Diverticulitis Insights in Aetiology and Treatment

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DIVERTICULITIS

INSIGHTS IN AETIOLOGY AND TREATMENT

Niels de Korte

VRIJE UNIVERSITEIT

DIVERTICULITIS

INSIGHTS IN AETIOLOGY AND TREATMENT

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor aan
de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
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in het openbaar te verdedigen
ten overstaan van de promotiecommissie
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Niels de Korte

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TABLE OF CONTENTS

CHAPTER 1

Introduction, aim and outline of the thesis

INTRODUCTION

Colonic diverticula are one of the most common disorders of the colonic wall in western countries and most frequently localized in the sigmoid colon. They are actually pseudodiverticula because they only involve the mucosa and submucosa and are mostly asymptomatic.[1] The incidence of diverticula increases with age occurring in 10% of individuals below the age of 40 and rising to 50-70% in people older than 80 years. Diverticulitis is the most common complication of diverticulosis (presence of diverticula), which is said to affect 10-25 % of patients.[2,3] The whole spectrum of complications and complaints arising from diverticula and diverticulitis, including bleeding, stenosis, fistula formation and chronic complaints, is sometimes called "diverticular disease".

Aetiology

The process of diverticula formation is attributed to increased intraluminal pressure and lacking of strength of the colonic wall. Fibre deficiency and abnormal colonic motility may be responsible for the increased intraluminal pressure whereas the weakening of the colonic wall is probably due to the aging process and connective tissue disorders. Diverticulosis is also characterized by shortening of the teniae and thickening of the circular muscle, aspects altogether known as myochosis.[4-6]

The traditional pathogenesis of diverticulitis has focused on the obstruction of diverticula by a faecolith that might induce a cascade of events including: distention of the sac, bacterial overgrowth, vascular compromise, and micro or macro perforations. In this multifactorial concept, the colonic microbiome may play a more important role than thus far has been recognized.[8-10] The microbiome is "the ecological community of commensal, symbiotic and pathogenic microorganisms that literally share our body space."[11] In the colon, this microbiome harvests up to 5000 individual microorganisms and changes in its composition and location may play an important role in health and disease.

In this thesis we shed some light on the colonic microbiome in patients with diverticulosis and diverticulitis to further unravel the aetiology of diverticulitis. Understanding the aetiology is a prerequisite for guiding prevention and treatment of diverticulitis.

Classification and management

Colonic diverticulitis and diverticular disease in general lack a universally adopted classification system. Numerous systems, such as the Hinchey[12] and modified Hinchey classification[13], based on the grade of inflammation or perforation and the Ambrosetti[14] classification based on the CT scan imaging exist and this complicates comparison of study results. Other systems have focused more on the whole spectrum of diverticular disease. A universally adopted classification system would greatly benefit future research and comparability of results.

The clinical presentation of diverticulits may vary from mild abdominal complaints to generalised peritonitis with sepsis. Treatment of mild disease usually consists of observation and antibiotics. The necessity of antibiotics however is controversial. Abscesses can often be drained percutaneously. Perforated disease is traditionally treated by a Hartmann's procedure although emerging evidence has suggested the safety of a primary anastomoses and in selected cases even laparoscopic lavage. Different international organizations have issued guidelines but recommendations on treatment have been largely based on retrospective series and expert opinion.[15-19] Large treatment variation exists for all stages of disease both internationally and in the Netherlands. The Dutch Diverticular Disease (3D) Collaborative Study Group incorporates 3 different randomized controlled trials (RCT) and tries to answer some of the current treatment controversies including the use of antibiotics (DIABOLO trial), treatment of perforated disease (Ladies trial) and the management of recurrent diverticulitis (Direct trial).

Treatment of diverticulitis with antibiotics

The lack of evidence is particularly true for the use of antibiotics in the treatment of uncomplicated diverticulitis. The use of antibiotics in treating uncomplicated diverticulitis is common practice in all countries except the Netherlands and Scandinavia, and its use is advised in all current international guidelines.[15-19] Its necessity remained controversial until the results of the DIABOLO trial, presented in this thesis. The main goal of this trial is to evaluate the need for antibiotics in uncomplicated diverticulitis patients in a RCT. Omitting antibiotic may also implicate no need for hospital admission and therefore reduce costs. Moreover, the ever-growing problem of antibiotic resistance warrants critical evaluation of the need for prescribing antibiotics. In 2014 the World Health Organization reported on its global surveillance of antimicrobial resistance and stated that antibiotic resistance is a serious worldwide threat to public health.[20]

Aim of the thesis

In this thesis we have investigated and tried to answer some fundamental questions concerning the aetiology and treatment of diverticulitis. The studies presented in this thesis try to address the following research questions:

- What is the colonic microbiome composition in patients with diverticulosis compared to a control population?
- Is the colonic microbiome in patients with diverticulitis different from healthy individuals?
- Are there histological changes in the mucosa of patients with diverticulosis?
- Which classification systems exist and what are the differences between the systems?

- What is the current approach to the diagnosis and treatment of diverticulitis in the Netherlands?
- What is the evidence base for diagnosing diverticulitis?
- Which risk factors predict treatment failure of diverticulitis in patients treated non-operatively?
- What is the value of treating uncomplicated diverticulitis with antibiotics?
- What controversies exist in the in the current management of diverticulitis?

OUTLINE OF THE THESIS

Chapter 1 comprises the introduction, outline and aim of the thesis.

Part I: Aetiology. Colonic microbiome and mucosal changes in patients with diverticulosis and diverticulitis
The composition of the colonic microbiome in diverticulosis and diverticulitis has never been studied before. Increased insight can enhance our understanding of its possible role in the development of diverticulitis. It has been suggested that low-grade mucosal inflammation may be a precursor stage of clinically manifest diverticulitis caused by an altered microbiome. Colonic mucosa therefore needs to be assessed. Evaluation of changes in the colonic microbiome can give new insights in the pathogenesis of diverticulitis and guide future research.

Chapter 2 describes the colonic microbiome in patients with diverticulosis and relates it to mucosal changes. **Chapter 3** evaluates the colonic microbiome in patients with diverticulitis as compared to a matched control group.

Part II: Current classification and management of diverticulitis
No universally accepted classification system exists for diverticulitis and diverticular disease. In **Chapter 4** the current classification systems for diverticular disease are reviewed. A new comprehensive classification is proposed that comprises all stages and includes diagnostic and treatment modalities.

Large variation exists in the diagnosis and treatment of diverticulitis in the Netherlands. **Chapter 5** reports on the current practice in the Netherlands concerning diagnosis and treatment of diverticulitis and evaluates the adherence to international guidelines. It is important to understand treatment variation and the controversies in management that exist, to guide future research.

Chapter 6 discusses the current evidence base for diagnosing diverticulitis. Rational imaging, incorporating the latest available evidence in diagnostic accuracy is needed to limit exposure to radiation and to lower costs were possible.

Diverticulitis can be managed non-operatively in the large majority of cases. **Chapter 7** evaluates the risk factors for treatment failure in a cohort of patients treated non-operatively. Insight in risk factors for treatment failure can guide more tailor-made treatment in the future.

Part III: Treatment of diverticulitis with antibiotics
The role of antibiotics in diverticulitis treatment is largely unclear. If safe, omitting antibiotics can reduce costs and is very important in the light of development of antibiotic resistance.

Chapter 8 is a systematic review on the use of antibiotics in diverticulitis.

Chapter 9 describes the effects of antibiotics in a cohort of diverticulitis patients.

Chapter 10 presents the protocol of the DIABOLO study, a RCT evaluating the use of antibiotics or not in uncomplicated diverticulitis.

Chapter 11 reports on the outcome of the DIABOLO study, a RCT comparing antibiotic treatment to no antibiotics in uncomplicated diverticulitis.

Chapter 12 is a review of current treatment strategies in diverticulitis and underscores the need for a less aggressive approach.

Chapter 13 comprises a summary, general discussion and future perspectives.

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PART I

Aetiology.

Colonic microbiome and mucosal changes in patients with diverticulosis and diverticulitis

CHAPTER 2

Gut mucosa and microbiota analysis in diverticulosis. Not different from a control population.

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ABSTRACT

Background

It has been suggested that the low fibre diet that may lead to diverticula formation could also alter the colonic microbiome and play a role in the development of diverticulitis. The altered microbiome may induce a form of chronic low grade inflammation, eventually leading to clinically manifest stages of disease. As a first step in further understanding the development of diverticulitis we compared the colonic microbiome of individuals with diverticulosis on colonoscopy, but without symptoms, and compared it to a population without diverticulosis. Furthermore we assesed mucosal inflammation on histology specimens to identify possible low grade inflammation.

Methods

A total of 43 patients were enrolled into the study of which 19 had diverticulosis and 24 did not have have diverticulosis on colonoscopy. To asses the microbiome a high-throughput PCR-based profiling technique (IS-pro) was performed on DNA isolates from histology samples. Differences in bacterial phylum abundance and diversity (Shannon index) of the resulting profiles were assessed by conventional statistics. Dissimilarity in microbiome composition was analyzed with principal coordinate analysis (PCoA) based on cosine distance measures. The presence of inflammatory changes was assessed by performing a neutrophile and lymphocyte count on 10 different colonic fields at 40-x magnification.

Results

We found that the microbiome of patients with diverticulosis is not different to that of a control population. This is true for the sigmoid colon as well as the transverse colon. The *Firmicutes* to *Bacteroidetes* ratio is commonly used to describe and characterize a dysbiosis of the gut microbiota. Therefore, we compared their relative abundance between patients and controls. For diverticulosis patients, *Bacteroidetes* represented 62% and *Firmicutes* 38% of the total abundance in the *Firmicutes/Bacteroidetes* PCR. Almost identical proportions were found for the patient group (*Bacteroidetes* 63%, *Firmicutes* 37%) with no statistical differences between the two groups (p=0.69, Students T-test). The total load of bacteria of the *Proteobacteria* phylum was also similar between patients and controls (*P*=0.56, Students T-test). On histological examination of the specimens no influx of neutrophilic granulocytes was seen at all. We furthermore found no differences in mean lymphocyte count neither in the whole crypt nor in the bottom of the crypts. This was true for the sigmoid colon as well as the transverse colon.

Conclusions

Diverticulosis patients do not have a higher diversity of faecal microbiota than controls without diverticulosis. Furthermore, no inflammatory changes in the colonic mucosa could be detected.

INTRODUCTION

It has long been believed that all forms of diverticulitis are the result of a colonic (micro) perforation due to an inpissated fecolith in the diverticular lumen. The original Hinchey classification is based on this premise.[1] Remarkably little however is known about the true etiology of diverticulitis. Recently a different pathogenesis has been proposed indicating that diverticulitis could be considered a form of inflammatory bowel disease.[2] Chronic sub-clinical inflammation may be a precursor stage to the clinically manifest stages of acute diverticulitis. Some research has been done on the mucosa of patients with varying degrees of diverticular disease. Tursi found signs of mucosal inflammation in specimens taken from the close proximity of diverticula in individuals without complaints and without endoscopic or systemic signs of inflammation.[3] These results however could not be substantiated in another study.[4]

Fibre deficiency in the Western diet, which leads to diverticula formation, could also lead to alterations in the gut microbiota[5] and play a role in the development of diverticulitis. It is known that the human endogenous microbiota plays an important role in health and disease.[6-10] Advances in nucleic acid sequencing methods have recently made it possible to reliably assess the entire fecal microbiome. It is believed that at the level of the individual up to 5000 different bacterial species may exist. Recently, the IS-pro technique, a 16S-23S based bacterial profiling technique validated for the intestinal microbiota,[11] was used to analyze the fecal microbiome in diverticulits patients. Here it was demonstrated for the first time that the fecal micobiome is different in patients with diverticulitis as compared to other individuals.[12] To date however no information is available on the fecal microbiome in individuals with diverticulosis.

Much unclarity therefore remains as to the real pathway of development of diverticulitis and it may well be multifactorial.[13] The aim of this study was to characterize mucosal inflammation and changes in colonic microbiome in individuals with diverticula as compared to a control population. This can contribute to further unravel the etiology of diverticulitis and guide future research on treatment and prevention.

MATERIALS AND METHODS

Study design

A prospective study was carried out in patients undergoing routine follow up colonoscopy for causes not related to diverticular disease or inflammatory bowel disease. Colonoscopy was performed by one gastroenterologist (JK). Prior to colonoscopy informed consent was obtained.

All patients underwent the same standard bowel preparation. When diverticula were encountered during colonoscopy a total of five biopsies were taken from the mucosa around

diverticula in the sigmoid colon and five biopsies were taken from the transverse colon as a control location. In the control group without diverticula on colonoscopy, five biopsies were taken from the sigmoid colon at random and from the transverse colon at random.

Subjects

Patients aged 18 years or older with hematochezia, gastrointestinal hemorrhage, unexplained changes in bowel habit, weight loss, iron-deficiency anemia, chronic constipation without succesfull conservative treatment, screening for and follow-up of colorectal cancer were eligible for recruitment.

Exclusion criteria were: suspicion of diverticular related complaints, proven history of symptomatic diverticular disease, use of coumarin derivates, unless stopped one week before colonoscopy, use of NSAID's unless stopped one week before colonoscopy, use of platelet aggregate inhibitors, including aspirin, unless stopped one week before colonoscopy, sedation before informed consent, history of inflammatory bowel disease.

The local ethics committee approved the study. All persons gave their informed consent before inclusion in the study.

Sample size calculation

Only one previous study was preformed on this subject.[3] This study found a difference in mean lymphocytic density count of 1.8 between individuals with endoscopic signs of diverticula and patients without diverticula. The mean lymphocytic density count in the diverticulosis group was 5.9 compared to 4.1 in the group without diverticula. The standard deviation was 1.7. To be able to reproduce this difference a minimal total of 2 x 17 individuals have to be included. We planned to enroll 2x 20 patients, one group with diverticula and one group without diverticula.

Histology samples

The presence of inflammatory changes was assessed as previously described by performing a neutrophile and lymphocyte count on 10 different colonic fields at 40-x magnification.[3] Hematoxylin and eosin staining was performed. To identify lymphocytes, antiCD3 antibodies (ready to use rabbit anti human polyclonal antibodies, Dako, Copenhagen, Denmark) were used and for neutrophils anti-CD15 antibodies. (Ready to use mouse antihuman monoclonal antibodies, Dako, Copenhagen, Denmark) The number of lymphocytes and neutrophils were scored both at the bottom and in the whole crypts.

For histological evaluation the means of lymphocyte and neutrophils infiltrate were compared using the Mann-Whitney test. A P value of <0.05 was considered statistically significant.

DNA isolation and amplification

Colonic biopsies used for analysis of the adherent microbiota were washed in PBS after harvesting to remove residual fecal material and non-adherent bacteria. Directly after this, biopsies were snap frozen in liquid nitrogen after which they were stored at -20°C.

After thawing of the samples, total DNA extraction was performed on all samples with the NucliSENS® easyMag® automated DNA isolation machine (Biomérieux, Marcy l'Etoile, France). One ml of nucliSENS® lysisbuffer, containing guanidine thiocyanate, was added to each vial containing a swab tip and the mixture was shaken at 1400rpm (Thermomixer comfort, Eppendorf, Hamburg, Germany) for five minutes. Afterwards, all samples were centrifuged for four minutes at 12.000g and added to the easyMag container. We have described exact DNA isolation previously.[11]

IS-profiling of the intestinal microbiota and data analysis

Amplification of IS-regions was performed with the IS-pro assay (IS-diagnostics, Amsterdam, the Netherlands). IS-profiling was done as described previously. All data were pre-processed with the IS-pro proprietary software suite (IS-Diagnostics, Amsterdam, the Netherlands). This process resulted in peak profiles with the length of each peak, measured in nucleotides, corresponding to a specific operational taxonomic unit (OTU), and a specific intensity, measured in relative fluorescence units (RFU), reflecting quantity of PCR product and corresponding to the abundance of that OTU. Finally, fluorescent labels categorize peaks into three phylogenetic groups: *Proteobacteria*, *Bacteroidetes* or *Firmicutes*/*Actinobacteria*/*Fusobacteria*/*Verrucomicrobia* (FAFV). All intensities were log2 transformed. Log2 transformation of complex profiles compacts the range of variation in peak heights, reducing the dominance of high peaks and including less abundant species of the microbiota in downstream analyses. This results in improved consistency of estimated correlation coefficient, lower impact of interrun variation and improved detection of less prominent species. This conversion was used in all downstream analyses.

Correlation and diversity analysis

To analyze similarities between samples, a correlation and a diversity analysis was performed. Correlation was analyzed by calculating Pearson correlations per phylum and for total microbiota within individuals (sigmoid versus transverse colon biopsies) and between individuals (sigmoid versus sigmoid colon) for control and diseased groups. Diversity was calculated both per phylum and for the overall microbial composition (by pooling all phyla together). Within-sample diversity was calculated using the Shannon index.[14] Dissimilarities between samples, or between-sample diversity, were represented in a dissimilarity matrix that was built using the cosine distance measure.[12] Diversity analysis was performed using the vegan software package in R.

Partial least squares discriminant analysis (PLS-DA)

A partial least squares discriminant analysis (PLS-DA) regression model[15] was used for the prediction of clinical status of samples; i.e. whether it belonged to a diverticulosis patient or to a control subject. The PLS-DA model was constructed on the basis of four different datasets: one for each of the three separate phylum groups and one for the overall microbial composition, by pooling all phyla. Only the top 25% most variable predictors were considered in the analysis.

PLS-DA model validation was carried out by a 10-fold cross validation procedure. The PLS-DA was described extensively in a previous study performed by us.[12] PLS-DA analysis was performed using the DiscriMiner package in R. All data visualizations were performed with the Spotfire software package (TIBCO, Palo Alto, CA, USA).

Clustered heat map

For a global analysis of all versus all samples, we generated a clustered heat map. First, a correlation matrix was generated by means of cosine correlation, and then clustering was done with the unweighted pair group method with arithmetic mean (UPGMA).

RESULTS

A total of 43 patients were enrolled into the study of which 19 had diverticulosis and 24 didn't have diverticulosis. Table 1 shows the baseline characteristics and table 2 the indications for colonoscopy.

Histology

On histological examination of the specimens no influx of neutrophilic granulocytes was seen at all. We furthermore found no differences in mean lymphocyte count neither in the whole crypt nor in the bottom of the crypts. This was true for the sigmoid colon as well as the transverse colon. (table 3.)

Intestinal microbiota analysis

The *Firmicutes* to *Bacteroidetes* ratio is commonly used to describe and characterize a dysbiosis of the gut microbiota.[17,29] Therefore, we compared their relative abundance between patients and controls. For diverticulosis patients, *Bacteroidetes* represented 62% and *Firmicutes* 38% of the total abundance in the *Firmicutes/Bacteroidetes* PCR. Almost identical proportions were found for the patient group (*Bacteroidetes* 63%, *Firmicutes* 37%) with no statistical differences between the two groups (p=0.69, Students T-test). The total load of bacteria of the *Proteobacteria* phylum was also similar between patients and controls (*P*=0.56, Students T-test).

Correlation and Diversity Analysis

A first approach to assessing differences in microbiota was by performing a correlation of microbiota profiles. To assess local diverticula-related variations in microbiota, we compared profiles from sigmoid and transverse colon within individuals for both patients and controls. Indeed, some variation was identified between the two locations, most outspokenly so for *Proteobacteria* and less so for *Firmicutes* and *Bacteroidetes*. However, the extent of these variations was similar in patients and controls. Furthermore, to get

Tabel 1 | Patient characteristics

	Diverticulosis N=19	No diverticulosis N=24
Sex (M)	14 (74%)	9 (38%)
Age (years)	66.0 (62.7-69.3)	56.4 (52.7-56.5)

Tabel 2 | Indications for colonoscopy

	Diverticulosis N=19	No diverticulosis N=24
Hematochezia	1	3
Change in bowel habit	2	2
Anemia eci	0	1
Obstipation	0	3
Screening and follow up colorectal carcinoma	2	4
Follow up after polypectomy	13	9
Other	1	2

Tabel 3 | Lymphocyte count

	Diverticulosis	No Diverticulosis	P value
Transverse colon Bottom of crypt	1.86	2.22	0,849
Transverse colon Whole crypt	9.56	8.39	0,261
Sigmoid colon Bottom of crypt	1.56	1.8	0,754
Sigmoid colon Whole crypt	6.95	7.12	0,765

a first impression of the presence of a specific diverticula-related microbiota in patients, we compared sigmoid colon samples from all patients to each other and we compared all sigmoid colon samples of controls to each other. In these inter-individual comparisons, correlations were generally low. Again, distribution of correlation coefficients was similar for patients and controls (Figure 1).

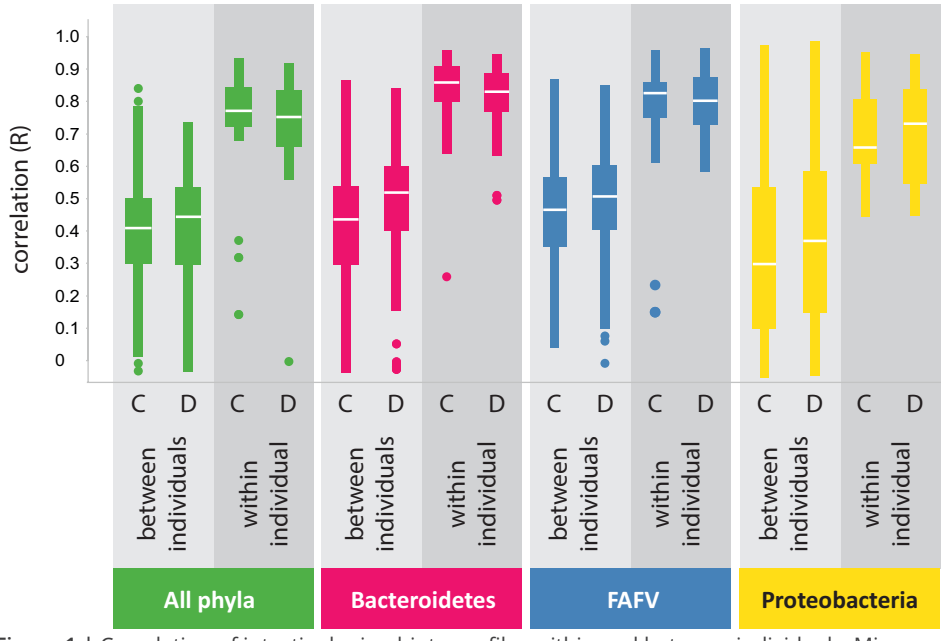

Figure 1 | Correlation of intestinal microbiota profiles within and between individuals. Microbiota profiles are highly similar within individuals for all phyla, regardless of disease status (C = control, D = diverticulosis). Between individuals microbiota profiles are dissimilar. If there was a specific diverticulosis signature, higher similarity within the diverticulosis (D) than control (C) group would be expected.

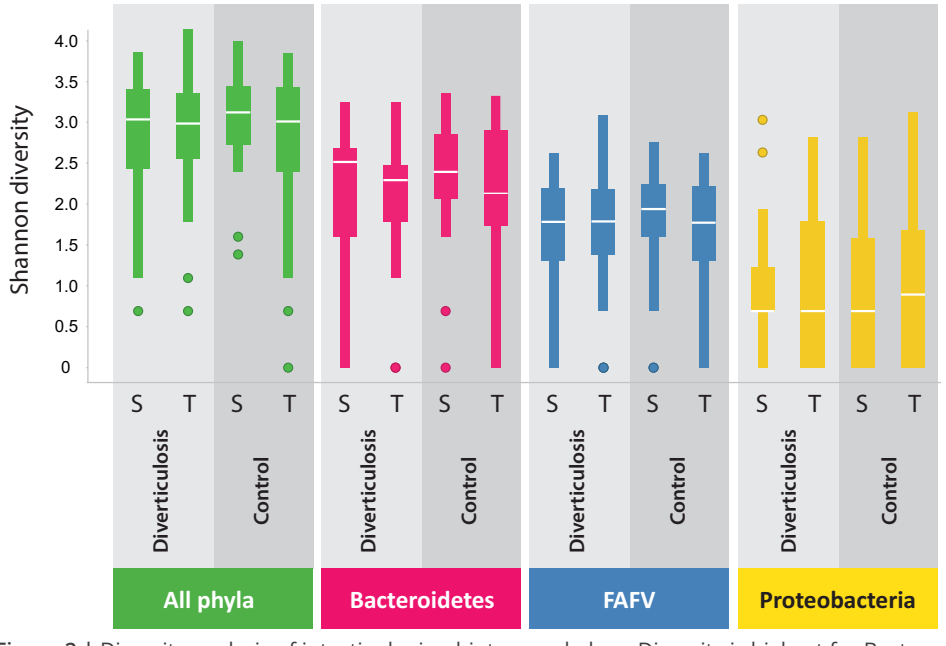

Figure 2 | Diversity analysis of intestinal microbiota per phylum. Diversity is highest for Bacteroidetes, followed by FAFV group and Proteobacteria. Diversity is not different in sigmoid and transverse colon or for diverticulosis patients or controls.

As diversity is a commonly applied measure to assess differences in microbiota, we performed a diversity analysis on all samples. Then, diversity indices for all phyla and sample types were compared to each other (Figure 2). This analysis showed that diversity was highest for *Bacteroidetes*, followed by *Firmicutes* and *Proteobacteria*. In this analysis too, no differences were found in different sample types or between patients and controls.

Partial least squares discriminant analysis (PLS-DA)

To identify individual species or sets of bacterial species related to the presence of diverticula, we performed a partial least squares discriminant analysis (PLS-DA). We were able to construct a model that had 74% accuracy in predicting clinical status, i.e. in 74% of samples the model was able to discriminate diverticulosis samples from healthy controls based on a selection of the most variable bacterial predictors. However, when the model was cross-validated, all predictive power was lost, indicating the absence of truly disease-specific bacterial species in this data set (Figure 3).

Clustered heat map

For a per-sample analysis of all data, we generated a clustered heat map (Figure 4). Here, it can be seen that most biopsies from the sigmoid colon show highest correlation to the corresponding transverse colon sample. Sometimes, samples show highest correlation to a sample from another individual. However, this is not disease-state specific. No clustering is apparent for diverticulosis or control samples

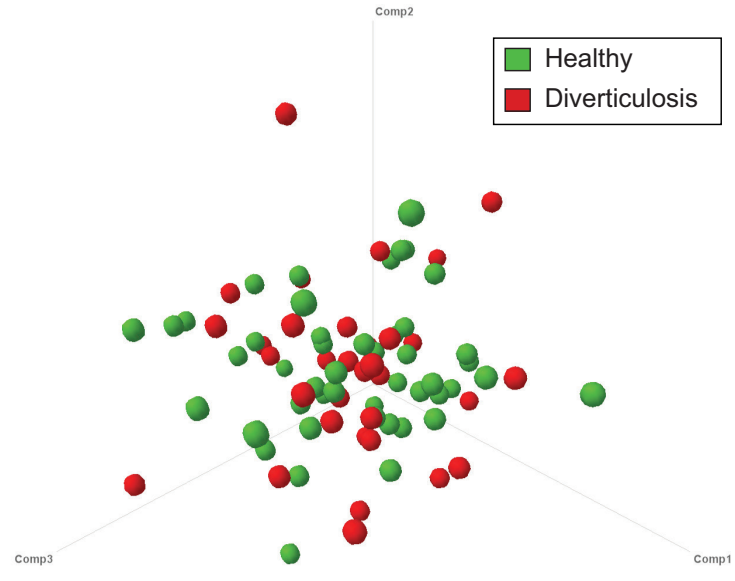

Figure 3 | Three dimensional PLS-DA scores plot of microbiota samples based on the most discriminative PLS components. It can be clearly seen that there is no separation, suggesting the absence of discriminative species for either state (healthy or diverticulosis)

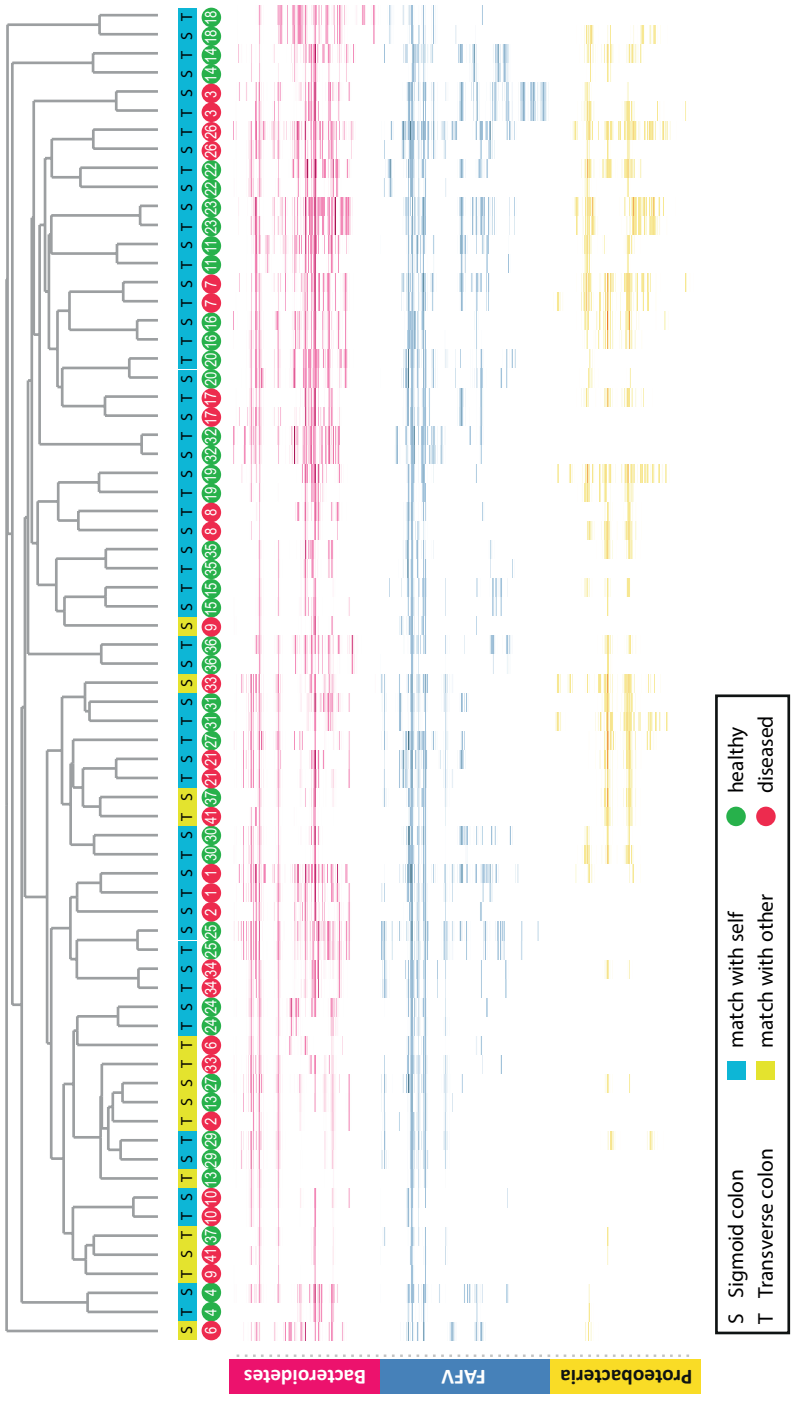

Figure 4 | Clustered heat map of all mucosal biopsy samples. Each column represents a sample from either sigmoid (S) or transverse (T) colon. Each band corresponds to an OTU, the intensity to its abundance, the color to its phylum group. Generally, microbiota of the sigmoid colon shows high correlation to the microbiota of the transverse colon of the same individual (all blue squares). Sometimes, correlation is stronger to a sample from another individual (yellow squares). However, no clear pattern can be seen here: samples from diverticulosis patients have a similar likelihood to having a low intra-individual correlation as control samples. Thus, random variation seems to be a more likely explanation here than an underlying biological phenomenon. Finally, there is no evident clustering of healthy or diseased individuals.

DISCUSSION

We demonstrated in this study that there are no evident changes in the mucosa or its associated microbiota in individuals with diverticula as compared to a control population.

The absence of inflammation of the mucosa is in line with a previous report on this subject [4] but in contrast with another study that did find a significant difference in lymphocyte infiltration in asymptomatic diverticular disease.[5] There are no previous reports on microbiota composition in diverticulosis. Our study is hampered by a few drawbacks. Firstly inflammation assessment was done by assessing lymphocyte and neutrophilic granulocyte influx in gut mucosa only. It would be interesting to see whether other inflammation markers or cytokines show any difference. Furthermore microbiota analysis was done on mucosal samples after bowel preparation, which has been shown to impact intestinal microbiota composition.[17] It can be debated if our results would be the same on rectal swabs or feces in unprepped subjects. Moreover, a larger sample size may yet reveal differences in microbiota composition. However, in a previous study we were able to clear microbiota signature in diverticulitis patients with the same technique and similar sample size.[12] Given this background, the absence of a microbiota signature for diverticulosis in this study seems highly indicative that there is no association between the presence of diverticula and microbiota.

In this study, we used a number of different techniques to identify changes in colonic microbiota associated with diverticulosis. If there would be local differences in microbiota related to diverticular disease, differences between sigmoid and transverse colon samples would be expected to be larger in patients than in controls. This was however not the case. What is more, inter-individual variation in sigmoid colon microbiota was similar for the patient group and the control group for all bacterial phyla. This indicated that there was no obvious diverticula-specific microbiota, as patient-related samples would then have been expected to be more similar than control samples. A specific diverticula-related microbiota or a pronounced structural difference in diverticula-associated microbiota could also not be identified by diversity analysis.

The PLS-DA analysis we performed is a technique that generally performs very well in identifying biomarkers associated to disease state in complex data. While the technique was not developed to demonstrate absence of differences, the lack of discriminating species found with this sensitive technique, does strongly suggest their absence in this data set.

Recent hypotheses have focused more on a multifactorial etiopathogenis of diverticulitis with an important role for a changed microbiome than on the old dogma of an inpissated fecolith causing a microperforation.[13] We recently demonstrated that the colonic microbiota in patients with diverticulitis differs from that of a control population.[12] Therefore it would be interesting to see whether this change in colonic microbiome is also present in individuals before they develop diverticulitis. This is the first study to date to evaluate the

colonic micobiome in patients with diverticula without symptoms.

In conclusion, there does not seem to be an evident change in microbiota or in mucosal inflammation in diverticulosis patients. Whether the changes in microbiota as identified in diverticulitis are a cause or the effect of the disease remains unclear and warrants more research.

CONFLICT OF INTEREST

Potential competing interest: AB and PS are involved in the IS-pro technology platform development. The other authors declare that no disclosures exist.

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CHAPTER 3

Fecal microbiome analysis as a diagnostic test for diverticulitis.

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ABSTRACT

Background

Disease specific variations in intestinal microbiome composition have been found for a number of intestinal disorders, but little is known about diverticulitis. The purpose of this study was to compare fecal microbiota of diverticulitis patients with control subjects from a general gastroenterological practice, and to investigate the feasibility of predictive diagnostics based on complex microbiota data.

Methods

Thirty-one patients with CT-proven left-sided uncomplicated acute diverticulitis were included and compared with 25 control subjects evaluated for a range of gastrointestinal indications. A high-throughput PCR-based profiling technique (IS-pro) was performed on DNA isolates from baseline fecal samples. Differences in bacterial phylum abundance and diversity (Shannon index) of the resulting profiles were assessed by conventional statistics. Dissimilarity in microbiome composition was analyzed with principal coordinate analysis (PCoA) based on cosine distance measures. To develop a prediction model for the diagnosis of diverticulitis, we used cross-validated partial least squares discriminant analysis (PLS-DA).

Results

Firmicutes/*Bacteroidetes* ratios and *Proteobacteria* load were comparable among patients and controls (P=0.20). The Shannon index indicated a higher diversity in diverticulitis for *Proteobacteria* (P<0.00002) and all phyla combined (P=0.002). PCoA based on *Proteobacteria* profiles resulted in visually separate clusters of patients and controls. The diagnostic accuracy of the cross-validated PLS-DA regression model was 84%. The most discriminative species derived largely from the family *Enterobacteriaceae*.

Conclusions

Diverticulitis patients have a higher diversity of faecal microbiota than controls from a mixed population, with the phylum *Proteobacteria* defining the difference. Analysis of intestinal microbiota offers a novel way to diagnose diverticulitis.

INTRODUCTION

The human endogenous intestinal microbiota is known to play a fundamental role in health and disease. Functions of the commensal gut flora include protection against direct epithelial cell injury[1] , regulation of host fat storage[2] as one of many metabolic functions, stimulation of intestinal angiogenesis[3] and influencing the development and function of the gut immune system.[4-5]

Nucleic acid sequencing methods have undergone tremendous developments,[6] and have provided a major advance in culture-independent analysis of the intestinal microbiota. However, these techniques are typically laborious and expensive for application on small batches of samples as is common in clinical practice. Profiling techniques are a cheap and reliable alternative. We have recently validated and optimized a specific profiling technique termed IS-pro for human intestinal microbiome analysis. It has proved to be a highly reproducible method suitable for high-throughput profiling of the human intestinal microbiota.[7]

With molecular techniques, it has been shown that the intestine harbours a complex bacterial community that consists largely (>95%) of 2 bacterial phyla, the *Bacteroidetes* and the *Firmicutes.*[8] Molecular genetics research suggests that at the level of the individual, the colonic microbiota may consist of up to 5000 different bacterial species.[9] The composition seems to be relatively stable in time and is more or less conserved throughout the colonic tract.[8, 10-12] Between individuals, however, the composition is highly variable.[8, 10, 13] There are also differences between mucosal and faecal communities.[14] Disease specific variations in the composition of the colonic microbiota have been identified, for example in inflammatory bowel disease (IBD)[3, 15-16] and metabolic syndrome.[17-18] Furthermore, specific bacterial species have been found to infiltrate the epithelium and submucosa in acute appendicitis.[19]

Diverticular disease (DD) patients have also been hypothesized to harbour a change in colonic flora that promotes disease and inflammation, either due to altering the immune process or by permitting an abnormal response to potentially harmful bacteria.[20] DD is a common condition in Western countries and defined as symptomatic disease associated with colonic diverticula. Diverticula are outpocketings of the colonic mucosa and submucosa through weaknesses of muscle layers in the colon wall. Acute diverticulitis develops in 10–25% of individuals with diverticula and imposes an impressive clinical and socioeconomic burden on health care resources.[21] Currently, we lack a clear understanding of the pathophysiologic mechanisms responsible for the progression from diverticulosis to diverticulitis. Theories are now shifting away from the traditional dogma that posits fecolith obstruction of a diverticulum to cause acute diverticulitis towards a view in which microbiota may play a central role. However, neither a diverticulitis specific microbiome nor a single causative microorganism has yet been found. Characterization of the colonic microbiota composition is the first step in elucidating their possible role in the etiopathogenesis of DD and its inflammatory complications.

The aim of our study was to characterize the faecal microbiota by means of IS-pro[7] in patients with a first episode of uncomplicated acute diverticulitis and compare these to the microbiota of controls. Identification of a diverticulitis-specific microbial composition could lead to clinical application of this technique in diagnosing disease. No published data on species composition during a first episode of uncomplicated acute diverticulitis are available yet.

METHODS

Study design

This study was ancillary to the 'DIABOLO Trial: A multicenter randomized clinical trial investigating the cost-effectiveness of treatment strategies with or without antibiotics for uncomplicated acute diverticulitis', which was approved by the Medical Ethics Committee, Academic Medical Center, Amsterdam, The Netherlands (no. 2009_233), and registered at ClinicalTrials.gov (no. NCT01111253)[22]. We carried out this prospective cohort study in three of the 22 participating centers (one academic and two teaching hospitals), based on practical grounds and logistics.

Subjects

Eligible diverticulitis patients were consecutive trial subjects from the three including centers of 18 years or older with a first episode of acute left-sided uncomplicated modified Hinchey 1A or 1B[23] diverticulitis demonstrated by computed tomography (CT). Included patients were recruited between August 2011 and September 2012. Informed consent was obtained from these trial subjects.

The control subjects were derived from an existing database of a mixed population of adult patients evaluated in another academic hospital for a range of gastrointestinal complaints, notably with no diagnosis of diverticulitis. Diverticulosis is a common finding at colonoscopy, with a prevalence of DD that increases with age from less than 10% in people younger than 40 years to 50-66% in octogenarians. The lifetime risk to develop diverticulitis is less than 25% in these patients.[24,25] Possibly a continuum in the microbiota composition exists in patients with diverticulosis and diverticulitis. To incorporate the possibility to distinguish mild diverticulitis from diverticulosis, the control group also included patients with diverticulosis.

The indications for and/or the diagnoses after colonoscopy in the control subjects were the following: follow-up after polypectomy (*n=1*), anaemia e.c.i. (*n=1*), benign neoplasm (*n=3*), malignant neoplasm (*n=1*), Morbus Crohn (*n=4*), ulcerative colitis (*n=2*), indeterminate colitis (*n=1*), irritable bowel syndrome (*n=2*), abdominal pain e.c.i. (*n=1*), surveillance for familial cancer susceptibility (*n=3*) and diverticulosis (*n=6*).

Rectal swabs

In the diverticulitis patients, sampling by means of a rectal swab (FLOQSwabs 552C, Copan, CA, USA) was performed at presentation on the emergency ward, prior to starting antibiotics when allocated to this treatment. The control subjects had their rectal swab taken prior to colonoscopy which was performed to evaluate their gastrointestinal complaints or for other indications. Rectal swabs were inserted into the anal canal, beyond the anal verge (±3 cm). Subsequently the tips of the swabs were gathered in sterile containers with 1ml of reduced transport fluid (RTF) medium[26] and stored at -20 °C within two hours of collection.

DNA isolation

After thawing of the samples, total DNA extraction was performed on all samples with the NucliSENS® easyMag® automated DNA isolation machine (Biomérieux, Marcy l'Etoile, France). One ml of nucliSENS® lysisbuffer, containing guanidine thiocyanate, was added to each vial containing a swab tip and the mixture was shaken at 1400rpm (Thermomixer comfort, Eppendorf, Hamburg, Germany) for five minutes. Afterwards, all samples were centrifuged for four minutes at 12.000g and added to the easyMag container. DNA extraction was performed on the easyMag machine with the Specific A protocol as described by the manufacturer. DNA was eluted in 110µl buffer and stored at 4°C until use for polymerase chain reaction (PCR) amplification.

IS-profiling of the intestinal microbiota

Amplification of IS-regions was performed with the IS-pro assay (IS-diagnostics, Amsterdam, the Netherlands). IS-pro involves bacterial species differentiation by the length of the 16S–23S rDNA interspace region with taxonomic classification by phylum-specific fluorescent labelling of PCR primers. Essentially, the IS-pro procedure consists of two multiplex PCRs: a first PCR for the phyla *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Fusobacteria* and *Verrucomicrobia* and a second PCR for the phylum *Proteobacteria*. The assay was performed according to the protocol provided by the manufacturer. Amplifications were carried out on a GeneAmp PCR system9700 (Applied Biosystems, Foster City, CA). After PCR, 5µl of PCR product was mixed with 19.8µl formamide and 0.2µl Mapmaker 1000 ROX-labeled size marker (BioVentures, Murfreesboro, TN, USA). DNA fragment analysis was performed on an ABI Prism 3130XL Genetic Analyzer (Applied Biosystems). Results are presented as color-labeled peak profiles (figure 1).

Data analysis

Log2 transformation and phylum abundance

All data were pre-processed with the IS-pro proprietary software suite (IS-Diagnostics, Amsterdam, the Netherlands). This process resulted in profiles consisting of a set of 1071 peaks with a specific length, measured in nucleotides, reflecting lengths of IS fragments, and a specific height, measured in relative fluorescence units (RFU), reflecting quantity of PCR product. In order to further analyze the data, we considered each peak in a profile as

an operational taxonomic unit (OTU) and its corresponding intensity as its abundance. All intensities were log2 transformed. Log2 transformation of complex profiles compacts the range of variation in peak heights, reducing the dominance of high peaks and including less abundant species of the microbiota in downstream analyses. This results in improved consistency of estimated correlation coefficient, lower impact of inter-run variation and improved detection of less prominent species. This conversion was used in all downstream analyses such as calculating within-sample and between-sample microbial diversity. A clustered heat map was made by generating a correlation matrix of all log2 transformed profile data followed by clustering with the unweighted pair group method with arithmetic mean (UPGMA).

Diversity Analysis

Diversity was calculated both per phylum and for the overall microbial composition (by pooling all phyla together). Within-sample diversity was calculated as the Shannon index [27]. Dissimilarities between samples, or between-sample diversity, was represented in a dissimilarity matrix that was built using the cosine distance measure. Given two vectors of attributes (two profiles in our case), A and B, the cosine dissimilarity is represented using a dot product and magnitude as:

$$dissimilarity = 1 - \cos\theta = 1 - \frac{\sum_i^n = 1\ A_i \times B_i}{\sqrt{\sum_i^n = 1\ (A_i)^2} \times \sqrt{\sum_i^n = 1\ (B_i)^2}}$$

The resulting dissimilarity matrix was summarized and visualized in a low-dimensional space using principal coordinate analysis (PCoA). Diversity analysis was performed using the vegan software package in R.

Partial least squares discriminant analysis (PLS-DA)

A partial least squares discriminant analysis (PLS-DA) regression model [28] was used for the prediction of clinical status of samples; i.e. whether it belonged to a diverticulitis patient or to a control subject. The PLS-DA model was constructed on the basis of four different datasets: one for each of the three separate phylum groups and one for the overall microbial composition, by pooling all phyla. Only the top 25% most variable predictors were considered in the analysis.

PLS-DA model validation was carried out by a 10-fold cross validation procedure. In practice, the dataset was split into 90% of samples for model construction (i.e. the training set) with the aim to predict the other 10% (i.e. the test set). This procedure was repeated for 10 iterations, where each sample served as a test sample exactly once. Accuracy rates, specificity and sensitivity were computed for the samples that were used as a test set in every iteration, and the model predictive power was further assessed using a receiver operating characteristic (ROC) curve, a function of the true positive rate (TPR or sensitivity) and false positive rate (FPR or 1-specificity).

PLS-DA provides a quantitative estimate of the discriminatory power of each descriptor by means of VIP (variable importance for the projection) parameters. VIP values rank the descriptors by their ability to discriminate different groups and is therefore considered an appropriate quantitative statistical parameter. We used the VIP criterion to rank the different OTUs based on their contribution to the response variable (clinical status, i.e. diverticulitis: yes or no) and PLS components. The OTUs with the highest contribution (VIP score > 1.2) were translated to most likely bacterial species by comparison to a database consisting of >1500 bacterial species and their associated IS lengths. Finally, to assess whether prediction of clinical status would be feasible with a set of specific qPCRs, we performed the same PLS-DA validation as mentioned above for a subset of the ten most discriminative OTUs (the ten OTUs with the highest VIP values).

PLS-DA analysis was performed using the DiscriMiner package in R (version 2.15.2). All data visualizations were performed with the Spotfire software package (TIBCO, Palo Alto, CA, USA).

Ethics

This study has been approved by the appropriate ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All persons gave their informed consent prior to their inclusion in the study.

RESULTS

Patient characteristics

Thirty-one patients diagnosed with a first episode of uncomplicated acute diverticulitis were included, of which 20 were males and 11 females, with a mean age of 58 years (95% Confidence Interval (CI): 54-62). In the control group, a total of 25 subjects were included, 12 males and 13 females, with a mean age of 53 years (95% CI: 47-59). Patients' characteristics are listed in Table 1.

Bacterial phylum abundance and profile clustering

The *Firmicutes* to *Bacteroidetes* ratio is commonly used to describe and characterize a dysbiosis of the gut microbiota.[17,29] Since these two phyla are being amplified in the same PCR reaction, we could compare their relative abundance between patients and controls. The phylogenetic characterization of samples from control subjects uncovered that *Bacteroidetes* represented 51% and *Firmicutes* 49% of the total abundance in the *Firmicutes/Bacteroidetes* PCR. Exactly the same proportions were found for the patient group. The total load of bacteria of the *Proteobacteria* phylum was relatively similar between patients and controls (10.2 ± 1.9 log2 RFU and 10.1 ± 2.0 log2RFU for patients and controls, respectively; *P*=0.20, Mann-Whitney U-test).

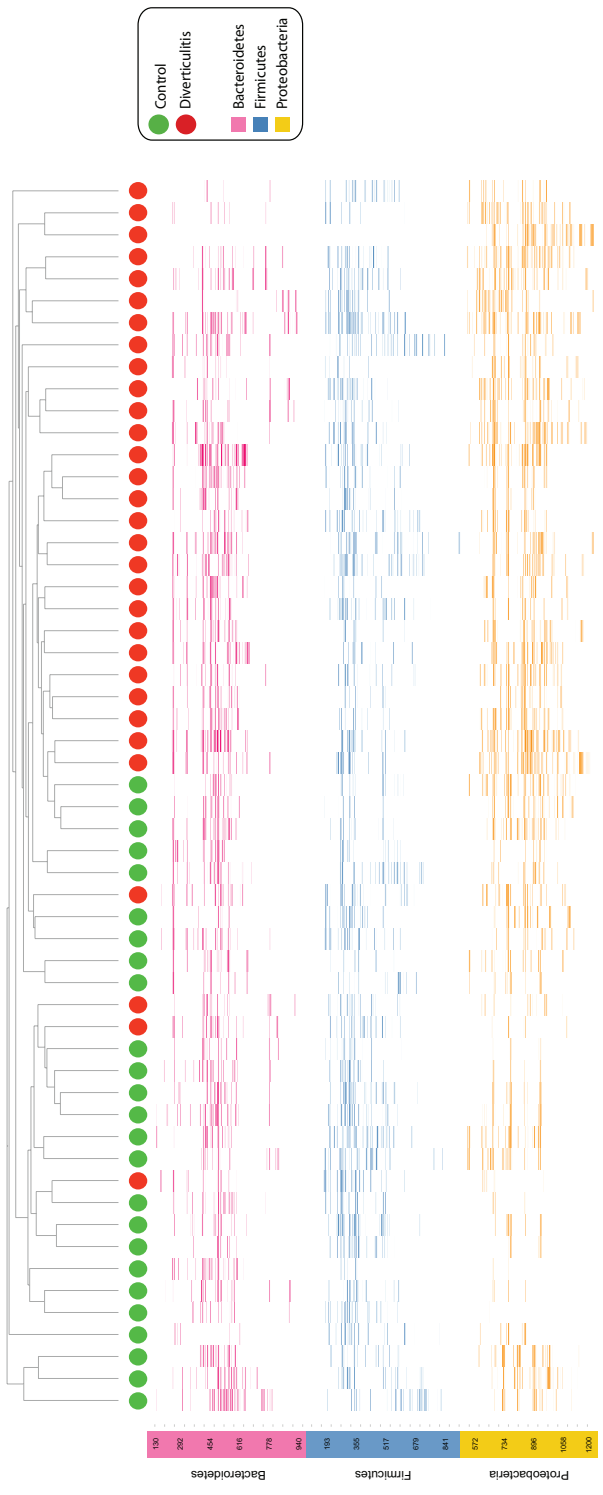

Figure 1 | Heatmap of all profiles sorted and colored by phylum. When profiles are clustered by total profile, it can be seen that there is a separation between profiles from diverticulitis patients and controls. *Proteobacteria* profiles can be seen to generally harbour more species in diverticulitis patients than in controls.

Table 1 | Demographic and baseline characteristics of diverticulitis patients and control subject

	Diverticulitis patients *(n=31)*	**Control subjects** *(n=25)*
Sex (M)	20 (64.5%)	12 (48%)
Age*(years)	57.8 (53.6-62.0)	52.6 (46.6-58.6)
ASA (I:II)	18 (58.1%) :13 (41.9%)	UK
BMI*(kg/m^2)	27.1(25.7-28.5)	26.7 (24.0-29.6)
Duration of complaints† (days)	2 (1-3)	UK
Restricted oral intake *2 missings*	11 (35.5%)	UK
Diarrhea	3 (9.7%)	UK
Temperature*(°C)	37.1 (36.8-37.4)	UK
CRP†(mg/dl)	89 (47.9-131.0)	UK
WBC*(11x10E9/L)	11.9 (10.7-13.1)	UK

Abbreviations: ASA, American Society of Anesthesiologists (physical status classification); BMI, body mass index; UK, unknown; CRP, C-reactive protein; WBC, white blood cell (count);
*Data are means with 95% confidence intervals (CI);
†Data are medians with interquartile ranges.

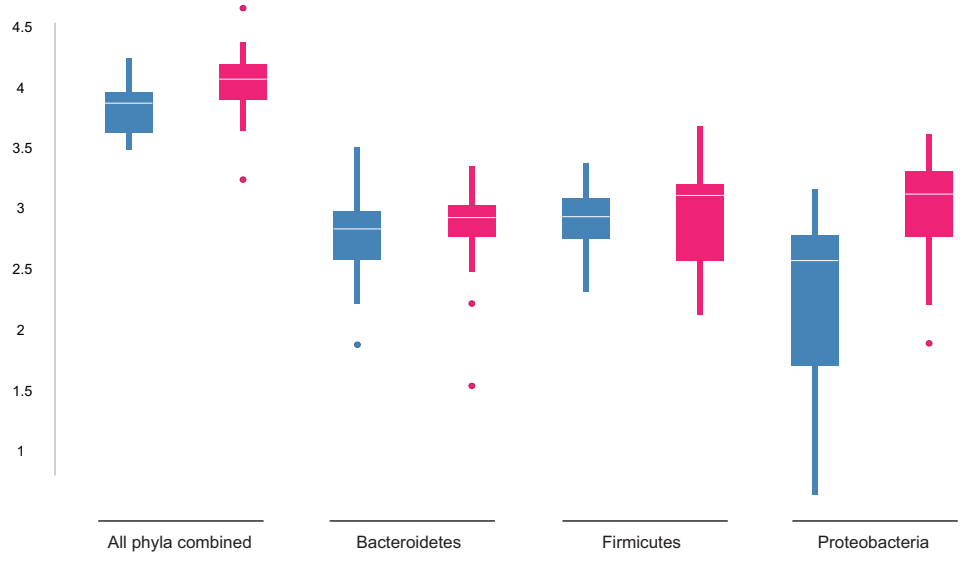

Figure 2 | Boxplot comparisons of within sample diversity as calculated by Shannon index all phyla combined and per phylum for diverticulitis patients and control subjects, with a significant higher diversity of the phylum *Proteobacteria*and all phyla combined in diverticulitis patients.

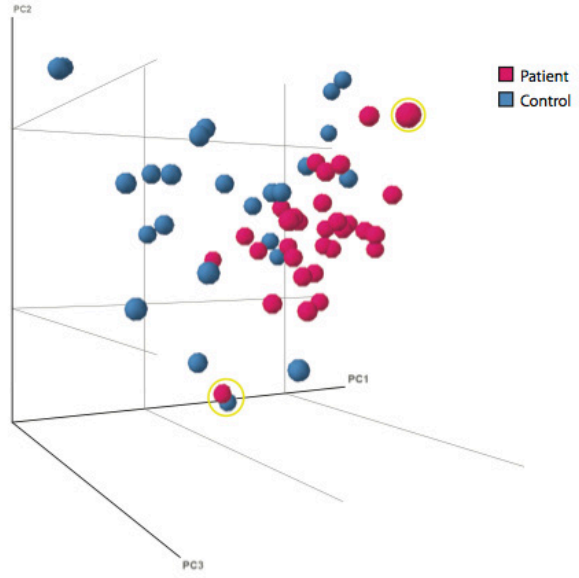

Figure 3 | Principle coordinate analysis (PCoA) scatterplot to express between sample diversity displays clustering of diverticulitis patients separate from control subjects for the phylum *Proteobacteria.* Three samples that were wrongly classified by PLS-DA are encircled

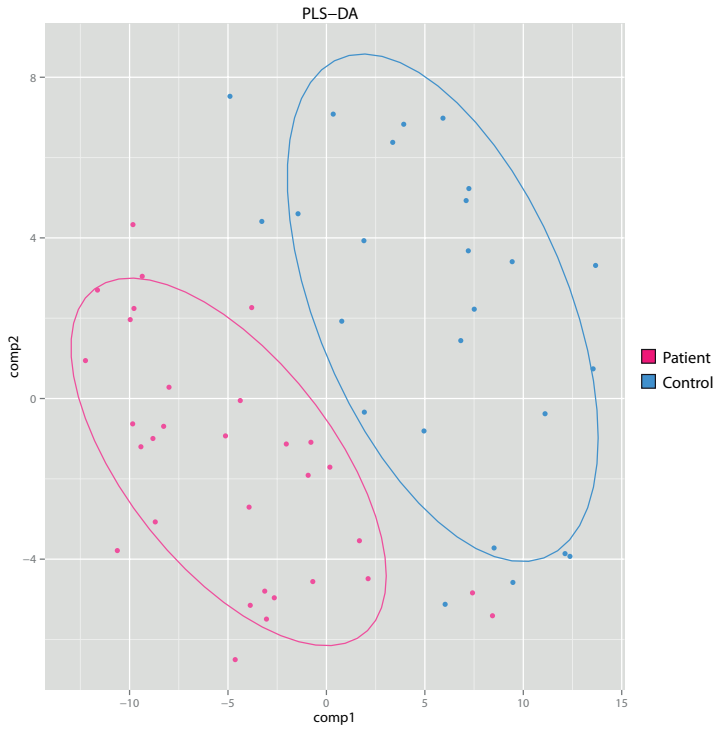

Figure 4 | The partial least square-discriminant analysis (PLS-DA) scores plot for the phylum *Proteobacteria* shows a clear differentiation between diverticulitis patients and control subjects.

A heat map was generated from all IS-profiles separated by phylum. IS-profiles showed a general separation of samples from diverticulitis patients and controls when clustering was performed on total profiles (*Fig. 1*).

Microbial diversity and composition in diverticulitis patients versus controls

While diversity of the phyla *Bacteroidetes* or *Firmicutes* did not differ between patients and controls, the Shannon index indicated that the diversity of the *Proteobacteria* phylum was significantly higher in patients compared to controls (2.6 [IQR: 1.07] and 3.2 [IQR: 0.5] for controls and patients respectively; $P<0.00002$, Mann-Whitney U-test), which also affected the difference in diversity measured when considering all phyla together (3.9[IQR: 0.3] and 4.1 [IQR: 0.3] for controls and patients respectively; $P<0.002$, Mann-Whitney U-test) (*Fig.2*).

PCoA did not segregate diverticulitis patients and controls into different groups for the phyla *Bacteroidetes* and *Firmicutes*. However, patients could be clustered separately from controls in a 3-dimensional space based on their *Proteobacteria* profiles (*Fig.3*).

Discriminative ability of PLS-DA

The use of an unsupervised approach for classification (PCoA) already demonstrated diagnostic potential of *Proteobacteria* profiles in predicting the health status of a given patient. This potential was born out in a supervised analysis, using PLS-DA, known to be suitable for high-dimensional data.[28,30-31] The PLS-DA model used 268 OTUs, representing the 25% most variable OTUs, as predictors and the clinical status of the samples (i.e. diverticulitis: yes or no) as the response variable. In order to quantify the discriminative ability of the model we first considered the full datasets (three individual phylum datasets, and one composed of all phyla). Taking the *Bacteroidetes* or *Firmicutes* data as input resulted in

Table 2 | Most discriminative OTUs based on a Variable Importance for Projection value >1.2

Species	Family
E.coli	Enterobacteriaceae
K. pneumoniae	Enterobacteriaceae
Enterobacter aerogenes	Enterobacteriaceae
S. marcescens	Enterobacteriaceae
Klebsiella variicola	Enterobacteriaceae
Providencia stuartii	Enterobacteriaceae
Desulfovibrio sp.	Desulfovibrionaceae
Xanthomonas sp.	Xanthomonadaceae
Stenotrophomonas	Xanthomonadaceae
Pseudomonas aeruginosa	Pseudomonadaceae
Burkholderia sp.	Burkholderiaceae
Aggregatibacter actinomycetemcomitans	Pasteurellaceae
Unknown Proteobacteria species*	Unknown

***11 types of unknown *Proteobacteria species* were identified

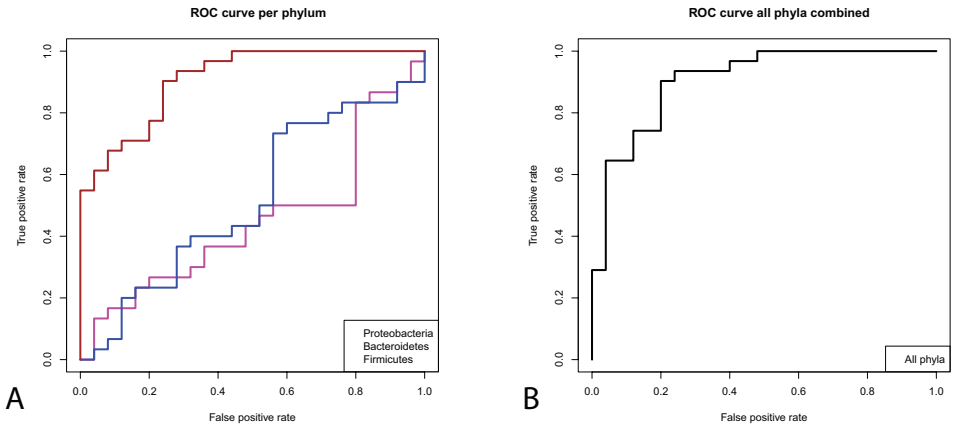

Figure 5 | ROC curves summarizing the predictive power of the PLS-DA modelfor clinical status per phylum (A) and for all phyla combined (B).

low predictive accuracy rates (55% and 53% for *Bacteroidetes* and *Firmicutes*, respectively; data not shown). Taking the *Proteobacteria* data as input resulted in a predictive accuracy rate of 95% (*Fig.4*). Three out of 56 samples were misclassified: one control and two patients, whose samples are the encircled ones in the PCoA scatterplot (*Fig. 3*). Resulting specificity was thus calculated to be 96% with a sensitivity of 94%. Taking the combined data set, composed of all three phyla, as input resulted in an accuracy rate of 96% with two misclassified controls, corresponding to a specificity of 92% and 100% sensitivity. The misclassified controls were two subjects with diverticulosis. The most discriminative OTUs were found to derive largely from the family *Enterobacteriaceae* (*Table 2*).

Prediction of diverticulitis using the PLS-DA model

The predictive ability of the model was assessed by cross-validation. The prediction results were pooled together and enabled us to estimate the performance of the model by means of predictive power. Taking account of the *Bacteroidetes* or the *Firmicutes* phylum only resulted in a low predictive accuracy. For both the *Bacteroidetes* and the *Firmicutes* the cross-validated accuracy rate was 51%. Considering only the *Proteobacteria*, we reached a cross-validated accuracy rate of 80%. Six controls and five patients were wrongly classified, which resulted in a specificity of 76% and a sensitivity of 84%. When we combined the three phyla, we could reach a diagnostic accuracy rate of 84% (spec=80%; sens=87%). Figure 5 summarizes the predictive power of the PLS-DA model by means of ROC curves. To evaluate whether a set of specific qPCRs might be able to attain similar predictive power, we performed PLS-DA analysis on a subset of the ten most discriminative OTUs. Here, a specificity of 71% and sensitivity of 77% was reached.

DISCUSSION

The results of our study suggest that the fecal microbiota diversity of patients with a first episode of acute uncomplicated left-sided diverticulitis differs significantly from control subjects from a general gastroenterological practice, with the *Proteobacteria* phylum mainly defining this difference. Furthermore, predictive diagnostics based on complex microbiota data seems feasible for diagnosing diverticulitis, with a diagnostic accuracy rate of 84%. The most discriminative species derived from the family *Enterobacteriaceae*. An approach based on a limited set of specific qPCRs is unlikely to attain the same diagnostic accuracy as IS-pro.

Several studies have identified characteristics of the intestinal microbiota that may be associated with disease, but clinical diagnostic tools based on microbiome analysis still need to be developed. Whereas most studies into microbiota composition in health and disease identified correlations, here we demonstrate an approach in which microbiota composition may be used as a clinical predictor. By employing a supervised algorithm in combination with cross-validation, we show how microbiota analysis may move towards prediction instead of correlation. PLS regression provides a dimension reduction strategy in situations where a set of response variables needs to be related to a set of predictor variables.[28] It is considered a supervised learning method since it uses the dependent (clinical status in this study) as well as the independent variables (OTUs) to construct variable selection and importance ranking. PLS-DA refers to the particular case where the response variable is a set of binary variables describing the categories of a categorical variable, e.g. disease states. This model is commonly used in the field of chemometrics and in the analysis of microarray expression data, as it is especially suited to deal with a much larger number of predictors than observations and with multi-colinearity.[30-33] In this study we encountered similar challenges; the number of OTUs is much larger than the number of samples and some of them are highly correlated. Due to the properties mentioned above, we found this approach also very appropriate to apply to IS-pro data. The VIP criterion was previously used in PLS-DA microarray analyses to assess which genes were useful to discriminate between different groups.[30,32-33]

Specific shifts in the phylum *Proteobacteria* -other than general measures like diversity- have not been found to be associated with disease before. This might be caused by the fact that *Proteobacteria* generally have a low relative abundance in the intestinal microbiota.[8,34] Because almost all current approaches to analyze the intestinal microbiota use universal bacterial amplification as a starting point, low abundant phyla such as the *Proteobacteria* remain relatively underexplored as other, more prevalent taxa will dominate the PCR reaction and following analyses. In contrast, the IS-pro molecular technique comprises two separate phylum-specific PCR reactions: one for the amplification of *Bacteroidetes/Firmicutes* and another for the specific amplification of *Proteobacteria*. While the separation of the different phyla in two PCRs prevents us from addressing all three phyla together

when presenting their relative abundances -consequently hampering direct comparisons of abundances- it does allow us to zoom in and analyze the *Proteobacteria* community composition in-depth.

Brook et al. retrospectively studied the aerobic and anaerobic microbiology of 110 specimens from the peritoneal cavity after intestinal perforation and in 22 specimens from abdominal abscesses of patients with complicated diverticulitis.[35] With conventional culture techniques they identified *E. coli* and *Streptococcus spp* as the predominant aerobic and facultative bacteria. The most frequently isolated anaerobes were *Bacteroides spp* (*B. fragilis* group), *Peptostreptococcus*, *Clostridium* and *Fusobacterium spp*. The only study up to date with PCR based sequencing of the microbiota in diverticulitis patients was conducted by Gueimonde et al.[36] They identified a significant higher occurrence of *Bifidobacterium longum* and *Bifidobacterium animalis* in patients with diverticulitis, and their overall conclusion was that aberrances in mucosa-associated microbiota are present in different intestinal diseases. However, in their study only nine diverticulitis patients were included. Resected mucosal samples were compared with those of 21 colon cancer patients and four inflammatory bowel disease patients, but no healthy controls. Surprisingly, they looked only at the genus *Bifidobacterium* and did not analyze the entire profile; they stated they used the bifidobacterial microbiota as an indicator of alterations in the mucosal colonization pattern. The bifidobacterial microbiota however, is known to constitute only a small fraction of the intestinal microbial composition in adults.

Currently, antibiotics are often used in the conservative treatment of uncomplicated diver-ticulitis despite the lack of sound evidence.[37,38] Cyclic administration of rifaximin has been proven to be effective in reducing symptoms and complications[39-42] and possibly prevents recurrence in patients after complicated diverticulitis.[43] Relatively new therapies, such as probiotic therapy, are proposed as well for the management of diverticular disease (DD). Indeed, a few small open label studies already show promising results[44-47] Considering that antibiotic and probiotic treatments are regularly prescribed to DD patients, it is striking that relatively few studies have been performed to improve our understanding of the composition of the colonic microbiota. The pathophysiology of diverticulitis was assumed to be clear and well understood but actually astonishingly little is known about causal factors for this disease. Our understanding of the effect of changes in microbiota abundance, diversity and composition is limited. Our study therefore, is a first step in further elucidating the etiopathogenesis of diverticular disease and its inflammatory complications.

Since a clinical diagnosis of diverticulitis can not be made with a high certainty without imaging [48], it seems appropriate to evaluate a test intended for making a specific clinical diagnosis against a patient group with variable clinical presentation. By taking a cross-section of patients in a general gastroenterological practice instead of a healthy control group, the specificity of the prediction becomes more meaningful.

This study has some limitations. First, we have data on only a small study group. As a result we are not able to estimate and optimize predictive ability robustly. The performance of a predictive tool is prone to be overestimated in its own study cohort. For diagnostics by microbiome to be applied in daily practice a study like this one should be externally validated and followed by a larger study to confirm results and calculate sensitivity and specificity more robustly. Second, as a consequence of a small sample size, we were not able to firmly compare diverticulitis patients with subjects with diverticulosis. It has been hypothesized that DD patients have a changed colonic microbiome. From an etiopathogenetic point of view, it would be informative to know to what extent the microbiome in diverticulosis resembles the microbiome in diverticulitis or health. Indeed, the two controls that were misclassified were subjects with diverticulosis. This seems to underline a shift in microbiota related to diverticular disease. It would be interesting to further investigate whether there is a gradual shift in microbiota composition from patients with diverticulosis towards diverticulitis. Such a phenomenon should be investigated in a larger study group. Further it should be noted that species identification was done by in-silico comparison of fragment lengths. While this technique generally gives consistent results, identification is not definitive.

Present study demonstrated that the diagnosis of diverticulitis can be done by microbiome analysis with relatively good accuracy. More generally, this study illustrates a proof of concept of how diagnostics based on complex microbiota data in a broader sense may be applied. This could lead to the use of fecal microbiota as diagnostic tool for diverticulitis, with possible patient stratification directing a personalized treatment strategy, whether or not to prescribe antibiotics, the type of antibiotic, and even to monitor disease course. Clinical application as a diagnostic tool could reduce the need for imaging to diagnose diverticulitis. Clinical applicability needs to be confirmed in a larger study.

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CONFLICT OF INTEREST / STUDY SUPPORT

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PART II

Current classification and management of diverticulitis

CHAPTER 4

Review of current classifications for diverticular disease and a translation into clinical practice.

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ABSTRACT

Background
Diverticular disease of the sigmoid colon prevails in Western society. Its presentation may vary greatly per individual patient, from symptomatic diverticulosis to perforated diverticulitis. Since publication of the original Hinchey classification, several modifications and new grading systems have been developed. Yet, new insights in the natural history of the disease, the emergence of the CT-scan and new treatment modalities plead for evolving classifications.

Methods
This article reviews all current classifications for diverticular disease.

Results
A three stage model is advanced for a renewed and comprehensive classification system for diverticular disease, incorporating up-to-date imaging and treatment modalities.

INTRODUCTION

Diverticular disease of the sigmoid colon is a common condition in Western society. It's presentation of it among patients may vary from symptomatic diverticulosis to perforated diverticulitis. The incidence for diverticulosis is 33-66%; of these patients 10-25% will develop an acute episode of diverticulitis.[1] Although diverticular disease is more common among elderly patients, a dramatic rise of its incidence is seen in the younger age groups.[2] Furthermore, depending on the severity of the disease, the treatments for the various presentations of the disease will differ. Accordingly, diagnostic tools, indications for surgery as well as treatment modalities have been evolving, resulting in more options in the therapy for diverticular disease.

Since Hinchey's traditional classification for perforated diverticulitis in 1978, several modifications and new grading systems have been presented to display a more contemporary overview of the disease.[3] Unfortunately, these different classifications of diverticular disease have led to conflicting terminology in current literature. Moreover, none of the classifications seems to sufficiently embrace the entire spectrum of the disease. This calls for a thorough review and a new parameter.

The current classifications of diverticular disease are based on clinical, radiological or operative findings, yet most lack a translation into daily clinical practice. Given a useful classification system ought to guide clinical decision making and management, this review serves to combine the available classifications with current knowledge of practice into a more useful practice parameter for treating diverticular disease.

METHODS

An extensive literature analysis was performed using the PubMed database. The following 'MeSH' terms were used during the first PubMed search: [diverticulitis], [classification] and [colonic diverticulosis], only a few classifications for diverticular disease were revealed. In most publications the results of a clinical study on imaging or treatment modalities are described, and rarely the proposal of a new classification system. A second analysis using manual cross reference search of the bibliographies of relevant articles located studies not found in the first search. The third strategy used the 'related article' function in PubMed to select articles not found in above searches. All articles in English, German and Dutch have been included. A total of nine classifications and modified classifications for diverticular disease were collected.

Classifications
A proper classification system can improve mutual communication between doctors of different specialties and support clinical decision making. This seems indispensible for the management of the wide spectrum of manifestations and many treatment modalities em-

Table 1 | Hinchey classification and modified Hinchey classification by Sher et al.

	Hinchey classification[3]		Modified Hinchey classification by Sher et al. [5]
I	Pericolic abscess or phlegmon	I	Pericolic abscess
II	Pelvic, intraabdominal or retroperitoneal abscess	IIa	Distant abscess amendable to percutaneous drainage
		IIb	Complex abscess associated with fistula
III	Generalized purulent peritonitis	III	Generalized purulent peritonitis
IV	Generalized fecal peritonitis	IV	Fecal peritonitis

Table 2 | Modified Hinchey classification by Wasvary et al. and CT-findings by Kaiser et al.

	Modified Hinchey classification by Wasvary et al.[6]	CT-findings by Kaiser et al.[20]
0	Mild clinical diverticulitis	Diverticuli ± colonic wall thickening
Ia	Confined pericolic inflammation or phlegmon	Colonic wall thickening with pericolic soft tissue changes
Ib	Pericolic or mesocolic abscess	Ia changes + pericolic or mesocolic abscess
II	Pelvic, distant intraabdominal or retroperitoneal abscess	Ia changes + distant abscess (generally deep in the pelvis or interloop regions)
III	Generalized purulent peritonitis	Free gas associated with localized or generalized ascites and possible peritoneal wall thickening
IV	Generalized fecal peritonitis	Same findings as III

Table 3 | Classification by Köhler et al.[7]

Symptomatic uncomplicated disease	Recurrent symptomatic disease	Complicated disease
• Hemorrhage • Abscess • Phlegmon	• Fistula • Perforation • Stricture	• Purulent and fecal peritonitis • Small bowel obstruction due to postinflammatory adhesions

braced by the term 'diverticular disease'. Uniform classification in clear subgroups of diverticular disease could help the clinician in predicting outcomes and prognosis more accurately.

In 1978 Hinchey et al. published their classification for acute diverticulitis.[3] The Hinchey classification has traditionally been used in international literature to distinguish four stages of perforated disease (see Table 1). This most widely used classification was actually based on an earlier clinical division of acute diverticulitis published by Hughes et al. (see Figure 1).[4] Since the introduction of the computed tomography (CT-scan) in the 1980's, this imaging modality has established itself as the primary diagnostic tool in the assessment of diverticular disease (see Figure 2). The much more detailed information provided by CT-scans led earlier to modifications of the original Hinchey classification. Subcategories could be defined by taking the radiological findings into account. Hence, in 1997 Sher et al. introduced the first modification for distinguishing between a pericolic abscesses (stage I), distant abscesses amendable for percutaneous drainage (stage IIa) and complex abscesses associated with a possible fistula (stage IIb).[5] This modification also implied the use of new treatment strategies, such as CT-guided percutaneous drainage of abscesses.

In 1999, Wasvary et al. published another modification, which since then has been widely adopted (see Table 2).[6] This modification broadened the original Hinchey classification by not only addressing perforated disease, but also including mild clinical disease (stage 0). Additionally, a difference was made between confined pericolic inflammation or phlegmon (stage Ia) and a confined pericolic abscess (stage Ib).

Also in 1999, Köhler et al. published a consensus statement drawn up by the European Association of Endoscopic Surgeons (EAES), entailing a clinical classification that differentiated symptomatic uncomplicated disease, recurrent symptomatic disease and complicated disease (see Table 3).[7]

In German literature since 1998, the Hansen/Stock classification has been mainly used. This is also a clinical classification accounting for asymptomatic diverticulosis as well as complicated diverticulitis in different stages, depending on the severity of the complications (see Table 4).[8] These aspects make it probably the most useful classification in clinical practice; however, it has rarely been adopted in international literature. Another German classification published in 1995 by Siewert et al. followed a similar delineation for complicated disease.[9]

Each classification accentuates different aspects of diverticular disease, creating its own strength and limitation. Moreover some of these classifications appear to be used at random in today's literature, thereby hampering adequate interpretation and comparison. Despite this variety of classifications, still a few clinical manifestations comprised by 'diverticular disease' seem to be lacking; for example recurrent diverticular bleeding and postinflammatory stenosis.

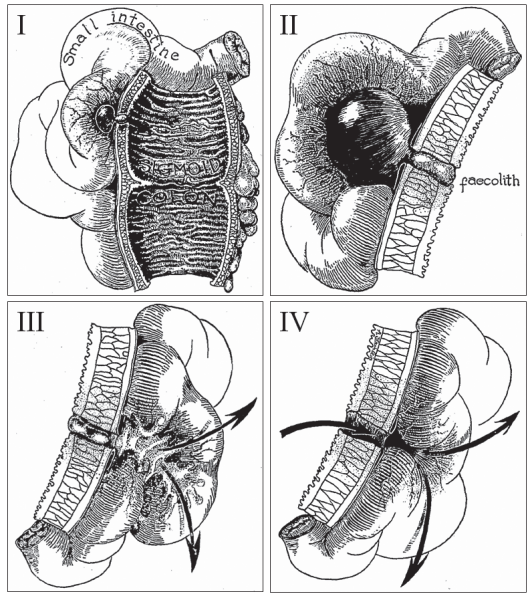

Figure 1 | Hughes classification
Hughes ESR et al. **The surgical management of acute diverticulitis.** MJA 1963; 50 (1): 780-782.

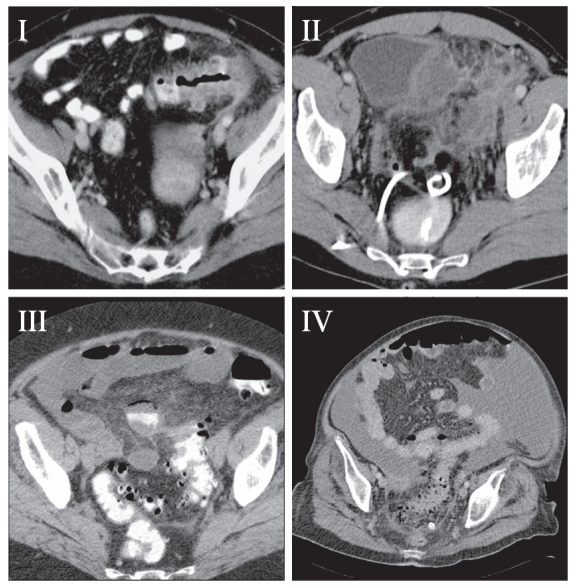

Figure 2 | CT-scan images resembling the four Hughes stages
I Pericolic phlegmon with small associated abscess
II Large intraabdominal abscess
III Small amounts of free air and fluid
IV Massive pneumoperitoneum and free fluid

Table 4 | Hansen/Stock and Siewert classification

	Hansen/Stock classification[8]		Siewert et al.[9]	
0	Diverticulosis			
I	Acute uncomplicated diverticulitis			
II	Acute complicated diverticulitis			
	a	Phlegmon, peridiverticulitis	I	Pericolic abscess or phlegmon
	b	Abscess, sealed perforation	II	Pelvic, intra-abdominal or retroperitoneal abscess
	c	Free perforation	III	Free perforation
III	Chronic recurrent diverticulitis			

Clinical presentation

As stated above, Köhler et al. presented a classification for diverticular disease based on the clinical severity and presentation of the disease. Although subjective complaints are obviously difficult to grade, Köhler et al. considered crampy pain in the left lower quadrant, fever, and changes in relief pattern to be symptomatic. One must consider that a large number of patients with complaints of pain in the left lower quadrant, fever and soiling are probably out of clinical sight, consulting only their general practitioner. Such complaints are considered to be self-limiting, sometimes assisted by antibiotic therapy. Published data on clinical episodes of diverticulitis do not account for these subjective complaints, leading to an underestimation of the real scale of these mild manifestations of diverticular disease. Furthermore limitations of the clinical diagnosis of diverticulitis have to be regarded.[10]

Clinical episodes are characterized by focus on more objective signs, like raised infectious parameters in laboratory tests and typical findings on CT-scan or colonoscopy.[1] Yet this does not discount the initial, subjective complaints. It is the combination of specific symptoms that still form the basis for a differential diagnosis and the indication for additional examinations. For instance, impaired passage of a stool is suggestive for a stenosis, in which a colonoscopy can differentiate between post-diverticulitis stenosis or cancer; diverticular bleeding is the most common cause of recurrent rectal blood loss, but again cancer should be ruled out by a colonoscopy; and pneumaturia is pathognomic for a colovesical fistula, usually a CT-scan will reveal its pathway. Furthermore a generalized peritonitis is only diagnosed by physical examination, the combination of the following symptoms are suspect: an ill patient, fever, absence of peristalsis, very tender abdomen on palpation, relief pain, défènce musculair. A CT-scan is often mandatory in uncovering its cause and confirming the absolute indication for surgery.

When elective surgery for diverticular disease is considered, indications are mainly determined by the impact of symptoms on patients lives. Complications such as stenosis, fistula or recurrent diverticular bleeding are clear indications for an elective sigmoid resection, but also the prevention of perforated diverticulitis by performing an elective sigmoid resection has been standard policy for several decades. Recently, these recommendations have been challenged because new data on the natural history of diverticulitis has shown that most perforations do not occur after recurrences, but at the first attack of acute diverticulitis.[11] Furthermore, conservative management of recurrent non-perforated diverticulitis is associated with low rates of morbidity and mortality. These new insights resulted in a more individual and conservative approach to mild diverticular disease, making the extent of subjective complaints even more important.[2,12]

Imaging

The original Hinchey classification was based on both clinical and surgical findings. Since then diagnostic tools have widely been improved and new modalities have been developed. The usual tests performed at the acute phase of diverticular disease are: water-soluble contrast enema, CT-scan, and ultrasound (US). Although US has been proven as a non-invasive, readily available, and well-performing tool for the diagnosis of acute diverticulitis, its drawbacks are the dependency on the level of the examiner's competence and the fact that images are unreadable for other physicians.[13]

In today's clinical practice regarding diverticular disease, CT-scans enhanced with intravenous and intrarectal contrast have, because of their superior sensitivity and specificity up to 100%, replaced contrast enemas as the most important imaging modality.[14,15] Especially when an associated abscess is suspected, a CT-scan can be very helpful to demonstrate its presence. Also the possibility of direct percutaneous drainage makes it a valuable attribute in the treatment of complicated diverticular disease.[16] In the case of diverticular bleeding, a CT-scan enhanced with intravenous contrast (CT-angio) may demonstrate a contrast blush, a limitation is that blood loss has to be at least two millilitres per minute. Furthermore it has to be considered that 80% of all diverticular bleeding is self-limiting. The role of interventional radiology is yet to be determined, occasional successes of highly selective arterial embolization are described.[17]

A colonoscopy is indicated when there is doubt about cancer, persisting or recurrent complaints in the left lower quadrant, suspicion of a stenosis or recurrent blood loss. Colonoscopy enables biopsies for histological diagnosis and cessation of diverticular bleeding may be attempted by endoscopic measures, such as clipping, coagulation or adrenaline injections. [18] Follow-up colonoscopy for ruling out malignancy is usually performed six weeks after an episode of acute diverticulitis. Routine colonoscopy divulges the majority finds of asymptomatic diverticular disease.

Table 5 | CT-findings by Ambrosetti et al.

CT-findings by Ambrosetti et al.[21]	
Moderate diverticulitis	Localized sigmoid wall thickening (< 5 mm)
	Pericolic fat stranding
Severe diverticulitis	Abscess
	Extraluminal air
	Extraluminal contrast

In recent years, Magnetic Resonance Imaging (MRI) has gained popularity, because it lacks the ionizing radiation of a CT-scan, yet matches its sensitivity and specificity.[19] Additional advantages of MRI over CT-scan are its better visualization of fistulae and the possibility of virtual colonoscopy, thereby making invasive colonoscopy unnecessary. To current date the availability of the MRI and experienced radiologists are often limited, and therefore not suitable for routine use.

The wide use of CT-scans initiated modifications to the Hinchey classification, but also several new radiological classifications for diverticular disease were developed. Kaiser et al. have published specific CT-findings per modified Hinchey stage (see Table 2), resulting in a guideline for objective observation and reporting of CT-scans.[20] The publications on the role of CT-scans in diverticular disease by Ambrosetti et al., allocate diverticulitis into severe or moderate disease (see Table 5). In this approach, the CT-scan provides the physician guidance in the treatment of acute complications, as well as a prognostic factor in the development of chronic complications after a first conservatively treated episode.[21]

Treatment

The wide spectrum of diverticular disease warrant a differentiated approach to the different manifestations. Treatment options for mild disease, associated abscesses, perforations, bleeding, and post-inflammatory complications are discussed separately. Also the role of elective or preventive sigmoid resection will be addressed.

Moderate cases of diverticular disease, such as phlegmon or small abscesses, can be treated conservatively. Initial prescriptions are often antibiotics and an easily digestible diet, although no clear evidence exists for both their beneficial actions. Preventive measures are thought to be more successful by several authors, high-fibre diet, prevention of obesity and treatment of comorbidities are the usual ingredients.[22-24] Newer insights into the pathophysiology of diverticular disease, comparable to inflammatory bowel disease, has led to research on the potentials of 5-aminosalicylic acid (Mesalazine) and probiotics as adjunctive treatments for diverticular disease. Tursi et al. have described promising results, but these medications are still only administered in experimental settings.[25,26]

Large abscesses, if amendable and usually larger than five centimetres, should be good candidates for CT-guided percutaneous drainage.[27] This procedure may relieve symptoms or function as a bridge to (elective) surgery. A purulent or faecal peritonitis results from a

perforation and is associated with high morbidity and mortality (10-35%).[28] In these severe circumstances acute surgical intervention is warranted. Hartmann's procedure used to be the treatment of choice for decades, but in recent literature a few interesting alternatives have emerged. Several authors consider a primary anastomosis a safe option in purulent peritonitis, with or without defunctioning stoma. Even in fecal peritonitis successful series of primary anastomosis have been published.[29] In 2008 Myers et al. introduced the concept of laparoscopic lavage for purulent peritonitis. This minimal invasive method provided resolution in 87% of patients and a reduction in mortality of up to 25% described for Hartmann's procedure to 3% for laparoscopic lavage. Since then several series have been published, but evidence from a randomized controlled trial is still to be awaited.[30]

In order to prevent complicated disease after two episodes of acute diverticulitis, it has been considered good practice for years, to perform elective sigmoid resection after two episodes of symptomatic diverticulitis and even doing so after one episode in the younger patients.[31] These recommendations drawn up by the American Society of Colorectal Surgeons (ASCRS) in 2000, have recently been challenged. It is now thought that after a conservatively treated episode, diverticular disease usually follows a rather benign course and that complications occur mostly at first presentation.[10,32,33] Therefore, elective sigmoid resections should be restricted for use in treating complicated disease, such as symptomatic stenosis, fistulas to a hollow organ or recurrent diverticular bleeding. Furthermore, recent publications on the natural course of diverticular disease suggest applying early elective sigmoid resection in high-risk patients, such as the use of immune suppression therapy, having chronic renal failure or collagen-vascular diseases. The management of diverticular disease in young patients remains controversial, a more hazardous course has been suggested. In contrast, opponents account the longer lifespan responsible for more recurrences and complications and thereby a higher cumulative risk of emergency surgery. An individual approach, weighing symptoms and peri-operative risks on a case by case basis, seems the most appropriate policy.[34,35]

Since the mid 1990s, laparoscopic sigmoid resections for diverticular disease have gained popularity. Several retrospective series after laparoscopic sigmoid resections suggested improvements in minor complication rates, earlier resumption of food and shorter hospital stay. [36-38] In January 2009 these beneficial effects were confirmed by a randomized controlled trial, the short-term results showed that a laparoscopic approach delivered a significant 15.4% reduction in major morbidity, less pain, shorter hospitalization and improved quality of life at the cost of a longer operating time.[39] After six months follow-up the reduction in major morbidity accumulated to 27%. Therefore laparoscopic sigmoid resection may well be the procedure of choice for patients requiring elective resection for diverticular disease.

Discussion and a proposal of a new classification

This review of the current classification systems for a condition as complex as diverticular disease raises the question: Is there a need for another classification? We acknowledge that the introduction of still another classification could be even more confusing. Consequently, the aim of this review is not to add another modification or new classification, but to combine the existing classifications and make a comprehensive translation of the findings for use in daily clinical practice. By doing so, new imaging and treatment modalities are to be incorporated. The clinical applicability of this three stage model has yet to be addressed by means of prospective data and expert panel validation.

We propose three stages of differentiating diverticular disease: A) Uncomplicated; B) Chronic complicated; C) Acute complicated (see Table 6). We thereby address clinical findings ('Presentation'), radiological findings ('Imaging') and treatment modalities ('Treatment') in different paragraphs. This stepwise approach resembles clinical decision making and forms the basis for a practice parameter on diverticular disease (see Table 6).

The three stages A, B, and C is in accordance with the clinical classification as devised by Köhler et al. and the German Hansen/Stock classification. An important difference is that since indications for elective resection no longer depend on the number of episodes, there is no further need to distinguish between 'symptomatic uncomplicated disease' and 'recurrent symptomatic disease'. Furthermore the category of 'complicated disease' found in both Köhler and Hansen/Stock classifications, embraces all possible complications of diverticular disease, both moderate and severe, and so may be confusing. In this classification complications are certified by severity and therapeutic options.

The original Hinchey classification for perforated diverticulitis and its modifications are mainly represented in stage C. Large abscesses (C1) and perforated disease (C4) are severe complications, but also massive diverticular (C3) bleeding and total bowel obstruction (C2) are entitled to acute interventions. In large abscesses, if amendable and usually larger than five centimetres, CT- or US-guided percutaneous drainage should be attempted as final treatment or bridge to surgery. Massive diverticular bleeding might be approached endoscopically (clipping, coagulation or adrenaline injections) or even endovascular (coiling), but in most centres a (laparoscopic) sigmoid resection is probably the final resolution. When a general peritonitis is suspected on physical examination, confirmed by CT-scan, surgical intervention is warranted. According to current literature, a safe strategy might be to primarily perform a diagnostic laparoscopy. In the case of a purulent peritonitis, either (laparoscopic) sigmoid resection with primary anastomosis (with or without defunctioning stoma) or even laparoscopic lavage may be considered in selected cases. When fecal contamination is discovered, Hartmann's procedure is still considered the safest option, but in select cases a primary anastomosis (with or without defunctioning stoma) might be a safe alternative.

Table 6 | Proposed classification

Classification		Presentation	Imaging	Treatment
A		**Uncomplicated disease**		**Conservative treatment**
		• Pain in left lower quadrant • Fever • Changes in relief pattern	CT-scan or US • Phlegmon • Small abscess in bowel wall • (<5 cm) Colonoscopy • Diverticulosis • Inflammation	Treatment acute episode • Antibiotics* • Low residue diet* Prevention • Fibers • Prevention of obesity • Treatment of comorbidity • *Mesalazine*
B		**Chronic complicated disease**		**Elective intervention**
		• Impaired passage of stool • Presence of fistula • Recurrent rectal blood loss • Incapacitating complaints • High-risk patients	CT-scan • Stenosis • Fistula Colonoscopy • Stenosis • Fistula • Blood in diverticula	Sigmoid resection with primary anastomosis • Open • Laparoscopically
C		**Acute complicated disease**		**Acute intervention**
	1	• Fever • Painful mass	• CT-scan • Large abscesses (>5cm)	• Percutaneous drainage
	2	• Ileus	• CT-scan • Intestinal obstruction	Sigmoid resection with primary anastomosis Hartmann's procedure
	3	• Massive rectal blood loss	• CT-angio • Contrast blush • Colonoscopy • Active diverticular bleeding	• Sigmoid resection with primary anastomosis • Open • Laparoscopically *Endoscopic intervention** *Endovascular coiling**
	4	• Generalized peritonitis	• CT-scan • Pneumoperitoneum • Extraluminal contrast • Free fluid	• Diagnostic laparotomy / laparoscopy • Resection with primary anastomosis • Hartmann's procedure • *Lavage and drainage**

** Experimental or non-evidence-based treatment*

In most classifications, post-inflammatory changes like stenosis or fistulas are not included. Patients may have serious complaints, but interventions can usually be postponed to an elective setting. Stage B includes non-acute complications of diverticular disease, such as symptomatic stenosis, fistulas to hollow organ, recurrent (self-limiting) diverticular bleeding and incapacitating complaints. This last group of patients covers mainly those young patients who are incapacitated by recurrent attacks and hospital admissions, which prevent them from having normal working careers and social life. In addition, high-risk patients, such as those immune compromised, using of NSAIDs and other immune suppressants or experiencing chronic renal failure, might be good candidates for early elective sigmoid resection. The planning of an elective operation, makes it possible to do a proper preoperative work-up to prevent unwelcome surprises during surgery. In cases of stenosis or recurrent rectal blood loss, it is advisable to perform a colonoscopy to rule out cancer. CT-scan is of superior diagnostic value in case of stenosis or fistula. During preoperative planning of complex fistula, MRI might have some benefit over CT-scan. Stage B disease forms indications for elective sigmoid resections, preferably laparoscopically.

Stage A contains symptomatic uncomplicated disease. Patients with subclinical complaints or recurrent hospital admission should not be considered differently, because both groups will fully recover with conservative measures. Acute episodes of stage A diverticulitis can mostly be resolved with antibiotics and a low residue diet. Recurrent episodes usually follow a benign course and risks of complications are low. At presentation a CT-scan or US (provided an experienced radiologist is available), has to be performed to rule out complicated disease, moreover these baseline findings are crucial if the patient deteriorates during conservative treatment. Small amounts of mucus or blood loss are generic signs of inflammation, whereby colonoscopy has to rule out other inflammatory bowel diseases or colon cancer. After a first attack, preventive measures have to be taken into account, such as high-fibre diet, weight loss and treatment of comorbid conditions. In the near future the prescription of Mesalazine might be added to this preventive strategy.

In conclusion, this manuscript provides an overview of current classification systems for diverticular disease. The proposed three-stage model provides a renewed and comprehensive classification system for diverticular disease, incorporating up-to-date imaging and (future) treatment modalities.

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CHAPTER 5

Management of diverticulitis. Results of a survey among gastroenterologists and surgeons.

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ABSTRACT

Background
The aim of this study is to investigate current management strategies for left-sided diverticulitis and compare it to current international guidelines. Furthermore differences between surgeons and gastroenterologists and between gastro-intestinal and non gastro-intestinal surgeons are assessed.

Methods
A survey concerning the different treatment options for uncomplicated and complicated diverticulitis was sent to all surgeons and gastroenterologists in the Netherlands. Only surgeons were surveyed about surgical strategies.

Results
A total of 292 surgeons and 87 gastroenterologists responded representing 92 % of all surgical departments and 46 % of all gastroenterology departments. 90% percent of respondents treat mild diverticulitis without antibiotics. A minority (18% of gastroenterologists and 39% of surgeons) view a CT scan as mandatory in the initial assessment. The majority of both surgeons and gastroenterologists use a form of bowel rest, would consider outpatient treatment and perform a colonoscopy on follow-up. For Hinchey 3 diverticulitis 78% of surgeons would consider a resection and primary anastomosis. Laparoscopic lavage is viewed as a valid alternative for Hinchey 3 diverticulitis by 30% of gastro-intestinal surgeons and 2% of non-gastrointestinal surgeons. For Hinchey 4 diverticulitis 46 % of gastro-intestinal surgeons and 72% of non-gastrointestinal surgeons would always perform a Hartmann procedure.

Conclusion
The treatment of diverticulitis in the Netherlands shows major discrepancies when compared to guidelines. Considerable variation in treatment exists for all stages of disease.

INTRODUCTION

Diverticular disease accounts for 312,000 hospital admissions, 1,5 million days of inpatient care and a total estimated cost 2,6 billion dollars each year in the United States imposing a substantial healthcare burden for a “benign” disease.[1]

Acute diverticulitis is usually graded as “complicated” or “uncomplicated” according to the classification of The European Association for Endoscopic Surgeons[2] , as “mild” or “severe” according to the Ambrosetti CT-criteria[3] , or according to the modified Hinchey classification.[4] For uncomplicated diverticulitis (Hinchey 1a) mortality is as low as 5% increasing to 42% for Hinchey 4 disease.[5] In the last decades the advent of CT scanning has allowed a more accurate disease classification and the development of percutaneous drainage techniques has resulted in more patients being treated without surgery.[6] When an operation is necessary there is evidence that a single stage resection is safe in Hinchey 3 diverticulitis and maybe even in Hinchey 4 diverticulitis.[7,8] Laparoscopic lavage has emerged as a very promising alternative in stage 3 disease.[9,10] There is now a vast body of literature on the treatment of diverticulitis but controversy still remains because high quality evidence is lacking.

A number of professional organizations have tried to condense the best available evidence into guidelines and practice parameters. All guidelines recommend the use of CT scanning as the preferred imaging modality. Restriction of oral intake and antibiotics are recommended for the treatment of uncomplicated disease. Less solid recommendations exist for the preferred surgical treatment of complicated disease but a resection and primary anastomosis is regarded as a save choice in selected cases.[11-15] Little is known about adherence to these guidelines. In the Netherlands no national guidelines exist.

The aim of our survey is to evaluate current practice in the treatment of diverticulitis among gastroenterologists and surgeons and to asses adherence to international guidelines and current literature.

METHODS

An e-mail request was sent to all surgeon members (n=1051) of the Association of Surgeons of the Netherlands and to all gastroenterologist members (n=284) of the Association of Gastroenterology of the Netherlands to participate in a web-based survey. Two e-mail reminders were sent. Data on respondent characteristics (subspecialty, number of years since registration, type of hospital and number of patients treated with diverticulitis) were noted. The survey consisted of questions concerning multiple aspects of the treatment of mild diverticulitis such as antibiotic use, diet prescribed, imaging modalities used, pain medication, other medication, outpatient treatment and colonoscopy in follow-up. Further-

more we surveyed the operative treatment for the different Hinchey stages of severe diverticulitis. On the survey website the Ambrosetti CT classification and modified Hinchey classification were shown to avoid confusion on the stage of disease and staging system used. Yes/no, multiple choice and multiple answer questions or were used. In multiple answer and multiple-choice questions there was a possibility to enter free text. The tables presented in the results section represent the questions asked in the survey.

Comparison of responses was done using Chi square test or Fisher exact test as appropriate. Continues variables are represented as means with standard deviation when normally distributed. Statistical significance was defined as p 0.05. Statistical analysis was performed using SPSS®, version 17.0(SPSS Inc., Chicago, IL).

RESULTS

Response

A total of 292/1051 surgeons and 87/ 284 gastroenterologists responded representing 92% (87 of 95 hospitals) of all surgical departments and 46 % (44 of 95 hospitals) of all gastroenterology departments in the Netherlands. From the responding surgeons 19 responses were excluded from analysis because more than half of the data were missing. 32 respondents indicated that because of ongoing sub-specialization they did not treat patients with diverticulitis anymore. Thus 240/292 surveys (82%) from surgeon respondents who treated patients with diverticulitis were eligible for final analysis. Of these respondents there were no missing data. Of the responding gastroenterologists all (87/87) of returned surveys were eligible for analysis and there was no missing data. Respondent characteristics are shown in table 1.

Respondent characteristics

Gastroenterologists were registered for a mean of 10 years and surgeons for a mean of 12 years. The majority of surgeons and gastroenterologist treat between 0 and 20 patients with diverticulitis each year. 63 percent of surgeons indicated gastrointestinal surgery as their subspecialty. Responses were obtained from all types of hospitals in the Netherlands.

Uncomplicated/ mild (Hinchey 1a) diverticulitis (table 2.)

Imaging

On initial presentation the majority of gastroenterologist (68%) and surgeons (62%) request a CT scan, although the majority of non-gastrointestinal surgeons (65%) use ultrasound. Sixteen percent of non-gastrointestinal surgeons use no imaging at all compared to 0 % of both gastrointestinal surgeons and gastroenterologists. (p<0.001) Eighteen percent of gastroenterologists consider a CT scan mandatory for every patient compared to 39% of surgeons (p=0.001). Most guidelines advice CT scanning as the preferred imaging modality.[9,10]

Table 1 | Respondent characteristics

	Surgeons N= 240	Gastroenterologists N=87
Number of years since registration (SD)	12 (±8)	10 (±8)
Number of patients with diverticulitis treated each Year		
0-20	168 (70%)	60 (74%)
20-50	62 (26%)	22 (27%)
50-100	7 (3%)	2 (2%)
>100	2 (1%)	1 (1%)
Surgical subspecialty		
Gastro-intestinal	151 (63%)	
Non- Gastro-intestinal	89 (37%)	
Type of hospital		
Regional	71 (30%)	14 (16%)
Teaching	120 (50%)	51 (58%)
Academic	48 (20%)	19 (22%)

Antibiotics

Only 9% of gastroenterologists and 10% of surgeons consider antibiotics mandatory in the treatment of uncomplicated or mild diverticulitis. When antibiotics are prescribed, the types of antibiotics differ considerably. The majority of surgeons would prescribe amoxicillin/clavulanate acid (27%), cefuroxim (37%), metronidazole (44%) or combinations of those. Most gastroenterologists use amoxicillin/clavulanate acid (42%), metronidazole (34%), ciprofloxacine (32%), cefuroxim (15%) or combinations of those.

All current guidelines recommend the use of broad-spectrum antibiotics in the treatment of uncomplicated or mild disease.[9-11]

Diet

Most gastroenterologists (88%) and surgeons (81%) prescribe some form of bowel rest when a patient is admitted for an acute attack of uncomplicated diverticulitis. After discharge most gastroenterologist (93%) and surgeons (88%) advice a fiber rich diet.

In all guidelines bowel rest is recommended during an acute attack and a fiber rich diet after recovery to prevent diverticula formation.[9-11]

Table 2 | Treatment of uncomplicated diverticulitis

	Gastro-enterologists N=87	All Surgeons N=240	P value	GI Surgeons N=151	Non GI Surgeons N=89	P value
Imaging on presentation (Multiple answers possible)						
Plain abdominal X-ray	3 (3%)	43 (18%)	**0.001**	21 (14%)	22 (25%)	**0.038**
Ulrasound	40 (46%)	95 (39%)	0.299	37 (25%)	58 (65%)	**<0.001**
CT scan	59 (68%)	149 (62%)	0.341	122 (81%)	27 (30%)	**<0.001**
No imaging	0 (0%)	14 (6%)	**0.021**	0 (0%)	14 (16%)	**<0.001**
CT scan mandatory for every patient						
Yes	16 (18%)	93 (39%)	**0.001**	58 (39%)	35 (40%)	0.832
No	71 (82%)	147 (61%)		93 (61%)	64 (60%)	
Antibiotics mandatory in mild or uncomplicated diverticulitis (Hinchey 1a)						
Yes	8 (9%)	23 (10%)	1	14 (9%)	9 (10%)	1
No	79 (91%)	217 (90%)		147 (91%)	80 (90%)	
Diet when admitted in hospital (Multiple choice answer)						
Some form of bowel rest	77 (88%)	195 (81%)	0.121	120 (79%)	75 (84%)	0.357
Normal diet	10 (12%)	46 (19%)	0.134	32 (21%)	14 (16%)	0.315
Diet advice after recovery from an attack						
Fiber rich				126 (83%)	84 (94%)	
Yes	81 (93%)	210 (88%)	0.168	25 (17%)	5 (6%)	0.150
No	6 (7%)	30 (12%)				

Table 2 | Continued

	Gastro-entero-logists N=87	All Surgeons N=240	P value	GI Surgeons N=151	Non GI Surgeons N=89	P value
Pain medication prescribed (Multiple answers possible)						
Paracetamol	75 (86%)	221 (92%)	0.134	142 (94%)	79 (89%)	0.215
NSAID's	13 (15%)	118 (49%)	**<0.001**	83 (55%)	35 (39%)	**0.023**
Morfine	13 (15%)	47 (20%)	0.419	30 (19%)	17 (19%)	1
None	0 (0%)	4 (2%)	0.347	2 (1%)	2 (2%)	0.629
Other medication prescribed (Multiple answers possible)						
Bulk producing laxatives	35 (40%)	84 (35%)	0.435	63 (42%)	21 (24%)	**0.050**
Osmotic laxatives	29 (37%)	45 (19%)	**<0.001**	24 (16%)	21 (24%)	0.171
Spasmolytic	28 (32%)	4 (3%)	**<0.001**	2 (1%)	2 (2%)	0.629
Mesasaline	6 (7%)	3 (1%)	**0.013**	2 (1%)	1 (1%)	1
Colonoscopy mandatory after recovery from first attack in follow up						
Yes	65 (75%)	178 (74%)	1	114 (76%)	64 (72%)	0.545
No	22 (25%)	62 (26%)		37 (24%)	25 (28%)	
Outpatient treatment possible for mild disease						
Yes	83 (95%)	198 (82%)	**0.003**	131 (87%)	67 (75%)	**0.034**
No	4 (5%)	42 (18%)		20 (13%)	22 (25%)	

Table is a copy of the questions in the survey. P values were calculated using two by two tables and Chi square test or Fisher exact test as appropriate.

Medication

Most gastroenterologists (86%) and surgeons (92%) prescribe paracetamol. Significantly more surgeons (49%)would prescribe NSAID's than gastroenterologists (15%, p<0.001). A minority of both surgeons (20%)and gastroenterologists (15%) use morfine. Only 7% of gastroenterologists and 1% of surgeons prescribe mesazaline.

The type of pain medication is not commented upon in guidelines as is mesazaline use.[9-11]

Follow up

The majority of both gastroenterologist (75%) and surgeons (74%) believe a colonoscopy is mandatory in the follow up after a first attack of diverticulitis.Some guidelines recommend performing a colonoscopy at follow-up to exclude a carcinoma.[8-9]

Outpatient treatment

The majority of both gastroenterologists (95%) and surgeons (82%) consider outpatient treatment for mild disease. Gastroenterologists are more likely to do so than surgeons and gastrointestinal surgeons more likely than non-gastrointestinal surgeons.

Outpatient treatment is not specifically mentioned in guidelines.[9-11]

Table 3 | Treatment of Hinchey 3 diverticulitis

	All surgeons *n=240*	GI surgeons *n=151*	Non GI surgeons *n=89*	P value
Hartmann procedure if there is a high risk of anastomotic leakage otherwise resection and anastomosis (with defunctioning ostomy on indication)	186 (78%)	119 (79%)	67 (75%)	0.527
Always Hartmann procedure	26 (10%)	7 (5%)	19 (21%)	<0.001
Always Resection and primary anastomosis (with defunctioning ostomy on indication)	14 (6%)	10 (7%)	4 (2%)	0.133
Laparoscopic lavage	47 (20%)	45 (30%)	2 (2%)	<0.001
Open lavage and defunctioning ostomy only	14 (6%)	10 (7%)	4 (5%)	0.497
All surgeons who consider primary anastomosis (with defunctioning ostomy on indication)	198 (82%)	129 (85%)	69 (78%)	0.159

Values ad up to more than 100% because more than one answer was possible.
P values were calculated using two by two tables and Chi square test or Fisher exact test as appropriate.

Complicated diverticulitis

The majority of both gastrointestinal (79%) and non gastro-intestinal surgeons (75%) would perform a primary anastomosis (with a defunctioning ostomy on indication) for a non high-risk patient. Twenty percent of all surgeons consider laparoscopic lavage. Gastrointestinal surgeons are more likely to consider laparoscopic lavage than non-gastrointestinal surgeons. (30% vs. 2%, P<0.001)

Values ad up to more than 100% because more than one answer was possible.
P values were calculated using two by two tables and Chi square test or Fisher exact test as appropriate.

The majority of surgeons (56%) always perform a Hartmann procedure, 45% would consider a primary anastomosis in selected patients. Gastrointestinal surgeons are more likely to perform a primary anastomosis than non-gastrointestinal surgeons. (54% vs. 30%, p=0.001)

Table 4 | Treatment of Hinchey 4 diverticulitis

	All surgeons *n=240*	GI surgeons *n=151*	Non GI surgeons *n=89*	P value
Hartmann procedure if there is a high risk of anastomotic leakage otherwise resection and anastomosis (with defunctioning ostomy on indication)	103 (43%)	76 (50%)	27 (30%)	0.003
Always Hartmann procedure	134 (56%)	70 (46%)	64 (72%)	<0.001
Always Resection and primary anastomosis (with defunctioning ostomy on indication)	5 (2%)	5 (3%)	0 (0%)	0.161
Open lavage and defunctioning ostomy	13 (5%)	5 (3%)	8 (9%)	0.014
Laparascopic lavage	5 (2%)	5 (3%)	0 (0%)	0.161
All surgeons who would consider a primary anastomosis (with defunctioning ostomy on indication)	108 (45%)	81 (54%)	27 (30%)	0.001

Values ad up to more than 100% because more than one answer was possible.
P values were calculated using two by two tables and Chi square test or Fisher exact test as appropriate.

DISCUSSION

Our survey is the first to evaluate possible different treatment options for uncomplicated and complicated diverticulitis in a nationwide survey. Also for the first time, preferences of both surgeons and gastroenterologists were assessed. The treatment of diverticulitis in the Netherlands shows major variation compared to published guidelines.

On of the drawbacks of all surveys is the risk of response bias. At hospital level the response rate was good for surgeons and average for gastroenterologists. At the individual level the response rate of about 30% was less good. Owing to sub-specialization in the Netherlands an increasing number of (general) surgeons do not treat patients with diverticulitis any more and it can be assumed that they formed an important portion of nonresponders. All academic centers have a specialized gastro-intestinal surgery unit and on call system and these are developing in an increasing number of other hospitals as well. Although we cannot provide exact numbers this does influence the response rate in a favorable way.

All different types of hospitals in the Netherlands are adequately represented in our survey. Surgical and gastroenterolgy groups in the Netherlands often work closely together, especially in academic and teaching hospitals, which comprise more than half of all hospitals in the Netherlands. Often protocols are in place and patient treatment is discussed on a daily basis among the whole group. To our opinion this also limits response bias.

CT scanning is recommended for the diagnosis of diverticulitis in all published guidelines.[11-15] It has a high sensitivity and specificity for the diagnosis of diverticulitis and can identify possible other causes of complaints.[16-18] Moreover it can identify abscesses and subsequent drainage can be performed. There is however evidence supporting the routine use of ultrasound, which has equally high sensitivity and specificity rates as CT scanning and has the advantage of not subjecting patients to ionizing radiation. [18] It has been proposed that CT scanning should be reserved for an inconclusive ultrasound examination or clinical deterioration.[17] The lack of evidence for routine use of CT scanning is reflected in our survey by the fact that a majority of respondents do not think CT scanning is mandatory for every patient suspected of having diverticulitis.

Contrary to all guidelines and practice parameters Dutch gastroenterologists and surgeons do not view antibiotics as mandatory in the treatment of uncomplicated diverticulitis of the sigmoid. In guidelines usually broad-spectrum antibiotics are recommended.[11-15] Evidence supporting the mandatory use of antibiotics is absent. In the Netherlands a long-standing tradition exists in treating mild diverticulitis without antibiotics. In 1996 van der Linde et al. for the first time described the results a cohort of patients with mild diverticulitis treated without antibiotics.[19] In 2007 Hjern et al. described a cohort of patients treated *with* antibiotics and compared it to a cohort treated *without* antibiotics and showed no difference in success rate or complications.[20] No prospective trials to date have compared the use of antibiotics to observation alone in patients with acute uncomplicated diverticulitis.

An overlap between diverticulitis and inflammatory bowel disease has been proposed.[22] Only recently has this been substantiated in a study that found a higher level of inflammation in tissue specimens taken from the mucosa around diverticula in asymptomatic individuals without endoscopic signs of inflammation.[22] Non-randomized studies show beneficial effects of mesazaline in the prevention and treatment of diverticulitis underscoring the concept of some form of chronic inflammation in diverticular disease. A low-fiber diet in the Western world is associated with a change in colonic flora and an increase in intracolonic pressure.[21] This increase in pressure could lead to the formation of diverticula. The altered colonic flora could also lead to a form of chronic subclinical inflammation in the mucosa around diverticula.[21,23,24] In our survey the majority of respondents recommend a high fiber diet after an acute episode but only a very small percentage uses mesazaline.

Bowel rest is usually recommended in an acute attack. There is no evidence in the literature whatsoever to substantiate this. The majority of respondents in our survey use some form of bowel rest although specific regimens varied.

The use of NSAID's in patients with diverticulitis is associated with a higher rate of perforation in some series.[26,27] NSAID's inhibit the cyclo-oxigenase enzyme and cause topical mucosal damage and thereby increasing colonic permeability. Furthermore they reduce prostaglandin synthesis, which plays a role in establishing a mucosal barrier.[27] Published practice parameters do not comment on analgesia but their use in acute diverticulitis is controversial. In our survey NSAID's are still widely used by surgeons and by a small minority of gastroenterologists.

The treatment of Hinchey 3 and 4 diverticulitis remains controversial. Recent retrospective and non-randomized studies have consistently shown the safety of a primary anastomosis even in the presence of fecal peritonitis.[7,8] This is partially reflected in our survey. The majority of all surgeons would consider a primary anastomosis in Hinchey 3 diverticulitis. No difference was found between non-gastro-intestinal surgeons and gastrointestinal surgeons. This is in contrast with other research showing that gastrointestinal surgeons are more likely to perform a single stage operation.[28] In the presence of a fecal peritonitis the majority of all surgeons in our survey would still perform a Hartmann procedure, but gastro-intestinal surgeons are more likely to perform a one-stage operation. Formal guidelines do not explicitly favor one procedure over the other because evidence is mostly retrospective or non-randomized and could suffer from a potentially large selection and inclusion bias.

In the present survey 30% of gastrointestinal surgeons would consider laparoscopic lavage in patients with Hinchey 3 diverticulitis although this is a recent development. Laparoscopic lavage is an appealing alternative because there is no chance of anastomotic leakage and there is no stoma formation. In the published series on laparoscopic lavage the mortality is much lower than in historical data on Hinchey 3 patients.[9,10]

The treatment of diverticulitis in the Netherlands shows major discrepancies compared with published guidelines in imaging strategies and antibiotic use were evidence for these recommendations is poor. The major change in the treatment of Hinchey 3 diverticulitis has been rapidly incorporated into practice even when not yet incorporated in formal guidelines. Considerable variation still exists in all fields of management *among* and *between* gastroenterologists and surgeons.

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CHAPTER 6

Rational imaging: Suspected left-sided diverticulitis.

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Wouter de Monyé
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LEARNING POINTS/ ABSTRACT

- Left-sided diverticulitis can be diagnosed by clinical findings and laboratory tests accurately in only a small number of patients thus imaging tests are necessary to confirm the diagnosis.
- CT and US have similar diagnostic accuracy, so when expertise is available the first line of imaging should be an US to confirm the diagnosis.
- In the case of a non-diagnostic or inconclusive ultrasound a CT scan should be performed, as CT is superior to ultrasound in identifying an alternative diagnosis.
- In a critically ill patient, with marked elevation of infection parameters or high fever a CT scan should be made without delay to rule out complicated diverticulitis and to guide therapy.

THE PATIENT

A 55-year-old male presented to the emergency department with a two-day history of progressive pain in the left lower quadrant. On physical examination he had a temperature of 38.0 degrees Celsius and marked tenderness in the left lower quadrant and some tenderness in the supra-pubic area. No rebound tenderness was present. Laboratory testing showed a CRP level of 80 and a white blood cell count of 13.8.

WHAT SHOULD BE THE NEXT INVESTIGATION?

This patient is suspected of having a left-sided diverticulitis. Diagnosis based solely on clinical and laboratory parameters has proven to be imperfect. The sensitivity for diagnosing acute diverticulitis on clinical grounds alone is only 68%.[1] A small subset of patients with pain only in the lower left quadrant, raised CRP and the absence of vomiting, has recently been identified in which diverticulitis can be diagnosed with a high degree of diagnostic accuracy without additio-nal imaging.[2-3] However, these results should be validated in a prospective cohort. Therefore, in patients suspected of having diverticulitis additional imaging is required to confirm the diagnosis.

Ultrasound (US)- Graded compression US has excellent diagnostic accuracy for diverticulitis with reported sensitivity of 92% and specificity of 90%. In Graded compression US interposing fat and bowel can be displaced or compressed by means of gradual compression to show underlying structures. If the bowel cannot be compressed, the non-compressibility itself is an indication of inflammation[4] US is widely available, cheap and lacks radiation exposure. It has been argued though that it requires a highly trained radiologist, who is not always available. However, a recent study showed that 2nd year residents had similar diagnostic accuracy as seasoned radiologists in diagnosing acute diverticulitis with ultrasound.[5] Despite the proven accuracy in demonstrating diverticulitis, complications such as very small abscesses, deep pelvic abscesses and small amounts of free air may be missed, although the only available evidence shows that US is as good as CT in identifying abscesses in diverticulitis . Only one study compared CT and US in complicated diverticulitis and found good kappa agreement between CT and US for abscesses (k=0.69).[6]

Furthermore, the technique is operator dependent and has severe limitations in obese patients and in some areas in the world like the United States CT is more readily available then US.

Computed Tomography (CT)- CT scanning has slightly higher diagnostic accuracy than US (sen-sitivity 94%, specificity 99%), although not statistically significant in a recent meta-analysis.[4] It is superior to US in diagnosing an alternative diagnosis, with a sensitivity between 50% and 100%, compared to a sensitivity of 33% and 78% for US.[4] Furthermore, it is more useful when planning percutaneous drainage of an abscess or surgery.[4] The main

drawback of CT is radiation exposure, however, newest generation CT-scanners using advanced reconstruction algorithms can reduce dose up to 50 %. Moreover low-dose unenhanced CT scanning offers equal diagnostic accuracy as normal dose scanning with oral or intravenous contrast.[7]

Magnetic Resonance Imaging (MRI)- MRI scanning could combine the advantages of CT scanning without the radiation exposure. Reported sensitivity rates vary between 86% and 100% and spe-cificity rates between 88% and 100%. [8] Limited availability, high costs, length of the examination and limited experience hamper the current use of MRI in diagnosing diverticulitis.

In the OPTIMA cohort study CT and US were compared head to head in patients with acute abdominal pain. A strategy of US first and CT only in inconclusive or negative US resulted in the best sensitivity and lowest exposure to radiation.[5]

In a patient suspected of having acute uncomplicated diverticulitis US can be performed if expertise is available, to confirm the diagnosis. This is the case in the majority of patients presenting with acute diverticulitis.[9] In a critically ill patient, with marked elevation of infection parameters of high fever suspected of having complicated diverticulitis a CT scan should be performed as the first choice examination.

OUTCOME

An ultrasound was performed which showed sigmoid bowel wall thickening and inflammation of the pericolic fat around a diverticulum consistent with sigmoid diverticulitis. (Figure 1.) The patient was admitted to the hospital with bowel rest and intravenous antibiotics were administered, although the necessity of antibiotics in uncomplicated diverticulitis is disputed.[10-11] After two days there was a marked rise in temperature to 39 degrees Celsius. On suspicion of complicated diverticulitis a CT was performed revealing a pericolic abscess consistent with Hinchey 1 b (table 1.) diverticulitis. (Figure 2.) Diverticulitis with pericolic abscess formation is generally treated with antibiotics alone.[12] In this patient the antibiotics were continued, the fe-ver subsided and infection parameters declined. He was followed up at the outpatient clinic with continuation of oral antibiotics for a total of 10 days. Four weeks after the initial presentation lab values had normalised, he was pain free and there were no problems with defecation.

Table 1 | Modified Hinchey classification of acute sigmoid diverticulitis

0	Mild clinical diverticulitis
Ia	Confined pericolic inflammation or phlegmon
Ib	Pericolic or mesocolic abscess
II	Pelvic, distant intraabdominal or retroperitoneal abscess
III	Generalized purulent peritonitis
IV	Generalized fecal peritonitis

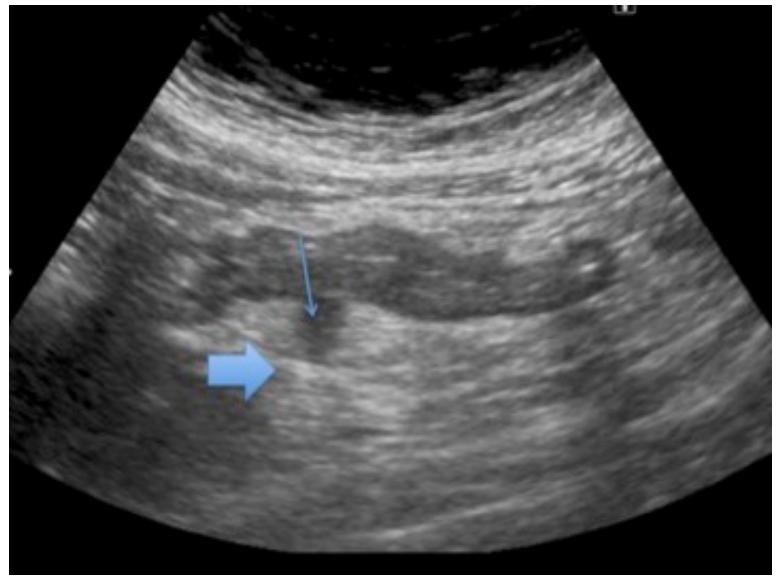

Figure 1 | Ultrasound
Graded compression ultrasound image showing a diverticulum (small arrow) with inflamed pericolic fat (large arrow).

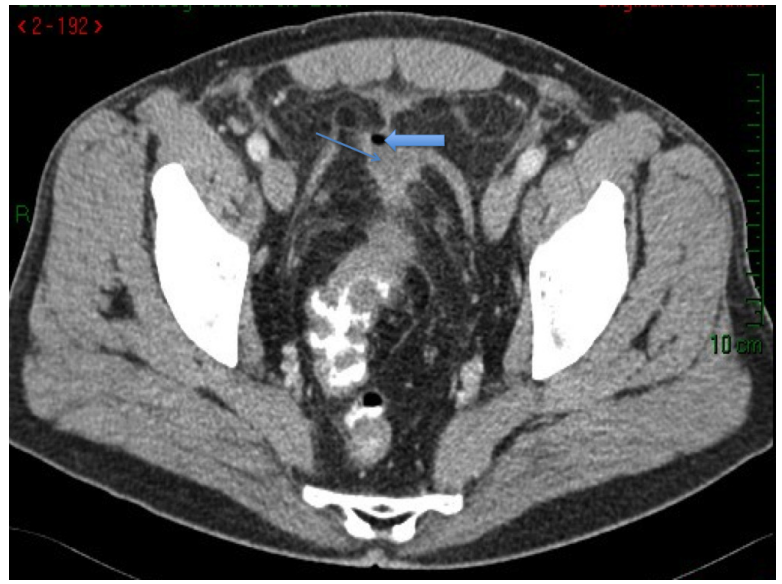

Figure 2 | CT scan
Computed tomogram showing a loop of sigmoid colon with pericolic abscess with fluid (small arrow) and air (large arrow).

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CHAPTER 7

Non-operative treatment of diverticulitis. NSAID use, ASA classification and abscess formation predict failure rates.

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Submitted

ABSTRACT

Background

Most patients with diverticulitis can be managed non-operatively. The literature on risk factors for treatment failure however is scarse. The aim of this study is to identify predictors for failure in patients treated non-operatively for acute diverticulitis.

Methods

Retrospective cohort analysis. Patients admitted with imaging confirmed acute left-sided diverticulitis in which the decision was made to treat them conservatively were analysed.

Results

A total of 318 patients were identified in which the decision was made to treat them non-operatively. A total of 20 patients (6%) failed treatment. On univariate analysis age above 70, ASA grade higher than 2, abscess formation on CT scan, steroid use and NSAID use were associated with an increased risk of treatment failure. Multivariate analysis showed abscess formation (odds ratio 8.76 [95% confidence interval 2.88-26.64]), NSAID use (odds ratio 13.35 [95% confidence interval 2.84-64.20]) and ASA grade (odds ratio 4.50 [95% confidence interval 1.52-13.33]) to be independent risk factors. There were 6 (2%) deaths in the entire cohort all of which were in the treatment failure group. When treatment failed mortality was as high as 31.6 percent.

Conclusions

Non-operative treatment of diverticulitis is highly successful. Patients with NSAID use, ASA classification >2 and abscess formation on CT scan however carry a high risk of failing treatment. Close monitoring and early intervention is warranted in these patient groups, because when treatment fails the mortality is very high.

INTRODUCTION

Diverticulosis is a common finding in the western world. Diverticular disease and its complications constitute a substantial healthcare burden and incidence rates, especially among younger patients, seem to be on the rise.[1,2]

Treatment and diagnoses of diverticulitis have changed dramatically over the last decades. The advent of CT scanning, percutaneous drainage techniques, antibiotics and supportive care have allowed for more patients to be treated without surgery.[3,4]

Conservative treatment of diverticulitis is usually successful with reported success-rates of 70-100%.[3,5] Predictors of treatment failure have rarely been studied and high quality evidence is lacking. When conservative treatment of acute diverticulitis fails, often an acute or urgent resection is needed in a critically ill patient. Reported mortality and morbidity rates in this patient group are very high[3,6-8] Identification of subsets of patients at high risk for treatment failure could allow for more closely monitoring them and consider early intervention in a period when the sequalae of abdominal sepsis have not yet fully developed.

The aim of our study is to identify predictors of failure in patients treated non-operatively for acute sigmoid diverticultis.

METHODS

Patients admitted to the Kennemer Gasthuis hospital and the VU University Medical Centre in the Netherlands between the 1st of January 2001 and 31st of December 2007 with a diagnosis of acute diverticulitis were identified from the prospective hospital patient and diagnosis registry using ICD-9 codes for diverticulitis. The Kennemer Gasthuis hospital is a large teaching hospital and the VU University Medical Centre is an academic centre that also serves as the primary referral hospital for its region. Patients admitted on all hospital wards were included (departments of surgery, internal medicine and gastroenterology). Paper charts and electronic medical charts were reviewed. Inclusion criteria for the study were imaging confirmed acute, diverticulitis of the sigmoid colon in which the decision was made to treat the patient non-operatively. Patient data were anonimised after being entered in the database. For this type of research approval of an institutional review board is not required in the Netherlands.

Hospitalisation

Data extracted on hospitalisation were Ambrosetti CT classification[9] , age, sex, ASA score, antibiotic use, drainage procedures and operations. A total of 21 co morbid conditions were registered. The Charlson score was calculated for each patient as an indicator for comorbidity. Recent research shows that the Charlson index is a predictor of disease severity in patients with acute diverticulitis.[10] The use of steroids, non-steroid anti-inflammatory drugs (NSAIDs), aspirin, oral anticoagulants, insulin and oral antidiabetics was noted.

Confirmation of diagnosis

Only patients with ultrasound or CT-scan proven diverticulitis of the sigmoid colon were included. Original ultrasound and CT-scan reports to assess classification of disease. The Ambrosetti[9] classification was used for classification of disease severity. Radiologists in both hospitals are well trained in the use of both ultrasound and CT scanning for abdominal imaging. Pathology records of operated patients were reviewed.

Treatment failure

Treatment failure was defined as the need for urgent or emergency surgery because of free perforation, clinical deterioration or bowel obstruction not responding to conservative therapy. When in the course of disease percutaneous drainage was performed and treatment thereafter was successful (without the need for an operation) this was noted but not considered a treatment failure.

Statistical analysis

Continues variables are expressed as means and were compared using Mann-Whitney U or students T tests as appropriate. Categorical variables were compared using Fisher exact test or chi-square test. Multivariate logistic regression was performed by incorporating all variables in a model to account for possible confounding. A backward conditional model was used. Statistical significance was defined as p 0.05. Results are presented as odd's ratios with 95% confidence intervals. Statistical analysis was performed using SPSS®, version 17.0(SPSS Inc., Chicago, IL).

RESULTS

A total of 444 patients admitted with a diagnosis of acute diverticulitis were identified and evaluated (Figure 1.). In six patients the diagnosis was not confirmed by imaging, five patients had right-sided diverticulitis on imaging and 115 patients required acute surgery on admission. These patients were excluded from further analysis. 318 patients had imaging confirmed diverticulitis of the sigmoid colon in which the decision was made to treat them non-operatively (e.g. by means of observation, antibiotics and/or percutaneous or transrectal drainage).

Patient and cohort characteristics are shown in table 1. One patient in the succesfull treatment group was excluded from further analysis because too many variables were missing. The mean age of patients was 61.3 years with a standard deviation of 14.1 years. Two thirds of patients were female (68.1%). A total of 20 patients (6%) failed treatment. On univariate analysis age above 70, ASA grade higher than 2, abscess formation on CT scan, steroid use and NSAID use were associated with an increased risk of treatment failure. Multivariate analysis showed abscess formation (odds ratio 8.76 [95% confidence interval 2.88-26.64]), NSAID use (odds ratio 13.35 [95% confidence interval 2.84-64.20]) and ASA grade (odds

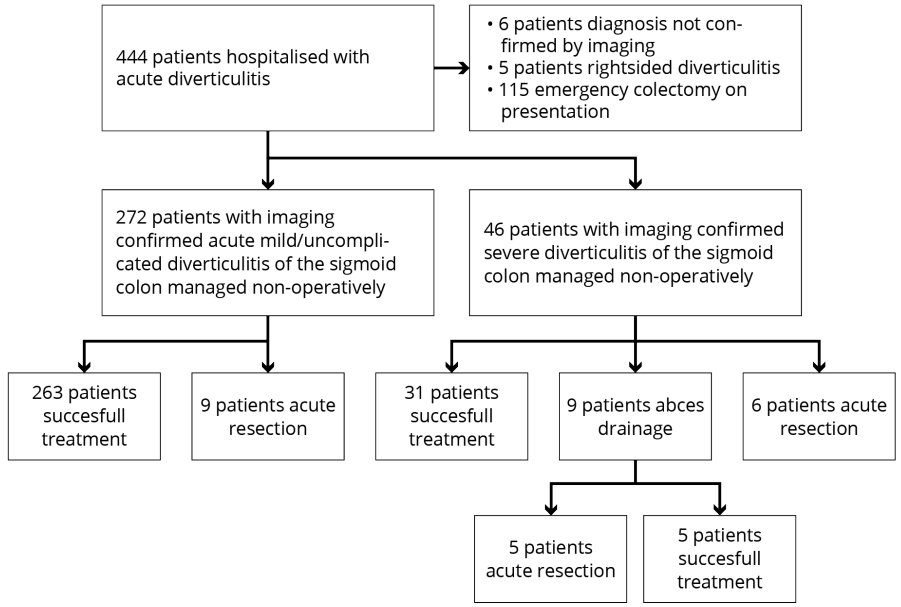

Figure 1 | Flowchart

ratio 4.50 [95% confidence interval 1.52-13.33]) to be independent risk factors. There were 6 (2%) deaths in the entire cohort all of which were in the treatment failure group. When treatment failed mortality was as high as 31.6 percent.

DISCUSSION

The main finding of the present study is that non-operative treatment of diverticulitis is successful but that patients who use NSAID's, have a high ASA classification or have severe diverticulitis on imaging are at high risk of failing treatment. When treatment fails mortality is as high as 31.6 percent.

Diverticular disease and its complications compose a serious healthcare problem. It already ranks 5th in total costs in gastrointestinal disease burdon with an estimated 315.000 admissions and a total annual cost of 2.6 billion dollars in the United States[11] and incidences seem to be rising.[1,2] Treatment for diverticulitis is evolving. CT scanning is recommended for verification of disease and to identify possible complications.[3,12] This has allowed for more patients to be treated non-operatively and most abscesses can now be drained percutaneously.[4] However, much remains unclear about the optimum treatment of diverticulitis. To our opinion treatment for diverticulitis has to be individualised and we need to identify high-risk groups for failing treatment using prediction models.

Table 1 | Patient characteristics

	Successful treatment N=297	(%)	Treatment failure N=20	(%)	P
Sex					
Male	95	(32)	6	(30)	
Female	202	(68)	14	(70)	0.854
Age					
<50	67	(22.6)	3	(15.0)	0.582
>70	83	(27.9)	11	(55)	0.010
ASA grade					
1	136	(45.8)	9	(45)	
2	118	(39.7)	3	(15)	
3	40	(13.5)	7	(35)	
4	3	(1.0)	1	(5.3)	0.011
Charlston score					
0	193	(65)	12	(60)	
1	64	(21.5)	3	(15)	
2	24	(8.1)	3	(15)	
3	7	(2.4)	2	(10)	
4	7	(2.4)	0	(0)	
5	2	(0.7)	0	(0)	0.309
CT scan					
Abcess	25	(8.4)	9	(45)	0.000
Extraluminal air	8	(2.7)	2	(10)	0.125
Antibiotics on admission					
Yes	94	(31.6)	7	(35)	
No	203	(68.4)	13	(65)	0.631
NSAID use	5	(1.7)	5	(25)	0.000
Steroid use	11	(3.7)	4	(20)	0.001
Aspirin use	41	(13.8)	2	(10)	1.000
Oral anticoagulant use	23	(7.8)	2	(10)	0.665
Insuline use	5	(1.7)	2	(10)	0.066
Oral antidiabetic use	18	(6.1)	1	(5)	1.000
Mortality	0	(0)	6	(31.6)	

The literature on treatment failure is scarse. Only one study has recently systematically evaluated risk factors for treatment failure in patients with diverticulitis who were treated non-operatively.[13] This study comprised a cohort of only outpatients and there is doubt as to whether this can be extrapolated to the entire population of patients who are treated conservatively with diverticulitis. It showed that free fluid on CT scan and female age are independent risk factors for treatment failure. Other studies have also identified severe diverticulitis as a risk factor for treatment failure.[9,14] In these studies however no multivariate analysis was preformed to account for confounding by other variables. In our study abscess formation on CT scan was also correlated to treatment failure on multivariate analysis. A recent review on the conservative treatment of abscesses complicating diverticulitis found a failure rate of 20-30%.[4] NSAID use had been shown to increase perforation risk in diverticular disease.[10,15,16] Our study is the first to identify it as an independent risk factor for treatment failure. Co-morbidity has been linked to severity of diverticulitis and risk of emergency colectomy in other studies. Yoo showed that the Charlson index was an independent predictor of severity in diverticulitis.[17] In our study we did not identify the Charlson index as a predictor of treatment failure, but we did found high ASA classification to be associated with a high risk of treatment failure. In patients with high ASA classification, treating physicians may be reluctant to carry out an acute resection because of the perceived higher operating risk. It can be tempting to try to manage these patients non-operatively. Our results however indicate that this group carries a much higher risk of failing treatment. Waiting until treatment fails, sometimes resulting in a full-blown abdominal sepsis, makes outcome of surgery even more dismal. Early surgical intervention when there is no clinical progression during optimal non-surgical treatment may be the preferred choice in this patient group.

Our study is the first to systematically evaluate risk factors for treatment failure in inpatients treated non-operatively for diverticulitis. A further strength of our study lies in the fact that all patients in this study had imaging confirmed diverticulitis. Only six patients in the entire cohort were excluded because of unconfirmed diagnosis. Including patients with an unconfirmed diagnosis leads to unacceptable high percentages of patients not having diverticulitis and no disease severity stratification is possible.[18] Furthermore patients in the present study were included from two different hospitals and from all medical specialties treating patients with diverticulitis, which increases the generalisability of the results.

This study has several drawbacks. Due to the retrospective nature there is always the possibility of bias. All patients in this cohort had imaging confirmed diverticulitis of which the severity was re-evaluated in the original reports and the variables of interest were well documented in the charts, so we believe this limits possible bias. The decision to operate on a patient is ultimately made by the treating surgeon based on numerous factors not easily identifiable in a retrospective study. This will however be difficult to identify even in a prospective study. We evaluated the addition of temperature on admittance, white blood cell count and C reactive protein to strengthen our model. In over 10% of the cases how-

Table 2 | Multivariate analysis: outcome = treatment failure

	Adjusted OR (95 CI)	
Age		
<50	0.68	(0.13-3.68)
>70	2.22	(0.60-9.31)
Sex		
Male	1.00	(reference)
Female	0.54	(0.18-1.99)
CT scan		
Extra luminal air	5.80	(0.93-36.41)
Abcess	8.76	(2.88-26.64)
ASA classification		
ASA 1-2	1.00	(reference)
ASA >2	4.50	(1.52-13.33)
Charlson score		
0	1.00	(reference)
1-2	0.17	(0.02-1.90)
>2	0.04	(0.00-1.27)
Antibiotics on admittance		
No antibiotics	1.00	(reference)
Antibiotics	1.60	(0.66-2.20)
NSAID use	13.35	(2.85-64.20)
Steroid use	5.20	(0.62-43.22)
Aspirin use	0.30	(0.04-2.45)
Oral anticoagulant use	2.29	(0.30-21.013)
Insuline use	5.20	(0.29-95.11)
Oral diabetic medication use	1.29	(0.29-95.11)

ever these data were not well documented or missing. In our opinion including only one value of the aforementioned variables in the prediction model can be misleading, because of fluctuations over time. We therefore decided not to incorporate these variables in our model. Ideally in future prediction models they should be registered sequentially over time.

In conclusion, non-operative treatment of diverticulitis is highly successful. Patients with NSAID use, higher ASA classification and abscess formation on CT scan however carry a high risk of failing treatment. Close monitoring and early intervention is warranted in these patient groups, because when treatment fails observed mortality is very high. More research is needed to further identify risk factors for treatment failure to customise non-operative treatment for diverticulitis.

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PART III

Treatment of diverticulitis with antibiotics

CHAPTER 8

Use of antibiotics in uncomplicated diverticulitis.

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ABSTRACT

Background

The value of antibiotics in the treatment of acute uncomplicated left-sided diverticulitis is not well esthablished. The aim of this review was to assess whether or not antibiotics contribute to the (uneventful) recovery from acute left-sided diverticulitis, and which types of antibiotic and route of administration are most effective.

Methods

Medline, the Cochrane Library and Embase databases were searched. Randomized clinical trials (RCT), prospective or retrospective cohort studies addressing conservative treatment of mild uncomplicated left-sided diverticulitis and use of antibiotics were included.

Results

No randomized or prospective studies were found on the topic of effect on outcome. One retrospective cohort study was retrieved that compared a group treated with antibiotics to observation alone. This study showed no difference in success rate between groups. Only one RCT of moderate quality compared intravenous and oral administration of antibiotics, and found no differences. One other RCT of very poor quality compared two different kinds of intravenous antibiotics and found no difference either. A small retrospective cohort study comparing antibiotics with and without anaerobe coverage showed no difference between group outcomes.

Conclusion

Evidence on the use of antibiotics in mild or uncomplicated diverticulitis is sparse and of very low quality. There is no evidence mandating the routine use of antibiotics in uncomplicated diverticulitis, although several guidelines recommend this.

INTRODUCTION

Diverticular disease is the most common disease of the colon being found in 1 in 3 people over the age of 60 in the western world.[1] The lifetime prevalence of diverticulitis is 10-25% among patients with diverticular disease and is increasing.[1,2]

Acute diverticulitis is usually graded as “complicated” or “uncomplicated” according to the classification of The European Association for Endoscopic Surgeons[3], as “mild” or “severe” according to the Ambrosetti CT-criteria[4], or according to the modified Hinchey classification.[5] As only 0-10% of admitted patients present with complicated disease and require surgery or percutaneous drainage, conservative treatment is the management of choice in the majority of patients.[1] The mainstay of treatment for uncomplicated diverticulitis has been bowel rest, intravenous fluids and antibiotics.[1] Usually coverage against both gram negative and anaerobic bacteria is recommended.[1, 6-9] Contrary to complicated disease, effect of treatment in uncomplicated disease has rarely been subject of research. Recommendations are based on expert opinions and medical dogmas.

Surveys conducted among American, British and Dutch surgeons and gastroenterologists show that the choice of antibiotics and the route of administration differ. Most American and British surgeons use antibiotics for the treatment of uncomplicated diverticulitis, but the majority of surgeons and gastroenterologists in the Netherlands believe antibiotics are not mandatory in the treatment of uncomplicated diverticulitis.[10-12]

First, to assess the grounds for use of antibiotics in uncomplicated diverticulitis guidelines issued by professional organisations worldwide were evaluated. The systematic review aimed to investigate (a) the overall effect of antibiotics on the treatment of diverticulitis, (b) the effect of administration route and (c) the effect of different types of antibiotics in the treatment of acute mild (uncomplicated) diverticulitis of the sigmoid colon in adult patients.

METHODS

The latest PRISMA guidelines for conducting and reporting a systematic review or a meta-analysis were used.[13]

Search strategy

Two reviewers (NdK and CU) independently searched the following databases: Medline (January 1966 to May 2010, search strategy: ((“Diverticulitis”[Mesh] OR “Diverticulitis, Colonic”[Mesh])) AND (“Anti-Bacterial Agents”[Mesh] OR “Anti-Bacterial Agents “[Pharmacological Action]))), Cochrane Database of Systematic Reviews, Cochrane Clinical Trials Register, Database of Abstracts on Reviews and Effectiveness (search strategy: Diverticulitis AND antibiotics) and EMBASE (January 1950 to May 2010, search strategy: (“Diverticulitis”) AND (“Anti-Bacterial Agents:))

After identifying relevant titles all abstracts were read and eligible articles were retrieved. A manual cross-reference search of the bibliographies of relevant articles was performed to identify other studies not found in the search. The "related articles" function in Pubmed was also used to identify articles not found in the original search. Clinical studies published in English, German, or Dutch were included. No unpublished data or abstracts were included. Last search update was 01-06-2010.

Inclusion and exclusion criteria

Studies

Because of the paucity of data on the conservative treatment of diverticulitis of the sigmoid colon we chose not only to include randomized clinical trials but all comparative studies addressing the conservative treatment of uncomplicated or mild diverticulitis of the sigmoid colon and the use of antibiotics.

Participants

Patients eighteen years or older diagnosed with acute uncomplicated or mild diverticulitis of the sigmoid colon.

Interventions and controls

Studies that compare (a) antibiotics versus observation alone, (b) different types of antibiotics or (c) oral versus intravenous regimens were included.

Outcome measures

Primary outcome parameter is success rate of the treatment.

Data collection process

Data were registered on preformatted sheets. The follwing information was extracted from each included study: characteristics of trial participants (including age, severity of disease, and method of diagnosis), and the trial's inclusion criteria; type of intervention (antibiotics versus observation, different types of antibiotics, and route of administration of antibiotics); and types of outcome measures.

Risk of bias in individual studies

Two authors (NdK and CU) independently assessed the methodological quality and bias of the RCT's using the Jadad score [14] and the checklist of the Cochrane collaboration[15]. Disagreement was resolved by consensus. For each individual study included other forms of bias were evaluated on a case-by-case basis. This was done specifically for method of diagnosing diverticulitis.

Statistical analysis and summary measures

The effectiveness of a specific therapy compared to its control group for the primary outcome measure success rate was expressed using odds ratios (ORs) with 95% confidence intervals (CIs), and calculated from the original data, if not provided. An OR of less than

1 favors the intervention group over the control group. Since none of the three research questions concerning antibiotic use in uncomplicated diverticulitis revealed more than one RCT, pooling of data was not possible or needed. Data analysis was performed using the Cochrane Review Manager (RevMan) version 5 (Cochrane Collaboration, Oxford, UK).

RESULTS

Published guidelines and practice parameters

A total of four guidelines were identified after searching Medline. The Society of Surgery of the Alimentary Tract [8], the American Society of Colon and Rectal Surgeons[7], the European Association for endoscopic Surgery [3] and the American College of Gastroenterology[6] published guidelines concerning the treatment of mild diverticulitis of the sigmoid colon and the use of antibiotics. A further search using Google identified one other guideline by the World Gastroenterology Organization.[16] All guidelines recommend the use of antibiotics, but references to original research are lacking. For the recommendation on the type of antibiotic only in two guidelines (the American Society of Colon and Rectal Surgeons and the American College of Gastroenterology) a reference to original research is given.[17] All guidelines indicate that antibiotics should be given intravenous, but that in mild disease where outpatient treatment is considered it can be given orally. Broad-spectrum antibiotics covering gram negatives and anaerobes are recommended in all guidelines. No references to original research are given.

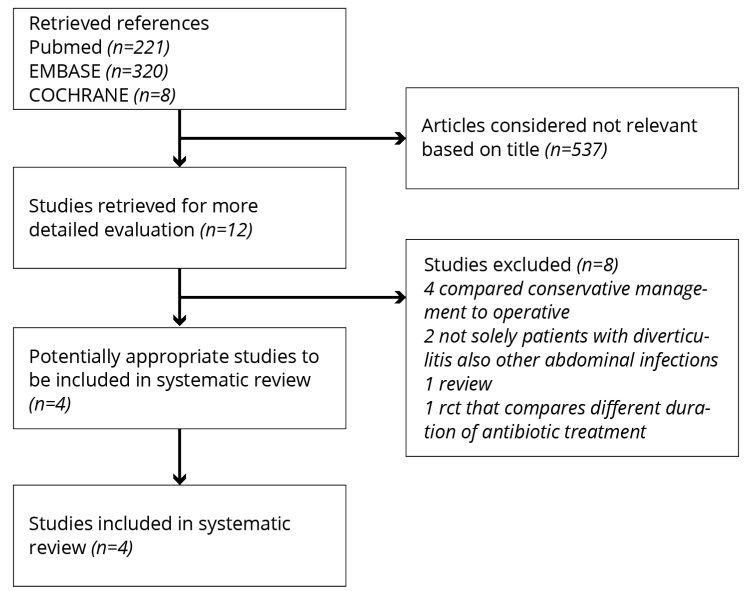

Figure 1 | Search strategy

Table 1 | Characteristics of included studies

	Reference	Design	Period	Country	Patients Age	Inclusion	Method of diagnosis	Group Intervention	n	Control	n	Total n
Studies comparing antibiotics to observation alone	18	Retro-spective comparative cohort study	2000-2002	Sweden	Adult patients	Acute diverti-culitis	CT	Antibiotics	118	Observa-tion alone	193	311
Studies comparing oral to intravenous regimens	20	RCT	2002-2004	UK	Adult patients	Acute diverti-culitis	Clinical grounds	Oral regimen	41	Intra-venous regimen	38	79
Studies comparing different types of antibiotics	17	RCT	1992	UK	Adult patients	Acute diverti-culitis	Combination of clinical grounds and radiology, pathology or surgical evidence of diverticular disease.	Cefoxitin	30	Genta-mycine-Clinda-mycine	21	51
	19	Retrospective comparative cohort study	1974-1978	USA	Adult patients	Acute diverti-culitis	Not stated	Anaerobic coverage	15	No anaerobic coverage	52	67

Systematic review

The first search resulted in a combined total of 545 articles in all databases combined. After reviewing the abstracts only 4 articles addressed the use of antibiotics specifically in colonic diverticulitis and met our inclusion criteria (Figure 1). A summary of includes studies is shown in table 1. Individual study quality assessment is listed per methodological item in table 2. Two randomized controlled trials were found. In addition, two studies were found that compared two cohorts of patients.

Antibiotics versus no antibiotics

No RCT's were found. Only one study was retrieved in the search strategy. Hjern et al. performed a retrospective case control study in a group of patients with diverticulitis treated without antibiotics and compared those to a group of patients treated with antibiotics.[18] The groups were comparable at baseline for age, sex and co-morbidity. Diagnosis was confirmed using CT. Disease severity was compared using laboratory parameters and Ambrosetti CT classification. The group that received antibiotics had significantly higher infection parameters and more severe diverticulitis on CT at baseline.

The primary outcome measure was success rate and it was similar between the antibiotics group (115 of 118, 97%) and the control group (186 of 193, 95%). No odds ratios or confidence intervals were reported for the primary outcome, but can be calculated. Calculated odds ratios for success of treatment without antibiotics is 1.44 (95%CI 0.37-5.69). Time to recovery also did not significantly differ between groups. Hospital stay was significantly shorter in the control group (3 days) compared with the antibiotics group (5 days, P<0.001). During follow-up, 29% of patients treated with antibiotics had further events (recurrent acute diverticulitis and/or subsequent surgery) compared with 28% of those treated without antibiotics. In a multivariable analysis, the risk of a further event was not influenced by prior antibiotic treatment (OR 1.03, CI 95% 0.61-1.74).

Different types of antibiotics

Only one RCT was found examining this question. Kellum et al. conducted a randomized trial comparing cefoxitin and gentamycine-clindamycine in the treatment of acute uncomplicated diverticulitis[17]. The primary outcome measure was success rate. No power calculation was reported. Diagnosis was based on clinical grounds and contrast enema or CT. The two patient groups were comparable with respect to baseline characteristics and clinical disease severity (fever, laboratory parameters and abdominal tenderness). No difference in success rate was found between patients treated with cefoxitin (27 of 30, 90%) versus gentamycin/clindamycin (18 of 21, 86%), P=0.48. No odds ratios or confidence intervals were reported, but can be calculated.

Calculated odds ratio for success of gentamycin/clindamycin treatment is 1.50 (95%CI 0.27-8.26). Quality assessment revealed a Jadad score of 0, indicating very poor quality.

Table 2 | Quality assessment

Refe-rence	Study design	Rando-mization?	Treatment Allocation Concealed?	Eligibility Criteria Specified?	Patient Blinded?	Outcome Assessor Blinded?
18	Retro-spective case control	No	No	Yes	No	Not stated
20	RCT	Yes	Yes	Yes	No	Not stated
17	RCT	Yes	No	Yes	No	Not stated
19	Retro-spective case control	No	No	Yes	No	Not stated

A retrospective study by Fink et al. evaluated two different intravenous antibiotic regimens with and without anaerobic coverage, defined as in vitro activity against Bacteroides fragilis[19]. The primary outcome measure used was success rate of treatment. The two groups were comparable with respect to baseline characteristics (age and sex). Fever, laboratory findings and abdominal tenderness were used to assess disease severity. How diverticulitis was diagnosed was not stated. The authors found no difference in success rate between the no anaerobic coverage group (34 of 52, 65%) and the anaerobic coverage group (10 of 15, 67%; P>0.05). No odds ratios or confidence intervals were reported for the primary outcome, but can be calculated. The calculated odds ratio for success of treatment with anaerobic coverage is 1.06 (0.31-3.57). The extremely small numbers of patients in this study, especially in the anaerobic group hampers interpretation of the data.

No pooling of data was possible for these two studies because of major differences in design and difference in antibiotic coverage used.

Oral versus intravenous regimens

Ridgeway et al. conducted a randomized controlled trial comparing an oral antibiotic regimen (N=41) with an intravenous regimen (N=38) of clindamycin and metronidazol in patients with uncomplicated diverticulitis.[20] Diagnosis was based solely on clinical grounds. The two patient groups were comparable with respect to baseline characteristics and laboratory infection parameters. Primary outcome parameter was resolution of disease. Resolution of left iliac fossa tenderness (by Wexford tenderness score), length of stay and failures of oral therapy (requiring supplemental parenteral therapy) were used as surrogate markers for resolution of disease or success of treatment. There was no significant difference in Wexford tenderness score on day 3 between the oral treatment arm (score 1.26) versus the intravenous arm (1.20, P=0.79). Hospital stay did not differ between oral regimen (5.5 days) and intravenous regimen (6.6 days, P=0.12). There was a 100 % success rate as both groups had no treatment failures, and no odds ratio calculation is possible for that reason. Quality assessment showed a Jadad score of 4 indicating moderate quality.

Table 2 | Continued

Care provider blinded?	Groups Similar at Baseline?	Follow Up?	Percentage of patients lost to FU	Intention to treat?	Trial stopped early?	Similar Non trial treatment?	Jadad score
No	No	Yes	0 %	No	No	Not stated	
No	Yes	Yes	0 %	Yes	No	Yes	4
No	Yes	Yes	Not stated	Not stated	No	Not stated	0
No	Yes	Yes	Not stated	No	No	Not stated	

DISCUSSION

Diverticulitis of the sigmoid colon is one of the most common disorders of the gastrointestinal tract, with a huge healthcare burden. Nevertheless, evidence on the use of antibiotics in mild uncomplicated diverticulitis is sparse and of very low quality. There is no evidence mandating the routine use of antibiotics in mild uncomplicated diverticulitis, although several guidelines recommend this.

In the present systematic review four studies were identified, shedding some additional light on the use of antibiotics in uncomplicated left-sided diverticulitis. A recent retrospective case control study found no advantage of antibiotics in patients with uncomplicated diverticulitis. There is some evidence from one randomized controlled trial that treatment of uncomplicated diverticulitis with oral antibiotics alone is as effective as treatment with intravenous antibiotics, although verification of the diagnosis of diverticulitis has been suboptimal in that study. High quality evidence as to what type of antibiotic is most effective is lacking.

It has long been believed that all forms of diverticulitis are the result of a colonic (micro) perforation. The original Hichey classification is based on this premise.[21] More recently a different or complementary pathogenesis of diverticulitis has been proposed, where diverticultitis is regarded as a form of inflammatory bowel disease.[22] This concept of some form of chronic inflammation (not infection) of the colon in the presence of diverticula has been substantiated recently in a study that showed inflammation in pathologic specimens taken from around the mucosa of diverticula in asymptomatic individuals without endoscopic findings of inflammation.[23] This chronic low-grade inflammation could be a precursor stage to the clinically manifest stages of diverticulitis. Recent success in preventing attacks of diverticulitis with probiotics and mezasaline contribute to this notion.[24, 25]

Uncomplicated diverticulitis could be a self-limiting disease in which the local host defence can eradicate the bacterial invasion of a diverticulum without antibiotics in immunocompetent individuals. Antibiotics may therefore not be necessary in the treatment of uncomplicated disease. Potential benefits of a more liberal treatment strategy for acute diverticulitis without antibiotics include shorter duration of hospital admission (no intravenous medication needed), cost reduction, less antibiotic resistance development and side effects. Antibiotic resistance in particular is becoming a serious and hard to combat health-care threat. In this light the cohort study of Hjern et al. is interesting, concluding that antibiotics might not be necessary in the majority of patients.[18] The study is, however, retrospective and non-randomized and affected by selection bias. No firm conclusions can be drawn, but this study does give some evidence to the common practice in some European countries that do not use antibiotics in the treatment of uncomplicated diverticulitis[12, 18]

Intra-abdominal infections have been studied extensively but recommendations on the use of antibiotics in diverticulitis are largely based on findings in studies not specifically investigating diverticulitis.[26] Only one study has tackled this subject for perforated diverticulitis and showed a similar microbiology in diverticulitis compared to other forms of intra-abdominal infections.[27] The two studies found in this review where of very poor quality and do not add to the existing narrative on antibiotic choice in intra-abdominal infections in general.

The only randomized trial performed comparing oral and intravenous antibiotics in mild diverticulitis is underpowered.[20] Their conclusion that treatment with oral antibiotics alone is as effective as treatment with intravenous antibiotics cannot be drawn without reservation. Results from this trial are however in line with recommendations from published guidelines. Recent literature shows that patients with mild diverticulitis are increasingly being treated safely as outpatients with oral regimens of antibiotics.[28] In addition, a prospective randomised trial for complicated intra-abdominal infections of all origins showed that a switch from intravenous to oral antibiotics is safe when oral intake was tolerated.[29]

One of the problems with the design of three of the four retrieved studies is the verification of the diagnosis of diverticulitis. Were the correct patients included in the studies? Diagnosis on clinical grounds alone leads to a high percentage of patients being included not having diverticulitis.[30, 31] CT or ultrasound should be the method of choice in identifying patients with diverticulitis.[32] Two recent papers state that there may be a subset of patients that can be positively diagnosed without imaging base on a decision rule.[33, 34] However, this decision rule first needs external validation.

Different classification and staging systems exist for diverticulitis and allow for stratification of disease severity. When diverticulitis is classified as “uncomplicated” there is no abscess formation or gross perforation. This correlates with de Ambrosetti CT classification[4]

in which this is classified as “mild”. This however not always fits the clinical picture. When there are signs of sepsis in a patient with “mild” diverticulitis on imaging this does not constitute a “mild” or “uncomplicated” diverticulitis. In three studies in the present review the assessment of disease severity was made partly or solely on clinical grounds. There are no classification systems that incorporate clinical features, but it suffices to say that when there are signs of sepsis antibiotics have to be administered and close observation is warranted despite the absence of evidence to support this in patients with diverticulitis. In the end the decision to give or omit antibiotics is ultimately made by the treating physician based on the complete clinical picture.

The treatment of mild uncomplicated left-sided diverticulitis lacks evidence. Future patients with mild diverticulitis could benefit from the results of prospective trials with sound criteria for diagnosis, with stratification of disease stage and adequate power, investigating one of the many unproven issues of diverticulitis treatment. Results of two randomised clinical trials (NCT01111253 and NCT01008488) in the Netherlands and Sweden randomising patients with uncomplicated diverticulitis to antibiotics or observation alone are not expected for several years. Until these results become available it is useful to note that current guidelines that advise the use of antibiotics in uncomplicated diverticulitis are not evidence-based. In the majority of patients with mild diverticulitis antibiotics can probably be omitted.

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CHAPTER 9

Mild colonic diverticulitis can be treated without antibiotics. A case-control study.

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ABSTRACT

Aim

Conservative treatment of mild colonic diverticulitis usually consists of observation, restriction of oral intake, intravenous fluids and antibiotics. The beneficiary effect of antibiotics remains unclear. The aim of this study is to evaluate the need for antibiotics in mild colonic diverticulitis.

Methods

A retrospective case-control study was performed in 272 patients with mild colonic diverticulitis admitted in two hospitals with distinctly different treatment regimes concerning antibiotic use.

Results

A total of 191 patients were treated without antibiotics and 81 with antibiotics. Groups were comparable at baseline with respect to age, sex, co-morbidity, NSAID, steroid and aspirin use. All patients had imaging confirmed diverticulitis. CRP and WBC levels did not differ significantly. In the antibiotics group there were significantly more patients with a temperature of 38.5 ° Celsius or higher on admission. (8% *versus* 19%, P=0.014). Treatment failure did not differ between groups (4% *versus* 6%, p=0.350). The risk of recurrence was higher in the antibiotics group on logistic regression analysis but did not reach statistical significance (odds ratio 2.04, CI 0.88-4.75, p=0.880). The only factor that increased the risk of recurrence was NSAID use (odds ratio 7.25, CI 1.22-46.88, p=0.037).

Conclusion

Antibiotics can be omitted in selected patients with mild colonic diverticulitis and should be given on indication only.

INTRODUCTION

Diverticular disease is the most common disease of the colon in the developed world and its incidence is increasing.[1,2] Approximately 10-25% of patients with diverticulosis will develop diverticulitis.[3] The majority of patients who present with acute colonic diverticulitis can be managed conservatively.[4] Conservative treatment of mild colonic diverticulitis usually consists of observation, restriction of oral intake, intravenous fluids and antibiotics.[4] Although all published guidelines recommend the use of antibiotics there is no evidence to support this.[5-9] On the contrary, the only study evaluating the efficacy of antibiotics in mild colonic diverticulitis showed omitting antibiotics had no effect on failure rate.[10]

Furthermore, recent studies on the aetiology of diverticular disease suggest that it maybe a form of inflammatory bowel disease and that not all forms of diverticulitis are the result of a colonic (micro) perforation.[11-13] Successful prevention of diverticulitis with anti-inflammatory drugs and probiotics contribute to this concept.[14-15] If this is indeed the case, the rationale behind prescribing antibiotics for the treatment of acute mild diverticulitis can be debated.

In the Netherlands a long-standing tradition exists to minimize the use of antibiotics whenever possible. A survey shows that the majority of Dutch surgeons and gastroenterologists do not routinely prescribe antibiotics in the treatment of mild diverticulitis.[16] The Dutch National Antibiotics Policy Committee also states that antibiotics are not mandatory in the treatment of colonic diverticulitis. [17] The ever-growing problem of antibiotic resistance, possible side effects and costs warrant further research on the effectiveness of antibiotics in acute diverticulitis.

The aim of this case-control study is to evaluate the effect of antibiotics on failure rates of conservative management of acute mild diverticulitis of the sigmoid colon.

METHODS

Patients admitted to the Kennemer Gasthuis hospital and the VU University Medical Centre in the Netherlands between the 1st of January 2001 and 31st of December 2007 with a diagnosis of acute diverticulitis were identified from the prospective hospital patient registry using ICD-9 codes for diverticulitis. Patients admitted on different hospital wards were included (departments of surgery, internal medicine and gastroenterology). Paper charts and electronic medical charts were reviewed. Inclusion criteria for the study were imaging confirmed (CT or ultrasound) acute, Ambrosetti[18] mild or Hinchey 1a[19] diverticulitis of the sigmoid colon in which the decision was made to treat the patient conservatively. To compare success rates the cohort was dived into a group treated with antibiotics and a group treated without antibiotics. Patient data were anonimised after being entered in the database. For this type of research approval of an institutional review board is not required in the Netherlands.

Hospital type and antibiotic use
The Kennemer Gasthuis hospital is a large teaching hospital. No formal protocol exists for the antibiotic treatment of mild diverticulitis. Antibiotics are not routinely given.

The VU University Medical Centre is an academic centre that also serves as the primary referral hospital for its geographic location. A protocol exists for the antibiotic treatment of diverticulitis. When patients are admitted on the surgical ward a combination of piperacilin and metronidazole is given intravenously. When patients are admitted on the internal medicine or gastroenterology wards amoxicillin-clavulanic acid is given intravenously. Antibiotics are continued 7-10 days depending on clinical status. In all cases the treating physicians decided to prescribe or to omit antibiotics on individual grounds.

In both hospitals the treating physician made the ultimate decision regarding the start or omission of antibiotics based on the clinical status.

Conservative treatment consisted of restriction of oral intake, intravenous fluid rehydration and observation. Restriction of oral intake varied but usually a liquid diet was prescribed when patients tolerated oral intake. When symptoms resided, a normal diet was started. No specific foods were avoided. Analgesics were given as appropriate, starting with acetaminophen and non-steroid anti-inflammatory drugs (NSAID's) as needed.

First hospitalisation
Data extracted on first hospitalisation were Ambrosetti and Hinchey classification, age, sex, ASA classification, history of previous attacks of diverticulitis, recurrence, drainage procedures and operations. A total of 21 co morbid conditions were registered. The use of steroids, NSAID's and aspirin was noted. The Charleston score was calculated for each patient as an indicator for comorbidity. Recent research shows that the Charlson index is a predictor of disease severity in patients with acute diverticulitis.[20]

Confirmation of diagnosis
Only patients with ultrasound or CT-scan proven diverticulitis of the sigmoid colon were included. Two authors (NDK, HBS) independently reviewed the original ultrasound and CT-scan reports to assess classification of disease. The Ambrosetti[18] and modified Hinchey classifications[19] were used for classification of disease severity. Radiologists in both hospitals are well trained in the use of both ultrasound and CT scanning for abdominal imaging. Pathology records of patients operated upon were reviewed.

Treatment failure
Treatment failure was defined as the need for urgent or emergency surgery and/or the need for percutaneous drainage of abscesses because of clinical deterioration. The addition of antibiotics in patients initially not treated with antibiotics was noted, but not considered a treatment failure, as this is an inherent part of a treatment protocol without antibiotics.

Follow-up
The mean length of follow up was 50 months (range 12-100). All recurrences and/or complications of diverticulitis were noted. A recurrence was defined as a readmission 8 weeks or more after the previous attack and after resolution of infection parameters. Diagnosis was confirmed by imaging with CT scanning in all cases.

Statistical analysis
Continues variables are expressed as medians with inter quartile range or means with range and were compared using Mann-Whitney U or students T tests as appropriate. Categorical variables were compared using Fisher exact test or chi-square test as appropriate. Multivariate logistic regression was performed to assess the risk of recurrence by incorporating age>70, age<50, sex, ASA grade >II, Carlson co morbidity index, corticosteroid use, NSAID use, aspirin use and antibiotics use in the primary episode in a model. A backward conditional method was used. Statistical significance was defined as p £0.05. Results are presented as odd's ratios with 95% confidence intervals. Statistical analysis was performed using SPSS®, version 17.0(SPSS Inc., Chicago, IL).

RESULTS

A total 272 patients were identified with imaging confirmed Ambrosetti mild or Hinchey 1a diverticulitis of the sigmoid colon. (Figure 1.) Diverticulitis was confirmed by ultrasound only in 15 patients, the other 257 patients all had CT confirmation of their diagnosis. Antibiotic treatment was started in 81 patients (AB group) and antibiotics were omitted in 191 patients (N-AB group). Patient characteristics are shown in table 1. The two groups are comparable with respect to age, sex, comorbidity as assed by ASA grade and Charlson score, corticosteroid use, NSAID use and aspirin use at baseline.

Index admission
Table 2 shows data on the index admission. The AB and N-AB groups were comparable with respect to CRP and WBC on admission. A significantly higher percentage of patients in the antibiotics AB group, however, had a temperature of 38.5° Celsius or higher on admission. (P=0.014). Treatment failure did not differ between groups. In the N-AB group 7 patients (4%) failed treatment. One patient underwent successful percutaneous drainage of an abscess and later had an elective laparoscopic sigmoid resection. One patient developed signs of bowel obstruction not responding to conservative therapy and underwent a Hartmann procedure. In six patients deterioration of the clinical condition warranted an acute operation and a Hartmann procedure was performed. One patient died of ongoing sepsis and multiple organ failure. In the N-AB group only in two patients eventually antibiotics were started because of high temperature.

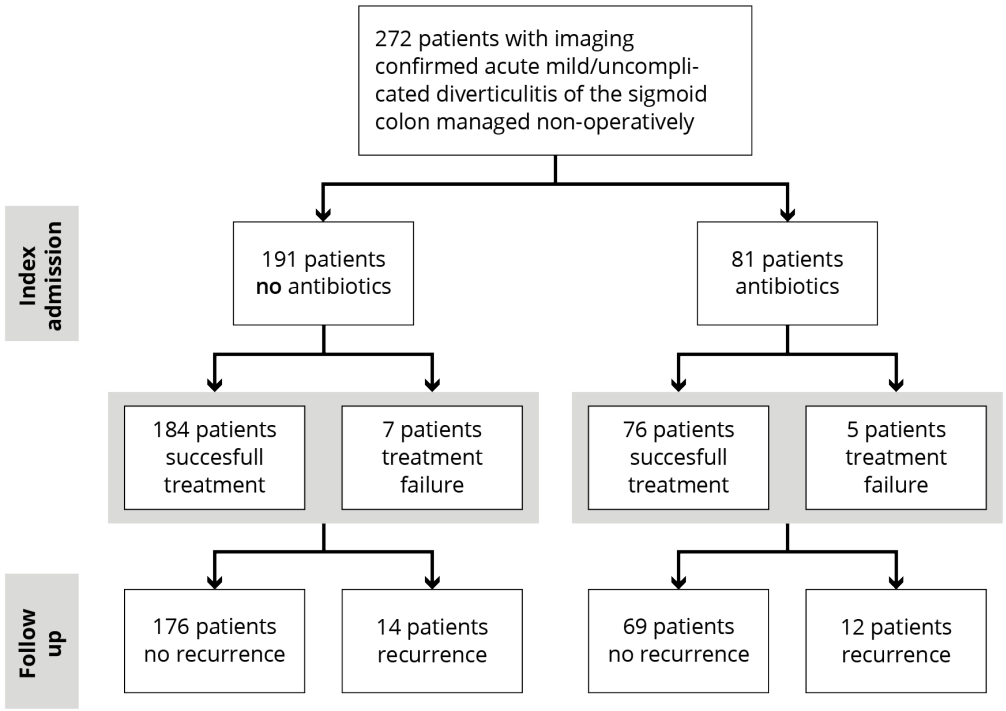

Figure 1 | Flowchart

In the AB group five patients (6%) failed conservative treatment. Two patients underwent successful percutaneous drainage of an abscess and settled without an operation. In the follow-up an elective laparoscopic sigmoid resection was performed. In three patients an acute operation was performed because of clinical deterioration. In two instances a resection and primary anastomosis was performed. One of these patients died because of ongoing sepsis and multiple organ failure. In the other patient a Hartmann procedure was performed.

There was no difference in treatment failure between the two hospitals. (8 of 208 patients versus 4 of 52 patients, P=0.276)

Follow up

In the N-AB group 14 patients (7%) had one or more recurrences requiring hospitalization. Of these 14 patients one required acute resection during follow- up and underwent a Hartmann procedure. Seven patients had complications requiring elective surgery, four had a symptomatic stenosis and three had a fistula. All underwent a resection and primary anastomosis. Of the AB group 12 patients had a recurrence (15%) of which one had emergency surgery. Four patients developed a symptomatic stenosis and one patient a fistula. All were managed by elective resection and primary anastomosis. (Table 2.)

Table 1 | Patient characteristics

	No antibiotics n=191		Antibiotics n=81		P value
Age (years)*	61	(27-92)	63	(34-94)	0.370§
Female	135	(71)	52	(64)	0.291‡
ASA classification					
I	90	(47)	33	(41)	
II	77	(40)	31	(38)	
III	22	(12)	16	(20)	
IV	2	(1)	1	(1)	
					0.341‡
Charlston score					
0	131	(69)	45	(55)	
1-2	52	(27)	29	(36)	
>2	8	(4)	7	(9)	
					0.084‡
Corticosteroid use	8	(4)	4	(5)	0.774‡
NSAID use	4	(2)	1	(1)	1.000‡
Aspirin use	25	(13)	13	(16)	0.505‡

Values in parentheses are percentages unless indicated otherwise; * values are means (range); ‡ Fischer's Exact test or χ^2 test as appropriate; § Student's T- test; WBC, white blood count; CRP, c reactive protein.

Table 2 | Results on index admission and follow-up

	No antibiotics n=191		Antibiotics n=81		P value
Temperature on admission ≥38.5 ° C	16	(8)	15	(19)	0.014‡
WBC on admission (x 10^9 cells/ml.)*	12.4	(4.7)	12.9	(5.1)	0.482§
CRP on admission (mg/l)*	99	(108)	109	(96)	0.395§
Treatment failure	7	(4)	5	(6)	0.350‡
Acute resection	6		3		
Percutaneous drainage	1		2		
Antibiotics added	2	(1)	-		-
Mortality	1	(0.5)	1	(1)	0.508‡
Hospital stay (days)*	7	(5)	7	(5)	0.666§
Recurrence	14	(7)	12	(15)	0.055‡
Acute resection	1		1		
Complications in follow up	7	(4)	5	(7)	0.347‡
Stenosis	4		4		
Fistula	3		1		

Values in parentheses are percentages unless indicated otherwise; * values are medians (Inter Quartile Range); ‡ Fischer's Exact test or χ^2 test as appropriate; § Mann-Whitney U test; WBC, white blood count; CRP, c reactive protein.

An elective resection for recurrent disease was performed in a total of 33 patients in the entire cohort. All operated patients had evidence of diverticular disease in their pathology specimens.

Risk of recurrence

Univariate analysis showed that treatment with antibiotics resulted in a higher risk of recurrence, although not statistically significant (7 % versus 15%, p=0.055). A model was constructed to assess other factors that could influence recurrences. Logistic regression analysis revealed no influence of antibiotic use on recurrence (odds ratio 2.04, CI 0.83-4.75, p=0.880). No other factors had influence on recurrence except NSAID use which showed a higher chance of recurrence (odds ratio 7.85, CI 1.22-46.88, p=0.037).

DISCUSSION

The results of this study indicate that it is safe to omit antibiotics in a selected group of patients with mild diverticulitis. The mandatory use of antibiotics in mild colonic diverticulitis has been a long-standing surgical dogma. Only four studies evaluate the use of antibiotics specifically in colonic diverticulitis.[10, 21-23] Two studies of poor quality compared different antibiotic regimens and found no difference in success rate.[21-22] In a recent prospective randomized trial, treatment of mild diverticulitis with oral antibiotics was as effective as treatment with intravenous antibiotics, although diagnosis was made on clinical grounds only.[23] Hjern et al. in 2007 for the first time questioned the usefulness of antibiotics in colonic diverticulitis in a cohort study and found no difference in success rate between the group treated with and the group treated without antibiotics.[10] The study suffered by the fact that 30% of patients admitted with a clinical diagnosis of diverticulitis were excluded because the diagnosis was not confirmed by imaging. Furthermore the groups significantly differed with respect to disease severity at baseline.

The current study has several limitations. Patients were not randomised to be treated with or without antibiotics so there is a possibility of selection bias. All patients however were comparable with respect to baseline characteristics, co-morbidity and medication use. All patients in this study had mild diverticulitis on imaging (Hinchey 1A), but the clinical presentation varied. We therefore used infection parameters and temperature as additional markers for severity to asses treatment bias. In the patient group treated with antibiotics, significantly more patients had a temperature of 38.5°C. or higher. However, only 11% of the entire cohort had a temperature of 38.5°C. or higher. Although not statistically different, the patients in the AB group had slightly higher WBC and CRP levels. This may indicate that in these patients the treating physicians were more reluctant to omit antibiotics because of a marked systemic inflammatory response. It is therefore not clear if antibiotics can be omitted in patients with mild diverticulitis on imaging, but with high fever and severely

elevated infection parameters. This underscores the need for a clinical staging system in mild diverticulitis incorporating serological markers and clinical signs. In future prospective studies this should be addressed. As this is an observational study there is always the possibility of a type II error. Given the high success rates of conservative treatment of mild colonic diverticulitis already, even without antibiotics, very large numbers of patients would have to be treated to prevent one treatment failure.

The rationale behind treating an episode of uncomplicated diverticulitis with antibiotics lies in the fact that is has long been believed that all forms of diverticulitis are the result of a colonic (micro) perforation caused by inpissated stool in a diverticulum.[24] In mild disease the body is able to contain the perforation. Antibiotics are given to combat this form of local peritonitis and to prevent subsequent abscess formation or progression to a free perforation. An overlap between diverticulitis and inflammatory bowel disease has long been recognized[25] but recently Floch[11] and Tursi[12] postulated that all diverticular disease could be a form of inflammatory bowel disease. This notion was substantiated by the fact that low-grade inflammation can be shown in the mucosa around diverticula in asymptomatic individuals.[12] An attack of acute diverticulitis might be the other end of this spectrum of chronic inflammation that in severe cases leads to a (micro) perforation. Altering the inflammatory response in cases of mild diverticulitis may be a more logical step than giving antibiotics.[12] In cases of complicated diverticulitis when perforation or abscess formation arises antibiotics can be given to lower the bacterial load and to treat septic complications. How this chronic inflammation is initiated remains unclear but an altered colonic micro ecology could play a role.[26] Research has shown that increased bran intake alters the anaerobic/aerobic ratio in the colon. The success of trials using ant-inflammatory drugs[27,28] and probiotics[15] to prevent recurrent diverticulitis and symptomatic diverticulosis are promising and contribute to the notion of some form of chronic inflammation in diverticular disease and diverticulitis. Antibiotics resistance is becoming a serious and increasingly hard to combat healthcare threat.[29,30] Furthermore, the risk of side effects and costs warrant selective use whenever possible.

In our study treatment regime did not significantly influence the risk of recurrence although patients in the AB group had a higher recurrence rate. The only factor significantly influencing recurrence on logistic regression analysis was the use of NSAID's. Although it has been reported to increase the risk of perforation in diverticular disease[31], to our knowledge this it the first report to associate it with a higher risk of recurrence.

Many cohort studies on diverticulitis to date are hampered by unconfirmed diagnosis through imaging. A diagnosis solely based on history and physical examination proofs to be imperfect as 30% of the clinically diagnosed patients does not have diverticulitis. CT scanning is now recommended for confirmation of the diagnosis, assessment of extent of disease and for evaluation of possible other diagnoses.[4] Ultrasound yields high sensitivity and specificity rates as well.[33] Moreover it has the advantage of not subjecting patients to

ionizing radiation, but quality is highly investigator dependent and pain, abdominal gas and obesity can hinder interpretation. In many countries ultrasound imaging by an experienced radiologist is not always available in the acute setting. The radiologists in our study are well trained in abdominal ultrasound and it was readily available. Almost all patients in this study, however, underwent a CT scan, which illustrates the fact that since 2000 it was customary in both hospitals to confirm diagnosis by means of CT scanning. Only six patients in this cohort were excluded from further analysis because of unconfirmed diagnosis. Interestingly two recent papers have identified a subset of patients in which the diagnosis of diverticulitis can be made based on a decision rule consisting of a combination of clinical and serological signs without imaging. However, this decision rule first needs to be externally validated.[34,35]

In conclusion, we believe the current evidence supports the notion that antibiotics can be omitted in selected patients with mild colonic diverticulitis. Antibiotic treatment may be beneficial when there is a marked elevation in temperature or infection parameters. Randomized clinical trials are needed to further evaluate the usefulness of antibiotics in mild diverticulitis and incorporate clinical and serological markers. Further research is also needed to unravel the etiology of diverticular disease and diverticulitis and to define the role of mesalazine and probiotics in treatment and prevention.

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CHAPTER 10

A multicenter randomized clinical trial investigating the cost-effectiveness of treatment strategies with or without antibiotics for uncomplicated acute diverticulitis (DIABOLO trial).

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ABSTRACT

Background

Conservative treatment of uncomplicated or mild diverticulitis usually includes antibiotic therapy. It is, however, uncertain whether patients with acute diverticulitis indeed benefit from antibiotics. In most guidelines issued by professional organizations antibiotics are considered mandatory in the treatment of mild diverticulitis. This advice lacks evidence and is merely based on experts' opinion. Adverse effects of the use of antibiotics are well known, including allergic reactions, development of bacterial resistance to antibiotics and other side-effects.

Methods

A randomized multicenter pragmatic clinical trial comparing two treatment strategies for uncomplicated acute diverticulitis. I) A conservative strategy with antibiotics: hospital admission, supportive measures and at least 48 hours of intravenous antibiotics which subsequently are switched to oral, if tolerated (for a total duration of antibiotic treatment of 10 days). II) A liberal strategy without antibiotics: admission only if needed on clinical grounds, supportive measures only. Patients are eligible for inclusion if they have a diagnosis of acute uncomplicated diverticulitis as demonstrated by radiological imaging. Only patients with stages 1a and 1b according to Hinchey's classification or "mild" diverticulitis according to the Ambrosetti criteria are included. The primary endpoint is time-to-full recovery within a 6-month follow-up period. Full recovery is defined as being discharged from the hospital, with a return to pre-illness activities, and VAS score below 4 without the use of daily pain medication. Secondary endpoints are proportion of patients who develop complicated diverticulitis requiring surgery or non-surgical intervention, morbidity, costs, health-related quality of life, readmission rate and acute diverticulitis recurrence rate. In a non-inferiority design 264 patients are needed in each study arm to detect a difference in time-to-full recovery of 5 days or more with a power of 85% and a confidence level of 95%. With an estimated one percent of patients lost to follow up, a total of 533 patients will be included.

Conclusion

A clinically relevant difference of more than 5 days in time-to-full recovery between the two treatment strategies is not expected. The liberal strategy without antibiotics and without the strict requirement for hospital admission is anticipated to be more a more cost-effective approach.

Trial registration

Trial registration number: NCT01111253.

BACKGROUND

Prevalence of diverticular disease increases with age, from less than 10% in people younger than age 40 to 50-66% in octogenarians, with similar frequency in men and women. Approximately three quarters of patients with diverticulosis remain asymptomatic throughout their lifetime. Asymptomatic disease is often an incidental finding during imaging or endoscopy for suspicion of colonic disorders. Of the 25% of patients who develop symptomatic diverticular disease, approximately three quarters develop diverticulitis.[1,2] Of all patients with diverticulitis, 75% have mild acute disease only and 25% develop complicated disease[3] . All and all about 5% of patients with diverticulosis will undergo an episode of complicated diverticulitis.

The cause of colonic diverticular disease has not yet been conclusively established. Epidemiologic studies have demonstrated associations between diverticulosis and diets that are low in dietary fiber and high in refined carbohydrates. Low intake of dietary fiber results in less bulky stools retaining less water and altering gastrointestinal transit time. These factors could increase intracolonic pressure (development of pressure zones that create diverticula alongside the vasa recta), and make evacuation of colonic contents more difficult.[4] Other factors that have been associated with an increased risk of diverticular disease include physical inactivity, constipation, obesity, smoking, and treatment with non-steroidal anti-inflammatory drugs.[5,6]

Although much has been learned about the development of diverticula, less is known about the pathogenesis of diverticular inflammation. As discussed earlier, a minority of patients with diverticulosis will develop symptomatic disease. Initial theories of diverticulitis focused on ideas about the pathogenesis of appendicitis; a diverticulum lumen becomes obstructed by a faecolith leading to increased intradiverticular pressure and eventually causing inflammation. Interest has been generated in the role of altered peridiverticular colonic flora and low-grade chronic inflammation leading to periods of symptomatic disease, similar to periods of exacerbation and remission in inflammatory bowel disease.[7]

The classical clinical presentation of diverticulitis in the western world includes left lower quadrant abdominal pain, tenderness, low-grade fever and leucocytosis. However, clinical features can be quite variable. Leucocytosis may only be present in 45-65% of the patients, and low-grade fever may be present in only 21%.[8]

For a reliable diagnosis additional imaging is usually necessary. Computed tomography (CT) is recommended as initial radiological examination. Positive findings in ultrasound (US) are equally accurate in the diagnosis of diverticulitis. However CT has an advantage in excluding alternative diagnoses and visualising complications of acute diverticulitis needing intervention. For both US and CT, sensitivity is as high as 90%, with a specificity of up to 99% for CT.[9]

The severity of diverticulitis is often graded with the use of modified Hinchey's criteria, based on CT imaging and on preoperative findings.[10,11] The Ambrosetti's criteria is based only on CT imaging, classifying in "mild" and "severe" diverticulitis. This classification system does not take into account the effects of coexisting conditions on disease severity or outcome.[12] (Table 1) Stage II disease is related to a large (> 5 cm) collection of pus, which is at distance (in the pelvis or the abdomen) of the sigmoid colon.[10] Stage II usually requires percutaneous drainage, while stages III and IV diverticulitis usually request surgery.

Conservative treatment of mild diverticulitis usually includes careful observation, restriction of oral intake, administration of intravenous fluids, and most patients receive antibiotic therapy. The majority of patients with mild diverticulitis improve with these conservative measures. Less than 10% need percutaneous or operative treatment for disease progression and/or complications.[13,14]

It is, however, uncertain whether patients with acute diverticulitis benefit from antibiotics, since evidence from prospective studies or randomized trials is lacking. In a recent review antibiotics are considered mandatory in the treatment of mild diverticulitis.[15] This advice lacks evidence and is based on experts' opinion only. Anaerobes are commonly isolated organisms in acute diverticulitis. Gram-negative aerobes, especially Escherichia coli, and facultative gram-positive bacteria, such as streptococci, are often cultured as well[16]. Therefore, broad-spectrum antibiotics are advised. Which antibiotic regimen should be used in diverticulitis is unclear.[17,18] There is scarse evidence that oral antibiotics are as effective as intravenous antibiotics.[19]

Only one study has investigated the use of antibiotics in the treatment of acute uncomplicated diverticulitis. In a retrospective study by Hjern et al[20], there was no significant benefit from antibiotics in the treatment of mild diverticulitis. However, this study was hampered by selection bias due to its retrospective design and small patient groups.

Moreover, there is major discrepancy in the use of antibiotics between countries in Northwest Europe and other countries, including the United States and United Kingdom. In the Netherlands and Scandinavian countries antibiotic use for this disease is less common compared to these other countries, where antibiotics are considered mandatory. A

Table 1 | Hinchey classification and modified Hinchey classification by Sher et al.

Hinchey classification		Modified Hinchey classification by Sher et al.	
I	Pericolic abscess or phlegmon	I	Pericolic abscess
II	Pelvic, intraabdominal or retroperitoneal abscess	IIa	Distant abscess amendable to percutaneous drainage
		IIb	Complex abscess associated with fistula
III	Generalized purulent peritonitis	III	Generalized purulent peritonitis
IV	Generalized fecal peritonitis	IV	Fecal peritonitis

Dutch survey showed that many gastro-enterologists prescribed antibiotics in the treatment of acute diverticulitis, but only a minority of Dutch surgeons did so.[21] In contrast, all UK surgeons responding to a survey prescribed antibiotics in the initial treatment of diverticulitis and 43% of them even for 7 days after hospital discharge.[22]

Six professional organisations have issued formal guidelines concerning the use of antibiotics in uncomplicated diverticulitis. Five of these guidelines advice the use of antibiotics. (Table 2).[23-28] Patients should start with intravenous antibiotics and after improvement within 2-4 days, oral antibiotics are continued to complete a 7-10 days treatment regimen. In the Netherlands, the Dutch Antibiotic Policy Committee considers antibiotics not primarily indicated in the treatment of uncomplicated diverticulitis.[28]

Adverse effects of antibiotics are well known, such as allergic reactions and development of antibiotic resistance of bacterial species. The frequency of toxicodermia is 7-8% with the use amoxicillin, allergy reactions are accounted for in 1% of the patients, and the incidence of anaphylactic shock is 0,01-0,04% with the use of penicillin. Therefore, efforts are made to minimize the use of antibiotics in various fields in clinical medicine.[29]

The lack of evidence for its use necessitates a scientific judgement of the role of antibiotics in the treatment of uncomplicated diverticulitis. Therefore, we initiated a randomized multicenter trial to investigate the effect of antibiotics on disease course in patients with mild acute diverticulitis.

METHODS/DESIGN

Objective

The main goal of the present study is to establish whether antibiotics are necessary in the primary treatment of acute mild diverticulitis, and whether a more liberal strategy without initial antibiotics is more cost-effective with respect to time-to-full recovery.

In daily practice there is an ongoing discussion about the relative benefits and disadvantages of a more conservative treatment strategy embracing the use of intravenous antibiotics. This strategy needs hospital admission and is, at least at the start, an in-hospital treatment regimen. A more liberal strategy, without antibiotics and without the strict requirement of hospital admission, may lead to a shorter hospital stay and reduced costs without compromising outcome.

Our hypothesis is that in uncomplicated (mild) acute diverticulitis, a liberal strategy treatment without antibiotics is a more cost-effective approach than conservative treatment strategy with hospital admission and antibiotics, outcome is measured by time-to-full recovery as primary outcome and diverticulitis-associated complication rates and patient well-being as secondary outcome.

Table 2 | Published guidelines and practise parameters

Organization	Year	Antibiotics Recommended	Original research cited	Which antibiotics	Original research cited	Route of administering	Original research cited
American College of Gastroenterology[23]	1999	Yes	None	Covering both Gram negative and anaerobes	Kellum[15]	Oral or intravenous, depending on clinical status	None
European Association for Endoscopic Surgery[25]	1999	Yes	None	Ciprofloxacin And Metronidazol	None	Oral or intravenous, depending on clinical status	None
American Society of Colon and Rectal Surgeons[24]	2006	Yes	None	Covering both Gram negative and anaerobes	Kellum[15]	Oral or intravenous, depending on clinical status	None
Society of Surgery of the Alimentary Tract[26]	2007	Yes	None	Broad spectrum antibiotics	None	Oral or intravenous, depending on clinical status	None
World Gastroenterology Organization[27]	2007	Yes	None	Covering both Gram negative and anaerobes	None	Oral or intravenous, depending on clinical status	None
SWAB[28]	2009	No, not primarily	None	Broad spectrum antibiotics	None	Oral or intravenous, depending on clinical status	

Study population

Inclusion criteria:

1. Only left-sided and primary (first attack) mild acute diverticulitis.
2. Diagnosis of diverticulitis by US and conditional CT. Diverticulitis-positive US findings are sufficiently accurate compared to CT findings.[9] In diverticulitis-negative US findings in clinically suspected patients, immediate i.v. contrast-enhanced CT is mandatory for confirmation of diverticulitis and exclusion of other pathology.
3. Staging of diverticulitis by CT. CT is needed for all patients for Hinchey/Ambrosetti classification (which is a CT-based classification system). In diverticulitis-positive US findings CT has to be performed within 24 hours. Staging diverticulitis is defined according the modified Hinchey/Ambrosetti staging. Only modified Hinchey stages 1a and 1b (1a Colonic wall thickening/Confined pericolic inflammation, 1b Confined small pericolic abscess) and Ambrosetti's "mild" diverticulitis stage are included. Figure 1 depicts a flow chart, showing the inclusion criteria and the steps after inclusion.[10-11]
4. Informed consent.

Exclusion criteria are summarized in Table 3.

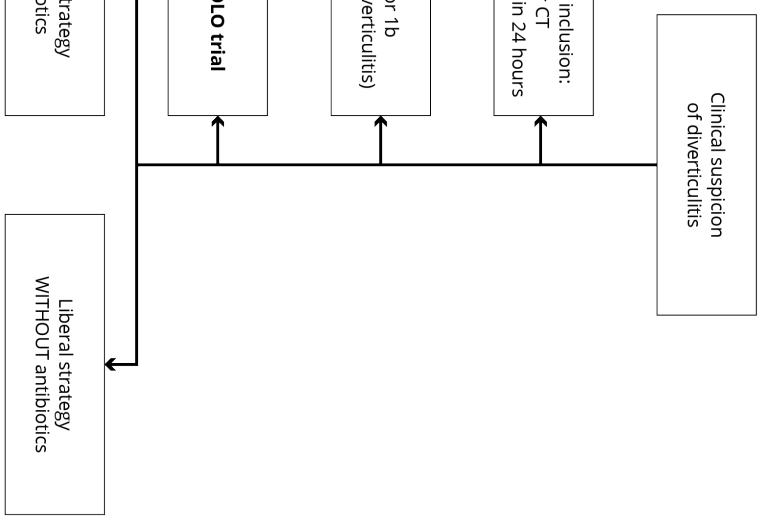

Figure 1 | Study flow chart

Table 3 | Exclsuion criteria

1. Previous radiological (US and/or CT) proven episode of diverticulitis;
2. US and/or CT suspicion of colonic cancer;
3. Inflammatory bowel disease (ulcerative colitis, Crohn's disease);
4. Hinchey stages 2, 3 and 4 or "severe" diverticulitis according to the Ambrosetti criteria, which require surgical or percutaneous treatment;
5. Disease with expected survival of less than 6 months;
6. Contraindication for the use of the study medication (e.g. patients with advanced renal failure or allergy to antibiotics used in this study);
7. Pregnancy;
8. ASA (American Society of Anesthesiologists) classification > III;
9. immunocompromised patient; (Haematological malignancies, AIDS patients with low CD4+ counts, Bone marrow transplantation, Splenectomy , Genetic disorders such as severe combined immunodeficiency.)
10. Clinical suspicion of bacteraemia (i.e. sepsis);
11. The ability of reading/understanding and filling in the questionnaires;
12. Antibiotic use in the 4 weeks prior to inclusion.

Table 4 | Treatment strategies

Conservative strategy with antibiotics	**Liberal strategy without antibiotics**
Hospital admission;	Admission only if discharge criteria are not met;
Intravenous fluids and at least 48 hours of intravenous antibiotics and subsequently switch to oral antibiotics if tolerated (otherwise continuation i.v.) to complete a full 10-day treatment duration;	No initial antibiotics;
Adequate pain relief;	Adequate pain relief;
Oral intake as tolerated;	Oral intake as tolerated;
Daily monitoring.	Daily monitoring when admitted to the hospital;
	Self monitoring at home.

Patients will be randomly allocated to one of the following two treatment strategies: Conservative strategy including immediate antibiotic treatment or liberal strategy without antibiotics (supportive measures only). (Table 4).

In the conservative strategy, the use of antibiotics will be intravenously for at least 48 hours after which route of administration can be switched to orally if tolerated. Hospital admission in the liberal strategy is needed for patients with nausea and vomiting, in need of intravenous fluids or for patients with excessive pain not properly reacting to oral pain medication.

The interval between start of symptoms of the patient and administration of antibiotics will be registered. Also the period after inclusion and the actual first administration of antibiotics will be registered.

In both strategies CT is repeated in case of clinical deterioration. For patients in the liberal strategy treatment arm, clinical deterioration and/or proven subsequent complicated diverticulitis and/or other infectious foci (e.g., pneumonia, infections) may dictate start of antibiotic treatment, instigated by the treating physician. Criteria to start antibiotics in the liberal arm are temperature > 39°C, positive blood cultures and clinical suspicion of bacteraemia (i.e. sepsis). Criteria for sepsis are set by the American College of Chest Physicians and the Society of Critical Care Medicine. Two or more symptoms are required: Body temperature < 36°C or > 38°C, heart rate higher than 100 beats a minute, respiratory rate higher than 20 breaths a minute and white blood cell count < 4×10^9 or > 12×10^9 cells/L [31] . Also another infectious focus (e.g., pneumonia, urinary tract infections) may dictate start of antibiotic treatment, instigated by the treating physician.

The following discharge criteria are applied in both strategies: normal diet (defined by tolerating solid food and more than 1L of fluid orally), temperature < 38.0°C, VAS (Visual Analoge Score) pain score < 4 (with paracetamol only), self support as compared to the pre-illness level, and acceptance by the patient.

All outpatients will daily monitor and register their body temperature. Written and oral instructions at discharge are given, and relevant telephone numbers and contact information will be provided. In case of fever above 38˚C, progression of pain above a VAS of 4 or other clinical signs of deterioration, patients can contact the hospital or emergency department immediately.

Antibiotics

For the choice and duration of antibiotics the practice guidelines of the Dutch Antibiotic Policy Committee[28] and the American Society of Colon and Rectal Surgeons [30] are followed. In both guidelines, a minimum of 7-14 days of broad-spectrum antibiotics is advised. In the present study amoxicillin-clavulanic acid is chosen as broad-spectrum antibiotic; duration of antibiotic treatment is 10 days. The dosage scheme for the study drug is 1200 mg i.v. 4

times daily with subsequent oral administration of 625 mg 3 times daily. In case of allergy (known or newly diagnosed), a switch will be made to the combination of ciprofloxacine and metronidazole; ciprofloxacine 2 times a day 400 mg i.v. and metronidazol 3 times daily 500 mg, with oral doses of ciprofloxacine being 500 mg 2 times a day and of metronidazol 3 times a day 500 mg.

Endpoints

The primary endpoint is time-to-full recovery within a follow-up period of 6 months. Full recovery is defined by the following criteria: discharged from the hospital (out-patient), normal diet (defined by tolerating solid food and more than 1L of fluid orally), temperature < 38.0°C, and VAS pain score < 4, no use of daily pain medication or back to pre-illness pain medication use, and resuming to pre-illness working activities; as assessed by questionnaires and out-patient clinic visits.

The secondary endpoints are: proportion of patients who develop complicated diverticulitis require surgery or non-surgical intervention; number of days outside the hospital in a 6 months period; direct and indirect medical costs at 6 months follow-up; occurrence of complicated diverticulitis defined as abscess, perforation, stricture and/or fistula; predefined side-effects of initial antibiotic treatment (e.g. antibiotic resistance/sensitivity pattern, allergy); morbidity (e.g. pneumonia, myocardial infarction, urinary tract infection); mortality; readmission rate within 6 months and acute diverticulitis recurrence rates at 12 and 24 months follow-up. Changes in health status and valuation over time will be measured using generic and disease specific quality of life questionnaires (Euro-Qol 5D, Short Form 36 (SF-36) and the Gastro-Intestinal Quality of Life Index (Giqli)) on admission and after 3, 6, 12 and 24 months.

A recurrence is defined as ultrasound- or CT-proven acute diverticulitis after complete resolution of symptoms more than 1 month after initial discharge from hospital. If a patient dies during follow-up, the reason for death will be recorded as related or unrelated to diverticular disease.

Randomization

Computerized block randomization for allocation of treatment group, stratified for center and for Hinchey 1a and 1b, will take place after all inclusion and exclusion criteria have been verified and informed consent has been obtained. A standardized case record from (CRF) will be used. This CRF is partially web-based via a secured internet module. A minimum of 10% of the CRF data will be verified with source data by an independent audit.

Sample size calculation and date analysis

A non-inferiority design was chosen. Time-to-full recovery in the liberal strategy arm must not exceed a clinically relevant difference of more than 5 days compared with the conservative strategy. When this condition is fulfilled, the potential advantages of the liberal

(non-antibiotic) strategy become dominant: patient well being when the need of hospital admission can be avoided, less costs, less antibiotic resistance and less other side effects. The study must have the power (superiority) to detect a difference in time-to-full recovery of 5 days.

The median time-to-full recovery is 21 days based on the National Dutch Hospital Registry data with an average of 7 days admission and an assumed additional median 14-day outpatient period to full recovery. To reject the null-hypothesis of a difference in time-to-full recovery of 5 days or less, using a time-to-event analysis with a power of 85% at a confidence level of 95%, an accrual period of 730 days and a follow-up period of 180 days, at least 264 patients need to be included in each treatment arm. With an estimated one percent of the trial patients lost to follow-up, a total 533 patients is needed.

The primary endpoint is time-to-full recovery. Kaplan-Meier curves depicting the proportion of patients with full recovery since randomization will be constructed for both strategies. The log rank test will be used to test for superiority of one strategy compared with the other. Testing for non-inferiority will be done by calculating the hazard ratio for the liberal strategy compared with the conservative strategy using Cox regression. We will calculate a one-sided 95% confidence interval for this ratio to determine whether it reaches outside the hazard ratio belonging to an equivalence limit of a difference of 5 days in median survival time.

For other endpoints data will be compared by the Student's t test, Wilcoxon rank sum test, Chi square test or Fischer exact test as appropriate. In superiority tests a two-tailed P value ≤ 0.05 will be considered statistically significant, whereas one-sided tests will be performed in non-inferiority testing. The main analyses will be based on the intention to treat principle. Predefined subgroup analyses to investigate whether treatment effects are different in subgroups will be performed for Hinchey classification 1a versus 1b and for participating center.

Cost analysis

All related costs will be estimated based on the actual input terms of resource use and personnel in the 6-month follow-up period after randomization. For all cost-items such as hospital admission, medication used, diagnostic tests, unit costs will be derived from the Dutch costing manual or determined in cooperation with the hospital administration. Direct medical costs will be recorded in the case record forms. Indirect costs arising from losses in productivity will be assessed by means of the Health and Labor questionnaire and will be calculated by means of the friction cost method.

Economic evaluation

The economic evaluation will be performed from a societal perspective as a cost-effectiveness and cost-utility analysis. The main analyses include costs per day reduction to

achieve full recovery and costs per QALY gained. Additional sensitivity analyses, regarding differences in possible subgroups, will be performed.

Safety monitoring

Adverse events are defined as any undesirable experience occurring to a subject during a clinical trial, whether or not considered related to the investigational drug. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded. A serious adverse event (SAE) is any untoward medical occurrence or effect that at any dose results in death; is life threatening (at the time of the event); requires hospitalization or prolongation of existing inpatients' hospitalization; results in persistent or significant disability or incapacity; is a congenital anomaly or birth defect; is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction, major safety finding from a newly completed animal study, etc. All SAEs will be reported to the accredited Medical Ethical Committee (MEC) that approved the protocol, according to the requirements of that MEC.

Suspected unexpected serious adverse reactions (SUSAR) are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are adverse reactions, of which the nature, or severity, is not consistent with the applicable product information.

The sponsor will report expedited the following SUSARs to the MEC; SUSARs that have arisen in the clinical trial that was assessed by the MEC; SUSARs that have arisen in other clinical trial of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the MEC. The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the MEC. This line listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.

The sponsor will report expedited all SUSARs to the competent authority, the Medicine Evaluation Board and the competent authorities in other Member States. The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report. There is no need to break any code in case of a SUSAR because due to the nature of the study in which neither participant nor treating physician are blinded.

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited MEC, competent authority, Medicine Evaluation Board and competent authorities of the concerned Member States. This safety report consists of: a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study; a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

An independent data and safety monitoring committee will evaluate the progress of the trial and will examine safety parameters at regular intervals (every 25 patients). The committee can unblind the data whenever deemed necessary based on reported adverse events. All involved physicians will repetitively be asked to report any potential adverse events caused by the study protocol. These adverse events will be listed and discussed with the monitoring committee. The monitoring committee can ask for a full report in order to discuss a specific adverse event. A copy of this report will be send to the central ethics board and to the involved physicians. All deceased patients will be evaluated by the safety committee for cause of death and possible trial related serious adverse effects. Every death will be reported to the central ethics board and the local ethics board. The Data Safety Monitoring Board will consist of an epidemiologist/statistician who is the chairman, an independent surgeon and an independent radiologist.

Ethics

This study is conducted in accordance with the principles of the Declaration of Helsinki and 'good clinical practice' guidelines. The Medical Ethical Committee of the Academic Medical Center in Amsterdam has approved the protocol. The Ethical Committees of the participating centers is applied for local feasibility. Prior to randomization, written informed consent will be obtained from all patients.

DISCUSSION

Diverticular disease is the most common disease of the colon being found in every 1 of 3 people over the age of 60 years. The overall prevalence of diverticular disease during endoscopy is 27%.[32] A recent task force convened by the American Gastroenterological Association confirmed that diverticular disease is a major clinical problem. Diverticular disease is fifth in the list of digestive diseases in terms of total costs.[33] Hospital admission rates for colonic diverticulitis have increased in the last decades. In the United States the population-adjusted numbers of domestic admissions for acute diverticulitis increased by 26%.[34]

Over the last decade there have been efforts made to minimize the prescription of antibiotics in various fields in clinical medicine. Patients with appendiceal inflammatory masses or acute cholecystitis are not treated primarily by antibiotics. This is also true for community-acquired infections, such as acute otitis media, upper respiratory tract infections and in paediatric medicine.[35] Bacterial resistance to antibiotics is a major public-

health problem and antibiotic use is being increasingly recognized as the main selective pressure driving this resistance.[36,37] Development of Clostridium-associated diarrhea is however one of the downsides of antibiotic use, and subject of this study. With the use of beta-lactam antibiotics, infection with Clostridium difficile is a potential problem for all hospitalized patients. Clostridium difficile is implicated in 20-30% of patients with antibiotic-associated diarrhea, in 50-70% of those with antibiotic-associated colitis and in more than 90% of those with antibiotic-associated pseudomembranous colitis.[38] Alternatively, there is no evidence or guideline dictating that support anti-anaerobic prophylaxis for hospitalized patients in general. Prophylactic metronidazol to prevent Clostridium-associated diarrhea is not standard practice and is therefore not considered for this trial.

There are some new treatment options for symptomatic diverticular disease under investigation, such as mesalazin and probiotics. For the present randomized trial these treatments were not considered a reasonable alternative. First, these treatment options are not yet widely used and are only applied in the context of clinical trials. These studies have dealt with the treatment of uncomplicated symptomatic diverticular disease, and not with acute diverticulitis. Patients with proven diverticulosis and at least one months of symptoms had been included. These trials have excluded diverticulitis patients.[39,40] Some studies have assessed meselazin in the prevention of recurrent diverticulitis but never as the actual treatment of acute diverticulitis itself.[41,42] Third and foremost, the main topic in daily practice is whether antibiotics are mandatory in the treatment of acute diverticulitis. Until now, no randomized controlled trial has investigated this matter. Before other treatment options become an issue, first the efficacy of antibiotics in diverticulitis needs to be investigated, as this is currently standard practice in many countries.

In the present study we chose for a more pragmatic approach to investigate the effect of antibiotics in the treatment of acute uncomplicated diverticulitis. A clinical randomized trial setting was chosen over a double-blind placebo controlled randomized trial. Our intention is to compare the contemporary treatment strategies in uncomplicated acute diverticulitis. In a pragmatic trial set-up the two possible treatment strategies can be investigated and the outcome will be more applicable in daily practice. In a double-blind placebo controlled trial the effect of antibiotics will be investigated in a more experimental setting were all patients will be admitted and the result will not be applicable to daily practice.

Not all patients with acute diverticulitis have to be admitted to the hospital. In 2005, Mizuki et al showed that outpatient treatment of patients with mild or uncomplicated diverticulitis is safe.[43] For this reason, in the present trial hospital admission is not mandatory in the liberal strategy arm when patients fulfill the 'discharge' criteria at time of study entry. Part of the conservative treatment is hospital admission and intravenous antibiotics as this is common practice. In both arms the same strict criteria for discharge apply.

We decided not to stratify for age, based on the prevalence of diverticulitis in the different age groups and on the latest literature on the outcome of diverticulitis. Diverticulitis occurs in 5-10% by the age of 40 years, in 10-30% by 50 years and in more than 60% by age 80. Recently, Hjern et al reviewed 234 patients with CT-confirmed diverticulitis. The rate of severe diverticulitis observed with CT was lower in the younger patients (2% versus 11.9%; P = 0.025). Surgical management during the first admission was similar in younger patients (2% versus 6.8%; P = 0.271); first episodes of acute diverticulitis being not more aggressive in younger patients.[13] Variables 'severity of disease' (Hinchey 1a (inflammation) versus 1b (plus micro abscesses)) and 'participating and including hospital' were deemed most important with respect to outcome and therefore in need of stratification. Stratification for more than two variables is highly uncommon in randomized control trials.

Right-sided diverticulitis is excluded because of uncertainty about the underlying factors that contribute to right-sided diverticulitis. In literature, a clear distinction is made between left and right-sided diverticulitis. In Western countries, diverticulitis mostly affects the left colon and the incidence of right-sided diverticulitis is estimated to be below 4%. However, in Asia and countries with a high Asian population, diverticular disease of the cecum and the ascending colon is a more widespread disease than the left-sided form of this disease. Sugihara et al reported on 615 Japanese patients with diverticular disease of the colon: 69.8% with right-sided and 15.9% with left-sided and 14.3% both-sided diverticular disease.[44] Left-sided diverticular disease is mainly based on pseudodiverticulae. The pathogenesis is based on a higher intraluminal pressure with consecutive hypertrophy of the colonic wall. In contrast, right-sided diverticulosis, typically is associated with normal intraluminal pressures and a tendency for bleeding rather than perforation, presumably owing to underlying connective tissue abnormality.[45] For the reason of uniformity of study population only left-sided diverticulitis will be included.

CONCLUSION

The DIABOLO trial is a multicenter randomized pragmatic trial (trialregister: NL29615.018.09, Clinicaltrial.gov: NCT01111253) comparing the cost-effectiveness of a conservative strategy (with admission and antibiotics) with a liberal treatment strategy (without antibiotics and no strict need for hospital admission) with respect to the primary endpoint time-to-full recovery.

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CHAPTER 11

A randomized clinical trial of observational versus antibiotic treatment for a first episode of uncomplicated acute diverticulitis.

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ABSTRACT

Background

It is uncertain whether antibiotics are necessary in the treatment of uncomplicated acute diverticulitis. To date, most guidelines advise the use of antibiotics. One randomized trial has been performed but included about 40% recurrent diverticulitis, and did not change clinical practice and guidelines. Importantly, use of antibiotics can lead to adverse effects and overuse results in escalating antimicrobial resistance.

Methods

In a multicenter, pragmatic, non-inferiority trial we randomly assigned 570 patients with CT-proven primary, left-sided, uncomplicated, acute diverticulitis to an observational or antibiotic treatment strategy. The primary endpoint was time-to-recovery at 6 months. An intention-to-treat analysis was done.

Results

At 6 months, median time-to-recovery of 528 analyzed diverticulitis patients was comparable among observational and antibiotic treatment strategies (14 days [interquartile range, 6 to 35] vs. 12 days [interquartile range, 7 to 30]; P=0.291 by the Log-Rank test), with a hazard ratio for recovery of 0.910 (upper limit one-sided 95% confidence interval, 1.059; P=0.151). Recovery occurred in 89.3% versus 93.2% of patients assigned to observation and antibiotics respectively (P=0.183). We found no significant between-group differences for main secondary endpoints readmission rate, complicated, ongoing and recurrent diverticulitis, need for sigmoid resection or for mortality and adverse event (AE) rates, except for antibiotics related AE.

Conclusions

Observational treatment for uncomplicated acute diverticulitis did not result in an increase in time-to-recovery, nor in higher rates of readmission, complicated, ongoing and recurrent diverticulitis and sigmoid resection. Observational treatment is without significant repercussions, which indicates that antibiotics can safely be omitted.

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BACKGROUND

Acute diverticulitis is an inflammatory complication that occurs in 10-25% of patients with colonic diverticular disease.[1,2] Diverticular disease is one of five most costly gastrointestinal diseases in the United States costing 2.5 billion dollars annually.[3] The increasing incidence of acute diverticulitis and dramatic rise in hospitalization rates impose a significant burden on Western health care resources.[3-5]

The natural history of acute diverticulitis is mild in 75% of patients [6] and most patients are treated successfully by conservative measures.[7-9] It is uncertain however, whether antibiotics are necessary in the treatment of a first episode of uncomplicated acute diverticulitis. Two comparative studies and one randomized trial have compared observational and antibiotic treatment in patients with uncomplicated acute diverticulitis.[10-12] These studies were either retrospective or included about 40% recurrent diverticulitis.[10-12] All three studies suggest that antibiotic treatment is not more successful than observational treatment in uncomplicated diverticulitis. International guidelines remained unchanged and still recommend antibiotics for uncomplicated diverticulitis.[13-15] Whether or not antibiotics are used varies between countries and disciplines.[16-18] In a recent review article on the management of acute diverticulitis it is stressed that further high-quality randomized controlled trials in this area are required for the decision on antibiotics.[19]

Importantly, antibiotic treatment is accompanied with several drawbacks. Besides costs there are the risks of adverse effects and allergic reactions. Escalating antimicrobial resistance due to antibiotic overuse is a global threat that already is addressed in several fields in clinical medicine.[20] In this pragmatic randomized trial, we compared the effectiveness of two strategies for the management of a first episode uncomplicated acute diverticulitis: with or without antibiotics.

METHODS

Trial design

The 'DIverticulitis: AntiBiotics Or cLose Observation?' (DIABOLO) trial was a multicenter (22 centers), open label, pragmatic, randomized, controlled trial of two strategies in patients with uncomplicated acute diverticulitis.[21] The study design reflects current clinical practice in which the two studied approaches co-exist as standards of care.

Study oversight

This trial was conducted in accordance with the principles of the Declaration of Helsinki and "Good Clinical Practice" guidelines and has been registered in the European Union Drug Regulating Authorities Clinical Trials database (EudraCT number, 2009-015004-26). The institutional review board (IRB) and Dutch Central Committee on Research

Involving Human Subjects (CCMO) approved the study protocol[21] . An independent Data and Safety Monitoring Board (DSMB) evaluated the progress of the trial and examined safety parameters at regular intervals. All serious adverse events (SAEs) were reported to the DSMB and the accredited IRB. An end-point assessment committee adjudicated all primary and main secondary endpoints. All authors take responsibility for the accuracy and completeness of the reported data and for the fidelity of the report to the study protocol.

Study population

Patients were eligible for the study if they had a first episode of left-sided, uncomplicated, acute diverticulitis, to be confirmed within 24 hours by Computed tomography (CT). Only modified Hinchey stages 1a-b and Ambrosetti's "mild" diverticulitis stage were included.[22,23] Main exclusion criteria were previous US and/or CT proven episode of diverticulitis, modified Hinchey stages 2, 3 and 4 or Ambrosetti's "severe" diverticulitis stage plus clinical suspicion of bacteremia (i.e. sepsis[24]), and antibiotic use in the four weeks prior to inclusion. A complete overview is provided in Table S1. All participants provided written informed consent before enrollment.

Randomization and Study Treatments

We assigned participants, in a 1:1 ratio, to either an observational or an antibiotic treatment strategy. Randomization was centrally controlled at the trial-coordinating center using a computerized system with a block design, with a random block size of 2 to 4 patients, stratified by Hinchey classification and center.

In the antibiotic treatment strategy, the use of antibiotics led to admittance of all patients due to the premise that antibiotics were given at least the first 48 hours intravenously (i.v.) after which the route of administration could be switched to orally if tolerated. Based on the practice guidelines of the Dutch Antibiotic Policy Committee[25] and the American Society of Colon and Rectal Surgeons [26], amoxicillin-clavulanic acid, with treatment duration of 10 days, was chosen as broad-spectrum antibiotic. In case of allergy, a switch was made to the combination of ciprofloxacin and metronidazole.

In both strategies CT was repeated in case of clinical deterioration. For patients in the observational treatment group, clinical deterioration, proven subsequent complicated diverticulitis or another infectious focus (e.g., pneumonia, urinary tract infection) dictated start of antibiotic treatment. Criteria to start antibiotics were: temperature > 39°C, positive blood cultures and clinical suspicion of bacteremia (i.e., sepsis [24]). Patients were discharged if they fulfilled discharge criteria.

Follow-up and Study Outcomes

The primary outcome was time-to-recovery during 6 months of follow-up. 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 < 38.0 °C, and 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.

Secondary outcomes were: days spent outside the 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 rate, need for sigmoid resection or other (non-)surgical intervention within 6 and 12 months follow-up, (serious) adverse events (e.g., urinary tract infection, pneumonia), predefined side-effects of initial antibiotic treatment (e.g., antibiotic resistance/sensitivity pattern, allergy) and all-cause mortality.

Details on the patients' adherence to the antibiotic regimen were obtained by telephone. At 2 and 6 months the patient visited the outpatient clinic and follow-up at 12 and 24 months was performed by telephone. A standardized case record form was used for collection of study variables. Oracle Clinical, with internet-based remote data capture version 4.5.3 (Oracle Corporation, Redwood Shores, CA 94065, U.S.A), was used for entering, managing and validating data from the investigative sites.

Statistical Analyses

A sample of 528 participants was enrolled to have 85% power at a confidence level of 95% to test the hypothesis that time-to-recovery would not be clinically relevant longer under the observational treatment strategy than under the antibiotic treatment strategy. A difference in time-to-recovery of less than 5 days was considered non-inferior, assuming a median time-to-recovery of 21 days based on 7-day admission duration and an additional 14-day outpatient period to full recovery. Because the drop-out rate was higher than the initially anticipated 1%, due to 39 wrongful inclusions (Table S2), the DSMB recommended extending the accrual period through October 2012 when 570 participants, of which 528 patients were evaluable for the primary endpoint, were enrolled to preserve statistical power (Table S3).

We performed all analyses following the intention-to-treat principle. Continuous variables are expressed as medians and presented with interquartile ranges since these data were not normally distributed; and Mann-Whitney-U test was used for comparison. For categorical variables numbers and percentages were calculated and compared by using the Chi-square test, Fisher's exact test or Linear-by-Linear Association, as appropriate.

For the primary outcome, time-to-recovery, time-to-event analyses were performed. We plotted Kaplan–Meier curves to determine the time-to-recovery in the two groups, and we used Log-Rank tests to test for differences between the observational and antibiotic treatment groups. Furthermore, a Cox proportional hazard regression was performed to obtain hazard ratios for the observational treatment strategy compared with the antibiotic treatment strategy[27], while adjusting for Hinchey classification and center. To assess differences within Hinchey classes and centers subgroup analyses were performed. For

each model, the Cox proportional-hazard assumption was tested by visually inspecting the log–log plots with no deviations detected. We calculated the upper limit of the one-sided 95% confidence interval for the hazard ratio using the upper limit of the two-sided 90% confidence interval[28]. Additionally, pre-specified subgroup analyses for the main secondary endpoints were performed. Multiple testing adjustment was done by using the Benjamini-Hochberg method to control the false discovery rate. P-values <0.05 were considered statistically significant. Statistical analyses were performed using SPSS, version 21.0 (SPSS Inc., Chicago, IL, USA) and adjustment for multiple testing was done in R (version 2.13.1).

RESULTS

Study Population

From June 1, 2010 through October 14, 2012, we screened 893 consecutive diverticulitis patients at surgical and gastroenterological departments of 22 Dutch centers. 570 patients were randomly assigned to observational treatment (283 patients) or antibiotic treatment (287 patients). Of these, 39 patients were wrongful inclusions and not eligible to participate in the study. A total of 528 patients were included in primary analyses, as is shown in the CONSORT flow diagram (Figure 1)[29]. Patients who underwent randomization had clinical characteristics mostly similar to those who were eligible but not randomized because they declined participation (Table S4). The reasons for non-enrollment, wrongful inclusion and the number of included patients per hospital are provided in Tables S5, S2 and S6, respectively.

Baseline characteristics were evenly distributed between the treatment groups, though ASA score was somewhat higher in the antibiotics group (P=0.036) (Table 1). The rate of positive blood cultures did not differ significantly between groups (5.9% vs. 2.8%; P=0.285). Bacterial resistance was noted twice; in one culture resistance to penicillin and clindamycin was found and in the other to metronidazole. For 22 patients 23 Clostridium toxin tests were performed on clinical indication, all of which were negative.

Study Treatment

All patients allocated to antibiotic treatment except for one (99.6% [265/266]) started antibiotics, with a median interval of 0 days from randomization to start of antibiotics. Amoxicillin/clavulanic acid was the most prescribed type of antibiotic (94.3% [250 of 265]) (Table S7). The median duration was 10.0 days (interquartile range, 10.0 to 10.0) and 94.7% (252 of 266) of patients from the antibiotic group completed the 10-day treatment course. In three patients (1.1%) antibiotic treatment was discontinued because of side effects or allergic reactions, of which one was an anaphylactic shock. In 5.0% (13 of 262) of patients in the observation group antibiotics were started on clinical grounds (Table S8), of which another focus of infection was the most common reason (N=4).

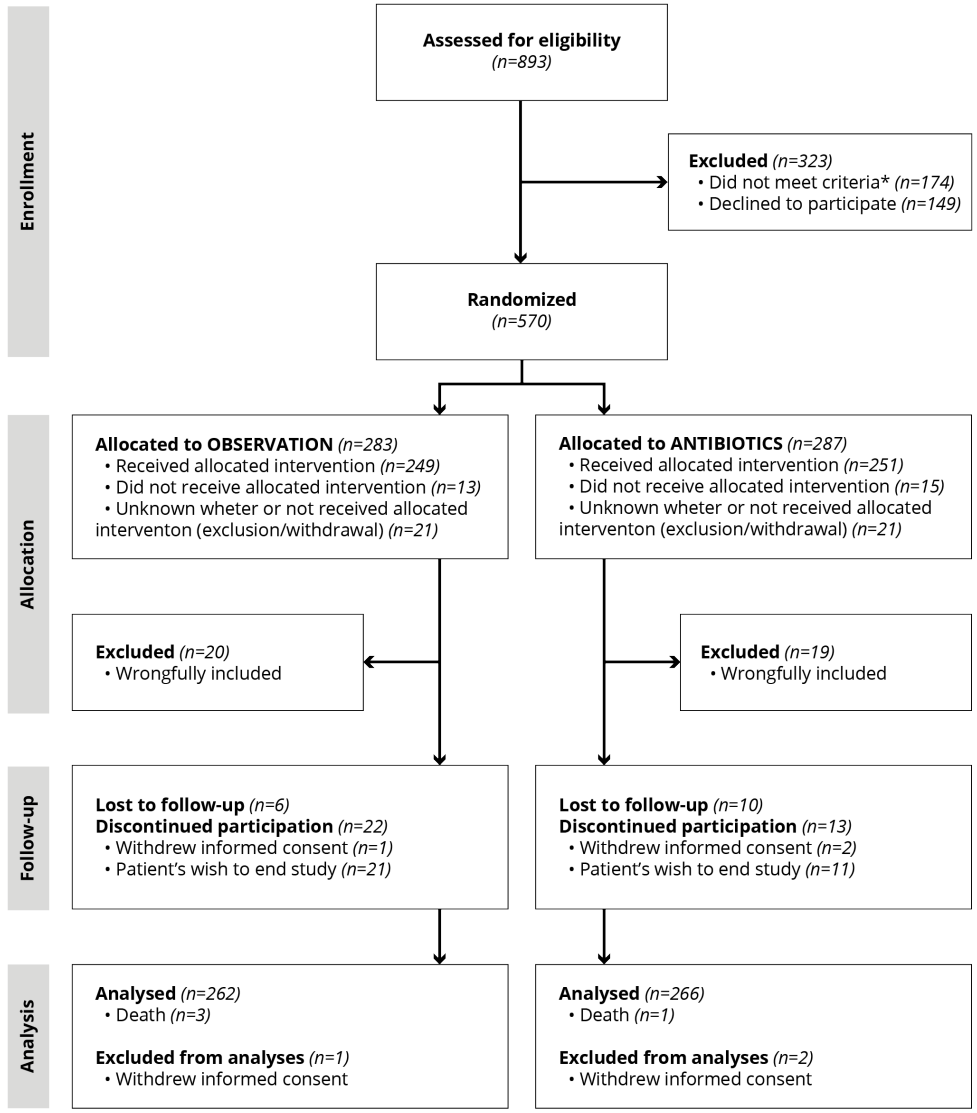

Figure 1 | CONSORT Flow Diagram for Trial Patient Progress

Table 1 | Baseline Characteristics of the Patients According to Study Group *

	Observation (N=262)		Antibiotics (N=266)	
Age – yr	57.4	(48.5-64.6)	56.3	(48.5-63.8)
Male sex – no (%)	135	(51.5%)	132	(49.6%)
Known antibiotic allergy – no (%)	36	(13.7%)	52	(19.5%)
Penicillin allergy – no (%)	5	(1.9%)	14	(5.3%)
Co-morbidity† – no (%)	113	(43.1%)	121	(45.5%)
ASA score ‡ – no (%)				
ASA 1	174	(66.4%)	156	(58.6%)
ASA 2	81	(30.9%)	96	(36.1%)
ASA 3	7	(2.7%)	14	(5.3%)
Body mass index – kg/m^2	26.4	(24.3-29.0)	27.2	(24.5-30.1)
(20 vs 16 missings)				
Duration of GI 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 §	6	(4-8)	6	(5-8)
(39 vs 47 missings)				
Localization abdominal pain – no (%)				
Left lower quadrant isolated	119	(45.4%)	125	(47.0%)
Vomiting – no (%)	20	(7.6%)	27	(10.2%)
White blood cell count – ×10^9 cells/L	12.5	(10.2-14.8)	12.0	(10.0-14.2)
C-reactive protein (CRP) – mg/L	73.0	(44.5-125.5)	82.7	(42.0-128.3)
CRP > 50 mg/L – no (%)	188	(72.0%)	191	(71.8%)
(1 missing in observation group)				
Imaging diagnosis – no (%)				
Ultrasonography (US)	171	(65.3%)	176	(66.2%)
Computed Tomography (CT)	258	(98.5%)	259	(97.4%)
Hinchey category 1a ¶ – no (%)	236	(90.1%)	250	(94.0%)

Abbreviations: ASA, American Society of Anesthesiologists (Physical Status Classification System); GI, gastrointestinal; VAS, Visual Analogue Scale;

* Data are medians with interquartile range since they were not normally distributed, or numbers with percentages in parentheses. P>0.05 for all comparisons, except for ASA score (P=0.036);

† Includes cardiovascular disease and/or pulmonary disease and/or renal failure and/or diabetes mellitus;

‡ ASA 1=Normal, healthy patient, ASA 2=Patient with a mild systemic disease, ASA 3=Patient with severe systemic disease;

§ Visual Analogue Scale score ranged 0 to 10;

¶ (Modified) Hinchey classification category 1a= Colonic wall thickening and/or confined pericolic inflammation, category 1b=Confined small pericolic abscess (≤ 5cm).

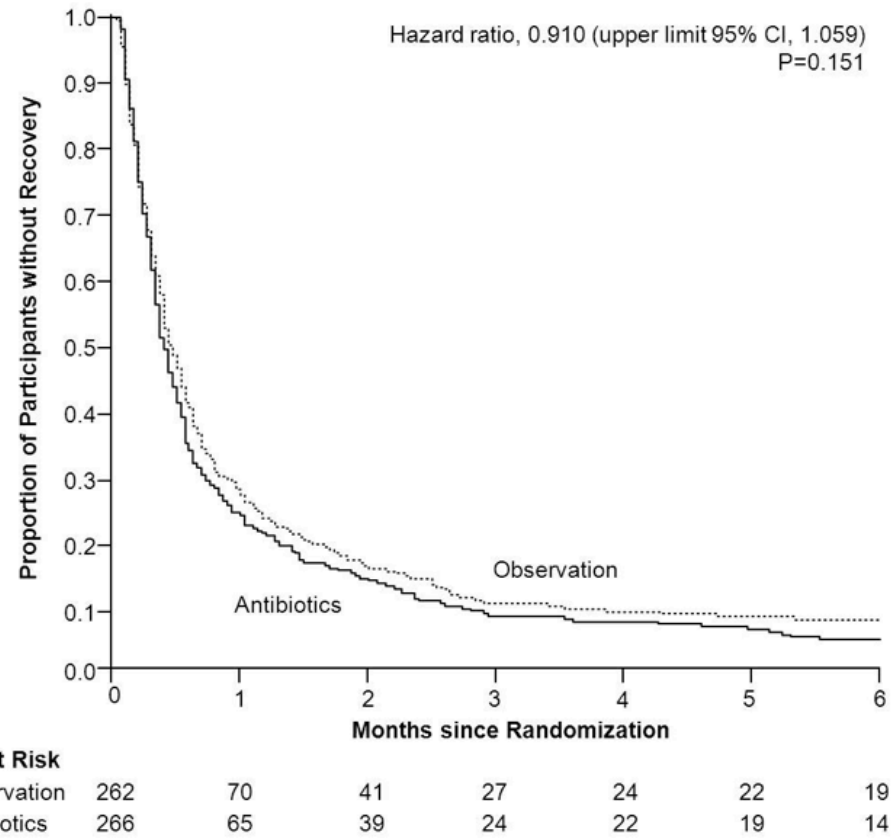

Figure 2 | Time-to-Recovery in Patients with Uncomplicated Acute Diverticulitis

Kaplan-Meier survival curves for time-to-recovery of patients with uncomplicated acute diverticulitis assigned to observational or antibiotic treatment strategy over 6 months of follow-up.

Primary Outcome

The median time-to-recovery during 6 months follow-up was not significantly different between the two treatment groups; 14.0 days (interquartile range, 6.0 to 35.0) for patients with observational treatment versus 12.0 days (interquartile range, 7.0 to 30.0) for patients with antibiotic treatment (P=0.291 by the Log-Rank test) (Figure 2). An observational treatment strategy, as compared with an antibiotic treatment strategy, was associated with a hazard ratio for recovery of 0.910 (upper limit one-sided 95% confidence interval [CI], 1.059; P=0.151). The hazard ratio was not affected by adjustment for Hinchey classification and center (hazard ratio, 0.895 [upper limit one-sided 95% CI, 1.044]).

Secondary Outcomes

Within 6 months 234 patients (89.3%) in the observational group versus 248 patients (93.2%) in the antibiotic group fulfilled the recovery criteria (P=0.183). In the observational

Table 2 | Secondary Outcomes among Patients with Uncomplicated Acute Diverticulitis assigned to an Observational or Antibiotic Treatment Strategy *

	Observation (N=262)	Antibiotics (N=266)	Unadjusted P-value	Adjusted P-value†
Outpatient treatment – no (%)	34 (13.0%)	1 (0.4%)	<0.001	**0.006**
Duration initial admission – days	2 (1-3)	3 (2-3)	<0.001	**0.006**
Recovery ≤ 6 months FU – no (%)	234 (89.3%)	248 (93.2%)	0.055	0.183
Readmission (≥1) ≤ 6 months FU – no (%)	46 (17.6%)	32 (12.0%)	0.037	0.148
Total number	66	35		
Days outside hospital ≤ 6 months FU – proportion of FU duration ‡	0.989 (0.978-0.994)	0.983 (0.978-0.989)	<0.001	**0.006**
Complicated diverticulitis (≥1) ≤ 6 months FU – no (%)	10 (3.8%)	7 (2.6%)	0.220	0.377
Type § – no (%)				
Abscess (> 5cm)	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%)	0.496	0.553
Bleeding	2 (0.8%)	0 (0.0%)	0.246	0.390
At index admission – no (%)	3 (1.1%)	6 (2.3%)	0.260	0.390
Intervention § – no (%)				
Percutaneous	2 (0.8%)	1 (0.4%)	0.494	0.553
Surgery	8 (3.1%)	5 (1.9%)	0.192	0.354
Ongoing diverticulitis (≥1) ≤ 6 months FU – no (%)	19 (7.3%)	11 (4.1%)	0.061	0.183
Imaging proven	10	5		
Needing admission	15	4		
Recurrent diverticulitis (≥1) ≤ 6 months FU – no (%)	9 (3.4%)	8 (3.0%)	0.391	0.494
Imaging proven	7	4		
Needing admission	4	5		
Sigmoid resection ≤ 6 months FU – no (%)	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

Table 2 | Continued

	Observation (N=262)	Antibiotics (N=266)	Unadjusted P-value	Adjusted P-value†
Morbidity § ¶ – no (%)	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
AB related morbidity	1 (0.4%)	22 (8.3%)	**<0.001**	**0.006**
Mortality ¶ – no (%)	3 (1.1%)	1 (0.4%)	0.306	0.432

* Data are numbers with or without percentages in parentheses or data are medians with interquartile range since these continuous variables had non-gaussian distributions;

† P-values after multiple testing adjustment by using Benjamini-Hochberg correction;

‡ 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 can have more than 1 type of complicated diverticulitis, intervention and morbidity;

¶ With a median duration of follow-up of 711 days (IQR, 366 to 732) in the observation group and 732 days (IQR, 366 to 732) in the antibiotic group (P=0.204).

group more patients were treated as outpatients after their evaluation at the emergency department (13% vs. 0.4%; P=0.006) and a shorter median duration of initial hospital stay was observed (2 vs. 3 days; P=0.006) due to the intravenous administration of antibiotics in the antibiotic group (Table 2). Readmission rates were comparable among treatment groups (17.6% vs. 12.0%; P=0.148). Almost all patients initially treated as outpatients 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 observational treatment group than in the antibiotic treatment group (0.989 vs. 0.983; P=0.006).

The proportion of patients developing complicated diverticulitis during 6 months follow-up was comparable among treatment groups (3.8% vs. 2,6%; P=0.377). The proportion of patients that progressed to complicated diverticulitis during initial admission was small (1.1% for observational vs. 2.3% for antibiotic treatment; P=0.390).

Ongoing diverticulitis was reported in 19 patients (7.3%) in the observation group and in 11 patients (4.1%) in the antibiotic group (P=0.183). Also the proportion of patients with recurrent diverticulitis (3.4% vs. 3.0%; P=0.494) and sigmoid resection (3.8% vs. 2.3%; P=0.323) were comparable among groups; both for emergency resection (0.8% vs. 1.1%; P=0.553) and elective resection (3.1% vs. 1.1%; P=0.254). In both groups the most frequent reason for performing sigmoid resection was colonic obstruction (30% vs. 33% of resections). Perforation was the other main reason (20% vs 33%) for resection (Table S9).

In the observational and antibiotic group 86.6% and 90.2% of patients, respectively, had a follow-up duration of 12 months or more. At 12 months follow-up the treatment groups were comparable for main secondary outcomes readmission rate, complicated diverticulitis, ongoing diverticulitis and acute diverticulitis recurrence rate and overall need for sigmoid resection (7.0% vs. 3.8%; P=0.057; Table S10). Elective resection, however, was performed significantly more often in the observation group at 12 months follow-up (6.6% vs. 2.9%; P=0.030; Table S11).

Adverse Events

No significant between-group differences in the occurrence of mild (P=0.086) and serious (P=0.354) adverse events were observed (Table 2). As expected, antibiotics related adverse events, of which all but one were graded as mild, were more frequent in the antibiotic group (0.4% vs. 8.3%; P=0.006). There were no differences between the groups regarding mortality rate (1.1% vs. 0.4%; P=0.432).

Subgroup Analyses

With respect to the primary outcome time-to-recovery no significant results were seen within subgroups of center and Hinchey classification (Figures S1 and S2). In the Hinchey 1a subgroup (N=486), secondary outcomes were in line with main analyses (Table S12). Results of per-protocol analyses were in accordance with the results of the intention-to-treat analyses (Tables S13-15 and Figure S3).

DISCUSSION

In this pragmatic, randomized controlled trial, we found that an observational treatment strategy for a first episode of CT-proven uncomplicated acute diverticulitis was not inferior to an antibiotic treatment strategy with respect to the primary outcome time-to-recovery during 6 months. The median time-to-recovery in patients who were assigned to observation was 14 days as compared to 12 days with antibiotics, but without significant repercussions. Analyses of secondary endpoints, such as proportions of complicated, ongoing or recurrent diverticulitis, overall sigmoid resections, readmission, adverse event and mortality rates, support these findings. In the antibiotic group the duration of initial admission was longer and the rate of antibiotics related adverse events was higher. These results indicate that antibiotics can be omitted in the treatment of patients with uncomplicated acute diverticulitis, and clinical guidelines can be adjusted accordingly.

Current guidelines recommend including antibiotics in the non-operative treatment of uncomplicated acute diverticulitis. Treatment for uncomplicated diverticulitis without antibiotics obviously is controversial, since clinical guidelines have remained unchanged despite evidence from two observational studies[10,11] and one randomized clinical trial[12] indicating antibiotics have no benefit. The one previous randomized clinical trial has

evaluated 623 patients with mild diverticulitis[12], but as has been discussed previously the methodological setup of this Swedish RCT is not ideal for a number of reasons[13,19]. Major limitations are inclusion of 40% of patients with recurrent instead of primary diverticulitis, a long accrual period of more than 6 years, no differentiation between ongoing diverticulitis and recurrent diverticulitis, and no standardized antibiotic treatment that could have resulted in performance bias.[12] In the latest Practice Parameters of the American Society of Colon and Rectal Surgeons (ASCRS)[13] the Swedish trial is discussed and deemed in need of confirmation. A recent Cochrane review has found no significant difference between antibiotics and no antibiotics for the treatment of uncomplicated diverticulitis, but states - as others did - that further research is required before an antibiotic-free treatment strategy can be adopted safely in clinical guidelines.[30]

Although at every other outcome variable the observational treatment was not inferior to antibiotic treatment, we saw an unexpected higher rate of elective sigmoid resections at 12 months (15 (6.6%) vs. 7 (2.9%) patients; P=0.030) but not at 6 months follow-up. Most elective resections in both arms were performed for persistent abdominal complaints. In the observation group more elective resections were performed for recurrent diverticulitis, but the recurrence rate as such was comparable among both groups (at 6 months: 3.4 vs. 3.0%, P=0.494; at 12 months: 8.4% vs. 7.9%, P=0.429). ASCRS states in their most recent guideline that elective sigmoid resection after recovery from uncomplicated acute diverticulitis should be made on a case-by-case basis.[13] Also the Dutch guideline concludes that patient-related factors are most important role in selecting patients for elective sigmoid resection.[31] This individualized approach could have resulted in variation in indications for elective surgery due to subjective assessment, and in small samples cause distortion of a secondary outcome variable.

This trial, as most trials, lacked power to detect smaller subgroup effects. Our results suggest that antibiotics may not be necessary also in patients with Hinchey 1b diverticulitis, but that subgroup constituted only of 42 patients. There were some other limitations noteworthy. First, accrual rates between participating hospitals were notably different. Selection bias could have been introduced. We anticipate that the high number of participating hospitals evened out these possible effects. Importantly, the study's block randomization and stratification by center should also prevent for such confounding. Secondly, in 8.3% of patients assigned to antibiotics treatment related adverse events were registered, but in only three patients these resulted in discontinuation of antibiotic treatment. Thirdly, no *Clostridium difficile* superinfection causing pseudomembranous colitis did occur in this study population, but fecal bacterial resistance patterns were not fully examined. Therefore, the extent of the potential clinical problem of resistance of bacteria associated with antibiotic treatment of diverticulitis could not be assessed. The World Health Organization (WHO) has long recognized antimicrobial resistance (AMR) as worldwide health threat and urged the international community to commit to combatting AMR. One of the main AMR containment strategies is to increase appropriate use of

antimicrobials, and to reduce misuse, since AMR is a consequence of antimicrobial use[20]. This so-called rational use of antibiotics could imply omitting them in uncomplicated acute diverticulitis based on present study results.

Present study was conducted according to the highest standards of randomized trials and can thereby answer the study question with considerable confidence. The short-term benefits of observational treatment, partly in outpatient setting, without significant short-term or medium long-term repercussions indicate that antibiotic treatment can safely be omitted in uncomplicated diverticulitis. A treatment strategy without antibiotics for uncomplicated acute diverticulitis can now be adopted in clinical guidelines.

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SUPPLEMENTARY APPENDIX

Table S1 | Exclusion Criteria

Exclusion criteria
Previous US and/or CT proven episode of diverticulitis
US 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 of less than six months
Contraindication for the use of the study medication (e.g. patients with advanced renal failure or allergy to all antibiotics used in this study),
Pregnancy, breastfeeding
ASA classification > III
Immunocompromised patients
Clinical suspicion of bacteremia (i.e. sepsis [24])
Inability of reading/understanding and filling in the questionnaires
Antibiotic use in the four weeks prior to inclusion

Abbreviations: US, ultrasonography; CT, computed tomography; ASA, American Society of Anesthesiologists.

Table S2 | Reasons for Wrongful Inclusion of Randomized Patients

	Observation (N=283)	**Antibiotics** (N=287)	***Total*** (N=570)
No confirmed diagnosis of diverticulitis	4 (1.4%)	3 (1.0%)	7 (1.2%)
Complicated diverticulitis *	4 (1.4%)	3 (1.0%)	7 (1.2%)
CRC < 3 months after randomization	2 (0.7%)	5 (1.7%)	7 (1.2%)
Antibiotics < 1 month before randomization	3 (1.1%)	3 (1.0%)	6 (1.1%)
Previous episode of diverticulitis	2 (0.7%)	3 (1.0%)	5 (0.9%)
No informed consent	3 (1.0%)	1 (0.3%)	4 (0.7%)
Immunocompromised	1 (0.4%)	1 (0.3%)	2 (0.4%)
IBD	1 (0.4%)	0 (0%)	1 (0.2%)
Total	20 (7.1%)	19 (6.6%)	39 (6.8%)

Abbreviations: CRC, colorectal carcinoma; IBD, inflammatory bowel disease;

***** Hinchey 2, 3 or 4, or diverticulitis with fistula or obstruction.

Table S3 | Major Protocol Amendments

Description amendment	Data approval by IRB
Change in the definition of recurrent diverticulitis with the aim to make a distinction between recurrent and ongoing diverticulitis* and reporting accordingly	October 26, 2012
Extension of the enrollment period to compensate for the unexpected high wrongful inclusion rate and to ensure sufficient evaluable patients	September 10, 2012
Change in DSMB charter: abstaining from interim-analyses	February 16, 2012
'Approval by patient' added to discharge criteria	March 4, 2010
Criteria / escape clauses for starting antibiotics in patients assigned to observational treatment	March 4, 2010
Additional secondary endpoint: number of days outside the hospital in a 6 month period	March 4, 2010

Abbreviations: IRB, institutional review board; DSMB, data safety and monitoring board;

* Definition recurrent diverticulitis: clinical picture of diverticulitis whether or not imaging proven AND interval of at least 3 months from randomization AND recovery during this time interval, when the last two criteria are not fulfilled the diagnosis is ongoing diverticulitis; which substituted the earlier definition of ultrasound- or CT-proven acute diverticulitis after complete resolution of symptoms more than 1 month after initial discharge from hospital.

Table S4 | Baseline Characteristics of the Patients According to Randomization Status *

	Randomized (N=570)		Not randomized eligible patients who declined participation (N=149)		P-value
Age – yr	56.6	(48.5-64.2)	57.8	(48.1-65.9)	0.633
Male sex – no (%)	277	(48.6%)	61	(40.9%)	0.095
Co-morbidity† – no (%) *(42 vs 7 missings)*	234	(44.3%)	45	(31.7%)	0.007
ASA score ‡ – no (%)					0.114
ASA 1	330	(62.5%)	99	(69.7%)	
ASA 2	177	(33.5%)	39	(27.5%)	
ASA 3	21	(4.0%)	4	(2.8%)	
(42 vs 7 missings)				(	
Body mass index – kg/m^2 *(78 vs 87 missings)*	26.8	(24.4-29.6)	26.7	(24.3-28.9)	0.528
Body temperature – °C *(42 vs 7 missings)*	37.3	(36.9-38.0)	37.2	(36.8-37.8)	0.077
Localization abdominal pain LLQ isolated – no (%) *(42 vs 7 missings)*	244	(46.2%)	102	(71.8%)	**<0.001**
Vomiting – no (%) *(42 vs 7 missings)*	47	(8.9%)	8	(5.6%)	0.208
White blood cell count – ×10^9 cells/L *(42 vs 7 missings)*	12.2	(10.1-14.5)	12.1	(10.0-14.8)	0.818
C-reactive protein – mg/L *(43 vs 8 missings)*	79.0	(43.0-128.0)	78.5	(46.7-131.0)	0.910
Hinchey category 1a § – no (%) (11 missings in the not randomized group)	507	(88.9%)	126	(91.3%)	0.420

Abbreviations: ASA, American Society of Anesthesiologists (Physical Status Classification System); LLQ, left lower quadrant;

* Data are medians with interquartile range since they were not normally distributed, or numbers with percentages in parentheses;

† Includes cardiovascular disease and/or pulmonary disease and/or renal failure and/or diabetes mellitus;

‡ ASA 1=Normal, healthy patient, ASA 2=Patient with a mild systemic disease, ASA 3=Patient with severe systemic disease;

§ (Modified) Hinchey classification category 1a=Colonic wall thickening and/or confined pericolic inflammation, category 1b=Confined small pericolic abscess (≤ 5cm).

Table S5 | Reasons for Non-Enrollment of Screened Patients *

N=323	
No informed consent	286 (88.5%)
No informed consent as only reason	149 (46.1%)
Antibiotics < 1 month before screening	65 (20.1%)
Previous episode of diverticulitis	46 (14.2%)
No left-sided mild diverticulitis	35 (10.8%)
No US and/or CT-proven diagnosis of Hinchey 1a or 1b diverticulitis	29 (9.0%)
Complicated diverticulitis †	19 (5.9%)
Inability of reading and/or understanding and/or filling in the questionnaires	12 (3.7%)
Immunocompromised	12 (3.7%)
Contraindication for all trial antibiotics	10 (3.1%)
Radiological suspicion for CRC	6 (1.9%)
Bacteraemia/sepsis	4 (1.2%)
Expected survival < 6 months	3 (0.9%)
IBD	2 (0.6%)
≥ ASA 4	2 (0.6%)
Pregnancy or breastfeeding	1 (0.3%)

Abbreviations: US, ultrasound; CT, computed tomography; CRC, colorectal carcinoma; IBD, inflammatory bowel disease; ASA, American Society of Anesthesiologists (Physical Status Classification System);

* One patient can have more than one reason for non-enrollment;

† Hinchey 2, 3 or 4, or diverticulitis with fistula or obstruction.

Table S6 | Number of Included Patients per Hospital*

	Observation		Antibiotics		Total
	ITT (N=262)	PP (N=264)	ITT (N=266)	PP (N=264)	(N=528)
Academic Medical Center	9 (3.4%)	8 (3.0%)	8 (3.0%)	9 (3.4%)	17 (3.2%)
VU Medical Center	3 (1.1%)	4 (1.5%)	4 (1.5%)	3 (1.1%)	7 (1.3%)
Kennemer Gasthuis Hosp.	17 (6.5%)	18 (6.8%)	14 (5.3%)	13 (4.9%)	31 (5.9%)
Spaarne Hospital	24 (9.2%)	22 (8.3%)	26 (9.8%)	28 (10.6%)	50 (9.5%)
Saint Lucas Andreas Hosp.	9 (3.4%)	10 (3.8%)	9 (3.4%)	8 (3.0%)	18 3.4%)
Meander Medical Center	35 (13.4%)	37 (14.0%)	37 (13.9%)	35 (13.3%)	72 (13.6%)
Máxima Medical Center	13 (5.0%)	12 (14.5%)	13 (4.9%)	14 (5.3%)	26 (4.9%)
Onze Lieve Vrouwe Gasthuis Hospital	8 (3.1%)	9 (3.4%)	9 (3.4%)	8 (3.0%)	17 (3.2%)
Gelre Hospital	8 (3.1%)	7 (2.7%)	8 (3.0%)	9 (3.4%)	16 (3.0%)
BovenIJ Hospital	5 (1.9%)	5 (1.9%)	4 (1.5%)	4 (1.5%)	9 (1.7%)
Red Cross Hospital	18 (6.9%)	19 (7.2%)	15 (5.6%)	14 (5.3%)	33 (6.2%)
Albert Schweitzer Hospital	25 (9.5%)	22 (8.3%)	26 (9.8%)	29 (11.0%)	51 (9.7%)
Tergooi Hospital	10 (3.8%)	12 (4.5%)	12 (4.5%)	10 (3.8%)	22 (4.2%)
Ziekenhuisgroep Twente Hospital	21 (8.0%)	23 (8.7%)	22 (8.3%)	20 (7.6%)	43 (8.1%)
Westfriesgasthuis Hospital	16 (6.1%)	15 (5.7%)	18 (6.8%)	19 (7.2%)	34 (6.4%)
Ikazia Hospital	6 (2.3%)	5 (1.9%)	6 (2.3%)	7 (2.7%)	12 (2.3%)
Saint Franciscus Gasthuis Hospital	10 (3.8%)	11 (4.2%)	10 (3.8%)	9 (3.4%)	20 (3.8%)
Slotervaart Hospital	1 (0.4%)	1 (0.4%)	2 (0.8%)	2 (0.8%)	3 (0.6%)
Reinier de Graaf Gasthuis Hospital	7 (2.7%)	7 (2.7%)	7 (2.6%)	7 (2.7%)	14 (2.7%)
Flevo Hospital	5 (1.9%)	5 (1.9%)	3 (1.1%)	3 (1.1%)	8 (1.5%)
Saint Antonius Hospital	12 (4.6%)	12 (4.5%)	13 (4.9%)	13 (4.9%)	25 (4.7%)

Abbreviations: ITT, intention to treat; PP, per protocol; Hosp., Hospital;

* One participating hospital did not contribute to patient inclusion, but screened six patients that were ineligible.

Table S7 | Type of Antibiotic Treatment prescribed

	Observation (N=13 of 262)		Antibiotics (N=265 of 266)	
Amoxicillin/clavulanic acid	1	(7.7%)	250	(94.3%)
Metronidazol + Ciprofloxacin	3	(23.1%)	14	(5.3%)
Cephalosporin ‡	3	(23.1%)	1	(0.4%)
Gentamicin	2	(15.4%)	0	(0.0%)
Unknown	4	(30.8%)	0	(0.0%)

‡ Cephalosporins prescribed: cefuroxime (N=2), ceftriaxone (N=1), cefotaxime (N=1).

Table S8 | Reasons for Protocol Deviation per Treatment Group

Reasons for starting antibiotics in patients assigned to observational treatment (13 of 262) *	
Other infectious focus	4 (1.5%)
Clinical deterioration or progression to complicated diverticulitis	3 (1.1%)
Body temperature >39°C	3 (1.1%)
Sepsis	2 (0.8%)
Positive blood culture	1 (0.4%)
Total	13 (5.0%)
Reasons for discontinuation of antibiotics in patients assigned to antibiotic treatment (15 of 266) †	
Incorrect prescription by treating physician	7 (2.6%)
Unclear instruction/patient's own decision	4 (1.5%)
Allergic reaction	2 (0.8%)
Side-effects	1 (0.4%)
Death	1 (0.4%)
Total	15 (5.6%)

* Defined as start of antibiotic treatment within 10 days after randomization;

† Defined as 5 or more days of missed antibiotic treatment within 10 days after randomization.

Table S9 | Indications for Sigmoid Resection at 6 Months Follow-up

	Observation (N=10 of 262)		Antibiotics (N=6 of 266)	
Obstruction/chronic ileus	3	(30.0%)	2	(33.3%)
Perforated diverticulitis	2	(20.0%)	2	(33.3%)
Ongoing diverticulitis	2	(20.0%)	1	(16.7%)
Persistent abdominal complaints	1	(10.0%)	1	(16.7%)
	1	(10.0%)	0	(0.0%)
Diverticular bleeding	1	(10.0%)	0	(0.0%)
Fistula	0	(0.0%)	0	(0.0%)
Recurrent diverticulitis	0	(0%)	0	(0%)
Total	10	(100%)	6	(100%)

Table S10 | Main Secondary Outcomes among Patients with Uncomplicated Acute Diverticulitis assigned to an Observational or Antibiotic Treatment Strategy at 12 Months Follow-up

	Observation (N=227* of 262)	Antibiotics (N=240* of 266)	P-value
Readmission (≥1) – no (%)	48 (21.1%)	49 (20.4%)	0.423
Complicated diverticulitis (≥1) – no (%)	9 (4.0%)	6 (2.5%)	0.185
Ongoing diverticulitis (≥1) – no (%)	17 (7.5%)	10 (4.2%)	0.062
Recurrent diverticulitis (≥1) – no (%)	19 (8.4%)	19 (7.9%)	0.429
Sigmoid resection – no (%)	16 (7.0%)	9 (3.8%)	0.057
Emergency	1 (0.4%)	2 (0.8%)	0.521
Elective	15 (6.6%)	7 (2.9%)	0.030

***** Number of patients with a follow-up duration of at least 12 months; in the observation and antibiotic group 86.6% and 90.2% of patients respectively had a follow-up duration of at least 12 months.

Table S11 | Indications for Sigmoid Resection at 12 Months Follow-up for Elective and Emergency Resections

	Elective resections (22 of 467*)		Emergency resections (3 of 467*)	
	Observation (N=15 of 227*)		Antibiotics (N=7 of 240*)	
Persistent abdominal complaints	5	(33.3%)	3	(42.9%)
	3	(20.0%)	1	(14.3%)
Recurrent diverticulitis	3	(20.0%)	1	(14.3%)
Obstruction/chronic ileus	2	(13.3%)	2	(28.6%)
Ongoing diverticulitis	1	(6.7%)	0	(0.0%)
Fistula	1	(6.7%)	0	(0.0%)
Diverticular bleeding	0	(0%)	0	(0%)
Total	15	(100%)	7	(100%)
	Observation (N=1 of 227*)		Antibiotics (N=2 of 240*)	
Perforated diverticulitis	1	(100%)	1	(50%)
Obstruction/chronic ileus	0	(0%)	1	(50%)
Total	1	(100%)	2	(100%)

* Number of patients with a follow-up duration of at least 12 months; in the observation and antibiotics group 86.6% and 90.2% of patients respectively had a follow-up duration of at least 12 months.

Table S12 | 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

	Hinchey 1a (N=486)				Hinchey 1b (N=42)			
Subgroup								
Treatment arm	**Obs** (N=241)	**AB** (N=245)	Un-adjust. **P-value**	Adjust.† **P-value**	**Obs** (N=23)	**AB** (N=19)	Un-adjust. **P-value**	Adjust.† **P-value**
Recovery ≤ 6 months FU – no (%)	211 (89.4%)	235 (94.0%)	0.033	0.163	23 (88.5%)	13 (81.2%)	0.413	0.508
Readmission (≥1) ≤ 6 months FU – no (%)	42 (17.8%)	31 (12.4%)	0.048	0.163	4 (15.4%)	1 (6.2%)	0.359	0.508
Days outside hospital ≤ 6 months FU – proportion of FU duration ‡	0.989 (0.978-0.994)	0.983 (0.978-0.989)	<0.001	0.009	0.989 (0.969-0.996)	0.983 (0.968-0.988)	0.044	0.432
Complicated diverticulitis (≥1) ≤ 6 months FU – no (%)	8 (3.4%)	4 (1.6%)	0.164	0.282	2 (7.7%)	3 (18.8%)	0.275	0.508
At index admission	2 (0.8%)	3 (1.2%)	0.527	0.527	1 (3.8%)	3 (18.8%)	0.146	0.467
Intervention §								
Surgery	6 (2.5%)	3 (1.2%)	0.224	0.317	2 (7.7%)	2 (12.5%)	0.495	0.528
Percut.	1 (0.4%)	0 (0.0%)	0.486	0.516	1 (3.8%)	1 (6.2%)	0.623	0.623
Treatment arm	**Obs** (N=236)	**AB** (N=250)	Un-adjust. **P-value**	Adjust.† **P-value**	**Obs** (N=26)	**AB** (N=16)	Un-adjust. **P-value**	Adjust.† **P-value**
Ongoing diverticulitis (≥1) ≤ 6 months FU – no (%)	17 (7.2%)	11 (4.4%)	0.093	0.264	2 (7.7%)	0 (0.0%)	0.377	0.508

Table S12 | Continued

Subgroup	Hinchey 1a (N=486)				Hinchey 1b (N=42)			
Recurrent diverticulitis (≥1) ≤ 6 months FU – no (%)	9 (3.8%)	7 (2.8%)	0.266	0.348	0 (0.0%)	1 (6.2%)	0.381	0.508
Sigmoid resection ≤ 6 months FU – no (%)	8 (3.4%)	4 (1.6%)	0.164	0.282	2 (7.7%)	2 (12.5%)	0.495	0.528
Emerg.	2 (0.8%)	1 (0.4%)	0.478	0.516	0 (0.0%)	2 (12.5%)	0.139	0.467
Elective	6 (2.5%)	3 (1.2%)	0.224	0.317	2 (7.7%)	0 (0.0%)	0.377	0.508
All morbidity § ¶ – no (%)	118 (50%)	136 (54.4%)	0.166	0.282	9 (34.6%)	9 (56.2%)	0.081	0.432
Mild	83 (35.2%)	107 (42.8%)	0.043	0.163	6 (23.1%)	7 (43.8%)	0.080	0.432
Serious	64 (27.1%)	56 (22.4%)	0.114	0.277	5 (19.2%)	5 (31.2%)	0.300	0.508
AB related	1 (0.4%)	21 (8.4%)	<0.001	0.009	0 (0%)	1 (6.2%)	0.381	0.508
Mortality ¶ – no (%)	3 (1.3%)	1 (0.4%)	0.290	0.352	NA	NA	NA	NA

Abbreviations: Obs, observation; AB, antibiotics; Unadjust, unadjusted; Adjust, adjusted; FU, follow-up; percut., percutaneous; emerg., emergency;

* Data are numbers with or without percentages in parentheses or data are medians with interquartile range since these continuous variables had non-gaussian distributions;

† Multiple comparison adjustment by using Benjamini-Hochberg correction;

‡ 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 can have more than 1 type intervention and morbidity;

¶ With a median duration of follow-up of 711 days (IQR, 366 to 732) in the observation group and 732 days (IQR, 366 to 732) in the antibiotic group (P=0.204).

Table S13 | Secondary Outcomes among Patients with Uncomplicated Acute Diverticulitis assigned to an Observational or Antibiotic Treatment Strategy according to Per-Protocol Analyses *

	Observation (N=264)	Antibiotics (N=264)	Un-adjusted P-value	Adjusted P-value†
Outpatient treatment – no (%)	33 (12.5%)	2 (0.8%)	<0.001	0.006
Duration initial admission – days	2 (1-3)	3 (2-3)	<0.001	0.006
Recovery ≤ 6 months FU – no (%)	239 (90.5%)	243 (92.0%)	0.269	0.416
Readmission (≥1) ≤ 6 months FU – no (%)	44 (16.7%)	34 (12.9%)	0.110	0.264
Total number	59	42		
Days outside hospital ≤ 6 months FU – proportion of FU duration ‡	0.989 (0.978-0.994)	0.983 (0.978-0.989)	<0.001	0.006
Complicated diverticulitis (≥1) ≤ 6 months FU – no (%)	6 (2.3%)	11 (4.2%)	0.109	0.264
Type § – no (%)				
Abscess (> 5cm)	1 (0.4%)	3 (1.1%)	0.312	0.416
Perforation	1 (0.4%)	5 (1.9%)	0.108	0.264
Obstruction	3 (1.1%)	3 (1.1%)	0.657	0.657
Fistula	0 (0.0%)	1 (0.4%)	0.500	0.512
Bleeding	2 (0.8%)	0 (0.0%)	0.250	0.416
At index admission– no (%)	0 (0.0%)	9 (3.4%)	0.002	0.010
Intervention § – no (%)				
Percutaneous	1 (0.4%)	2 (0.8%)	0.500	0.512
Surgery	4 (1.5%)	9 (3.4%)	0.130	0.284
Ongoing diverticulitis (≥1) ≤ 6 months FU – no (%)	16 (6.1%)	14 (5.3%)	0.354	0.447
Imaging proven	7	8		
Needing admission	12	7		
Recurrent diverticulitis (≥1) ≤ 6 months FU – no (%)	10 (3.8%)	7 (2.7%)	0.230	0.416
Imaging proven	8	3		
Needing admission	4	5		
Sigmoid resection ≤ 6 months FU – no (%)	7 (2.7%)	9 (3.4%)	0.306	0.416
Emergency	1 (0.4%)	4 (1.5%)	0.186	0.372
Elective	6 (2.3%)	5 (1.9%)	0.381	0.457

Table S13 | Continued

	Observation (N=264)	Antibiotics (N=264)	Unadjusted P-value	Adjusted P-value†
Morbidity § ¶ – no (%)	125 (47.3%)	147 (55.7%)	0.028	0.103
Mild	91 (34.5%)	112 (42.4%)	0.030	0.103
Serious	64 (24.2%)	66 (25.0%)	0.420	0.480
AB related morbidity	4 (1.5%)	19 (7.2%)	0.001	0.006
Mortality ¶ – no (%)	3 (1.1%)	1 (0.4%)	0.312	0.416

* Data are numbers with or without percentages in parentheses or data are medians with interquartile range since these continuous variables had non-gaussian distributions;

† P-values after multiple testing adjustment by using Benjamini-Hochberg correction;

‡ 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 can have more than 1 type of complicated diverticulitis, intervention and morbidity;

¶ With a median duration of follow-up of 726 days (IQR, 366 to 732) in the observation group and 732 days (IQR, 366 to 732) in the antibiotics group (P=0.073).

Table 14 | Main Secondary Outcomes among Patients with Uncomplicated Acute Diverticulitis according to Per-Protocol Analyses at 12 Months Follow-up

	Observation (N=229* of 264)	Antibiotics (N=238* of 264)	P-value
Readmission (≥1) – no (%)	47 (20.5%)	50 (21.0%)	0.449
Complicated diverticulitis (≥1) – no (%)	6 (2.6%)	9 (3.8%)	0.239
Ongoing diverticulitis (≥1) – no (%)	14 (6.1%)	13 (5.5%)	0.382
Recurrent diverticulitis (≥1) – no (%)	18 (7.9%)	20 (8.4%)	0.415
Sigmoid resection – no (%)	13 (5.7%)	12 (5.0%)	0.381
Emergency	1 (0.4%)	2 (0.8%)	0.514
Elective	12 (5.2%)	10 (4.2%)	0.298

* Number of patients with a follow-up duration of at least 12 months; in the observation and antibiotic group 86.7% and 90.2% of patients respectively had a follow-up duration of at least 12 months.

Table S15 | Subgroup Analyses of Main Secondary Outcomes for Hinchey Categories 1a and 1b among Patients with Uncomplicated Acute Diverticulitis according to Per-Protocol Groups

Subgroup	Hinchey 1a (N=486)				Hinchey 1b (N=42)			
Treatment arm	**Obs** (N=241)	**AB** (N=245)	Un-adjust. **P-value**	Adjust.† **P-value**	**Obs** (N=23)	**AB** (N=19)	Un-adjust. **P-value**	Adjust.† **P-value**
Recovery ≤ 6 months FU – no (%)	218 (90.5%)	228 (93.1%)	0.148	0.359	21 (91.3%)	15 (78.9%)	0.128	0.341
Readmission (≥1) ≤ 6 months FU – no (%)	41 (17.0%)	32 (13.1%)	0.112	0.317	3 (13.0%)	2 (10.5%)	0.593	0.678
Days outside hospital ≤ 6 months FU – proportion of FU duration ‡	0.989 (0.978-0.994)	0.983 (0.978-0.989)	<0.001	0.009	0.989 (0.978-0.994)	0.978 (0.922-0.989)	0.009	0.112
Complicated diverticulitis (≥1) ≤ 6 months FU – no (%)	6 (2.5%)	6 (2.4%)	0.489	0.510	0 (0.0%)	5 (26.3%)	0.014	0.112
At index admission	0 (0.0%)	5 (2.0%)	0.032	0.181	0 (0.0%)	4 (21.1%)	0.035	0.118
Intervention §								
Surgery	4 (1.7%)	5 (2.0%)	0.510	0.510	0 (0.0%)	4 (21.1%)	0.035	0.118
Percut.	1 (0.4%)	0 (0.0%)	0.496	0.510	0 (0.0%)	2 (10.5%)	0.199	0.346
Treatment arm	**Obs** (N=241)	**AB** (N=245)	Un-adjust. **P-value**	Adjust.† **P-value**	**Obs** (N=23)	**AB** (N=19)	Un-adjust. **P-value**	Adjust.† **P-value**
Ongoing diverticulitis (≥1) ≤ 6 months FU – no (%)	15 (6.2%)	13 (5.3%)	0.332	0.510	1 (4.3%)	1 (5.3%)	0.706	0.706

Table S13 | Continued

Subgroup	Hinchey 1a (N=486)				Hinchey 1b (N=42)			
Recurrent diverticulitis (≥1) ≤ 6 months FU – no (%)	9 (3.7%)	7 (2.9%)	0.294	0.510	1 (4.3%)	0 (0.0%)	0.548	0.678
Sigmoid resection ≤ 6 months FU – no (%)	6 (2.5%)	6 (2.4%)	0.489	0.510	1 (4.3%)	3 (15.8%)	0.234	0.346
Emerg.	1 (0.4%)	2 (0.8%)	0.506	0.510	0 (0.0%)	2 (10.5%)	0.199	0.346
Elective	5 (2.1%)	4 (1.6%)	0.490	0.510	1 (4.3%)	1 (5.3%)	0.706	0.706
All morbidity § ¶ – no (%)	118 (49.0%)	136 (55.5%)	0.074	0.251	7 (30.4%)	11 (57.9%)	0.037	0.118
Mild	85 (35.3%)	105 (42.9%)	0.044	0.187	6 (26.1%)	7 (36.8%)	0.227	0.346
Serious	60 (24.9%)	60 (24.5%)	0.459	0.510	4 (17.4%)	6 (31.6%)	0.238	0.346
AB related	3 (1.2%)	19 (17.8%)	<0.001	0.009	1 (4.3%)	0 (0.0%)	0.548	0.678
Mortality ¶ – no (%)	3 (1.2%)	1 (0.4%)	0.306	0.510	NA	NA	NA	NA

Abbreviations: Obs, observation; AB, antibiotics; Unadjust, unadjusted; Adjust, adjusted; FU, follow-up; percut., percutaneous; emerg., emergency;

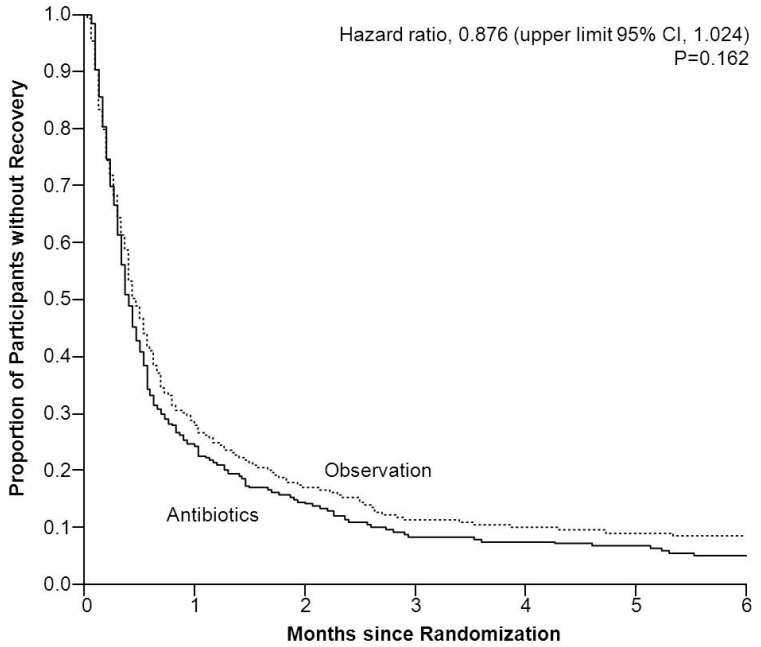
* Data are numbers with or without percentages in parentheses or data are medians with interquartile range since these continuous variables had non-gaussian distributions;

† Multiple comparison adjustment by using Benjamini-Hochberg correction;

‡ 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 can have more than 1 type intervention and morbidity;

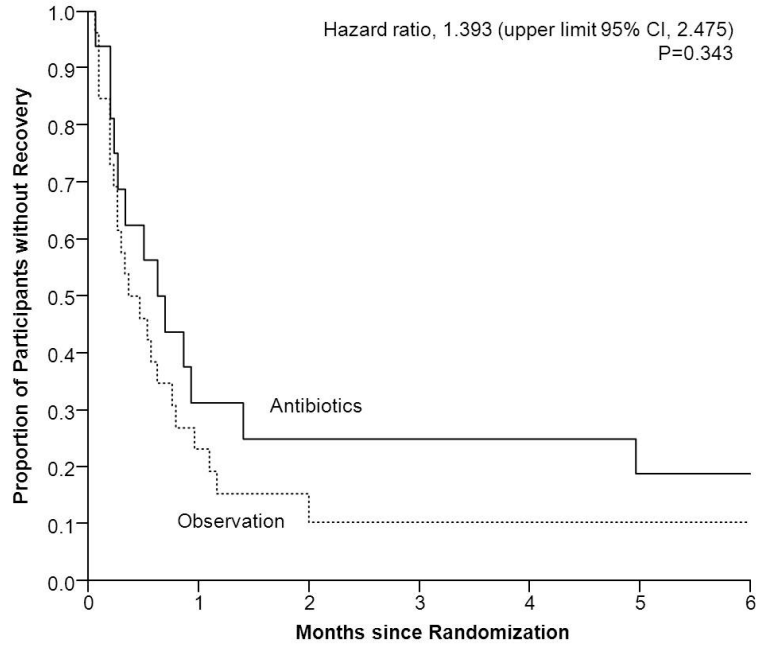
¶ Median follow-up within Hinchey 1A subgroup: in observation arm 731 days (IQR, 366 to 732) and antibiotics arm 732 days (IQR, 366 to 732) (P=0.189); within Hinchey 1B subgroup: in observation arm 397 days (IQR, 366 to 732) and antibiotics arm 659 days (IQR, 366 to 732) (P=0.189).



No. at Risk							
Observation	236	64	39	25	22	20	17
Antibiotics	250	60	35	20	18	16	11

Figure S1 | Time-to-Recovery in Patients with Uncomplicated Acute Diverticulitis within the Subgroup Hinchey 1a

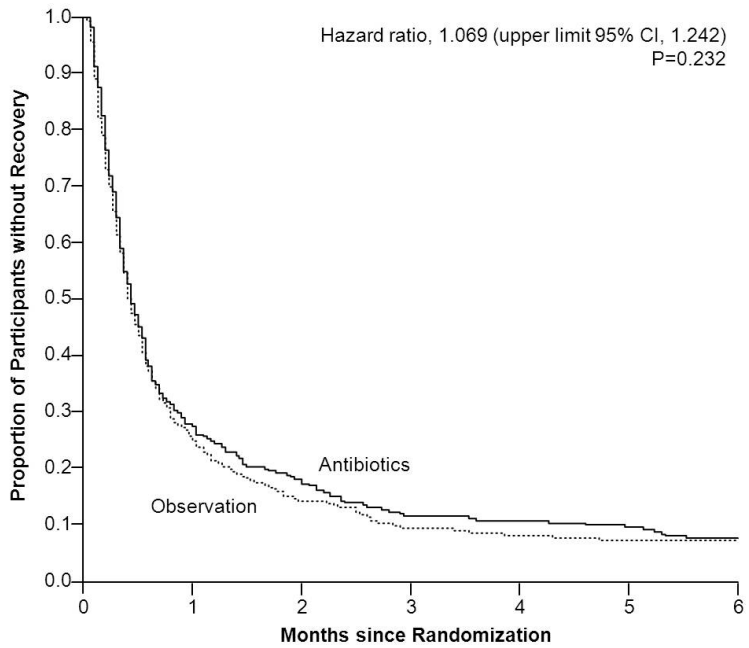
Kaplan-Meier survival curves for time-to-recovery of patients with uncomplicated acute diverticulitis assigned to an observational or antibiotic treatment strategy within the subgroup Hinchey 1a over 6 months of follow-up.



No. at Risk							
Observation	26	6	6	2	2	2	2
Antibiotics	16	5	5	4	4	3	3

Figure S2 |Time-to-Recovery in Patients with Uncomplicated Acute Diverticulitis within the Subgroup Hinchey 1b

Kaplan-Meier survival curves for time-to-recovery of patients with uncomplicated acute diverticulitis assigned to an observational or antibiotic treatment strategy within the subgroup Hinchey 1b over 6 months of follow-up.



No. at Risk

Observation	264	63	35	22	19	17	15
Antibiotics	264	72	45	29	27	24	18

Figure S3 | Time-to-Recovery in Patients with Uncomplicated Acute Diverticulitis according to Per-Protocol Group

Kaplan-Meier survival curves for time-to-recovery of patients with uncomplicated acute diverticulitis according to per-protocol group over 6 months of follow-up.

CHAPTER 12

Overtreatment of sigmoid diverticulitis: a plea for a less aggressive approach.

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ABSTRACT

A less invasive approach to the treatment of left-sided colonic diverticulitis has emerged in the last decade. The standard of care for perforated or complicated diverticulitis evolved from a Hartmann's procedure, to resection and primary anastomosis, to treatment with antibiotics and percutaneous drainage in a carefully selected (Hinchey grade 2) patient subset. Recently laparoscopic lavage emerged as a promising less invasive treatment for selected cases of Hinchey 3 patients. Likewise for non-perforated or uncomplicated diverticulitis the approach is becoming less aggressive with a change from intravenous antimicrobial therapy, starvation and admission, to oral antibiotics and finally to observation and outpatient treatment. This less invasive or aggressive approach is due to expanding evidence on optimal treatment and congruent with an increasing understanding that diverticulitis comprises different disease entities with heterogeneity between patients. The disease should be targeted by specific approaches likewise, after a meticulous assessment of the diverticulitis stage, and tailored to an individual basis. Avoidance of overtreatment has obvious benefits: less in hospital treatment, cost reduction, diminished development of antimicrobial resistance, reduction in complication rate and side effects and presumably a better quality of life for the patient. In conclusion one might say we overtreated the majority of diverticulitis patients for decades. More research is needed to explain the pathogenesis and multifactorial aetiology and in the nearby future hopefully several unanswered questions regarding the optimal management of patients with different stages of diverticulitis will be answered by various ongoing trials.

INTRODUCTION

A less invasive approach to the treatment of left-sided diverticulitis has emerged in the last decade. In the beginning of the last century the three stage approach was the standard for emergency left-sided colonic surgery. In 1921, Henri Hartmann described an operative procedure for the treatment of rectosigmoid carcinoma[1] which was adopted by Boyden in 1950 for patients with acute diverticulitis.[2] In the 1970s the Hartmann's procedure became increasingly applied since advantages like immediate resection of the diseased colon, avoidance of anastomosis and a more rapid recovery outweighed the disadvantages of the risk of a permanent stoma and complications associated with the second stage.[3-6] Past diagnostic challenges required early resection because of the difficulty in ruling out malignancy. Meanwhile, there have been major developments in imaging, (interventional) radiologists' expertise, antibiotic therapy and as well in intensive care management and anaesthesia.

Since then standard of care for perforated or complicated diverticulitis evolved from a Hartmann's procedure[7], to resection and primary anastomosis[8] and to treatment with antibiotics and percutaneous drainage in a carefully selected (Hinchey grade 2) patient subset.[9] Recently laparoscopic lavage emerged as a promising less invasive treatment for selected cases of Hinchey 3 patients.[10-14] Likewise for non-perforated or uncomplicated diverticulitis the approach is becoming less aggressive with a change from intravenous antimicrobial therapy, starvation and admission, to oral antibiotics[15,16] and finally to observation[17-19] and outpatient treatment.[20-23] This more conservative approach is in line with the evolvement of less invasive management strategies for other intra abdominal infections such as appendicitis, and pancreatitis. These shifts in care are a reflection of the conception that diverticulitis comprises a broad spectrum of diseases and not just one uniform clinical picture. Furthermore, evidence on optimal treatment is expanding. This paper aims to address the available evidence for contemporary operative and non-operative management of colonic diverticulitis.

Understanding the disease

Diverticulosis is a common condition in Western society with an incidence of 33–66% and carries a high socioeconomic burden. Of these patients 10–25% will develop an acute episode of diverticulitis.[24] Gaining better insight in the natural history of diverticular disease, its clinical picture and the results of follow-up after treatment has had great influence on management strategies.

Current evidence suggests that dietary deficiency (of fibre), colonic pressure, motility changes and colonic structural alterations may collectively contribute to diverticula formation[25] ,although these hypotheses remain largely unproven. Some connective tissue disorders, mainly part of genetic disorders, have been associated with a predisposition towards this formation but literature is ambiguous on this matter.[26,27] Possibly, increasing mitochondrial dysfunction plays a role in the pathogenesis of diverticular disease.[28] Know-

ledge on the pathogenesis of diverticular inflammation is also scarce and uncertain. Hinchey postulated in his original classification that all forms of diverticulitis are the result of a (micro)perforation due to an inspissated fecalith.[29] This hypothesis however remains unproven. Changes in intestinal microbiota composition, colonization or entrapment of pathogenic bacteria within diverticula through impacted faeces and stimulation of mucosal immune responses have recently been postulated as mechanisms in the pathogenesis of symptoms and complications. Recent studies suggest that it maybe a form of inflammatory bowel disease (IBD).[30-32]

DEVELOPMENT IN MANAGEMENT

Uncomplicated disease

Mild diverticulitis may in majority of cases be a self-limiting process[17,19] but antibiotics are usually prescribed. Apart from recommendations in several guidelines there is no evidence mandating the routine use of antibiotics in uncomplicated diverticulitis and this advice mainly is based on medical dogma and expert opinion. A randomized clinical trial (RCT) that compared an oral versus an intravenous antibiotic regimen[15], studies that compared two different kinds of antibiotics and antibiotics with and without anaerobe coverage[33,34] and two recent retrospective case-controlled studies that compared treatment with and without antibiotics[17,19] could not establish differences in outcome between the groups. Therefore, antibiotics can probably be omitted in selected patients with mild colonic diverticulitis and should be given on indication only. Hence the main goal of the DIABOLO trial[35], an actively accruing multicenter RCT, is to establish whether antibiotics are necessary in the primary treatment of acute mild diverticulitis and whether a strategy without initial antibiotics is more cost-effective with respect to time-to-full recovery. The results of this and a similar RCT, both comparing antibiotics with observation alone in mild diverticulitis, are awaited for definitive answers.[35-37]

The advent of antibiotics almost 70 years ago resulted in a major decline in the incidence of life-threatening infections, but inappropriate treatment and overuse have contributed to the emergence of antimicrobial resistance (AMR). Several international organizations actively address this global threat to our ability to cope with infections and the World Health Organization (WHO) selected combating AMR as the theme for World Health Day 2011. WHO issued an international call for concerted action to halt the spread of antimicrobial resistance and recommended a six-point policy package for governments.[38]

Ambulatory treatment of uncomplicated acute diverticulitis seems to be safe, effective and applicable to most patients with tolerance to oral intake, without severe comorbidity and having appropriate family support.[20,22,23] A cohort study of 96 patients showed that ambulatory treatment with oral antibiotics is applicable in more than 70% of patients and the majority (97%) will complete the treatment successfully with resolution of the

inflammatory process and without complications. [20] Similarly, in a retrospective analysis of a cohort of 693 patients it was found that outpatient treatment was effective (94%), but that women (OR 3,08) and patients with free fluid on CT scan (OR 3,19) were at significantly higher risk for treatment failure.[23]

Complicated disease

For acute complicated diverticular disease differences of opinion still exist about the best approach to the surgical treatment. In a retrospective study in 60 patients primary anastomosis with defunctioning stoma and the Hartmann's procedure after resection of the diseased sigmoid were compared. It was concluded that both regimens are accepted treatments but because of morbidity during the second stage (anastomotic leaks), the longer hospital stay, the longer follow-up with a stoma, and morbidity in terms of stomal dysfunction and a permanent stoma after the Hartmann's procedure primary anastomosis with covering stoma should be the preferred treatment option.[39]

A retrospective analysis of 1.073.397 diverticulitis patients showed a trend toward increased use of primary anastomosis for acute operations and laparoscopic techniques for elective operations.[40] Laparoscopic resection for both symptomatic and perforated diverticulitis have been shown to be as safe and effective as conventional open techniques[41,42] and the results of a cost-effectiveness analysis of a laparoscopic approach compared with open sigmoid resection were similar.[43,44]

Regardless of selected strategy, emergency operations for acute perforated diverticulitis are associated with substantial morbidity and mortality.[45] Recently laparoscopic lavage emerged as an alternative for patients with perforated diverticulitis with purulent peritonitis.[10] Prospective cohort studies and retrospective case series show promising results, with high efficacy, low mortality, low morbidity and a minimal need for a colostomy.[11-14] Laparoscopic lavage for perforated purulent diverticulitis has great potential and its performance and use is gradually inclining since its introduction in 1996. Currently, the LapLAND study from Ireland and the DILALA and SCANDIV study from Scandinavia are comparing laparoscopic lavage versus resection for Hinchey 3 diverticulitis in an RCT and are currently recruiting patients.[46-49] Furthermore, the Ladies trial, a two-armed RCT from the Netherlands, is including patients to investigate whether laparoscopic lavage and drainage is a safe and effective treatment for patients with purulent peritonitis and what the optimal resectional strategy is in patients with a purulent or faecal peritonitis.[47]

Elective resection

For years it has been considered good practice to perform elective sigmoid resection after two episodes of acute diverticulitis and even after one episode in younger patients[50], in order to prevent complicated disease. Acute diverticulitis has a recurrence rate of 36%, rarely progresses to complications; complicated recurrences occur in only 3,9%-10%.[51,52] During the first episode the risk of free perforation is 25,3%, during the second 12,7% and

the third 5,9%.[53] Patients who present with a family history of diverticulitis, long segment of involved colon, and/or retroperitoneal abscess are at higher risk for recurrent disease.[51] The majority of patients who develop a recurrence do so in a similar mode and location, but in 35% of patients recurrent diverticulitis occurs at a different location.[52]

Current indications for elective sigmoid resection are symptomatic stenosis, fistulas or recurrent diverticular bleeding. Furthermore, an elective resection might be justified in high-risk patients, after a conservatively treated episode of diverticulitis, who use immunosuppression therapy and have chronic renal failure or collagen-vascular diseases. As stated, the risk of free perforation in acute sigmoid diverticulitis significantly decreases with the number of previous episodes, which suggests that elective surgery may be unnecessary after conservatively treated diverticulitis. The number of recurrent episodes alone should not be a leading factor.[42]

Patients with persisting abdominal complaints, which is not uncommon after an episode of diverticulitis, and patients with frequent recurrences suffer greatly from their disease. Both conservative and operative management are applied but it is undetermined which is superior. Therefore, currently a RCT comparing these two treatment strategies is conducted and results are to be awaited.[54]

Prevention

Conservative treatment has become the primary choice in the prevention of a recurrent episode of diverticulitis. This approach mainly comprises dietary advises and medical therapies. High-fibre diet is still recommended in several guidelines despite the fact that high-quality evidence for a high-fibre diet in the treatment of diverticular disease is lacking, and most recommendations are based on inconsistent level 2 and mostly level 3 evidence.[55] Lifestyle factors seem to have impact on the course of diverticular disease. Several prospective cohort studies and a number of retrospective studies have found positive associations between obesity and diverticular complications.[56] Smoking also increases the likelihood of complications in diverticulitis.[57] Lifestyle modification should maybe have a larger role in the (preventive) management of diverticular disease and its complications.

Besides for the management of symptomatic uncomplicated diverticular disease antibiotics are also applied for prevention of recurrent diverticulitis. A retrospective study of 505 patients, in which the cyclic administration of the non-absorbable antibiotic rifaximin to prevent recurrence after complicated diverticulitis was studied, showed a significant lower readmission and operation rate in the antibiotic group.[58] Last few years new medical therapies, such as probiotics and 5-aminosalicylic acid (5-ASA), have been studied. Probiotics, by affecting intestinal microbial flora, have been shown to have a positive effect on various gastrointestinal conditions. Probiotics seem a promising therapy for symptomatic diverticular disease and prevention of recurrence of diverticulitis, but data are limited and well designed randomized trials with adequate sample size are needed to

confirm preliminary findings.[59-62] 5-ASAs are widely and effectively used for the treatment of inflammatory bowel disease (IBD) and, since it has been postulated that inflammation in diverticular disease is similar to the inflammation in IBD, patients may benefit from treatment with anti-inflammatory medication such as 5-ASA. A review of 6 RCTs showed that patients treated with 5-ASA had significantly better outcomes and that mesalazine scheduled daily was superior to cyclic administration to prevent relapse of diverticular disease, so it seems that 5-ASAs may have a role in the management of diverticular disease.[63]

Classification

Since Hinchey's traditional classification for perforated diverticulitis in 1978[29], several modifications and new grading systems have been presented to display a more contemporary overview of the disease but none seems to sufficiently embrace the entire spectrum of the disease. A new classification system, which proposes three stages of differentiating diverticular disease (A—uncomplicated, B—chronic complicated, and C—acute complicated) addresses clinical findings, radiological findings and treatment modalities and could be of great value in the clinical decision making and management of a condition as complex as diverticular disease.[64] A new universally used classification system would greatly enhance the comparability of outcome in future research.

WHAT'S NEXT?

Despite the fact that there still is controversy about the appropriate management of the various stages of the disease and its complications, one cannot help but noticing a shift away from invasive, operative treatment for both uncomplicated and complicated diverticulitis towards a less aggressive, non-operative approach. Moreover this has not led to an increased incidence of complicated disease.[64]

In conclusion one might say we overtreated the majority of diverticulitis patients for decades. The trend towards a less aggressive approach is a recent development congruent with an increasing understanding that diverticulitis comprises different disease entities with heterogeneity between patients. As a result the disease should be targeted by specific approaches likewise and tailored to an individual basis. For this purpose a meticulous assessment of the diverticulitis stage is essential and imaging is indispensable to complement clinical assessment and physical examination. A systematic review and meta-analysis on diagnostic accuracy showed no statistically significant difference in accuracy of ultrasonography (US) and computed tomography (CT) in diagnosing acute colonic diverticulitis. Both can be used as initial diagnostic tool, however CT is more likely to identify alternative diseases.[66] In the future there possibly is a role for magnetic resonance imaging in differentiating between diverticulitis stages.

Avoidance of overtreatment has obvious benefits: less in hospital treatment, cost reduction, diminished development of antimicrobial resistance, reduction in complication rate and side effects and presumably a better quality of life for the patient. Still many aspects of diverticular disease and its complications remain poorly understood. More research is needed to explain its pathogenesis and multifactorial aetiology and could lead to new targets for treatment. Several unanswered questions regarding the management of patients with diverticulitis will hopefully be answered in the nearby future by various ongoing trials that address the optimal treatment of different stages of diverticulitis.[35-37,46-49,54]

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CHAPTER 13

Summary, general discussion
and future perspectives.

SUMMARY

Colonic diverticulosis is one of the most common disorders of the gastro-intestinal tract. Diverticulitis is a common complication of diverticulosis and imposes a significant health care burden. International guidelines until now have been based on low-level evidence. No universal classification system exists and still much debate exists over optimum treatment strategies. Furthermore the aetiology of diverticulitis remains unclear; especially in relation to the colonic microbiome.

In this thesis we have tried to answer a number of questions concerning the aetiology, current treatment of diverticulitis and the use of antibiotics. All research questions postulated in the introduction are answered separately below.

PART I: AETIOLOGY. COLONIC MICROBIOME AND MUCOSAL CHANGES IN PATIENTS WITH DIVERTICULOSIS AND DIVERTICULITIS.

What is the colonic microbiome composition in patients with diverticulosis compared to a control population?

Chapter 2 presents the results of the PADIFLORA study. As a first step in further understanding the development of diverticulitis we compared the colonic microbiome of individuals with diverticulosis on colonoscopy, but without symptoms, and compared it to a matched control population. It has been suggested that a low fibre diet that may lead to diverticula formation could also alter the colonic microbiome. A high-throughput polymerase chain reaction (PCR)-based profiling technique (IS-pro) was performed on DNA isolates from mucosal samples. We found that the microbiome of patients with diverticulosis is not different to that of a control population. This is true for the sigmoid colon as well as the transverse colon. The *Firmicutes* to *Bacteroidetes* ratio is commonly used to describe and characterize a dysbiosis of the gut microbiota. Therefore, we compared their relative abundance between patients and controls. For diverticulosis patients, *Bacteroidetes* represented 62% and *Firmicutes* 38% of the total abundance in the *Firmicutes/Bacteroidetes* PCR. Almost identical proportions were found for the patient group (*Bacteroidetes* 63%, *Firmicutes* 37%) (p=0.69 vs patients). The total load of bacteria of the *Proteobacteria* phylum was also similar between patients and controls (*P*=0.56).

Are there histological changes in the mucosa of patients with diverticulosis?

Chapter 2 also describes the histological evaluation of the colonic mucosa in a group of patients with diverticula on colonoscopy compared to individuals with no diverticula. It has been hypothesized that clinically manifest forms of diverticulitis could have a precursor stage with a form of low grade mucosal inflammation not leading to clinical manifest symptoms yet. To assess this, mucosal biopsies were taken from individuals with diverticulosis on colonoscopy but without symptoms and compare this to the mucosa of patients

without diverticula. The presence of inflammation was assessed. We found no difference in mean lymphocyte count between the groups, neither in the bottom of the crypts or in the whole crypts. This was also true for the sigmoid colon as well as the transverse colon.

Is the colonic microbiome in patients with diverticulitis different from healthy individuals?

Chapter 3 describes the results of the DIBIOTA study. Thirty-one patients with Computed Tomography (CT) proven left-sided, uncomplicated diverticulitis were included and compared with 25 matched control subjects evaluated for a range of other gastrointestinal indications.

Differences in bacterial phylum abundance and diversity (Shannon index) of the resulting profiles were assessed by conventional statistics. Dissimilarity in microbiome composition was analysed with principal coordinate analysis (PCoA) based on cosine distance measures. To develop a prediction model for the diagnosis of diverticulitis, we used cross-validated partial least squares discriminant analysis (PLSDA). Firmicutes/Bacteroidetes ratios and Proteobacteria load were comparable among patients and controls (p=0.20). The Shannon index indicated a higher diversity in diverticulitis for Proteobacteria (p<0.00002) and all phyla combined (p= 0.002). PCoA based on Proteobacteria profiles resulted in visually separate clusters of patients and controls. The diagnostic accuracy of the cross-validated PLS-DA regression model was 84 %. The most discriminative species derived largely from the family Enterobacteriaceae.

Diverticulitis patients have a higher diversity of faecal microbiota than controls from a mixed population, with the phylum Proteobacteria defining the difference. The analysis of intestinal microbiota offers a novel way to diagnose diverticulitis and may play a role in the aetiology of diverticulitis.

In conclusion, much remains unclear in the aetiology of diverticulitis and the role the colonic microbiome plays in it.

PART II: CURRENT CLASSIFICATION AND MANAGEMENT OF DIVERTICULITIS

Which classification systems exist and what are the differences between the systems?

Chapter 4 reviews the current classification systems for diverticulitis. A total of nine different classification systems were identified. Some were only based on imaging and some incorporated all aspects of diverticular disease including chronic complications and bleeding.

A new classification system more in line with current evidence incorporating all aspects of complicated diverticular disease, imaging and its treatment is proposed.

What is the current approach to the diagnosis and treatment of diverticulitis in the Netherlands?

Chapter 5 describes the results of a questionnaire on the treatment and diagnosis of diverticulitis in the Netherlands among gastro-enterologists and surgeons. Eighteen percent of gastro-enterologists consider a CT mandatory for every patient compared to 39% of surgeons (p=0.001). A CT however is considered mandatory in all guidelines. 90% percent of respondents (both gastro-enterologists and surgeons) treat mild diverticulitis *without* antibiotics, although antibiotics are recommended in all international guidelines. The majority of both surgeons and gastroenterologists use a form of bowel rest, would consider outpatient treatment, and perform a colonoscopy at follow-up. For Hinchey 3 diverticulitis 78% of surgeons would consider a resection and primary anastomosis. Laparoscopic lavage is viewed as a valid alternative for Hinchey 3 diverticulitis by 30% of gastro-intestinal surgeons and 2% of non-gastrointestinal surgeons. For Hinchey 4 diverticulitis 46 % of gastro-intestinal surgeons and 72% of non-gastrointestinal surgeons would always perform a Hartmann procedure.

Recent publications show that bowel rest and antibiotics are not needed for mild diverticulitis, follow-up colonoscopy is not needed, and primary anastomosis after resection for complicated diverticulitis is usually safe and feasible. Much of these new insights are not widely practiced.

What is the evidence base for diagnosing diverticulitis?

Chapter 6 reports a case vignette study in which the current evidence base for diagnosing diverticulitis is evaluated.

A strategy of ultrasound first followed by Computed Tomography (CT) in case of inconclusive ultrasound is a safe strategy and results in the lowest exposure to radiation. In case of a critically ill patient a CT should be performed as the first choice. The role of Magnetic Resonance Imaging (MRI) for diverticulitis remains unclear.

Which risk factors predict treatment failure of diverticulitis in patients treated non-operatively?

In chapter 7 a cohort of patients with diverticulitis treated non-operatively is described. A total of 20 patients (6%) failed treatment. On univariate analysis age above 70, ASA grade higher than 2, abscess formation on CT scan, steroid use and NSAID use were associated with an increased risk of treatment failure. Multivariate analysis showed abscess formation (odds ratio 8.76 [95% confidence interval 2.88-26.64]), NSAID use (odds ratio 13.35 [95% confidence interval 2.84-64.20]) and ASA grade (odds ratio 4.50 [95% confidence interval 1.52-13.33]) to be independent risk factors. There were 6 (2%) deaths in the entire cohort, all of which were in the treatment failure group. When treatment failed mortality was as high as 31.6 percent.

A more aggressive approach should be considered in a high-risk group of patients.

PART III: TREATMENT OF DIVERTICULITIS WITH ANTIBIOTICS

What is the value of treating uncomplicated diverticulitis with antibiotics?

Chapter 8 is the result of a systematic review on the use of antibiotics in uncomplicated diverticulitis. The results show that evidence for antibiotic treatment of diverticulitis is extremely sparse. The review concludes that there is no evidence supporting the use of antibiotics in uncomplicated diverticulitis.

Chapter 9 describes a retrospective cohort study in which a group of patients with uncomplicated diverticulitis is treated with antibiotics and one is treated without antibiotics. A total of 191 patients were treated without antibiotics and 81 with antibiotics. Groups were comparable at baseline with respect to age, sex, co-morbidity, NSAID, steroid and aspirin use. All patients had imaging confirmed diverticulitis. C-reactive protein and white blood cell counts levels did not differ significantly. Treatment failure did not differ between groups (4% *versus* 6%, p=0.350).

Chapter 10 is the presentation of the protocol of the DIABOLO study, a randomized controlled trial comparing a regimen of antibiotics and hospital admission to observation alone in patients with uncomplicated diverticulitis.

Chapter 11 reports on the outcome of the DIABOLO study. The trial shows that there is no differences in time to recovery at six months follow up. 570 patients were randomly assigned to observation or antibiotics. Complete recovery occurred in 234 (89.3%) of patients assigned to the observation arm and in 248 (93.2%) patients assigned to the antibiotic arm (P=0.183) Over a median follow-up period of 731 days we found, after adjusting for multiple comparisons, no significant differences between both treatment strategies for main and secondary endpoints. Hospital stay was significantly shorter in the observation group.

In conclusion, omitting antibiotics in uncomplicated diverticulitis is safe. In the light of ever growing antibiotic resistance this is an important finding. Based on all research currently available, international guidelines should be amended.

What controversies exist in the current management of diverticulitis?

A review of the current management strategies for the treatment of diverticulitis is addressed in **chapter 12**. The use of antibiotics is controversial in the treatment of uncomplicated diverticulitis and according to the outcome of the DIABOLO trial not necessary. In complicated diverticulitis there is still much debate on the treatment of Hinchey 3 (purulent peritonitis) and Hinchey 4 diverticulitis (fecal peritonitis). A resection and anastomosis may be a save option as is laparoscopic lavage in selected cases. A less aggressive approach for all stages is advocated.

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

This thesis focusses on several aspects of aetiology, classification and treatment of diverticulitis, where progress and clarification is needed. This has been one of the main reasons of the formation of the Dutch Diverticular Disease (3D) collaborative study group, addressing some of the most controversial aspects of management.

The aetiology of diverticulitis still remains partly unsolved. In this thesis we have tried to shed some light on the role of the colonic microbiome in the development of diverticulitis. For the first time in diverticulosis and diverticulitis patients we assessed the microbiome using the latest DNA technologies. We found that although the microbiome in diverticulis has changed significantly, this is not the case yet in asymptomatic diverticulosis. These findings need to be validated on a much larger set of patients with diverticulitis, and the cause and effect of a changed microbiome in this setting needs to be assessed. Furthermore, it would be interesting to know whether the microbiome changes again after diverticulitis subsides. Studies in children indicate that antibiotic use may alter the microbiome permanently, and this may be the case in adults as well. Along these lines of reasoning, antibiotic-induced changes superimposed upon an already altered microbiome in diverticular disease may play a role in the pathophysiology of recurrent episodes of diverticulitis. For future research the colonic microbiome can be evaluated using rectal swabs instead of mucosal biopsies. Evaluation in asymptomatic patients with diverticula but without the possible confounding of colonic lavage (as preparation for colonoscopy) is necessary to define whether shifts in the microbiome occur already before symptoms start. Furthermore, the microbiome inside diverticula may be different from the microbiome in the colonic lumen. Therefore, assessment of diverticula specimens of resected sigmoid for other reasons than diverticular disease may be an interesting approach.

The colonic microbiome harvests more than 5000 individual bacterial species and is a largely uncharted field for future research. In the coming years our understanding of the role of the microbiome in health and disease needs to increase. What is its role in the prevention, development and disease course of diverticulitis; which micro-organisms and which shifts in microbiome are important?

We found no inflammatory changes in the mucosa of symptom-free diverticulosis patients as had been suggested by others. Future research could focus on identifying changes in regulatory pathways of mucosal cytokines in individuals with diverticulosis that could play a role in developing clinically manifest diverticulitis.

A universally adopted classification system is paramount for standardizing diagnosis and treatment of a disease, for evaluation of new imaging and treatment advances, and for international comparison of study results. For diverticulitis this is however not the case. We reviewed all classification systems and propose a new system incorporating all elements of diagnosis and treatment of diverticular disease. Future research must evaluate and validate this new comprehensive classification and other promising new classification systems like the Dharmarajam classification in prospective series. Research on diverticular disease would benefit greatly if a classification system would be universally adopted, as has been the case for the international TNM system in cancer.

In this thesis we demonstrated large variations in diagnosis and treatment of diverticulitis in the Netherlands. Large practice variations of a condition are unwanted both from a medical and a socio-economical point of view. Surgical societies and health care insurers could play an important role in making these differences clear by providing data on the sort of diagnostic modality and treatment used in individual hospitals and comparing them to other hospitals and guidelines. Since the publication of our survey a guideline on the treatment of diverticulitis has been issued. It would be interesting to see whether emerging evidence and guidelines alter treatment for diverticulitis. Limited funds for diverticulitis research, as for other non-malignant diseases, are a problem that needs to be addressed. The health care burden of diverticulitis is enormous and research resources should not by predominantly aimed at cancer research.

It appears that although mild or uncomplicated diverticulitis usually runs a benign course of disease, when comorbidity, NSAID use or abscess formation is present, failure of conservative treatment may result in high mortality. Further research should focus on these risk factors and determine the best treatment strategy for them. Ideally treatment choices should be tailored to a patients individual risk profile. National prospective audits, similar to cancer treatment, may prove a valuable quality control method in evaluating diverticulitis treatment in the future.

The use of antibiotics in the treatment of uncomplicated diverticulitis has been a long-standing dogma. Until only a few years ago there was no evidence whatsoever to justify this. The Dutch surgeon Roumen, already in 1996, was the first who published data on the use of antibiotics in diverticulitisin the Netherlands Journal of Surgery. His prospective DIVAN trial however proved difficult to complete. More than 15 years later we completed the DIABOLO trial which together with the Swedish AVOD study by Chabok et al. and two retrospective cohort studies, of which one is presented in this thesis, firmly prove the safety of omitting antibiotics in uncomplicated diverticulitis. The recently published Dutch national guideline does not advise the use of antibiotics in uncomplicated diverticulitis and more emphasis on restrictive use is appearing currently in review articles on diverticulitis. The next update of the Dutch national guideline should include the evidence of the DIABOLO trial. International guidelines however appear to be rigid and still recommending the use of antibiotics. This should be altered in upcoming updates. Restrictive use of antibiotics is extremely important in the light of ever growing antibiotic resistance. In 2014 the World Health Organization stated that antibiotic resistance is a serious worldwide threat to public health that should be firmly combated. The use of antibiotics without evidence and published clinic benefit should be banned.

The Dutch LOLA trial and three other foreign trials evaluate the use of laparoscopic lavage in Hinchey 3 diverticulitis. Furthermore the Dutch DIVA trial examines primary anastomosis versus Hartmann's procedure in Hinchey 3 and 4 diverticulitis. In the near future these trials hopefully will provide more definitive answers to the many other unsolved questions regarding the treatment of diverticulitis.

All and all, recent years have seen a shift from an approach of the disease with antibiotic use, hospitalization, resection and stoma formation to a *less aggressive* approach without antibiotic use and with outpatient treatment in uncomplicated disease and the possibility of primary anastomosis or peritoneal lavage in selected cases of complicated disease.

SAMENVATTING IN HET NEDERLANDS

Diverticulose van de dikke darm is een van de meest voorkomende aandoeningen van de tractus digestivus. Diverticulitis is de meest voorkomende complicatie van diverticulose en vormt een belangrijke ziektelast voor het gezondheidssysteem. Er bestaat geen universeel geaccepteerd classificatiesysteem voor diverticulitis en er bestaat nog steeds veel verschil van inzicht over de beste behandeling. Verder is de ontstaanswijze van diverticulitis nog steeds onduidelijk, zeker in relatie tot het microbioom van het colon. Dit proefschrift beantwoordt een aantal onderzoeksvragen betreffende de etiologie, de huidige behandeling en het gebruik van antibiotica bij de behandeling van diverticulitis.

DEEL I: ETIOLOGIE VAN DIVERTICULITIS

Hoe ziet het microbioom van het colon eruit in individuen met diverticulosis in vergelijking tot een controle groep van individuen zonder diverticulosis?
In **hoofdstuk 2** worden de resultaten van de PADIFLORA studie gepresenteerd. Als een eerste stap in het verder begrijpen van het ontstaan van diverticulitis hebben we het microbioom van patinten met divertikels, maar zonder klachten, vergeleken met een controle groep van patiënten zonder divertikels. Een “high-throughput” polymerase chain reaction (PCR) profiling technique (IS-PRO) werd gedaan op DNA isolaten van mucosale biopten. Het blijkt dat het microbioom van het colon niet anders is in individuen met diverticulosis vergeleken met een controle groep.

Zijn er histologische veranderingen zichtbaar in de darm mucosa van individuen met diverticulosis?
Hoofdstuk 2 beschrijft de evaluatie van de mucosa van de dikke darm van een patiënten groep met en een zonder diverticulosis. Er zijn aanwijzingen dat het ontstaan van diverticulitis wordt voorafgegaan door een stadium van laag-gradige mucosale inflammatie zonder dat individuen hier klachten van ondervinden. Om dit te onderzoeken zijn mucosale biopten genomen van een groep individuen zonder divertikels en een groep met divertikels. Het blijkt dat er geen verschillen zijn in gemiddelde lymfocyten dichtheid tussen deze twee groepen. Dit geld zowel voor de bodem van de crypten als voor de hele crypt.

Is het microbioom van het colon anders in patiënten met diverticulitis dan in een gezonde populatie?
In hoofdstuk 3 worden de resultaten van de DIBIOTA studie beschreven. Eenendertig patiënten met Computer Tomografie (CT) bewezen diverticulitis werden geïncludeerd en vergeleken met 25 controle individuen. Een “high-throughput” polymerase chain reaction (PCR) profiling technique (IS-PRO) werd gedaan op DNA isolaten van feces monsters. De resultaten laten zien dat patiënten met diverticulitis meer diversiteit in het microbioom van hun colon hebben dan de controle populatie en dat het phylum Proteobacteriën het verschil voornamelijk definieert. De analyse van intestinale microbiota vormt een nieuwe manier om diverticulitis te diagnosticeren en kan een rol spelen in het verder ontrafelen van de ontstaanswijze van diverticulitis.

Concluderend blijft er nog veel onduidelijkheid over de ontstaanswijze van diverticulitis en de rol van het microbioom van de dikke darm hierin.

DEEL II: HUIDIGE BEHANDELING VAN DIVERTICULITIS

Welke classificatiesystemen bestaan er voor diverticulitis?
Hoofdstuk 4 geeft een overzicht van de huidige classificatiesystemen voor diverticulitis en beschrijft een voorstel voor een nieuw classificatiesysteem dat meer in lijn is met de huidige inzichten van behandeling en welke alle aspecten van divertikelziekte en zijn mogelijke complicaties behelst.

Wat is de huidige behandeling van diverticulitis in Nederland?
Hoofdstuk 5 beschrijft de resultaten van een enquête betreffende de diagnostiek en behandeling van diverticulitis die naar alle Nederlandse chirurgen en maag-darm-leverartsen is gestuurd. Er werd een groot verschil in behandeling gezien in diagnose en behandeling zowel tussen chirurgen als tussen chirurgen en maag-darm-leverartsen voor alle stadia van diverticulitis. Verder bleek dat de behandeling aanzienlijk verschilde van internationale richtlijnen. Achttien procent van de maag-darm-lever artsen en 39% van de chirurgen vonden een CT scan een vereiste in de diagnostiek van diverticulitis. Een CT scan wordt echter aanbevolen in alle internationale richtlijnen. De meerderheid van zowel maag-darm-leverartsen als chirurgen behandeld diverticulitis zonder antibiotica, hoewel alle internationale richtlijnen dit wel aanbevelen. De meerderheid van maag-darm leverartsen en chirurgen behandeld patiënten poliklinisch en doet een coloscopie in de follow-up. Voor Hinchey 3 diverticulitis wordt 78% van de chirurgen een resectie en primaire anastomose overwogen. Laparoscopische lavage wordt door 30% van de gastro-intestinale chirurgen en 2% van de niet gastro-intestinale chirurgen als een alternatief gezien. Bij een Hinchey 4 divericulitis zou 46% van de gastro-intestinaal chirurgen en 72% van de niet gastro-intestinaal chirurgen een Hartmann procedure uitvoeren.

Wat is de beste manier om diverticulitis te diagnosticeren?
Hoofdstuk 6 beschrijft met behulp van een klinische casus de huidige literatuur met betrekking tot de beste manier om diverticulitis aan te tonen.

Een strategie waarbij eerst een echo wordt gemaakt en alleen een CT scan bij een niet conclusieve echo is een veilige strategie die lijdt tot de minste stralenbelasting. De rol van Magnetic Resonance Imaging (MRI) bij het diagnosticeren van diverticulitis is nog onduidelijk.

Welke risicofactoren voorspellen het niet slagen van een conservatieve behandeling van diverticulitis?
In hoofdstuk 7 wordt een cohort patiënten beschreven welke conservatief zijn behandeld in verband met een diverticulitis van het sigmoïd. Het blijkt dat NSAID gebruik, ASA score en abces vorming onafhankelijke risicofactoren zijn voor het falen van een conservatief

beleid. Als het conservatieve beleid bij deze groep faalt, is de mortaliteit 30%. In patiënten met deze risicofactoren lijkt een meer agressievere benadering bij het dreigen te falen van het conservatieve beleid te rechtvaardigen.

DEEL III: BEHANDELING VAN DIVERTICULITIS MET ANTIBIOTICA

Wat is de waarde van antibiotica bij de behandeling van diverticulitis?

Hoofdstuk 8 is een systematische review naar de waarde van antibiotica bij de behandeling van ongecompliceerde diverticulitis. Het blijkt dat er zeer weinig bewijs is voor de noodzaak tot het toedienen van antibiotica bij ongecompliceerde diverticulitis.

Hoofdstuk 9 beschrijft een cohort patiënten met ongecompliceerde diverticulitis waarvan een deel met en een deel zonder antibiotica is behandeld. Totaal werden 191 patiënten met en 81 zonder antibiotica behandeld. De groepen waren vergelijkbaar wat betreft leeftijd, geslacht, comorbiditeit, NSAID gebruik, steroïd gebruik en aspirine gebruik. Alle patiënten hadden met beeldvorming bewezen diverticulitis. Er bleek geen verschil te zijn tussen de twee groepen voor wat betreft het falen van de behandeling of het voorkomen van complicaties.

Hoofdstuk 10 is het protocol van de DIABOLO studie, een RCT welke de behandeling van diverticulitis met antibiotica vergelijkt met alleen observatie.

Hoofdstuk 11 beschrijft de uitkomsten van de DIABOLO studie. Het blijkt dat er geen verschil is in tijd tot volledig herstel tussen beide groepen. 570 patiënten zijn uiteindelijk gerandomiseerd. Volledig herstel trad op bij 234 (89.3 %) patiënten in de observatiegroep en bij 248 (93.2%) van de patiënten in de antibiotica groep. Bij een mediane follow-up van 731 dagen waren er geen significante verschillen in primaire en secundaire uitkomstmaten. Het verblijf in het ziekenhuis was duidelijk korter bij de groep die geen antibiotica kreeg.

Concluderend blijkt het achterwege laten van antibiotica bij de behandeling van ongecompliceerde diverticulitis een veilige behandelstrategie. In het licht van de alsmaar groeiende antibioticaresistentie is dit een zeer belangrijke vinding. Op basis van het huidige beschikbare bewijs zouden internationale richtlijnen moeten worden aangepast.

Welke controversen spelen er bij de behandeling van diverticulitis?

In hoofdstuk 12 worden in een review de huidige behandelstrategieën besproken. Het gebruik van antibiotica bij ongecompliceerde diverticulitis is controversieel en is waarschijnlijk niet noodzakelijk. Bij gecompliceerde diverticulitis is er verschil van inzicht over de beste manier van het behandelen van Hinchey 3 (purulente peritonitis) en 4 (fecale peritonitis) diverticulitis. Resectie en anastomose lijken veilige opties, evenals laparoscopische lavage in sommige gevallen. Een minder agressieve aanpak van alle stadia van ziekte wordt gepropageerd.

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CURRICULUM VITAE

Niels de Korte was born on the 6th of May 1977 in Amsterdam. After attending the Alkwin Kollege in Uithoorn he started his Bachelor in medical biology at the VU University in Amsterdam. The year after he was admitted to medical school at the same university. In that period he performed his research thesis in Paramaribo, Surinam, South America on the variety of symptoms in Surinam general practice.

After graduating from medical school in 2003 he started as an emergency physician in the Lange Land Hospital in Zoetermeer. Nine months later he was accepted for general surgery training. He started his training in the Kennemer Gasthuis (Dr. H.L.F. Brom/Dr. H. Rijna). His academic rotation was performed at the VU University Medial Center (Prof. J.A. Rauwerda/Dr. D. van der Peet).

During his residency and fellowship he was trained in laparoscopic gastro-intestinal surgery, surgical oncology and trauma surgery. He now is board certified in all three fields and works as a consultant surgeon in the Spaarne Gasthuis in Hoofddorp and Haarlem.

During his residency he laid the groundwork for his dissertation and was one of initiators of the DIABOLO trial and one of the founders of the Dutch Diverticular Disease (3D) Collaborative Study Group. Furthermore he is one of the authors of the guideline “Diagnosis and treatment of acute colonic diverticulitis” of the Dutch Society of Surgeons.

He lives in Haarlem with Klarke Boor and their two children Jaap en Liesje.