Treatment of acute diverticulitis and appraisal of evidence

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CHAPTER 3

Long-term effects of omitting antibiotics in uncomplicated acute diverticulitis

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ABSTRACT

Background

Traditionally uncomplicated acute diverticulitis was routinely treated with antibiotics, although evidence for this strategy was lacking. Recently, two randomized clinical trials (AVOD trial and DIABOLO trial) published short-term results of omitting antibiotics compared to routine antibiotic treatment. Both showed no significant differences regarding recovery from the initial episode, as well as rates of complicated or recurrent diverticulitis and sigmoid resection. However, both studies showed a trend of higher rates of sigmoid resection in the observational groups. Here, the long-term effects of omitting antibiotics in first episode uncomplicated acute diverticulitis were assessed.

Methods

A total of 528 patients with CT-proven, primary, left-sided, uncomplicated acute diverticulitis were randomized to either an observational or an antibiotic treatment strategy (DIABOLO trial). Outcome measures were complicated diverticulitis, recurrent diverticulitis and sigmoid resection at 24 months' follow up. Differences between the groups were explored and risk factors were identified using multivariable logistic regression.

Results

Complete case analyses showed no difference in rates of recurrent diverticulitis (15.4% in the observational group versus 14.9% in the antibiotic group; $p = 0.885$), complicated diverticulitis (4.8% versus 3.3%; $p = 0.403$) and sigmoid resection (9.0% versus. 5.0%; $p = 0.085$). Young patients (<50 years) and patients with a pain score at presentation of 8 or higher on a visual analogue pain scale were at risk for complicated or recurrent diverticulitis. In this multivariable analysis, treatment type (with or without antibiotics) was not an independent predictor for complicated or recurrent diverticulitis.

Conclusion

Omitting antibiotics in the treatment of uncomplicated acute diverticulitis did not result in more complicated diverticulitis, recurrent diverticulitis or sigmoid resections at long-term follow up. As the DIABOLO trial was not powered for these secondary outcome measures, some uncertainty remains whether (small) non-significant differences could be true associations.

INTRODUCTION

Acute diverticulitis occurs in four per cent of patients with colonic diverticular disease as its inflammatory complication, and is among the top ten diagnoses of patients with acute abdominal pain presenting to the general physician or at the emergency department.[1,2] Despite this frequent occurrence in Western countries, contradictory views on the pathogenesis and treatment strategies remain.[3,4]

One of those contradictory views is whether uncomplicated acute diverticulitis should be routinely treated with antibiotics. A recent survey among experts from four continents could not reach consensus on this topic based on the previously published retrospective series and one randomized clinical trial (RCT), the AVOD trial.[3,5-7] This same split in opinions takes place in international guidelines.[4]

Recently, a randomized clinical trial (DIABOLO trial) including 528 patients with a first episode of computed tomography (CT) proven uncomplicated acute diverticulitis, showed no short-term repercussions of omitting antibiotics.[8] Observational treatment did not result in longer time to recovery or higher rates of readmission, complicated, ongoing and recurrent diverticulitis and sigmoid resection at short-term follow up. Both RCT's on this topic, the AVOD trial and the DIABOLO trial, only reported 1-year follow-up results. Despite that no significant differences were found between an observational and antibiotic treatment strategy, both trials showed a non-significant trend towards more cases of complicated diverticulitis and elective sigmoid resections. Therefore, long-term data may provide valuable information on the safety of omitting antibiotics in mild diverticulitis. Here, long-term effects are reported of the DIABOLO trial.

METHODS

Study design and patient population

The DIABOLO trial was a multicenter, pragmatic, non-inferiority, randomized clinical trial, taking place in 22 clinical sites in the Netherlands during 2010–2012. A total of 528 patients with CT-proven, first episode, left-sided and uncomplicated acute diverticulitis were randomized to either an observational (262 patients) or an antibiotic (266 patients) treatment strategy. The antibiotic regimen consisted of amoxicillin-clavulanic acid in a 10-day course with intravenous administration for at least 48 h, after which the route could be switched—if tolerated—to oral administration. Uncomplicated acute diverticulitis was defined as modified Hinchey stages 1a and b and Ambrosetti's "mild" diverticulitis stage.[9,10]

Data collection and outcomes

Follow-up was performed by outpatient clinic visits or by telephone at 12 and 24 months and all hospital records were reviewed, data collection was done using standardized case record forms. First, the antibiotic and observational treatment strategy groups were compared in a complete case analysis regarding rates of recurrent diverticulitis, complicated diverticulitis and sigmoid resection. Between 6 months (primary endpoint of the DIABOLO trial) and the end of 2-year follow-up patients were allowed to be enrolled in another Dutch randomized clinical trial (DIRECT trial)[11] comparing surgical or conservative treatment of patients with 3 or more episodes of recurrent diverticulitis or persistent complaints for at least 3 months after an episode of acute diverticulitis. Since this potentially introduced bias for the outcome measure sigmoid resection, patients were censored for this outcome at the time of their enrollment in the DIRECT trial. Second, differences among treatment groups were explored and risk factors for complicated diverticulitis and recurrent diverticulitis were identified. The association between complicated or recurrent diverticulitis and elective sigmoid resection was visualized using lasagna plots. Lasagna plots can visualize longitudinal patters of multiple outcomes within one figure. The methods of creating lasagna plots have been described before.[12] Full recovery was defined by meeting the following criteria: discharge from the hospital, normal diet (tolerating solid food and more than 1 L of fluid orally), temperature <38°C, VAS pain score <4 (with no use of daily pain medication) and resuming to pre-illness working activities; as assessed by a daily patient diary. Recurrent diverticulitis was defined as a clinical picture of diverticulitis whether or not imaging proven with an interval of at least 3 months from randomization. Only recurrent episodes diagnosed by a physician (general practitioner or hospital physician) were recorded. There were no pre-specified criteria for a clinical diagnosis of recurrent diverticulitis, but diagnoses were established as in daily practice. A recurrent episode was treated with or without antibiotics according to daily practice, treatment allocation by randomization was not maintained throughout the follow up. The study protocol and some protocol amendments were published previously.[8,13]

Statistical analysis

For categorical variables, numbers and percentages were calculated and compared using the χ^2-test or Fisher's exact test, as appropriate. Multivariable logistic regression was used to identify independent risk factors. Variables that were significant or approached significance ($p \leq 0.10$) in the univariable analyses, were entered into the multivariable logistic analyses. Some numerical variables (e.g., age and pain scores) were converted into dichotomous categorical variables defined by clinically relevant thresholds, making them more easy to interpret and more easy to use in daily practice. All risk estimates are expressed in odds ratios (OR). Since a non-inferiority margin was only established for the primary outcome of the RCT (time to recovery), analysis of long-term (secondary) outcomes in the present study was performed using a superiority approach. A two-sided $p<0.05$ was considered statistically significant. TRIPOD guidelines for reporting were followed.[14] All analyses were performed using SPSS, version 23.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Observational versus antibiotic treatment strategy

A total of 227 patients (86.6% of 262; 3 patients died and 32 were lost to follow up) in the observational group and 241 patients (90.6% of 266; 1 patient died and 24 were lost to follow up) in the antibiotic group completed the 24 months of follow up and were included in the complete case analysis. This analysis showed similar proportions of patients with one or more episodes of recurrent acute diverticulitis during 2-year follow up; 15.4% (35/227) in the observational group and 14.9% (36/241) in the antibiotic group ($p = 0.885$). Comparison of only imaging-proven recurrent diverticulitis yielded comparable results; 11.0% (25/227) in the observational group and 7.9% (19/241) in the antibiotic group ($p = 0.246$). The proportion of patients that developed one or more episodes of complicated diverticulitis was comparable among groups (4.8% (11/227) versus 3.3% (8/241); $p = 0.403$). In addition, rates of different types of complicated diverticulitis and interventions performed because of complicated diverticulitis were comparable among groups (Table 1).

Chapter 3

Table 1. Intention-to-treat analyses of main secondary outcomes among patients with uncomplicated acute diverticulitis assigned to an observational or antibiotic treatment strategy at 24 months follow-up.

	Observation (N=227* of 262)	**Antibiotics** (N=241* of 266)	**P-value**
Recurrent diverticulitis (≥1)# – no (%)	35 (15.4%)	36 (14.9%)	0.885
Only imaging proven recurrences	25 (11.0%)	19 (7.9%)	0.246
Complicated diverticulitis (≥1)# – no (%)	11 (4.8%)	8 (3.3%)	0.403
Type † – no (%)			
Abscess (>5cm)	2 (0.9%)	3 (1.2%)	
Perforation	5 (2.2%)	2 (0.8%)	
Obstruction	4 (1.8%)	2 (0.8%)	
Fistula	1 (0.4%)	1 (0.4%)	
Diverticular bleeding (≥1)# – no (%)	3 (1.3%)	0 (0.0%)	0.113
Intervention for complicated diverticulitis (≥1) – no (%)	11 (4.8%)	7 (2.9%)	0.275
Type † – no (%)			
Percutaneous	2 (0.9%)	2 (0.8%)	
Surgery	10 (4.4%)	5 (2.1%)	
Sigmoid resection – no (%)$	20 (9.0%)	12 (5.0%)	0.085
Type Emergency	3 (1.4%)	2 (0.8%)	
Elective	17 (7.7%)	10 (4.2%)	

* Number of patients that completed the full 24 months of follow-up; 86.6% in the observational group and 90.6% in the antibiotic group.

Number of patients with one or more episodes of recurrent diverticulitis

† Patients can have more than 1 type of complicated diverticulitis

$ Due to censoring of 6 patients that were dually enrolled in the DIRECT trial, the total number of patients in this comparison was 221 in the observational group and 241 in the antibiotic group

Although no differences in the proportion of complicated and recurrent diverticulitis were found, the proportion of patients undergoing sigmoid resection was non-significantly higher in the observational group (9.0% (20/221) versus 5.0% (12/241); $p = 0.085$). This trend is explained by a higher number of elective sigmoid resections in the observational group (7.7%; 17/227) compared to the antibiotic group (4.2%; 10/241). The rates of emergency sigmoid resections, however, were comparable (1.3% (3/227) and 0.8% (2/241), respectively; Table 1). In the observational group, all three emergency resections were performed because of perforated diverticulitis. In the antibiotic group, one emergency was performed because of perforated diverticulitis and the other one because of sigmoid obstruction.
Since this complete case analysis only included patients that completed the entire 24 months of follow up, attrition bias might have been introduced. Three analyses were done to assess the risk of attrition bias by exploring differences in baseline characteristics and clinical disease course. First, baseline characteristics were comparable among the complete case analysis population and lost to follow-up population (Supplementary Table 1). Second, only minimal changes in rates of complications at 6 months in favor of the antibiotic group were observed when the current complete case study population was compared to the original intention-to-treat population (Supplementary Table 2).[8] Third, the time to recovery in observational patients was significantly longer in the lost to follow-up group compared with the complete case group (median 24 days versus 13 days, respectively; $p = 0.004$), whereas the time to recovery in antibiotic patients was only slightly but not significantly longer in the lost to follow-up group (median 15 days versus 11 days, respectively; $p = 0.106$). This implies that patients in the observational group tended to drop out of follow-up sooner than patients in the antibiotic group when recovery of the initial diverticulitis episode was prolonged.

Complicated and recurrent diverticulitis

Figures 1 and 2 show the long-term effects of observational or antibiotic treatment of the initial episode of diverticulitis on the occurrence of complicated and recurrent diverticulitis. No clear distinctive pattern of distribution over time between the observational and antibiotic groups could be recognized for both complicated diverticulitis and recurrent diverticulitis.

Risk factors for the development of complicated or recurrent diverticulitis were identified using univariable and multivariable logistic regression. Independent risk factors for the development of complicated or recurrent diverticulitis were younger age (<50 years; adjusted odds ratio (OR) 1.86; 95% confidence interval (CI) 1.05–3.32) and an initial pain score at first presentation of a visual analogue score (VAS) 8 or higher (adjusted OR 1.89; 95% CI 1.06–3.35). Treatment type by itself was not an independent risk factor for complicated or recurrent diverticulitis (adjusted OR of 1.18 (95% CI 0.69–2.02) for

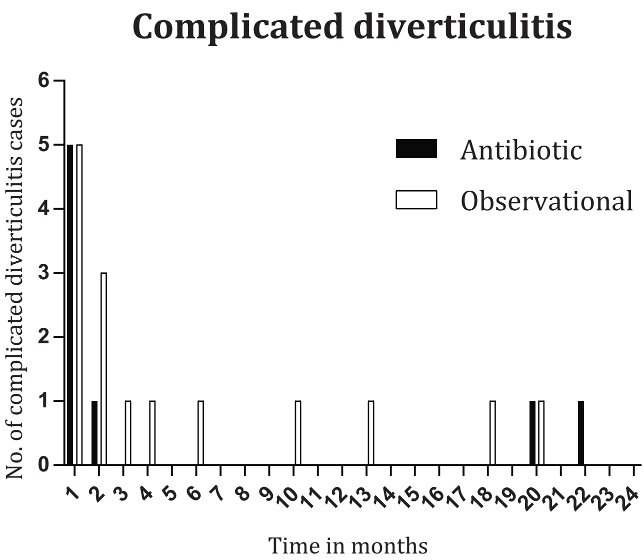

Figure 1. Number of complicated diverticulitis episodes in each month for the 24 months after randomization, comparing the observational (N=227) and antibiotic (N=241) treatment groups. Patients can have more than 1 episode of complicated diverticulitis.

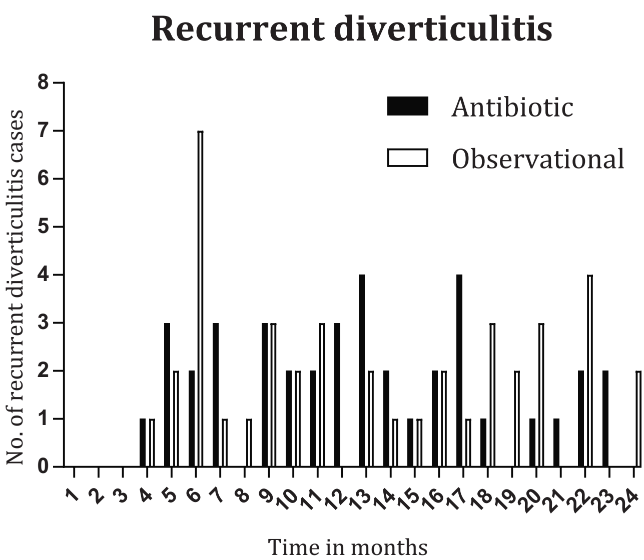

Figure 2. Number of recurrent diverticulitis episodes in each month for the 24 months after randomization, comparing the observational (N=227) and antibiotic (N=241) treatment groups. Patients can have more than 1 episode of recurrent diverticulitis.

Table 2. Univariable and multivariable analyses of risk factors (odds ratio) associated with 1 or more episodes of complicated diverticulitis or recurrent diverticulitis in patients that completed the 24 months of follow-up.

	No. of patients at risk for complicated diverticulitis or recurrence	Complicated diverticulitis or recurrence N (%)	Univariable OR (95% CI)	Multivariable OR (95% CI)
Gender				
Male	227	41 (18.1%)	0.93 (0.59-1.49)	
Female	241	46 (19.1%)		
BMI				
< 30 kg/m^2	352	59 (16.8%)		
> 30 kg/m^2	96	23 (24.0%)	1.57 (0.91-2.70)	
Age				
< 50 years	136	35 (25.7%)	1.87 (1.15-3.03)	**1.86 (1.05-3.32)**
≥ 50 years	332	52 (15.7%)		
ASA score				
I	297	62 (20.9%)		
II or III	171	25 (14.6%)	0.65 (0.39-1.08)	0.84 (0.45-1.54)
Smoking				
Yes	106	26 (24.5%)	1.65 (0.97-2.80)	1.51 (0.84-2.71)
No	334	55 (16.5%)		
Alcohol ≥ 2 units/day				
Yes				
No	80	17 (21.3%)	1.13 (0.61-2.10)	
	249	48 (19.3%)		
Pain score at presentation				
VAS < 8	298	47 (15.8%)		
VAS ≥ 8	101	26 (25.7%)	1.85 (1.07-3.19)	**1.89 (1.06-3.35)**
Hinchey				
1a	435	81 (18.6%)		
1b	33	6 (18.2%)	0.97 (0.39-2.43)	
Treatment type				
Observational	227	44 (19.4%)	1.11 (0.70-1.76)	1.18 (0.69-2.02)
Antibiotic	241	43 (17.8%)		

Abbreviations: BMI, Body Mass Index. ASA, American Society of Anesthesiologists. VAS, Visual Analogue Score.

observational treatment compared to antibiotic treatment; Table 2). Only younger age (<50 years) was an independent risk factor for recurrent diverticulitis (adjusted OR 1.80; 95% CI 1.05–3.11; Table 3).

Elective sigmoid resection

The trend towards more elective sigmoid resection rates (7.7% in the observational group versus 4.2% in the antibiotic group) could not be explained by specific indications for surgery. (Table 4) Indications for elective sigmoid resection were mostly comparable

Table 3. Univariable and multivariable analyses of risk factors (odds ratio) associated with 1 or more episodes of recurrent diverticulitis in patients that completed the 24 months of follow-up.

	No. of patients at risk for recurrence	Recurrence N (%)	Univariable OR (95% CI)	Multivariable OR (95% CI)
Gender				
Male	227	34 (15.0%)	0.97 (0.59-1.61)	
Female	241	37 (15.4%)		
BMI				
< 30 kg/m²	352	46 (13.1%)		
> 30 kg/m²	96	20 (20.8%)	1.75 (0.98-3.13)	1.67 (0.92-3.02)
Age				
< 50 years	136	30 (22.1%)	2.01 (1.19-3.38)	**1.80 (1.05-3.11)**
≥ 50 years	332	41 (12.3%)		
ASA				
I	297	51 (17.2%)		
II or III	171	20 (11.7%)	0.64 (0.37-1.11)	
Smoking				
Yes	106	19 (17.9%)	1.33 (0.74-2.39)	
No	334	47 (14.1%)		
Alcohol ≥ 2 units/day				
Yes	80	13 (16.3%)	1.05 (0.53-2.07)	
No	249	39 (15.7%)		
Pain score at presentation				
VAS < 8	298	41 (13.8%)		
VAS ≥ 8	101	20 (19.8%)	1.55 (0.86-2.79)	
Hinchey				
1a	435	69 (15.9%)		
1b	33	2 (6.1%)	0.34 (0.08-1.46)	
Treatment type				
Observational	227	35 (15.4%)	1.04 (0.63-1.72)	1.05 (0.62-1.78)
Antibiotic	241	36 (14.9%)		
Time-to-recovery				
< 28 days	342	48 (14.0%)		
≥ 28 days	126	23 (18.3%)	1.37 (0.79-2.36)	

Abbreviations: BMI, Body Mass Index. ASA, American Society of Anesthesiologists. VAS, Visual Analogue Score.

among both groups. Although, recurrent diverticulitis and colonic obstruction were slightly more often the reason for elective surgery whereas the number of patients that had one or more episodes of recurrent diverticulitis (35 patients in the observational group and 36 in the antibiotic group) and colonic obstruction (4 patients in the observational group and 2 in the antibiotic group) were comparable.

The patients' hospital was no contributing factor since multivariable logistic regression demonstrated comparable odds ratios for sigmoid resection with (OR 1.89; 95% CI 0.90–

Table 4. Indications for elective sigmoid resection at 24 months follow-up.

	Observation (N=221*)	**Antibiotics** (N=241*)
Perforated diverticulitis	0	0
Obstruction/chronic ileus	4	1
Ongoing diverticulitis	2	0
Persistent abdominal complaints	4	6
Recurrent diverticulitis	5	2
Diverticular bleeding	1	0
Fistula	1	1
Total	17	10

* Number of patients that completed the full 24 months of follow-up; 86.6% in the observational group and 90.6% in the antibiotic group. Six observational patients were censored due to dual enrollment in the DIRECT trial.

3.98) or without adjustment (OR 1.90; 95% CI 0.91–3.98) for center. A lower threshold to perform a sigmoid resection after an adverse event in the observational group may have played a role which is illustrated by the lasagna plots in Fig. 3. The occurrence of either complicated or recurrent diverticulitis was equally distributed throughout the 2 years of follow up and comparable rates were seen at 2 years after randomization (18.1% in the observational group versus 17.4% in the antibiotic group). Despite these comparable rates, slightly more patients underwent an elective sigmoid resection after an episode of complicated or recurrent diverticulitis. These lasagna plots also show the vast majority of patients did not experience any diverticulitis related complications during the 2 years after their initial episode.

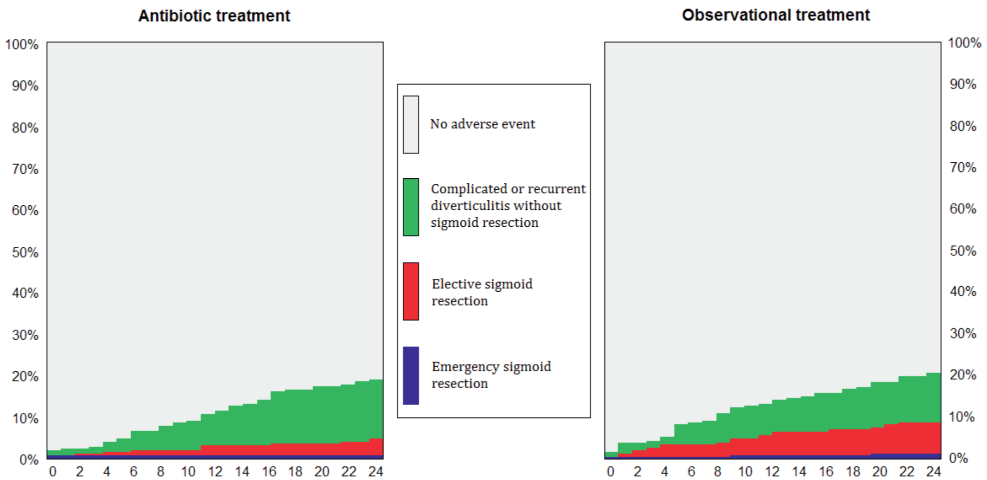

Figure 3. Sorted lasagna plots showing 24 months of follow-up after randomization of an observational (N=227) and antibiotic (N=241) treatment strategy. The plots are within-column sorted, thereby displaying group-level patterns. The light grey area represents patients with no episode of complicated or recurrent diverticulitis, nor sigmoid resection. The green area represents patients that had one or more episodes of complicated or recurrent diverticulitis, but did not undergo sigmoid resection (yet). The red area represents patients that underwent elective sigmoid resection and the blue area represents patients that underwent emergency sigmoid resection. Therefore, a patient that had an episode of complicated or recurrent diverticulitis is represented by the green area, but after an elective sigmoid resection the patient is represented by the red area and no longer by the green area.

DISCUSSION

Long-term follow-up results of a randomized clinical trial comparing an observational and antibiotic treatment strategy for a first episode of uncomplicated acute diverticulitis revealed no difference in recurrent diverticulitis rates and complicated diverticulitis rates. Slightly, but not significantly, more elective sigmoid resections were performed in the observational group, although the number of patients with complicated or recurrent diverticulitis was comparable in both study groups.

Most results are in line with the only other RCT on this topic, the AVOD trial.[7] This Scandinavian study found 16.2% recurrent diverticulitis in the observational group and 15.8% in the antibiotic group, both at a follow-up duration of 12 months. These rates were slightly higher at only half the follow-up duration of the present study. Presumably, this is caused by the 40% of patients that had recurrent rather than primary diverticulitis at inclusion in the AVOD trial. Furthermore, also the AVOD trial found a non-significantly higher rate of complicated diverticulitis, 1.9% in the observational group versus 1.0% in the antibiotic group ($p = 0.302$). As in both studies few events occurred, discriminating between causal association and a non-significant difference by chance seems impossible. Furthermore, the AVOD trial only reported perforation and abscess as complicated diverticulitis types. Therefore, comparisons of other types of diverticulitis related complications (obstruction, fistula and diverticular bleeding) between the studies could not be made.

Although not significant, the slightly higher proportion of patients undergoing elective sigmoid resection in the observational group may be a new perspective in the treatment dilemma of antibiotics or not for mild diverticulitis. The AVOD trial has only reported resection rates up to 12 months follow up. These rates were also, however not significantly higher in the observational group (1.9% versus 0.6%, $p = 0.148$). These percentages represent sigmoid resections during follow up. Whether emergency resections are part of these follow-up resections is not stated. Apart from these two randomized trials, only one retrospective study with similar follow-up duration (mean 30 months) reported elective sigmoid resection rates.[5] In contrast to the present study, this retrospective study found more elective sigmoid resections in the antibiotic group (1.1% of patients in the observational group versus 8.7% of patients in the antibiotic group). Although, the inevitable bias that has been introduced by the non-randomized nature of this study makes these results only illustrative rather than comparable to the present study.

In contrast to the other available RCT, indications for elective sigmoid resections were listed in the DIABOLO trial. This revealed that most indications for elective surgery were comparable among groups. In the observational group recurrent diverticulitis and colonic obstruction were mentioned more often as a reason for sigmoid resection. Since rates of adverse events were comparable among groups, surgeon and/or patient preference with a lower threshold for surgery in the observational group may have played a role. An explanation for this different threshold could be the open-label study design in which patients may feel they did not receive treatment (being antibiotics) during their initial episode and demand treatment when disease recurs, albeit being more invasive treatment. Another explanation could be the minor (non-significant) differences to the disadvantage of observational treatment that were observed such as time to recovery (median 14 versus 12 days), ongoing diverticulitis (7.3% versus 4.1%) and complicated diverticulitis (4.8% versus 3.3%) (See Supplementary Figure 1 for a visualization of all short-term and long-term outcomes of the DIABOLO trial). Although all these differences were by enlarge non-significant, in theory they could have caused by a slightly less favourable disease course in the observational group, accumulating into a disease status that leaned more towards sigmoid resection. Although, the subjective evaluation leading to an elective sigmoid resection limits the value and generalizability of this finding.

A strength of this study is the source of the data; a randomized clinical trial conducted according to the highest standards of randomized trials. The study was prospective and data collection was standardized. An inherent limitation of data from a RCT is the possible selection of patients. However, as reported previously, patients eligible to participate that were not randomized had clinical characteristics mostly similar to the patients that were randomized.[8] Another limitation is the insufficient sample size to assess outcome measures with few events and subgroups that might benefit from antibiotics, as the sample size of this trial was calculated on the time-to-recovery comparison between an observational and antibiotic treatment strategy. One more limitation is the possible risk of attrition bias. In a complete case analysis, only patients that completed the entire follow-up duration were included. Patients can become lost to follow up because of certain baseline characteristics or because of a deviant clinical course, both may influence the results of the analyses. In the present study, baseline characteristics did not seem to be a contributing factor. Also outcomes of patients included in the 6 months analysis and patients included in the complete case analysis were comparable. Patients lost to follow up in the observational group however, did have a longer time to recovery than patient not lost to follow up. The open-label study design presumably caused patients in the observational group to drop out of follow-up sooner. Nonetheless, since prolonged time to recovery did not seem to have a significant effect on rates of events during follow up in the risk factor analyses, the impact on outcomes is considered to be limited. In summary, the risk of attrition bias seems limited and, if present, would probably have resulted in slightly underestimated rates of complications in the observational group. Furthermore, outcomes of patients that were dually enrolled in the DIRECT trial[11] (comparing surgery and conservative treatment for persisting complaints after acute diverticulitis) were biased. Therefore, these patients, six from the observational group, were censored at the time of their enrolment in the DIRECT trial. In the DIRECT trial, four of these six patients were randomized to conservative treatment and two of six were randomized to sigmoid resection. However, two of the patients randomized to conservative treatment did eventually undergo sigmoid resection because of worsening symptoms. If these patients would not have been excluded from the present study, the rate of elective sigmoid resection would have been slightly higher in the observational group. Since all dually enrolled patients – both surgical patients and conservative patients that underwent resection because of worsening symptoms later – were biased by that study, these patients were excluded from the present study.

In parallel with the comparable time to recovery between observational and antibiotic treatment reported in the short-term results of the DIABOLO trial[8], this study found at long-term follow up no differences in recurrent diverticulitis, complicated diverticulitis and sigmoid resection rates. The non-significant higher rate of elective sigmoid resections in the observational group seems to have been caused by a lower threshold for surgery in this group. However, the subjective evaluation leading to an elective sigmoid resection limits the value and generalizability of this finding. Since the DIABOLO trial was not powered on the secondary outcomes, some uncertainty remains whether (small) non-significant differences could be true associations. If future research would show any beneficial effect of antibiotics for a subset of long-term outcome parameters, these should be compared with the disadvantages of antibiotics as reported in the initial DIABOLO paper[8]; patients treated with antibiotics developed antibiotic related morbidity in 8.3% of patients, whereas patients without antibiotic treatment could be treated as outpatients in 13.0% of cases and if admitted, length of hospital stay was significantly shorter compared with antibiotic patients.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Baseline characteristics of patients in complete case analysis and patient not in complete case analysis (lost to follow-up).

	Complete case analysis (N=468)	**Lost to follow-up** (N=60)
Age (years)*	57.4 (49.8-65.0)	53.2 (41.2-65.3)
Sex ratio (M:F)	227:241	40:20
Co-morbidity†	211 (45.1%)	23 (38.3%)
BMI (kg/m^2)*	26.6 (24.1-29.1)	27.5 (15.0-30.0)
Body temperature (°C)*	37.3 (36.3-38.4)	37.2 (36.2-38.2)
White blood cell count (x 10^9 cells/l)*	12.3 (10.1-14.5)	11.7 (9.3-14.1)
C-reactive protein (mg/l)*	79.0 (37.0-121.0)	73.5 (33.5-113.5)
Hinchey category 1a	435 (92.9%)	51 (85.0%)

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; ASA American Society of Anesthesiologists; BMI Body Mass Index

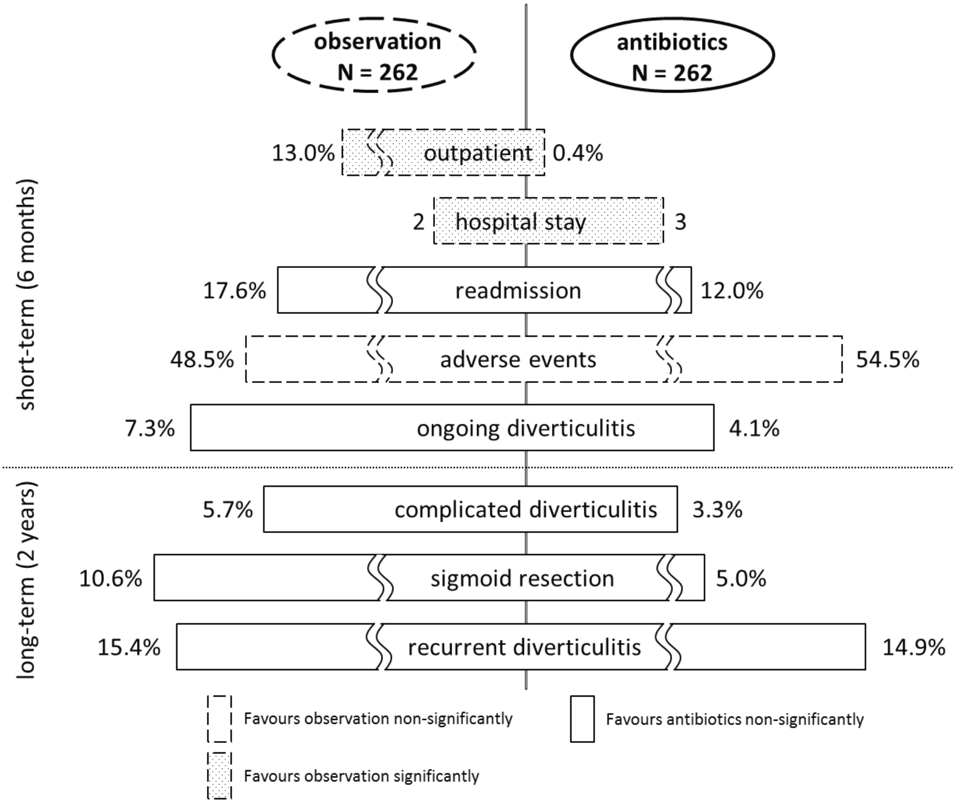
Supplementary Table 2. Assessment of potential attrition bias. Comparison of main secondary outcome measures at 6 months of follow-up between the group of patients that was included in the short-term results paper[8] (all 528 patients in the study) (Supplementary Table 2a) and the group of patients that was included in the present long-term intention-to-treat results paper (only patients that completed the entire 24 months of follow-up) (Supplementary Table 2b).

Supplementary Table 2a

	Observation (N=262)	**Antibiotics** (N=266)
Recurrent diverticulitis (≥1) – no (%)	9 (3.4%)	8 (3.0%)
Complicated diverticulitis (≥1) – no (%)	10 (3.8%)	7 (2.6%)
Sigmoid resection – no (%)	10 (3.8%)	6 (2.3%)

Supplementary Table 2b

	Observation (N=227*)	**Antibiotics** (N=241*)
Recurrent diverticulitis (≥1) – no (%)	8 (3.5%)	6 (2.5%)
Complicated diverticulitis (≥1) – no (%)	9 (4.0%)	6 (2.5%)
Sigmoid resection – no (%)	8 (3.5%)	4 (1.7%)



Supplementary Figure 1. Visualization of short-term (≤ 6 months) outcomes (outpatient treatment, length of hospital stay in days, readmission, adverse events and ongoing diverticulitis) and long-term (2 year) outcomes (complicated diverticulitis, sigmoid resection and recurrent diverticulitis) for observational and antibiotic treatment of uncomplicated acute diverticulitis.