Treatment, follow-up and microbiota in acute diverticulitis
Daniels, L.

Citation for published version (APA):
Daniels, L. (2015). Treatment, follow-up and microbiota in acute diverticulitis

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.

UvA-DARE is a service provided by the library of the University of Amsterdam (http://dare.uva.nl)
UITNODIGING

Voor het bijwonen van de openbare verdediging van het proefschrift

TREATMENT, FOLLOW-UP AND MICROBIOTA IN ACUTE DIVERTICULITIS

Door Lidewine Daniels

Vrijdag 24 april 2015
om 12.00 uur in de Agnietenkapel
Universiteit van Amsterdam
Oudezijds Voorburgwal 231
Amsterdam

Aansluitend bent u van harte uitgenodigd voor de receptie ter plaatse

Lidewine Daniels
Sumatrakade 867
1019 RA Amsterdam
lidosaurus@hotmail.com
06-14517454

PARANIMFEN

Eveline Boeker
e.b.boeker@outlook.com
06-18822203

Diane van Diemen
dianevandiemen@hotmail.com
06-27054384
TREATMENT, FOLLOW-UP AND MICROBIOTA IN ACUTE DIVERTICULITIS

Lidewine Daniels
Treatment, follow-up and microbiota in acute diverticulitis
Thesis, University of Amsterdam, The Netherlands

Paranimfen: Diane van Diemen, Eveline Boeker

ISBN: 978-94-6259-623-8
Cover design: Persoonlijkproefschrift.nl
Lay-out: Persoonlijkproefschrift.nl
Printed by: Ipskamp Drukkers BV

© L. Daniels, Amsterdam, The Netherlands, 2015

No part of this thesis may be reproduced, stored or transmitted, in any form or by any means, without prior permission of the author.

The DIABOLO trial was financially supported by: the Netherlands Organization for Health Research and Development, Health Care Efficiency Research program (ZonMw grant number 80-82310-97-10039) and the Dutch Digestive Diseases Foundation (MLDS grant number WO 08-54).

Financial support for the printing of this thesis was kindly provided by: Wetenschappelijk Fonds Chirurgie AMC; Nederlandse Vereniging voor Gastroenterologie; Academisch Medisch Centrum; Westfriesleerhuis; Astellas Pharma B.V.; IS-Diagnostics Ltd.; ChipSoft B.V.; Olympus Nederland B.V.; EuroTec B.V.
TREATMENT, FOLLOW-UP AND MICROBIOTA IN ACUTE DIVERTICULITIS

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit van Amsterdam op gezag van de Rector Magnificus prof. dr. D.C. van den Boom ten overstaan van een door het college voor promoties ingestelde commissie, in het openbaar te verdedigen in de Agnietenkapel op vrijdag 24 april 2015, te 12:00 uur

door

Lidewine Daniels

geboren te Woerden
PROMOTIECOMMISSIE

Promotor  Prof. dr. M.A. Boermeester

Co-promotores  Dr. H.B.A.C. Stockmann  Dr. M.G.W. Dijkgraaf

Overige Leden  Prof. dr. M.D. de Jong  Prof. dr. O.R.C. Busch  Prof. dr. R.J. de Haan  Prof. dr. H.G. Gooszen  Prof. dr. E. Dekker  Prof. dr. M.A. Cuesta

Faculteit der Geneeskunde
<table>
<thead>
<tr>
<th>TABLE OF CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>General introduction and outline of the thesis</td>
</tr>
</tbody>
</table>

**PART 1  TREATMENT**

**Chapter 1**  Overtreatment of sigmoid diverticulitis: plea for a less aggressive approach.  
*Dig Dis 2012;30(1):86-91*  
Page 21

**Chapter 2**  A multicenter randomized clinical trial investigating the cost-effectiveness of treatment strategies with or without antibiotics for uncomplicated acute diverticulitis (DIABOLO trial).  
*BMC Surg 2010;10:23*  
Page 35

**Chapter 3**  Observational versus antibiotic treatment for a first episode of CT-proven uncomplicated acute diverticulitis.  
*Submitted*  
Page 55

**PART 2  FOLLOW-UP**

**Chapter 4**  Routine colonoscopy after left-sided acute uncomplicated diverticulitis: a systematic review.  
*Gastrointest Endosc 2014;79(3):378-89*  
Page 93

**Chapter 5**  Yield of colonoscopy after recent CT-proven uncomplicated acute diverticulitis: a comparative cohort study.  
*Surg Endosc 2014 [Epub ahead of print]*  
Page 119

**Chapter 6**  Systematic review of medical therapy to prevent recurrent diverticulitis.  
*Int J Colorectal Dis 2012;27(9):1131-6*  
Page 139

**PART 3  MICROBIOTA**

**Chapter 7**  A hypothesis: important role for gut microbiota in the etiopathogenesis of diverticular disease.  
*Dis Colon Rectum 2014;57(4):539-43*  
Page 155

**Chapter 8**  Fecal microbiome analysis as a diagnostic test for diverticulitis.  
*Eur J Clin Microbiol Infect Dis 2014;33(11):1927-36*  
Page 167

Summary and future perspectives  
Page 189

Nederlandse samenvatting  
Page 199

List of publications  
Page 209

PhD Portfolio  
Page 213

Dankwoord  
Page 219

Curriculum Vitae  
Page 225
General introduction & outline of the thesis
**GENERAL INTRODUCTION**

**Diverticular disease**
Colonic diverticular disease comprises a spectrum of conditions. Diverticulosis is defined as asymptomatic uninflamed colonic diverticula. These diverticula are pockets of mucosa, bounded by muscularis mucosae and covered with a thin layer of submucosa, that herniate through weak points in the muscle wall at the sites of penetration of the vasa recta. Uncomplicated diverticular disease signifies symptomatic disease associated with mild symptoms such as abdominal pain and/or change in bowel habit. Complicated diverticular disease is diverticulitis with more severe clinical symptoms and evidence of inflammation. Finally, abscess, perforation, peritonitis, fistula, bleeding, stricture, or obstruction accompanies complicated diverticulitis. Several grading systems exist for acute diverticulitis, of which the Ambrosetti and Modified Hinchey classification are most widely used.

**Epidemiology**
The prevalence of diverticulosis increases with age, ranging from approximately 10 percent in adults aged younger than 40 years to 50 to 70 percent among octogenarians and older people. Most people with diverticulosis remain asymptomatic. Older publications report that approximately 10 to 25 percent of patients with diverticulosis develop left-sided acute diverticulitis, but given the extremely high prevalence of diverticulosis these are unlikely figures. The majority of patients with diverticulitis has a mild acute course of disease. Diverticular disease has an increasing incidence and consequent rise in hospitalization rates and costs. In the Netherlands a 40 percent increase in admission rate for diverticular disease was noticeable in 2010 compared to 2008. It is one of five most costly gastrointestinal diseases in the United States. Thus, diverticular disease imposes a high socioeconomic burden on Western countries.

**Pathogenesis**
To date, the cause of diverticulosis and the pathogenesis of diverticulitis have not been conclusively established. Since Painter and Burkitt, over 40 years ago, put forth their hypothesis that a “low-residual diet”, high in refined carbohydrates and low in fiber, and increased colonic intraluminal pressure were responsible for the development of colonic diverticula, conflicting data on the role of fiber in the development of diverticular disease have emerged. Nevertheless, based on this long-held fiber hypothesis patients with diverticular disease are still recommended to increase their dietary fiber intake. Most likely, dietary factors, structural changes to the colonic wall, functional changes but also genetic changes and aging all play roles that are related to each other. Similarly for diverticulosis as for the development of diverticulitis old dogmatic theories, which state that fecalith obstruction of a diverticulum causes bacterial overgrowth, diverticular inflammation and focal necrosis resulting in a microscopic or macroscopic perforation of a diverticulum, are losing ground. It has been suggested that this condition should be regarded as a form of
inflammatory bowel disorder (IBD) based on common histologic findings. The chronic component in some patients with symptomatic diverticular disease indeed resembles periods of exacerbation and remission in IBD. So existing pathophysiologic concepts are being challenged and new research implicates a role for low-grade inflammation and alterations of gut microbiota in the development of diverticular disease.

**Microbiota**
Nucleic acid sequencing methods have provided a major advance in culture-independent analysis of the gut microbiota. It is known that the human endogenous microbiota play a fundamental role in health and disease. The microbial layer in the gut mucosa contributes to the gut barrier function. It provides resistance to pathogens, thereby controlling homeostasis of the immune system. Disease specific variations in the composition of the colonic microbiota have been identified, for example in IBD. Diverticular disease patients have also been hypothesized to harbor a change in gut microbiota that promotes disease and inflammation, either due to altering the immune process or by permitting an abnormal response to potentially harmful bacteria. However until now, no studies analyzing the entire gut profile of diverticulosis or diverticulitis patients have been performed.

**Treatment**
Controversy exists about the appropriate management of the various stages of diverticular disease. The last decade the management of diverticulitis is evolving. Surgical interventions for acute diverticulitis are becoming less invasive. Further, indications for recurrent diverticulitis are becoming limited. This has not led to an increased incidence of complicated disease though. For uncomplicated diverticulitis a shift away from aggressive treatment with admission and antibiotics towards a more liberal approach can be noticed. The natural history of acute diverticulitis is mild in the vast majority of patients, and most patients are treated successfully by conservative measures. Whether or not antibiotics are used varies between countries and disciplines. It is uncertain however, whether antibiotics are necessary in the treatment of a first episode of uncomplicated acute diverticulitis. At the start of the research described in this thesis two non-randomized studies comparing observational and antibiotic treatment in patients with uncomplicated acute diverticulitis were published; results suggest that antibiotic treatment is not more successful. Internationally antibiotics are recommended for uncomplicated diverticulitis. Omitting antibiotics could be a more cost-effective treatment and at the same time in line with the World Health Organization’s strategy to combat escalating antimicrobial resistance by reducing antibiotic overuse. Randomized controlled trials this area are required if management is to be evidence-based.
General introduction

Follow-up colonoscopy
Currently, most international and clinical practice guidelines recommend routine follow-up colonoscopy after non-operatively treated acute diverticulitis. The rationale is to confirm the diagnosis and exclude underlying malignancy or advanced colonic neoplasia. This recommendation dates back to the time the diagnosis was primarily based on clinical examination and laboratory results with frequent use of barium enema. In today’s clinical practice however, abdominal computed tomography (CT) is widely used for diagnosing diverticulitis. Because CT has a high sensitivity and specificity and a low inter observer variability for the diagnosis diverticulitis, the need for follow-up colonoscopy may therefore be questioned. The latest Dutch diverticulitis guideline advises not to routinely perform endoscopy after an episode of diverticulitis, but stands alone among the guidelines of other countries. The results of several studies on the yield of colonoscopy after an episode of acute diverticulitis as well as a recent systematic review, although including studies of moderate methodological quality, cast doubt on current international practice. Since colonoscopy is accompanied by disadvantages as invasiveness, risk of perforation and additional costs, it is important to know whether there is a justified indication for colonoscopy after a confident diagnosis of acute diverticulitis.

Prevention of recurrent diverticulitis
After an episode of diverticulitis patients are at risk for developing recurrent disease. Traditionally, elective resection was advised after two documented episodes of uncomplicated diverticulitis requiring hospitalization and/or after one episode of complicated diverticulitis. The rationale was a high recurrence rate of up to 60 percent as reported in old studies. Simultaneously it was thought that patients with a recurrence had higher complication and mortality rates and were less likely to respond to medical treatment. In recent literature however, the reported recurrence rates are much lower, a consequence of wider use of imaging modalities to confirm the diagnosis. The recurrence rate of conservatively treated patients is approximately 25 percent. Furthermore, recent studies have demonstrated that most patients with complicated diverticulitis are facing their first attack and a small minority develops complicated diverticulitis during subsequent attacks. Consequently, recurrent diverticulitis is at present not necessarily an indication for elective resection, all the more so since the operation itself carries a risk of morbidity, colostomy, mortality and the risk for recurrence is not eliminated. Hence, a conservative approach is advised after an episode of diverticulitis, to improve symptoms and prevent recurrences. Several therapies have been proposed, such as high-fiber diet, antibiotics, 5-aminosalicylic acid and probiotics. It is unclear however whether these therapies prevent recurrent diverticulitis.
Aim of the thesis

In summary, there are several controversies in the approach to patients with acute diverticulitis. First, the pathogenesis of diverticular disease remains poorly understood, and new research drives theories away from the traditional dogmas towards views with a proposed role for low-grade inflammation and alterations of gut microbiota. Second, the appropriate management of the various stages of the disease and its complications is still under debate, though a shift away from invasive treatment towards a less aggressive approach is noticeable. Although most current international guidelines advise the use of antibiotics it is uncertain whether antibiotics are necessary in the treatment of uncomplicated acute diverticulitis. The lack of evidence mandates a scientific judgment. At the core of this thesis therefore is the DIABOLO trial, a randomized multicenter trial our research group initiated to investigate the effect of antibiotics on disease course in patients with uncomplicated acute diverticulitis. Furthermore, the use of routine colonoscopy after an episode of acute diverticulitis remains controversial because of conflicting study results. Lastly, the value of conservative treatment after an episode of diverticulitis to prevent recurrent diverticulitis remains unclear. In this thesis we present several reviews, the DIABOLO trial study protocol and clinical results, a hypothesis and retrospective and prospective studies ancillary to the DIABOLO trial. The aim of this thesis is to add clarity to the existing controversies in the management and follow-up of patients with acute diverticulitis, and to provide new insight on the pathogenesis of this disease.
OUTLINE OF THE THESIS

This thesis addresses several aspects of the treatment, follow-up and microbiota in acute diverticulitis. We divided this thesis in three parts.

The first part of this thesis focuses on the treatment of diverticulitis. In Chapter 1 we present a narrative review that describes the emergence of a less aggressive approach to the management of colonic diverticulitis in the last decade. The understanding we might have overtreated the majority of diverticulitis patients for decades has led to various randomized clinical trials regarding the optimal management of patients with different stages of diverticulitis, amongst which the DIABOLO trial. In Chapter 2 the study protocol and rationale of the DIABOLO trial are described. This study was designed to evaluate the cost-effectiveness of treatment strategies with or without antibiotics for uncomplicated acute diverticulitis. The clinical results of this randomized clinical trial are reported in Chapter 3.

The second part of this thesis evaluates the follow-up after uncomplicated diverticulitis. To assess the need for routine follow-up colonoscopy we first present a systematic review in Chapter 4, reporting the outcomes of colonoscopy after left-sided acute uncomplicated diverticulitis. Second, in Chapter 5, we describe the results of the first cohort study that directly compared the diagnostic yield for advanced colonic neoplasia of follow-up colonoscopy after CT-proven uncomplicated acute diverticulitis with the yield of screening colonoscopy in an asymptomatic screening population. To evaluate whether medical or dietary therapies can prevent recurrent diverticulitis, in Chapter 6 we critically review the worldwide literature available on conservative measures after a primary episode of acute diverticulitis.

The third part of this thesis concentrates on the role of microbiota in diverticulitis. In Chapter 7, we propose a new hypothesis for the etiopathogenesis of diverticular disease and diverticulitis in particular, in which we aim to integrate known factors and the new player in the field, gut microbiota, in a multifactorial theory. This hypothesis has led to the study described in Chapter 8, in which we characterized the gut microbiome in diverticulitis by comparing the fecal microbiota composition of diverticulitis patients with the composition of control subjects.
REFERENCES


General introduction and outline of the thesis


General introduction and outline of the thesis


General introduction and outline of the thesis


PART 1

TREATMENT
Chapter 1

Overtreatment of sigmoid diverticulitis: 
Plea for a less aggressive approach

Daniels L
de Korte N
Winter D
Boermeester MA
Stockmann HB

Dig Dis 2012;30(1):86-91
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 nonperforated 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 is congruent with an increasing understanding that diverticulitis comprises different disease entities with heterogeneity between patients. The disease should be targeted by specific approaches, 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 have overtreated the majority of diverticulitis patients for decades. More research is needed to explain the pathogenesis and multifactorial etiology and in the near 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. At 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, which was adopted by Boyden in 1950 for patients with acute diverticulitis. In the 1970s, the Hartmann 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. 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 as well as intensive care management and anesthesia.

Since then, standard of care for perforated or complicated diverticulitis evolved from a Hartmann’s procedure, to resection and primary anastomosis and 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 nonperforated 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 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 nonoperative 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. 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 fiber), colonic pressure, motility changes and colonic structural alterations may collectively contribute to diverticula formation, 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 the literature is ambiguous on this matter.
increasing mitochondrial dysfunction plays a role in the pathogenesis of diverticular disease. Knowledge on the pathogenesis of diverticular inflammation is also scarce and uncertain. Hinchey et al. postulated in their original classification that all forms of diverticulitis are the result of a (micro)perforation due to an inspissated fecalith. This hypothesis, however, remains unproven. Changes in intestinal microbiota composition, colonization or entrapment of pathogenic bacteria within diverticula through impacted feces and stimulation of mucosal immune responses have recently been postulated as mechanisms in the pathogenesis of symptoms and complications. Recent studies suggest that it may be a form of inflammatory bowel disease (IBD).

**Development in Management**

**Uncomplicated Disease**

Mild diverticulitis may in a majority of cases be a self-limiting process 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, studies that compared two different kinds of antibiotics and antibiotics with and without anaerobe coverage and two recent retrospective case-controlled studies that compared treatment with and without antibiotics, 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, 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.

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. Several international organizations actively address this global threat to our ability to cope with infections and the World Health Organization (WHO) selected combating antimicrobial resistance as the theme for World Health Day 2011. The WHO issued an international call for concerted action to halt the spread of antimicrobial resistance and recommended a six-point policy package for governments.

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. 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.\textsuperscript{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 a significantly higher risk for treatment failure.\textsuperscript{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.\textsuperscript{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.\textsuperscript{40} Laparoscopic resection for both symptomatic and perforated diverticulitis have been shown to be as safe and effective as conventional open techniques\textsuperscript{41, 42} and the results of a cost effectiveness analysis of a laparoscopic approach compared with open sigmoid resection were similar.\textsuperscript{43, 44}

Regardless of selected strategy, emergency operations for acute perforated diverticulitis are associated with substantial morbidity and mortality.\textsuperscript{45} Recently, laparoscopic lavage emerged as an alternative for patients with perforated diverticulitis with purulent peritonitis.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 purulent or fecal peritonitis.\textsuperscript{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\textsuperscript{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%.\textsuperscript{51, 52} During the first episode the risk of free perforation is 25.3%, during the second 12.7%
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. 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.

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, that 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.

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 an RCT comparing these two treatment strategies is being conducted and the results are still awaited.

Prevention

Conservative treatment has become the primary choice in the prevention of a recurrent episode of diverticulitis. This approach mainly comprises dietary advice and medical therapies. A high-fiber diet is still recommended in several guidelines despite the fact that high quality evidence for a high-fiber diet in the treatment of diverticular disease is lacking, and most recommendations are based on inconsistent level 2 and mostly level 3 evidence. 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. Smoking also increases the likelihood of complications in diverticulitis. Lifestyle modification should perhaps have a larger role in the (preventive) management of diverticular disease and its complications.

Besides being given 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 nonabsorbable antibiotic rifaximin to prevent recurrence after complicated diverticulitis was studied, showed a significant lower readmission and operation rate in the antibiotic group. In the 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.\textsuperscript{59-62} 5-ASAs are widely and effectively used for the treatment of 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.\textsuperscript{63}

\textbf{Classification}

Since Hinchey’s traditional classification for perforated diverticulitis in 1978\textsuperscript{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.\textsuperscript{64} A new universally used classification system would greatly enhance the comparability of outcome in future research.

\textbf{What’s Next?}

Despite the fact that there is still controversy about the appropriate management of the various stages of the disease and its complications, one cannot help but notice a shift away from invasive, operative treatment for both uncomplicated and complicated diverticulitis towards a less aggressive, nonoperative approach. Moreover, this has not led to an increased incidence of complicated disease.\textsuperscript{65}

In conclusion, one might say that we have 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 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 and computed tomography in diagnosing acute colonic diverticulitis. Both can be used as the initial diagnostic tool; however, computed tomography is more likely to identify alternative diseases.\textsuperscript{66} In the future, there is the possibility for 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 etiology 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
REFERENCES


Chapter 2

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

Unlü Ç
de Korte N
Daniels L
Consten EC
Cuesta MA
Gerhards MF
van Geloven AA
van der Zaag ES
van der Hoeven JA
Klicks R
Cense HA
Roumen RM
Eijsbouts QA
Lange JF
Fockens P
de Borgie CA
Bemelman WA
Reitsma JB
Stockmann HB
Vrouenraets BC
Boermeester MA

For the Dutch Diverticular Disease 3D Collaborative Study Group

BMC Surg 2010;10:23
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.
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 visualizing 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{10} Stage II usually requires percutaneous drainage, while stages III and IV diverticulitis usually request surgery.

<table>
<thead>
<tr>
<th>Hinchey classification and modified Hinchey classification of acute diverticulitis\textsuperscript{10,12}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hinchey</strong></td>
</tr>
<tr>
<td>I. Pericolic abscess or phlegmon</td>
</tr>
<tr>
<td>I. Pelvic, intraabdominal, or retroperitoneal abscess</td>
</tr>
<tr>
<td>III. Generalized purulent peritonitis</td>
</tr>
<tr>
<td>IV. Generalized fecal peritonitis</td>
</tr>
</tbody>
</table>

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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{16} Therefore, broad-spectrum antibiotics are advised. Which antibiotic regimen should be used in diverticulitis is unclear.\textsuperscript{17,18} There is scarce evidence that oral antibiotics are as effective as intravenous antibiotics.\textsuperscript{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\textsuperscript{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 Dutch survey showed that many gastro-enterologists prescribed antibiotics in the treatment of acute diverticulitis, but only a minority of Dutch surgeons did so. 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.

Six professional organizations have issued formal guidelines concerning the use of antibiotics in uncomplicated diverticulitis. Five of these guidelines advice the use of antibiotics. (Table 2) 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.

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.

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.
<table>
<thead>
<tr>
<th>Organization</th>
<th>Year</th>
<th>Antibiotics Recommended</th>
<th>Original research cited</th>
<th>Which antibiotics</th>
<th>Original research cited</th>
<th>Route of administering</th>
<th>Original research cited</th>
</tr>
</thead>
<tbody>
<tr>
<td>American College of Gastroenterology(^{20})</td>
<td>1999</td>
<td>Yes</td>
<td>None</td>
<td>Covering both Gram negative and anaerobes</td>
<td>Kellum(^{15})</td>
<td>Oral or intravenous, depending on clinical status</td>
<td>None</td>
</tr>
<tr>
<td>European Association for Endoscopic Surgery(^{20})</td>
<td>1999</td>
<td>Yes</td>
<td>None</td>
<td>Ciprofloxacin and Metronidazol</td>
<td>None</td>
<td>Oral or intravenous, depending on clinical status</td>
<td>None</td>
</tr>
<tr>
<td>American Society of Colon and Rectal Surgeons(^{20})</td>
<td>2006</td>
<td>Yes</td>
<td>None</td>
<td>Covering both Gram negative and anaerobes</td>
<td>Kellum(^{15})</td>
<td>Oral or intravenous, depending on clinical status</td>
<td>None</td>
</tr>
<tr>
<td>Society of Surgery of the Alimentary Tract(^{20})</td>
<td>2007</td>
<td>Yes</td>
<td>None</td>
<td>Broad spectrum antibiotics</td>
<td>None</td>
<td>Oral or intravenous, depending on clinical status</td>
<td>None</td>
</tr>
<tr>
<td>World Gastroenterology Organization(^{17})</td>
<td>2007</td>
<td>Yes</td>
<td>None</td>
<td>Covering both Gram negative and anaerobes</td>
<td>None</td>
<td>Oral or intravenous, depending on clinical status</td>
<td>None</td>
</tr>
<tr>
<td>SWAB(^{20})</td>
<td>2009</td>
<td>No, not primarily</td>
<td>None</td>
<td>Broad spectrum antibiotics</td>
<td>None</td>
<td>Oral or intravenous, depending on clinical status</td>
<td>None</td>
</tr>
</tbody>
</table>
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.

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.\(^{10-12}\)
4. Informed consent.

Exclusion criteria are summarized in Table 3.
Part 1 | Treatment

Clinical suspicion of diverticulitis

For diagnosis and inclusion:
- acute US or CT

For staging:
- CT within 24 hours

Hinchey 1a or 1b
(uncomplicated diverticulitis)

Inclusion DIABOLO trial

Conservative strategy
WITH antibiotics

Liberal strategy
WITHOUT antibiotics

Figure 1 | Study flow chart

Table 3 | Exclusion 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. Other 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; (i.e., haematological malignancies, AIDS patients with low CD4+ counts, transplantation, chemotherapy, splenectomy, long-term corticosteroid use and 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
Study outline

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.

Table 4 | Treatment strategies

<table>
<thead>
<tr>
<th>Conservative strategy with antibiotics</th>
<th>Liberal strategy without antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital admission</td>
<td>Admission only if discharge criteria are not met</td>
</tr>
<tr>
<td>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</td>
<td>No initial antibiotics</td>
</tr>
<tr>
<td>Adequate pain relief (VAS &lt; 4)</td>
<td>Adequate pain relief (VAS &lt; 4)</td>
</tr>
<tr>
<td>Oral intake as tolerated</td>
<td>Oral intake as tolerated</td>
</tr>
<tr>
<td>Daily monitoring</td>
<td>Daily monitoring when admitted to the hospital</td>
</tr>
<tr>
<td>Self monitoring at home after discharge</td>
<td>Self monitoring at home</td>
</tr>
<tr>
<td>Out patient follow-up at regular intervals</td>
<td>Out patient follow-up at regular intervals</td>
</tr>
</tbody>
</table>

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 bacteremia (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 × 10⁹ or > 12 × 10⁹ cells/L. 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 Analogue 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 and the American Society of Colon and Rectal Surgeons 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 ciprofloxacin and metronidazole; ciprofloxacin 2 times a day 400 mg i.v. and metronidazole 3 times daily 500 mg, with oral doses of ciprofloxacin being 500 mg 2 times a day and of metronidazole 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 form (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 data 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 (nonantibiotic) 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. Records of 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%.\(^3\) 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.\(^3\) 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%.\(^4\)

Over the last decade there have been efforts made to minimize the prescription of antibiotics in various fields in clinical medicine. Patients with appendicular 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 pediatric medicine.\(^5\) 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.\(^6,^7\) 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.\(^8\) Alternatively, there is no evidence or guideline dictating that support anti-anaerobic prophylaxis for hospitalized patients in general. Prophylactic metronidazole 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 mesalazine 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 month of symptoms had been included. These trials have excluded diverticulitis patients.\(^9,^10\) Some studies have assessed meselazine in the prevention of recurrent diverticulitis but never as the actual treatment of acute diverticulitis itself.\(^11,^12\) 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. 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. 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. 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. 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.

Acknowledgements

The Netherlands Organization for Health Research and Development, Health Care Efficiency Research program, (ZonMw grant: 80-82310-97-10039) and the Dutch Digestive Diseases Foundation (MLDS grant: WO 08-54) funded the DIABOLO trial.
REFERENCES


27. World Gastroenterology Organisation. Available at: [http://www.worldgastroenterology.org].


Chapter 3

Observational versus antibiotic treatment for a first episode of CT-proven uncomplicated acute diverticulitis -
A Randomized, Controlled trial

Daniels L
Ünlü Ç
de Korte N
van Dieren S
Stockmann HB
Vrouwenraets BC
Consten EC
van der Hoeven JA
Eijsbouts QA
Faneyte IF
Bemelman WA
Dijkgraaf MG
Boermeester MA

For the Dutch Diverticular Disease (3D) Collaborative Study Group

BMC Surg 2010;10:23
ABSTRACT

Background
It is uncertain whether antibiotics are necessary in the treatment of uncomplicated acute diverticulitis. To date, use of antibiotics is advised in most guidelines. Importantly, use of antibiotics can lead to adverse effects and overuse results in escalating antimicrobial resistance. Objectives: The DIABOLO (DIVerticulitis: AntiBiotics Or cLOSE Observation) trial compared the effectiveness of two strategies with or without antibiotics for the management of a first episode of uncomplicated acute diverticulitis.

Methods
Design: Randomized, open-label, non-inferiority trial. Setting: 22 clinical sites, randomization between June 1, 2010 and October 14, 2012. Patients: 528 patients with CT-proven, primary, left-sided, uncomplicated, acute diverticulitis. Intervention: Random assignment to an observational (262 patients) or antibiotic (266 patients) treatment strategy. Measurements: The primary endpoint was time-to-recovery at 6 months. Main secondary endpoints were readmission rate, complicated, ongoing and recurrent diverticulitis, sigmoid resection and mortality. An intention-to-treat analysis was done.

Results
Median time-to-recovery was comparable among observational and antibiotic treatment strategies (14 days [IQR 6 to 35] vs 12 days [IQR 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% CI, 1.059; \( P = 0.151 \)). We found no significant between-group differences for the main secondary endpoints. Hospital stay was significantly shorter in the observational strategy without antibiotics (\( P < 0.01 \)).

Conclusion
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.
INTRODUCTION

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 and most patients are treated successfully by conservative measures.\(^6,7-9\) 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 with or without antibiotics for the management of a first episode of uncomplicated acute diverticulitis.

METHODS

Design Overview

The ‘Diverticulitis: AntiBiotics Or cLose Observation?’ (DIABOLO) trial was a multicenter (22 clinical sites), open label, pragmatic, randomized, controlled trial of two strategies in patients with uncomplicated acute diverticulitis.\(^21\) We chose not to perform a double-blind placebo controlled trial since the effect of antibiotics would then be investigated in a more experimental setting were all patients have to be admitted, whereas a pragmatic trial is more applicable to daily practice. The study design reflects current clinical practice in which the two studied approaches co-exist as standards of care.
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. 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.

Setting and Participants
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. 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 as defined by the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM)), and antibiotic use in the four weeks prior to inclusion. A complete overview is provided in Appendix Table 1. All participants provided written informed consent before enrollment.

Randomization and Interventions
We randomly 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. The trial was open label, but outcome assessors and investigators analyzing data were masked to treatment allocation until analyses were finished and definite.

Based on the practice guidelines of the Dutch Antibiotic Policy Committee and the American Society of Colon and Rectal Surgeons amoxicillin-clavulanic acid was chosen as broad-spectrum antibiotic for the treatment of patients allocated to the antibiotic treatment strategy. The antibiotic regimen consisted of a 10-day course, with i.v. administration of 1200 mg 4 times daily for at least 48 hours, after which the route could be switched to oral administration of 625 mg 3 times daily if tolerated. In case of allergy, a switch was made to the combination of ciprofloxacin and metronidazole.

In the antibiotic treatment strategy, the use of antibiotics led to admittance of all patients due to the premise that antibiotic treatment was started intravenously (i.v.). Hospital admission in the observational treatment strategy was needed only for patients with nausea and vomiting requiring intravenous fluids, for patients with excessive pain not properly reacting to oral pain medication, or when CT confirmation of diagnosis could
not be completed in the emergency department. Patients allocated to the observational strategy could be treated directly in an outpatient setting when the following discharge criteria were met: tolerating a normal diet (defined as solid food and more than 1L of fluid orally), temperature < 38.0°C, VAS (Visual Analogue Score) pain score < 4 (with paracetamol at the most), self-support as compared to the pre-illness level, and acceptance by the patient.

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 dictated start of antibiotic treatment. Criteria to start antibiotics were: temperature > 39°C, positive blood cultures and clinical suspicion of bacteremia (i.e., sepsis as defined by the ACCP/SCCM). Patients were discharged if they fulfilled aforementioned discharge criteria.

Outcomes and Follow-up
The primary outcome was time-to-recovery during 6 months of follow-up. Full recovery was defined by meeting the following criteria: discharge from 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 Analysis
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 extracted from the National Dutch Hospital Registry data and an assumed additional 14-day outpatient
Part 1 | Treatment

period to full recovery. Because the drop-out rate was higher than the initially anticipated 1%, due to 39 wrongful inclusions (Appendix Table 2), 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 (Appendix Table 3).

We performed all analyses following the intention-to-treat principle. Continuous variables are expressed as medians and presented with interquartile ranges (IQR) 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 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. 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).

Role of the Funding Source
The Netherlands Organisation for Health Research and Development (ZonMw) and Digestive Diseases Foundation (Maag Lever Darm Stichting, MLDS) provided financial support to the trial, but had no involvement in trial design, conduct or reporting.
Chapter 3 | Antibiotic treatment or not for uncomplicated diverticulitis

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). Patients who underwent randomization had clinical characteristics mostly similar to those who were eligible but not randomized because they declined participation (Appendix Table 4). The reasons for non-enrollment, wrongful inclusion and the number of included patients per hospital are provided in Appendix Tables 5, 2 and 6, respectively.

Baseline Characteristics
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]) (Appendix Table 7). The median duration was 10.0 days (IQR, 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 (Appendix Table 8), of which another focus of infection was the most common reason (N=4).

Time-to-Recovery
The median time-to-recovery during 6 months follow-up was not significantly different between the two treatment groups; 14.0 days (IQR, 6.0 to 35.0) for patients with observational treatment versus 12.0 days (IQR, 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 (HR) was not affected by adjustment for Hinchey classification and center (HR, 0.895 [upper limit one-sided 95% CI, 1.044]).
Assessed for eligibility (n=893)

Excluded (n=323)
- Did not meet criteria* (n=174)
- Declined to participate (n=149)

Randomized (n=570)

Allocated to OBSERVATION (n=283)
- Received allocated intervention (n=249)
- Did not receive allocated intervention (n=13)
- Unknown whether or not received allocated intervention (exclusion/withdrawal) (n=21)

Excluded (n=20)
- Wrongfully included

Allocated to ANTIBIOTICS (n=287)
- Received allocated intervention (n=251)
- Did not receive allocated intervention (n=16)
- Unknown whether or not received allocated intervention (exclusion/withdrawal) (n=21)

Excluded (n=19)
- Wrongfully included

Lost to follow-up (n=6)
- Discontinued participation (n=2)
- Withdrew informed consent (n=1)
- Patient’s wish to end study (n=3)

Analysed (n=262)
- Death (n=3)
- Excluded from analyses (n=1)

Lost to follow-up (n=10)
- Discontinued participation (n=3)
- Withdrew informed consent (n=2)
- Patient’s wish to end study (n=5)

Analysed (n=266)
- Death (n=1)
- Excluded from analyses (n=2)
- Withdrew informed consent

Figure 1 | CONSORT flow diagram for trial patient progress

* Patients could have more than one reason for ineligibility for the study
### Table 1: Baseline characteristics of the patients according to study group

<table>
<thead>
<tr>
<th></th>
<th>Observation (N=262)</th>
<th>Antibiotics (N=266)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age — yr</strong></td>
<td>57.4 (48.5-64.6)</td>
<td>56.3 (48.5-63.8)</td>
</tr>
<tr>
<td><strong>Male sex — no (%)</strong></td>
<td>135 (51.5%)</td>
<td>132 (49.6%)</td>
</tr>
<tr>
<td><strong>Known antibiotic allergy — no (%)</strong></td>
<td>36 (13.7%)</td>
<td>52 (19.5%)</td>
</tr>
<tr>
<td>Penicillin allergy — no (%)</td>
<td>5 (1.9%)</td>
<td>14 (5.3%)</td>
</tr>
<tr>
<td><strong>Co-morbidity † — no (%)</strong></td>
<td>113 (43.1%)</td>
<td>121 (45.5%)</td>
</tr>
<tr>
<td><strong>ASA score ‡ — no (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA 1</td>
<td>174 (66.4%)</td>
<td>156 (58.6%)</td>
</tr>
<tr>
<td>ASA 2</td>
<td>81 (30.9%)</td>
<td>96 (36.1%)</td>
</tr>
<tr>
<td>ASA 3</td>
<td>7 (2.7%)</td>
<td>14 (5.3%)</td>
</tr>
<tr>
<td><strong>Body mass index – kg/m²</strong></td>
<td>26.4 (24.3-29.0)</td>
<td>27.2 (24.5-30.1)</td>
</tr>
<tr>
<td></td>
<td>(20 vs 16 missings)</td>
<td></td>
</tr>
<tr>
<td><strong>Duration of GI complaints – days</strong></td>
<td>2 (1-4)</td>
<td>3 (1-5)</td>
</tr>
<tr>
<td><strong>Body temperature – °C</strong></td>
<td>37.3 (36.9-38.0)</td>
<td>37.3 (36.9-38.0)</td>
</tr>
<tr>
<td><strong>Abdominal pain – VAS score §</strong></td>
<td>6 (4-8)</td>
<td>6 (5-8)</td>
</tr>
<tr>
<td></td>
<td>(39 vs 47 missings)</td>
<td></td>
</tr>
<tr>
<td><strong>Localization abdominal pain – no (%)</strong></td>
<td>119 (45.4%)</td>
<td>125 (47.0%)</td>
</tr>
<tr>
<td>Left lower quadrant isolated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting – no (%)</td>
<td>20 (7.6%)</td>
<td>27 (10.2%)</td>
</tr>
<tr>
<td><strong>White blood cell count – ×10⁹ cells/L</strong></td>
<td>12.5 (10.2-14.8)</td>
<td>12.0 (10.0-14.2)</td>
</tr>
<tr>
<td><strong>C-reactive protein (CRP) – mg/L</strong></td>
<td>73.0 (44.5-125.5)</td>
<td>82.7 (42.0-128.3)</td>
</tr>
<tr>
<td>CRP &gt; 50 mg/L – no (%)</td>
<td>188 (72.0%)</td>
<td>191 (71.8%)</td>
</tr>
<tr>
<td></td>
<td>(1 missing in observation group)</td>
<td></td>
</tr>
<tr>
<td><strong>Imaging diagnosis – no (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultrasonography (US)</td>
<td>171 (65.3%)</td>
<td>176 (66.2%)</td>
</tr>
<tr>
<td>Computed Tomography (CT)</td>
<td>258 (98.5%)</td>
<td>259 (97.4%)</td>
</tr>
<tr>
<td><strong>Hinchey category 1a ¶</strong></td>
<td>236 (90.1%)</td>
<td>250 (94.0%)</td>
</tr>
</tbody>
</table>

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 periocolic inflammation, category 1b=Confined small periocolic abscess (≤ 5cm).
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 group more patients were treated as outpatients after their evaluation at the emergency department (13.0% 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; \( P = 0.006 \)).

![Figure 2: Time-to-recovery in patients with uncomplicated acute diverticulitis](image)

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.
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 (Appendix Table 9).

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%; \( P = 0.057 \); Appendix Table 10).

**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 and Per-Protocol Analyses**

With respect to the primary outcome time-to-recovery no significant results were seen within subgroups of center and Hinchey classification (Appendix Figure 1 and 2). In the Hinchey 1a subgroup (N=486), secondary outcomes were in line with main analyses (Appendix Table 11). Results of per-protocol analyses were in accordance with the results of the intention-to-treat analyses (Appendix Tables 12-14 and Appendix Figure 3).
Table 2 | Secondary outcomes among patients with uncomplicated acute diverticulitis assigned to an observational or antibiotic treatment strategy*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Observation (N=262)</th>
<th>Antibiotics (N=266)</th>
<th>Unadjusted P-value</th>
<th>Adjusted P-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outpatient treatment – no (%)</strong></td>
<td>34 (13.0%)</td>
<td>1 (0.4%)</td>
<td>&lt;0.001</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Duration initial admission – days</strong></td>
<td>2 (1-3)</td>
<td>3 (2-3)</td>
<td>&lt;0.001</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Recovery ≤ 6 months FU – no (%)</strong></td>
<td>234 (89.3%)</td>
<td>248 (93.2%)</td>
<td>0.055</td>
<td>0.183</td>
</tr>
<tr>
<td><strong>Readmission (≥1) ≤ 6 months FU – no (%)</strong></td>
<td></td>
<td></td>
<td>0.037</td>
<td>0.148</td>
</tr>
<tr>
<td>Total number</td>
<td>46 (17.6%)</td>
<td>32 (12.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Days outside hospital ≤ 6 months FU – proportion of FU duration ‡</strong></td>
<td>0.989 (0.978-0.994)</td>
<td>0.963 (0.978-0.989)</td>
<td>&lt;0.001</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Complicated diverticulitis (≥1) ≤ 6 months FU – no (%)</strong></td>
<td>10 (3.8%)</td>
<td>7 (2.6%)</td>
<td>0.220</td>
<td>0.377</td>
</tr>
<tr>
<td><strong>Type § – no (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abscess (&gt; 5cm)</td>
<td>2 (0.8%)</td>
<td>2 (0.8%)</td>
<td>0.682</td>
<td>0.682</td>
</tr>
<tr>
<td>Perforation</td>
<td>3 (1.1%)</td>
<td>3 (1.1%)</td>
<td>0.650</td>
<td>0.678</td>
</tr>
<tr>
<td>Obstruction</td>
<td>4 (1.5%)</td>
<td>2 (0.8%)</td>
<td>0.336</td>
<td>0.448</td>
</tr>
<tr>
<td>Fistula</td>
<td>1 (0.4%)</td>
<td>0 (0.0%)</td>
<td>0.496</td>
<td>0.553</td>
</tr>
<tr>
<td>Bleeding</td>
<td>2 (0.8%)</td>
<td>0 (0.0%)</td>
<td>0.246</td>
<td>0.390</td>
</tr>
<tr>
<td><strong>At index admission – no (%)</strong></td>
<td>3 (1.1%)</td>
<td>6 (2.3%)</td>
<td>0.260</td>
<td>0.390</td>
</tr>
<tr>
<td><strong>Intervention § – no (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percutaneous</td>
<td>2 (0.8%)</td>
<td>1 (0.4%)</td>
<td>0.494</td>
<td>0.553</td>
</tr>
<tr>
<td>Surgery</td>
<td>8 (3.1%)</td>
<td>5 (1.9%)</td>
<td>0.192</td>
<td>0.354</td>
</tr>
<tr>
<td><strong>Ongoing diverticulitis (≥1) ≤ 6 months FU – no (%)</strong></td>
<td>19 (7.3%)</td>
<td>11 (4.1%)</td>
<td>0.061</td>
<td>0.183</td>
</tr>
<tr>
<td>Imaging proven</td>
<td>10</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Needing admission</td>
<td>15</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Recurrent diverticulitis (≥1) ≤ 6 months FU – no (%)</strong></td>
<td>9 (3.4%)</td>
<td>8 (3.0%)</td>
<td>0.391</td>
<td>0.494</td>
</tr>
<tr>
<td>Imaging proven</td>
<td>7</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Needing admission</td>
<td>4</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sigmoid resection ≤ 6 months FU – no (%)</strong></td>
<td>10 (3.8%)</td>
<td>6 (2.3%)</td>
<td>0.148</td>
<td>0.323</td>
</tr>
<tr>
<td>Emergency</td>
<td>2 (0.8%)</td>
<td>3 (1.1%)</td>
<td>0.507</td>
<td>0.553</td>
</tr>
<tr>
<td>Elective</td>
<td>8 (3.1%)</td>
<td>3 (1.1%)</td>
<td>0.106</td>
<td>0.254</td>
</tr>
<tr>
<td><strong>Morbidity § ¶ – no (%)</strong></td>
<td>127 (48.5%)</td>
<td>145 (54.5%)</td>
<td>0.083</td>
<td>0.221</td>
</tr>
<tr>
<td>Mild</td>
<td>89 (34.0%)</td>
<td>114 (42.9%)</td>
<td>0.018</td>
<td>0.086</td>
</tr>
<tr>
<td>Serious</td>
<td>69 (26.3%)</td>
<td>61 (22.9%)</td>
<td>0.182</td>
<td>0.354</td>
</tr>
<tr>
<td><strong>A3 related morbidity</strong></td>
<td>1 (0.4%)</td>
<td>22 (8.3%)</td>
<td>&lt;0.001</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Mortality ¶ – no (%)</strong></td>
<td>3 (1.1%)</td>
<td>1 (0.4%)</td>
<td>0.306</td>
<td>0.432</td>
</tr>
</tbody>
</table>
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 and one randomized clinical trial indicating antibiotics have no benefit. The one previous randomized clinical trial has evaluated 623 patients with mild diverticulitis, but some drawbacks of its methodological design may have caused a lack in change of clinical practice. The problems comprise 40% of patients with a recurrent instead of primary diverticulitis, a long accrual period, and no standardized antibiotic treatment that may have resulted in performance bias. In the latest Practice Parameters of the American Society of Colon and Rectal Surgeons (ASCRS) the Swedish trial is discussed and deemed in need of confirmation.

This trial, as most trials, lacked power to detect smaller subgroup effects. Our results suggest that antibiotics may not be necessary in patients with Hinchey 1a as well as 1b diverticulitis, but the Hinchey 1b subgroup constituted only of 42 patients. The inclusion of Hinchey 1b patients may be considered controversial but small absceses are usually managed without percutaneous drainage. Apart from present study there are no reports on observational versus antibiotic management of (Hinchey 1b) small abscesses. This could be focus of future research.
Part 1 | Treatment

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, though patients with a previous US and/or CT proven episode of diverticulitis were excluded, patients with an undetected previous episode without visiting medical care or treated by general practitioners without a definitive diagnosis were not excluded by definition. Thirdly, although 8.3% of patients assigned to antibiotics treatment experienced related adverse events, in only three patients antibiotic treatment was discontinued. Finally, no *Clostridium difficile* super infection 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. 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. Hospital stay was significantly shorter in the observational strategy than in the antibiotic strategy. A treatment strategy without antibiotics for uncomplicated acute diverticulitis can now be adopted in clinical guidelines.

**Acknowledgements**

The Netherlands Organisation for Health Research and Development (ZonMw) and Digestive Diseases Foundation (Maag Lever Darm Stichting, MLDS) provided financial support to the trial. We thank the patients who participated in the study, the members of the data and safety monitoring board (Patrick Bossuyt, Prof., chair; Hein Gooszen, Prof.; and Jan van der Meer, M.D., Ph.D.) and the investigators, coordinators, clinicians and (research) nurses at the clinical sites.
REFERENCES


SUPPLEMENTARY APPENDIX

List of Collaborators - Dutch Diverticular Disease (3D) Collaborative Study Group

Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands: Boermeester MA, Daniels L, Ünlü Ç, Van Dieren S, Dijkgraaf MG, Bemelman WA, Glaap CEM and Croonen A

VU University Medical Center, Amsterdam, The Netherlands: Cuesta MA

Kennemer Gasthuis Hospital, Haarlem, The Netherlands: Stockmann HB, Kuijvenhoven JP, Buijsman R, Den Uil S

Spaarn Hospital, Hooftdorp, The Netherlands: De Korte N, Eijsbouts QA, De Reuver PR

Saint Lucas Andreas Hospital, Amsterdam, The Netherlands: Vrouwenraets BC, Tuynman JB

Meander Medical Center, Amersfoort, The Netherlands: Consten EC, Van de Wall BJM, Stam MAW

Máxima Medical Center, Veldhoven, The Netherlands: Roumen RMH, Truin W, Wijn R

Onze Lieve Vrouw Gasthuis Hospital, Amsterdam, The Netherlands: Gerhards MF, Kuhlmann KFD

Gele Hospital, Apeldoorn, The Netherlands: Van der Zaag ES, Biemond JE

BovenIj Hospital, Amsterdam, The Netherlands: Klicks RJ, Dhar N

Red Cross Hospital, Beverwijk, The Netherlands: Cense HA, De Groot GH, Pikoulin Y, Van Ramshorst GH, Hoornweg LL

Albert Schweitzer Hospital, Dordrecht/Zwijndrecht, The Netherlands: Van der Hoeven JA, Koet L

Tergooi Hospital, Hilversum, The Netherlands: Van Geloven AAW, Emous M

Ziekenhuisgroep Twente Hospital, Almelo/Hengelo, The Netherlands: Faneyte IF, Claassen ATPM, Mollink S

Westfriesgasthuis Hospital, Hoorn, The Netherlands: Sonneveld DJA, Bouvé L, Diepenhorst GMP

Ikazia Hospital, Rotterdam, The Netherlands: Vles WJ, Toorenhviet BR

Erasmus University Medical Center, Rotterdam, The Netherlands: Lange JF

Saint Franciscus Hospital, Rotterdam, The Netherlands: Mannaerts GHH, Grotenhuis BA, De Vos tot Nederveen Cappel RJ, Deerenberg EB

Slotervaart Hospital, Amsterdam, The Netherlands: Depla ACTM, Bruin S, Vos X

Reinier de Graaf Gasthuis Hospital, Delft, The Netherlands: Scheepers JJP

Flevo Hospital, Almere, The Netherlands: Boom MJ

Saint Antonius Hospital, Nieuwegein, The Netherlands: Boerma D, Van Esser S, Pruim J

Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht, The Netherlands: Reitsma JB
Chapter 3 | Antibiotic treatment or not for uncomplicated diverticulitis

Appendix Table 1 | Exclusion criteria

<table>
<thead>
<tr>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous US and/or CT proven episode of diverticulitis</td>
</tr>
<tr>
<td>US and/or CT suspicion of colonic cancer</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>Modified Hinchey stages 2, 3 and 4 or Ambrosetti’s “severe” diverticulitis stage, which require surgical or percutaneous treatment</td>
</tr>
<tr>
<td>Other disease with expected survival of less than six months</td>
</tr>
<tr>
<td>Contraindication for the use of the study medication (e.g. patients with advanced renal failure or allergy to all antibiotics used in this study),</td>
</tr>
<tr>
<td>Pregnancy, breastfeeding</td>
</tr>
<tr>
<td>ASA classification &gt; III</td>
</tr>
<tr>
<td>Immunocompromised patients</td>
</tr>
<tr>
<td>Clinical suspicion of bacteremia (i.e. sepsis)</td>
</tr>
<tr>
<td>Inability of reading/understanding and filling in the questionnaires</td>
</tr>
<tr>
<td>Antibiotic use in the four weeks prior to inclusion</td>
</tr>
</tbody>
</table>

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

Appendix Table 2 | Reasons for wrongful inclusion of randomized patients

<table>
<thead>
<tr>
<th>Reasons for wrongful inclusion</th>
<th>Observation (N=283)</th>
<th>Antibiotics (N=287)</th>
<th>Total (N=570)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No confirmed diagnosis of diverticulitis</td>
<td>4 (1.4%)</td>
<td>3 (1.0%)</td>
<td>7 (1.2%)</td>
</tr>
<tr>
<td>Complicated diverticulitis *</td>
<td>4 (1.4%)</td>
<td>3 (1.0%)</td>
<td>7 (1.2%)</td>
</tr>
<tr>
<td>CRC &lt; 3 months after randomization</td>
<td>2 (0.7%)</td>
<td>5 (1.7%)</td>
<td>7 (1.2%)</td>
</tr>
<tr>
<td>Antibiotics &lt; 1 month before randomization</td>
<td>3 (1.1%)</td>
<td>3 (1.0%)</td>
<td>6 (1.1%)</td>
</tr>
<tr>
<td>Previous episode of diverticulitis</td>
<td>2 (0.7%)</td>
<td>3 (1.0%)</td>
<td>5 (0.9%)</td>
</tr>
<tr>
<td>No informed consent</td>
<td>3 (1.0%)</td>
<td>1 (0.3%)</td>
<td>4 (0.7%)</td>
</tr>
<tr>
<td>Immunocompromised</td>
<td>1 (0.4%)</td>
<td>1 (0.3%)</td>
<td>2 (0.4%)</td>
</tr>
<tr>
<td>IBD</td>
<td>1 (0.4%)</td>
<td>0 (0.0%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Total</td>
<td>20 (7.1%)</td>
<td>19 (6.6%)</td>
<td>39 (6.8%)</td>
</tr>
</tbody>
</table>

Abbreviations: CRC, colorectal carcinoma; IBD, inflammatory bowel disease; * Hinchey 2, 3 or 4, or diverticulitis with fistula or obstruction.
### Appendix Table 3 | Major protocol amendments

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

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.
### Appendix Table 4 | Baseline characteristics of the patients according to randomization status *

<table>
<thead>
<tr>
<th></th>
<th>Randomized (N=570)</th>
<th>Not randomized eligible patients who declined participation (N=149)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong> – yr</td>
<td>56.6 (48.5-64.2)</td>
<td>57.8 (48.1-65.9)</td>
<td>0.633</td>
</tr>
<tr>
<td><strong>Male sex</strong> – no (%)</td>
<td>277 (48.6%)</td>
<td>61 (40.9%)</td>
<td>0.095</td>
</tr>
<tr>
<td><strong>Co-morbidity† – no (%)</strong> (42 vs 7 missings)</td>
<td>234 (44.3%)</td>
<td>45 (31.7%)</td>
<td><strong>0.007</strong></td>
</tr>
<tr>
<td><strong>ASA score ‡ – no (%)</strong></td>
<td></td>
<td></td>
<td>0.114</td>
</tr>
<tr>
<td>ASA 1</td>
<td>330 (62.5%)</td>
<td>99 (69.7%)</td>
<td></td>
</tr>
<tr>
<td>ASA 2</td>
<td>177 (33.5%)</td>
<td>39 (27.5%)</td>
<td></td>
</tr>
<tr>
<td>ASA 3</td>
<td>21 (4.0%)</td>
<td>4 (2.8%)</td>
<td></td>
</tr>
<tr>
<td><strong>Body mass index – kg/m²</strong> (78 vs 87 missings)</td>
<td>26.8 (24.4-29.6)</td>
<td>26.7 (24.3-28.9)</td>
<td>0.528</td>
</tr>
<tr>
<td><strong>Body temperature – °C</strong> (42 vs 7 missings)</td>
<td>37.3 (36.9-38.0)</td>
<td>37.2 (36.8-37.8)</td>
<td>0.077</td>
</tr>
<tr>
<td><strong>Localization abdominal pain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LLQ isolated – no (%)</td>
<td>244 (46.2%)</td>
<td>102 (71.8%)</td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td>Vomiting – no (%) (42 vs 7 missings)</td>
<td>47 (8.9%)</td>
<td>8 (5.6%)</td>
<td>0.208</td>
</tr>
<tr>
<td><strong>White blood cell count – ×10⁹ cells/L</strong> (42 vs 7 missings)</td>
<td>12.2 (10.1-14.5)</td>
<td>12.1 (10.0-14.8)</td>
<td>0.818</td>
</tr>
<tr>
<td><strong>C-reactive protein – mg/L</strong> (43 vs 8 missings)</td>
<td>79.0 (43.0-128.0)</td>
<td>78.5 (46.7-131.0)</td>
<td>0.910</td>
</tr>
<tr>
<td><strong>Hinchey category 1a § – no (%)</strong> (11 missings in the not randomized group)</td>
<td>507 (88.9%)</td>
<td>126 (91.3%)</td>
<td>0.420</td>
</tr>
</tbody>
</table>

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).
## Appendix Table 5 | Reasons for non-enrollment of screened patients*

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

*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.
# Appendix Table 6 | Number of included patients per hospital*  
<table>
<thead>
<tr>
<th>Hospital</th>
<th>Observation (N=262)</th>
<th>Antibiotics (N=266)</th>
<th>Total (N=528)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Academic Medical Center</td>
<td>9 (3.4%)</td>
<td>8 (3.0%)</td>
<td>17 (3.2%)</td>
</tr>
<tr>
<td>VU Medical Center</td>
<td>3 (1.1%)</td>
<td>4 (1.5%)</td>
<td>7 (1.3%)</td>
</tr>
<tr>
<td>Kennemer Gasthuis Hospital</td>
<td>17 (6.5%)</td>
<td>14 (5.3%)</td>
<td>31 (5.9%)</td>
</tr>
<tr>
<td>Spaarne Hospital</td>
<td>24 (9.2%)</td>
<td>26 (9.8%)</td>
<td>50 (9.5%)</td>
</tr>
<tr>
<td>Saint Lucas Andreas Hospital</td>
<td>9 (3.4%)</td>
<td>9 (3.4%)</td>
<td>18 (3.4%)</td>
</tr>
<tr>
<td>Meander Medical Center</td>
<td>35 (13.4%)</td>
<td>37 (13.9%)</td>
<td>72 (13.6%)</td>
</tr>
<tr>
<td>Maxima Medical Center</td>
<td>13 (5.0%)</td>
<td>13 (4.9%)</td>
<td>26 (4.9%)</td>
</tr>
<tr>
<td>Onze Lieve Vrouwe Gasthuis Hospital</td>
<td>8 (3.1%)</td>
<td>9 (3.4%)</td>
<td>17 (3.2%)</td>
</tr>
<tr>
<td>Gelre Hospital</td>
<td>8 (3.1%)</td>
<td>8 (3.0%)</td>
<td>16 (3.0%)</td>
</tr>
<tr>
<td>BovenIJ Hospital</td>
<td>5 (1.9%)</td>
<td>4 (1.5%)</td>
<td>9 (1.7%)</td>
</tr>
<tr>
<td>Red Cross Hospital</td>
<td>18 (6.9%)</td>
<td>15 (5.6%)</td>
<td>33 (6.2%)</td>
</tr>
<tr>
<td>Albert Schweitzer Hospital</td>
<td>25 (9.5%)</td>
<td>26 (9.8%)</td>
<td>51 (9.7%)</td>
</tr>
<tr>
<td>Tergooi Hospital</td>
<td>10 (3.8%)</td>
<td>12 (4.5%)</td>
<td>22 (4.2%)</td>
</tr>
<tr>
<td>Ziekenhuisgroep Twente Hospital</td>
<td>21 (8.0%)</td>
<td>22 (8.3%)</td>
<td>43 (8.1%)</td>
</tr>
<tr>
<td>Westfriesgasthuis Hospital</td>
<td>16 (6.1%)</td>
<td>18 (6.8%)</td>
<td>34 (6.4%)</td>
</tr>
<tr>
<td>Ikazia Hospital</td>
<td>6 (2.3%)</td>
<td>6 (2.3%)</td>
<td>12 (2.3%)</td>
</tr>
<tr>
<td>Saint Franciscus Gasthuis Hospital</td>
<td>10 (3.8%)</td>
<td>10 (3.8%)</td>
<td>20 (3.8%)</td>
</tr>
<tr>
<td>Slotervaart Hospital</td>
<td>1 (0.4%)</td>
<td>2 (0.8%)</td>
<td>3 (0.6%)</td>
</tr>
<tr>
<td>Reinier de Graaf Gasthuis Hospital</td>
<td>7 (2.7%)</td>
<td>7 (2.6%)</td>
<td>14 (2.7%)</td>
</tr>
<tr>
<td>Flevo Hospital</td>
<td>5 (1.9%)</td>
<td>3 (1.1%)</td>
<td>8 (1.5%)</td>
</tr>
<tr>
<td>Saint Antonius Hospital</td>
<td>12 (4.6%)</td>
<td>13 (4.9%)</td>
<td>25 (4.7%)</td>
</tr>
</tbody>
</table>

Abbreviations: ITT, intention to treat; Hosp., Hospital;  
* One participating hospital did not contribute to patient inclusion, but screened six patients that were ineligible.
### Appendix Table 7 | Type of antibiotic treatment prescribed

<table>
<thead>
<tr>
<th>Type of Antibiotic Treatment</th>
<th>Observation (N=13 of 262)</th>
<th>Antibiotics (N=265 of 266)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin/clavulanic acid</td>
<td>1 (7.7%)</td>
<td>250 (94.3%)</td>
</tr>
<tr>
<td>Metronidazole + Ciprofloxacin</td>
<td>3 (23.1%)</td>
<td>14 (5.3%)</td>
</tr>
<tr>
<td>Cephalosporin ‡</td>
<td>3 (23.1%)</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>2 (15.4%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (30.8%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

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

### Appendix Table 8 | Reasons for protocol deviation per treatment group

#### Reasons for starting antibiotics in patients assigned to observational treatment (13 of 262) *

<table>
<thead>
<tr>
<th>Reason</th>
<th>Count (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other infectious focus</td>
<td>4 (1.5%)</td>
</tr>
<tr>
<td>Clinical deterioration or progression to complicated diverticulitis</td>
<td>3 (1.1%)</td>
</tr>
<tr>
<td>Body temperature &gt;39°C</td>
<td>3 (1.1%)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>2 (0.8%)</td>
</tr>
<tr>
<td>Positive blood culture</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>13 (5.0%)</strong></td>
</tr>
</tbody>
</table>

#### Reasons for discontinuation of antibiotics in patients assigned to antibiotic treatment (15 of 266) †

<table>
<thead>
<tr>
<th>Reason</th>
<th>Count (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incorrect prescription by treating physician</td>
<td>7 (2.6%)</td>
</tr>
<tr>
<td>Unclear instruction/patient’s own decision</td>
<td>4 (1.5%)</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>2 (0.8%)</td>
</tr>
<tr>
<td>Side-effects</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>15 (5.6%)</strong></td>
</tr>
</tbody>
</table>

* 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.
Chapter 3 | Antibiotic treatment or not for uncomplicated diverticulitis

Appendix Table 9 | Indications for sigmoid resection at 6 month

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

Appendix Table 10 | Main secondary outcomes among patients with uncomplicated acute diverticulitis assigned to an observational or antibiotic treatment strategy at 12 months follow-up

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Observation (N=227* of 262)</th>
<th>Antibiotics (N=240* of 266)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Readmission (≥1) – no (%)</td>
<td>48 (21.1%)</td>
<td>49 (20.4%)</td>
<td>0.423</td>
</tr>
<tr>
<td>Complicated diverticulitis (≥1) – no %)</td>
<td>9 (4.0%)</td>
<td>6 (2.5%)</td>
<td>0.185</td>
</tr>
<tr>
<td>Ongoing diverticulitis (≥1) – no (%)</td>
<td>17 (7.5%)</td>
<td>10 (4.2%)</td>
<td>0.062</td>
</tr>
<tr>
<td>Recurrent diverticulitis (≥1) – no (%)</td>
<td>19 (8.4%)</td>
<td>19 (7.9%)</td>
<td>0.429</td>
</tr>
<tr>
<td>Sigmoid resection – no (%)</td>
<td>16 (7.0%)</td>
<td>9 (3.8%)</td>
<td>0.057</td>
</tr>
</tbody>
</table>

* 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.
### Appendix Table 11 | 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

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>Subgroup</th>
<th>Hinchey 1a (N=486)</th>
<th></th>
<th>Hinchey 1b (N=42)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Obs (N=236)</td>
<td>AB (N=250)</td>
<td>Unadjust. P-value</td>
<td>Adjust† P-value</td>
</tr>
<tr>
<td>Recovery ≤ 6 months FU – no (%)</td>
<td>211 (89.4%)</td>
<td>235 (94.0%)</td>
<td>0.033</td>
<td>0.163</td>
<td>23 (88.5%)</td>
</tr>
<tr>
<td>Readmission (≥1) ≤ 6 months FU – no (%)</td>
<td>42 (17.8%)</td>
<td>31 (12.4%)</td>
<td>0.048</td>
<td>0.163</td>
<td>4 (15.4%)</td>
</tr>
<tr>
<td>Days outside hospital ≤ 6 months FU – proportion of FU duration ‡</td>
<td>0.989 (0.978-0.994)</td>
<td>0.983 (0.978-0.989)</td>
<td>&lt;0.001</td>
<td>0.009</td>
<td>0.989 (0.969-0.996)</td>
</tr>
<tr>
<td>Complicated diverticulitis (≥1) ≤ 6 months FU – no (%)</td>
<td>8 (3.4%)</td>
<td>4 (1.6%)</td>
<td>0.164</td>
<td>0.282</td>
<td>2 (7.7%)</td>
</tr>
<tr>
<td>At index admission Intervention §</td>
<td>2 (0.8%)</td>
<td>3 (1.2%)</td>
<td>0.527</td>
<td>0.527</td>
<td>1 (3.8%)</td>
</tr>
<tr>
<td>Surgery</td>
<td>6 (2.5%)</td>
<td>3 (1.2%)</td>
<td>0.244</td>
<td>0.317</td>
<td>2 (7.7%)</td>
</tr>
<tr>
<td>Percut.</td>
<td>1 (0.4%)</td>
<td>0 (0.0%)</td>
<td>0.466</td>
<td>0.516</td>
<td>1 (3.8%)</td>
</tr>
<tr>
<td>Ongoing diverticulitis (≥1) ≤ 6 months FU – no (%)</td>
<td>17 (7.2%)</td>
<td>11 (4.4%)</td>
<td>0.093</td>
<td>0.264</td>
<td>2 (7.7%)</td>
</tr>
<tr>
<td>Recurrent diverticulitis (≥1) ≤ 6 months FU – no (%)</td>
<td>9 (3.8%)</td>
<td>7 (2.8%)</td>
<td>0.266</td>
<td>0.348</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Sigmoid resection ≤ 6 months FU – no (%)</td>
<td>8 (3.4%)</td>
<td>4 (1.6%)</td>
<td>0.164</td>
<td>0.282</td>
<td>2 (7.7%)</td>
</tr>
<tr>
<td>Emerg.</td>
<td>2 (0.8%)</td>
<td>1 (0.4%)</td>
<td>0.478</td>
<td>0.516</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Elective</td>
<td>6 (2.5%)</td>
<td>3 (1.2%)</td>
<td>0.224</td>
<td>0.317</td>
<td>2 (7.7%)</td>
</tr>
</tbody>
</table>
### Table 3.1

<table>
<thead>
<tr>
<th>All morbidity § ¶ – no (%)</th>
<th>118 (50.0%)</th>
<th>136 (54.4%)</th>
<th>0.166</th>
<th>0.282</th>
<th>9 (34.6%)</th>
<th>9 (56.2%)</th>
<th>0.081</th>
<th>0.432</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>83 (35.2%)</td>
<td>107 (42.8%)</td>
<td>0.043</td>
<td>0.163</td>
<td>6 (23.1%)</td>
<td>7 (43.8%)</td>
<td>0.080</td>
<td>0.432</td>
</tr>
<tr>
<td>Serious</td>
<td>64 (27.1%)</td>
<td>56 (22.4%)</td>
<td>0.114</td>
<td>0.277</td>
<td>5 (19.2%)</td>
<td>5 (31.2%)</td>
<td>0.300</td>
<td>0.508</td>
</tr>
<tr>
<td>AB related</td>
<td>1 (0.4%)</td>
<td>21 (8.4%)</td>
<td>&lt;0.001</td>
<td>0.009</td>
<td>0 (0.0%)</td>
<td>1 (6.2%)</td>
<td>0.381</td>
<td>0.508</td>
</tr>
<tr>
<td>Mortality ¶ – no (%)</td>
<td>3 (1.3%)</td>
<td>1 (0.4%)</td>
<td>0.290</td>
<td>0.352</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

*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>
<thead>
<tr>
<th></th>
<th>Observation (N=264)</th>
<th>Antibiotics (N=264)</th>
<th>Unadjusted P-value</th>
<th>Adjusted P-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outpatient treatment – no (%)</strong></td>
<td>33 (12.5%)</td>
<td>2 (0.8%)</td>
<td>&lt;0.001</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Duration initial admission – days</strong></td>
<td>2 (1-3)</td>
<td>3 (2-3)</td>
<td>&lt;0.001</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Recovery ≤ 6 months FU – no (%)</strong></td>
<td>239 (90.5%)</td>
<td>243 (92.0%)</td>
<td>0.269</td>
<td>0.416</td>
</tr>
<tr>
<td><strong>Readmission (≥1) ≤ 6 months FU – no (%)</strong></td>
<td>44 (16.7%)</td>
<td>34 (12.9%)</td>
<td>0.110</td>
<td>0.264</td>
</tr>
<tr>
<td><strong>Total number</strong></td>
<td>59</td>
<td>42</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Days outside hospital ≤ 6 months FU – proportion of FU duration ‡</strong></td>
<td>0.989 (0.978-0.994)</td>
<td>0.983 (0.978-0.989)</td>
<td>&lt;0.001</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Complicated diverticulitis (≥1) ≤ 6 months FU – no (%)</strong></td>
<td>6 (2.3%)</td>
<td>11 (4.2%)</td>
<td>0.109</td>
<td>0.264</td>
</tr>
<tr>
<td><strong>Type § – no (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abscess (&gt; 5cm)</td>
<td>1 (0.4%)</td>
<td>3 (1.1%)</td>
<td>0.312</td>
<td>0.416</td>
</tr>
<tr>
<td>Perforation</td>
<td>1 (0.4%)</td>
<td>5 (1.9%)</td>
<td>0.108</td>
<td>0.264</td>
</tr>
<tr>
<td>Obstruction</td>
<td>3 (1.1%)</td>
<td>3 (1.1%)</td>
<td>0.657</td>
<td>0.657</td>
</tr>
<tr>
<td>Fistula</td>
<td>0 (0.0%)</td>
<td>1 (0.4%)</td>
<td>0.500</td>
<td>0.512</td>
</tr>
<tr>
<td>Bleeding</td>
<td>2 (0.8%)</td>
<td>0 (0.0%)</td>
<td>0.250</td>
<td>0.416</td>
</tr>
<tr>
<td><strong>At index admission – no (%)</strong></td>
<td>0 (0.0%)</td>
<td>9 (3.4%)</td>
<td>0.002</td>
<td>0.010</td>
</tr>
<tr>
<td><strong>Intervention § – no (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percutaneous</td>
<td>1 (0.4%)</td>
<td>2 (0.8%)</td>
<td>0.500</td>
<td>0.512</td>
</tr>
<tr>
<td>Surgery</td>
<td>4 (1.5%)</td>
<td>9 (3.4%)</td>
<td>0.130</td>
<td>0.284</td>
</tr>
<tr>
<td><strong>Ongoing diverticulitis (≥1) ≤ 6 months FU – no (%)</strong></td>
<td>16 (6.1%)</td>
<td>14 (5.3%)</td>
<td>0.354</td>
<td>0.447</td>
</tr>
<tr>
<td><strong>Imaging proven</strong></td>
<td>7</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Needling admission</strong></td>
<td>12</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Recurrent diverticulitis (≥1) ≤ 6 months FU – no (%)</strong></td>
<td>10 (3.8%)</td>
<td>7 (2.7%)</td>
<td>0.230</td>
<td>0.416</td>
</tr>
<tr>
<td><strong>Imaging proven</strong></td>
<td>8</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Needling admission</strong></td>
<td>4</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sigmoid resection ≤ 6 months FU – no (%)</strong></td>
<td>7 (2.7%)</td>
<td>9 (3.4%)</td>
<td>0.306</td>
<td>0.416</td>
</tr>
<tr>
<td><strong>Emergency</strong></td>
<td>1 (0.4%)</td>
<td>4 (1.5%)</td>
<td>0.186</td>
<td>0.372</td>
</tr>
<tr>
<td><strong>Elective</strong></td>
<td>6 (2.3%)</td>
<td>5 (1.9%)</td>
<td>0.381</td>
<td>0.457</td>
</tr>
<tr>
<td><strong>Morbidity § ¶ – no (%)</strong></td>
<td>125 (47.3%)</td>
<td>147 (55.7%)</td>
<td>0.028</td>
<td>0.103</td>
</tr>
<tr>
<td><strong>Mild</strong></td>
<td>91 (34.5%)</td>
<td>112 (42.4%)</td>
<td>0.030</td>
<td>0.103</td>
</tr>
<tr>
<td><strong>Serious</strong></td>
<td>64 (24.2%)</td>
<td>66 (25.0%)</td>
<td>0.420</td>
<td>0.480</td>
</tr>
<tr>
<td><strong>AB related morbidity</strong></td>
<td>4 (1.5%)</td>
<td>19 (7.2%)</td>
<td>0.001</td>
<td>0.008</td>
</tr>
<tr>
<td><strong>Mortality ¶ – no (%)</strong></td>
<td>3 (1.1%)</td>
<td>1 (0.4%)</td>
<td>0.312</td>
<td>0.416</td>
</tr>
</tbody>
</table>
Chapter 3 | Antibiotic treatment or not for uncomplicated diverticulitis

Table 2 | Continued

* 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 ($P = 0.073$).

Appendix Table 13 | Per-protocol analyses of main secondary outcomes at 12 months follow-up among patients with uncomplicated acute diverticulitis.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Observation (N=229* of 264)</th>
<th>Antibiotics (N=238* of 264)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Readmission (≥1) – no (%)</td>
<td>47 (20.5%)</td>
<td>50 (21.0%)</td>
<td>0.449</td>
</tr>
<tr>
<td>Complicated diverticulitis (≥1) – no (%)</td>
<td>6 (2.6%)</td>
<td>9 (3.8%)</td>
<td>0.239</td>
</tr>
<tr>
<td>Ongoing diverticulitis (≥1) – no (%)</td>
<td>14 (6.1%)</td>
<td>13 (5.5%)</td>
<td>0.382</td>
</tr>
<tr>
<td>Recurrent diverticulitis (≥1) – no (%)</td>
<td>18 (7.9%)</td>
<td>20 (8.4%)</td>
<td>0.415</td>
</tr>
<tr>
<td>Sigmoid resection – no (%)</td>
<td>13 (5.7%)</td>
<td>12 (5.0%)</td>
<td>0.381</td>
</tr>
</tbody>
</table>

* 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.
**Appendix Table 14** | Per-protocol subgroup analyses of main secondary outcomes for Hinchey categories 1a and 1b among patients with uncomplicated acute diverticulitis

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>Subgroup</th>
<th>Hinchey 1a (N=486)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>Hinchey 1b (N=42)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Obs(N=241)</td>
<td>AB(N=245)</td>
<td>Unadjust. P-value</td>
<td>Adjust.† P-value</td>
<td>Obs(N=23)</td>
<td>AB(N=19)</td>
<td>Unadjust. P-value</td>
<td>Adjust.† P-value</td>
<td></td>
</tr>
<tr>
<td>Recovery ≤ 6 months FU – no (%)</td>
<td>218 (90.5%)</td>
<td>228 (93.1%)</td>
<td>0.148</td>
<td>0.359</td>
<td>21 (91.3%)</td>
<td>15 (78.9%)</td>
<td>0.128</td>
<td>0.341</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Readmission (≥1) ≤ 6 months FU – no (%)</td>
<td>41 (17.0%)</td>
<td>32 (13.1%)</td>
<td>0.112</td>
<td>0.317</td>
<td>3 (13.0%)</td>
<td>2 (10.5%)</td>
<td>0.593</td>
<td>0.678</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days outside hospital ≤ 6 months FU – proportion of FU duration ‡</td>
<td>0.989 (0.978-0.994)</td>
<td>0.983 (0.978-0.989)</td>
<td>&lt;0.001</td>
<td>0.009</td>
<td>0.989 (0.978-0.994)</td>
<td>0.978 (0.922-0.989)</td>
<td>0.009</td>
<td>0.112</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complicated diverticulitis (≥1) ≤ 6 months FU – no (%)</td>
<td>6 (2.5%)</td>
<td>6 (2.4%)</td>
<td>0.489</td>
<td>0.510</td>
<td>0 (0.0%)</td>
<td>5 (26.3%)</td>
<td>0.014</td>
<td>0.112</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At index admission</td>
<td>0 (0.0%)</td>
<td>5 (2.0%)</td>
<td>0.032</td>
<td>0.181</td>
<td>0 (0.0%)</td>
<td>4 (21.1%)</td>
<td>0.035</td>
<td>0.118</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention §</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>4 (1.7%)</td>
<td>5 (2.0%)</td>
<td>0.510</td>
<td>0.510</td>
<td>0 (0.0%)</td>
<td>4 (21.1%)</td>
<td>0.035</td>
<td>0.118</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percut.</td>
<td>1 (0.4%)</td>
<td>0 (0.0%)</td>
<td>0.496</td>
<td>0.510</td>
<td>0 (0.0%)</td>
<td>2 (10.5%)</td>
<td>0.199</td>
<td>0.346</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ongoing diverticulitis (≥1) ≤ 6 months FU – no (%)</td>
<td>15 (6.2%)</td>
<td>13 (5.3%)</td>
<td>0.332</td>
<td>0.510</td>
<td>1 (4.3%)</td>
<td>1 (5.3%)</td>
<td>0.706</td>
<td>0.706</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent diverticulitis (≥1) ≤ 6 months FU – no (%)</td>
<td>9 (3.7%)</td>
<td>7 (2.9%)</td>
<td>0.294</td>
<td>0.510</td>
<td>1 (4.3%)</td>
<td>0 (0.0%)</td>
<td>0.548</td>
<td>0.678</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sigmoid resection ≤ 6 months FU – no (%)</td>
<td>6 (2.5%)</td>
<td>6 (2.4%)</td>
<td>0.489</td>
<td>0.510</td>
<td>1 (4.3%)</td>
<td>3 (15.8%)</td>
<td>0.234</td>
<td>0.346</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emerg.</td>
<td>1 (0.4%)</td>
<td>2 (0.8%)</td>
<td>0.506</td>
<td>0.510</td>
<td>0 (0.0%)</td>
<td>2 (10.5%)</td>
<td>0.199</td>
<td>0.346</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elective</td>
<td>5 (2.1%)</td>
<td>4 (1.6%)</td>
<td>0.490</td>
<td>0.510</td>
<td>1 (4.3%)</td>
<td>1 (5.3%)</td>
<td>0.706</td>
<td>0.706</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### All morbidity

<table>
<thead>
<tr>
<th>Category</th>
<th>No (%)</th>
<th>With (%)</th>
<th>p-value 1</th>
<th>p-value 2</th>
<th>p-value 3</th>
<th>p-value 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>118 (49.0%)</td>
<td>136 (55.5%)</td>
<td>0.074</td>
<td>0.251</td>
<td>7 (30.4%)</td>
<td>11 (57.9%)</td>
</tr>
<tr>
<td>Serious</td>
<td>85 (35.3%)</td>
<td>105 (42.9%)</td>
<td>0.444</td>
<td>0.187</td>
<td>6 (26.1%)</td>
<td>7 (36.8%)</td>
</tr>
<tr>
<td>AB related</td>
<td>60 (24.9%)</td>
<td>60 (24.5%)</td>
<td>0.459</td>
<td>0.510</td>
<td>4 (17.4%)</td>
<td>6 (31.6%)</td>
</tr>
<tr>
<td>Mortality</td>
<td>3 (1.2%)</td>
<td>19 (7.8%)</td>
<td>&lt;0.001</td>
<td>0.009</td>
<td>1 (4.3%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

| 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 of 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). |
Appendix Figure 1 | 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.
Appendix Figure 2 | 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 26 6 6 2 2 2 2
Antibiotics 16 5 5 4 4 3 3

Proportion of Participants without Recovery
Antibiotics
3
Appendix Figure 3 | Per-protocol analysis results of time-to-Recovery in patients with uncomplicated acute diverticulitis

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.

Hazard ratio, 1.069 (upper limit 95% CI, 1.242)  
P=0.232

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Observation</th>
<th>Antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>264</td>
<td>264</td>
</tr>
<tr>
<td>0-1 Months</td>
<td>63</td>
<td>72</td>
</tr>
<tr>
<td>1-2 Months</td>
<td>35</td>
<td>45</td>
</tr>
<tr>
<td>2-3 Months</td>
<td>22</td>
<td>29</td>
</tr>
<tr>
<td>3-4 Months</td>
<td>19</td>
<td>27</td>
</tr>
<tr>
<td>4-5 Months</td>
<td>17</td>
<td>24</td>
</tr>
<tr>
<td>5-6 Months</td>
<td>15</td>
<td>18</td>
</tr>
</tbody>
</table>

Proportion of Participants without Recovery

Antibiotics  Observation
PART 2

FOLLOW-UP
Chapter 4

Routine colonoscopy after left-sided acute uncomplicated diverticulitis:
A systematic review

Daniels L
Ünlü Ç
de Wijkerslooth TR
Dekker E
Boermeester MA

Gastrointest Endosc 2014;79(3):378-89
BACKGROUND

The use of routine colonoscopy after an episode of acute diverticulitis (AD) remains a point of debate. Most international and clinical practice guidelines advise endoscopy after conservatively treated diverticulitis.\(^1\)\(^-\)\(^4\)\) The rationale has always been to exclude an underlying malignancy or advanced colonic neoplasia (ACN). However, this is based merely on expert opinion. A recent article indicated that presently this may be different with increased use of abdominal CT imaging of diverticulitis.\(^7\) Furthermore, the yield of colonoscopy in patients after an episode of AD also cast doubt on current international practice.\(^5\)\(^-\)\(^20\)

Routine colonoscopy after an uncomplicated episode of diverticulitis dates from a time where the diagnosis was primarily based on clinical examination and laboratory results with frequent use of barium enema.\(^21\) However, in today’s clinical practice, CT is widely used for the diagnosis of diverticulitis, with the possibility to assess potential adverse events such as abscess, fistula, obstruction, or perforation as well. Because of high sensitivity of 94%, a specificity of 99%, and a low interobserver variability, this modality is currently preferred for the diagnosis of diverticulitis, although US also has a good sensitivity.\(^22\)\(^,\)\(^23\) Nevertheless, it remains uncertain if the prevalence of colorectal carcinoma (CRC) and advanced adenoma (AA) in patients with imaging-proven diverticulitis is higher than in an average-risk population. Apart from diagnosing CRC, the detection of AA is of great importance because it bears the potential to progress to carcinoma.

Colonoscopy is accompanied by such disadvantages as invasiveness and discomfort, potential adverse events such as perforation, and additional costs. It is important to know what the yield of routine colonoscopy is after a confident diagnosis of AD (ie, is there a justified indication?) Therefore, the aim of this systematic review was to determine the pooled prevalence of ACN, thus CRC and/or AA, as detected with colonoscopy in patients after an imaging-proven diagnosis of AD.
METHODS

Review protocol and study eligibility
A review protocol, for which the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist served as a guideline, was used by 2 authors (L.D. and C.U.) for the execution of this systematic review.

Eligibility criteria
Definitions
Diverticulitis is complicated diverticular disease with clinical symptoms and evidence of inflammation, confirmed by US or CT imaging. ACN comprises AA and/or CRC. An AA is defined as an adenoma ≥ 10 mm, ≥ 25% villous features (also classified as tubulovillous or villous histology), or with high-grade dysplasia. Right-sided is defined as proximal to the splenic flexure.

Types of studies
There were no predetermined limits of design types or language. Articles were eligible for inclusion when the following criteria were met: studies dealing with follow-up colonoscopy after US- or CT-proven left-sided diverticulitis, human studies, and studies of which the full text and data were available. The following exclusion criteria were used for study selection: studies without follow-up colonoscopy but with CT-colonography or contrast barium enemas instead or with outcome based on surgically obtained pathology specimens.

Types of participants
Patients aged 18 years or older with a recent diagnosis of uncomplicated AD were included. This diagnosis had to be confirmed by US and/or CT imaging.

Types of outcome measures
Primary outcome measure was the detection of ACN: AA and/or CRC. Secondary outcomes were detection of adenomas and serrated polyps (hyperplastic, sessile serrated adenoma/polyp, and traditional serrated adenoma). Adverse events of colonoscopy were also registered if described.

Literature search
An electronic literature search was performed to identify relevant records. The MEDLINE database was searched for articles published between January 1966 and July 2013, with the following search strategy: ((“Diverticulitis”[Mesh] OR “diverticulitis”[All Fields]) AND (“Colonoscopy”[Mesh] OR “Colonoscopy”[All Fields] OR “Colonography, Computed Tomographic”[Mesh])) AND (“1966/01/01”[Date -Publication]: “3000”[Date - Publication])). Free text words were also used instead of MeSH terms to avoid missing recent articles that had not yet been given a MeSH label. EMBASE database was searched for records published between 1974 and July 2013 with the following terms: diverticulitis and...
colonoscopy. The CINAHL database was also checked with the same key words. In addition, the Cochrane database of Systematic Reviews was searched with the following words: diverticular disease.

**Selection**

After removal of duplicate records, 2 reviewers screened the initial literature search based on title and abstract. After identifying potentially relevant records, the full-text articles of these were retrieved. Additionally, a manual cross-reference search of the reference lists of relevant articles was performed, and electronic links to related articles were hand searched as well to identify other studies not found in the initial search. They were all assessed for eligibility by applying the inclusion and exclusion criteria. Articles that reported on (parts of) the same study population were excluded from the review.

**Data extraction**

Data from each included study were extracted by 2 reviewers independently, using a standard form. These data included authors, year of publication, country, study design, inclusion period, type of patients, type of imaging for the diagnosis of AD, definition used for AD and ACN/AA, interval between diagnosis AD and colonoscopy, study endpoints, follow-up period, number of patients, patient age, number of complete colonoscopies, number of adverse events, number of patients with neoplastic lesions, number of (patients with) polyps, number of (patients with) adenomas (including AA), number of (patients with) AA, number of (patients with) CRC, number of (patients with) ACN, localization of ACN, age at diagnosis ACN, and any additional relevant information.

**Assessment of susceptibility to bias**

Two reviewers independently assessed the methodological quality of the studies and susceptibility to bias using the MINORS quality score, an instrument designed to assess the methodological quality of nonrandomized surgical studies, with a global ideal score of 16 for non-comparative studies.26

**Statistical analysis**

The primary outcome of this systematic review was the percentage of patients with ACN, and thus CRC and/or AA, as detected with follow-up colonoscopy, after an episode of imaging-proven diverticulitis. Therefore, for each included study, we calculated the 95% confidence intervals (CIs) around the proportions of ACN, CRC, and AA. We calculated the estimated pooled prevalence and 95% CIs based on a random effects model using Meta-Analyst version Beta 3.13 (Tufts Medical Center, Boston, MA, USA). We determined the presence of heterogeneity between the studies by using a forest plot and by performing a χ² (‘chi-squared’) heterogeneity test, and the I²-index was calculated. To assess publication bias, we performed a funnel plot asymmetry test by using Meta-Analyst version Beta 3.13 as well.
RESULTS

Study selection

A total of 959 records was initially identified in the literature search (Figure 1). Of these, 234 records were excluded because they were duplicate articles. From the 725 remaining records, screened based on title and abstract, another 694 were excluded because of irrelevance. Most studies were irrelevant because they covered other subjects, among others performance and findings of CT-colonography, screening colonoscopy, comparison of standard colonoscopy versus colonoscopy with transparent cap, management of diverticulitis, and sigmoidovesical fistula. Thirty-one full text articles were retrieved for more detailed examination; 1 additional article was found in reference lists. These were assessed for eligibility. The application of our inclusion and exclusion criteria resulted in 8 relevant studies. Twenty-three articles were excluded because they were abstracts only, case report, contained duplicate data, or failed to meet our inclusion criteria. The 2 reviewers completely agreed on inclusion of studies.

Figure 1 | PRISMA flow diagram showing selection of articles for review and analysis
Study characteristics and risk of bias
Eight studies met our inclusion criteria and were reviewed (Table 1).\(^8\)\textsuperscript{−15}\footnote{The studies were executed on 4 different continents within the time frame 2000 to 2010. All studies were retrospective cohort studies, except for the studies of Chabok et al\(^9\) and Lahat et al.\(^15\) They compared acceptance and diagnostic accuracy of CT-colonography versus colonoscopy and early versus late colonoscopy respectively. Many of these retrospective cohort studies attempted an indirect comparison with published data on high- and average-risk asymptomatic individuals derived from screening studies.\(^27\) Lau et al\(^14\) compared their CRC rate with that published by the WA Cancer Registry for all Western Australians; however, these data were not based on population colonoscopic screening.\(^28\) In all studies, the diagnosis of AD was imaging proven: CT proven in 6 studies, US and/or CT proven in one\(^10\) and US or CT confirmed in another.\(^11\) The radiologic definition used for diverticulitis was described in 5 studies.\(^10,12-15\) The histologic definition for ACN was described in only 3 studies.\(^10,12,13\) The number of patients enrolled per study ranged from 86 to 402. The studies were of moderate to good quality using the MINORS scoring scale, with total scores ranging from 10 to 14 (Table 2).

Patient cohort and results of individual studies
The clinical characteristics and outcome are summarized in Table 3. A total of 1796 patients, aged around 60, had an imaging-proven diagnosis of uncomplicated diverticulitis with endoscopic evaluation in follow-up. Reported colonoscopy completion rates ranged from 85.4%\(^13\) to 93.4%.\(^14\) More than half of the studies did not mention adverse events; the 3 that did so stated to have experienced none. One in 5 patients (20.2%; 363 of 1796) had at least 1 polyp. All but 3 studies\(^8,12,14\) referred to the most advanced lesion detected. Chabok et al\(^9\), Schout et al\(^11\), and Lahat et al\(^15\) did not mention hyperplastic polyps. None of the included studies described the number of (patients with) sessile serrated adenomas/polyps and traditional serrated adenomas. In 236 of 1695 patients (14%), adenomas were detected. The exact number of patients may have been slightly different because 1 study did not report on adenomas\(^8\) and therefore was left aside. Another study\(^12\) mentioned a total number of 36 adenomatous polyps and not patients. Thirty-three of 915 patients (3.6%) were found to have AA; 3 studies did not report on patients with AA and consequently were disregarded in this calculation.\(^8,9,11\) Twenty-nine of 1796 patients (1.6%) had CRC detected in follow-up with colonoscopy. In 3 studies, no CRC was found.\(^8,12,15\) When we take into account only studies that reported on both AA and CRC, a total of 45 of 915 patients were diagnosed with ACN (4.9%), comprising either AA or CRC, with a range of 3.4% to 6% between studies. Localization of ACN, specified in 4 studies, was found in all cases except for 1 left-sided or, more specifically, the sigmoid colon. Lau et al\(^14\) presented a 5.6% rate of ACN and was the only study to conclude that routine colonoscopy is mandatory in uncomplicated diverticulitis.
<table>
<thead>
<tr>
<th>Study, year and country</th>
<th>Study design</th>
<th>Inclusion period</th>
<th>Type of patients</th>
<th>Radiological diagnosis AD</th>
<th>Definition AD ACN(AA)</th>
<th>Interval AD – colonoscopy</th>
<th>Endpoint(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elmi et al. 2013, United States</td>
<td>Retrospective</td>
<td>Jan 2000 - Dec 2004</td>
<td>Acute (un)complicated diverticulitis in patients older than 49 years, without a history of CRC</td>
<td>CT</td>
<td>No</td>
<td>5.3 years (1 month - 11 years, 34.8% &lt; 6 months)*</td>
<td>Sensitivity, specificity, and predictive values of CT parameters for prediction of CRC.</td>
</tr>
<tr>
<td>Chabok et al. 2013, Sweden</td>
<td>Prospective comparative</td>
<td>Oct 2005 - Jan 2007</td>
<td>Acute left-sided colonic diverticulitis (without a colorectal examination during the last 2 years)</td>
<td>CT</td>
<td>No</td>
<td>6 - 8 weeks</td>
<td>Patient acceptence and diagnostic accuracy of CTC vs colonoscopy for DD, adenomas and CRC</td>
</tr>
<tr>
<td>Van de Wall et al. 2012, NL</td>
<td>Retrospective crosssectional</td>
<td>Jan 2007 - Jan 2010</td>
<td>Primary episode diverticulitis (84.5% Hinchey I) and/or US</td>
<td>CT (61%)</td>
<td>Yes</td>
<td>8.9 weeks ± 10.6*</td>
<td>Detection rate of hyperplastic polyps, adenomas and ACN</td>
</tr>
<tr>
<td>Schout et al. 2012, NL</td>
<td>Retrospective</td>
<td>2000 - 2010</td>
<td>Diverticulitis with or without intra-abdominal abscess</td>
<td>CT or US</td>
<td>No</td>
<td>NR</td>
<td>Number of malignant and benign colon tumours detected by FU programme</td>
</tr>
<tr>
<td>Schmilovitz-Weiss et al. 2012, Israel</td>
<td>Retrospective</td>
<td>Jun 2002 - Sep 2009</td>
<td>Acute diverticulitis (exclusion if questionable CT findings and/or hemorrhage)</td>
<td>CT</td>
<td>Yes</td>
<td>4 - 6 weeks</td>
<td>Yield of early colonoscopy and correlation between imaging results and scopy outcomes</td>
</tr>
<tr>
<td>Westwood et al. 2011, New Zealand</td>
<td>Retrospective longitudinal</td>
<td>Jan 2004 - Dec 2008</td>
<td>Acute uncomplicated diverticulitis (exclusion if complicated or mass lesions)</td>
<td>CT</td>
<td>Yes</td>
<td>‘After’ AD or &lt; 2 years before AD</td>
<td>Yield of ACN with colonoscopy/ CTC</td>
</tr>
<tr>
<td>Lau et al. 2011, Australia</td>
<td>Retrospective</td>
<td>Jan 2003 - Jun 2009</td>
<td>(Un)complicated left-sided diverticulitis</td>
<td>CT</td>
<td>Yes</td>
<td>70 days</td>
<td>No of patients in whom CRC were diagnosed and other incidental findings</td>
</tr>
<tr>
<td>Lahat et al. 2007, Israel</td>
<td>Prospective (RCT early vs late colonoscopy)</td>
<td>Jan 2004 - Jun 2006</td>
<td>Acute diverticulitis (exclusion if adjacent peritoneal air or fluid or free perforation)</td>
<td>CT</td>
<td>Yes</td>
<td>5.2 days (3-11) † vs 7.8 weeks (6-19) †</td>
<td>Feasibility, endoscopic findings and compliance rates and risk (adverse events)</td>
</tr>
</tbody>
</table>

NR, not reported; AD, Acute diverticulitis; ACN, Advanced colonic neoplasia; AA, Advanced adenoma; CRC, Colorectal carcinoma; CT, Computed Tomography; CTC, CT-colonography; DD, Diverticular Disease; NL, The Netherlands; US, Ultrasonography; FU, Follow-up; RCT, Randomized Controlled Trial.

*Values are means ± standard deviations (± SD).
†Values are medians (range).
### Table 2 | Assessment for risk of bias

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. A clearly stated aim</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>2. Inclusion of consecutive patients</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>3. Prospective collection of data</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>4. Endpoints appropriate to the aim of the study</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>5. Unbiased assessment of the study endpoint</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>6. FU period appropriate to the aim of the study</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>7. Loss to FU less than 5%</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>8. Prospective calculation of the study size</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total score†</strong></td>
<td>11</td>
<td>14</td>
<td>12</td>
<td>10</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>14</td>
</tr>
</tbody>
</table>

FU, Follow-up.

*The items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate); items 9-12 were left out since they only apply to comparative cohort studies.

†Maximal total score 16 for non-comparative studies.
### Table 3 | Clinical characteristics and outcomes of included studies

<table>
<thead>
<tr>
<th>Study, year</th>
<th>No of patients</th>
<th>Age (years)</th>
<th>Complete study</th>
<th>No of patients with neoplastic lesions (inclusive of polyps)</th>
<th>No of patients with adenoma</th>
<th>No of patients with ACN</th>
<th>CRC</th>
<th>AA</th>
<th>Age at diagnosis ACN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elmi et al.</td>
<td>402</td>
<td>63.3 (range 50 - 94)*</td>
<td>NR</td>
<td>78 (19.4%) 21 (5.2%) hyperplastic 2 (0.5%) polypoid granulations</td>
<td>55 (13.7%)</td>
<td>NR</td>
<td>9 (2.2%)</td>
<td>NR</td>
<td>68.1*</td>
</tr>
<tr>
<td>Chabok et al.</td>
<td>101</td>
<td>56 (range 27 - 84)†</td>
<td>100 (of 110 = 90.9%)</td>
<td>20 (20%)</td>
<td>NR</td>
<td>NR</td>
<td>0 (0%)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Van de Wall et al.</td>
<td>205</td>
<td>57.3 ± 13.2*</td>
<td>146</td>
<td>40 (19.5%)</td>
<td>23 (11.2%) 18 (8.8%) adenomas 2 tubular adenomas &gt; 1 cm 1 adenoma with HGD 2 adenomas &gt; 25% villous</td>
<td>7 (3.4%)</td>
<td>62.7 (37-83)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schout et al.</td>
<td>378</td>
<td>NR</td>
<td>NR</td>
<td>47 (12.4%)</td>
<td>39 (10.3%)</td>
<td>NR</td>
<td>8 (2.1%)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Schmiliowitz-Weiss et al.</td>
<td>100</td>
<td>61.8 ± 13.3*</td>
<td>NR</td>
<td>32 (32%)(42 lesions) 5 hyperplastic</td>
<td>NR (36 adenomas)†</td>
<td>6 tubulovillous adenomas, 1 of which &gt; 1 cm 30 tubular adenomas</td>
<td>6 (6%)</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>
### Table 3 | Continued

| Study, year | No of patients | Age (years) | Complete 
scopy | No of patients with neoplastic lesions (inclusive of polyps) | No of patients with adenoma | No of patients with ACN CRC AA | Age at diagnosis ACN |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Westwood et al. 2011</td>
<td>205</td>
<td>60 (23-95)†</td>
<td>175 (85.4%)</td>
<td>50 (24.4%)</td>
<td>29 (14.1%)</td>
<td>11 (5.4%)</td>
<td>63 (46–82)†</td>
</tr>
<tr>
<td>Lau et al. 2011</td>
<td>319</td>
<td>59.8 ± 15.2*</td>
<td>298 (93.4%)</td>
<td>91 (28.5%)</td>
<td>49 (15.4%)</td>
<td>18 (5.6%)</td>
<td>NR</td>
</tr>
<tr>
<td>Lahat et al. 2007</td>
<td>86</td>
<td>60.5 ±11.4*</td>
<td>75 (87.2%)</td>
<td>5 (5.8%)</td>
<td>5 (5.8%)</td>
<td>3 (3.5%)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>45 ‘early’</td>
<td>60.3 ±14.7*</td>
<td>vs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>41 ‘late’</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ACN, Advanced Colonic Neoplasia; CRC, Colorectal Carcinoma; AA, Advanced Adenoma; HGD, high grade dysplasia; NR, not reported.

*Values are means ± standard deviations (± SD).
†Values are medians (range).
‡Total number of adenomas instead of number of patients with adenoma was reported.
Pooled prevalence
As shown in Figures 2, 3, and 4, the estimated pooled prevalence was 5.0% (95% CI, 3.8%-6.7%) for ACN, 1.5% (95% CI, 1.0%-2.3%) for CRC, and 3.8% (95% CI, 2.7%-5.3%) for AA as detected at follow-up after an episode of imaging-confirmed AD. There was limited evidence of heterogeneity among included studies for the detection of CRC ($I^2 = 32\%$) and none for ACN ($I^2 < 0.01\%$) and AA ($I^2 < 0.01\%$). Results of the funnel plot asymmetry tests are presented in Figure 5 and show some asymmetry that could be indicative of publication bias.

Excluded studies
Of the 23 excluded studies, most failed to meet our inclusion criteria and/or were abstracts only. Three studies were excluded because they concerned bowel thickening on CT scan and only a fraction of the included patients (2.8%-29.3%) were diagnosed with diverticulitis or diverticular disease.\textsuperscript{29-31} Three studies dealt with complicated\textsuperscript{20,32} or persistent\textsuperscript{33} diverticulitis. It was concluded that early colonoscopy is mandatory and safe. One study that compared colonoscopy with CT-colonography was excluded because not all included patients had imaging-proven diverticulitis.\textsuperscript{34} Four studies appeared to meet the eligibility criteria but were excluded because they were abstracts only and not published to date.\textsuperscript{16-19} Despite inclusion of patients with CT patterns of tumour-like lesions of the sigmoid (5.5%) and sigmoid stenosis (8.3%), Alatawi et al\textsuperscript{18} found low diagnostic rates for adenomas, AAs, and CRC. The excluded studies, which were considered a relevant addition to obtain a complete overview on current literature, are summarized in Table 4.

DISCUSSION
The purpose of this review was to determine the prevalence of ACN as detected with colonoscopy in patients after a diagnosis of AD confirmed by imaging. In our systematic review, the estimated pooled prevalence was 5.0% (95% CI, 3.8%-6.7%) for ACN, 1.5% (95% CI, 1.0%-2.3%) for CRC, and 3.8% (95% CI, 2.7%-5.3%) for AA. The overall adenoma detection rate (ADR) was 14%.

In 2012 a systematic review was published concerning colonoscopy after CT diagnosis of AD to exclude colon cancer.\textsuperscript{7} Sai et al included 10 studies of which only 2 met our inclusion criteria. By including patients with radiologic features suspicious for neoplasia, namely atypical findings such as colonic wall thickening and mass lesions, it can be expected to have resulted in a higher yield of CRC at subsequent colonoscopy. Their included studies had follow-up by surgery in most cases; colonoscopy exclusively, on the other hand, was the method of follow-up in only 4 studies.
Figure 2 | Forest plot of the included studies and the prevalence of advanced colonic neoplasia

Proportion: 95% Confidence Interval

<table>
<thead>
<tr>
<th>Study Name</th>
<th>N</th>
<th>Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>van de Wall et al (2012)</td>
<td>205</td>
<td>0.034 (0.016, 0.070)</td>
</tr>
<tr>
<td>Scmilovitz-Weiss et al (2012)</td>
<td>100</td>
<td>0.060 (0.027, 0.127)</td>
</tr>
<tr>
<td>Westwood et al (2011)</td>
<td>205</td>
<td>0.054 (0.030, 0.094)</td>
</tr>
<tr>
<td>Lau et al (2011)</td>
<td>319</td>
<td>0.056 (0.036, 0.088)</td>
</tr>
<tr>
<td>Lahat et al (2007)</td>
<td>86</td>
<td>0.035 (0.011, 0.103)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>0.050 (0.038, 0.067)</td>
</tr>
</tbody>
</table>

Figure 3 | Forest plot of the included studies and the prevalence of colorectal carcinoma

Proportion: 95% Confidence Interval

<table>
<thead>
<tr>
<th>Study Name</th>
<th>N</th>
<th>Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elni et al (2013)</td>
<td>402</td>
<td>0.022 (0.012, 0.042)</td>
</tr>
<tr>
<td>Chabok et al (2013)</td>
<td>101</td>
<td>0.000 (0.000, 0.073)</td>
</tr>
<tr>
<td>van de Wall et al (2012)</td>
<td>205</td>
<td>0.010 (0.002, 0.038)</td>
</tr>
<tr>
<td>Schout et al (2012)</td>
<td>378</td>
<td>0.021 (0.011, 0.042)</td>
</tr>
<tr>
<td>Schmilovitz-Weiss et al (2012)</td>
<td>100</td>
<td>0.000 (0.000, 0.074)</td>
</tr>
<tr>
<td>Westwood et al (2011)</td>
<td>205</td>
<td>0.005 (0.001, 0.034)</td>
</tr>
<tr>
<td>Lau et al (2011)</td>
<td>319</td>
<td>0.006 (0.002, 0.025)</td>
</tr>
<tr>
<td>Lahat et al (2007)</td>
<td>86</td>
<td>0.000 (0.000, 0.085)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>0.015 (0.010, 0.023)</td>
</tr>
</tbody>
</table>
Chapter 4 | Routine colonoscopy: a systematic review

**Figure 4** | Forest plot of the included studies and the prevalence of advanced adenoma

<table>
<thead>
<tr>
<th>Study Name</th>
<th>N</th>
<th>Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>van de Wall et al (2012)</td>
<td>205</td>
<td>0.024 (0.010, 0.057)</td>
</tr>
<tr>
<td>Schmilovitz-Weiss et al (2012)</td>
<td>100</td>
<td>0.060 (0.027, 0.127)</td>
</tr>
<tr>
<td>Westwood et al (2011)</td>
<td>205</td>
<td>0.049 (0.026, 0.088)</td>
</tr>
<tr>
<td>Lau et al (2011)</td>
<td>319</td>
<td>0.028 (0.015, 0.053)</td>
</tr>
<tr>
<td>Lahat et al (2007)</td>
<td>86</td>
<td>0.035 (0.011, 0.103)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>0.038 (0.027, 0.053)</td>
</tr>
</tbody>
</table>

**Figure 5A** | Results of the funnel plot asymmetry test for advanced colonic neoplasia; ○ = study; Σ = pooled estimate line
Figure 5B | Results of the funnel plot asymmetry test for colorectal carcinoma; • = study; ‖ = pooled estimate line

Figure 5C | Results of the funnel plot asymmetry test for advanced adenoma; • = study; ‖ = pooled estimate line
### Table 4 | Characteristics of excluded studies (of which it was expected that these could be included)

<table>
<thead>
<tr>
<th>Study year (and country)</th>
<th>Study design</th>
<th>Reason(s) for exclusion</th>
<th>No of patients</th>
<th>Type of patients</th>
<th>Age</th>
<th>ACN CRC AA</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahmeidat et al. <strong>16</strong> 2012</td>
<td>Retrospective</td>
<td>Abstract only</td>
<td>44</td>
<td>CT-confirmed AD</td>
<td>61 (19-92)†</td>
<td>NR</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Alexandersson et al. <strong>17</strong> 2012</td>
<td>Retrospective</td>
<td>Abstract only</td>
<td>118</td>
<td>CT-verified diverticulitis</td>
<td>57 (50-67)†</td>
<td>1 (0.8%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Alatawi et al. <strong>18</strong> 2012</td>
<td>Retrospective</td>
<td>Abstract only</td>
<td>121</td>
<td>CT diagnosis AD (in 7 tumor-like lesions)</td>
<td>62*</td>
<td>3 (2.4%)</td>
<td>1 (0.8%)</td>
</tr>
<tr>
<td>Daker et al. <strong>19</strong> 2012</td>
<td>Retrospective</td>
<td>Abstract only</td>
<td>47</td>
<td>CT confirmed diverticulitis</td>
<td>NR</td>
<td>NR</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Elramah et al. <strong>20</strong> 2010</td>
<td>Retrospective</td>
<td>Abstract only</td>
<td>130</td>
<td>CT confirmed diverticulitis (mass-like lesion, abscess, perforation included)</td>
<td>63.7*</td>
<td>NR</td>
<td>3 (2.3%)</td>
</tr>
<tr>
<td>Kraft et al. <strong>21</strong> 2010</td>
<td>Prospective</td>
<td>Abstract only</td>
<td>45</td>
<td>CT proven diverticulitis (19 Hinchey II, 3 stenosis/fistula)</td>
<td>NR</td>
<td>NR</td>
<td>1 (2.2%)</td>
</tr>
<tr>
<td>Lahat et al. <strong>22</strong> 2008, Israel</td>
<td>Prospective</td>
<td>1. Duplicate data (Lahat et al. <strong>23</strong> 2007) 2. Persistent diverticulitis</td>
<td>23</td>
<td>Persistent course of CT confirmed AD</td>
<td>NR</td>
<td>NR</td>
<td>3 (13%)</td>
</tr>
<tr>
<td>Study, year (and country)</td>
<td>Study design</td>
<td>Reason(s) for exclusion</td>
<td>No of patients</td>
<td>Type of patients</td>
<td>Age</td>
<td>ACN CRC AA</td>
<td>Conclusion</td>
</tr>
<tr>
<td>---------------------------</td>
<td>--------------</td>
<td>-------------------------</td>
<td>---------------</td>
<td>----------------</td>
<td>-----</td>
<td>-----------</td>
<td>------------</td>
</tr>
<tr>
<td>Hjern et al., 2007, United States</td>
<td>Prospective comparative (control group: CTC)</td>
<td>Not all CT diagnosis (3 based on clinical signs and 3 on surgical findings instead)</td>
<td>57</td>
<td>Recent episode of acute diverticulitis</td>
<td>NR</td>
<td>NR</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

ACN, Advanced Colonic Neoplasia; CRC, Colorectal Carcinoma; AA, Advanced Adenoma; CT, Computed Tomography; AD, Acute Diverticulitis; NR, not reported; FU, Follow-up; CTC, CT-colonography; DD, Diverticular disease.

*Values are means (± SD).
†Values are medians (range).
As a result of surgical follow-up, another selection bias might have been introduced because a minority of patients needs surgery after AD. Barium enema, a follow-up method used in 2 studies, is less reliable. Full bowel preparation is needed and test performance is low: sensitivity for lesions ≥ 10 mm and ≥ 6 mm was only 48% and 35%, respectively, in a high-risk cohort.\textsuperscript{36} Sai et al\textsuperscript{7} presented an estimated pooled CRC prevalence of 2.1% (95% CI, 1.2%-3.2%), which is somewhat higher than the 1.5% in the current review. Based on a comparison with a prevalence of 0.68% as calculated in a general population in the United States, their conclusion was that there are limited data to support the recommendation to perform colonoscopy after a diagnosis of AD. Since acceptance of Sai et al’s review in December 2011, several articles and abstracts have been published on this topic. Therefore, our systematic review can provide a more up-to-date and reliable answer.

Most studies included in our review were of moderate methodological quality and pooled data with limited evidence of heterogeneity. Statistical power calculations were not done in the included studies. As a consequence, the relatively small number of patients included in the studies might cause a beta error in the conclusion that the yield of colonoscopy is equal or lower in patients after imaging-proven diverticulitis as compared with the yield in a general population, because a huge number of patients are needed to detect a significant difference.

A drawback of the available studies was the study design. Because there was a lack of an adequate control group in all included studies, namely a cohort of average risk healthy individuals of similar age, the main question still remains whether patients with diverticulitis have an increased ACN rate or not. To answer this question, most studies compared their prevalence with previous published data concerning colonic screening in asymptomatic populations or with epidemiologic data found in population-based registries, as we did. The number of colonoscopies that need to be performed in patients with an imaging-proven diagnosis of AD to detect 1 extra CRC is 122 (1/[0.015-0.0068]), based on our study’s pooled prevalence of 1.5% and a general population prevalence of 0.68%.

Another important limitation of this study is selection bias in individual studies. First, in 2 studies the diagnosis of AD was not solely made by CT but was based on US as well.\textsuperscript{10,11} As a result, because this modality is more dependent on the accuracy of radiology interpretation, adverse events of AD could have been underestimated and smaller malignant lesions missed. Second, there is also a possibility of selection bias because the overall detection rate could have been higher in those patients with CT findings of complicated features of diverticulitis. Schout et al\textsuperscript{11} also included patients with intra-abdominal abscesses and reported a CRC prevalence of 2.1%. Lau et al\textsuperscript{14} concluded that a significantly higher proportion of CRC was found in patients with abscess, local perforation, or fistula noted on the CT report compared with those without abscess.
Elramah et al\textsuperscript{20}, an excluded study, found that patients with a mass effect as an atypical CT finding were at greatest risk. Not all studies described the histologic definitions of ACN and AA clearly; as a result, detection bias could have arisen. Moreover, 3 studies did not report on AA yield, and therefore ACN prevalence could not be extracted.\textsuperscript{5,9,11}

There is marked heterogeneity in types of reported data in included studies, thereby limiting the information that could be extracted. Age is an important known risk factor for developing ACN. Increasing age has a weak, but significant, association with ACN detected by colonoscopy with an odds ratio of 1.06 per year (95% CI, 1.03-1.10).\textsuperscript{36} Age was reported incompletely. A higher age at colonoscopy could have led to an overestimation of our reported ACN prevalence. Lau et al\textsuperscript{14}, however, described that the incidence rate ratios for CRC appear to be much higher in the younger age group (aged 40-64 years) compared with older patients. Another limitation is the inability to know in which studies patients had undergone colonoscopy before AD because not all studies reported these data. The expected incidence rate of neoplasia may be higher in individuals who have not undergone prior colonoscopy. Furthermore, more than half of the studies did not mention adverse events because of colonoscopy, thereby limiting our ability to assess safety of colonoscopy after AD. Colonoscopy, however, is not without risk, with the most serious adverse event being perforation at nearly 0.1\%.\textsuperscript{37} In a prospective study on early colonoscopy in complicated sigmoid diverticulitis, no endoscopy-related adverse events occurred,\textsuperscript{32} although in patients with diverticulitis there is a potential risk of turning a sealed perforation into a free one while performing colonoscopy.

The interpretation of this systematic report might be hampered by publication bias because all funnel plots are asymmetrical. In several studies no publications were found, only congress abstracts. We excluded abstracts in this study because not all data can be obtained or verified. Moreover, selective reporting never can be excluded.

Our review does not involve the possible higher lifetime risk of developing CRC. There are 2 studies concerning the lifetime relationship between diverticulitis and CRC.\textsuperscript{38,39} One described a longitudinal case-control study in 7,159 patients with a prior diverticulitis and a follow-up of at least 20 years in which they find an increased risk (odds ratio, 4.2) for left-sided CRC.\textsuperscript{38} The other study was a cross-sectional retrospective study, analyzing the colonoscopy reports of complete colonoscopies and pathohistological results of all patients referred for colonoscopy in a period of 3 months in 18 hospitals in The Netherlands.\textsuperscript{39} No increased risk for polyps or CRC was found in patients with diverticulitis. Despite common etiologic factors, similar epidemiological characteristics, and corresponding disease localization between both disease entities, results on a possible association were contradictory.

A meta-analysis performed in 2008 involving 68,324 participants, aiming to determine the diagnostic yield of colonic evaluation in asymptomatic populations of 50 years and
older, demonstrated that the overall prevalence of ACN was 5.8% (95% CI, 4%-6%) and of CRC 0.78% (95% CI, 0.13%-2.97%). Recent studies, however, suggest a higher prevalence of ACN and CRC. German registries reported ACN prevalence of 7.9% in the German colonoscopy screening program, more or less comparable with a recent Dutch invitational population-based screening program that demonstrated ACN prevalence of 8.7%. Quintero et al reported an ACN rate of 10.8% in a Spanish colonoscopy screening program. The results of our review therefore suggest that patients with imaging-proven uncomplicated AD have a prevalence of ACN less than that of the general population but a prevalence of CRC somewhat higher. A possible explanation for this remarkable finding may be the quality of the follow-up colonoscopy. First, only 3 studies had an adequate cecal intubation rate ≥ 90%, as defined by Rex et al. Incomplete colonoscopies are not unusual in patients with diverticular disease. In patients with diverticulitis, the failures mostly result from excessive pain. Luminal narrowing, spasm, muscular hypertrophy, and fixation can be the cause of technical difficulties in intubating the sigmoid. Thus, the ACN detection rate can be underestimated in our review because of incomplete colonoscopies. This is reflected by the relatively low ADR of less than 15%. Some studies only reported the most advanced detected lesion. Our reported ADR could therefore be an underestimation of the true prevalence. Withdrawal time is a modifiable factor related to the ADR in CRC screening colonoscopies. Included studies, however, did not present their withdrawal times. Most studies did not identify who performed the colonoscopy, although most authors were from surgical departments. Provider specialty is related to colonoscopy effectiveness; a colonoscopy performed by a gastroenterologist is more likely to result in the removal of polyps than a colonoscopy performed by providers who are not gastroenterologists. In average-risk populations, ADRs of less than 20% are associated with interval CRC. Therefore, quality guidelines proposed this percentage as the lower achievable limit. The low ADR in this review suggests low-quality follow-up colonoscopies and therefore an underestimation of polyp detection, as well as ACN detection. Finally, colonoscopy is not infallible: tandem studies have shown that 2% of large adenomas and 22% of all adenomas are missed during colonoscopy.

Most included studies reported periods between AD and follow-up colonoscopy of less than 6 months. Elmi et al, however, had a longer period of 5.3 years (34.8% was performed within 6 months). This could possibly have resulted in a higher ACN rate because of the development of interval CRC. Indeed, the CRC rate was 2.2%, which was relatively high. Other included studies, apart from Westwood et al, who did not present exact data on the period, presented periods of less than 6 months. Therefore, we believe the proportion of patients who may have developed interval cancers after their diagnosis of AD to be minimal. None of studies mentioned results on serrated polyps, although these account for 10% to 20% of all CRC and more than 30% of interval cancers in average-risk individuals.
In conclusion, the available data presented in this systematic review suggest that the malignancy rate as detected with colonoscopy after imaging-proven uncomplicated AD is low; the ACN rate is lower and the CRC rate somewhat higher than in asymptomatic populations. Convincing data are lacking, however, because of limitations of included studies, such as moderate methodological quality, lack of an adequate control group, selection bias, and low quality of colonoscopies. The available data, although limited, do not support the current recommendation to routinely perform colonoscopy after uncomplicated diverticulitis. We believe a more refined approach to the general recommendation of colonoscopy after an imaging proven diagnosis of AD may be considered. The question arises whether follow-up colonoscopy should be targeted to higher-risk patients. These might be cases with complicated diverticulitis, suspicious radiological findings, or a protracted clinical course. Patients who have not undergone age-appropriate screening recently can safely undergo colonoscopy after AD, because an increased risk of adverse events has not been documented in these patients. A definitive study would require a large prospective cohort of patients with colonoscopy after an episode of AD compared with an asymptomatic screening cohort with an appropriate power analysis and colonoscopies that fulfilled the criteria as advised in colonoscopy quality guidelines.
REFERENCES


Chapter 5

Yield of colonoscopy after recent CT-proven uncomplicated acute diverticulitis: A comparative cohort study

Daniels L
Ünlü Ç
de Wijkerslooth TR
Stockmann HB
Kuipers EJ
Boermeester MA
Dekker E

Surg Endosc 2014 [Epub ahead of print]
ABSTRACT

Background
Current guidelines recommend routine follow-up colonoscopy after acute diverticulitis to confirm the diagnosis and exclude malignancy. Its value, however, has recently been questioned because of contradictory study results. Our objective was to compare the colonoscopic detection rate of advanced colonic neoplasia (ACN), comprising colorectal cancer (CRC) and advanced adenoma (AA), in patients after a CT-proven primary episode of uncomplicated acute diverticulitis with average risk participants in a primary colonoscopy CRC screening program.

Methods
A retrospective comparison was performed of prospectively collected data from cohorts derived from two multicenter randomized clinical trials executed in the Netherlands between 2009 and 2013. 401 uncomplicated diverticulitis patients and 1,426 CRC screening participants underwent colonic evaluation by colonoscopy. Main outcome was the diagnostic yield for ACN, calculated as number of diverticulitis patients and screening participants with ACN relative to their totals, with differences expressed as odds ratios (OR). The histopathology outcome of removed lesions during colonoscopy was used as definitive diagnosis.

Results
AA detection was similar [5.5 vs. 8.7%; OR 0.62 (95% CI 0.38-1.01); \( P = 0.053 \)]. CRC was detected in 1.2% (5/401) of diverticulitis patients versus 0.6% (9/1,426) of screening participants [OR 1.30 (95% CI 0.39-4.36); \( P = 0.673 \)]. ACN was diagnosed in 6.7% (27/401) of diverticulitis patients versus 9.1% (130/1,426) of screening participants [OR 0.71 (95% CI 0.45-1.11); \( P = 0.134 \)]. ORs were adjusted for age, family history of CRC, smoking, BMI, and cecal intubation rate.

Conclusions
ACN detection does not differ significantly between patients with recent uncomplicated diverticulitis and average risk screening participants. Routine follow-up colonoscopy after primary CT-proven uncomplicated left-sided acute diverticulitis can be omitted; these patients can participate in CRC screening programs. Follow-up colonoscopy may be beneficial when targeted at high-risk patients, but such an approach first needs prospective evaluation.
INTRODUCTION

Current international guidelines recommend the use of ultrasonography (US) or computed tomography (CT) to diagnose acute diverticulitis, grade the severity of disease and assess for complications. \(^1-4\) Subsequent colonic evaluation, preferably colonoscopy, is advised to confirm the diagnosis and exclude other diagnoses, colorectal carcinoma (CRC) in particular. \(^1-3,5-9\) Importantly, the recommendation for colonoscopy is merely based on expert opinion and dates back to the time before widespread use of CT to diagnose acute diverticulitis. With high sensitivity (94%) and specificity (99%) of CT for diagnosing diverticulitis, and a sensitivity ranging between 50% and 100% for the identification of alternative diseases, the need for routine colonoscopy after CT-proven acute diverticulitis can be questioned. \(^10\) Recently several, mostly retrospective, studies assessing the yield of routine colonic evaluation after an episode of acute diverticulitis have been published. \(^11-25\) The results are contradictory but some authors deem current practice unnecessary. Furthermore, colonoscopy is invasive, burdensome, costly, time-consuming, can be accompanied by procedure-related morbidity \(^26\), and its availability is limited.

Therefore, it is important to clarify whether it is justified to prioritize patients with a CT diagnosis of acute diverticulitis above those eligible for population-based screening for CRC. We hypothesized that the detection of advanced colonic neoplasia (ACN), comprising CRC and advanced adenoma (AA), in diverticulitis patients is equivalent to or lower than in individuals eligible for primary colonoscopy screening. In a prospective, comparative cohort study, we compared the diagnostic yield of patients following a CT-proven episode of uncomplicated acute diverticulitis with average risk participants in a primary colonoscopy screening program for CRC. Hereby, conclusions on the indication and current recommendation for routine colonoscopy after a primary episode of uncomplicated acute diverticulitis can be drawn.

METHODS

Design

This study was a retrospective comparison of prospectively collected data of two cohorts: a primary colonoscopy screening population and a cohort of uncomplicated acute diverticulitis patients. The cohorts were derived from two multicenter randomized clinical trials (RCTs) that were performed in the Netherlands in the period June 2009–August 2010 and June 2010–April 2013, respectively. \(^27,28\) Ethical approval for both trials was obtained and all participants gave informed consent. Both trials were registered in the Netherlands Trial Registry: NTR1829 and NTR2069, respectively, (http://www.trialregister.nl) and the DIABOLO trial also at ClinicalTrials.gov: NCT01111253.
Participants
Data for the screening cohort were collected in the randomized, multicenter ‘Colonoscopy or Colonography for Screening’ (COCOS) trial. This cohort consisted of individuals from the general population, randomly selected from the regional municipal administration, aged 50–75 years, and living in the wider Amsterdam and Rotterdam regions. Only those participants who were randomly invited for primary colonoscopy screening and decided to participate were included in the current study. The overall design of this study as well as its main results in terms of participation and diagnostic yield have been published before.

The diverticulitis cohort consisted of adult patients with CT-proven uncomplicated left-sided acute diverticulitis. None of the included patients had a previous attack of diverticulitis; all patients had a primary episode. These patients were included in one of 22 hospitals, all teaching hospitals from different regions in the Netherlands and two large academic tertiary referral centers, participating in the DIABOLO Trial. This trial was a multicenter RCT investigating the cost-effectiveness of treatment strategies with or without antibiotics for uncomplicated acute diverticulitis. Patients who had undergone follow-up colonoscopy within 6 months were included in this study. Collected data were stored anonymously.

Colonoscopy
Colonoscopies in the screening cohort were performed at one of two participating centers by a dedicated study team of experienced gastroenterologists (≥ 1,000 colonoscopies) and done according to the standard quality indicators as defined by the society of gastrointestinal endoscopy. A strict study protocol was used and research staff attended all colonoscopies and prospectively recorded (in case report forms) colonoscopy quality indicators and data on polyp detection, as the main outcome of the COCOS trial was the yield of colonoscopy.

In the diverticulitis cohort, all colonoscopies were performed according to local protocol by experienced gastroenterologists and/or colorectal surgeons. The colonoscopy findings were collected prospectively as well, though polyp removal and registration were not protocoled. At the time both trials were performed, there was no national CRC screening program in The Netherlands.

Study parameters and outcomes
Baseline characteristics in the screening individuals were collected from the regional municipal administration, asked via a pre-colonoscopy consultation and through a questionnaire. Data regarding diverticulitis patient baseline characteristics were collected from hospital admission forms and a questionnaire. Furthermore, the hospital records of all diverticulitis patients were reviewed to identify patients who underwent colon surgery and were diagnosed with CRC. CT reports were used to determine the modified Hinchey
classification and extract CT signs suggestive of complicated disease or malignancy. The interval between the acute diverticulitis episode and colonoscopy was registered.

In both cohorts, the quality of the colonic evaluation was determined by assessing the endpoint of colonoscopy, colon visualization, and reasons for an incomplete procedure. Procedure-related adverse events were recorded as well.

The primary outcome was the diagnostic yield of colonoscopy for ACN, comprising CRC and AA. This was calculated as number of acute diverticulitis patients and screening individuals with ACN, relative to the total number of patients and individuals, respectively. We used the histopathology outcome of removed lesions as definitive diagnosis. All polyps were recorded and lesions were subsequently classified as 1: serrated polyp, including hyperplastic polyps, sessile serrated lesions, and/or traditional serrated lesions, 2: adenoma, including tubular adenoma, tubulovillous adenoma, and/or villous adenoma, or 3: carcinoma. Dysplasia was assessed as either low or high grade. Histology was defined according to the Vienna criteria. AA was defined as an adenoma ≥ 10 mm, or with a ≥ 25% villous component, or with high-grade dysplasia. ACN comprised CRC and AA altogether. Of all lesions, localization was recorded. All parameters were collected in case report forms.

Sample size calculation
We hypothesized that the rate of ACN, as detected with colonoscopy, in the diverticulitis cohort would lie at or below the rate in the screening population. Therefore, we used a non-inferiority design. The screening cohort ACN rate was 9%. We considered a 2% absolute increase in ACN (increase from 9 to 11%) in the diverticulitis cohort to be a clinically relevant difference and to be inferior. For the alternative hypothesis, we assumed the ACN rate in the diverticulitis cohort would be lower than the rate in the screening cohort. We would then expect the ACN rate in the diverticulitis cohort to be 6.75%. Sample sizes of 350 patients in the diverticulitis cohort and 1,400 individuals in the screening cohort would provide an 80% power to detect a non-inferiority margin difference of 2% between the group rates. The power was computed for the case when the actual diverticulitis cohort rate would be 6.75%. The test statistic used was the one-sided Z test (pooled). The significance level of the test was targeted at $P < 0.05$.

Statistical analysis
Continuous variables were summarized as either means with corresponding standard deviations or medians with interquartile range depending on normality. Student t test was used for comparing continuous variables when data were normally distributed; in other cases, Mann–Whitney U test was used. Normality was assessed using Q–Q plots and by performing the Shapiro–Wilk test. Categorical variables were compared using the Chi-Square, Fisher’s exact test, or Linear-by-Linear Association when appropriate. Differences in diagnostic yield of colonoscopy for the primary outcome were expressed as odds ratios (OR) with 95% confidence intervals (CI), and ORs were also calculated.
adjusted for significant patient and endoscopy characteristics. Statistical significance was defined as a two-sided $P < 0.05$. Statistical analysis was performed using SPSS, version 21.0 (SPSS Inc., Chicago, IL, USA).

**RESULTS**

**Subject inclusion**

During the study period, 570 patients presented at the emergency department with clinical suspicion of uncomplicated acute diverticulitis. Of these, 57 were excluded on the basis of DIABOLO trial exclusion criteria and premature termination of study. Of 513 remaining patients with a CT-proven diagnosis of primary left-sided uncomplicated acute diverticulitis, another 112 patients were excluded since they did not undergo follow-up endoscopy at all, not within a 6-month interval or they were evaluated by means of sigmoidoscopy, leaving 401 patients for analysis. Of the 6,600 individuals from the general population invited for screening colonoscopy, 1,426 participated in the screening program (Figure 1).

**Patient characteristics**

The clinical characteristics of included and excluded diverticulitis patients were similar, with the exception of a shorter duration of gastrointestinal complaints in excluded patients [median duration, 3 (IQR 1–5) vs. 3 (IQR 2–5); $P = 0.039$]. Table 1 compares the characteristics of the diverticulitis patients with the screening individuals. The diverticulitis patients were significantly younger (median age, 57 vs. 60 years; $P < 0.001$), had a higher body mass index (median 26.9 vs. 26.0; $P = 0.002$), and were more often smokers or ex-smokers ($P < 0.001$). Significantly, more screening individuals had a family history of CRC; 15.3% as compared to 9.5% in the diverticulitis cohort ($P = 0.003$). The median duration of gastrointestinal complaints in the diverticulitis patients was 3 days. The majority (92.5%) was classified as Hinchey 1A diverticulitis, and most patients (84.3 %) were recovered at the time of endoscopy.
Patients with clinical suspicion of uncomplicated acute diverticulitis

Patients excluded
- 25 Excluded from DIABOLO Trial
- 2 Diverticulitis-negative CT
- 6 Immunosuppressed
- 6 Antibiotic use in the 4 weeks prior to inclusion
- 4 Previous episode AD
- 6 Complicated diverticulitis
- 6 No informed consent
- 32 Premature end of study

Diverticulitis patients included in the analysis

Colonoscopy characteristics

The median time interval between the diagnosis diverticulitis and colonoscopy was 55 days. In 92.3% (370/401) of diverticulitis patients, diverticula were described in the endoscopy report. The cecum was intubated in 91.3% (366/401) of the diverticulitis patients compared to in 98.2% (1,401/1,426) of the screening individuals (P < 0.001). In a total of 79 subjects, visualization of the colon was incomplete—in 14.2% (57/401) of diverticulitis patients and 1.5% (22/1,426) of screening individuals (P < 0.001). In 42% (24/57) of diverticulitis patients and in 23% (5/22) of screening individuals with incomplete visualization, fecal contamination was the cause. Furthermore, difficult anatomy of the colon was the cause of incomplete visualization in 37% (21/57) of diverticulitis patients versus in 36% (8/22) of screening individuals. In the diverticulitis cohort, stricture or stenosis was accountable for this difficult anatomy in majority of cases. In the screening cohort, pain was an important cause as well and accounted for 27% (6/22) of cases of incomplete visualization, whereas in the diverticulitis patients, pain was the cause in only 14% (8/57).

The number of procedure-related serious adverse events did not differ significantly between the two cohorts; 0.7% (3/401) in the diverticulitis cohort versus 0.4% (5/1,426) in the screening cohort (P = 0.384). In each cohort, two post-polypectomy bleedings occurred. No colonic perforations were reported.
Table 1 | Characteristics of diverticulitis patients and screening individuals*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Diverticulitis patients (N=401)</th>
<th>Screening individuals (N=1426)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57 (49-65)</td>
<td>60 (55-65)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Male</td>
<td>191 (47.6%)</td>
<td>726 (50.9%)</td>
<td>0.246 †</td>
</tr>
<tr>
<td>Family history of CRC ‡</td>
<td>38 (9.5%)</td>
<td>218 (15.3%)</td>
<td>0.003 †</td>
</tr>
<tr>
<td>Smoking (14 vs 9 missing)</td>
<td></td>
<td></td>
<td>&lt; 0.001 †</td>
</tr>
<tr>
<td>Never</td>
<td>169 (42.1%)</td>
<td>890 (62.4%)</td>
<td></td>
</tr>
<tr>
<td>Stopped</td>
<td>113 (28.2%)</td>
<td>312 (21.9%)</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>105 (26.2%)</td>
<td>215 (15.1%)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.9 (24.5-30.3)</td>
<td>26.0 (23.8-28.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>Duration of complaints (days)</td>
<td>3.0 (2.0-5.0)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Modified Hinchey classification†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1a</td>
<td>371 (92.5%)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>1b</td>
<td>30 (7.5%)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Recovery at endoscopy §</td>
<td>338 (84.3%)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

CRC, colorectal carcinoma; BMI, body mass index; AD, acute diverticulitis; NA, not applicable; † Group differences were tested with the Fisher’s Exact test, Pearson χ² test or Linear-by-Linear Association, as appropriate; ‡ A family history of CRC was defined as having at least one affected first-degree relative; § Recovery was defined by all of the following criteria: outpatient, normal diet (defined by tolerating solid food and more than 1L of fluid orally), temperature < 38.0 °C, and Visual Analog Scale pain score < 4, with no use of daily pain medication and resuming to pre-illness working activities.

Main outcomes

Table 2 presents main outcomes and additionally the total number of lesions and its characteristics for the two cohorts. The number of subjects with polyps (38.7 vs. 49.6%), serrated polyps (13.2 vs. 27.2%), and adenoma (19.0 vs. 29.4%) detected at colonoscopy was significantly lower in the diverticulitis cohort than in the screening cohort (P < 0.001). Further, AA was detected less often in the diverticulitis cohort [5.5 vs. 8.7%; crude OR 0.61 (95% CI 0.38–0.97); P = 0.036 and adjusted OR 0.62 (95% CI 0.38–1.01); P = 0.053]. CRC was diagnosed in 1.2% (5/401) of diverticulitis patients and 0.6% (9/1,426) of screening individuals [crude OR 1.99 (95% CI 0.66–5.97); P = 0.205 and adjusted OR 1.30 (95% CI 0.39–4.36); P = 0.673]. The number of subjects with ACN did not differ significantly between both cohorts; 6.7% (27/401) of diverticulitis patients versus 9.1% (130/1,426) of screening individuals [crude OR 0.72 (95% CI 0.47–1.11); P = 0.132 and adjusted OR 0.71 (95% CI 0.45–1.11); P = 0.134]. ORs were adjusted for age, family history of CRC, smoking, BMI, and cecal intubation rate, since these characteristics were significantly different between groups.
We also analyzed the data only for those with a completion colonoscopy: 91.3% (366/401) of the diverticulitis patients and 98.2% (1,401/1,426) of the screening individuals. The results were similar to the results of the analyses of the total cohort, with ORs now adjusted for age, family history of CRC, smoking, and BMI. The adjusted OR for AA was 0.66 (95% CI 0.40–1.08; \(P = 0.095\)), the adjusted OR for CRC was 0.75 (95% CI 0.16–3.53; \(P = 0.711\)), and the adjusted OR for ACN was 0.68 (95% CI 0.42–1.10; \(P = 0.115\)).

Most lesions were localized left sided; 100% (5/5) versus 77.8% (7/9) of CRCs (\(P = 0.505\)), and 77.4% (24/31) versus 71.5% (123/172) of ACNs (\(P = 0.498\)) in diverticulitis patients and screening individuals, respectively. The median age at diagnosis ACN did not differ significantly between the two cohorts (61 vs. 62 years; \(P = 0.554\)).

**ACN and CRC patients in the diverticulitis cohort**

The median time interval between the initial diagnosis diverticulitis and the diagnoses CRC and ACN was 48 days (IQR 35–91) and 66 days (IQR 48–84) respectively (Table 2). Of five CRCs (in three men and two women), four were diagnosed by colonoscopy within 3 months; one was detected with an interval of 130 days. Of 27 ACN patients in all but five, the diagnosis was made within a 3-month interval.

In only one CRC patient, diverticula were described in the endoscopy report. Review of the CT reports showed that in all five CRC patients inflammation involving the sigmoid colon was described, with diverticulitis designated as potential diagnosis by the radiologist, but without diverticula being reported. Furthermore, other CT signs inconsistent with uncomplicated diverticulitis were present: two patients were classified with a small abscess (Hinchey 1b), three had localized perforation, one had free fluid, three had suspicious lymph nodes, and in two CRC was specifically mentioned by the radiologist as alternative diagnosis for diverticulitis. Two CRC patients did not meet the criteria for recovery within the 6-month follow-up period.
### Table 2 | Outcomes compared on subject level and total numbers of lesions with characteristics within cohorts

<table>
<thead>
<tr>
<th>Lesion type (and characteristics)</th>
<th>Diverticulitis patients (N=401)</th>
<th>Screening individuals (N=1426)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N with lesion</td>
<td>Total lesions</td>
<td>N with lesion</td>
</tr>
<tr>
<td>Polyp</td>
<td>155 (38.7%)</td>
<td>330</td>
<td>707 (49.6%)</td>
</tr>
<tr>
<td>Serrated polyp</td>
<td>53 (13.2%)</td>
<td>113</td>
<td>388 (27.2%)</td>
</tr>
<tr>
<td>Hyperplastic</td>
<td>109</td>
<td></td>
<td>633</td>
</tr>
<tr>
<td>Sessile</td>
<td>4</td>
<td>111</td>
<td>1</td>
</tr>
<tr>
<td>Traditional</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Adenoma</td>
<td>76 (19.0%)</td>
<td>103</td>
<td>419 (29.4%)</td>
</tr>
<tr>
<td>Tubular</td>
<td>87</td>
<td>675</td>
<td></td>
</tr>
<tr>
<td>Tubulovillous</td>
<td>15</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>Villous</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>(Missing 0 vs 16)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesion size ≥ 10mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HG dysplasia</td>
<td>10 (2.5%)</td>
<td>11</td>
<td>95 (6.7%)</td>
</tr>
<tr>
<td>AA</td>
<td>4 (1.0%)</td>
<td>7</td>
<td>34 (2.4%)</td>
</tr>
<tr>
<td>Time to diagnosis (days)†</td>
<td>71 (53-85)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>CRC</td>
<td>5 (1.2%)</td>
<td>5</td>
<td>9 (0.6%)</td>
</tr>
<tr>
<td>Time to diagnosis (days)†</td>
<td>48 (35-91)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>ACN</td>
<td>27 (6.7%)</td>
<td>31</td>
<td>130 (9.1%)</td>
</tr>
<tr>
<td>Time to diagnosis (days)†</td>
<td>66 (48-84)</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

HG, high-grade; AA, advanced adenoma; NA, not applicable; CRC, colorectal carcinoma; ACN, advanced colonic neoplasia;

* Group differences between diverticulitis patients with lesions and controls with lesions were tested with the Pearson χ² test or Fisher’s Exact test, as appropriate, and P-values are unadjusted;

† Values are medians with interquartile ranges (IQR);

‡ Not significant anymore (P=0.053) after adjustment for age, family history of CRC, smoking, BMI and cecal intubation rate.
DISCUSSION

We compared the colonoscopic yield of ACN, comprising CRC and AA, between patients with a recent primary episode of CT-proven uncomplicated left-sided acute diverticulitis and average risk participants in a population CRC screening program by colonoscopy. The detection rate of CRC, AA, and ACN did not differ significantly between the groups.

This study is the first cohort study that directly compared the diagnostic yield of follow-up colonoscopy after uncomplicated acute diverticulitis with the yield of screening colonoscopy in an asymptomatic population with adequate power. The control cohort in this study was relatively homogenous. We included participants who were randomly selected from the population registry and who all underwent a primary screening colonoscopy. The diverticulitis cohort consisted of consecutive patients from more than 20 large teaching hospitals throughout the Netherlands. Therefore, our results are representative for the general Dutch population and most likely for other large urban health region populations. Further, research staff prospectively recorded various data ensuring accurate and optimal data registry.

A number of potential limitations should also be acknowledged. We did not include patients with complicated diverticulitis. As a consequence, our results cannot be extrapolated to this category of diverticulitis patients. Further, the cohorts in our study were different for some baseline characteristics. The diverticulitis patients were significantly younger than the screening individuals, but ages at diagnosis ACN did not differ significantly between the two cohorts. Higher age is a known risk factor for the development of ACN. A lower age in the diverticulitis cohort could therefore have led to a lower ACN rate. Furthermore, the two cohorts were unbalanced with regard to the BMI, which was significantly higher in diverticulitis patients. Overweight and obesity are known to be moderately associated with an increased risk of CRC in men and similar trends exist for adenoma. The results of a recent nested case–control study performed within a large Italian CRC screening program indicate that this association exists, but for right-sided CRC only, which was not found in our diverticulitis cohort. Smoking and family history positive of CRC, also known risk factors significantly associated with ACN detected by colonoscopy, were unevenly distributed between the cohorts and could have effected detection rates. However, we do not expect these differences have influenced our results since similar outcomes were obtained when ORs were adjusted for these confounding factors.

The cecal intubation rate was significantly lower in the diverticulitis cohort than in the screening cohort. Also several earlier, mostly retrospective, cohort studies evaluating the yield of colonoscopy after acute diverticulitis reported similar completion rates of about 90%. Although the 95% quality indicator level was not reached in our diverticulitis cohort, the cecal intubation rate was well above the 80.7% achieved in a series of 12,835 colonoscopies in an Italian prospective study of routine clinical practice.
In our study, inadequate bowel preparation (i.e. fecal contamination) was found to be the most frequent reason for incomplete visualization (42% vs. 23% in the screening cohort). Fecal contamination, luminal narrowing, and stenosis as encountered in our cohort, and not unusual in diverticulitis patients, are known factors related to cecal intubation failure. Diverticulosis also is known to be associated with lower completion rates. This may have led to an underestimation of the true colonic neoplasia prevalence in the diverticulitis cohort. Further, endoscopists who participated in the diverticulitis study did not remove all detected lesions as they were considered benign or irrelevant, which is according to daily practice. Endoscopists in the screening cohort were instructed to remove all detected lesions. Lastly, withdrawal time was not registered in the diverticulitis group. This may have resulted in a shorter inspection time and in worse polyp detection in this group, consequently.

The CRC rate in our diverticulitis cohort is lower than the pooled prevalence of three recent meta-analyses. In 2012, Sai et al. published a systematic review concerning colonoscopy after a CT diagnosis of acute diverticulitis to exclude CRC. Patients with follow-up by means of surgery or barium enema were included as well. Their meta-analysis of 771 patients resulted in an estimated pooled CRC prevalence of 2.1% (95% CI 1.2–3.2). After comparison with a calculated estimated prevalence of 0.68% among United States adults older than 55 years their conclusion was that there are limited data to support the recommendation to perform colonoscopy after a CT diagnosis of acute diverticulitis. By including patients with radiological features suspicious for neoplasia, it can be expected this has resulted in a higher yield of CRC at subsequent colonoscopy. More recently, Sharma et al. performed a similar meta-analysis of 1,970 diverticulitis patients with colonic evaluation by means of sigmoidoscopy, CT colonography, colonoscopy, or contrast enema studies. They found a pooled proportional estimate of 1.6% (95% CI 0.9–2.8) and concluded the risk of CRC after a radiological proven episode of uncomplicated acute diverticulitis is low. Some of included studies in these meta-analyses dealt with patients without an imaging-proven diagnosis, with complicated or persistent diverticulitis, or with patients with CT patterns of tumor-like lesions and are in our opinion not comparable to our population. But most cohorts are more or less comparable to ours since authors included mainly patients with an imaging proven diagnosis of uncomplicated acute diverticulitis and found CRC and ACN rates of 0–2.7 and 3.4–9.2%, respectively, in accordance with the results of our study. A third recent meta-analysis included only patients with a recent diagnosis of uncomplicated acute diverticulitis that had to be confirmed by US and/or CT imaging, and thus diverticulitis patients that are comparable to ours. In 1,796 patients, an estimated pooled CRC prevalence of 1.5% (95% CI 1.0–2.3) was found. Importantly, most studies included in these meta-analyses were retrospective, all lacked an adequate control group and in none statistical power calculations were done.
When we consider the CRC patients in our diverticulitis cohort, we can notice that none had diverticula described in the CT report. Furthermore, three CRC patients had one or more signs at CT that could have raised suspicion for malignancy. Nevertheless, in these cases the radiologist reported diverticulitis as most likely potential diagnosis. Although occasionally diverticulitis may occur concomitantly with CRC, in some cases of a presumed episode of diverticulitis, especially when diverticula are absent both on imaging and endoscopy, you may conclude afterward the diagnosis acute diverticulitis was a wrongful diagnosis and CRC was missed at primary assessment. The diagnostic approach should be different between patients with 'clear diverticulitis' and with 'doubtful diverticulitis,' i.e. when a diagnostic dilemma exists.

In summary, we showed that colonoscopic detection of ACN after uncomplicated acute diverticulitis is comparable to that in an average risk screening cohort. This study may have some clinical implications; follow-up colonoscopy after a primary episode of CT-proven uncomplicated left-sided acute diverticulitis can be omitted. Follow-up colonoscopy may be beneficial when targeted at high-risk patients, but uniform description of ‘high risk’ is challenging and such an approach first needs prospective evaluation. This will result in less patient burden and colonoscopy-related adverse events. Further, it will restrict national health care costs. Patients with uncomplicated acute diverticulitis patients may then participate in a national CRC screening program after adequate therapy and the disappearance of symptoms.

Acknowledgment
The COCOS trial, from which the screening cohort for this study was derived, was funded by the Netherlands Organisation for Health Research and Development of the Dutch Ministry of Health (ZonMw No. 120720012), Centre for Translational Molecular Medicine (CTMM DeCoDe-project), and the Nuts Ohra Foundation (Amsterdam, The Netherlands). The DIABOLO trial, from which the diverticulitis patient cohort was derived, was also funded by ZonMw (No. 171002303) and by the Dutch Maag Lever Darm Stichting (MLDS No. WO08-54). The funders had no role in study design, data collection and analysis, data interpretation, decision to publish, writing or preparation of the manuscript.
 REFERENCES


Obesity and heavy alcohol consumption are independently 
associated with an increased risk 
of colorectal cancer: a nested case-
control study. Abstract United European 
Gastroenterology Week 2013, Berlin. 
Available at http://www.elearning. 
ueg.eu/documents-view.html?no_ 
cache=1&eprs%5Br% 5D=20787; 

37. Hazewinkel Y, Dekker E. Colonoscopy: 
basic principles and novel techniques. 
Nat Rev Gastroenterol Hepatol 
2011;8(10):554-64.

38. Radaelli F, Meucci G, Sgroi G, Minoli 
G; Italian Association of Hospital 
Gastroenterologists (AIGO). Technical 
performance of colonoscopy: the key 
role of sedation/analgesia and other 
quality indicators. Am J Gastroenterol 

39. Dafnis G, Granath F, Påhlman L, 
Ekborn A, Blomqvist P. Patient 
factors influencing the completion 
rate in colonoscopy. Dig Liver Dis 

40. Loffeld RJ, van der Putten AB. The 
completion rate of colonoscopy 
in normal daily practice: factors 
associated with failure. Digestion 

41. Anderson JC, Messina CR, Cohn W, 
Gotfried E, Ingber S, Bernstein G, 
Coman E, Polito J. Factors predictive 
of difficult colonoscopy. Gastrointest 

42. Jover R, Zapater P, Poliania E, Bujanda 
L, Lasas A, Herno JA, Cubiella J, Ono 
A, González-Méndez Y, Peris A, Pellisé 
M, Seoane A, Herreros-de-Tejada A, 
Ponce M, Marin-Gabriel JC, Chaparro 
M, Cacho G, Fernández-Diez S, Arenas 
J, Sopeña F, de-Castro L, Vega-Villaamil 
P, Rodríguez-Soler M, Carballo F, Salas 
D, Morillas JD, Andreu M, Quinto E, 
Castells A; COLONPREV study 
investigators. Modifiable endoscopic 
factors that influence the adenoma 
detection rate in colorectal cancer 
screening colonoscopies. Gastrointest 

43. Barclay RL, Vicari JJ, Doughty AS, 
Johanson JF, Greenlaw RL. 
Colonoscopic withdrawal times 
and adenoma detection during 

44. Sai VF, Velayos F, Neuhaus J, 
Westphalen AC. Colonoscopy after CT 
diagnosis of diverticulitis to exclude 
colon cancer: a systematic literature 

45. Sharma PV, Eglinton T, Hider P, 
Frizelle F. Systematic review and 
meta-analysis of the role of routine 
colonoscopic evaluation after radiologically 
confirmed acute diverticulitis. Ann 

46. Daniels L, Unlü C, de Wijkerslooth TR, 
Dekker E, Boerremeester MA. Routine 
colonoscopy after left-sided acute 
uncomplicated diverticulitis: a 
systematic review. Gastrointest Endosc 

47. Goh V, Halligan S, Taylor SA, Burling D, 
Bassett P, Bartram CI. Differentiation 
between diverticulitis and colorectal 
cancer: quantitative CT-perfusion 
measurements versus morphologic 
criteria, initial experience. Radiology 
Part 2 | Follow-up


Chapter 6

Systematic review of medical therapy to prevent recurrent diverticulitis

Ünlü Ç
Daniels L
Vrouenraets BC
Boermeester MA

Int J Colorectal Dis 2012;27(9):1131-6
ABSTRACT

Background
One of today’s controversies remains the prevention of recurrent diverticulitis. Current guidelines advise a conservative approach, based on studies showing low recurrence rates and a high operative morbidity and mortality. Conservative measures in prevention recurrence are dietary advises and medical therapies, including probiotics and 5-aminosalicylic acid. The aim of this systematic review was to assess whether medical or dietary therapies can prevent recurrent diverticulitis after a primary episode of acute diverticulitis.

Methods
We searched different databases for papers published between January 1966 and January 2011. Clinical studies were eligible for inclusion if they assessed the prevention of recurrent diverticulitis with a medical or dietary therapy. Studies without a control group were excluded.

Results
Three randomized controlled trials (RCT), all with a Jadad quality score of 2 out of 5, were included in this systematic review. Mesalazine results in significantly less disease recurrence and fewer symptoms after an acute episode. The use of probiotics decreases symptoms but does not reduce recurrence. No difference in effect is seen when Balsalazide is added to probiotics compared to probiotics only. No relevant studies on dietary therapy/advices or antibiotics for prevention of recurrent diverticulitis were found.

Conclusion
The evidence that supports medical therapy to prevent recurrent diverticulitis is of poor quality. Treatment with 5-aminosalicylic acid seems promising. Based on current data, no recommendation of any non-operative relapse prevention therapy for diverticular disease can be made.
INTRODUCTION

One of today’s controversies remains the management of recurrent diverticulitis. Until recently the guideline was based on the assumption that recurrent episodes (2 or more) of diverticulitis will lead to complicated diverticulitis and higher mortality. The data used to support this assumption were based on only a few small older studies that reported recurrence rates of more than 40% after one episode of diverticulitis with complications occurring in 30–60% of patients. Nowadays, due to advances in accuracy of diagnostic modalities and modified surgical techniques, both management and outcome of diverticulitis have changed. Current guidelines advise a more conservative approach, based on several more recent studies, showing lower recurrence rates. Moreover, multiple episodes of diverticulitis do not seem to be associated with increased mortality or an increased risk of complicated diverticulitis. The overall mortality rate for patients with a prior history of diverticulitis was 2.5%, comparing favorably with a mortality rate of 10% for patients with a first presentation of complicated diverticulitis. In addition, 78% of patients with perforated diverticulitis had no prior history of diverticulitis. Elective sigmoid resection for diverticulitis is associated with risks of mortality and colostomy as high as 2.3% and 14.2%, respectively. Furthermore, the risk of recurrent diverticulitis is not eliminated after sigmoid resection with recurrence rates between 2.6% and 10.4%. For all these reasons, conservative treatment has become the preferred choice after an episode of diverticulitis. Conservative measures in prevention of diverticulitis recurrence are dietary advises and medical therapies, including the use of probiotics and 5-aminosalicylic acid. However, the value of these conservative measures is unclear. A systematic review of these dietary and medical management to prevent recurrent diverticulitis is given.

METHODS

Systematic review

Literature search

Two authors (CU, LD) performed a literature search to identify studies investigating the effectiveness of a medical therapy in human subjects to prevent recurrence of diverticulitis. We searched MEDLINE databases for papers published between January 1966 and January 2011, using the following keywords: “Diverticulitis, Colonic” [Mesh] and “Recurrence” [Mesh] and “Therapeutics” [Mesh]. EMBASE database was searched with the following terms: diverticulitis and recurrence and therapeutics. CINAHL database was also checked for relevant studies with the following keywords: (“Diverticulitis” and “Recurrence” and “Therapy”). The Cochrane database of Systematic Reviews was searched with the following words: Diverticular disease and recurrence.
Validity assessment

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. Only clinical studies published in English were included. No unpublished data were included. A full search strategy is available at request. Two authors independently assessed the methodological quality of the articles using the Jadad score and the checklist of the Cochrane collaboration. The Jadad score is a well-known instrument assigning a numerical score between 0 and 5 to each study, reflecting its quality (0 indicating poor quality and 5 high quality). 1

Definition

In order to be able to reliably compare the data, uncomplicated diverticular disease was defined as symptomatic disease associated with colonic diverticula. This is associated with mild symptoms, usually abdominal pain and/or change in bowel habit, but without clinical features of inflammation. Diverticulosis is asymptomatic colonic diverticula. Diverticulitis is complicated diverticular disease with clinical symptoms and evidence of inflammation. Recurrent disease is characterized by the reappearance of these symptoms. Complicated diverticulitis is perforation, abscess, fistula, bleeding or stricture/obstruction, usually needing surgical or percutaneous intervention. Medical treatment is defined as any non-operative relapse prevention therapy. The following were found, dietary fibre therapy, antibiotics, probiotics and 5-aminosalicylic acid.

Inclusion and exclusion criteria

Types of studies

Clinical studies were eligible for inclusion if they assessed the medical prevention of recurrent diverticulitis. The following exclusion criteria were used for study selection: non-English literature, studies without comparison with a control group and studies that (also) included patients who were operated because of an episode of complicated diverticulitis.

Types of participants

Patients of 18 years or older diagnosed with diverticulitis were included. The diagnosis of diverticular disease had to be confirmed by radiologic evidence (Barium enema or CT scan) or colonoscopy. A diagnosis of diverticulitis on clinical grounds was allowed.

Types of interventions

All studies (prospective, retrospective, case-controlled, cohort) that assessed medical treatment to prevent recurrence were searched.

Types of outcome measures

Primary endpoint parameters for inclusion were the occurrence of recurrent diverticulitis.
RESULTS

Systematic review

The first search resulted in a combined total of 84 articles. After reviewing the abstracts, 12 articles were retrieved for more detailed information. Only three articles met our inclusion criteria and were used for this systematic review (Figure 1).

Figure 1 | Potentially relevant articles identified and screened (n=84)

Dietary fibre

No dietary fibre study met the inclusion criteria of this systematic review.

5-Aminosalicylic acid and probiotics

In a study in 2002, a total of 218 consecutive patients (131 males, 87 females age 64.3 years, range 51–79) with recurrent diverticulitis, after two attacks of diverticulitis in the same year, were monitored. Diagnosis of diverticulitis, defined as inflammation and/or infection associated with diverticula of the colon, was done by colonoscopy (123 patients) or by double contrast X-ray study of the colon (95 patients), by the presence of abdominal pain, bowel disorders and/or fever and leukocytosis. The intensity of the symptoms and bowel habits were quantified with a scale from 0 to 4.

After assessment of the acute diverticulitis attacks, patients were randomly assigned to two different groups, after giving informed consent: Group A (109 patients): rifaximin 400 mg bid plus mesalazine 800 mg tid for 7 days, followed by rifaximin 400 mg bid plus mesalazine 800 mg bid for 7 days every month; Group B (109 patients): rifaximin 400 mg bid for 7 days, followed by rifaximin 400 mg bid for 7 days every month.
Colonoscopy was performed after 3, 6 and 12 months of therapy. At end of follow-up, 193 patients were fully compliant to therapy. Recurrence of diverticulitis was evaluated on the basis of clinical and endoscopic examination. Neither diagram to show enrolment and randomization process nor sample size calculation were given. Severity of symptoms and bowel habits improved significantly in group A compared to group B, and symptomatic recurrence of diverticulitis occurred significantly less in group A (Table 1).

Table 1 | Results of Tursi et al.12

<table>
<thead>
<tr>
<th>Results of Tursi et al.12</th>
<th>Group A (Mesalazine + Rifaximin)</th>
<th>Group B (only Rifaximin)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular bowel habits</td>
<td>82 (78.8%)</td>
<td>53 (59.5%)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Symptom free</td>
<td>89 (85.6%)</td>
<td>44 (44.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recurrence of diverticulitis</td>
<td>3 (2.7%)</td>
<td>16 (18.0%)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

In 2004, the effect of probiotics on recurrent diverticulitis has been compared to no treatment after an acute attack.13 The study was carried out on 83 consecutive patients (31 males, 52 females; mean age 64.3, range 49–78) suffering from recurrent diverticulitis and with at least two attacks in the previous year. The diagnosis of diverticular disease was performed by colonoscopy or double contrast X-ray study, or both. The diagnosis of diverticulitis was based on clinical grounds. All patients were treated during the acute period of diverticulitis with oral rifaximin or with intravenous ciprofloxacin for 7–14 days, until the complete remission of laboratory findings and symptoms improvement.

After clinical recovery, 43 patients were randomly assigned to receive (group A) an oral polybacterial lysate suspension containing $80 \times 10^9$ Escherichia coli (strains 01, 02, 055 and 0111) and $1 \times 10^9$ Proteus vulgaris (Colifagina S). The study medication was administered as a twice-daily 5 ml oral medication for 2 weeks every month, within 3 months after an acute attack. The other patients were the control group. All patients received adequate dietary rules. The patients were to fill in a score-point schedule for abdominal symptoms and the intensity of symptoms was quantified on a scale from 0 to 3. The diagnostic criteria for recurrence were the same as for inclusion.

Seven out of the total 83 patients (8.4%) had a recurrence within the 3 months of the study. Two patients belonged to group A (4.6%) and 5 to group B (12.5%). The authors state that the difference between the recurrence rates in the two groups was significant ($P < 0.05$), using a Student’s t test for paired data. However, in statistical comparison of proportions a chi-square test should be used. The chi-square test of the difference is not significant ($P = 0.28$). Complete results are summarized in Table 2.
Table 2 | Results of Dughera et al.13

<table>
<thead>
<tr>
<th></th>
<th>Group A (Probiotic group) after 3 months (N=43)</th>
<th>Group B (control group) after 3 months (N=40)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent abdominal pain score</td>
<td>64</td>
<td>113</td>
<td>&lt;0.01 (ANOVA one way)</td>
</tr>
<tr>
<td>Intermittent diarrhea score</td>
<td>58</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>Abdominal bloating score</td>
<td>69</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>10</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Recurrent diverticulitis</td>
<td>2 (5%)</td>
<td>5 (12%)</td>
<td>0.28*</td>
</tr>
</tbody>
</table>

*Recalculation with chi square; published P value was P<0.05 with inappropriate use of paired t test.

In a recent small study by Tursi et al., 30 consecutive patients (19 males, 11 females; mean age 60 years, range 47–75 years) affected by uncomplicated diverticulitis of the colon were monitored. The aim was to investigate whether a combination Balsalazide and/or VSL#3, a probiotic mixture containing several billions of different bacterial strains (mainly Lactobacillus and Bifidobacteria), is effective in preventing diverticulitis recurrence.

After obtaining remission, the patients were randomly assigned to: group A, Balsalazide 2.25 g daily for 10 days every month plus VSL#3 450 billions per day for 15 days every month and group B, VSL#3 alone 450 billions per day for 15 days every month. Primary end-point was remission throughout a 12-month follow-up. Diverticulitis recurrence was evaluated on the basis of clinical and/or endoscopic examination. Secondary end-points were overall scores at the end of the follow-up and the effect on symptom score component. The intensity of the symptoms was quantified on a scale of 0–10 according to worsening of symptoms.

In Table 3, the results at the end of follow-up are summarized. No side effects were recorded throughout the follow-up in both groups. The authors have concluded that the combination of probiotic/Balsalazide is better than probiotic treatment alone in the prevention of recurrent diverticulitis. This conclusion is inappropriate since no significant difference was found.
Table 3 | Results of Tursi et al.\textsuperscript{14}

No significant difference between the Balsalazide/VSL3\# and the VSL3\# group.

<table>
<thead>
<tr>
<th></th>
<th>Group A (Balsalazide + VSL#3 after 12 months N=15)</th>
<th>Group B (VSL#3 after 12 months N=15)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent diverticulitis</td>
<td>1 (7%)</td>
<td>2 (13%)</td>
<td>ns</td>
</tr>
<tr>
<td>Symptom-free</td>
<td>11 (73%)</td>
<td>8 (60%)</td>
<td>ns</td>
</tr>
</tbody>
</table>

Antibiotics

No study evaluating the use of antibiotics meeting the inclusion criteria of this systematic review was found.

Quality assessment of the included studies

This assessment is shown in Table 4 and demonstrates the moderate quality of the available evidence (Jadad score 2 out of 5).

Table 4 | Quality assessment and study design of RCTs

<table>
<thead>
<tr>
<th>Reference</th>
<th>Tursi et al.\textsuperscript{12}</th>
<th>Dughera et al.\textsuperscript{13}</th>
<th>Tursi et al.\textsuperscript{14}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>RCT</td>
<td>RCT</td>
<td>RCT</td>
</tr>
<tr>
<td>Intervention/comparison</td>
<td>Mesalazine/Rifaximin vs Rifaximin</td>
<td>Polybacterial lysate suspension vs control group</td>
<td>Balsalazide/VSL#3 vs VSL#3</td>
</tr>
<tr>
<td>Number intervention/number comparison</td>
<td>109/109</td>
<td>41/35</td>
<td>15/15</td>
</tr>
<tr>
<td>Randomization?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Treatment allocation concealed?</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Eligibility criteria specified?</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Patient blinded?</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Outcome assessor blinded?</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Care provider blinded?</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Groups similar at baseline?</td>
<td>Yes</td>
<td>Yes</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Follow-up?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Intention to treat?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Jadad score?</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>
DISCUSSION

New medical treatment options have been introduced to lower recurrence rates after an episode of diverticulitis.\(^5,6\) In this systematic review, we present an overview of medical therapy options for the prevention of recurrence of diverticulitis. With 5-aminosalicylic acid (mesalazine) significant less disease recurrence and fewer symptoms were found.\(^12\) Probiotics decreased symptoms without an effect on diverticulitis recurrence.\(^13\) No effect was seen when Balsalazide was added to probiotics compared to probiotics only.\(^14\)

Dietary therapy for uncomplicated diverticular disease is based on the theory that decreased fibre intake may result in decreased intestinal contents and decreased size of the lumen. This results into increased pressure on the wall, which leads to the formation of diverticula at the weakest point in the wall, the so-called vasa recta being the site of penetration by blood vessels.\(^15\) Dietary therapy will increase stool transit time and decrease pressure and hypothetical therefore may prevent recurrence. In our literature search, no dietary fibre study was found enrolling patients with acute diverticulitis. A study of Hyland et al.\(^16\) enrolled 100 patients with acute diverticular disease of which 25 patients had been operated. It is not clear from that publication whether patients had diverticulitis or symptomatic diverticular disease, suggesting a mixed study population. Patients were reviewed 5 to 7 years after admission and 91 \% of the patients on high fibre diet had remained symptom-free during that period. It was concluded that high fibre diet may have a protective role and prevent further complications.

The last few decades, the pathogenesis theory of diverticular disease has changed.\(^17\) It has been suggested that the type of inflammation is similar to that occurring in chronic idiopathic inflammatory bowel disease, suggesting that patients may benefit from anti-inflammatory medication.\(^18-20\) Some studies have evaluated this theory.\(^21-24\) All studies included patients with symptomatic uncomplicated diverticular disease and excluded patients with diverticulitis. These studies reveal that mesalazine may improve symptoms and bowel habits significantly and maybe a new medical therapy for diverticular disease. Balsalazide is a pro-drug needing bacterial action to liberate the active 5-ASA molecules. Thus far, one low quality study has evaluated the effect of Balsalazide on recurrence after an episode of acute diverticulitis and showed no advantage.\(^14\)

The theory that inflammation is chronic in the formation of diverticulitis also raises the hypothesis that probiotics could be effective by stimulating immunologic processes that restore an altered microflora of the colon. This alteration of the microbial environment could result in a low grade colitis, which has then a potential to progress to acute diverticulitis.\(^25-28\) There is only one comparative study studying the effect of probiotics on recurrence of diverticulitis.\(^13\) This low quality study (Jadad <3) has shown no clear benefit of probiotics.
Antibiotics are commonly used in the treatment of inflammatory complications of diverticular disease. Apart from recommendations in several guidelines there is no evidence mandating the routine use of antibiotics in mild diverticulitis. Antibiotics have also been studied for their effect on prevention of recurrent diverticulitis. Several clinical studies suggest a role of long-term cyclic administration of the non-absorbable antibiotic drug rifaximin in the management of symptomatic uncomplicated diverticular disease of the colon. Only one study was found that studied the cyclic administration of rifaximin to prevent recurrence of lower rate of operations of 73% in the antibiotic group. The proportion of patients with primary or recurrent diverticulitis is not given, thereby prohibiting definitive conclusions on the effectiveness of rifaximin to prevent recurrence of diverticulitis. Another possible bias is that all studies included patients on mostly clinical grounds. It is known that the clinical diagnosis of acute diverticulitis is in only 43–68% of the patients correct. This could be a reason for the difference in recurrence rates (12%, 13% vs 18%) in the three studies. An explanation for this variance can be the clinical inter-observer variation of the diagnosis diverticulitis.

In conclusion, the evidence of medical treatment to prevent recurrence of diverticulitis is scarce. Studies are of poor quality. It is too early to promote the medical options such as mesalazine, probiotics or antibiotics. Future patients could benefit from the results of prospective trials. Until then, the treatment of choice after a first episode of acute diverticulitis remains a wait and see policy.
REFERENCES


PART 3
MICROBIOTA
Chapter 7

A hypothesis: Important role for gut microbiota in the etiopathogenesis of diverticular disease

Daniels L, Philipszoon LE, Boermeester MA

Dis Colon Rectum 2014;57(4):539-43
BACKGROUND

Epidemiology, Terminology, and Pathophysiology of Diverticular Disease

Diverticular disease (DD) inflicts a high socioeconomic burden on Western and industrialized countries because of an increasing incidence worldwide and, consequently, increasing admission rates and costs.1 DD is composed of a spectrum of conditions. Patients with diverticulosis have asymptomatic colonic diverticula. Uncomplicated DD is defined as symptomatic disease, associated with mild symptoms, such as abdominal pain and/or change in bowel habit. Complicated DD is diverticulitis with severe clinical symptoms and evidence of inflammation. Complicated diverticulitis is accompanied by an abscess, perforation, peritonitis, fistula, bleeding, stricture, or obstruction.

The epidemiology and pathophysiology are assumed to be clear and well understood. However, theories are currently shifting away from the traditional dogma stating that low dietary fiber predisposes to diverticulosis and fecalith obstruction of a diverticulum causes acute diverticulitis. DD was once regarded as a relatively asymptomatic disorder hampered by acute, often self-limited, attacks of diverticulitis.

More recently, the chronic component in some patients with symptomatic DD received attention, and it was suggested this condition should be regarded as a form of inflammatory bowel disorder. New research implicates a role for low-grade inflammation and alterations of gut microbiota in this group of diseases.2 Other than known factors, such as age, diet, fecalith entrapment, and bacterial overgrowth,2 gut microbiota may play a role in the development of diverticula and (complicated) DD.3

Microbiota as a New Player in the Field

A new hypothesis encompasses the roles of altered gut microbiota and low-grade chronic inflammation leading to periods of symptomatic DD and perhaps even as triggers of acute diverticulitis. Several lines of indirect evidence support a potential association between these factors and DD. The initial hypothesis by Painter and Burkitt4 with a key role for fiber deficiency in the etiology of DD, as well as outdated views on the pathogenesis of inflammation, needs some revision. Based on current literature, we aim to integrate known factors and the new player in the field, gut microbiota, and propose a valid hypothesis on the etiopathogenesis of DD in which an important role is reserved for the microbiome factor.

Gut Microbiota Function and Characterization

A symbiotic relationship exists between intestinal microbiota and the host. The gut microbiota have a direct impact on the morphology of the gut and are involved in protective functions. The microbial layer in the gut mucosa contributes to the gut barrier function. The gut mucosal barrier effect causes resistance to pathogens, thereby controlling epithelial cell proliferation and homeostasis of the immune system. Moreover, the gut mucosal barrier has a metabolic function in the fermentation of non-digestible dietary residues into short-chain fatty acids.5
Characterization of gut microbiota was formerly performed almost exclusively by cultivation methods. However, the large majority of organisms are refractory to cultivation, and the true diversity of the microbial communities is not reflected. Presently the highly conserved 16S ribosomal RNA gene is used for taxonomic purposes. Nowadays nucleic acid sequencing methods allow for differentiation of bacteria at species and subspecies levels.

**Normal Gut Microbiome Composition**

The initial colonization after birth is very important with respect to the final composition of the permanent flora in adults. A healthy intestinal microbiome can be defined as the normal individual microbiota that maintain and propagate wellbeing and absence of disease.\(^6\) The intestine harbors a complex bacterial community that consists almost entirely (>95%) of 2 bacterial phyla, Bacteroidetes and Firmicutes.\(^7\) The genera *Bacteroides*, *Bifidobacterium*, *Eubacterium*, *Clostridium*, *Peptococcus*, *Peptostreptococcus*, and *Ruminococcus* are predominant. The intestinal tract of every individual contains several hundred different species belonging to these genera. Each individual has a particular combination of predominant species that is distinct from that found in other individuals, the microbiome fingerprint.\(^8\)

Gut microbiota stability is controlled by several factors, among others: pH, temperature, microbial interaction, peristalsis, bile acid, drug therapy, and immune responses. An individual’s microbiome composition can fluctuate under some circumstances, for instance, with acute diarrheal illnesses, antibiotic treatment, or, to a lesser extent, dietary interventions.\(^5\)

**Changes in Gut Microbiome in Relation to Disease**

Disease-specific variations in the composition of the colonic microbiome have been found as well. A descriptive study in humans has mapped fecal flora composition and has found a high risk for colon cancer in the presence of *Bacteroides vulgatus* and *B stercoris* and a low risk with *Lactobacillus acidophilus*, *L S06*, and *Eubacterium aerofaciens*. Although the evidence is not conclusive, colonic flora could play a part in initiation of colon cancer through the production of carcinogens, cocarcinogens, or procarcinogens.\(^9\)

In sections of acute appendicitis, Fusobacteria are a specific component of epithelial and submucosal infiltrates in 62% of patients, and its presence positively correlates with the severity of the appendicitis.\(^10\) For conditions with some similarities to DD, such as irritable bowel syndrome (IBS) and IBD, and also for obesity, a known risk factor for diverticulitis, intestinal microbiota shifts have been observed.
IBS and Gas-Related Syndrome

IBS is a disorder with a multifactorial and largely undetermined pathophysiology. A changed composition of microbiota is thought to be the underlying causative factor for nonspecific gastrointestinal symptoms, such as bloating, borborygmus, flatulence, abdominal distension, and discomfort. This so-called gas-related syndrome is caused by overproduction of gastrointestinal gas and may be related to an altered gut microbiome. Decreased *Clostridium*, *Lactobacilli*, and *Bifidobacteria* have been demonstrated in the feces of IBS patients. In terms of symptomatology, there is considerable overlap between DD and IBS.

Obesity, Microbiome, and Diverticulitis

Obesity has been established as a major risk factor for diverticulitis. The exact mechanism that links these 2 conditions is unclear. An altered cytokine profile, increased intra-abdominal pressure, altered diet, and altered gut microbiome may play a role. Ley et al. showed that the relative proportion of Bacteroidetes is decreased in obese people in comparison with lean people and that this proportion increases with weight loss on 2 types of low-calorie diets. Therefore, obesity may affect inflammatory responses either directly or indirectly, and thereby contribute to the development of diverticulitis.

IBD and Changes in Intestinal Microbiota

IBD is a spectrum of diseases characterized by chronic gastrointestinal inflammation. Compositional and functional changes in the intestinal microbiota, host genotype, and immune disequilibrium may play a role in the development and progression of disease. Comparison of clone libraries has revealed significant differences between the microbiota of patients with Crohn's disease (CD) and ulcerative colitis and those of non-IBD controls. Patients with IBD have higher amounts of bacteria attached to their epithelial surfaces and a predominant colonic phenotype of anaerobic commensal enteric microbiota compared with healthy people. Direct interaction between commensal microflora and intestinal mucosa can stimulate inflammatory activity in the gut lesions. After induction of colitis, some anaerobes invade the mucosa. Intestinal microflora of patients with IBD produce greater amounts of metabolic products than the microflora of healthy controls. Uninhibited activation of the intestinal immune system by elements of the gut flora could be a causative factor in the pathophysiology of IBD.

Inflammatory Similarities Between IBD and DD

The interest in similarities between IBD and DD is growing. The coming and going of symptoms in DD is similar to periods of exacerbation and remission in IBD. A possible overlap between chronic diverticular inflammation and IBD has been suggested more than once. Studies in biopsy material indicate that DD is associated with degrees of chronic inflammation. Floch demonstrated that diverticula are associated with an increase in microscopic colitis. Biopsy material of left-sided diverticula showed mild-to-moderate lymphocytic infiltrates and chronic inflammation in areas of diverticula. Gledhill
and Dixon\textsuperscript{13} have found histologic features of CD and diverticulitis in colonic resection specimens of 11 patients. All of the cases demonstrated mural thickening, hypertrophy of the muscularis propria with diverticula, and peridiverticular abscesses typical of DD. Microscopy revealed transmural granulomatous inflammation and ulceration typical of CD, with crypt abscess formation and fissuring ulceration in most cases. The authors concluded that a CD-like inflammatory response can be a localized reaction to diverticulitis and does not necessarily indicate chronic IBD.\textsuperscript{13} A small subset of patients with DD may develop segmental colitis associated with diverticulitis. This is recognized as a unique form of chronic colitis limited to areas of the colon with diverticular formation that is often mistakenly diagnosed as IBD.\textsuperscript{14} It is generally accepted that segmental colitis associated with diverticulosis is a distinct clinicopathologic entity that has much in common with idiopathic IBD.

**Altered Microbiota and Inflammation in DD**

Chronic diverticular symptoms, such as abdominal pain, bloating, tenesmus, and diarrhea, may be caused by low-level mucosal inflammation similar to that occurring in chronic idiopathic IBD. Chronic inflammation is related to relatively increased levels of proinflammatory cytokines. This may be triggered, at least in part, by altered peridiverticular microflora. *Bifidobacterium longum* and *B animalis* are found to be significantly more frequent and more abundant in patients with diverticulitis than in patients with colon cancer or IBD. *B adolescentis* is only found in the mucosa of patients with colon cancer and not in patients with diverticulitis.\textsuperscript{15}

Some anaerobes induce immune responses that are associated with accumulation of collagen in the tissue. Moreover, increased elastin deposition is found in the colonic wall of patients with DD.\textsuperscript{2} These findings could lead to the assumption that inflammation causes weakness of the colonic wall and results in diverticula formation.

**Fiber Deficiency Causes Both Diverticula and Microbiome Changes**

Fiber deficiency, attributed to a Western diet, is seen as a crucial pathogenic factor of DD. In this widely accepted hypothesis, the resulting smaller-volume stool is said to cause alterations in colonic motility and to increase segmental contractions of the colonic circular muscle. Resulting increased intracolonic pressure then generates increased outward force on the colonic wall. At areas of potential weakness, where penetrating arteries are localized, mucosal herniation results in a diverticulum.\textsuperscript{4}

Studies comparing cultures of gut flora in a rural African population eating a high-fiber diet with an English population eating a low-fiber diet found much higher levels of Bacteroides and lower levels of Bifidobacteria within the population eating the low-fiber diet.\textsuperscript{16} Indeed, DNA sequencing confirmed that fecal microbiota composition is affected by consumption of supplemental fibers.\textsuperscript{17}
Therapeutic Advances in DD
The presence of chronic inflammation suggests that some patients may benefit from treatment with nonabsorbable enteral antibiotics, anti-inflammatory medications, probiotics, or a combination of these.

Rifaximin, a poorly absorbable antibiotic, decreases the metabolic activity of the intestinal bacterial flora and the degradation of dietary fiber. Cyclic administration of rifaximin with dietary fiber supplementation is more effective in reducing both symptom and complication frequency than simple dietary fiber supplementation in patients with DD.\textsuperscript{18}

The 5-aminosalicylic acid mesalazine is an anti-inflammatory drug typically used in IBD.\textsuperscript{19} Probiotics are ingested living microorganisms which, when administered in adequate concentration, should confer a health benefit on the host. Probiotics antagonize the inflammatory effect triggered by an altered bacterial microenvironment because they have competitive metabolic interactions with proinflammatory organisms and downregulate proinflammatory cytokines. Mesalazine significantly improves patient symptoms and a global sense of wellbeing and is highly effective in obtaining and maintaining remission of symptoms. Probiotics improve abdominal symptoms and prolong the remission period. Patients receiving a combination of mesalazine and the probioticum \textit{L. casei} are more likely to remain in remission compared with patients receiving a single treatment.\textsuperscript{20} Hence, based on these therapeutic effects, it can be concluded that low-grade inflammation is associated with DD symptoms and plays a role in the progression to acute diverticulitis.

Composing a Hypothesis
\textit{Figure 1} displays the hypothesis that changes in intestinal microbiota composition play a role in the development of DD and its complications because of uninhibited activation of intestinal immune responses. Interestingly, a chronic low-grade inflammation can be found in patients with asymptomatic diverticulosis. Changed stability control factors or genetic variations could have led to these changes in intestinal microbiota composition. The onset of inflammation in diverticulitis shows similarities to the induction of inflammation in IBD. Deficiencies of host immune defenses and dysfunction of the barrier effect result in increased mucosal adherence of bacteria and promote translocation. A pathogenic immune response is activated and inflammation induced by the formation and topical release of proinflammatory cytokines. Inflammatory and/or functional changes lead to abdominal symptoms, such as lower abdominal pain/discomfort, bloating, tenesmus, and diarrhea. Evidence that supports the assumption that microbiota and low-grade inflammation play important roles in DD derives from studies demonstrating the efficacy of rifaximin, 5-aminosalicylic acid, and probiotics in achieving symptom relief and disease remission.
A changed microbiota composition can cause diverticulitis without the presence of an inspissated fecalith, in contrast to what generally is hypothesized. When diverticula are present, microbiota are able to cause diverticulitis. However, it is assumable that the presence of a fecalith accelerates the onset of diverticulitis because of stasis or obstruction in the narrow-necked diverticulum resulting in bacterial overgrowth and local tissue ischemia.

One could even speculate on a role for microbiota in the development of diverticula. Most risk factors for this are indirectly related to microbiota composition or even directly able to influence the microbiota composition. For instance, consider the mentioned differences in microbiota composition between people with a low-fiber and high-fiber diet. A disturbed anaerobic/aerobic bacteria ratio can induce immune responses associated with accumulation of collagen resulting in structural colonic alterations. Furthermore, a low-fiber diet not only causes colonic motility changes but can inflict a change in microbiota composition that can lead to small-bowel overgrowth and induction of gas-producing bacteria. These could alter the colonic pressure leading to a diverticulum and, additionally, could even cause symptomatic DD. Changes in microbiota composition could be the result of a known risk factor. A plausible explanation is that the microbiota composition can also make the host more vulnerable to DD risk factors. When a risk factor then occurs, a person with aberrant intestinal microbiota will develop a diverticulum because of an abnormal response. It is likely that a changed microbiota composition and risk factors for DD interact with each other, which may even lead to additive effects.
Figure 1 | A proposed hypothesis: important role for changed microbiota composition in the etiopathogenesis of diverticular disease. NSAID = nonsteroidal anti-inflammatory drug.
CONCLUSION

A changed microbiota composition is a plausible etiopathogenetic factor in DD. A solitary role for microbiota is not likely, however; the pathogenesis is more likely multifactorial and the result of complex interactions. There may well be some missing links, yet to be discovered, other than a changed microbiome and subsequent activation of immune responses that are necessary for the development of DD and/or its complications. The pathophysiologic significance of these changes in gut microbiome is still uncertain. Importantly, it needs to be determined whether changes in the gut microbiome indeed are a cause or just a consequence of DD. If the exact role of gut microbiota in DD is determined, this could be of great clinical value in the diagnosis and prevention of disease, treatment options, targeting of treatment, and in measuring the effect of therapy.
REFERENCES


Chapter 8

Fecal microbiome analysis as a diagnostic test for diverticulitis

Daniels L
Budding AE
de Korte N
Eck A
Bogaards JA
Stockmann HB
Consten EC
Savelkoul PH
Boermeester MA

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 the 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 computed tomography (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 polymerase chain reaction (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 crossvalidated partial least squares discriminant analysis (PLSDA).

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.

Conclusion
Diverticulitis patients have a higher diversity of fecal 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.
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 the 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 harbors a complex bacterial community that consists largely (>95%) of two 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 5,000 different bacterial species.\(^9\) The composition seems to be relatively stable over 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 fecal 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 harbor a change in colonic flora that promotes disease and inflammation, due either 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 is 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 fecalith 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 fecal microbiota by means of IS-pro7 in patients with a first episode of uncomplicated acute diverticulitis and compare these to the microbiota of controls. The 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.

MATERIALS AND 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 included centers aged 18 years or older with a first episode of acute left-sided uncomplicated modified Hinchey 1A or 1B23 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 old 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 as follows: follow-up after polypectomy (n=1), anemia 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, Murrieta, CA, USA) was performed at presentation to 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 1 ml of reduced transport fluid (RTF) medium\textsuperscript{26} and stored at −20 °C within 2 h of collection.

DNA isolation
After thawing of the samples, total DNA extraction was performed on all samples with the NucliSENS\textsuperscript{®} easyMag\textsuperscript{®} automated DNA isolation machine (bioMérieux, Marcy l’Etoile, France). One milliliter of nucliSENS\textsuperscript{®} lysis buffer, containing guanidine thiocyanate, was added to each vial containing a swab tip and the mixture was shaken at 1,400 rpm (Thermomixer comfort, Eppendorf, Hamburg, Germany) for 5 min. Afterwards, all samples were centrifuged for 4 min 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 110 μl of buffer and stored at 4 °C until use for polymerase chain reaction (PCR) amplification.

IS-profiling of the intestinal microbiota
The 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 labeling of PCR primers. Essentially, the IS-pro procedure consists of two multiplex PCRs: a first PCR for the phyla \textit{Firmicutes}, \textit{Bacteroidetes}, \textit{Actinobacteria}, \textit{Fusobacteria}, and \textit{Verrucomicrobia}, and a second PCR for the phylum \textit{Proteobacteria}. The assay was performed according to the protocol provided by the manufacturer. Amplifications were carried out on a GeneAmp PCR System 9700 (Applied Biosystems, Foster City, CA, USA). After PCR, 5 μl of PCR product was mixed with 19.8 μl of formamide and 0.2 μl of MapMarker 1000 ROX-labeled size marker (BioVentures, Murfreesboro, TN, USA). DNA fragment analysis was performed on an ABI Prism 3130xl Genetic Analyzer (Applied Biosystems). The results are presented as color labeled peak profiles (Figure 1).
Proteobacteria profiles can be seen to generally harbor more species in diverticulitis patients than in controls.

Figure 1 | Heat map of all profiles sorted and colored by phylum. When profiles are clustered by the 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 harbor more species in diverticulitis patients than in controls.
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 1,071 peaks with a specific length, measured in nucleotides, reflecting the lengths of IS fragments, and a specific height, measured in relative fluorescence units (RFU), reflecting the 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 the 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). The 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:

\[
dissimilarity = 1 - \cos \theta = 1 - \frac{\sum_{i=1}^{n} A_i \times B_i}{\sqrt{\sum_{i=1}^{n} (A_i)^2} \times \sqrt{\sum_{i=1}^{n} (B_i)^2}}
\]

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 the 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 ten 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 variable importance for the projection (VIP) parameters. VIP values rank the descriptors by their ability to discriminate different groups and are, 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 the most likely bacterial species by comparison to a database consisting of > 1,500 bacterial species and their associated IS lengths. Finally, to assess whether prediction of the 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 were 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, comprising 12 males and 13 females, with a mean age of 53 years (95% CI: 47–59). The patients’ characteristics are listed in Table 1.
Chapter 8 | Fecal microbiome analysis as diagnostic test

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

<table>
<thead>
<tr>
<th></th>
<th>Diverticulitis patients (N=31)</th>
<th>Control subjects (N=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M)</td>
<td>20 (64.5%)</td>
<td>12 (48%)</td>
</tr>
<tr>
<td>Age* (years)</td>
<td>57.8 (53.6-62.0)</td>
<td>52.6 (46.6-58.6)</td>
</tr>
<tr>
<td>ASA (I:II)</td>
<td>18 (58.1%) :13 (41.9%)</td>
<td>UK</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.1(25.7-28.5)</td>
<td>26.7 (24.0-29.6)</td>
</tr>
<tr>
<td>Duration of complaints† (days)</td>
<td>2 (1-3)</td>
<td>UK</td>
</tr>
<tr>
<td>Restricted oral intake</td>
<td>11 (35.5%)</td>
<td>UK</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (9.7%)</td>
<td>UK</td>
</tr>
<tr>
<td>Temperature* (°C)</td>
<td>37.1 (36.8-37.4)</td>
<td>UK</td>
</tr>
<tr>
<td>CRP† (mg/dl)</td>
<td>89 (47.9-131.0)</td>
<td>UK</td>
</tr>
<tr>
<td>WBC* (11x10⁹/L)</td>
<td>11.9 (10.7-13.1)</td>
<td>UK</td>
</tr>
</tbody>
</table>

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.

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 revealed 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 log2 RFU for patients and controls, respectively; P = 0.20, Mann–Whitney U-test). A heatmap 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 the total profiles (Figure 1).
Figure 2 | Boxplot comparisons of within-sample diversity as calculated by the Shannon index of all phyla combined and per phylum for diverticulitis patients and control subjects, with a significantly higher diversity of the phylum Proteobacteria and all phyla combined in diverticulitis patients.

Microbial diversity and composition in diverticulitis patients versus controls

While the 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) (Figure 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 three-dimensional space based on their Proteobacteria profiles (Figure 3).
Chapter 8 | Fecal microbiome analysis as diagnostic test

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

**Discriminative ability of PLS-DA**

The use of an unsupervised approach for classification (PCoA) already demonstrated the 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.\textsuperscript{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 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% (Figure 4). Three out of 56 samples were misclassified: one control and two patients, whose samples are the encircled ones in the

---

\textsuperscript{28} For details on the PLS-DA model parameters, please refer to the original publication.

\textsuperscript{30} Additional analysis was performed to validate the classification outcomes.

\textsuperscript{31} The discriminative ability was strengthened further by incorporating a larger sample size.
PCoA scatterplot (Figure 3). The resulting specificity was thus calculated to be 96%, with a sensitivity of 94%. Taking the combined dataset, 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).

Figure 4 | The PLS-DA scores plot for the phylum Proteobacteria shows a clear differentiation between diverticulitis patients and control subjects.
Table 2 | Most discriminative OTUs based on a Variable Importance for Projection value > 1.2

<table>
<thead>
<tr>
<th>Species</th>
<th>Family</th>
</tr>
</thead>
<tbody>
<tr>
<td>E.coli</td>
<td>Enterobacteriaceae</td>
</tr>
<tr>
<td>K. pneumoniae</td>
<td>Enterobacteriaceae</td>
</tr>
<tr>
<td>Enterobacter aerogenes</td>
<td>Enterobacteriaceae</td>
</tr>
<tr>
<td>S. marcescens</td>
<td>Enterobacteriaceae</td>
</tr>
<tr>
<td>Klebsiella varicola</td>
<td>Enterobacteriaceae</td>
</tr>
<tr>
<td>Providencia stuartii</td>
<td>Enterobacteriaceae</td>
</tr>
<tr>
<td>Desulfovibrio sp.</td>
<td>Desulfovibrionaceae</td>
</tr>
<tr>
<td>Xanthomonas sp.</td>
<td>Xanthomonadaceae</td>
</tr>
<tr>
<td>Stenotrophomonas</td>
<td>Xanthomonadaceae</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>Pseudomonadaceae</td>
</tr>
<tr>
<td>Burkholderia sp.</td>
<td>Burkholderiaceae</td>
</tr>
<tr>
<td>Aggregatibacter actinomycetemcomitans</td>
<td>Pasteurellaceae</td>
</tr>
<tr>
<td>Unknown Proteobacteria species*</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

*Eleven types of unknown Proteobacteria species were identified

**Prediction of diverticulitis using the PLS-DA model**

The predictive ability of the model was assessed by crossvalidation. The prediction results were pooled together, which enabled us to estimate the performance of the model by means of the 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* phyla, the cross-validated accuracy rate was 51 %. Considering only the *Proteobacteria* phylum, 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 % (specificity = 80 %; sensitivity = 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 a 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.\(^\text{28}\) 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 chemo-metrics 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 multicollinearity.\textsuperscript{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 that this approach is 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.\textsuperscript{30,32,33}

Specific shifts in the phylum \textit{Proteobacteria}\textemdash other than general measures like diversity\textemdash have not previously been found to be associated with disease. This might be caused by the fact that \textit{Proteobacteria} generally have a low relative abundance in the intestinal microbiota.\textsuperscript{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 \textit{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 \textit{Bacteroidetes/Firmicutes} and another for the specific amplification of \textit{Proteobacteria}. While the separation of the different phyla in two PCRs prevents us from addressing all three phyla together when presenting their relative abundances\textemdash consequently hampering direct comparisons of abundances\textemdash it does allow us to zoom in and analyze the \textit{Proteobacteria} community composition in depth.

Brook and Frazier 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.\textsuperscript{35} With conventional culture techniques, they identified \textit{E. coli} and \textit{Streptococcus spp.} as the predominant aerobic and facultative bacteria. The most frequently isolated anaerobes were \textit{Bacteroides spp.} (\textit{B. fragilis} group), \textit{Peptostreptococcus, Clostridium,} and \textit{Fusobacterium spp.} The only study to date using PCR-based sequencing of the microbiota in diverticulitis patients was conducted by Gueimonde et al.\textsuperscript{36} They identified a significantly higher occurrence of \textit{Bifidobacterium longum} and \textit{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 \textit{Bifidobacterium} and did not analyze the entire profile; they stated that 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 diverticulitis, despite the lack of sound evidence.\textsuperscript{37,38} Cyclic administration of rifaximin has been proven to be effective in reducing symptoms and complications\textsuperscript{39-42} and possibly prevents recurrence in patients after complicated diverticulitis.\textsuperscript{43} Relatively new therapies,
such as probiotic therapy, are proposed as well for the management of DD. Indeed, a few small open-label studies already show promising results\(^4\)\(^4\)\(^7\). 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 the 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 DD and its inflammatory complications.

Since a clinical diagnosis of diverticulitis cannot be made with a high certainty without imaging\(^4\)\(^8\), 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 the 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 DD. 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.

The 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 a 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.
Acknowledgments
We thank all the physicians and nurses in the participating centers (Academic Medical Center, Amsterdam; Meander Medical Center, Amersfoort; and Kennemer Gasthuis Hospital, Haarlem) for the accrual of patients and performing rectal swabs. We thank Malieka Degen for performing DNA isolation and the IS-pro procedure on all fecal samples.
REFERENCES


Summary & future perspectives
SUMMARY

Part 1 A less aggressive approach to the treatment of left-sided colonic diverticulitis can be noticed, but there still is controversy about the appropriate management of the various stages of the disease. Conservative treatment for uncomplicated acute diverticulitis traditionally includes antibiotic treatment, and most international guidelines recommend accordingly. At the start of the research described in this thesis however, it was uncertain whether these patients indeed benefit from antibiotics, since evidence from prospective studies or randomized trials was lacking.

Chapter 1 presents a narrative review that addresses the emergence of a less aggressive approach to the management of colonic diverticulitis 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 2) patient subset. More recently, laparoscopic lavage has been posed as a promising less invasive treatment for selected cases of Hinchey 3 patients, while others dispute this. Likewise, for uncomplicated diverticulitis the approach has become less aggressive with a change from intravenous antimicrobial therapy, starvation and admission to the hospital, to oral antibiotics and finally to observation and outpatient treatment. This changing approach is due to expanding evidence on optimal treatment and is congruent with an increasing understanding that diverticulitis comprises different disease entities with heterogeneity among patients. 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. We conclude by stating we might have overtreated the majority of diverticulitis patients for decades.

Chapter 2 describes a study protocol for a multicenter randomized clinical trial investigating the cost-effectiveness of treatment strategies with or without antibiotics for uncomplicated acute diverticulitis (DIABOLO trial). A pragmatic trial set-up is chosen over a double-blind placebo controlled randomized trial. By comparing two contemporary treatment strategies, instead of investigating the effect of antibiotics in a more experimental setting in which all patients will be admitted, the outcome will be more applicable in daily practice. Patients are eligible for inclusion if they have a primary diagnosis of acute uncomplicated diverticulitis, with stages 1a and 1b according to the Modified Hinchey classification or “mild” diverticulitis according to the Ambrosetti criteria, as demonstrated by radiological imaging. The primary endpoint is time-to-full recovery within a 6-month follow-up period. A clinically relevant difference of more than 5 days in time-to-full recovery between the two treatment strategies is not expected. In a non-inferiority design a total of 533 patients need to be included. 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...
Summary

and acute diverticulitis recurrence rate. The observational strategy without antibiotics is anticipated to be a more cost-effective approach.

In Chapter 3 the results of the DIABOLO trial are presented. This study was performed in 22 clinical sites in the Netherlands. Between June 2010 and October 2012 528 patients with CT-proven, primary, left-sided, uncomplicated, acute diverticulitis were randomly assigned to an observational (262 patients) or antibiotic (266 patients) treatment strategy. An intention-to-treat analysis was done. Median time-to-recovery was comparable among observational and antibiotic treatment strategies (14 days [IQR, 6 to 35] vs 12 days [IQR, 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% CI, 1.059; \( P = 0.151 \)). We found no significant between-group differences for the main secondary endpoints. Hospital stay was significantly shorter in the observational strategy without antibiotics (\( P < 0.01 \)). Results of per-protocol analyses were in accordance with the results of the intention-to-treat analyses. In conclusion, observational treatment for uncomplicated acute diverticulitis does not result in an increase in time-to-recovery, nor in higher rates of readmission, complicated, ongoing and recurrent diverticulitis and sigmoid resection. This trial therefore shows observational treatment is without significant repercussions, which indicates that antibiotics can safely be omitted.

Part 2 focuses on the follow-up after an episode of uncomplicated acute diverticulitis. Current guidelines recommend routine follow-up colonoscopy after acute diverticulitis to confirm the diagnosis and exclude underlying malignancy. This recommendation merely is based on expert opinion and dates back to the time before widespread use of abdominal CT. The value of colonoscopy has recently been questioned because of contradictory study results on the yield of colonoscopy. Another one of today’s controversies in the follow-up is the management of recurrent diverticulitis. Conservative treatment has become the preferred choice because elective resection has been abandoned as standard therapy for recurrent diverticulitis since it is now known that multiple episodes of diverticulitis do not seem to be associated with increased mortality or an increased risk of complicated diverticulitis. However, the value of different medical therapies that have been developed for the prevention of recurrent diverticulitis is unclear.

We performed a systematic review with the aim to assess the need for routine colonoscopy after acute diverticulitis. The results are presented in Chapter 4. A literature search was done in MEDLINE, EMBASE, CINAHL databases and the Cochrane database of Systematic Reviews. Two authors performed selection and data-extraction. Articles dealing with follow-up colonoscopy after a recent episode of imaging proven left-sided acute diverticulitis in adults were eligible for inclusion. The methodological quality and susceptibility to bias of the studies were assessed. We calculated the estimated pooled prevalence and 95% confidence intervals of advanced colonic neoplasia (ACN), comprising colorectal carcinoma (CRC) and/or advanced adenoma (AA), as detected with
colonoscopy after acute diverticulitis, based on a random effects model. Eight studies of moderate methodological quality with a total of 1,796 patients met the inclusion criteria. There was limited heterogeneity among included studies. The estimated pooled prevalence of ACN, CRC and AA was 5.0% (CI, 3.8-6.7%), 1.5% (CI, 1.0-2.3%) and 3.8% (CI, 2.7-5.3%) respectively. In conclusion, in patients with colonoscopy after imaging proven acute diverticulitis the prevalence of ACN is low, though the prevalence of CRC is somewhat higher than in asymptomatic populations. These data do not support current practice of performing follow-up colonoscopy in these patients. Definitive conclusions however cannot be drawn, due to limitations of included studies, of which lack of an adequate control group is the most important.

In Chapter 5 the results of the first cohort study that directly compared the diagnostic yield of follow-up colonoscopy after CT-proven uncomplicated acute diverticulitis with the yield of screening colonoscopy in an asymptomatic population from a primary screening program for CRC are presented. A total of 401 patients with uncomplicated diverticulitis was compared with 1,426 screening participants, derived from cohorts of two multicenter randomized clinical trials executed in the Netherlands between 2009 and 2013. The histopathology outcome of removed lesions during colonoscopy was used as definitive diagnosis. The detection rate of CRC [1.2% vs 0.6%; OR, 1.30 (95% CI, 0.39-4.36); \( P = 0.673 \)], AA [5.5% vs 8.7%; OR, 0.62 (95% CI, 0.38-1.01); \( P = 0.053 \)], and ACN [6.7% vs 9.1%; OR, 0.71 (95% CI, 0.45-1.11); \( P = 0.134 \)] did not differ significantly between the groups. Our findings suggest that routine follow-up colonoscopy after primary CT-proven uncomplicated left-sided acute diverticulitis can be omitted. Follow-up colonoscopy may be beneficial when a diagnostic dilemma exists and may be targeted at high-risk patients, but such an approach first needs prospective evaluation.

In Chapter 6, the existing literature on conservative measures for the prevention of recurrent diverticulitis after a primary episode of acute diverticulitis published between January 1966 and January 2011 was systematically reviewed. Conservative measures were defined as dietary advises and medical therapies. The search resulted in the inclusion of three randomized controlled trials. One study, comparing Rifaximin plus Mesalazine (5-aminosalicylic acid) with Rifaximin alone, found that the combination therapy with Mesalazine results in significantly less disease recurrence and fewer symptoms after an acute episode. Another study showed that the use of probiotics decreases abdominal symptoms but does not reduce recurrence. In the third study no difference in effect is seen when Balsalazide is added to probiotics compared to probiotics only. No studies assessing the use of dietary fibre or antibiotics for prevention of recurrent diverticulitis were found. In conclusion, the evidence of medical treatment to prevent recurrence of diverticulitis is scarce and the available studies are of moderate quality. It is therefore too early to recommend any non-operative relapse prevention therapy, though treatment with 5-aminosalicylic acid seems promising.
Part 3 concentrates on the involvement of gut microbiota in diverticulitis. 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 fecalith obstruction of a diverticulum to cause acute diverticulitis towards a view in which microbiota may play a central role. To date however, the gut microbiome of diverticulitis patients has not yet been characterized.

In Chapter 7 a new hypothesis, encompassing important roles for altered gut microbiota and low-grade chronic inflammation in the etiopathogenesis of diverticular disease, is proposed. The onset of inflammation in diverticulitis shows similarities to the induction of inflammation in inflammatory bowel disease, a spectrum of diseases with known changes in gut microbiota. Based on current literature, we integrated known factors and the new player in the field, gut microbiota, in a multifactorial theory. Several lines of indirect evidence support a potential association of altered gut microbiota and low-grade chronic inflammation with diverticular disease and its complications. It is concluded that a changed microbiota composition is a plausible etiopathogenetic factor in diverticular disease. A solitary role for microbiota and immune response activation is not likely though and the pathogenesis is more likely multifactorial and the result of complex interactions.

Characterization of the gut microbiome composition is the first step in elucidating a possible role for gut microbiota in the etiopathogenesis of diverticulitis. In Chapter 8 the fecal microbiota composition of 31 patients with a first episode of CT-proven left-sided uncomplicated acute diverticulitis is compared with the composition of 25 control subjects evaluated for a range of gastrointestinal indications. A high-throughput polymerase chain reaction (PCR)-based profiling technique (IS-pro) was performed on DNA isolates from fecal samples. Firmicutes/Bacteroidetes ratios and Proteobacteria load were comparable among patients and controls. In diverticulitis higher fecal microbiota diversity was noted, with the Proteobacteria phylum mainly defining this difference. The diagnostic accuracy of the cross-validated partial least squares discriminant analysis regression model was 84%. The most discriminative species derived largely from the family Enterobacteriaceae. In conclusion, diverticulitis patients have higher diversity of fecal microbiota than controls from a mixed population. Furthermore, our study demonstrates that the diagnosis of diverticulitis can be done by microbiome analysis with relatively good accuracy. The analysis of intestinal microbiota therefore offers a novel way to diagnose diverticulitis.
The Dutch Surgical Society (Nederlandse Vereniging voor Heelkunde) pursues an evidence-based policy with regards to the optimal treatment of both uncomplicated and complicated diverticulitis. On that account it has since 2009 provided a platform to promote the ongoing Dutch Diverticular Disease Group trials and present its study results at the annual national congresses. The 2012 Dutch guideline on diverticulitis internationally took the lead on controversial issues by progressively stating there is no evidence for the routine administration of antibiotics in patients with uncomplicated diverticulitis and stating there is no indication for routine endoscopic examination after an episode of diverticulitis.\textsuperscript{1} The scientific evidence for these recommendations at that time was limited.

Last years, considerable progress has been made in the scientific field regarding diverticulitis; surgical approaches have become less invasive and traditional treatment principles are being studied extensively. Despite these developments, there still is room for further improvement and many questions have yet to be answered. The research reported in this thesis aims to contribute to the optimization of the approach to patients with uncomplicated diverticulitis. For complicated diverticulitis results of several ongoing trials will add to present knowledge and possible change treatment choices as well.

The outcomes of the DIABOLO trial confirm the results of the Scandinavian randomized clinical trial, which also investigated the need for antibiotic treatment in acute uncomplicated diverticulitis and was published in 2012. They have found that antibiotic treatment neither accelerates recovery nor prevents complications or recurrence, but the study included a large proportion of patients with recurrent diverticulitis.\textsuperscript{2} In a recent review therefore it is reluctantly concluded antibiotic treatment may not be required in all patients.\textsuperscript{3} In both this review as in a Cochrane systematic review it is stated that first confirmation by further high-quality randomized controlled trials is needed, if management is to be evidence-based.\textsuperscript{3,4} Recent international guidelines and practice parameters remained unchanged and also conclude that further research is required before adopting an antibiotic-free treatment strategy.\textsuperscript{5,6} With the results of the DIABOLO trial – presented in this thesis –, now a second randomized trial indicates that antibiotics are of no additional value. With the knowledge that the present trial only included primary episodes of mild acute diverticulitis there now is sufficient evidence available for the implementation of an observational treatment strategy without antibiotics for uncomplicated diverticulitis in international guidelines.

Omitting antibiotics in the treatment of uncomplicated acute diverticulitis should for the time being be limited to patients classified with Hinchey 1a diverticulitis. Though the results of the DIABOLO trial suggest this recommendation may be applicable to patients with Hinchey 1b diverticulitis as well, caution is advised within this subgroup of patients with a small pericolic or mesocolic abscess. In literature there are no high-quality papers about the treatment of diverticulitis patients with abscess formation and an observational
strategy has never been evaluated. Therefore prospective samples, considerably larger than the 42 patients in our study, are required before definitive conclusions can be drawn for optimal treatment strategy in patients with Hinchey 1b diverticulitis. As well, patients with significant comorbidity, inflammatory bowel disease, pregnancy, clinical suspicion of sepsis and immune compromised patients should be excluded from this recommendation. It is important to investigate further which features may predict which patients could benefit from an antibiotic treatment strategy and define subgroups.

The patient load will most likely rise in the nearby future, therefore, further optimization of treatment strategies and facilitation of cost-effective care are the main challenges. The DIABOLO trial was also intended to compare cost-effectiveness of an observational strategy with an antibiotic strategy. These analyses are currently in the final phase, and results to be awaited. A combination of an antibiotic-free and outpatient treatment may lead to further optimization of the treatment strategy for uncomplicated acute diverticulitis.\textsuperscript{7,8}

Gaining better insight in the natural history of diverticular disease, its clinical picture and the results of follow-up after treatment already had great influence on management strategies. The treatment of diverticulitis though, can only be optimally tailored to the individual patient when the unknown pathophysiology of diverticulitis is clarified. Recent publications on diverticular disease have challenged long-standing disease concepts and management strategies. New research, including our own, implicates an important role for alterations of gut microbiota. Our study demonstrated that the fecal microbiota of diverticulitis patients differs significantly from controls and diagnosis of diverticulitis could be done by microbiome analysis. Although these results need external validation, exciting new perspectives lie in their clinical applicability such as the possibilities of using fecal transplantation (bacteriotherapy) for the prevention of recurrent diverticulitis.

Further studies need to determine whether changes in the gut microbiome indeed are a cause or just a consequence of diverticular disease. From an etiopathogenetic point of view, it would be interesting to further investigate whether there is a gradual shift in microbiota composition from diverticulosis towards diverticulitis. If the exact role of gut microbiota in diverticular disease is determined this could also be of great clinical value in prevention of disease and targeting of treatment. Currently, we are trying to gain insight in the course fecal microbiota composition takes in patients with a first episode of uncomplicated acute diverticulitis and the effects of antibiotic therapy on this course.

The pathogenesis most likely is multifactorial and the result of complex interactions. There may well be some missing links, yet to be discovered, other than a changed microbiome and subsequent activation of immune responses that are necessary for the development of diverticular disease and/or its complications. It is of paramount importance to gain a better understanding of the pathophysiology of diverticular disease; this could lead to better targeting and even new targets of treatment.
REFERENCES


Nederlandse samenvatting
Deel 1 Bij de behandeling van linkszijdige colon diverticulitis is een minder agressieve aanpak zichtbaar, maar er bestaat nog steeds controverse over de behandeling van de verschillende stadia van de ziekte. Conservatieve behandeling van ongecompliceerde acute diverticulitis bestaat van oudsher uit antibiotische behandeling, en de meeste internationale richtlijnen bevelen dit dan ook aan. Bij aanvang van het onderzoek beschreven in dit proefschrift was het echter onzeker of deze patiënten gebaat zijn bij antibiotica, gezien wetenschappelijk bewijs van prospectieve of gerandomiseerde studies ontbrak.

Hoofdstuk 1 bevat een beschrijvende review die de opkomst in de laatste tien jaar van een minder agressieve aanpak voor de behandeling van colon diverticulitis behandelt. De standaard behandeling voor geperforeerde of gecompliceerde diverticulitis ontwikkelde zich van een Hartmann procedure, naar resectie met primaire anastomose, naar behandeling met antibiotica en percutane drainage in een zorgvuldig geselecteerde (Hinchey 2) patiënten categorie. Meer recentelijk werd laparoscopische lavage voorgesteld als veelbelovende minder invasieve behandeling van geselecteerde Hinchey 3 patiënten, terwijl anderen dit in twijfel trokken. Voor ongecompliceerde diverticulitis is de aanpak eveneens minder agressief verworden; met een verandering van intraveneuze antibiotische behandeling, geen orale belasting en ziekenhuis opaname, in orale antibiotica en uiteindelijk poliklinische behandeling. Deze kentering in de aanpak is het gevolg van een toename van wetenschappelijk bewijs en loopt parallel aan de opvatting dat diverticulitis verschillende ziekte entiteiten omvat met heterogeniteit tussen patiënten. Het vermijden van overbehandeling heeft duidelijke voordelen: minder ziekenhuis opnames, reductie in kosten, minder ontwikkeling van antimicrobiële resistentie, afname van complicaties en bijwerkingen, en vermoedelijk een betere kwaliteit van leven voor de patiënt. We concluderen met te stellen dat we waarschijnlijk tientallen jaren de meeste diverticulitis patiënten te agressief behandeld hebben.

Hoofdstuk 2 beschrijft het onderzoeksprotocol voor een multicentrische gerandomiseerde klinische studie die de kosten-effectiviteit onderzoekt van behandelstrategieën met of zonder antibiotica voor ongecompliceerde acute diverticulitis (DIABOLO). Een pragmatische studie opzet is verkozen boven een dubbel-blinde placebo-gecontroleerde studie. Door twee alledaagse behandelstrategieën met elkaar te vergelijken, in plaats van het effect van antibiotica in een meer experimentele setting te onderzoeken waarbij alle patiënten opgenomen zijn, zal de uitkomst beter toepasbaar zijn in de dagelijkse praktijk. Patiënten komen in aanmerking voor inclusie wanneer zij een eerste diagnose acute ongecompliceerde diverticulitis hebben; stadium 1a en 1b volgens de Gemodificeerde Hinchey classificatie of ‘mild’ volgens de Ambrosetti criteria, bevestigd middels beeldvorming. De primaire uitkomstmaat is de tijd-tot-volledig-herstel bij 6 maanden follow-up. Een klinisch relevant verschil in tijd-tot-volledig-herstel van meer dan
Samenvatting

5 dagen tussen de twee behandelstrategieën wordt niet verwacht. Om non-inferioriteit aan te kunnen tonen dienen in totaal 533 patiënten te worden geïncludeerd. Secundaire uitkomstmaten zijn het aantal patiënten met gecompliceerde diverticulitis waarvoor een (non-)chirurgische interventie nodig is, morbiditeit, kosten, ziekte-gerelateerde kwaliteit van leven, aantal patiënten met heropnames en recidieven. De hypothese is dat een observationele strategie zonder antibiotica een kosten-effectievere behandeling is.

In Hoofdstuk 3 worden de resultaten van de DIABOLO trial gepresenteerd. Deze studie is uitgevoerd in 22 ziekenhuizen in Nederland. Tussen juni 2010 en oktober 2012 werden 528 patiënten met een CT-bewezen, primaire, linkszijdige, ongecompliceerde, acute diverticulitis gerandomiseerd voor een observationele (262 patiënten) of antibiotische (266 patiënten) behandelstrategie. De analyses waren volgens het ‘intention-to-treat’ principe. De mediane tijd-tot-herstel bij observationele behandeling was vergelijkbaar met antibiotische behandeling (14 dagen [IQR, 6 - 35] vs 12 dagen [IQR, 7 - 30]; \( P = 0.291 \) met de Log-Rank test), met een hazard ratio voor herstel van 0.910 (bovengrens eenzijdig 95% betrouwbaarheidsinterval (BI), 1.059; \( P = 0.151 \)). De groepen waren eveneens niet significant verschillend voor de belangrijke secundaire uitkomstmaten. De ziekenhuis opnameduur was significant korter in de observationele strategie zonder antibiotica (\( P < 0.01 \)). De resultaten van de per-protocol analyse waren in overeenstemming met de resultaten van de intention-to-treat analyse. Concluderend, observationele behandeling voor ongecompliceerde acute diverticulitis gaat niet gepaard met een langere tijd-tot-herstel, noch met meer heropnames, gecompliceerde, ongoing en recidiverende diverticulitis of sigmoid resectie. Deze trial toont daarmee aan dat observationele behandeling zonder significante repercussies is, waaruit opgemaakt kan worden dat antibiotica veilig weggelaten kunnen worden.

Deel 2 richt zich op de follow-up na een episode van ongecompliceerde acute diverticulitis. Huidige richtlijnen adviseren routinematig follow-up colonoscopie te verrichten na acute diverticulitis om de diagnose te bevestigen en onderliggende maligniteit uit te sluiten. Deze aanbeveling is voornamelijk gebaseerd op expert opinion en dateert van voor het wijdverbreid gebruik van abdominale CT. De waarde van colonoscopie wordt sinds kort betwijfeld gezien resultaten van studies naar de diagnostische opbrengst van colonoscopie tegenstrijdig zijn. Een van de andere huidige controverses ten aanzien van de follow-up is de aanpak van recidiverende diverticulitis. Conservatieve behandeling is inmiddels de eerste keus behandeling gezien electieve resectie als standaard therapie voor recidiverende diverticulitis verlaten is omdat we nu weten dat meerdere episodes niet geassocieerd zijn met een hogere mortaliteit of een groter risico op gecompliceerde diverticulitis. Niettemin, de waarde van verschillende medische behandelingen die zijn ontwikkeld ter preventieve van recidiverende diverticulitis is niet bekend.
We hebben een systematische review verricht met het doel de waarde van routine colonoscopie na diverticulitis te onderzoeken. De resultaten worden beschreven in Hoofdstuk 4. Literatuur werd gezocht in MEDLINE, EMBASE, CINAHL databases en de Cochrane database of Systematic Reviews. Twee auteurs voerden de selectie en data extractie uit. Artikelen over follow-up colonoscopie na een recente episode van middels beeldvorming bewezen linkszijige acute diverticulitis bij volwassenen kwamen in aanmerking voor inclusie. De methodologische kwaliteit en risico op bias van de studies werd beoordeeld. We berekenden de geschatte gepoolde prevalenties met 95% betrouwbaarheidsintervallen (BI) van geavanceerde colorectale neoplasie (ACN), welke colorectaal carcinoom (CRC) en/of geavanceerd adenoom (AA) omvat, zoals gedetecteerd door colonoscopie na acute diverticulitis, gebaseerd op een random effects model. Acht studies van matige methodologische kwaliteit met in totaal 1,796 patiënten voldeden aan de inclusie criteria. Er was beperkte heterogeniteit tussen de studies. De geschatte gepoolde prevalentie van ACN, CRC en AA was respectievelijk 5.0% (BI, 3.8-6.7%), 1.5% (BI, 1.0-2.3%) en 3.8% (BI, 2.7-5.3%). Concluderend, de prevalentie van ACN is laag bij patiënten met colonoscopie na acute diverticulitis bewezen met beeldvorming, de prevalentie van CRC is echter iets hoger dan in asymptomatische individuen. Deze data ondersteunen de huidige praktijk, follow-up colonoscopie te verrichten in deze patiënten, niet. Definitieve conclusies kunnen echter niet getrokken worden door limitaties van de geïncludeerde studies, waarvan het ontbreken van een adequate controle groep de voornaamste is.

In Hoofdstuk 5 worden de uitkomsten gerapporteerd van de eerste cohort studie die de diagnostische opbrengst van follow-up colonoscopie na CT-bewezen ongecompliceerde acute diverticulitis direct vergeleken heeft met de opbrengst van screening colonoscopie in een asymptomatische populatie uit een primair screening programma voor CRC. Een totaal van 401 patiënten met ongecompliceerde diverticulitis werd vergeleken met 1,426 screening participanten, afkomstig van de cohorten van twee multicentrische gerandomiseerde klinische trials uitgevoerd in Nederland tussen 2009 en 2013. De histopathologie uitslag van de verwijderde lesies bij colonoscopie werd gebruikt als definitieve diagnose. De detectie van CRC [1.2% vs 0.6%; OR, 1.30 (95% BI, 0.39-4.36); P = 0.673], AA [5.5% vs 8.7%; OR, 0.62 (95% BI, 0.38-1.01); P = 0.053], en ACN [6.7% vs 9.1%; OR, 0.71 (95% BI, 0.45-1.11); P = 0.134] was niet significant verschillend tussen de groepen. Onze bevindingen suggereren dat routine follow-up colonoscopie na primaire CT-bewezen ongecompliceerde linkszijige acute diverticulitis achterwege gelaten kan worden. Follow-up colonoscopie is mogelijk van toegevoegde waarde indien er een diagnostisch dilemma bestaat en zou gericht kunnen worden op hoog-risico patiënten, echter deze aanpak moet eerst prospectief geëvalueerd worden.

In Hoofdstuk 6 hebben we de bestaande literatuur over conservatieve therapieën ter preventie van recidiverende diverticulitis na een primaire episode van acute diverticulitis, gepubliceerd tussen januari 1966 en januari 2011, systematisch gereviewed. Conservatieve
therapieën werden gedefinieerd als diët therapieën en medische therapieën. De search resulteerde in de inclusie van drie gerandomiseerde gecontroleerde trials. Een studie, waarin Rifaximin plus Mesalazine (5-aminosalicylzuur) met alleen Rifaximin vergeleken werd, vond dat de combinatie therapie met Mesalazine significant tot minder recidieven en minder symptomen na een acute episode leidde. Een andere studie liet zien dat de toepassing van probiotica abdominale symptomen verminderde maar niet het aantal recidieven. In een derde studie werd geen verschil in effect gezien tussen de combinatie probiotica plus Balsalazide en alleen probiotica. Er werden geen studies gevonden die vezels of antibiotica voor de preventie van recidiverende diverticulitis onderzochten.

Concluderend, er is weinig wetenschappelijk bewijs beschikbaar ten aanzien van medische therapieën voor de preventie van recidiverende diverticulitis en de bestaande studies zijn van matige kwaliteit. Het is dus nog voorbarig een van de niet-operatieve preventieve therapieën aan te bevelen, hoewel de behandeling met 5-aminosalicyliczuur veelbelovend lijkt te zijn.

Deel 3 concentreert zich op de betrokkenheid van darm microbiota bij diverticulitis. Thans ontberen we het complete inzicht in de pathofysiologische mechanismen die verantwoordelijk zijn voor de progressie van diverticulose naar diverticulitis. Theorieën verschuiven momenteel van het traditionele dogma, dat stelt dat obstructie van een divertikel door een fecaliet tot acute diverticulitis leidt, naar een visie waarin microbiota mogelijk een centrale rol spelen. Tot op heden echter, is het darm microbioom van diverticulitis patiënten nog niet in kaart gebracht.

In Hoofdstuk 7 wordt een nieuwe hypothese voorgesteld, waarin belangrijke rollen zijn weggelegd voor een veranderde samenstelling van darm microbiota en laaggradige chronische inflammatie in de etiopathogenese van divertikelziekte. De ontstaanswijze van inflammatie bij diverticulitis toont overeenkomsten met de inductie van inflammatie bij inflammatoire darmziekten, een spectrum van ziekten met bekende veranderingen in darm microbiota. Gebaseerd op de huidige literatuur kunnen bekende factoren en de nieuwe factor, darm microbiota, geïntegreerd worden in een multifactoriële theorie. Er is divers indirect bewijs dat een potentiële associatie tussen een veranderde samenstelling van darm microbiota en laaggradige chronische ontsteking met divertikelziekte en complicaties onderschrijft. Er wordt geconcludeerd dat een veranderde microbiota samenstelling een plausibele etiopathogenetische factor is voor divertikelziekte. Louter rollen voor microbiota en activatie van de immuun respons is echter onwaarschijnlijk en de pathogenese is waarschijnlijker multifactorieel en het resultaat van complexe interacties.

Het in kaart brengen van het darm microbioom is de eerste stap in het verhelderen van een mogelijke rol van darm microbiota in de etiopathogenese van diverticulitis. In Hoofdstuk 8 wordt de fecale microbiota samenstelling van 31 patiënten met een eerste episode CT-bewezen, linkszijdige, ongecompliceerde, acute diverticulitis vergeleken met de samenstelling van 25 controles die wegens diverse gastrointestinale indicaties geëvalueerd
werden. Een ‘high-throughput’, op polymerase kettingreactie (PCR)-gebaseerde, profiling techniek (IS-pro) werd uitgevoerd op DNA verkregen uit fecale samples. Firmicutes/Bacteroidetes ratio’s en hoeveelheid Proteobacteria waren vergelijkbaar tussen patiënten en controles. Bij diverticulitis was een hogere fecale microbiota diversiteit waarnembaar, waarbij het phylum Proteobacteria voornamelijk dit verschil bepaalde. De diagnostische accuratesse van het cross-gevalideerde ‘partial least squares discriminant analysis’ regressie model was 84%. De meest discriminatoire species waren grotendeels afkomstig van de familie Enterobacteriaceae. We concluderen dat diverticulitis patiënten een hogere diversiteit van fecale microbiota hebben dan controles uit een gemengde populatie. Verder laat onze studie zien dat de diagnose diverticulitis met relatief goede accuratesse gesteld kan worden middels microbioom analyse. Zodoende biedt analyse van de darm microbiota een nieuwe manier om de diagnose diverticulitis te stellen.

TOEKOMSTPERSPECTIEVEN

De Nederlandse Vereniging voor Heelkunde streeft een evidence-based beleid na ten aanzien van de optimale behandeling van zowel ongecompliceerde als gecompliceerde diverticulitis. Zodoende heeft de Vereniging vanaf 2009 voorzien in een platform om de lopende Dutch Diverticula Disease Group trials te promoten en de studie resultaten te presenteren tijdens het jaarlijkse landelijke congres. De Nederlandse diverticulitis richtlijn uit 2012 nam internationaal het voortouw ten aanzien van controversiële punten door progressief te stellen dat er geen bewijs is voor het routinematig toedienen van antibiotica bij patiënten met ongecompliceerde diverticulitis en dat er geen indicatie is voor routine endoscopische evaluatie na een episode diverticulitis. Het wetenschappelijke bewijs voor deze aanbevelingen was toenertijd minimaal.

In de laatste jaren is er een aanzienlijke vooruitgang geboekt op het wetenschappelijke gebied van diverticulitis; chirurgische behandelingen werden minder invasief en traditionele behandelpri ncipes worden uitvoerig onderzocht. Ondanks deze ontwikkelingen is er nog steeds ruimte voor verdere verbetering en moeten er nog vele vragen worden beantwoord. Het onderzoek dat in dit proefschrift is beschreven heeft als doel bij te dragen aan de optimalisatie van de aanpak van patiënten met ongecompliceerde diverticulitis. Voor gecompliceerde diverticulitis zullen de resultaten van verschillende lopende trials een bijdrage aan de huidige kennis leveren en mogelijk keuze opties veranderen. De uitkomsten van de DIABOLO trial bevestigen de resultaten van de Scandinavische gerandomiseerde klinische trial, die eveneens de waarde van antibiotische behandeling voor acute ongecompliceerde diverticulitis heeft onderzocht en in 2012 is gepubliceerd. Zij vonden dat antibiotische behandeling noch het herstel versnelde noch complicaties of recidieven voorkwam, maar de studie includeerde een groot aantal patiënten met recidiverende diverticulitis. In een recent review artikel wordt derhalve met tegenzin
Toekomstperspectieven

geconcludeerd dat antibiotische behandeling mogelijk niet nodig is bij alle patiënten.\textsuperscript{3} Maar in zowel deze review als in een Cochrane systematische review wordt aangegeven dat eerst bevestiging door andere gerandomiseerde gecontroleerde trials van goede kwaliteit nodig is, als de behandeling evidence-based moet zijn.\textsuperscript{3,4} Recente internationale richtlijnen bleven ongewijzigd en concludeerden ook dat meer onderzoek nodig is alvorens een antibiotica-vrije behandelstrategie in te voeren.\textsuperscript{5,6} Met de resultaten van de DIABOLO trial – gepresenteerd in deze thesis –, is er nu een tweede gerandomiseerde trial die uitwijst dat antibiotica niet van toegevoegde waarde zijn. Met de kennis dat de huidige trial alleen eerste episodes van milde acute diverticulitis heeft geïncludeerd, is er nu voldoende bewijs beschikbaar voor de implementatie in internationale richtlijnen van een observationele behandelstrategie zonder antibiotica.

Het achterwege laten van antibiotica bij de behandeling van diverticulitis dient vooral nog beperkt te blijven tot patiënten met Hinchey 1a diverticulitis. Hoewel de resultaten van de DIABOLO trial suggereren dat de aanbeveling mogelijk ook toepasbaar is op patiënten met Hinchey 1b diverticulitis, is voorzichtigheid geboden binnen deze subgroep met een klein peri- of mesocolisch abces. In de literatuur zijn er geen high-quality papers over de behandeling van diverticulitis patiënten met abcesvorming en een observationele strategie is nooit onderzocht. Zodoende zijn er prospectieve cohorts nodig, met een grootte van meer dan de 42 patiënten zoals in onze studie, voordat er definitieve conclusies getrokken kunnen worden voor wat betreft de optimale behandelstrategie voor patiënten met Hinchey 1b diverticulitis. Eveneens dienen patiënten met significante comorbiditeit, inflammatoire darmziekten, zwangerschap, klinische verdenking op sepsis en immuungecompromitterde patiënten uitgesloten te worden van deze aanbeveling. Het is belangrijk verder te onderzoeken welke kenmerken mogelijk voorspellen welke patiënten voordeel zouden kunnen hebben van een antibiotische behandelstrategie en subgroepen te definiëren.

Het aantal diverticulitis patiënten zal in de nabije toekomst meest waarschijnlijk verder toenemen. Daarom zijn het verder optimaliseren van behandelstrategieën en faciliteren van kosten-effectieve zorg de grote uitdagingen. De DIABOLO trial is ook opgetzet om de kosten-effectiviteit van een observationele strategie met een antibiotische strategie te vergelijken. Deze analyses zijn momenteel in de laatste fase en de resultaten worden verwacht. Een combinatie van een antibiotica-vrije en poliklinische behandelstrategie leidt mogelijk tot verder optimaliseren van de behandelstrategie voor ongecompliceerde acute diverticulitis.\textsuperscript{7,8}

Beter inzicht verkrijgen in het natuurlijke beloop van divertikelziekte, het klinische beeld en de resultaten van follow-up na behandeling zijn reeds van grote invloed geweest op behandelstrategieën. Echter, de behandeling van diverticulitis kan alleen optimaal afgestemd worden op de individuele patiënt wanneer we de onbegrepen pathofysiologie van diverticulitis ontrafeld hebben. In recente publicaties over divertikelziekte worden
Appendices

Lang bestaande ziekte concepten en behandelstrategieën betwist. Nieuw onderzoek, waaronder ons eigen onderzoek, dicht een belangrijke rol toe aan veranderingen in darm microbiota. Onze studie toonde aan dat fecale microbiota van diverticulitis patiënten significant verschilt van controles en dat de diagnose diverticulitis gesteld kan worden middels analyse van het microbiom. Hoewel deze resultaten extern gevalideerd moeten worden, zijn er spannende nieuwe perspectieven in hun klinische toepasbaarheid zoals de mogelijkheden van feces transplantatie (bacteriotherapie) voor de preventie van recidiverende diverticulitis.

Verdere studies dienen te kijken of veranderingen in de samenstelling van het darm microbiom inderdaad een oorzaak of juist een gevolg van divertikelziekte zijn. Vanuit een etiopathogenetisch perspectief zou het interessant zijn verder te onderzoeken of er een graduale verschuiving in microbiota samenstelling is van diverticulose naar diverticulitis. Wanneer de exacte rol van darm microbiota in divertikelziekte opgehelderd is dan zou dit eveneens van grote klinische waarde kunnen zijn in preventie van ziekte en gerichtere behandeling. Momenteel pogen wij inzicht te verkrijgen in het verloop dat fecale microbiota samenstelling heeft in patiënten met een eerste episode van ongecompliceerde acute diverticulitis en welke effecten antibiotische therapie heeft op dit verloop.

De pathogenese is meest waarschijnlijk multifactorieel en het resultaat van complexe interacties. Er zijn mogelijk ontbrekende schakels, die nog ontdekt moeten worden, andere dan een veranderd microbiom en de daarop volgende activatie van immuun respons die nodig zijn voor de ontwikkeling van divertikelziekte en/of de complicaties ervan. Het is van het grootste belang de pathofysiologie van divertikelziekte beter te begrijpen; dit zou tot gerichtere behandeling en zelfs nieuwe aangrijpingspunten voor behandeling kunnen leiden.
Toekomstperspectieven


REFERENTIES
LIST OF PUBLICATIONS

Yield of colonoscopy after recent CT-proven uncomplicated acute diverticulitis: a comparative cohort study
Daniels L, Unlü C, de Wijkerslooth TR, Stockmann HB, Kuipers EJ, Boermeester MA, Dekker E.

Fecal microbiome analysis as a diagnostic test for diverticulitis
Daniels L, Budding AE, de Korte N, Eck A, Bogaards JA, Stockmann HB, Consten EC, Savelkoul PH, Boermeester MA

Overschatting van optimale timing van antibiotagebruik ter preventie van postoperatieve wondinfecties
Daniels L, de Jonge SW, Boermeester MA
Ned Tijdschr Geneeskd. 2014;158:A7071

A hypothesis: important role for gut microbiota in the etiopathogenesis of diverticular disease
Daniels L, Philipszoon LE, Boermeester MA
Dis Colon Rectum. 2014 Apr;57(4):539-43

Routine colonoscopy after left-sided acute uncomplicated diverticulitis: a systematic review
Daniels L, Unlü C, de Wijkerslooth TR, Dekker E, Boermeester MA
Gastrointest Endosc. 2014 Mar;79(3):378-89

External validation of two tools for the clinical diagnosis of acute diverticulitis without imaging
Dig Liver Dis. 2014 Feb;46(2):119-24

Systematic review of medical therapy to prevent recurrent diverticulitis
Unlü C, Daniels L, Vrouwenraets BC, Boermeester MA
Int J Colorectal Dis. 2012 Sep;27(9):1131-6

Overtreatment of sigmoid diverticulitis: plea for a less aggressive approach
Daniels L, de Korte N, Winter D, Boermeester MA, Stockmann HB
A systematic review of high-fibre dietary therapy in diverticular disease
Ünlü C, Daniels L, Vrouenraets BC, Boermeester MA
Int J Colorectal Dis. 2012 Apr;27(4):419-27

Endoscopic type 2 endoleak repair following endovascular aortic aneurysm repair: acute results and follow-up experience
Linsen MA, Daniels L, Cuesta MA, Wisselink W

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

Hybrid treatment of aberrant right subclavian artery and its aneurysms.
Daniels L, Covieliers HM, Hoksbergen AW, Nederhoed JH, Wisselink W

Galsteenileus: diagnose en behandeling
Daniels L, Wiarda BM, Houdijk APJ

Catheter-delivered transducer-tipped ultrasound thrombolysis of a chronically occluded aortic stentgraft limb
Daniels L, Hoksbergen AWJ, Covieliers HME, Lely RJ, Nederhoed JH, Wisselink W
EJVES Extra. 2010;19:e25-e27
PhD Portfolio
### PhD Portfolio

**Name PhD student:** L. Daniels  
**PhD period:** December 2009 – January 2014  
**Name PhD supervisor:** Prof. dr. M.A. Boermeester

<table>
<thead>
<tr>
<th>1. PhD training</th>
<th>Year</th>
<th>Workload (ECTS)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General courses</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Reference Manager</td>
<td>2010</td>
<td>0.1</td>
</tr>
<tr>
<td>- Web of Science</td>
<td>2010</td>
<td>0.1</td>
</tr>
<tr>
<td>- Evidence Based Searching</td>
<td>2010</td>
<td>0.1</td>
</tr>
<tr>
<td>- PubMed Biomedical Sciences</td>
<td>2010</td>
<td>0.1</td>
</tr>
<tr>
<td>- Developing a Cochrane Systematic Review</td>
<td>2010</td>
<td>0.3</td>
</tr>
<tr>
<td>- The AMC World of Science</td>
<td>2010</td>
<td>0.7</td>
</tr>
<tr>
<td>- Clinical Data Management</td>
<td>2010</td>
<td>0.3</td>
</tr>
<tr>
<td>- Practical Biostatistics</td>
<td>2010</td>
<td>1.1</td>
</tr>
<tr>
<td>- Good Clinical Practice</td>
<td>2010</td>
<td>0.2</td>
</tr>
<tr>
<td>- Basic Course in Legislation and Organization for Clinical Researchers (BROK)</td>
<td>2010</td>
<td>0.9</td>
</tr>
<tr>
<td>- Oral Presentation in English</td>
<td>2011</td>
<td>0.8</td>
</tr>
<tr>
<td>- Clinical Epidemiology</td>
<td>2012</td>
<td>0.6</td>
</tr>
<tr>
<td>- Scientific Writing in English for Publication</td>
<td>2012</td>
<td>1.5</td>
</tr>
<tr>
<td><strong>Specific courses</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Advanced Topics in Biostatistics</td>
<td>2012</td>
<td>2.1</td>
</tr>
<tr>
<td><strong>Seminars, workshops and master classes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Weekly department seminars</td>
<td>2010-2014</td>
<td>4</td>
</tr>
<tr>
<td>- Master class by Prof. J. Powell</td>
<td>2012</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>(Inter)national conferences</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- NVvH Chirurgendagen</td>
<td>2010-2014</td>
<td>1.25</td>
</tr>
<tr>
<td>- Falk Symposium Diverticular Disease</td>
<td>2011</td>
<td>0.25</td>
</tr>
<tr>
<td>- NVvH Najaarsvergadering</td>
<td>2012</td>
<td>0.25</td>
</tr>
<tr>
<td>- NVGE Najaarsvergadering</td>
<td>2013</td>
<td>0.25</td>
</tr>
<tr>
<td>- Surgical Infection Society Europe</td>
<td>2011-2014</td>
<td>1.0</td>
</tr>
<tr>
<td>- United European Gastroenterology Week</td>
<td>2012, 2014</td>
<td>0.5</td>
</tr>
<tr>
<td>Presentations</td>
<td>Year</td>
<td>Workload (ECTS)</td>
</tr>
<tr>
<td>------------------------------------------------------------------------------</td>
<td>-------</td>
<td>-----------------</td>
</tr>
<tr>
<td>- Good Clinical Practice driven 3D studies - Symposium 3D Study Group</td>
<td>2010</td>
<td>0.5</td>
</tr>
<tr>
<td>NVvH Chirurgendagen, Veldhoven</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Diverticulitis: AntiBiotics Or Close Observation? – Protocol presentation</td>
<td>2010</td>
<td>0.5</td>
</tr>
<tr>
<td>Gutclub, Amsterdam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Wel of geen antibiotica voor ongecompliceerde diverticulitis? 1 trial is geen trial - Symposium 3D Study Group</td>
<td>2012</td>
<td>0.5</td>
</tr>
<tr>
<td>NVvH Chirurgendagen, Veldhoven</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Overtreatment of sigmoid diverticulitis: a plea for a less aggressive approach</td>
<td>2012</td>
<td>0.5</td>
</tr>
<tr>
<td>SIS-E Congress, Lund, Sweden</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Altered faecal microbiota composition in patients with a first episode of acute uncomplicated diverticulitis</td>
<td>2013</td>
<td>0.5</td>
</tr>
<tr>
<td>NVvH Chirurgendagen, Veldhoven</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SIS-E Congress, Prague, Czech Republic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NVGE Najaarsvergadering, Veldhoven</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Overview of results of the DIABOLO trial and its substudies - Symposium 3D Study Group</td>
<td>2014</td>
<td>0.5</td>
</tr>
<tr>
<td>NVvH Chirurgendagen, Veldhoven</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- A systematic review of routine colonoscopy after left-sided acute uncomplicated diverticulitis</td>
<td>2014</td>
<td>0.5</td>
</tr>
<tr>
<td>SIS-E, Vienna, Austria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- A prospective comparative cohort study on the prevalence of advanced colonic neoplasia after uncomplicated acute diverticulitis versus primary screening colonoscopy</td>
<td>2014</td>
<td>0.5</td>
</tr>
<tr>
<td>NVvH Chirurgendagen, Veldhoven</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SIS-E, Vienna, Austria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- A randomized clinical trial of observational versus antibiotic treatment for a first episode of uncomplicated acute diverticulitis (DIABOLO trial)</td>
<td>2014</td>
<td>0.5</td>
</tr>
<tr>
<td>NVvH Chirurgendagen, Veldhoven</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UEGW, Vienna, Austria</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### 2. Teaching

<table>
<thead>
<tr>
<th>Supervising</th>
<th>Year</th>
<th>Workload (ECTS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D.K. van Santen, trial nurse DIABOLO trial</td>
<td>2011</td>
<td>0.5</td>
</tr>
<tr>
<td>C.E.M. Glaap, trial nurse DIABOLO trial</td>
<td>2011-2012</td>
<td>2.0</td>
</tr>
<tr>
<td>L. Philipszoon, Microbiota etiopathogenetic factor in diverticular disease: a proposed hypothesis, Dept. of Surgery</td>
<td>2011-2012</td>
<td>1.0</td>
</tr>
<tr>
<td>A.H. Koch, Pilot study on timing of pre-operative antibiotic prophylaxis in relation to surgical site infection and accuracy of OR foot traffic registration, Dept. of Surgery</td>
<td>2012-2014</td>
<td>1.0</td>
</tr>
<tr>
<td>A. Croonen, research assistant DIABOLO trial</td>
<td>2013</td>
<td>0.5</td>
</tr>
<tr>
<td>L. Philipszoon, Compliance to a bundle of safety measures and the risk of surgical site infection, Dept. of Surgery</td>
<td>2013-2014</td>
<td>1.0</td>
</tr>
<tr>
<td>A.L.L. Vergunst, Fraction of inspired oxygen and surgical site infection, Dept. of Surgery</td>
<td>2013-2014</td>
<td>1.0</td>
</tr>
<tr>
<td>S.W. de Jonge, Timing of antibiotic prophylaxis and surgical site infection, Dept. of Surgery</td>
<td>2013-2014</td>
<td>1.0</td>
</tr>
</tbody>
</table>

### 3. Parameters of Esteem

<table>
<thead>
<tr>
<th>Grants</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>UEGW Travel Grant</td>
<td>2014</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Awards and Prizes</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>UEG Week Top Abstract Prize</td>
<td>2014</td>
</tr>
</tbody>
</table>