Treatment of acute diverticulitis and appraisal of evidence

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CHAPTER 2

Individual patient data meta-analysis of observational versus antibiotic treatment of acute uncomplicated diverticulitis

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ABSTRACT

Background

Two RCTs (AVOD and DIABOLO) showed no difference in recovery or adverse outcomes when omitting antibiotics for acute uncomplicated diverticulitis. Both trials however showed non-significantly higher rates of complicated diverticulitis and sigmoid resection in the non-antibiotics groups. Since the trials lacked statistical power to detect differences in secondary outcomes, meta-analysis of individual patient data was performed, aiming to identify patients at risk for complications that may benefit from antibiotic treatment.

Methods

Individual patient data of patients with uncomplicated diverticulitis from two RCTs comparing observational and antibiotic treatment were pooled; 545 patients in the observational group and 564 patients in the antibiotic group. Risk factors for adverse outcomes and the effect of observational management on the risk of adverse outcomes were assessed using logistic regression analyses. P<0·025 was considered statically significant due to multiple testing adjustment.

Findings

No statistical differences were found in 1-year follow-up rates of ongoing diverticulitis (observational 7·2% versus antibiotics 5·0%; p=0·062), recurrent diverticulitis (observational 8·6% versus antibiotics 9·6%; p=0·610), complicated diverticulitis (observational 4·0% versus antibiotics 2·1%; p=0.079) and sigmoid resection (observational 5·0% versus antibiotics 2·5%; p=0·214). An initial pain score >7, white blood cell counts >13·5x10^9/L and previous acute diverticulitis at presentation were risk factors for adverse outcomes. Antibiotic treatment did not prevent adverse outcomes in patients at high-risk for adverse events.

Interpretation

Observational management of acute uncomplicated diverticulitis is safe, given the comparable rates of adverse events up to 1 year compared to routine antibiotic treatment Some statistical uncertainty may remain depending on thresholds of clinical relevance as the sample size of the meta-analysis was insufficient to detect small differences. However, in risk factor analyses no patient subgroup could be identified that could potentially benefit from antibiotic treatment.

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INTRODUCTION

Acute uncomplicated diverticulitis has been routinely treated with antibiotics for decades, although evidence in favour of antibiotic treatment has always been lacking. Recently two randomized clinical trials (RCT) demonstrated the safety of omitting antibiotics in the treatment of acute uncomplicated diverticulitis up to 1 year of follow-up.[1,2] First, the AVOD trial[1] showed comparable rates of complicated diverticulitis, recurrent diverticulitis and sigmoid resection between observational and antibiotic treatment. Second, the DIABOLO trial[2] found no significant differences regarding time-to-recovery, complicated diverticulitis, recurrent diverticulitis and sigmoid resection. However, both RCTs showed somewhat – by enlarge non-significant – higher rates of complicated diverticulitis and sigmoid resections in the non-antibiotic group. Since the studies were not both powered for these secondary outcomes, uncertainty remained whether these small differences could potentially be true causal associations, the consequence of patient selection or findings by chance in accordance with statistical non-significance. A regular meta-analysis of the two RCTs would not be able to account for different follow-up durations and different outcome definitions that were provided in the result papers of both studies. In contrast, a meta-analysis on individual patient data level (IPDMA) can not only account for these differences but additionally provides an opportunity using the increased sample size of both trials combined. The aim was to identify patients at risk for complications who may benefit from antibiotic treatment.

METHODS

Study design and patient population

Individual patient data from two open-label randomized clinical trials (AVOD trial and DIABOLO trial) were pooled in the present study. The AVOD trial[1] was conducted in 11 hospitals in Sweden and Iceland during 2003-2010. The DIABOLO trial[2] was conducted in 22 hospitals in the Netherlands during 2010 – 2012. Both included only left-sided, computed tomography (CT) proven acute uncomplicated diverticulitis patients, and excluded immunocompromised patients, pregnant patients, and patients with signs of sepsis. Patients with small pericolic abscesses (Hinchey stage 1b[3]) from the DIABOLO trial were excluded in the present study, since the AVOD trial included only patients without abscesses and the number of Hinchey 1b patients in the DIABOLO trial was low (42 out of 528). Patients from both studies were

treated in the AVOD trial with broad-spectrum antibiotics, intravenously or orally for seven days, and in the DIABOLO trial for at least 48 hours intravenously with a total of ten days. In the AVOD trial, all patients were admitted after which patients were discharged based on the assessment of the attending surgeon in both study groups. In the DIABOLO trial, patients in the observational group could be treated as outpatients when predefined criteria were met whereas patients in the antibiotic group were all admitted on the premise that treatment was started intravenously and were only considered for outpatient treatment after 48 hours. Table 1 shows a summary of study characteristics of the DIABOLO trial and the AVOD trial.

Outcomes and follow-up

Outcome measures in the present study were length of hospital stay, and rates of ongoing diverticulitis, recurrent diverticulitis, complicated diverticulitis and sigmoid resection. Three outcomes were redefined in order to create definitions as homogeneous as possible. In the DIABOLO trial, ongoing diverticulitis and recurrent diverticulitis were distinct outcomes since symptoms of acute diverticulitis within three months of randomization were considered a prolongation of the initial diverticulitis episode instead of a true recurrent, hence new, episode. As the AVOD trial analyzed all disease activity after discharge from hospital as recurrent episodes, all episodes within three months after randomization were redefined as ongoing diverticulitis episodes. All subsequent episodes later than three months after randomization were considered recurrent episodes. Also, in the AVOD trial diverticular bleeding was not recorded as complicated diverticulitis. Therefore, diverticular bleeding cases in the DIABOLO trial were excluded as complicated diverticulitis event in the present study.

Another difference between the studies was the moment of last follow-up; 12 months in the AVOD trial and 24 months in the DIABOLO trial. In order to analyse results of the studies equally, outcomes were assessed at 12 months of follow-up. Since patients were contacted after a minimum of 12 months in the AVOD trial, most follow-up contacts took place in the 13th month after randomization. Therefore, results from both trials were assessed up to 13 months after randomization.

Statistical analysis

Observational and antibiotic treatment were compared following the intention-to-treat principle and contrasts were assessed for superiority. For categorical variables numbers and percentages were calculated and continuous variables are expressed as median and interquartile range (IQR) as these data are not normally distributed. Since the data in this meta-analysis is clustered by study, comparison between treatment groups was corrected for this clustering. For each outcome measure a generalized linear mixed model was fitted. For dichotomous outcomes a logistic regression mixed model was used, for the only continuous

Table 1. Summary of study characteristics of included studies.

		DIABOLO	AVOD
Study design		Open-label randomized clinical trial	Open-label randomized clinical trial
Study setting		22 hospitals in the Netherlands during 2010-2012	11 hospitals in Sweden and Iceland during 2003-2010
Patients		528 patients (262 in observational group and 266 in antibiotic group)	623 patients (309 in observational group and 314 in antibiotic group)
Inclusion criteria		CT-proven, left-sided acute uncomplicated (Hinchey stage 1a and 1b) diverticulitis	CT-proven, left-sided, acute uncomplicated (without any sign of complications such as abscess, free air or fistula), temperature ≥38°C at admission or during the last 12h before admission, raised WBC and CRP or increased WBC if short history
Exclusion criteria		Previous diverticulitis, pregnancy, inflammatory bowel disease, ASA fitness grade >III, immunocompromised, clinical suspicion of bacteremia (sepsis[12])	Pregnancy, immunosuppressive therapy, high fever, affected general condition, peritonitis or sepsis
Intervention	**Antibiotic treatment**	10-day course of amoxicillin clavulanic acid, with intravenous administration for at least 48h, switch to oral administration if tolerated, admission of all patients on the premise that treatment was started intravenously, discharge when meeting criteria: toleration of a normal diet, temperature less than 38°C, pain score <4, capable of self-support at same level as before illness, and patient acceptance	7-day course of intravenous or oral broad-spectrum antibiotics according to the participating centers' routines, admission of all patients, discharge based on assessment of attending surgeon with improvement in clinical status as well as a reduction in WBC and CRP and absence of fever
	Observational treatment	Supportive care, outpatient treatment when meeting criteria for outpatient treatment alike the antibiotic group	Supportive care, intravenous fluids only, admission of all patients, discharge when meeting criteria alike the antibiotic group

Outcomes	**Ongoing diverticulitis**	Clinical picture of diverticulitis, within 3 months from randomization or no recovery between randomization and subsequent diverticulitis	Not recorded separately
	Recurrent diverticulitis	Clinical picture of diverticulitis, and interval of at least 3 months from randomization, and recovery during this time interval	Clinical picture of diverticulitis demanding readmission to hospital
	Complicated diverticulitis	Abscess, perforation, obstruction, fistula or diverticular bleeding	Abscess, perforation, obstruction or fistula
Follow-up		Last follow-up contact and patient record assessment at 24 months	Last follow-up contact and patient record assessment after a minimum of 12 months

Abbreviations: CT, computed tomography; ASA, American society of anesthesiologists, WBC, white blood cell count; CRP, C-reactive protein.

outcome (length of hospital stay) a gamma regression distribution was chosen due to the right-skewed data. Both treatment allocation and study were entered into the model as fixed effects. This meta-analysis tested the outcomes of both trials - although some were slightly modified - additionally to the initial analysis of both trials. Therefore, correction for multiple testing was appropriate and a two-sided $p<0{\cdot}025$ was considered statistically significant. For some relevant outcome measures a post-hoc power calculation was performed using the results from unequal groups and without continuity correction.

Multivariable logistic regression was used to identify independent risk factors. Variables that were significant or approached significance ($p<0{\cdot}05$) in the univariable analyses, were entered into the multivariable logistic regression analyses. To provide insight in the effect of clustering of the data, the univariable analyses were repeated with adjustment for study. All multivariable analyses were adjusted for study. In order to assess the effect of omitting antibiotics on outcomes in patient subgroups and thereby identifying potential subgroups that may benefit from antibiotics, the interactions between observational treatment and risk factors that met the criteria for entering the multivariable logistic regression analyses were assessed. For each risk factor a multivariable logistic regression model was created containing both the main effects of observational treatment and the risk factor, as the interaction effect of these variables. Next, the effect of omitting antibiotics in patient subgroups with multiple risk factors was assessed in a full factorial analysis. This multivariable logistic regression model included the main effects of observational treatment and all variables that were univariably associated ($p<0{\cdot}05$) with that outcome, and all possible interaction (including 2^{nd}, 3^{rd} level interactions) effects between observational treatment and the risk factors. Backward selection, with a $p>0{\cdot}05$ significance level for removal of predictors, was used to identify potential significant predictors or interactions. These analyses were also corrected for clustering of the data by including study as covariable in all models. All risk estimates are

expressed in odds ratios (OR) with 97·5% confidence intervals (97·5% CI).

Numerical variables were converted into dichotomous categorical variables, making them more easy to interpret and more easy to use in daily practice. The most common cut-off values in literature were used to dichotomise some variables; 30kg/m^2 (obesity or no obesity) in case of body mass index (BMI), 50 years in case of age, and 38°C (fever or no fever) in case of body temperature. For other numerical variables the optimal cut-off was determined using ROC-curves (at value of highest combined sensitivity and specificity); pain score on a visual analogue scale (VAS), C-reactive protein (CRP) and white blood cell count (WBC) at presentation of the initial acute diverticulitis episode (at randomization). TRIPOD guidelines for reporting were followed.[4] All analyses were performed using SPSS, version 24·0 (SPSS Inc., Chicago, IL, USA).

Role of the funding source

The funding sources had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

RESULTS

This IPDMA included 1,109 patients with 545 patients in the observational group and 564 patients in the antibiotic group. Follow-up durations were made comparable among groups with 12·3 months (IQR 12·1-13·0) in the observational group and 12.4 months (IQR 12·1-13·0) in the antibiotic group. Also, baseline characteristics were mostly comparable among groups. Only patients with primary diverticulitis were slightly but significantly more common in the antibiotic group. (Table 2)

Table 2. Baseline characteristics of patients according to study group.

	Observation (N=545)	**Antibiotics** (N=564)	**P value**
Age (years)*	58·3 (47·9-65·8)	57·6 (48·5-65·5)	0·827
Sex ratio (M:F)	228:317	230:334	0·721
Co-morbidity†	170 (31·0)	190 (33·7)	0·375
BMI (kg/m^2)*	27·4 (24·6-29·7)	27·3 (24·6-30·5)	0·569
Body temperature (°C)*	38·0 (37·2-38·3)	38·0 (37·2-38·3)	0·775
White blood cell count (x 10^9 cells/l)*	12·2 (10·3-14·2)	12·4 (10·4-14·3)	0·773
C-reactive protein (mg/l)*	76·0 (44·0-122·8)	86·0 (48·0-130·0)	0·066
Primary diverticulitis	408 (74·9)	454 (80·5)	0·024

Values in parentheses are percentages unless indicated otherwise; *values are median (IQR); †Includes cardiovascular disease and/or pulmonary disease and/or renal failure and/or diabetes mellitus; BMI, Body Mass Index

Observational versus antibiotic treatment

The length of stay of the initial hospital admission was slightly but significantly shorter in the observational group (median 2 versus 3 days respectively; p=0·037). (Table 3) Furthermore, 33 of 1,109 patients (3·0%) were treated as outpatients from the start of treatment. The rate of ongoing diverticulitis (observational 7·2% (39/545) versus antibiotics 5·0% (28/564); p=0·062) differed somewhat but this difference failed to reach statistical significance. The rates of recurrent diverticulitis (observational 8·6% (47/545) versus antibiotics 9·6% (54/564); p=0·610) were comparable. Complicated diverticulitis and sigmoid resection rates were recorded during the acute disease stage (within one month) and at one-year follow-up. Rates of complicated diverticulitis within one month were comparable among groups (observational 1·8% (10/545) versus antibiotics 1·1% (6/564); p=0·204) and differed somewhat (10 patients) but non-significantly at one-year follow-up (observational 4·0% (22/545) versus antibiotics 2·1% (12/564); p=0·079). Furthermore, rates of sigmoid resection were not different between groups at one month (observational 0·6% (3/545) versus antibiotics 0·7 (4/564); p=0·818) nor at one year (observational 5·0% (27/545) versus antibiotics 2·5% (14/564); p=0·214).

Table 3. Intention-to-treat analyses among patients with Hinchey stage 1a acute diverticulitis assigned to an observational or antibiotic treatment strategy at a total follow-up duration of median 12.3 months (IQR 12.1-13.0); follow-up duration in observational group median 12.3 months (IQR 12.1-13.0) and in antibiotic group median 12.4 months (IQR 12.1-13.0).

	Observation (N=545)	**Antibiotics** (N=564)	**P-value**
Length of hospital stay (days)	2 (2-3)	3 (2-3)	**0·037**
Ongoing diverticulitis (≥1)	39 (7·2)	28 (5·0)	0·062
Recurrent diverticulitis (≥1)	47 (8·6)	54 (9·6)	0·610
Complicated diverticulitis (≥1) within 1 month	10 (1·8)	6 (1·1)	0·204
Type† Abscess (>5cm)	3	1	
Perforation	5	5	
Obstruction	2	0	
Complicated diverticulitis (≥1) at end follow-up	22 (4·0)	12 (2·1)	0·079
Type† Abscess (>5cm)	7	4	
Perforation	8	5	
Obstruction	5	3	
Fistula	3	0	
Sigmoid resection within 1 month	3 (0·6)	4 (0·7)	0·818
Sigmoid resection at end follow-up	27 (5·0)	14 (2·5)	0·214
Type Emergency	8	4	
Elective	19	10	

Values in parentheses are percentages unless indicated otherwise; † Patients can have more than 1 type of complicated diverticulitis

Although rates of complicated diverticulitis and sigmoid resection at the end of follow-up were not statistical significantly different, one may consider the differences (4·0% versus

2·1% and 5·0% versus 2·5% in observational vs. antibiotic group, respectively) clinically relevant. The number needed to treat to prevent one case of complicated diverticulitis would be 52 (95% CI minus 52 - plus 782) and the number needed to treat to prevent one sigmoid resection would be 40 (95% CI 21-411). Since the DIABOLO trial did not power on these secondary outcomes and the AVOD trial only powered on complicated diverticulitis, a post-hoc power analysis was performed for these two outcomes based on the combined results in the present study. For the difference in complicated diverticulitis rates, this comparison had a power of 34%. To achieve a power of 80%, which is generally considered adequate for intervention trials, a sample size of 3106 patients would have been needed. For the difference in sigmoid resection rates, this comparison had a power of 48% and a hypothetical power of 80% would have needed a sample size of 2189 patients.

Risk factors and the role of antibiotics in the prevention of adverse outcomes

Although no statistical significant differences were found among treatment groups, some of the differences in adverse event rates may be considered clinically relevant. If so, statistical power appeared to be insufficient. Furthermore, even if antibiotic treatment is not effective for the entire study group, some patients possibly benefit from antibiotic treatment nevertheless. Therefore, additional analyses were performed to assess the potential role of antibiotics in the prevention of these adverse outcomes. Risk factors for the development of ongoing diverticulitis, complicated diverticulitis and sigmoid resection were assessed. Additionally, to maximize power in the logistic regression analyses, risk factors to develop ongoing diverticulitis, complicated diverticulitis or undergoing a sigmoid resection were evaluated as one adverse outcome group. (Table 4; Supplemental tables 1 to 4 show the full results of the univariable logistic regression models) A primary episode of diverticulitis instead of recurrent diverticulitis appeared to be a protective factor for the development of ongoing diverticulitis (OR 0·29; 97·5% CI 0·13-0·66). Risk factors for the development of complicated diverticulitis were pain score on a visual analogue scale of more than 7 (OR 2·78; 97·5% CI 1·18-6·54) and a white blood cell count higher than 13·5 x 10^9/L (OR 2·62; 97·5% CI 1·11-6·18). A pain score of more than 7 was also a risk factor for sigmoid resection (OR 2·32; 97·5% CI 1·05-5·10). Analyses of all three adverse outcomes as one adverse event group yielded no additional risk factors; again pain score of more than 7 and white blood cell count higher than 13·5 x 10^9/L were found as risk factors and primary diverticulitis as protective factor.

Subsequently, the influence of omitting antibiotics on all risk factors, that had been entered in the multivariable analyses, was evaluated to assess whether antibiotic treatment could alter the risk in patients susceptible for any adverse outcome and potentially prevent these adverse outcomes in specific patient subgroups. Observational management did not significantly increase the risk of adverse outcomes in all subgroups of patients. (Table 5) Furthermore, observational treatment failed to influence outcomes in all possible

Table 4. Results from multivariable analyses of risk factors (odds ratio and 97.5% confidence intervals) associated with ongoing diverticulitis, complicated diverticulitis, sigmoid resection or all three outcomes combined. Variables that were assessed univariably but were not entered in the multivariable analyses were: sex, body mass index >30kg/m^2, age >50, present comorbidity and C-reactive protein at presentation.

	No. of patients at risk	Ongoing diverticulitis	Complicated diverticulitis	Sigmoid resection	Ongoing or complicated diverticulitis, or sigmoid resection
VAS at presentation‡					
≤ 7	650				
> 7	261		**2·78 (1·18-6·54)**	**2·32 (1·05-5·10)**	**1·98 (1·18-3·34)**
Temperature at presentation					
≤ 38·0 °C	643				
> 38·0 °C	462			0·66 (0·25-1·70)	
WBC at presentation‡					
≤ 13·5 x10^9/L	736				
> 13·5 x10^9/L	370		**2·62 (1·11-6·18)**		**1·76 (1·05-2·95)**
Primary diverticulitis					
No	247				
Yes	862	**0·29 (0·13-0·66)**			**0·33 (0·16-0·71)**

† Includes cardiovascular disease and/or pulmonary disease and/or renal failure and/or diabetes mellitus; ‡ Cut-off at optimal sensitivity and specificity according to ROC curve analysis

Abbreviations: BMI, Body Mass Index; VAS, Visual Analogue Score; CRP, C-reactive protein; WBC, white blood cell count.

combinations of risk factors in the full factorial analysis. Therefore, no patient subgroup that could potentially benefit from antibiotic treatment was identified.

Table 5. Interaction between observational treatment and risk factors that were univariably associated (p<0.05) with one of the outcomes, assessed with multivariable logistic regression analyses.

	Ongoing diverticulitis	Complicated diverticulitis	Sigmoid resection	Ongoing or complicated diverticulitis, or sigmoid resection
VAS at presentation‡				
≤ 7				
> 7		0·20 (0·02-1·62)	0·24 (0·04-1·50)	0·94 (0·33-2·68)
Temperature at presentation				
≤ 38·0 °C				
> 38·0 °C			2·48 (0·34-17·93)	
WBC at presentation‡				
≤ 13·5 x10^9/L				
> 13·5 x10^9/L		0·99 (0·18-5·36)		1·22 (0·46-3·22)
Primary diverticulitis				
No				
Yes	0·91 (0·27-3·05)			1·19 (0·42-3·37)
Significant interaction terms after backward selection in full factorial analyses	None	None	None	None

‡ Cut-off at optimal sensitivity and specificity according to ROC curve analysis

Abbreviations: VAS, Visual Analogue Score; WBC, white blood cell count.

Reasons for sigmoid resection

Complications of acute diverticulitis (perforation, abscess or bowel obstruction) as the reason for sigmoid resection were mostly comparable among groups. (Table 6) Outcomes that represent a prolonged or recurrent – but not complicated – disease course (ongoing diverticulitis, persistent abdominal complaints and recurrent diverticulitis) as reason for sigmoid resection appeared to be more common in the observational group.

Table 6. Registered reasons for sigmoid resection according to treatment allocation.

	Observation	Antibiotics
Diverticular abscess	1	0
Perforated diverticulitis	5	4
Obstruction/chronic ileus	4	3
Ongoing diverticulitis	4	2
Persistent abdominal complaints	5	3
Recurrent diverticulitis	6	2
Diverticular bleeding	1	0
Fistula	1	0
Total	27	14

DISCUSSION

This individual patient data meta-analysis of two randomized clinical trials demonstrated that omitting antibiotics does not increase the risk of ongoing diverticulitis, recurrent diverticulitis, complicated diverticulitis and sigmoid resection. Although some risk factors for adverse events were identified, antibiotic treatment failed to improve outcomes in patients at risk for adverse events.

Earlier reported results of the DIABOLO trial[2] and AVOD trial[1] showed no significant differences among groups for all outcomes. However, some outcomes at six or 12 months showed a trend toward a potential benefit from antibiotics, as suggested by others.[5] These trends could not be confirmed in the present meta-analysis of one year follow-up results; all outcomes were not statistically different between groups. Since the present meta-analysis repeated some analyses from the original study papers, a correction for multiple testing was applied. Although even without this correction results would have been comparable. Only the length of hospital stay would have been statistical significantly shorter in the observational group but the small difference would have made this finding clinically irrelevant. Although not statistical significantly different, the small differences in complicated diverticulitis and sigmoid resection rates may be considered clinically relevant. The sample size of the meta-analysis appeared to be insufficient to detect such small differences. However, a statistical power of 80% would need over 3000 patients to test the difference in complicated diverticulitis rates and over 2000 patients to test the difference in sigmoid resection rates. Since the AVOD trial and DIABOLO are the only available RCTs on this topic, it is very unlikely that a sufficient sample size will be achieved with studies yet to be performed any time soon.

Whereas uncomplicated acute diverticulitis has been treated with antibiotics routinely for decades, several guidelines have adapted their recommendations meanwhile. Guidelines published in recent years state that antibiotics should not be used routinely or that

antibiotics can be avoided.[6-10] Some guidelines however state that antibiotics "should be used selectively" (American Gastroenterological Association Institute guideline[10]), antibiotics "should be given to patients with risk indications of a complicated course" (German guideline[8]) or antibiotics "on a case-by-case basis should possibly be considered" (Italian guideline[7]). Little is known however about risk factors for a complicated course of initially uncomplicated acute diverticulitis. Therefore guidelines cannot recommend antibiotics for specific patients subgroups, besides subgroups that were excluded from studies on this topic such as immunocompromised and pregnant patients. The present meta-analysis showed several risk factors for one or more adverse outcomes that can guide this selection of patients that may benefit from antibiotics. However, results showed that omitting antibiotics does not increase the risk of adverse outcomes in these high-risk patients. Therefore, prevention of these adverse outcomes with antibiotic treatment may not be warranted.

A strength of this meta-analysis is the usage of individual patient data from the only two available randomized clinical trials on this topic. A regular meta-analysis would have only been able to pool results at the (different) follow-up durations reported in the results papers. Also, not all necessary information about for instance the proportion of emergency or elective surgery was reported in both result papers and definitions of outcome measures differed between studies. Usage of individual patient data resolved these issues and therefore analyses were more accurate and complete. Although differences between the studies were dissolved as much as possible, remaining differences could have influenced the results. Acute diverticulitis cases within 3 months of randomization were considered ongoing rather than recurrent episodes. In the AVOD trial however, ongoing diverticulitis was not an outcome measure and recurrent episodes within three months were converted into ongoing episodes despite no data was available whether patients were recovered in between. Also, in order to make the trials as homogenous as possible, all patients with small pericolic abscesses from the DIABOLO trial were excluded. The AVOD trial did not include this type of patients, therefore including these Hinchey 1b patients in the meta-analysis would not have any added value toward the DIABOLO results paper and the number of Hinchey 1b patients would still be too small to draw conclusions. Furthermore, follow-up durations were made as comparable as possible but some differences probably still exist. The last follow-up moment in the AVOD trial took place at different moments in the thirteenth month whereas in the DIABOLO trial for most patients follow-up of the entire thirteenth month was available. Therefore, the follow-up duration in DIABOLO patients was slightly longer than AVOD patients. However, if all DIABOLO adverse events from the thirteenth month would have been excluded (0 cases of complicated diverticulitis, 5 cases of recurrent diverticulitis (3 observational and 2 antibiotic) and 3 sigmoid resections (2 observational and 1 antibiotic)), results would not have changed. Another limitation is the low number of events in adverse outcomes in acute uncomplicated diverticulitis patients. Therefore, statistical power is limited for the analysis of these secondary outcomes leading

to imprecision and may be a reason for downgrading the level of evidence like the American Gastroenterological Association Institute guideline.[11]

The decision to treat an acute uncomplicated diverticulitis patient with or without antibiotics does not depend on a single outcome measure. All reasons in favour of antibiotics and all reasons in favour of omitting antibiotics should be taken into account. Omitting antibiotics did not increase the risk of ongoing diverticulitis, recurrent diverticulitis, complicated diverticulitis or sigmoid resection and is therefore a safe treatment strategy. Insufficient statistical power to detect small differences in complicated diverticulitis and sigmoid resection may leave some room for discussion if one may consider these small differences clinically relevant. Furthermore, the use of antibiotics should be limited as much as possible to constrain the global treat of rising microbial resistance and to prevent antibiotic-related morbidity (8·3% of all patients in the DIABOLO trial), including potentially life threatening allergic reactions. In the end, individual patient characteristics or preferences may act as decisive factors in the decision making process. However, in subgroups of patients with independent risk factors for adverse outcome (high pain scores, high white blood cell counts and a history of acute diverticulitis at presentation) no beneficial role for antibiotics in the prevention of such adverse outcomes was found.

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SUPPLEMENTARY MATERIAL

Supplemental table 1. Univariable and multivariable analyses of risk factors (odds ratio) associated with 1 or more episodes of ongoing diverticulitis or complicated diverticulitis, or sigmoid resection.

	No. of patients at risk for ongoing, complicated diverticulitis or sigmoid resection	Ongoing, complicated diverticulitis or sigmoid resection N (%)	Univariable (unadjusted for study) OR (97.5% CI)	Univariable (adjusted for study) OR (97.5% CI)	Multivariable (adjusted for study) OR (97.5% CI)
Sex					
Female	651	58 (8.9)			
Male	458	45 (9.8)	1.11 (0.70-1.78)	1.08 (0.67-1.73)	
BMI					
≤ 30 kg/m^2	636	65 (10.2)			
> 30 kg/m^2	222	17 (7.7)	0.73 (0.39-1.38)	0.74 (0.39-1.40)	
Age					
≤ 50 years	332	37 (11.1)			
> 50 years	777	66 (8.5)	0.74 (0.46-1.20)	0.74 (0.46-1.21)	
Comorbidity[†]					
No	749	76 (10.1)			
Yes	360	27 (7.5)	0.72 (0.43-1.21)	0.66 (0.38-1.13)	
VAS at presentation[‡]					
≤ 7	650	51 (7.8)			
> 7	261	37 (14.2)	1.94 (1.16-3.25)	1.96 (1.17-3.28)	**1.98 (1.18-3.34)**
Temperature at presentation					
≤ 38.0 °C	643	66 (10.3)			
> 38.0 °C	462	37 (8.0)	0.76 (0.47-1.23)	0.81 (0.48-1.37)	
CRP at presentation[‡]					
≤ 132 mg/L	861	76 (8.8)			
> 132 mg/L	247	27 (10.9)	1.27 (0.75-2.16)	1.28 (0.75-2.18)	
WBC at presentation[‡]					
≤ 13.5 x10^9/L	736	57 (7.7)			
> 13.5 x10^9/L	370	45 (12.2)	1.65 (1.03-2.64)	1.64 (1.02-2.62)	**1.76 (1.05-2.95)**
Primary diverticulitis					
No	247	32 (13.0)			
Yes	862	71 (8.2)	0.60 (0.36-1.00)	0.38 (0.19-0.74)	**0.33 (0.16-0.71)**

[†] Includes cardiovascular disease and/or pulmonary disease and/or renal failure and/or diabetes mellitus; [‡] Cut-off at optimal sensitivity and specificity according to ROC curve analysis

Abbreviations: BMI, Body Mass Index; VAS, Visual Analogue Score; CRP, C-reactive protein; WBC, white blood cell count.

Supplemental table 2. Univariable and multivariable analyses of risk factors (odds ratio) associated with 1 or more episodes of ongoing diverticulitis.

	No. of patients at risk for ongoing diverticulitis	Ongoing diverticulitis N (%)	Univariable (unadjusted for study) OR (97.5% CI)	Univariable (adjusted for study) OR (97.5% CI)	Multivariable (adjusted for study) OR (97.5% CI)
Sex					
Female	651	40 (6.1)			
Male	458	27 (5.9)	0.96 (0.54-1.70)	0.95 (0.53-1.70)	
BMI					
≤ 30 kg/m^2	636	44 (6.9)			
> 30 kg/m^2	222	10 (4.5)	0.64 (0.28-1.42)	0.62 (0.28-1.40)	
Age					
≤ 50 years	332	24 (7.2)			
> 50 years	777	43 (5.5)	0.75 (0.42-1.36)	0.75 (0.42-1.36)	
Comorbidity[†]					
No	749	49 (6.5)			
Yes	360	19 (5.0)	0.75 (0.40-1.42)	0.73 (0.38-1.40)	
VAS at presentation[‡]					
≤ 7	650	37 (5.7)			
> 7	261	21 (8.0)	1.45 (0.77-2.74)	1.45 (0.77-2.74)	
Temperature at presentation					
≤ 38.0 °C	643	44 (6.8)			
> 38.0 °C	462	23 (5.0)	0.71 (0.39-1.29)	0.69 (0.36-1.30)	
CRP at presentation[‡]					
≤ 132 mg/L	861	47 (5.5)			
> 132 mg/L	247	20 (8.1)	1.53 (0.82-2.84)	1.53 (0.82-2.85)	
WBC at presentation[‡]					
≤ 13.5 x10^9/L	736	39 (5.3)			
> 13.5 x10^9/L	370	28 (7.6)	1.46 (0.82-2.60)	1.46 (0.82-2.60)	
Primary diverticulitis					
No	247	25 (10.1)			
Yes	862	42 (4.9)	0.46 (0.25-0.82)	0.29 (0.13-0.66)	**0.29 (0.13-0.66)**

[†] Includes cardiovascular disease and/or pulmonary disease and/or renal failure and/or diabetes mellitus; [‡] Cut-off at optimal sensitivity and specificity according to ROC curve analysis

Abbreviations: BMI, Body Mass Index; VAS, Visual Analogue Score; CRP, C-reactive protein; WBC, white blood cell count.

Supplemental table 3. Univariable and multivariable analyses of risk factors (odds ratio) associated with 1 or more episodes of complicated diverticulitis.

	No. of patients at risk for complicated diverticulitis	Complicated diverticulitis N (%)	Univariable (unadjusted for study) OR (97.5% CI)	Univariable (adjusted for study) OR (97.5% CI)	Multivariable (adjusted for study) OR (97.5% CI)
Sex					
Female	651	19 (2.9)			
Male	458	15 (3.3)	1.13 (0.51-2.47)	1.19 (0.54-2.63)	
BMI					
≤ 30 kg/m^2	636	19 (3.0)			
> 30 kg/m^2	222	6 (2.7)	0.90 (0.31-2.62)	0.86 (0.30-2.52)	
Age					
≤ 50 years	332	10 (3.0)			
> 50 years	777	24 (3.1)	1.03 (0.44-2.42)	1.02 (0.43-2.41)	
Comorbidity[†]					
No	749	24 (3.2)			
Yes	360	10 (2.8)	0.86 (0.37-2.03)	0.95 (0.39-2.28)	
VAS at presentation[‡]					
≤ 7	650	14 (2.2)			
> 7	261	15 (5.7)	2.77 (1.18-6.48)	2.75 (1.18-6.44)	**2.78 (1.18-6.54)**
Temperature at presentation					
≤ 38.0 °C	643	16 (2.5)			
> 38.0 °C	462	18 (3.9)	1.59 (0.73-3.48)	1.46 (0.63-3.40)	
CRP at presentation[‡]					
≤ 132 mg/L	861	25 (2.9)			
> 132 mg/L	247	9 (3.6)	1.27 (0.52-3.07)	1.25 (0.51-3.03)	
WBC at presentation[‡]					
≤ 13.5 x10^9/L	736	16 (2.2)			
> 13.5 x10^9/L	370	17 (4.6)	2.17 (0.98-4.80)	2.19 (0.99-4.86)	**2.62 (1.11-6.18)**
Primary diverticulitis					
No	247	12 (4.9)			
Yes	862	22 (2.6)	0.51 (0.23-1.17)	0.54 (0.20-1.42)	

[†] Includes cardiovascular disease and/or pulmonary disease and/or renal failure and/or diabetes mellitus; [‡] Cut-off at optimal sensitivity and specificity according to ROC curve analysis

Abbreviations: BMI, Body Mass Index; VAS, Visual Analogue Score; CRP, C-reactive protein; WBC, white blood cell count.

Supplemental table 4. Univariable and multivariable analyses of risk factors (odds ratio) associated with sigmoid resection.

	No. of patients at risk for sigmoid resection	Sigmoid resection	Univariable (unadjusted for study)	Univariable (adjusted for study)	Multivariable (adjusted for study)
		N (%)	OR (97.5% CI)	OR (97.5% CI)	OR (97.5% CI)
Sex					
Female	651	23 (3.5)			
Male	458	18 (3.9)	1.12 (0.54-2.29)	0.96 (0.46-1.98)	
BMI					
≤ 30 kg/m^2	636	28 (4.4)			
> 30 kg/m^2	222	7 (3.2)	0.71 (0.27-1.85)	0.79 (0.30-2.08)	
Age					
≤ 50 years	332	15 (4.5)			
> 50 years	777	26 (3.3)	0.73 (0.35-1.54)	0.74 (0.35-1.57)	
Comorbidity[†]					
No	749	31 (4.1)			
Yes	360	10 (2.8)	0.66 (0.29-1.52)	0.48 (0.21-1.12)	
VAS at presentation[‡]					
≤ 7	650	19 (2.9)			
> 7	261	16 (6.1)	2.17 (1.00-4.73)	2.25 (1.03-4.94)	**2.32 (1.05-5.10)**
Temperature at presentation					
≤ 38.0 °C	643	31 (4.8)			
> 38.0 °C	462	10 (2.2)	0.44 (0.19-1.00)	0.65 (0.27-1.57)	0.66 (0.25-1.70)
CRP at presentation[‡]					
≤ 132 mg/L	861	32 (3.7)			
> 132 mg/L	247	9 (3.6)	0.98 (0.41-2.32)	1.02 (0.43-2.43)	
WBC at presentation[‡]					
≤ 13.5 x10^9/L	736	26 (3.5)			
> 13.5 x10^9/L	370	14 (3.8)	1.07 (0.50-2.29)	1.03 (0.48-2.21)	
Primary diverticulitis					
No	247	11 (4.5)			
Yes	862	30 (3.5)	0.77 (0.35-1.73)	0.06 (0.01-0.60)	

[†] Includes cardiovascular disease and/or pulmonary disease and/or renal failure and/or diabetes mellitus; [‡] Cut-off at optimal sensitivity and specificity according to ROC curve analysis

Abbreviations: BMI, Body Mass Index; VAS, Visual Analogue Score; CRP, C-reactive protein; WBC, white blood cell count.