replaced the originally published sample size calculation, mainly because the observed median time to recovery following antibiotic treatment as the reference strategy was considerably shorter than that anticipated at the time of study design[16]. Furthermore, the published sample size calculation was inaccurate (by reporting 21 days to recovery as the reference case where it should have been 19 days). In addition, the hazard ratio of recovery corresponding to a non-inferiority margin of 5 days or less has been spelled out here.

With at least 262 patients observed in each group based on intention to treat and a one-sided 0·05 significance level, an exponential maximum likelihood test of equality of time-to-recovery curves had more than 99 per cent power to detect a difference between a recovery rate under observational treatment of 0·0408 and a recovery rate under antibiotic treatment of 0·0578 (constant hazard ratio of recovery 0·706) within a follow-up period of 180 days. The hazard ratio of full recovery below 0·706 corresponds to a difference between a median above 17 days to recovery in the observational treatment group and the observed median of 12 days to recovery in the antibiotic group. With at least 255 patients in each group based on a per-protocol approach, the test had a power of 98 per cent.

The target sample size of 528 evaluable patients in the original protocol was achieved after extension of the accrual period to October 2012 following the recommendation of the DSMB to compensate for a higher drop-out rate than the 1 per cent initially anticipated, owing to incorrect inclusions (*Table S1*, supporting information).

All analyses followed the intention-to-treat principle. Continuous variables are expressed as median (i.q.r.) as these data are not normally distributed, with analysis using Mann–Whitney *U* test. Categorical variables were compared by means of χ^2 test, Fisher's exact test or linear-by-linear association, as appropriate.

For the primary outcome, Kaplan–Meier time-to-recovery curves were plotted and median (i.q.r.) times reported. A Cox proportional hazards regression was used to obtain hazard ratios for the observational treatment strategy compared with the antibiotic strategy, without and with adjustment for Hinchey classification and centre.

Subgroup analyses were performed to assess differences within Hinchey classes and centres. For each model, the Cox proportional hazards assumption was tested by inspecting the log–log plots visually, with no deviations detected. The lower limit of the one-sided 95 per cent confidence interval for the hazard ratio was calculated using the lower limit of the two-sided 90 per cent c.i.[22]. Supplementary analyses and considerations relating to log rank testing and on ignoring censored observations in the present data set are provided in *Appendix S1* (supporting information). The difference in VAS scores between the groups was assessed using the area under the curve and, given the normal distribution, tested using a Student's *t* test.

Prespecified subgroup analyses for the main secondary endpoints and per-protocol analyses were carried out. Multiple testing adjustment was done by using the Benjamini–Hochberg method to control for the false discovery rate. $P < 0{\cdot}050$ was considered statistically significant. Statistical analyses were carried out using SPSS® version 21.0 (IBM, Armonk, New York, USA) and adjustment for multiple testing was done in R version 2.13.1 (R Foundation for Statistical Computing, Vienna, Austria).

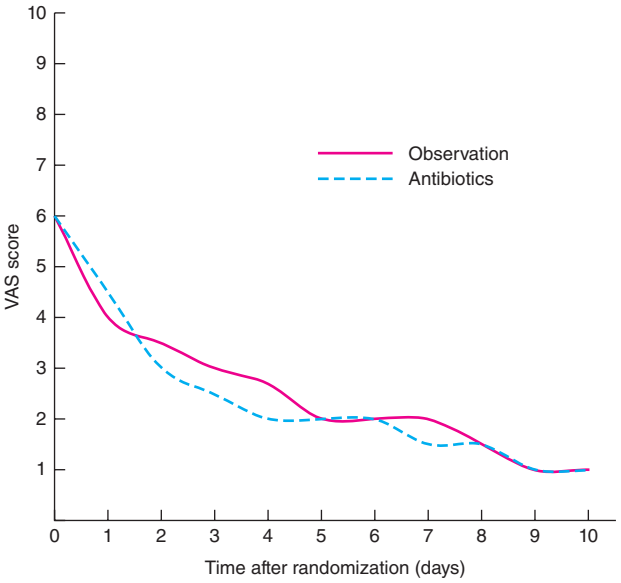

Fig. 2 Median scores for abdominal pain measured on a visual analogue scale (VAS) (range 0–10) from admission until day 10 for patients with uncomplicated acute diverticulitis assigned to an observational or antibiotic treatment strategy. $P = 0{\cdot}379$ (Student's *t* test)

Results

From 1 June 2010 to 14 October 2012, 893 consecutive patients with diverticulitis were screened at surgical and gastroenterological departments in 22 Dutch centres (*Fig. 1*)[23]. Some 323 patients were excluded (*Table S2*, supporting information) and the remaining 570 patients were assigned randomly to observational (283) or antibiotic (287) treatment. Of these, 39 patients were wrongly included and were not eligible to participate (*Table S3*, supporting information). Primary analyses included 528 patients (*Table S4*, supporting information). Clinical characteristics of patients who underwent randomization were mostly similar to those of patients who were eligible but not randomized because they declined participation (*Table S5*, supporting information)

Baseline characteristics were distributed evenly, though ASA fitness grade was somewhat higher in the antibiotic group ($P = 0{\cdot}036$) (*Table 2*). VAS scores declined rapidly in both groups within the 10 days from time of admission (*Fig. 2*) and there were no significant differences in VAS pain score over time ($P = 0{\cdot}379$). The rate of positive blood cultures did not differ significantly: 5·9 per cent in the observation *versus* 2·8 per cent in the antibiotic group ($P = 0{\cdot}285$). Bacterial resistance was noted twice: in one culture to penicillin and clindamycin, and in another to metronidazole. Twenty-three *Clostridium* toxin tests were performed on clinical indication in 22 patients (14 patients in the observation and 8 in the antibiotic group); all were negative.

Study treatment

All except one patient allocated to antibiotic treatment (265 of 266, 99·6 per cent) started antibiotics, with a median interval of 0 days from randomization. Amoxicillin–clavulanic acid was the most prescribed antibiotic (250 of 265, 94·3 per cent) (*Table S6*, supporting information). The median duration was 10·0 (i.q.r. 10·0–10·0) days and 94·7 per cent (252 of 266) completed the 10-day treatment course. In three patients (1·1 per cent) antibiotics were discontinued because of side-effects or allergic reactions, including anaphylactic shock in one patient. Antibiotics were discontinued incorrectly in 11 patients (4·1 per cent of 266) assigned to antibiotic treatment (*Table S7*, supporting information).

Time to recovery

The median time to recovery during 6 months' follow-up was 14 (i.q.r. 6–35) days for patients who had observational treatment *versus* 12 (7–30) days among those in the antibiotic treatment group. An observational treatment strategy, compared with an antibiotic treatment strategy,

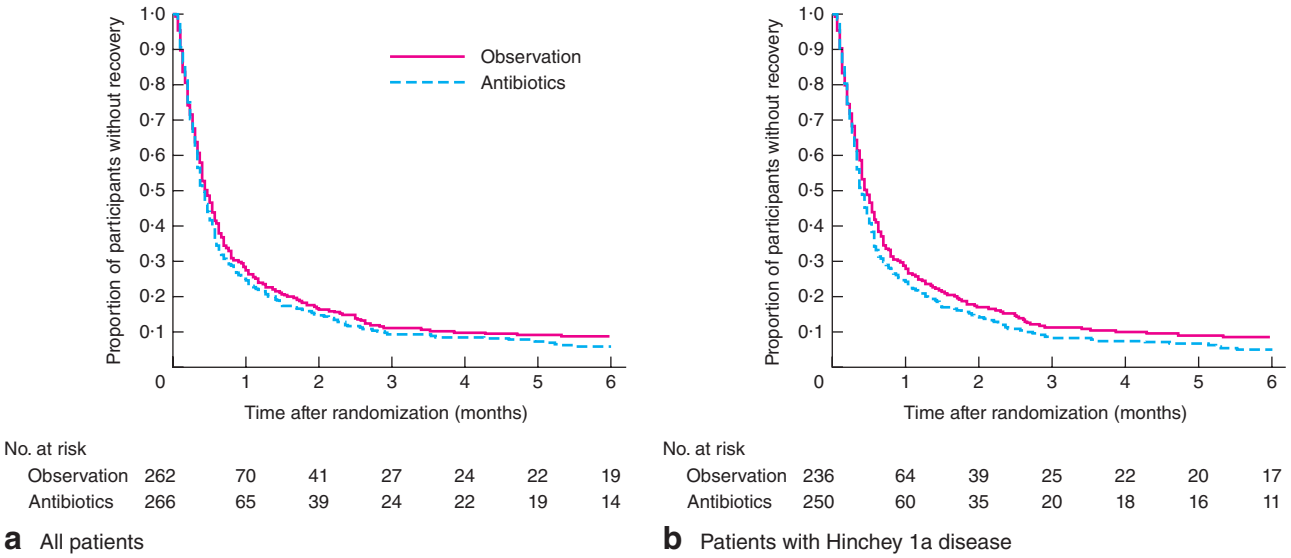

Fig. 3 Kaplan–Meier survival curves for time to recovery in intention-to-treat analyses: **a** all patients and **b** patients with Hinchey 1a disease. **a** $P = 0{\cdot}151$, **b** $P = 0{\cdot}081$ (1-sided P values for hazard ratio determined by Cox regression analysis)

was associated with a hazard ratio for full recovery of 0·91 (lower limit of 1-sided 95 per cent c.i. 0·78; $P = 0{\cdot}151$) (*Fig. 3a*). The hazard ratio was not affected by adjustment for Hinchey classification and centre (hazard ratio 0·90, lower limit of 1-sided 95 per cent c.i. 0·77; $P = 0{\cdot}118$). Within the Hinchey 1a subgroup, with a median time to recovery of 14 (6–35) in the observational and 12 (6–28) days in the antibiotic group, the hazard ratio for recovery was 0·88 (lower limit of 1-sided 95 per cent c.i. 0·75; $P = 0{\cdot}081$) (*Fig. 3b*).

Secondary outcomes

Within 6 months, 234 patients (89·3 per cent) in the observation group and 248 (93·2 per cent) in the antibiotic group fulfilled the recovery criteria ($P = 0{\cdot}183$). In the observation group more patients were treated as outpatients after evaluation in the emergency department (13·0 *versus* 0·4 per cent; $P = 0{\cdot}006$), and median duration of initial hospital stay was shorter owing to the intravenous administration of antibiotics in the antibiotic group (2 *versus* 3 days; $P = 0{\cdot}006$) (*Table 3*). Readmission rates were comparable; 17·6 per cent in the observation *versus* 12·0 per cent in the antibiotic group ($P = 0{\cdot}148$). Of the 34 patients in the observation group treated as outpatients, 32 were never admitted within the first 6 weeks after randomization. The number of days spent outside the hospital, expressed as proportion of the follow-up duration of 180 days, was higher in the observation group (0·989 *versus* 0·983; $P = 0{\cdot}006$); however, this difference may not be of clinical significance. [Correction added on 17 November 2016, after first online publication: $P = 0{\cdot}00$ should be $P = 0{\cdot}006$.]

Complicated diverticulitis rates during 6 months' follow-up were comparable: 3·8 per cent in the observation *versus* 2·6 per cent in the antibiotic group ($P = 0{\cdot}377$). The proportion of patients whose disease progressed to complicated diverticulitis during the initial admission was small (1·1 and 2·3 per cent respectively; $P = 0{\cdot}390$). Ongoing diverticulitis was noted in 19 patients (7·3 per cent) in the observation group and 11 (4·1 per cent) in the antibiotic group ($P = 0{\cdot}183$). The proportion of patients with recurrent diverticulitis was similar in the two groups (3·4 *versus* 3·0 per cent; $P = 0{\cdot}494$). Rates of sigmoid resection were comparable (3·8 *versus* 2·3 per cent; $P = 0{\cdot}323$), for both emergency resection (0·8 *versus* 1·1 per cent; $P = 0{\cdot}553$) and elective resection (3·1 *versus* 1·1 per cent; $P = 0{\cdot}254$). In both groups the most common reason for sigmoid resection was colonic obstruction (3 of 10 in observation group *versus* 2 of 6 in antibiotic group), followed by perforation (2 of 10 *versus* 2 of 6) (*Table S8*, supporting information).

Some 86·6 and 90·2 per cent of patients in the observation and antibiotic groups respectively had a follow-up duration of 12 months or more. At 12 months, treatment groups were comparable in terms of the main secondary outcomes readmission rate, complicated, ongoing and recurrent diverticulitis rate, and overall need for sigmoid resection (7·0 per cent *versus* 3·8 per cent; $P = 0{\cdot}057$) (*Table S9*, supporting information).

Table 3 Intention-to-treat analyses of secondary outcomes among patients with uncomplicated acute diverticulitis assigned to an observational or antibiotic treatment strategy

	Observation ($n = 262$)	Antibiotics ($n = 266$)	Unadjusted P¶	Adjusted P**
Outpatient treatment	34 (13·0)	1 (0·4)	< 0·001	0·006
Duration of initial admission (days)*	2 (1–3)	3 (2–3)	< 0·001#	0·006
Recovery within 6 months	234 (89·3)	248 (93·2)	0·055	0·183
Readmission within 6 months	46 (17·6)	32 (12·0)	0·037	0·148
Total number of readmissions	66	35		
Proportion of time outside hospital within 6 months	0·989 (0·978–0·994)	0·983 (0·978–0·989)	< 0·001#	0·006
Complicated diverticulitis within 6 months‡	10 (3·8)	7 (2·6)	0·220	0·377
Abscess (> 5 cm)	2 (0·8)	2 (0·8)	0·682	0·682
Perforation	3 (1·1)	3 (1·1)	0·650	0·678
Obstruction	4 (1·5)	2 (0·8)	0·336	0·448
Fistula	1 (0·4)	0 (0)	0·496	0·553
Bleeding	2 (0·8)	0 (0)	0·246	0·390
At index admission	3 (1·1)	6 (2·3)	0·260	0·390
Intervention‡				
Percutaneous	2 (0·8)	1 (0·4)	0·494	0·553
Surgery	8 (3·1)	5 (1·9)	0·192	0·354
Ongoing diverticulitis within 6 months	19 (7·3)	11 (4·1)	0·061	0·183
Imaging-proven	10	5		
Needing admission	15	4		
Recurrent diverticulitis within 6 months	9 (3·4)	8 (3·0)	0·391	0·494
Imaging-proven	7	4		
Needing admission	4	5		
Sigmoid resection within 6 months	10 (3·8)	6 (2·3)	0·148	0·323
Emergency	2 (0·8)	3 (1·1)	0·507	0·553
Elective	8 (3·1)	3 (1·1)	0·106	0·254
Morbidity‡§	127 (48·5)	145 (54·5)	0·083	0·221
Mild	89 (34·0)	114 (42·9)	0·018	0·086
Serious	69 (26·3)	61 (22·9)	0·182	0·354
Antibiotic-related	1 (0·4)	22 (8·3)	< 0·001	0·006
Mortality§	3 (1·1)	1 (0·4)	0·306	0·432

Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r.). †With a maximum follow-up duration of 180 days, without adjusting for a median 1 day longer index admission in the antibiotic treatment group. ‡Patients could have more than one type of complicated diverticulitis, intervention and morbidity. §At a median duration of follow-up of 711 (i.q.r. 366–732) days in the observation group and 732 (366–732) days in the antibiotic group ($P = 0·204$). ¶χ^2 or Fisher's exact test, except #Mann–Whitney U test. **Multiple comparison adjustment using Benjamini–Hochberg correction. [Correction added on 17 November 2016, after first online publication: update made to sixth entry in first column.]

Adverse events

No significant between-group differences were observed in the occurrence of mild ($P = 0·086$) and serious ($P = 0·354$) adverse events (*Table 3*). As expected, antibiotic-related adverse events, of which all but one were graded as mild, were more frequent in the antibiotic group (0·4 *versus* 8·3 per cent; $P = 0·006$). Mortality rates were no different (1·1 *versus* 0·4 per cent; $P = 0·432$).

Subgroup and per-protocol analyses

No significant differences in the primary outcome, time to recovery, were seen within subgroups of centre and Hinchey classification (*Fig. 3b*; *Fig. S1*, supporting information). In the Hinchey 1a subgroup (486 patients) secondary outcomes were in line with those of the main analyses, but in the Hinchey 1b subgroup (42) no significant differences were found between the two groups (*Table S10*, supporting information).

A total of 517 patients were included in the per-protocol analyses. Results were in accordance with those of intention-to-treat analyses. The median time to recovery was 14 (i.q.r. 6–35) days with observation and 12 (7–31) days with antibiotics (*Fig. S2*, supporting information), associated with a hazard ratio for recovery of 0·93 (lower limit of 1-sided 95 per cent c.i. 0·80; $P = 0·200$). This was not affected by adjustment for Hinchey classification and centre (hazard ratio 0·91, lower limit of 1-sided 95 per cent c.i. 0·78; $P = 0·158$). Within the Hinchey 1a subgroup, with a median time to recovery of 14 (6–35) days in the observation and 12 (6–31) days in the antibiotic group, the hazard ratio for recovery was 0·89 (lower limit of 1-sided

95 per cent c.i. 0·76; $P = 0·113$). The secondary outcomes were similar to those of the intention-to treat analyses (*Tables S11–S13*, supporting information).

Discussion

In this pragmatic RCT, an observational strategy for a first episode of CT-proven uncomplicated acute diverticulitis was not inferior to treatment with antibiotics. The duration of initial admission was longer and the rate of antibiotic-related adverse events higher in the antibiotic group. These results suggest that antibiotics can be omitted in patients with a first episode of uncomplicated (Hinchey I), left-sided acute diverticulitis.

Treatment without antibiotics is controversial, as guidelines have remained unchanged despite evidence from two observational studies[5,6] and one RCT[7] indicating that antibiotics have no benefit. The previous RCT evaluated 623 patients, but some drawbacks of its methodological design may account for the lack of change in clinical practice[7]. The problems were: 40 per cent of patients had recurrent rather than primary diverticulitis, there was a long accrual period, and no standardized antibiotic treatment may have resulted in performance bias[7,8,14]. The possibility that uncomplicated diverticulitis may not require antibiotic treatment has been raised in recent literature[24]. In the latest ASCRS practice parameters[8], the Swedish trial is discussed and deemed in need of confirmation. Meanwhile, two retrospective cohort studies[25,26] have confirmed that a no-antibiotic policy for acute uncomplicated diverticulitis is feasible and safe.

There were some noteworthy limitations. Accrual rates between centres were notably different. Selection bias could have been introduced. The authors anticipate that the large number of participating hospitals evened out these possible effects. Importantly, the study's block randomization and stratification by centre should also control for such confounding. Although patients with recurrent diverticulitis were excluded, patients who had experienced an undetected previous episode without receiving medical care, or who had been treated by general practitioners without a definitive diagnosis, were not excluded by definition. Owing to multiple endpoints, the possibility of a type II error existed and the rate of every negative outcome was higher in the observation group. Therefore, groups were compared for a composite endpoint, with no significant differences found.

This trial, like most others, lacked power to detect smaller subgroup effects. The present results suggest that antibiotics may also not be necessary in patients with Hinchey 1b diverticulitis. The inclusion of 1b disease may be considered controversial, but small abscesses are usually managed without percutaneous drainage[27]. There are no other reports on observational *versus* antibiotic management of Hinchey 1b disease. Omitting antibiotics in the treatment of uncomplicated acute diverticulitis should be limited to Hinchey 1a until larger Hinchey 1b samples have been examined. Moreover, recommendations for patients with significant co-morbidity or inflammatory bowel disease, and those who are pregnant or immunocompromised, cannot be made based on the present results. Patients with body temperature exceeding 39°C, sepsis[24] and/or positive blood cultures warrant antibiotic treatment.

Collaborators

Members of the 3D Collaborative Study Group are: M. A. Boermeester, L. Daniels, Ç. Ünlü, S. Van Dieren, M. G. Dijkgraaf, W. A. Bemelman, C. E. M. Glaap, A. Croonen (Academic Medical Centre, University of Amsterdam, Amsterdam); M. A. Cuesta (VU University Medical Centre, Amsterdam); H. B. Stockmann, J. Kuijvenhoven, R. Buijsman, S. Den Uil (Kennemer Gasthuis Hospital, Haarlem); N. De Korte, Q. A. Eijsbouts, P. R. De Reuver (Spaarne Hospital, Hoofddorp); B. C. Vrouenraets, J. B. Tuynman (Saint Lucas Andreas Hospital, Amsterdam); E. C. Consten, B. J. M. Van de Wall, M. A. W. Stam (Meander Medical Centre, Amersfoort); R. M. H. Roumen, W. Truin, R. Wijn (Máxima Medical Centre, Veldhoven); M. F. Gerhards, K. F. D. Kuhlmann (Onze Lieve Vrouw Gasthuis Hospital, Amsterdam); E. S. Van der Zaag, J. E. Biemond (Gelre Hospital, Apeldoorn); R. J. Klicks, N. Dhar (BovenIJ Hospital, Amsterdam); H. A. Cense, G. H. De Groot, Y. Pikoulin, G. H. Van Ramshorst, L. L. Hoornweg (Red Cross Hospital, Beverwijk); J. A. Van der Hoeven, L. Koet (Albert Schweitzer Hospital, Dordrecht/Zwijndrecht); A. A. W. Van Geloven, M. Emous (Tergooi Hospital, Hilversum); I. F. Faneyte, A. T. P. M. Claassen, S. Mollink (Ziekenhuisgroep Twente Hospital, Almelo/Hengelo); D. J. A. Sonneveld, L. Bouvé, G. M. P. Diepenhorst (Westfriesgasthuis Hospital, Hoorn); W. J. Vles, B. R. Toorenvliet (Ikazia Hospital, Rotterdam); J. F. Lange (Erasmus University Medical Centre, Rotterdam); G. H. H. Mannaerts, B. A. Grotenhuis, R. J. De Vos tot Nederveen Cappel, E. B. Deerenberg (Saint Franciscus Hospital, Rotterdam); A. C. T. M. Depla, S. Bruin, X. Vos (Slotervaart Hospital, Amsterdam); J. J. G. Scheepers (Reinier de Graaf Gasthuis Hospital, Delft); M. J. Boom (Flevo Hospital, Almere); D. Boerma, S. Van Esser, J. Pruim (Saint Antonius Hospital, Nieuwegein); J. B. Reitsma (Julius Centre for Health Sciences and Primary Care, University Medical Centre, Utrecht).

Acknowledgements

The authors thank the patients who participated in the study, members of the DSMB (P. Bossuyt, Chair; H. Gooszen; J. van der Meer) and investigators, coordinators, clinicians and (research) nurses. The DIABOLO trial was funded by the Netherlands Organization for Health Research and Development (ZonMw; 171002303) and the Digestive Diseases Foundation (Maag Lever Darm Stichting, MLDS WO08-54). The funders had no involvement in trial design, conduct or reporting.
Disclosure: The authors declare no conflict of interest.

References

1 Sarin S, Boulos PB. Long-term outcome of patients presenting with acute complications of diverticular disease. *Ann R Coll Surg Engl* 1994; **76**: 117–120.
2 Dharmarajan S, Hunt SR, Birnbaum EH, Fleshman JW, Mutch MG. The efficacy of nonoperative management of acute complicated diverticulitis. *Dis Colon Rectum* 2011; **54**: 663–671.
3 Hjern F, Josephson T, Altman D, Holmström B, Johansson C. Outcome of younger patients with acute diverticulitis. *Br J Surg* 2008; **95**: 758–764.
4 Shaikh S, Krukowski ZH. Outcome of a conservative policy for managing acute sigmoid diverticulitis. *Br J Surg* 2007; **94**: 876–879.
5 Hjern F, Josephson T, Altman D, Holmström B, Mellgren A, Pollack J *et al*. Conservative treatment of acute colonic diverticulitis: are antibiotics always mandatory? *Scand J Gastroenterol* 2007; **42**: 41–47.
6 De Korte N, Kuyvenhoven JP, van der Peet DL, Felt-Bersma RJ, Cuesta MA, Stockmann HB. Mild colonic diverticulitis can be treated without antibiotics. A case–control study. *Colorectal Dis* 2012; **14**: 325–330.
7 Chabok A, Påhlman L, Hjern F, Haapaniemi S, Smedh K; AVOD Study Group. Randomized clinical trial of antibiotics in acute uncomplicated diverticulitis. *Br J Surg* 2012; **99**: 532–539.
8 Feingold D, Steele SR, Lee S, Kaiser A, Boushey R, Buie WD *et al*. Practice parameters for the treatment of sigmoid diverticulitis. *Dis Colon Rectum* 2014; **57**: 284–294.
9 Agresta F, Ansaloni L, Baiocchi GL, Bergamini C, Campanile FC, Carlucci M *et al.* Laparoscopic approach to acute abdomen from the Consensus Development Conference of the Societa Italiana di Chirurgia Endoscopica e nuove tecnologie (SICE), Associazione Chirurghi Ospedalieri Italiani (ACOI), Societa Italiana di Chirurgia (SIC), Societa Italiana di Chirurgia d'Urgenza e del Trauma (SICUT), Societa Italiana di Chirurgia nell'Ospedalita Privata (SICOP), and the European Association for Endoscopic Surgery (EAES). *Surg Endosc* 2012; **26**: 2134–2164.
10 Sartelli M, Viale P, Catena F, Ansaloni L, Moore E, Malangoni M *et al*. 2013 WSES guidelines for management of intra-abdominal infections. *World J Emerg Surg* 2013; **8**: 3.
11 Van de Linde MJ, Wikkeling M, Driessen WM, Croiset van Uchelen FA, Roumen RM. Is er een rol voor antibiotica bij de conservatieve behandeling van acute diverticulitis coli? *Ned Tijdschr Heelk* 1996; **5**: 194–197.
12 De Korte N, Klarenbeek BR, Kuyvenhoven JP, Roumen RM, Cuesta MA, Stockmann HB. Management of diverticulitis: results of a survey among gastroenterologists and surgeons. *Colorectal Dis* 2011; **13**: e411–e417.
13 Munikrishnan V, Helmy A, Elkhider H, Omer AA. Management of acute diverticulitis in the East Anglian region: results of a United Kingdom regional survey. *Dis Colon Rectum* 2006; **49**: 1332–1340.
14 Humes DJ, Spiller RC. Review article: the pathogenesis and management of acute colonic diverticulitis. *Aliment Pharmacol Ther* 2014; **39**: 359–370.
15 World Health Organization. *The Evolving Threat of Antimicrobial Resistance: Options for Action*; 2012. http://whqlibdoc.who.int/publications/2012/9789241503181_eng.pdf?ua=1 [accessed 7 October 2013].
16 Unlü C, de Korte N, Daniels L, Consten EC, Cuesta MA, Gerhards MF *et al*.; Dutch Diverticular Disease 3D Collaborative Study Group. A multicenter clinical trial investigating the cost-effectiveness of treatment strategies with or without antibiotics for uncomplicated acute diverticulitis (DIABOLO trial). *BMC Surg* 2010; **10**: 23.
17 Wasvary H, Turfah F, Kadro O, Beauregard W. Same hospitalization resection for acute diverticulitis. *Am Surg* 1999; **65**: 632–635.
18 Ambrosetti P, Grossholz M, Becker C, Terrier F, Morel P. Computed tomography in acute left colonic diverticulitis. *Br J Surg* 1997; **84**: 532–534.
19 American College of Chest Physicians/Society of Critical Care Medicine. Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992; **20**: 864–874.
20 Stichting Werkgroep Antibiotica Beleid. *Nationale Antibiotica Boekje: Diverticulitis adviezen*. http://swabid.nl/node/7320 [accessed 2009 and 7 October 2013].
21 Rafferty J, Shellito P, Hyman NH, Buie WD; Standards Committee of American Society of Colon and Rectal Surgeons. Practice parameters for sigmoid diverticulitis. *Dis Colon Rectum* 2006; **49**: 939–944.
22 Piaggio G, Elbourne DR, Altman DG, Pocock SJ, Evans SJ; CONSORT Group. Reporting of noninferiority and equivalence trials: an extension of the CONSORT statement. *JAMA* 2006; **295**: 1152–1160.
23 *CONSORT Transparent Reporting of Trials*. http://www.consort-statement.org/consort-statement/ [accessed 7 October 2013].
24 McDermott FD, Collins D, Heeney A, Winter DC. Minimally invasive and surgical management strategies tailored to the severity of acute diverticulitis. *Br J Surg* 2014; **101**: e90–e99.
25 Isacson D, Andreasson K, Nikberg M, Smedh K, Chabok A. No antibiotics in acute uncomplicated diverticulitis: does it work? *Scand J Gastroenterol* 2014; **49**: 1441–1446.
26 Brochmann N, Schultz JK, Jakobsen GS2, Øresland T. Management of acute uncomplicated diverticulitis without antibiotics: a single centre cohort study. *Colorectal Dis* 2016; [Epub ahead of print].
27 Dharmarajan S, Hunt SR, Birnbaum EH, Fleshman JW, Mutch MG. The efficacy of nonoperative management of acute complicated diverticulitis. *Dis Colon Rectum* 2011; **54**: 663–671.

Supporting information

Additional supporting information may be found in the online version of this article:

Appendix S1 Supplementary analyses and considerations (Word document)

Table S1 Major protocol amendments (Word document)

Table S2 Reasons for non-enrolment of screened patients (Word document)

Table S3 Reasons for wrongful inclusion of randomized patients (Word document)

Table S4 Number of included patients per hospital (Word document)

Table S5 Baseline characteristics of the patients according to randomization status (Word document)

Table S6 Type of antibiotic treatment prescribed (Word document)

Table S7 Reasons for discontinuation of antibiotics in patients assigned to antibiotic treatment (Word document)

Table S8 Indications for sigmoid resection within 6 months (Word document)

Table S9 Intention-to-treat analyses of main secondary outcomes at 12 months' follow-up among patients with uncomplicated acute diverticulitis assigned to an observational or antibiotic treatment strategy (Word document)

Table S10 Intention-to-treat subgroup analyses of main secondary outcomes for Hinchey categories 1a and 1b among patients with uncomplicated acute diverticulitis assigned to an observational or antibiotic treatment strategy (Word document)

Table S11 Per-protocol analyses of secondary outcomes among patients with uncomplicated acute diverticulitis assigned to an observational or antibiotic treatment strategy (Word document)

Table S12 Per-protocol analyses of main secondary outcomes at 12 months' follow-up among patients with uncomplicated acute diverticulitis (Word document)

Table S13 Per-protocol subgroup analyses of main secondary outcomes for Hinchey categories 1a and 1b among patients with uncomplicated acute diverticulitis (Word document)

Fig. S1 Intention-to-treat analysis of time to recovery in patients with uncomplicated acute diverticulitis in the Hinchey 1b subgroup (Word document)

Fig. S2 Per-protocol analysis of time to recovery in patients with uncomplicated acute diverticulitis (Word document)