New Insights in the Management of (Uncomplicated) Diverticulitis

Towards More Cost-Effective Diverticulitis Care

Hendrike Elisabeth Bolkenstein

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New insights in the management of (uncomplicated) diverticulitis

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A stylized, light gray line drawing of a plant stem with several leaves and a flower bud at the bottom. The stem curves from the top left towards the bottom right. The leaves are arranged in a spiral pattern along the stem. The flower bud is located at the bottom left of the stem.

Chapter 1

General introduction and
thesis outline

This thesis describes different aspects of the management of diverticulitis. It focusses mainly on determinants of negative outcome (complications) in patients with diverticulitis as well as the optimal treatment strategy in patients with uncomplicated (recurrent) diverticulitis. With this thesis we hope to improve the quality of treatment as well as the cost-effectiveness.

Epidemiology

Diverticulosis is primarily seen in the Western population with the prevalence increasing with age. At forty, approximately 10% of the Western population will have diverticulosis, while this number increases up to 70% in octogenarians. About 7% of people with diverticulosis will develop diverticulitis of which 25% present with complications such as abscess or perforation.¹⁻⁴ Recent studies show a slightly higher incidence of diverticulitis in women, with an average of 60% female.^{5,6}

Etiology

Diverticula are protrusions of the colon wall, which in the Western population mostly occur in the descending colon and sigmoid.⁷ These diverticula are actually considered “false” diverticula since the mucosa and submucosa herniate through the muscularis propria without involving all layers of the colon wall. The protrusions occur mostly at the points where the vasa recta penetrate the colon wall to supply this region. The true pathogenesis of diverticulosis has yet to be clarified. Multiple factors might play a role in developing diverticulosis, such as age (increased collagen crosslinking and progressive elastosis), low-fibre diet, colon structure and motility. A low-fibre diet increases the transit time which stimulates the colonic circular muscle. It is thought that high intracolonic pressure, due to exaggerated contractions of the colonic circular muscle, generates increased outward force on the colon wall, resulting in mucosal herniation.^{8,9} While most etiology studies focussed on the colon wall structure and motility of the colon, few examined the three-dimensional (3D) geometrical colon properties in relation to diverticulosis.¹⁰ In **chapter 2** we look at the relation between 3D geometrical colon properties and the presence of diverticulosis. We aimed to acquire quantitative information on 3D colon geometry (length and tortuosity (amount of twists)) with non-invasive colon examination using computed tomography (CT) data and relate them to the presence or absence of diverticulosis. A common complication of diverticulosis is diverticulitis. The etiology of this inflammatory episode is also speculative. It has been described that fecalith either lodges in the diverticular neck or scrapes the mucosal layer and causes secondary inflammation. Subsequently proliferation

of bacteria, diverticular distension and localised ischemia will occur, which can eventually lead to perforation.⁹

Diagnosis

Acute uncomplicated diverticulitis is thought to be a primarily clinical diagnosis with pain in the lower left abdomen, C-reactive protein level of >50 mg/L and absence of vomiting being the strongest clinical features for predicting the presence of diverticulitis.¹¹ These three features are however present in only 25% of the patients with diverticulitis. In clinical practice, a radiological approach is often used to diagnose diverticulitis. Ultrasound (US) imaging is an effective and non-invasive approach with an overall sensitivity of 77% and specificity of 99%. In acute uncomplicated diverticulitis the sensitivity is 96%.¹² The optimal radiologic approach to identify diverticulitis is however still CT. CT has a sensitivity up to 97% and can distinguish between the different stages of complicated diverticulitis (abscess, free air, free fluid, fistula formation).^{13,14} As uncomplicated diverticulitis is usually a mild and self-limiting disease, it should primarily be seen and treated in primary care. However, general practitioners usually do not have access to the above described secondary care diagnostics and therefore the distinction between uncomplicated and complicated diverticulitis is difficult to make, resulting in unnecessary referrals to secondary care. Our aim was to give general practitioners a tool based on clinical parameters to decide which patients are at risk of complicated diverticulitis and should therefore be referred to secondary care for further evaluation by US or CT. In **chapter 3** a systematic review and meta-analysis is performed to identify clinical risk factors for complicated diverticulitis. In **chapter 4** we subsequently developed a diagnostic prediction model based on clinical parameters to predict the presence of complications in patients presenting with diverticulitis. The goal was to safely rule out complicated diverticulitis with this model, so that clinical practitioners can use it to select patients that are suitable to be treated at home. This could ultimately improve cost-effectiveness of diverticulitis care as unnecessary referrals to secondary care can be reduced.

Classification

Traditionally diverticulitis is divided in two categories: “uncomplicated” or “mild” diverticulitis and “complicated” diverticulitis. Ambrosetti et al made this classification based on CT-findings.¹⁴ The most commonly used classification is the modified Hinchey classification. This system categorises diverticulitis in five categories (zero to four). Hinchey zero is a clinical diagnosis. Hinchey one to four is based on CT-findings where Hinchey Ia (only pericolic inflammation and fat

straining) is usually considered as “uncomplicated” or “mild” and Hinchey Ib (with small abscess <5cm), two (large abscess ≥5cm), three (perforated diverticulitis with purulent peritonitis) and four (perforated diverticulitis with faecal peritonitis) as complicated diverticulitis.¹⁵⁻¹⁷ The differentiation between uncomplicated and complicated diverticulitis is important because complicated diverticulitis has higher morbidity and mortality. Therefore it demands a more aggressive therapeutic approach. For uncomplicated diverticulitis the mortality is almost zero, but perforated purulent or faecal diverticulitis has a mortality rate up to 20%.¹⁸⁻²¹ The above mentioned classification systems do not describe the patient group that presents with signs of (a small amount of) isolated pericolic air on CT-scan without signs of peritonitis or sepsis. Some authors describe this entity as a “covered perforation”.²¹ More recent classification systems do include the presence of pericolic air bubbles or localized pneumoperitoneum in their classification.²²⁻²⁴ The clinical relevance of pericolic air is however not well understood. In **chapter 6** we analyze the disease course of uncomplicated diverticulitis (Hinchey 1A) patients presenting with pericolic air and the outcome of a conservative treatment strategy without antibiotics in this patient group. We hypothesize that patients with isolated pericolic air (without clinical signs of sepsis or peritonitis) do not differ from “uncomplicated” diverticulitis patients and should be treated as such.

Treatment of uncomplicated diverticulitis

Two recent randomized controlled trials have demonstrated that uncomplicated diverticulitis (Hinchey 1A) can be treated conservatively without antibiotics.^{25,26} Moreover, recent studies have provided strong evidence that the outpatient treatment of uncomplicated diverticulitis patients is safe and effective even without oral antibiotics.²⁷⁻³² However, these studies do report treatment failure rates of 3-24% and due to high risk of selection and detection bias the results are less applicable to daily practice.³⁰ It remains uncertain which uncomplicated diverticulitis patients are eligible for non-antibiotic treatment and which uncomplicated diverticulitis patients are more susceptible for a complicated course (treatment failure) and should therefore receive antibiotic treatment and closer surveillance. In **chapter 5** we aim to identify clinical risk factors that can predict a complicated course in uncomplicated diverticulitis patients to select patients who are eligible for non-antibiotic treatment.

Treatment of complicated diverticulitis

Diverticular abscesses can be treated conservatively, surgically and by percutaneous abscess drainage.^{23,33,34} Nowadays, nonsurgical treatment is still frequently considered a bridge to surgery in these patients and there is no clear consensus regarding the optimal treatment strategy.³⁵ In **chapter 7** we assess both the short- and long-term outcomes of initial nonsurgical treatment strategies for acute complicated diverticulitis with abscess formation (Hinchey Ib and II) in a multicenter retrospective cohort. Factors associated with the need for emergency or elective surgery after initial nonsurgical treatment are identified to select patients for whom nonsurgical treatment with or without percutaneous drainage, followed by an expectant policy without elective surgery, is adequate enough. Perforated diverticulitis with peritonitis (Hinchey 3 or 4) is mostly treated with emergency surgery (sigmoid resection with or without ileostomy or Hartmann procedure) or in some cases laparoscopic lavage.³⁶⁻³⁸ This thesis will not further discuss the treatment of perforated diverticulitis (Hinchey 3 or 4).

Recurrent diverticulitis and persistent complaints

The relapse rate of medically treated diverticulitis varies in the literature from 2%-42%, but averages on 20%. Persistent complaints can occur in up to 30% of diverticulitis patients.³⁹⁻⁴⁴ A number of risk factors for developing recurrent diverticulitis have been described in previous literature such as; age, BMI, elevated CRP, elevated leucocyte count, free air or fluid on CT, length of affected colon, comorbidity (renal failure, collagen vascular disease), family history and previous episodes of diverticulitis.^{40,45-48}

The treatment of recurrent diverticulitis or ongoing complaints has been topic of debate. Traditionally, guidelines recommended that patients with ≥ 2 episodes of diverticulitis should receive elective sigmoid resection to reduce recurrence rate and associated complications.⁴⁹ Latest evidence however shows that recurrent diverticulitis does not have a more complicated course than a first episode. This undermines the old rationale for elective surgery as a preventive treatment, based mainly on concerns that recurrence would result in a progressively increased risk of sepsis or the need for a colostomy.⁵⁰ Latest guidelines therefore recommend a tailored approach for each individual patient where the impact of multiple recurrences and ongoing complaints on quality of life should form the most decisive factor in the decision whether or not to operate.^{51,52} The effect of elective resection on quality of life in this patient group is however not well understood. Only low quality data have been available on the operative and conservative management of recurrent diverticulitis and/or ongoing complaints,

with both treatment strategies being reported as effective.³⁹ The DIRECT trial was a randomized controlled trial comparing surgical (elective sigmoidectomy) treatment with conservative treatment in patients with recurrent diverticulitis and/or ongoing complaints, with quality of life as the primary outcome measure. The short term (six months) results showed that operative treatment leads to increased quality of life compared to conservative treatment.⁵³ **Chapter 8 and 9** describe the long-term outcome and cost-effectiveness of operative treatment.

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Chapter 2

The relation between diverticulosis and
colon length- and tortuosity:
analysis based on 3D modelling

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Abstract

Aim

Most etiology studies on diverticulosis focus on colon wall structure and motility. The aim of the present study is to acquire quantitative information on 3D colon geometry (length and tortuosity) with non-invasive colon examination using computed tomography (CT) data and relate them to diverticulosis.

Methods

A retrospective cohort study was performed comparing abdominal CT data between patients with and without diverticulosis. Exclusion criteria were previous colon surgery (resection or colostoma), clinical or radiological suspicion of colonic malignancy and for the diverticulosis group active diverticulitis at the moment of imaging. Colon centerlines were delineated with 3Mensio Vascular and length and tortuosity was evaluated using Matlab.

Results

Sixty patients were included in the study; 30 diverticulosis patients and 30 controls without diverticulosis. Mean total colon length was longer in the control group (136 ± 20 cm) compared to the diverticulosis group (120 ± 19 cm) ($p=0.002$), which can be attributed to a longer transverse colon (39 ± 8 cm vs 31 ± 7 cm) and sigmoid colon (34 ± 10 cm vs 28 ± 9 cm). Mean tortuosity of the transverse and the descending colon was higher in the control group 0.59 ± 0.1 vs 0.54 ± 0.08 ($p=0.045$) and 0.56 ± 0.12 vs 0.46 ± 0.11 ($p=0.002$) respectively. Although not statistically significant ($p=0.074$) total colon tortuosity seemed higher in the control group (0.63 ± 0.07) compared to the diverticulosis group (0.59 ± 0.08).

Conclusion

Patients with diverticulosis seem to have a less tortuous and shorter colon than patients without diverticulosis. Although the pathophysiologic mechanisms behind this relation have yet to be clarified, these results could contribute to the further understanding of the pathogenesis of diverticulosis.

Introduction

Diverticulosis has a high prevalence in the Western population, increasing with age. At the age of forty the prevalence is approximately 10%, while this number increases up to 70% in octogenarians. Diverticula are outpouchings that occur at weak points in the colonic wall where the vasa recta penetrate the circular muscle layer. They are most frequently found in the distal part of the colon, with 90% of patients having the sigmoid colon involved.^{1,2} About 7% of people with diverticulosis will develop diverticulitis. One in four will develop complications such as abscess, perforation, peritonitis, stenosis or fistula.³ Despite its high prevalence and impact, the true pathogenesis of diverticulosis has yet to be clarified. There are multiple factors that might play a role in the development of diverticulosis, such as a low-fibre diet, thickening of the colon musculature, disordered motility and (age-related) weakening of the colon wall connective tissue (increased collagen crosslinking and progressive elastosis).⁴⁻⁶ A low-fibre diet increases the transit time which stimulates the colonic circular muscle.⁷ It is thought that exaggerated contractions of the colonic circular muscle raise the intracolonic pressure and increase the outward force on the colonic wall, resulting in mucosal herniation.^{8,9} While most etiological studies focussed on the colonic wall structure and motility of the colon, few examined the three-dimensional (3D) geometrical colon properties in relation to diverticulosis.¹⁰ Two historical studies described an inverse relation of a redundant colon with diverticulosis.^{11,12} A redundant colon is commonly described as a chronically distended, elongated, tortuous colon without obvious cause. It occurs mostly in the sigmoid part of the colon.¹³⁻¹⁵ Recently, Cuda et al. conducted a study on the correlation between a redundant colon and diverticulosis. They confirmed the earlier described inverse relation.¹⁶ However, the used definition for redundant colon was based on a subjective finding of the endoscopist during colonoscopy. Moreover, the geometry of the colon is affected by the forces exerted by endoscope to the colon wall, making the results less reliable. The aim of the present study is to acquire quantitative information on 3D colon geometry (length and tortuosity) with non-invasive colon examination using abdominal computed tomography (CT) data and relate them to the presence or absence of diverticulosis.

Methods

Study design and study population

A retrospective cohort study was performed comparing abdominal CT data between patients with and without diverticulosis. The study was approved by the local Institutional Review Board of the Meander Medical Centre. A diagnostic specific code was used to identify patients with diverticulosis who received CT-imaging of the abdomen between January 2010 and May 2014. Patients in the control group (without diverticulosis) were randomly selected from a patient population who received CT-imaging of the abdomen in the same time period as the diverticulosis group. Since the absence of diverticulosis is not always explicitly mentioned in the CT-report, all patients in the control group had to have had a colonoscopy where the absence of diverticulosis was confirmed. Moreover, as the prevalence of diverticulosis increases with age, only non-diverticulosis patients who were at least 45 years of age at the time of CT-imaging were included to minimise the chance of them developing diverticulosis in a later stadium (and thus actually not belonging to the control group). Exclusion criteria were previous colon surgery (resection or colostoma), clinical or radiological suspicion of colonic malignancy and for the diverticulosis group active inflammation (diverticulitis) at the moment of imaging as these factors influence the 3D colon anatomy.

Data collection and processing

Imaging was performed using spiral CT scanners (Siemens SOMATOM: Sensation 16, Definition AS, Definition Flash) with the patient in supine position. Axial slices were spaced at 3 millimetres (mm) (Definition AS / Flash) or 5 mm (Sensation 16) intervals and contained 512 x 512 pixels. Intravenous contrast (Xenetix 300/350, Guerbet, The Netherlands) was administered and bowel preparation took place with oral contrast-enhancing fluid (CEF; Telebrix Gastro, Guerbet, The Netherlands) 1 hour before start of the CT examination (unless the patient had a contraindication for intravenous or oral contrast).

The study design for colon geometry analysis in abdominal CTs is based on vascular imaging, where the geometry of arterial structures is analyzed in computed tomography angiography (CTA) data for pre-operative planning of several endovascular interventions. The basis of that analysis is the centreline (the line drawn through the center point) of the blood vessel. Then, at every location along the centerline, the lumen area is determined perpendicular to the centerline. In this way, a complete lumen area profile of the vessel can be reconstructed. In the present study, we applied the same strategy to assess the

colon geometry in abdominal CTs. Professional vascular post-processing software (3mensio Vascular, Pie Medical Imaging, Maastricht, The Netherlands) was used for colon centerline positioning and for colon (segment) length measurements. The colon centerline was defined from the anus to the caecum by manual point clicking in the axial CT slices. The positioning of all centerline points was evaluated on precision in three planes simultaneously (axial, coronal and sagittal) and was adjusted when necessary. The spatial distribution of the centerline points was then evaluated and centerline points were removed or added in over or under sampled areas respectively to ensure reproducible tortuosity calculations. Colon (segment) length measurements were performed with the distance measurement tool in the stretched colon view. The following colon segments were defined: ascending, transverse, descending, sigmoid, rectum and diverticulosis area (based on radiologic findings). All distances were measured from the proximal end (caecum) to the segment junctions (hepatic flexure, lienal flexure, colo-sigmoid junction, recto-sigmoid junction and proximal/distal diverticulosis area border respectively). Colon segment junctions were defined as described in **table 1**.^{17,18} The location of the hepatic flexure, lienal flexure and the colo-sigmoid junction was determined in the 3D centerline view. The location of the recto-sigmoid junction was determined in the sagittal slices along the centerline. Finally, the centerline 3D coordinates were sampled at 1 mm intervals.

Table 1 *Colon Junction Definitions*

Colon junction	Description
Hepatic flexure	The centerline bending point of the ascending colon to the transverse colon.
Lienal flexure	The centerline bending point of the transverse colon to the descending colon.
Colo-sigmoid junction	The centerline bending point of the descending colon to the direction of the medial plane.
Recto-sigmoid junction	The centerline point perpendicular to the S3 vertebra (at this point, the colon loses its peritoneum and becomes rectum). ^{18,19}
Proximal/distal diverticulosis area border	Based on details from the radiology report and image interpretation of the observer.

Tortuosity evaluation

Tortuosity is a property of a curve being tortuous (twisted; having many turns). Mathematically, tortuosity can be defined with several different metrics. To select the optimal tortuosity metric to analyze colon tortuosity we assessed and implemented five different mathematical tortuosity metrics in MATLAB (R2017b, MathWorks, Inc.). These were the 'Distance Metric' (DM)^{19,20}, the 'Second derivative Metric' (SDM)²⁰, the 'Frenet-Serret metric (FSM)^{19,21}, the 'Sum of Angles Metric' (SOAM)²⁰ and the 'Inflection Count Metric' (ICM)¹⁹. The first four metrics all calculate local tortuosity along a 3D space curve (the colon centerline in our study). Averaging these local tortuosity values along the length of the curve results in a tortuosity index (TI). The ICM method only counts the number of inflection points along a curve. This number can be used as a multiplying factor to assign extra weight to the TI in case of present inflections. Moreover, all tortuosity metrics can be calculated on multiple scales. The choice of scale is important as the local tortuosity is calculated based on the samples within a specific distance from the current curve point while ignoring other samples. This allows curves of a specific size to be detected or highlighted.²¹ Therefore, we started with selecting the best tortuosity metric and scale based on colon centerline data of five test patients. First, for every test patient, all local tortuosity metrics (DM, SDM, FS and SOAM) were calculated on a varying scale from 11 to 151 mm in steps of 20 mm. Local tortuosity was expressed on a colour scale in a 3D visualization of the centerline curve (**figure 1**).

The best scale was selected based on the detection of relevant colon curves (e.g. sharp turns, sigmoid-like turns). Second, local tortuosity was calculated and expressed for every local tortuosity metric with its corresponding optimal scale (**figure 2**). The best tortuosity metric was again selected based on the detection of relevant colon curves. The final selected local tortuosity metric was the SDM with corresponding scale 31 mm. This method was used to calculate the colon (segment) TI results of all study patients.

Statistical analysis

Descriptive statistics were provided of all variables. Continuous variables are presented as means (with standard deviation (SD)) or medians (with inter quartile range (IQR)) according to their distribution. For categorical variables counts and percentages are presented. Continuous variables were compared using the independent T test or the Mann-Whitney U test, as appropriate. Categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate. All analyses were performed using the statistical software package SPSS 24.0 (IBM Corporation, New York, USA).

Figure 1 Example of local curvature expression of centerline data with the SD metric at different scales

Figure 2 Local curvature expression of centerline data with different metrics and corresponding optimal scales

Results

Study population

Between January 2010 and June 2014, 199 diverticulosis patients received abdominal CT-imaging. Of these, 169 patients had an active episode of diverticulitis and were excluded from the study. In total, 60 patients were included in the study; 30 diverticulosis patients and 30 controls without diverticulosis. The 30 patients in the diverticulosis group received CT-imaging of the abdomen for follow-up after a diverticulitis episode or ongoing complaints (without signs of active inflammation). The 30 patients in the control group received CT-imaging of the abdomen for various reasons; abdominal pain (n=9), herniation of the abdominal wall (n=2), testicular cancer (n=1), stomach cancer (n=1), ovarian cancer (n=3), renal cancer (n=1), adrenal cancer (n=1), gastrointestinal stromal tumour of the ileum, neuroendocrine tumour of the duodenum (n=1), appendicitis (n=1), pancreatitis (n=2), rectal blood loss (n=1), anaemia (n=1), lipoma (n=1), caecum polyp (n=1),

uterus myoma (n=1), kidney stone (n=2) and obstipation (n=1). **Table 2** shows the patient characteristics. The mean age was 61 ± 11 years and 40 % of the patients were male. The mean Body Mass Index (BMI) was 27.6 ± 6.6 kg/m². There were more men in the diverticulosis group (57%) compared to the control group (23%). Mean age was higher in the control group (64 ± 11 years) compared to the diverticulosis group (58 ± 9 years).

Table 2 Patient characteristics

	Diverticulosis N=30	Non-diverticulosis N=30	p-value
Patient characteristics			
Age (years)	58 (9)	64 (11)	0.037
Sex (N (%) male)	17 (57%)	7 (23%)	0.008
BMI	27.6 (5.0)	30.0 (8.0)	0.18

*Data are presented as mean (SD) unless stated otherwise
Abbreviations; BMI: Body Mass Index, SD: Standard Deviation*

Colon length and tortuosity

Table 3 shows the mean colon length and tortuosity of both groups. **Figure 3** illustrates the length of the colon segments in both groups. Mean total colon length was significantly longer in the control group (136 ± 20 centimetres (cm)) compared to the diverticulosis group (120 ± 19 cm) ($p=0.002$). The mean length of the transverse colon and the sigmoid colon were both longer in the control group compared to the diverticulosis group; 39 ± 8 cm vs 31 ± 7 cm ($p<0.001$) and 34 ± 10 cm vs 28 ± 9 cm ($p=0.028$) respectively. Mean tortuosity of the transverse and the descending colon was higher in the control group compared to the diverticulosis group; 0.59 ± 0.11 vs 0.54 ± 0.11 ($p=0.045$) and 0.56 ± 0.12 vs 0.46 ± 0.11 ($p=0.002$) respectively. Mean rectum tortuosity was lower in the control group 0.66 ± 0.16 vs 0.75 ± 0.16 ($p=0.041$). Although not statistically significant ($p=0.074$) total colon tortuosity seemed higher in the control group (0.63 ± 0.07) compared to the diverticulosis group (0.59 ± 0.08). The median (IQR) length of the diverticulosis segment in the diverticulosis patients was 51 (32-97) cm.

Table 3 Colon length and tortuosity

	Diverticulosis N=30	Non-diverticulosis N=30	p-value
Length (cm)			
Total colon	120 (19)	136 (20)	0.002
Ascending colon	21 (5)	21 (6)	0.89
Transverse colon	31 (7)	39 (8)	< 0.001
Descending colon	29 (7)	32 (6)	0.13
Sigmoid colon	28 (9)	34 (10)	0.028
Rectum	10 (2)	10 (22)	0.99
Tortuosity (SDM)			
Total colon	0.59 (0.08)	0.63 (0.07)	0.074
Ascending colon	0.59 (0.15)	0.57 (0.13)	0.60
Transverse colon	0.54 (0.11)	0.59 (0.11)	0.045
Descending colon	0.46 (0.11)	0.56 (0.12)	0.002
Sigmoid colon	0.74 (0.22)	0.75 (0.13)	0.79
Rectum	0.75 (0.16)	0.66 (0.16)	0.041

Data are presented as mean (SD) unless stated otherwise
Abbreviations; cm; centimetre, SD: Standard Deviation, SDM: Second Derivative Metric

Figure 3 Total colon length and colon segments per group

Discussion

To our knowledge, this study is the first to examine the 3D geometry (in terms of length and tortuosity) of the colon in relation to diverticulosis using abdominal CT data. Our results show that diverticulosis patients have a shorter colon (which can be attributed to a shorter sigmoid and transverse colon) and that their descending and transverse colon are less tortuous compared to patients without diverticulosis. Although not statistically significant, total colon tortuosity also seemed lower in diverticulosis patients.

Colon anatomy has previously been studied in live patients (in vivo studies) as well as in cadavers (in vitro studies). In vitro studies²²⁻²⁵ report mean colon lengths varying from 131 cm to 169 cm and in vivo studies²⁶⁻³¹ from 109 to 211 cm, which is in line with the results of the present study. The results from these studies vary due to different techniques and different definitions of colon segments. Previously used techniques all have different disadvantages. The obvious disadvantage of in vitro studies is the fact that these measurements are done on cadavers and might provide an inadequate presentation of the normal anatomy. Ahrens et al²⁶ described the process where intestinal length shortens directly after death and lengthens again when autolysis sets in. This could influence the measurements of colon length. In vivo studies used different techniques varying from barium enema³⁰, laparotomy²⁸ to CT colonography³¹. Saunders et al³⁰ measured the colon length and mobility in men and women with barium enema to find an explanation why performing a colonoscopy is more difficult in women. Results showed a median total colon length of 155 cm in women and 145 cm in men ($p=0.045$). They concluded that this might be the reason that colonoscopy is more difficult in women as a longer colon tends to predispose to loop formation, difficulty in passing the colonoscope and patient discomfort during intubation. However, barium enema is an imprecise tool to measure the length and tortuosity of the colon as the colon trajectory can only be measured in 2D instead of 3D. Moreover, the finding that women have a longer colon, is not supported by Philips et al²⁵ who analyzed colon length in cadavers and found no correlation with height, sex or age. Hanson et al³¹ compared CTC findings in patients with complete colonoscopy versus incomplete colonoscopy to identify anatomical features associated with inability to reach the cecum with colonoscopy. Mean colon length was 167 cm in patients with complete colonoscopy compared to 211 cm in patients with incomplete colonoscopy ($p<0.0001$). CTC is a more precise tool than barium enema, but produces an inadequate presentation of the normal anatomy since this is disturbed by the inflation of gas. A recently published study³² analyzed colon

length in healthy individuals using MRI-scan and electromagnetic capsules which were recorded while progressing through the colon. By using 3D-coordinates of the centerline they could estimate colon length and found a mean colorectal length of 95 cm, which is shorter than most reported studies. These methods look promising as they provide non-invasive accurate measurements of the colon but do have several limitations such as expense (MRI and electromagnetic capsules are expensive and time consuming), signal loss and poor quality of the electromagnetic recordings and inaccurate or incomplete segmentation (which is needed for MRI assessment of the centreline).³² Moreover, none of the above mentioned studies related the morphology of the colon to the presence or absence of diverticulosis.

There are a few studies that analyzed the relation between the anatomy of the colon and diverticulosis. Meneghelli et al³³ analyzed barium enemas of 243 patients with and without megacolon and found a significantly higher incidence of diverticulosis in patients without megacolon. Moreover, they found that among the patients with association of megacolon and diverticulosis, the diverticula were always located in the nondilated portions of the large bowel. Cuda et al¹⁶ conducted a study on geometrical properties of the colon related to diverticulosis using colonoscopy. They reported an inverse relation of redundant colon with diverticulosis.¹⁶ However, measurements during colonoscopy are influenced by telescoping and straightening that foreshorten insertion length, making these results less reliable.³¹ In the present study quantitative information on colon geometry was acquired by non-invasive colon examination (CT) to overcome the shortcomings of previously used techniques. Interestingly, the results of our study are in line with previous literature describing an inverse relation of redundant colon with diverticulosis^{11,12,16}, since we also found that patients with diverticulosis tend to have a shorter and less tortuous colon.

Although we developed our final method with the highest possible precision, the measured colon (segment) length and tortuosity are still influenced by the manual positioning of the colon centerline and the colon segment junctions, the selected tortuosity metric and the variable geometry of the colon over time. It was not possible to automate the positioning of the colon centerline. For automatic centerline detection, segmentation of the colon in the CT data is necessary, but the low contrast of the colon with the surrounding tissue impedes this. Regarding the tortuosity evaluation, it was difficult to determine what type of tortuosity would be relevant in relation to the presence of diverticulosis. Previous clinical applications of tortuosity derived from medical image data vary from 2D planar tortuosity analysis of nerves³⁴, vascular networks (retinal, tumor, mesenterial)³⁵⁻³⁷,

to the analysis of 3D arterial trajectories.^{20,21,38} There is however not a clear definition for tortuosity. Mathematically, it can be defined with several different metrics. Some of these metrics only take curvature into account, others focus on torsion, but a combination is possible as well. In the present study the SDM metric was selected as the best tortuosity metric based on the detection of the relevant colon turns in a 3D visualisation of the centerline curve. As this is, to our knowledge, the first study to analyze colon tortuosity using this method it remains unclear how to interpret the measured colon tortuosity. Nevertheless, the finding that patients with diverticulosis might have a less tortuous colon compared to patients without diverticulosis is in accordance with results of previous studies.¹⁶ The present study is the first to use clinical CT data to analyze colon length, giving more accurate in vivo measurements of colon length. The findings of the present study therefore provide important new information on colon anatomy. Moreover, these findings can provide important information for gastro-intestinal surgeons who perform colonic (left hemi- or sigmoid) resection on diverticulitis or diverticulosis patients. If diverticulosis patients indeed have a shorter and less tortuous colon, one should emphasize to mobilize the splenic flexure to gain enough colon length for a tensionless anastomosis in these patients. Also, the finding that the diverticulosis segment is on average 51 (IQR 32-97) centimetre may provide background information on resection strategy and recurrence. The sample size of the present study was quite small with only 30 patients in each group, therefore statistical power might have been insufficient to detect differences between the two groups. Patients in the control group were older, due to the fact that younger patients were excluded to minimise the chance of them developing diverticulosis in a later stadium (and thus not belonging to the non-diverticulosis group). There were also significantly more women in the control group, which is a coincidence as they were randomly selected. These factors (age and sex) could be confounders although previous studies report conflictingly about the correlation between colon length and age and sex.^{22-25,27,31} Nevertheless we did find a statistically longer and more tortuous colon in non-diverticulosis patients. Previous studies have described megacolon or redundant colon to have an inverse relation with diverticulosis. The pathophysiologic mechanisms behind this relation have yet to be clarified. It is thought that high intracolonic pressure generates increased outward force on the colonic wall, resulting in diverticula.^{8,9} Perhaps a shorter and less tortuous colon leads to increased intracolonic pressure causing the formation of diverticula. This mechanism can however not be derived from our data.

This study found that diverticulosis patients have a less tortuous and shorter colon than patients without diverticulosis. These results could contribute to the further understanding of the pathogenesis of diverticulosis.

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Chapter 3

Risk factors for
complicated diverticulitis:
Systematic review & meta-analysis

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ABSTRACT

Purpose

The aim of this systematic review is to identify risk factors that can predict complicated diverticulitis. Uncomplicated diverticulitis is a self-limiting and mild disease, but 10% of patients with diverticulitis develop complications requiring further treatment. It is important to estimate the risk of developing complicated diverticulitis at an early stage to set the right treatment at initial presentation.

Methods

Embase, MEDLINE and Cochrane databases were searched for studies reporting on risk factors for complicated diverticulitis. Complicated diverticulitis was defined as Hinchey $\geq$ Ib or severe diverticulitis according to the Ambrosetti criteria. Meta-analyses were performed when at least four studies reported on the outcome of interest. This study was conducted according to the PRISMA guidelines.

Results

A total of twelve studies were included with a total of 4619 patients. Most were of reasonable quality. Only the risk factors "age" and "sex" were eligible for meta-analysis, but none showed a significant effect on the risk for complicated diverticulitis. There was reasonable quality of evidence suggesting that high C-reactive protein, white blood cell count, clinical signs including generalised abdominal pain, constipation and vomiting, steroid usage, a primary episode and comorbidity are risk factors for complicated diverticulitis.

Conclusion

Although high level evidence is lacking, this study identified several risk factors associated with complicated diverticulitis. Individually these risk factors have little value in predicting the course of diverticulitis. The authors propose a prognostic model combining these risk factors which might be the next step to aid the physician in predicting the course of diverticulitis and setting the right treatment at initial presentation.

Introduction

In the Netherlands approximately 22.000 patients per year are referred to secondary care with diverticulitis.^{1,2} Ten percent of these patients will develop complications such as abscess or perforation and require further treatment in the form of close observation, antibiotics, percutaneous drainage or surgery. Uncomplicated diverticulitis is however a self-limiting and relatively mild disease.^{3,4} Recent literature has indicated that the outpatient treatment of uncomplicated diverticulitis is safe and effective.^{5,6} This implies that uncomplicated diverticulitis can be safely treated in primary care. The National Guideline for general practitioners (NHG standard) considers diverticulitis a clinical diagnosis based on the following signs; the development of persistent sharp, stabbing pain in the lower left abdomen within a couple of days and pressure or rebound tenderness only in the lower left abdomen. CRP level above 20 mg/L and body temperature >38.0°C could support the diagnosis. Ultrasound or CT scan is deemed unnecessary in the primary care setting when the above mentioned symptoms are present. The NHG standard advises only to refer patients with a suspicion of complicated diverticulitis to secondary care.¹ However, a considerable amount of patients with uncomplicated diverticulitis are still referred to secondary care, resulting in unnecessary diagnostics (ultrasound, CT-scan) and treatment (antibiotics, hospital admittance). To reduce the annual health care costs of diverticulitis and improve diverticulitis care, these unnecessary referrals should be reduced. Such a strategy would demand a proper prognostic tool to help estimate the risk of developing complicated diverticulitis, since this estimation will influence the course of action of the treating physician. If the treating physician can more accurately predict the course of the disease after setting the diagnosis, he/she will feel more comfortable to treat patients at home. To this day there are no prognostic models that can predict the severity of diverticulitis. More evidence on risk factors for complicated diverticulitis is needed to establish such a model and aid the treating physician in predicting the course of diverticulitis and setting the right treatment at initial presentation. Therefore a systematic review and meta-analysis was performed to identify risk factors for complicated diverticulitis.

Material and methods

Search strategy

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines and was executed in May 2016.⁷ The databases Pubmed, Embase and Cochrane library

were searched using synonyms for domain (diverticulitis), determinant (risk factors) and outcome (complicated diverticulitis). The used search terms are listed in **appendix 1**. The search results were filtered for doubles and the remaining articles were screened for title and abstract. All studies that did not report on the domain (diverticulitis) and outcome (complicated diverticulitis) were excluded. All non-English publications and studies performed before 1990 were also excluded. The remaining articles were read for full text. Only studies comparing patients with uncomplicated to complicated diverticulitis were included in this review. Case-reports, expert-opinions, reviews and studies on right-sided diverticulitis were excluded. The references of all selected studies were hand-searched for other relevant studies. Ambiguities were resolved by consultation with the senior authors.

Data extraction

Data regarding study characteristics and all relevant risk factors were extracted. A risk factor for complicated diverticulitis encompassed all patient characteristics (medical history, age, gender, body mass index, race), clinical signs (pain, nausea, vomiting, rectal bleeding, diarrhea, constipation), physical signs (guarding, palpable mass, signs of bowel obstruction), vital signs (body temperature, heart rate, blood pressure, respiratory rate) and laboratory parameters (C reactive protein (CRP) white blood cell (WBC) count, sodium).

Uncomplicated diverticulitis was defined as Hinchey Ia diverticulitis or “mild diverticulitis” according to the Ambrosetti classification. Complicated diverticulitis was defined as Hinchey $\geq$ Ib or severe diverticulitis according to the Ambrosetti criteria. (see appendix 2&3)

Critical appraisal

All selected articles were critically appraised by H. Bolkenstein. Cross sectional studies were assessed on relevance and quality using the cross sectional appraisal tool from wordpress.com.⁸ Longitudinal studies were assessed using the Scottish Intercollegiate Guidelines Network (SIGN) Methodology Checklist.⁹ Studies that were considered poorly were excluded to ensure the quality of the systematic review and minimize risk of confounding and bias. Ambiguities were resolved by consultation with the senior authors.

Data analysis

Review Manager (RevMan) software version 5.1 was used for the meta-analysis. Pooling of data was only performed of studies reporting mean and standard

deviation and when at least four studies reported on the outcome of interest. The remaining outcomes were described qualitatively. Pooled RR comparing uncomplicated diverticulitis to complicated diverticulitis were calculated using a random-effects model allowing for variation beyond chance in estimates across studies. The I² statistic was used to quantify the amount of heterogeneity. To obtain insight on the absolute cumulative risk of determinants the authors used the average risk across studies.

Results

Search and critical appraisal

Search results and study selection are described in **figure 1**. A total of twelve articles were critically appraised.¹⁰⁻²¹ Most studies were rated as reasonable to good quality based on the cross sectional appraisal tool from wordpress.com and the Scottish Intercollegiate Guidelines Network (SIGN) Methodology Checklist.^{8,9} Studies were mostly downgraded due to lack of control of possible confounders. None of the studies were graded high quality since the studies were of retrospective design and/or had small patient numbers and/or poor presentation of results.

Figure 1 Search Results

Table 1 Study characteristics

Study	Design	Quality assessment ¹ SIGN checklist* Cross sectional appraisal tool**	Number of patients	Men %	Age (years)	Study population	Definition complicated diverticulitis	UC	C
Cologne 2014	Retrospective cohort	+	1019	13.1	49.8	Radiologically confirmed diverticulitis, any episode	Hinchey >1A or "severe" diverticulitis according to Ambrosetti criteria	838	181
Faria 2011	Retrospective cohort	+/-	157	43.3	60	Radiologically or pathologically confirmed diverticulitis, any episode	Hinchey >1A	107	50
Hall 2010	Retrospective cohort	+/-	932	48	61	Radiologically confirmed diverticulitis, any episode	"severe" diverticulitis according to Ambrosetti criteria	806	126
Hjern 2008	Retrospective cohort	+/-	234	NR	59	Radiologically or pathologically confirmed diverticulitis, any episode	"severe" diverticulitis according to Ambrosetti criteria	212	22
Kotzampassakis 2010	Retrospective cohort	+/-	271	52.4	60	Radiologically confirmed diverticulitis, any episode	"severe" diverticulitis according to Ambrosetti criteria	166	105
Longstreth 2012	Retrospective cross sectional	+	741	43.7	57.2	Radiologically confirmed diverticulitis, any episode	Hinchey >1A	649	92
Makela 2015	Retrospective cross sectional	+	350	42	60	Radiologically confirmed diverticulitis, first episode	Hinchey >1A	169	181
Nizri 2013	Retrospective cross sectional	+	295	NR	NR	Radiologically confirmed diverticulitis, any episode	Hinchey >1A	243	52
Pisanu 2013	Retrospective cohort	+/-	80	56.2	60	Radiologically confirmed diverticulitis, any episode	Hinchey >1A	30	50
Tursi 2008	Prospective cross sectional	+/-	50	42	63.6	Radiologically confirmed diverticulitis, any episode	Hinchey >1A	39	11
Van de Wall 2012	Retrospective Cross-sectional	+	426	NR	NR	Radiologically confirmed diverticulitis, any episode	Hinchey >1A	364	62
West 2003	Retrospective cohort	+/-	64	NR	45.5	Radiologically or pathologically confirmed diverticulitis	"severe" diverticulitis according to Ambrosetti criteria	38	26

UC = Uncomplicated diverticulitis, C = Complicated diverticulitis

*Scottish Intercollegiate Guidelines Network (SIGN) Methodology Checklist

**Cross sectional appraisal tool. <https://reachefiles.wordpress.com/2010/03/cross-sectional-appraisal-tool.pdf> based on: Guyatt GH, Sackett DL, Cook DJ, Users' guides to the medical literature. II. How to use an article about therapy or prevention. JAMA 1993; 270 (21): 2598-2601 and JAMA 1994; 271(1):59-63¹ ++ = high quality, + = good, +/- = reasonable. - = poor

The results of the critical appraisal are depicted in **table 1**.

Baseline characteristics

Study characteristics of the included studies are shown in **table 1**. Of the twelve included studies, four had a retrospective cross-sectional design^{15-17,20} and seven had a retrospective cohort design^{10-14,18,21}. There was one prospective cross sectional study¹⁹. The twelve included articles evaluated a total of 4619 patients with diverticulitis. In all studies the diagnosis (complicated) diverticulitis was proven by computed tomography (CT) or pathological examination. A total of 3661 (79%) patients had uncomplicated diverticulitis and 958 (21%) had complicated diverticulitis.

Main outcome – risk factors for complicated diverticulitis

Age

Ten studies reported on age as a risk factor for complicated diverticulitis.^{11-18,20,21} A pooled data analysis was performed on studies that reported age as a dichotomous variable (older or younger than 50 years).^{11-14,18,21} The pooled analysis showed no significant difference. The pooled risk ratio was 0.74 (95% CI 0.27 – 2.02) in a random effects model ($I^2 = 95\%$), as depicted in **figure 2**. Makela et al reported the influence of age on the risk for complicated diverticulitis

Figure 2 Meta-analysis Age

in three groups (<50 years, 50-70 years and > 70 years). They found a significant effect of old age (>70 years) on the risk of complicated diverticulitis ($p=0.008$).¹⁶ Pooling of studies that described age as a continuous variable (mean and standard deviation) was not possible due to the fact some studies did not report the required standard deviation of the mean age. There was no consensus amongst these studies on the effect of age on the severity of diverticulitis. Van de Wall et al found that patients with complicated diverticulitis were of a significantly ($p<0.05$) higher age (63.9 years) as compared with patients with an uncomplicated episode

(57.1 years).²⁰ Nizri et al and Longstreth et al however did not find a significant effect. They respectively found a mean age of 63 an 57.3 years in patients with an uncomplicated episode compared to 59.3 and 56.6 years in patients with complicated diverticulitis (p= 0.182 and 0.71 respectively).^{15,17}

Gender

Four studies reported on gender.^{15-17,20} Pooled analysis demonstrated no significant difference in risk for complicated diverticulitis. The pooled risk ratio was 0.85 (95%CI 0.69 – 1.06) in a random effects model ($I^2 = 60\%$), as depicted in **figure 3**. The absolute risk of developing complicated diverticulitis varied from 9% to 46% in women with an estimated average of 21%. In men the absolute risk of

Figure 3 Meta-analysis Sex (number of men)

developing complicated diverticulitis varied from 16% to 59% with an estimated average of 25%.

History of previous attacks

Two studies reported on history of previous attacks as a risk factor for complicated diverticulitis.^{17,20} Nizri et al found that a primary episode of diverticulitis was at greater risk to be accompanied by complications compared to recurrent episodes (RR 1.98, 95% CI 1.26 -3.11).¹⁷ Van de Wall et al did not find a significant effect of previous attacks on the severity of diverticulitis. Twelve percent of the patients who presented with uncomplicated diverticulitis had had previous attacks, compared to 14% of the patients presenting with complicated diverticulitis.²⁰

Clinical signs and physical examination

Three studies reported on clinical signs (such as nausea, vomiting, bloating) as risk factors for complicated diverticulitis.^{15,19,20} Longstreth et al found that significantly more patients with complicated diverticulitis had signs of constipation (OR 2.32, 95%CI 1.27-4.23). Furthermore patients with complicated diverticulitis presented less frequently with localised pain in the lower left abdomen (OR 0.54, 95%CI 0.29-0.99). These patients had more generalized abdominal pain.¹⁵

Van de Wall et al found that patients with a complicated episode presented more frequently with vomiting (26% versus 11%) and diffuse abdominal pain (20% versus 9%) than patients with an uncomplicated episode.²⁰

Tursi et al investigated the severity of symptoms in uncomplicated and complicated diverticulitis graded on a quantitative scale. They found that patients with complicated diverticulitis had more severe constipation, abdominal pain and, when present, more severe rectal blood loss.¹⁹

Body temperature

Body temperature at presentation was reported in three studies. Tursi et al found that a temperature greater than 37°C was associated with complicated diverticulitis. Almost all patients (9 out of 11) with complicated diverticulitis presented with a temperature greater than 37°C while all the patients with uncomplicated diverticulitis (39 out of 39) had a temperature below 37°C.¹⁹

Longstreth et al demonstrated that patients presenting with a temperature greater than 37.5°C had a higher risk of having complicated diverticulitis (OR 2.13, 95%CI 1.27-3.57). Van de Wall reported on mean body temperature and did not find a significant effect. The mean temperature in patients with uncomplicated diverticulitis was 37.5°C (36.2-38.9) and 37.6°C (36.3-39.0) for complicated cases.¹⁵

C-reactive protein

Four studies reported on CRP level as a risk factor for complicated diverticulitis.^{16,17,19,29} All studies found a significant effect of CRP level on the risk of complicated diverticulitis. The overall mean CRP among patients with uncomplicated diverticulitis was 68 mg/L with a range of 25 mg/L to 96 mg/L. This was 186 mg/L with a range of 134 mg/L to 224 mg/L among patients with complicated diverticulitis. Three studies calculated the optimal threshold value of CRP level to distinguish uncomplicated from complicated diverticulitis. Makela et al found an optimal cut-off point of 149.5 mg/L (sensitivity 65%, specificity 85%).¹⁶ The studies of Nizri et al and van de Wall et al found an optimal cut-off point of 90 mg/L (sensitivity 88%, specificity 75%) and 175 mg/L (sensitivity 61%, specificity 82%) respectively.^{17,20}

White blood cell count

Four studies reported on this risk factor.^{15,16,19,20} Tursi et al and van de Wall et al reported on WBC as a continuous variable showing a significant effect of WBC on the risk of complicated diverticulitis. Average mean WBC count was $10.4 \times 10^9/L$ (range $8.7 - 12.0 \times 10^9/L$) in uncomplicated diverticulitis and $14.4 \times 10^9/L$ (range $12.5 - 15.3 \times 10^9/L$) in complicated diverticulitis.^{19,20}

Two studies reported WBC as a dichotomous value.^{15,16} Makela et al reported a sensitivity of 51% and specificity of 46% for a cut-off value of $10 \times 10^9/L$ ($p=0.672$).¹⁶ Longstreth et al found a sensitivity of 82% and specificity of 45% for a cut-off value of $11 \times 10^9/L$ ($p<0.0001$).¹⁵

Body mass index

Only one study reported on body mass index (BMI) as a risk factor for complicated diverticulitis. Longstreth et al found no significant difference between patients with a BMI greater or smaller than 25 (OR 1.00 (CI 0.96-1.04)).¹⁵

Comorbidity

One study reported on comorbidity and found that the group of patients with complicated diverticulitis consisted of patients with a higher ASA classification (ASA I 26%; ASA II 65%; ASA III 10%) compared to the group with uncomplicated diverticulitis (ASA I 41%; ASA II 51%; ASA III 8%).²⁰

Diabetes Mellitus

The effect of Diabetes Mellitus (DM) on the risk of complicated diverticulitis was reported in one retrospective cohort study. Approximately 16% of the patients without DM had complicated diverticulitis compared to 27% of the patients with DM ($p<0.003$).¹⁰

Steroid use and immunosuppression

One study reported on the use of steroids. Patients with complicated diverticulitis more frequently used steroids compared to patients with uncomplicated diverticulitis (7.3% versus 3.3%; $p=0.015$).¹⁷

Discussion

This systematic review and meta-analysis included twelve studies with a total of 4619 patients. Few studies were found that accurately described risk factors for complicated diverticulitis. Most of the studies were of retrospective design and did not account for confounders in their analyses. The evidence in the current literature for risk factors for complicated diverticulitis is therefore not strong. Considering the high incidence of this disease and the high impact on health, quality of life and health care costs this topic deserves more attention. This systematic review found that CRP, WBC count and clinical signs (constipation, generalised abdominal pain and vomiting) are risk factors for complicated diverticulitis. Comorbidity, number of episodes and steroid usage were suggested as possible risk factors, but evidence for these parameters was not very strong. Only the parameters “age”

and “sex” were eligible for meta-analysis. None of these parameters showed a significant difference in the risk for complicated diverticulitis.

There are some limitations of this study that should be taken in account when interpreting the results. In this systematic review there was significant heterogeneity in the design and methods of the included studies. We accounted for this problem by using a random-effects model which yields a more conservative estimate in case of heterogeneity. Additionally we only included studies with the same definition of complicated diverticulitis, thus minimizing the heterogeneity in outcome encountered in previously published reviews.

Most risk factors were not eligible for meta-analysis since less than four studies reported them. The outcome of these risk factors could therefore only be described qualitatively and should be interpreted carefully.

We expected to find that CRP and WBC count were related to complicated diverticulitis. A higher degree of inflammation generally correlates to higher levels of inflammatory parameters. Determining the optimal threshold for use in clinical practice, however, remains a point of debate. Several studies calculated the optimal threshold for CRP level and found cut-off values ranging from 50mg/L to >175mg/L.^{16,17,20} Optimal cut-off values for WBC count were not reported. Generally WBC levels were higher among patient with complicated diverticulitis ($10,4 \times 10^9/L$ (range 8.7 - $12.0 \times 10^9/L$) vs $14,4 \times 10^9/L$ (range 12.5 – $16.3 \times 10^9/L$).^{19,20}

As expected, patients with complicated diverticulitis present with more severe symptoms than patients with uncomplicated diverticulitis (diffuse vs localised abdominal pain). This could be accounted for by the presence of diffuse peritonitis.^{15,19,20}

For the other study parameters (comorbidity, DM, BMI, history of previous attacks, steroid use) very little evidence was found. Primary episode, comorbidity, DM and steroid use could be predictors of complicated diverticulitis.^{10,17,20} BMI did not show a significant difference in the risk for complicated diverticulitis.¹⁵ In general patients with (severe) comorbidities are more prone to complications since the underlying illnesses (cardiovascular, pulmonary) could lead to impaired tissue oxygenation and perfusion, which again could lead to an increased risk of perforation. Therefore the physician should be more vigilant of complicated diverticulitis in these patients. Moreover, the use of steroids abolishes the value of CRP level since steroids suppress the immune system in the inflammatory response. Physicians should take this in consideration when evaluating a patient.¹⁷ Recently a systematic review of predictors of acute diverticulitis severity was published. Tan et al concluded that comorbidity, steroid usage, first presentations

and CRP level of >175mg/L are predictive of a more severe disease process with higher likelihood for complications and resultant prolonged clinical course.²² This is similar to our findings, although we found different cut-off points for CRP level (90 mg/L, 149.5mg/L and 175 mg/L). A major difference between Tan's review and the present review is the fact that we used one definition for complicated diverticulitis according the Hinchey classification or Ambrosetti criteria. Tan et al employed multiple definitions such as risk of surgery, risk of medical treatment failure and length of hospital stay. This might cause considerable heterogeneity. For this reason and the fact that the Hinchey and Ambrosetti criteria are commonly used in clinical practice, we chose to define our outcome according to these classification systems.

In the past decade, our understanding of diverticulitis has increased. The majority of patients have uncomplicated diverticulitis and recover without the use of antibiotics or dietary restrictions. Some studies even suggest treating these uncomplicated cases in a primary care setting.⁴⁻⁶ A prognostic model would facilitate this vision and may ultimately lead to lower health care costs for a currently costly disease with high incidence. No studies have previously attempted to develop such a model. This review aimed to identify risk factors for complicated diverticulitis, as a component of such a prognostic model. In our opinion, these risk factors individually have little discriminative value for truly estimating the risk of developing complicated diverticulitis. Combining these risk factors in a full prognostic model might be the next step to aid the treating physician in predicting the course of diverticulitis and setting the right treatment at initial presentation.

We propose a prognostic model in which the following parameters will be included; first episode of diverticulitis, vomiting, constipation, diffuse abdominal pain, rebound tenderness, *défense musculaire* (as a clinical sign of peritonitis), comorbidity (ASA>I), steroid usage and CRP level (see **figure 4**). We chose these parameters based on the results of this systematic review and their applicability in clinical practice for primary care physicians. The weight of each parameter is based on the odds ratio's, relative risks, sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) as reported by the included studies. We aimed for the highest sensitivity and NPV since the model should safely rule out complicated diverticulitis in patients suspected of acute diverticulitis. Next, we will carry out a study in a diverticulitis patients cohort to construct a nomogram to calculate the probability of complicated diverticulitis in patients with a suspicion of acute diverticulitis based on the selected parameters. By constructing a nomogram we can evaluate and support our proposal for a clinical scoring system to make in applicable in clinical practice.

RISK FOR COMPLICATED DIVERTICULITIS	
PARAMETER	SCORE
ANAMNESIS	
Pain	
- Localized abdominal pain	0
- Generalized abdominal pain	2
Constipation	2
Vomiting	2
Steroid usage	1
PATIENT HISTORY	
First episode of diverticulitis	2
ASA $\geq$ II	1
ASA $\geq$ III	2
PHYSICAL EXAMINATION	
Rebound tenderness	2
Défense musculaire	5
LABORATORY PARAMETERS	
CRP	
- 0-50	0
- 50-150	2
- >150	4
TOTAL SCORE	
0-4 Low risk of complicated diverticulitis	
5-8 medium risk for complicated diverticulitis	
>8 high risk for complicated diverticulitis	

Patients with total score ≥ 5 points should be referred to secondary care

Figure 4 Proposal for a clinical scoring system to estimate the risk for complicated diverticulitis

Although high level evidence is lacking, this study demonstrates that CRP level, WBC count, clinical signs (generalised abdominal pain, constipation, vomiting), steroid use, number of episodes and comorbidity are risk factors for complicated diverticulitis. Individually these risk factors have little value for truly estimating the risk of developing complicated diverticulitis. Combining them in a prognostic model as proposed by the authors might be the next step to aid the physician in predicting the course of diverticulitis and setting the right treatment at initial presentation.

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APPENDIX

Appendix 1 Search terms

Domain	Determinant	Outcome
diverticulitis	Age	"Clinical symptoms"
	Young	BMI
	Old	"Body Mass Index"
	Sex	Obesity
	gender	Obese
	Women	ASA
	Men	"American Society of
	Man	Anaesthesiologists"
	Woman	Co-morbidity
	Female	comorbidity
	Male	"Associated disease"
	Race	"Charlson score"
	Ethnicity	NSAID
	CRP	"Nonsteroidal anti-inflammatory drugs"
	"C reactive protein"	"Non-steroidal anti-inflammatory
	Leucocytes	drugs"
	Leucocyte	Immunosuppression
	Leucocytosis	Immunosuppressed
	Fever	"Risk factors"
	Temperature	Riskfactors
	Sodium	"Risk factor"
	Hyponatremia	riskfactor
	hyponatraemia	risk
	History	"Alarm symptoms"
	Pain	Prognosis
	"Acute abdomen"	prognostic
	"Clinical picture"	Predictor
	"Clinical feature"	predictors
		prediction

Appendix 2 Hinchey classification

Hinchey	Modified Hinchey
	0 Mild clinical diverticulitis
I Pericolic abscess or phlegmone	Ia Colonic wall thickening and/or confined pericolic inflammation
	Ib Confined small pericolic abscess (≤ 5cm)
II Pelvic, distant intra-abdominal, or retroperitoneal abscess	II Pelvic, distant intra-abdominal, or retroperitoneal abscess
III Generalised purulent peritonitis	III Generalised purulent peritonitis
IV Generalised faecal peritonitis	IV Generalised faecal peritonitis
	Fistula
	Obstruction

Hinchey EJ, Schaal PG, Richards GK. Treatment of perforated diverticular disease of the colon. Adv Surg. 1979;12: 85-109

Appendix 3 *Ambrosetti criteria*

Mild diverticulitis	Severe diverticulitis
Localised wall thickening of the bowel wall (≥5mm)	Bowel wall thickening (≥5mm) and inflammation of pericolic fat + one of the following:
Inflammation of pericolic fat	Abscess
	Extraluminal air
	Extraluminal contrast

Ambrosetti P, Becker C, Terrier F. Colonic diverticulitis: impact of imaging on surgical management—a prospective study of 542 patients. Eur Radiol. 2002;12:1145–1149

Chapter 4

Development and validation of a
diagnostic prediction model distinguishing
complicated from uncomplicated
diverticulitis

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ABSTRACT

Objectives

Most diverticulitis patients (80%) who are referred to secondary care have uncomplicated diverticulitis (UD) which is a self-limiting disease and can be treated at home. The aim of this study is to develop a diagnostic model that can safely rule out complicated diverticulitis (CD) based on clinical and laboratory parameters to reduce unnecessary referrals.

Methods

A retrospective cross-sectional study was performed including all patients who presented at the emergency department with CT-proven diverticulitis. Patient characteristics, clinical signs and laboratory parameters were collected. CD was defined as >Hinchey 1A. Multivariable logistic regression analyses were used to quantify which (combination of) variables were independently related to the presence or absence of CD. A diagnostic prediction model was developed and validated to rule out CD.

Results

A total of 942 patients were included of whom 171 (18%) had CD. The dataset was randomly split into a derivation and validation set. The derivation dataset contained 475 patients of whom 82 (18%) patients had CD. Age, vomiting, generalized abdominal pain, change in bowel habit, abdominal guarding, C-reactive protein and leucocytosis were univariably related to CD. The final validated diagnostic model included abdominal guarding, C-reactive protein and leucocytosis (AUC 0.79 (95% CI 0.73-0.84)). At a CD risk threshold of $\leq 7.5\%$ this model had a negative predictive value of 96%.

Conclusion

This proposed prediction model can safely rule out complicated diverticulitis. Clinical practitioners could cautiously use this model to aid them in the decision whether or not to subject patients to further secondary care diagnostics and/or treatment.

Introduction

Diverticulitis is a very common disease, which poses a great financial burden on health care. It is one of the most costly gastro-intestinal diseases worldwide. In the United States the costs are estimated at 2.1 billion dollars per year.¹ Most patients (80%) have uncomplicated diverticulitis (UD) which is a self-limiting disease.^{2,3} In the past years evidence which justifies a more conservative approach towards this costly disease has been arising. Two recent randomized clinical trials showed that the use of antibiotics in patients with UD does not provide a beneficial effect and this is now considered obsolete.^{4,5} Moreover, recent studies have indicated that UD patients can be safely treated in an outpatient setting.⁶⁻⁹ The Dutch primary care guideline 'Diverticulitis' recommends to only refer patients who are at risk of complicated diverticulitis (CD) to secondary care (emergency department) for evaluation by surgeon or gastroenterologist.¹⁰ However, a considerable number of patients who present with UD in primary care (general/family practice) are still referred to secondary care, with the consequence of unnecessary diagnostics (ultrasound, CT-scan), treatment and hospital admission. To reduce the health care costs of diverticulitis, these unnecessary referrals should be reduced.¹¹ Such a strategy would demand a proper diagnostic tool to help distinguish UD from CD at presentation.

The aim of this study is to identify clinical and laboratory parameters that can predict the presence or absence of CD in order to develop and validate a diagnostic model that can be used for adequate and safe selection of patients at risk of CD.

Materials and methods

Study design

A retrospective cross-sectional study was performed in the Meander Medical Centre, a large regional teaching hospital in the Netherlands. Data were collected between January 2005 and January 2017. The study was approved by the local Institutional Review Board.

Study population

All adult (>18 years) patients presenting with a first episode of diverticulitis in the emergency department were eligible for inclusion. The diagnosis had to be proven by a Computed Tomography (CT) scan or surgical report. Potentially eligible patients were searched for by using a diagnostic specific code (DBC or DRG), ICD-9 (International Classification of Disease), or ICD-10 codes in the hospital database. In the Meander hospital all (suspected) diverticulitis patients who present at the ED are primarily evaluated by surgical trainees supervised by a surgeon.

Definition of complicated diverticulitis and secondary care diagnostics/treatment

The primary endpoint was complicated diverticulitis (CD), which was defined as Hinchey >1A based on the radiological reports or surgical reports.¹²⁻¹⁴ Secondary care diagnostics are considered as additional imaging in the form of ultrasound and/or CT-scan. Secondary care treatment might consist of careful observation, analgesics, laxatives, antibiotic treatment, percutaneous abscess drainage and possibly operative intervention, depending on the severity of diverticulitis.

Baseline characteristics

Patient characteristics, clinical signs and symptoms, American Society of Anesthesiologists (ASA) Physical Status classification scores, physical examination, laboratory parameters, CT-findings and initial treatment strategy (e.g. surgery, abscess drainage, antibiotic treatment, careful observation), were collected from the hospital records. The review of all medical records was done by H. Bolkenstein and B. van de Wall. If the ASA score wasn't reported explicitly in the patient record it was assessed retrospectively from the patient notes (based on comorbidity).

Selection of candidate diagnostic predictors

The most promising diagnostic predictors for CD were preselected based on previous literature^{15,16}: three from patient history (gender, age and ASA classification), six from signs and symptoms (duration of symptoms, nausea, vomiting, location of abdominal pain (left lower quadrant or generalized), change in bowel habit and rectal blood loss), three from physical examination (rebound tenderness, abdominal guarding and temperature) and two standard blood tests (C-reactive protein (CRP) and leucocytes). Abdominal guarding was defined as diffuse muscular rigidity on palpation.

Data analysis

All analyses were performed using the statistical software package SPSS 24.0 (IBM Corporation, New York, USA). Results are reported according to the TRIPOD statement.¹⁷ The dataset was randomly split into a derivation and validation set. Multiple imputation techniques were used to impute missing data points in order to avoid selection bias (multivariable imputation by chained equations, 10 datasets, 25 iterations, healthy convergence). Data were assumed to be missing at random. All reported results are based on the imputed data, where the estimates of interests at the final computational step were combined across the imputed datasets using Rubin's rules.¹⁸ Descriptive statistics are provided for all variables. Continuous variables are presented as means (with standard deviation (SD)) or

medians (with inter quartile range (IQR)) according to their distribution. For the categorical variables the counts and percentages are presented. In the initial analysis the differences in patient characteristics, signs, symptoms and additional blood tests between patients with and without CD were assessed. Univariable logistic regression analyses were used to calculate the crude odds ratios (OR) with 95% confidence interval (CI) of the independent predictors. Multivariable logistic regression analyses were used in combination with receiver operator curves (ROC) , to quantify which (combination of) variables from patient history, physical examination and laboratory measurements are independently related to the presence or absence of CD. Inclusion of the relevant diagnostic items in the multivariable model was based on clinical knowledge and p-values (p-value <0.05). In the first step, all relevant diagnostic predictors from history taking (patient demographics as well as signs and symptoms) were included. Next, physical examination predictors were added to this selected set of predictors while keeping the patient history variables selected. Then, the history and physical model was extended by adding (separately and in combination) the blood test results to determine their incremental diagnostic value, both in terms of increase in area under the curve (AUC) and in terms of fewer false positive and notably false negative diagnoses. The adjusted OR with 95% CI of the final model were calculated. Nagelkerke's R^2 is presented to illustrate the explained variance of the model. This final diagnostic model was then validated in the validation data set, using the same setting, inclusion criteria, outcome and predictors. Diagnostic probability thresholds were introduced based on clinically acceptable percentages of notably false negative diagnoses to define which combination and order of diagnostic tests yielded the highest diagnostic accuracy (in terms of false negative (and positive) diagnoses).¹⁹ Ultimately a model was developed to predict which patients have an acceptable low probability of CD and can safely be withheld secondary care diagnostic tests and/or treatment. Thresholds for C-reactive protein (CRP) and leucocytes were introduced in order to assign points to each variable, based on its regression coefficient. By assigning points to each variable, a scoring system was developed using the method demonstrated by the Framingham Risk Score. In this method a points system is developed from a multiple logistic regression model.²⁰

Results

Study population

A total of 1514 consecutive patients presented to the emergency department between January 2005 and January 2017 with a clinically suspected episode of

diverticulitis. Of these, 572 patients were excluded because they underwent sonography only (n=476) or they had no radiological examination at all (n=96). A total of 942 patients were included of whom 171 (18%) had CD and 771 (82%) had UD. The dataset was randomly split into a derivation and validation set. The validation dataset contained 467 patients of whom 90 (19%) had CD. The derivation dataset contained 475 patients of whom 82 (18%) patients had CD. The Hinchey classification of the complicated cases in the derivation dataset were as follows; 37 (8%) Hinchey IB, 17 (4%) Hinchey II, 23 (5%) Hinchey III and 5 (1%) Hinchey IV. Of the uncomplicated cases, 250 (64%) patients were treated as inpatients and 99 (26%) patients received antibiotics. Of the complicated cases, 76 (93%) patients were treated as inpatients and 65 (79%) patients received antibiotics. Complicated cases that did not receive antibiotics were all Hinchey IB patients. Patient characteristics are shown in **table 1**.

Missing data

All candidate predictors had missing data except for age, gender and ASA classification. The percentage of missing data per predictor was between 1% (CRP) and 7% (nausea and vomiting). In total 221 (4%) data items were imputed and 375 (79%) patients had a complete dataset for all candidate predictors.

Initial evaluation of candidate predictors

Table 1 shows the diagnostic accuracy of the individual candidate predictors. In the initial evaluation none of the candidate predictors could safely rule out CD individually. Based on the univariable analysis the following predictors were selected for inclusion in the multivariable regression analysis; age, vomiting, generalized abdominal pain, change in bowel habit, abdominal guarding, CRP and leucocytes.

Initial model

Table 2 shows the development of the model. In the initial model four predictors from patient history were retained; age, vomiting, change in bowel habit and generalized abdominal pain. The AUC of this model was 0.70 (95%CI 0.64-0.76). In the next step abdominal guarding was added to the model. When added to the initial model, this predictor was significantly related to CD. Adding the variable only slightly increased the AUC compared to the initial model to 0.71 (95%CI 0.65-0.76). Vomiting did not remain significantly related in this model and was therefore removed in the next step.

Table 1 Distribution and association of individual predictors with complicated diverticulitis^{1,2}

Diagnostic Variable ³	Distribution in RISICO study		P-value	OR (95%CI)
	Total N = 475	UD N = 393 (82%)		
Patient history: demographics				
Female gender; N (%)	283 (60)	229 (58)	54 (66)	1.38 (0.84-2.27)
Age in years; mean (SD)	61 (14)	60 (13)	65 (15)	1.03 (1.01-1.05)
ASA score >2 ⁴ ; N (%)	56 (12)	44 (11)	12 (15)	1.36 (0.68-2.71)
Patients history: Signs and symptoms				
Duration of symptoms in days; median (IQR)	3 (1-7)	3 (1-5)	4 (2-7)	1.01 (0.98-1.03)
Nausea; N (%)	219 (46)	177 (45)	42 (51)	1.25 (0.77-2.03)
Vomiting; N (%)	65 (14)	43 (11)	22 (27)	2.90 (1.58-5.31)
Abdominal pain in lower left quadrant; N (%)	256 (54)	218 (55)	38 (46)	0.98 (0.41-2.37)
Generalized abdominal pain; N (%)	34 (3)	20 (5)	14 (18)	3.96 (1.91-8.22)
Change in bowel habit; N (%)				
Diarrhea	84 (18)	60 (15)	24 (29)	2.75 (1.51-5.01)
Obstipation	79 (17)	64 (16)	15 (18)	1.61 (0.82-3.19)
Alternating	28 (6)	20 (5)	8 (10)	2.67 (1.09-6.55)
Rectal blood loss (%)	36 (8)	33 (8)	3 (4)	0.47 (0.14-1.54)
Physical examination				
Rebound tenderness (%)	164 (34)	140 (36)	24 (29)	0.73 (0.42-1.27)
Abdominal guarding (%)	11 (2)	4 (1)	7 (9)	10.81 (2.53-46.15)
Temperature in Celsius, mean (SD)	37.5 (0.8)	37.5 (0.8)	37.5 (0.8)	1.01 (0.75-1.37)
Blood tests				
CRP (mg/L), median (IQR)	103 (54-166)	96 (51-145)	198 (102-269)	1.01 (1.01-1.01)
Leucocytes (10 ⁹ /L), mean (SD)	12.3 (4.3)	11.9 (3.7)	14.6 (5.7)	1.14 (1.08-1.21)

¹All results in this table are results of multiple imputation and are based on univariable evaluation; ²complicated diverticulitis is defined as >Hinchey 1A; ³Variables are coded such that the reported category indicate a higher risk of complicated diverticulitis; ⁴Cut-off value based on previous literature; ⁵Chi²-test; ⁶Fisher exact Test; ⁷independent T-test; ⁸Mann-Whitney-U-test

Abbreviations: UD = uncomplicated diverticulitis, CD = complicated diverticulitis, ASA = American Society of Anesthesiologists, OR = odds ratio, SD = standard deviation, IQR = interquartile range, CI = confidence interval, CRP = C-reactive protein

Table 2 Adjusted Odds Ratios with 95% CI for the probability of complicated diverticulitis^{1,2}

Variable	β coefficient ³	OR	95% CI	p-value	AUC (95%CI)	R ²
Model (I) Patient history						
Age	0.02	1.02	1.00-1.04	0.07	0.70 (0.64-0.76)	0.11
Vomiting	0.67	1.96	1.00-3.85	0.05		
Change in bowel habit						
Diarrhea	0.75	2.12	1.12-4.00	0.02	0.71 (0.65-0.76)	0.14
Obstipation	0.30	1.35	0.66-2.77	0.41		
Alternating	0.72	2.06	0.81-5.25	0.13		
Generalized abdominal pain	1.03	2.81	1.29-6.13	0.01		
Model (II) Patient history and physical examination						
Age	0.02	1.02	1.00-1.04	0.09	0.79 (0.74-0.85)	0.27
Vomiting	0.51	1.66	0.81-3.41	0.17		
Change in bowel habit						
Diarrhea	0.79	2.21	1.16-4.22	0.02	0.79 (0.74-0.85)	0.27
Obstipation	0.25	1.29	0.61-2.69	0.51		
Alternating	0.75	2.12	0.81-5.57	0.13		
Generalized abdominal pain	0.97	2.63	1.18-5.88	0.02		
Abdominal guarding	1.99	7.34	1.53-35.15	0.01		
Model (III) Patient history, physical examination and inflammatory parameters						
Age	0.02	1.02	1.00-1.04	0.13	0.79 (0.74-0.85)	0.27
Change in bowel habit						
Diarrhea	0.52	1.69	0.84-3.39	0.14		
Obstipation	0.13	1.13	0.52-2.46	0.75		
Alternating	1.07	2.93	1.05-8.11	0.04		
Generalized abdominal pain	0.89	2.43	1.00-5.91	0.05		
Abdominal guarding	2.04	7.70	1.51-39.35	0.02		
CRP mg/L	0.01	1.01	1.00-1.01	<0.01		
Leucocytes 1x10 ⁹ /L	0.09	1.10	1.03-1.17	0.01		

¹ All results in this table are results of multiple imputation and analyses are based on multivariable logistic regression analysis with ENTER stepwise selection procedures; ² Complicated diverticulitis is defined as >Hinchey IA; ³ β coefficients are expressed per 1 unit increase for the continuous variables and for the condition present in dichotomous variables

Abbreviations: OR = Odds ratio, CI = confidence interval, AUC = Area under the receiver operating characteristic curve, R² = Nagelkerke's R², CRP = C-reactive protein

Added value of inflammatory parameters

When added to the model, CRP and leucocytes were both positively and significantly related to CD risk, both in isolation and when added in combination. The addition of these inflammatory parameters significantly increased the AUC compared to the second model (with predictors from patient history and physical examination) from 0.71 (95% CI 0.65-0.76) to 0.79 (95% CI 0.74-0.85) and led to the development of the final diagnostic model (model III) as depicted in **table 2**. This final model (model III) was then validated in the validation data set by entering all significant predictors that remained in the final model (change in bowel habit, abdominal guarding, CRP and leucocytes) in a multivariable logistic regression analysis. Upon this validation, only three predictors remained significantly related to CD: abdominal guarding, CRP and leucocytes. **Table 3** shows the final validated model. The AUC of this model was 0.79 (95% CI 0.73-0.84).

Table 3 Validated final Model¹

Variable	β coefficient ²	OR	95% CI	p-value	AUC (95% CI)	R ²
Abdominal guarding	2.17	8.79	2.28-33.84	<0.01		
CRP mg/L	0.01	1.01	1.01-1.01	<0.01		
Leucocytes 1x10 ⁹ /L	0.08	1.09	1.02-1.16	0.01		
					0.79 (0.73-0.84)	0.29

¹Analyses based on multivariable logistic regression analysis with ENTER stepwise selection procedures; ² β coefficients are expressed per 1 unit increase for the continuous variables and for the condition present in dichotomous variables

Abbreviations: OR = Odds ratio, CI = confidence interval, AUC = Area under the receiver operating characteristic curve, R² = Nagelkerke's R², CRP = C-reactive protein

Ruling out CD and risk score

Table 4 shows the diagnostic accuracy of the model at different probability thresholds for CD. A CD risk of $\leq 7.5\%$ was considered as a clinically acceptable percentage of notably false negative diagnoses. At this threshold, the final diagnostic model would prevent secondary care diagnostics/treatment in 25% of all patients, with a NPV of 96%. Five CD patients would have been missed, of whom 4 patients had Hinchey 1B. All these Hinchey 1B patients were treated conservatively, without further complications. One patient was classified as Hinchey 3, who presented late in the evening with complaints present since one hour. It is likely that due to the short presence of disease the inflammatory parameters were not yet elevated. The inflammatory parameters were in fact

Table 4 Diagnostic accuracy when basing secondary care diagnostics/treatment on varying complicated diverticulitis probability thresholds

CD risk threshold	% secondary care diagnostics/ treatment (95%CI)	CD detected (n)	CD missed (n)			Diagnostic accuracy for CD					
			Hinchey IB	Hinchey II	Hinchey III	Hinchey IV	Total	Sensitivity % (95%CI)	Specificity % (95%CI)	PPV % (95%CI)	NPV % (95%CI)
≤5%	93 (90-95)	88	2	0	0	0	2	98 (92-100)	8 (6-12)	20 (17-24)	94 (80-99)
≤7.5%	75 (70-78)	85	4	0	1	0	5	94 (88-98)	30 (26-35)	24 (20-29)	96 (90-99)
≤10%	60 (55-64)	78	4	3	5	0	12	87 (78-93)	47 (42-52)	28 (23-34)	94 (89-97)

Abbreviations: CD = complicated diverticulitis defined as >Hinchey 1A; PPV = positive predictive value; NPV = negative predictive value; CI = confidence interval

elevated the next morning, and if we introduce these values the model would classify this patient as CD. The patient received a CT-scan the next morning and went for surgery after confirmation of perforated diverticulitis. When lowering the CD risk threshold to $\leq 5\%$, the sensitivity would increase to 98% but the NPV would decrease to 94% and in only 7% of all patients secondary care diagnostics/treatment would be prevented. Increasing the threshold to $\leq 10\%$ would prevent secondary care diagnostics/treatment in 40% of the patients, but would result in 12 missed CD cases. **Table 5** shows a risk score which can be used to calculate the predicted CD risk when combining the individual parameters. The risk score illustrates that when a diverticulitis patient presents with a CRP <100 mg/L, leucocytes $<15.0 \times 10^9/L$ and no signs of abdominal guarding (diffuse muscular rigidity on palpation), the risk for CD is very low (4%). Patients presenting with abdominal guarding and/or a CRP >100 mg/L have a much higher risk for CD (16-25%).

Table 5 Scoring system to identify complicated diverticulitis

Diagnostic variable	Points
Abdominal guarding present	4
CRP mg/L	
0-100	0
101-150	3
151-200	4
201-250	5
> 250	7
Leucocytes $\times 10^9/L$	
0-15.0	0
15.1-20.0	1
> 20.0	2
Point total	Estimate of CD risk (%)
0	4.2
1	6.8
2	10.7
3	16.6
4	24.7
5	35.0
6	47.1
7	59.5
8	70.7
9	79.9
10	86.8
11	91.6
12	94.7
13	96.7

CD = complicated diverticulitis defined as Hinchey $>1A$

CRP= C-reactive protein

Discussion

This study showed that abdominal guarding at physical examination and inflammatory parameters (CRP and leucocytes) are predictors of CD in patients presenting at the ER with a first episode of diverticulitis. Use of a diagnostic model combining these parameters could safely rule out CD with a NPV of 96% at a 7.5% probability for CD. A scoring system was provided in order to illustrate the predicted CD risk when combining the individual parameters, which can be easily used in clinical practice. The risk score illustrates that when a diverticulitis patient presents with a CRP <100 mg/L, leucocytes <15.0 x10⁹/L and no signs of abdominal guarding (diffuse muscular rigidity on palpation), the risk for a CD is very low (4%). These patients can be safely withheld secondary care diagnostics and/or treatment. It should however be noted that the predicted CD risk derived from the scoring system is less accurate than the predicted CD risk derived from the actual prediction model, since the model uses the more accurate continuous values of the individual variables.

There is strong evidence for the safety and cost-effectiveness of outpatient treatment for uncomplicated diverticulitis. Multiple studies have compared outpatient treatment with in hospital treatment and all conclude that there is no difference between the two groups in morbidity, mortality or patient outcome.⁶⁻⁸ The next step in increasing the cost-effectiveness of diverticulitis care is to decrease the number of referrals to secondary care. A major concern of not referring patients to secondary care and withholding additional imaging is that the diagnosis 'diverticulitis' cannot be assumed with 100% certainty. Lameris et al²¹ studied all patients who presented in the ER with abdominal pain and developed a clinical prediction model for diagnosing acute diverticulitis. They concluded that in a patient who presents with abdominal pain in the lower left quadrant, CRP of >50mg/L and absence of vomiting, additional imaging can safely be withheld since the combination of these symptoms can accurately diagnose 'acute diverticulitis' with a specificity of 98% and a PPV of 88%. However only a quarter of patients with suspected diverticulitis presented with these three symptoms.²¹ Moreover, the model does not distinguish between UD and CD. Toorenvliet et al²² also analyzed the accuracy of clinical diagnosis for diverticulitis and conclude that this is low (PPV 65%, NPV 98%). Ultrasound and CT have superior diagnostic accuracy (PPV 95%, NPV 99%), but rarely change the initial management proposal based on clinical examination.²² Moreover, since only patients who are at risk of CD should be referred to secondary care for additional imaging and/or treatment,¹⁰ it is pertinent that we identify clinical and laboratory parameters (which are at the

disposal of primary care doctors) that can help primary care doctors to diagnose (complicated) diverticulitis.

In a recent systematic review, CRP, leucocytes and clinical signs (constipation, generalized abdominal pain and vomiting) were found to be risk factors for CD.¹⁶ The evidence in the current literature for these findings is however weak. The primary aim of the present study was to develop a clinical prediction model, which can safely rule out CD. The ultimate goal is to decrease the number of unnecessary diverticulitis referrals to secondary care, thus improving cost-effectiveness of diverticulitis care. When we started our quest to develop such a model we aimed to conduct a prospective nationwide study including all patients with a suspicion of diverticulitis in primary care who are referred to secondary care, since this is the population of interest. However, in the initiation of this study we encountered several practical issues which made the execution of such a study design not feasible. Considering the large sample size that would be required for this study (at least 600 patients) we would need to include 300 general practitioner (GP) practices since an average GP practice sees only 2 diverticulitis patients per year. Moreover the definition 'suspicion of diverticulitis' is subjective and this would result in a heterogeneous study population. We therefore chose to develop the model in our own population, and accepted subsequent limitations of this study. Because this study was conducted in secondary care it cannot directly be translated to primary care. Moreover, only patients with CT-proven diverticulitis were included and therefore we missed all patients suspected having diverticulitis who had gotten other diagnosis after CT. The model is therefore not applicable to all patients presenting with abdominal pain in the emergency department and when applying the risk score, clinical practitioners should be wary of other (serious) diagnoses. The model can however safely select patients that can be withheld further secondary care diagnostics and/or treatment. If we would combine our results and the results of Lameris et al²¹, we might conclude that patients who have localized left lower quadrant pain, in absence of vomiting and abdominal guarding should be screened by primary care doctors for CRP and leucocyte level. If CRP is less than 100mg/L and leucocyte count is less than $15 \times 10^9/L$ these patients may be refrained from additional imaging and referral to a secondary care center. Emergency physicians could also use these findings to select patients that can be discharged home from the emergency department with follow-up with their primary care doctors.

A major strength of this study is the large study population. Following existing guidance for required number of patients in studies aiming to develop prediction models, we needed to include 80-90 subjects with complicated diverticulitis in order to have sufficient power to identify predictors for complicated diverticulitis. With 82 complicated cases in the derivation dataset and 90 complicated cases in the validation dataset our study population was therefore sufficient to develop a prediction model. Although the study was of a retrospective design, the number of missing values was relatively low (with the highest percentage of missing data per predictor being 7% and a total of 4% missing data). Moreover we used multiple imputation techniques to prevent selection bias. A prediction model was developed and validated in a cohort of non-overlapping patients, increasing the robustness of the model.

A limitation of the study is that we did not re-analyze all CT scans to confirm the presence of (un)complicated diverticulitis but collected this from the initial CT report. Previous studies have shown that re-evaluation can give more accurate answers regarding occurrence of complications in diverticulitis. It could therefore be that a few complications were missed.^{23,24} Another limitation that is subsequent to the retrospective design is the fact that physical examination was performed by many doctors with different level of competence and intersect (and different ways to express the assessment in the records). Especially abdominal guarding can be interpreted differently by different doctors. The primary outcome of this study was CD defined as >Hinchey 1A. We chose this classification as it is the most commonly used in clinical practice. It is however questionable whether Hinchey 1B patients should be considered as 'complicated'. Most patients with small abscesses are treated without percutaneous drainage or surgery and recover quickly without further complications.²⁵ However, in order to develop a safe prediction model we felt it was pertinent to retain a strict definition of CD which is why we chose to define Hinchey 1B patients as complicated.

Immunosuppression and signs of sepsis were not considered in the present study. As sepsis is associated with high morbidity and mortality and immunosuppression can increase the complication rate, it stands to reason that these patients should receive secondary care diagnostics and treatment.²⁶ The present study focussed on the clinical diagnosis of complicated diverticulitis and not the optimal treatment strategy. As stated above, secondary care treatment might consist of careful observation, analgesics, laxatives, antibiotic treatment and possibly operative intervention, depending on the severity of diverticulitis. Previous studies have shown that uncomplicated diverticulitis can be treated at home without antibiotics. Adequate follow-up is however advisable to detect any complications that might arise.⁴⁻⁹

Conclusion

This study has proven that the proposed prediction model can distinguish uncomplicated from complicated diverticulitis. We suggest that clinical practitioners could use this model in clinical practice to assess the risk of complicated diverticulitis at presentation and aid them in the decision whether or not to subject patients to further secondary care diagnostics and/or treatment.

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Chapter 5

Treatment of acute uncomplicated
diverticulitis without antibiotics; risk
factors for treatment failure

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Abstract

Purpose

Conservative treatment strategy without antibiotics in patients with uncomplicated diverticulitis (UD) has proven to be safe. The aim of the current study is to assess the clinical course of UD patients who were initially treated without antibiotics and to identify risk factors for treatment failure.

Methods

A retrospective cohort study was performed including all patients with a CT-proven episode of UD (defined as modified Hinchey 1A). Only non-immunocompromised patients who presented without signs of sepsis, were included. Patients that received antibiotics within 24 hours after or two weeks prior to presentation were excluded from analysis. Patient characteristics, clinical signs and laboratory parameters were collected. Treatment failure was defined as (re)admittance, mortality, complications (perforation, abscess, colonic obstruction, urinary tract infection, pneumonia) or need for antibiotics, operative intervention or percutaneous abscess drainage within 30 days after initial presentation. Multivariable logistic regression analyses were used to quantify which variables are independently related to treatment failure.

Results

Between January 2005 and January 2017, 751 patients presented at the emergency department with a CT-proven UD. Of these, 186 (25%) patients were excluded from analysis because of antibiotic treatment. A total of 565 patients with UD were included. Forty-six (8%) patients experienced treatment failure. In the multivariable analysis a high CRP level (>170 mg/L) was a significant predictive factor for treatment failure.

Conclusion

UD patients with a CRP level >170 mg/L are at higher risk for non-antibiotic treatment failure. Clinical physicians should take this finding in consideration when selecting patients for non-antibiotic treatment.

Introduction

Diverticulitis is a common and costly disease. It is now ranked as the third most common gastrointestinal discharge diagnosis and an estimate of 2,1 billion dollars per year are spent on inpatient costs in the United States.¹ Most patients (75%) have uncomplicated diverticulitis (UD), which is defined by the absence of abscess, perforation, fistula or bleeding.² Traditionally, UD was treated in hospital with antibiotics and bowel rest.^{3,4} In the past years evidence has been presented which justifies a more liberal approach. Two recent randomized clinical trials comparing antibiotic treatment with non-antibiotic treatment in UD patients showed no beneficial effect of antibiotic treatment in this patient group.^{5,6} Moreover, recent studies have provided strong evidence that the outpatient treatment of UD patients is safe and effective even without oral antibiotics.⁷⁻¹² However, these studies do report treatment failure rates of 3-24% and due to high risk of selection and detection bias the results are less applicable to daily practice.¹⁰ The question remains which UD patients are eligible for non-antibiotic treatment and which UD patients are more susceptible for a complicated course (treatment failure) and should therefore receive antibiotic treatment and closer surveillance. Few studies have investigated clinical risk factors for treatment failure in patients with UD. In the few studies that are available, all patients received antibiotics.^{8,9} The aim of the current study is to assess the clinical course of UD patients who were initially treated without antibiotics and to identify risk factors for treatment failure in this patient group.

Methods

Study design

A retrospective cohort study was performed in the Meander Medical Centre, the Netherlands. Data were collected between January 2005 and January 2017. The study was approved by the local Institutional Review Board.

Study population

A diagnostic specific code was used to identify all adult (≥ 18 years of age) patients presenting with a first episode of acute UD in the emergency department. The diagnosis had to be proven by a Computed Tomography (CT) scan. UD was defined as the absence of perforation (extravasation of contrast on CT), abscess, bleeding or signs of peritonitis, which corresponds to the modified Hinchey classification 1A.¹³⁻¹⁵ Only non-immunocompromised patients who presented without signs of sepsis were included in the study. Patients that received antibiotics within 24 hours after or two weeks prior to presentation were excluded from analysis.

Outcome measures

Patient characteristics, clinical signs and symptoms, American Society of Anesthesiologists (ASA) Physical Status classification scores, physical examination, laboratory parameters, CT-findings and treatment data (e.g. surgery, abscess drainage, antibiotic treatment, watchful waiting), were collected from the hospital records. Treatment failure was defined as (re)admittance, mortality, complications (perforation, abscess, colonic obstruction, urinary tract infection, pneumonia) or need for antibiotic treatment, operative intervention or percutaneous abscess drainage within 30 days after initial presentation.

Statistical analysis

Multiple imputation techniques were used to impute missing data points in order to avoid selection bias. Data were assumed to be missing at random. All reported results are based on the imputed data, where the estimates of interests at the final computational step were combined across the imputed datasets using Rubin's rules.¹⁶ Descriptive statistics were provided of all variables. Continuous variables are presented as means (with standard deviation(SD)) or medians (with inter quartile range (IQR)) according to their distribution. For the categorical variables the counts and percentages are presented. In the initial analysis the differences in patient characteristics, signs, symptoms and additional tests between patients with and without treatment failure were assessed. Univariable logistic regression analyses were used to calculate the crude odds ratios (OR) with 95% confidence interval (CI) of the independent predictors. These analyses were used to quantify which (combination of) variables are independently related to treatment failure. Inclusion of the relevant diagnostic items in the multivariable model were based on clinical knowledge and p-values (p-value <0.10). To correct for a possible treatment effect, hospitalization (hospital admittance within 24 hours after presentation) was included in the multivariable regression model. All analyses were performed using the statistical software package SPSS 24.0 (IBM Corporation, New York, USA).

Results

Patient demographics and initial treatment strategy

Figure 1 shows the patient flow throughout the study. Between January 2005 and January 2017, 751 patients presented at the emergency department with a CT-proven Hinchey 1A diverticulitis.¹³⁻¹⁵ Of these, 186 (25%) patients received antibiotics within 24 hours after or two weeks prior to presentation and were excluded from analysis. A total of 565 patients with CT-proven Hinchey 1A

Figure 1 Patient flow throughout study

diverticulitis¹³⁻¹⁵ were included. Patient demographics are shown in **table 1**. The average age was 58 (SD 13) years and 60% of the patients were female. 301 patients (53%) were admitted to the hospital within 24 hours after presentation. Patients who were admitted to the hospital within 24 hours after presentation presented more often with nausea (43% vs 34%), vomiting (12% vs 5%) and active muscle resistance at physical examination (19% vs 12%) compared to patients who were treated as outpatients. Temperature (mean 37.4 °C vs 37.2 °C) leucocytes (mean $12.3 \times 10^9/L$ vs $11.3 \times 10^9/L$) and C-reactive protein (CRP) level (mean 104 mg/L vs 84 mg/L) were also higher at presentation in patients admitted to the hospital.

Missing data

All candidate predictors had missing data except for age, gender and ASA classification. The percentage of missing data per predictor was between 1% (pericolic free air on CT) and 7% (temperature, nausea and vomiting). In total 304 (3%) data items were imputed. 461 (82%) patients had a complete dataset for all candidate predictors.

Treatment failure

In total, 46 (8%) patients experienced treatment failure of which 34 patients were admitted to the hospital within 24 hours after presentation. Twelve patients were initially treated as out-patients but were admitted to the hospital because

Table 1 Characteristics of UD patients treated without antibiotics

Variable	All patients N = 565	Outpatient treatment N = 264 (47%)	Inpatient treatment ¹ N = 301 (53%)	p-value
Patient history				
Gender (N (%) female)	338 (60)	162 (61)	176 (58)	0.48 ²
Age in years; mean (SD)	58 (13)	57 (12)	59 (13)	0.08 ⁴
ASA score >2, N (%)	53 (9)	22 (8)	31 (10)	0.47 ²
Duration of symptoms in days; median (IQR)	3 (1-6)	3 (1-5)	3 (1-6)	0.73 ⁵
Nausea, N (%)	221 (39)	91 (34)	130 (43)	0.03 ²
Vomiting, N (%)	46 (8)	12 (5)	35 (12)	<0.01 ²
Generalized abdominal pain, N (%)	34 (6)	12 (5)	22 (7)	0.17 ²
Feces, N (%)				0.14 ²
Diarrhea	77 (14)	36 (14)	41 (14)	
Obstipation	85 (15)	30 (11)	55 (18)	
Alternating	42 (7)	19 (7)	23 (8)	
Rectal blood loss, N (%)	39 (7)	14 (5)	25 (8)	0.12 ²
Physical examination				
Rebound tenderness, N (%)	193 (34)	90 (34)	103 (34)	0.86 ²
Active muscle, N resistance (%)	90 (16)	32 (12)	57 (19)	0.03 ²
Temperature in Celsius ; mean (SD)	37.3 (0.7)	37.2 (0.6)	37.4 (0.7)	<0.01 ⁴
Laboratory parameters				
CRP mg/L; mean (SD)	94 (68)	84 (55)	104 (77)	<0.01 ⁴
Leucocytes x10 ⁹ /L; mean (SD)	11.8 (3.5)	11.3 (3.1)	12.3 (3.7)	<0.01 ⁴
CT-findings				
Pericolic free air, N (%)	41 (7)	13 (5)	28 (9)	0.04 ²

¹ Hospital admittance within 24 hours after presentation²Chi²-test ³Fisher exact Test ⁴independent T-test ⁵Mann-Whitney-U- test

Abbreviations: UD = uncomplicated diverticulitis defined as Hinchey 1A, ASA = American Society of Anesthesiologists, SD = standard deviation, IQR = inter quartile range, OR = odds ratio, CI = confidence interval, CRP = C-reactive protein

of complications or severe complaints. Seventeen patients were readmitted to the hospital within 30 days after initial presentation because of complications or severe complaints. Eighteen patients developed complications; abscess (n=5), perforation (n=8), urinary tract infection (n=2), fistula (n=1), pneumonia (n=1) and colonic obstruction (n=1). Twenty-six patients needed antibiotic treatment due to complications or deterioration of disease. Two patients needed percutaneous

abscess drainage. Fourteen patients were operated on within 30 days after presentation of which ten patients were operated in an emergency setting. Indications for operation were perforation (n=8), fistula (n=1), stenosis (n=4) and progression of disease (n=1). Three patients died, one due to perforation and two deaths were not diverticulitis related but died from underlying illness (heart failure and acute myocardial ischemia).

Risk factors for treatment failure

Table 2 shows the univariable analysis of all candidate predictors. The following variables were included in the multivariable analysis; age, gender, (absence of) rebound tenderness, CRP level and hospitalization. The results of the multivariable analysis are shown in **table 3**. One clinical variable remained as a statistically significant ($p < 0.05$) predictor for treatment failure. Higher CRP (mg/L) level was positively related with treatment failure. Thresholds were introduced for CRP level to further illustrate the predictive value of this parameter. A CRP level of $>170\text{mg/L}$ yielded the highest diagnostic accuracy with a positive predictive value (PPV) of 17% (95%CI 8-29), a negative predictive value (NPV) of 93% (95%CI 90-95), a specificity of 20% (95%CI 9-34) and a sensitivity of 91% (95%CI 89-94) at a 10% risk for treatment failure.¹⁷ A subgroup analysis of only those patients with complete datasets showed similar results (data not shown).

Patients excluded from analysis

There were 186 UD patients who received antibiotics within 24 hours after or two weeks prior to presentation. Of these, 27 (15%) patients experienced treatment failure. Patients who received antibiotics generally presented with higher inflammation parameters (temperature (mean 37.8°C (SD 0.9) vs 37.4°C (SD 0.7), $p < 0.01$), CRP level (mean 130 mg/L (SD 92) vs 94 mg/L (SD 86), $p < 0.01$) and leucocyte count (mean $12.8 \times 10^9/\text{L}$ (SD 4.5) vs $11.9 \times 10^9/\text{L}$ (SD 3.4), $p < 0.01$)) and a higher ASA score (15% $>\text{ASA } 2$ vs 9% $>\text{ASA } 2$, ($p = 0.02$)) compared to patients who were treated without antibiotics. A multivariable analysis including all 751 UD patients (non-antibiotic and antibiotic treatment), showed that a high ASA score (>2) and higher CRP level were significant ($p < 0.05$) predictors for treatment failure. When corrected for hospitalization and antibiotic treatment, these predictors remained statistically significant (data not shown).

Table 2 Distribution and association of individual predictors with treatment failure¹

Treatment success N = 519 (92%)						Treatment failure N = 46 (8%)	
Diagnostic Variable ²	Frequency (%) ⁴	Frequency (%)	P-value	OR (95%CI)			
Patient history							
Female gender, N (%)	305 (59)	33 (72)	0.09 ³	1.78 (0.92-3.46)			
Age in years, mean (SD)	58 (13)	63 (12)	0.02 ⁵	1.03 (1.01-1.06)			
ASA score >2, N (%)	45 (9)	8 (17)	0.05 ³	2.22 (0.98-5.04)			
Duration of complaints in days, median (IQR)	3 (1-5)	3 (1-10)	0.34 ⁶	1.03 (1.002-1.05)			
Nausea, N (%)	203 (39)	18 (39)	0.82 ³	1.04 (0.55-1.97)			
Vomiting, N (%)	40 (8)	7 (15)	0.13 ³	2.01 (0.79-5.11)			
Generalized abdominal pain, N (%)	30 (6)	4 (9)	0.43 ³	1.55 (0.52-4.62)			
Change in bowel habit							
Diarrhea, N (%)	69 (13)	8 (17)	0.65 ⁴	1.43 (0.62-3.28)			
Obstipation, N (%)	79 (15)	6 (13)		0.85 (0.32-2.24)			
Alternating, N (%)	37 (7)	4 (10)		1.41 (0.47-4.17)			
Rectal blood loss, N (%)	33 (6)	5 (11)	0.18 ³	1.93 (0.72-5.17)			
Physical examination							
No Rebound tenderness, N (%)	336 (65)	36 (78)	0.06 ³	2.02 (0.94-4.33)			
Active muscle resistance, N (%)	81 (16)	9 (20)	0.53 ³	1.28 (0.58-2.82)			
Temperature in Celsius, mean (SD)	37.3 (0.7)	37.3 (0.6)	0.76 ⁵	0.93 (0.60-1.46)			
Blood tests							
CRP (mg/L), mean (SD)	92 (66)	121 (85)	0.01 ⁵	1.01 (1.001-1.01)			
Leucocytes(10^9/L), mean (SD)	11.8 (3.4)	12.3 (3.6)	0.37 ⁵	1.04 (0.96-1.13)			
CRP findings							
Pericolic free air, N (%)	35 (7)	6 (13)	0.12 ³	2.06 (0.82-5.19)			
Treatment							
Hospital admittance, N (%) ⁷	267 (51)	34 (74)	<0.01 ³	2.67 (1.35-5.28)			

¹All results in this table are results of multiple imputation and based on univariable logistic regression; ²Variables are coded such that the reported category indicate a higher risk of treatment failure; ³Chi²-test ⁴Fischer exact Test ⁵independent T-test ⁶Mann-Whitney-U- test ⁷within 24 hours after presentation
Abbreviations: ASA = American Society of Anesthesiologists, SD = standard deviation, IQR = inter quartile range, OR = odds ratio, CI = confidence interval, CRP = C-reactive protein

Table 3 Multivariable analysis of factors associated with treatment failure¹

Variable	β coefficient ²	Adjusted OR	95% CI	P-value
Female gender	0.60	1.83	0.92-3.65	0.09
Age	0.02	1.02	0.99-1.04	0.24
ASA score >2	0.63	1.88	0.78-4.53	0.16
No rebound tenderness	0.72	2.05	0.95-4.43	0.07
CRP (mg/L)	0.01	1.01	1.001-1.01	0.02
Hospitalization ³	0.89	2.44	1.21-4.90	0.01

¹ All results in this table are results of multiple imputation and analyses are based on multivariable logistic regression analysis, corrected for hospitalization; ² β coefficients are expressed per 1 unit increase for the continuous variables and for the condition present in dichotomous variables; ³ within 24 hours after presentation

Abbreviations: OR = Odds ratio, CI = confidence interval, ASA = American Society of Anesthesiologists CRP = C-reactive protein

Discussion

This study assessed the implementation of non-antibiotic treatment in UD patients and identified risk factors for treatment failure in this patient group. The majority (75%) of patients presenting with UD were initially treated without antibiotics and treatment failure was seen in 8% of these patients. Moreover, only 12 patients (2%) had severe complications requiring invasive interventions such as percutaneous abscess drainage (n=2) or emergency surgery (n=10). This shows that the implementation of a more conservative approach without antibiotics has been successful. Patients with a high CRP level (>170 mg/L) were at significantly higher risk for treatment failure.

Hjern et al¹⁸ was the first to describe non-antibiotic treatment in UD patients and concluded that non-antibiotic treatment is feasible in a selected group of patients. This finding was recently supported by the results of two randomized clinical trials comparing antibiotic treatment with non-antibiotic treatment in UD patients.^{5,6} Current guidelines on treatment of UD are however still ambiguous when it comes to antibiotic treatment. Guidelines published by the American Society of Colon and Rectal Surgeons (ASCRS) in 2014 still recommend antibiotics as part of conservative treatment.¹⁹ The guideline of the World Society of Emergency Surgery (WSES) in 2016 advises to avoid antibiotic therapy in non-immunocompromised UD patients without systemic signs of infection.²⁰ The guideline of the Dutch association of surgery (NVvH) on acute diverticulitis recommends to start antibiotic treatment in patients with a temperature of >38.5 °C, signs of sepsis, deteriorating symptoms,

immunocompromised patients and patients on non-steroidal anti-inflammatory drugs.²¹ In the present study we found no supporting evidence for these criteria. Only CRP level remained as a significant predictor in the multivariable analysis and temperature was not a significant predictor for treatment failure ($p=0.76$). Immunocompromised patients and patients presenting with signs of sepsis were not included in the present study. As sepsis is associated with high morbidity and mortality and immunosuppression can increase the complication rate, it stands to reason that these patients should receive antibiotic treatment.²⁰

Clinical risk factors for treatment failure in UD patients have been scarcely investigated before. Treatment failure rates of 3-24% are reported, depending on the definition of treatment failure.⁷⁻¹² Reported risk factors for treatment failure are female gender, free fluid or free air around the colon on CT-scan, comorbidity (Ambrosetti score >3) and an ER admission time between midnight and 6 AM.^{8,9} These studies are however hampered by the fact that all patients received antibiotics, which is now considered a redundant treatment strategy. One recent study did analyze the feasibility of nonantibiotic treatment in acute uncomplicated diverticulitis and reported a treatment failure rate of 4%. However, this study did not identify risk factors for treatment failure.²² To our knowledge, the present study is the first to analyze clinical risk factors in UD patients treated without antibiotics. The retrospective design of this study comes with natural limitations. Fifty-three percent of the patients were directly admitted to the hospital. The decision to admit a patient to the hospital was made by the attending physician based on individual patient characteristics. Patients who were directly admitted to the hospital were at higher risk for treatment failure ($p<0.01$). This could however be the result of confounding by indication as clinical physicians might sooner be inclined to admit patients to the hospital who have a predisposition for treatment failure. It remains unclear if direct hospital admittance has an influence on the outcome of interest (treatment failure). We chose to include both inpatients and outpatients in our analysis as previous literature has provided strong evidence that in hospital treatment of UD patients does not have a beneficial effect compared to outpatient treatment.⁷⁻¹² To correct for a possible treatment effect, we included hospital admittance in the multivariable analysis.

Twenty-five percent of all UD patients presenting at the ER were excluded from the main analysis because they received antibiotic treatment within 24 hours after or two weeks prior to presentation. These patients generally presented with higher inflammation parameters and a higher ASA score. Apparently physicians consider these features a reason to start antibiotics. There were more patients

in the antibiotic group with treatment failure (15%) compared to the non-antibiotic group (8%). Because this is a retrospective study, there is a high risk of confounding by indication and no conclusions can be made from this comparison. In a separate analysis including the patient group treated with antibiotics, a high ASA score (>2) and higher CRP level were found to be risk factors for treatment failure. This could explain for the high risk of treatment failure in the antibiotic group since patients with a high ASA score and higher CRP level were more likely to receive antibiotics.

As we still found a non-antibiotic treatment failure rate of 8%, it is pertinent to adequately select patients who are suitable for a non-antibiotic treatment strategy. To resolve this problem, the present study tried to identify clinical risk factors for treatment failure, which can guide the decision whether or not to treat UD patients with antibiotics. Based on our results we conclude that UD patients with a CRP level >170 mg/L are at higher risk for treatment failure. Although not significant in the non-antibiotic group, a high ASA score (>2) could also be a risk factor for treatment failure. Clinical physicians should take these findings in consideration when selecting patients for non-antibiotic treatment.

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Chapter 6

Conservative treatment in diverticulitis patients with isolated pericolic air and the role of antibiotics as part of the treatment strategy

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Abstract

Background

Recently published studies advocate a conservative approach with observation and antibiotic treatment in diverticulitis patients with pericolic air on computed tomography (CT). The primary aim of this study was to assess the clinical course of initially conservatively treated diverticulitis patients with isolated pericolic air and to identify risk factors for conservative treatment failure. The secondary aim was to assess the outcome of non-antibiotic treatment.

Methods

Patient data from a retrospective cohort study on risk factors for complicated diverticulitis were combined with data from the DIABOLO trial, a randomized controlled trial comparing non-antibiotic with antibiotic treatment in patients with uncomplicated diverticulitis. The present study identified all patients with Hinchey 1A diverticulitis with isolated pericolic air on CT. Pericolic air was defined as air located <5 cm from the affected segment of colon. The primary outcome was failure of conservative management which was defined as need for percutaneous abscess drainage or emergency surgery within 30 days after presentation. Multivariable logistic regression analyses of clinical, radiological, and laboratorial parameters with respect to treatment failure were performed.

Results

A total of 109 patients was included in the study. Fifty-two (48%) patients were treated with antibiotics. Nine (8%) patients failed conservative management, seven (13%) in the antibiotic treatment group and two (4%) in the non-antibiotic group ($p=0.083$). Only (increased) CRP level at presentation was an independent predictor for treatment failure.

Conclusions

Conservative treatment in diverticulitis patients with isolated pericolic air is a suitable treatment strategy. Moreover, non-antibiotic treatment might be reasonable in selected patients.

Introduction

Colonic diverticulosis is primarily seen in the Western population with prevalence increasing with age. At forty years of age, approximately 10% of the Western population has diverticulosis, while this number increases up to 70% in octogenarians. About 4-7% of patients with diverticulosis will develop diverticulitis.^{1,2} Twenty-five per cent of diverticulitis patients develops complications such as abscess or colonic perforation.³ Uncomplicated diverticulitis is usually treated conservatively, whereas complicated diverticulitis is treated with percutaneous abscess drainage or operative intervention (emergency resection or laparoscopic lavage).⁴ Most classification systems that categorise diverticulitis are based on computed tomography (CT) findings, such as fluid collections, extraluminal contrast leakage or free air.⁵⁻⁸ The clinical relevance of free air on CT remains unclear. Distant free air on CT is usually considered a sign of diffuse peritonitis and an absolute indication for operative intervention, whereas patients who present with isolated pericolic air may be treated conservatively.⁹ Current guidelines on treatment of diverticulitis do not describe uncomplicated diverticulitis patients with isolated pericolic air nor do they advise on the optimal treatment strategy.¹⁰ Recently published studies advocate a conservative approach with observation and antibiotic treatment. These studies are however hampered by small or heterogeneous study populations (including patients with pericolic and distant free air) or inadequate outcome parameters (not including percutaneous drainage as a treatment failure), hindering direct translation to clinical practice.¹¹⁻¹⁵ The primary aim of the present study was therefore to assess the course of uncomplicated diverticulitis patients with isolated pericolic air seen on CT imaging and to identify risk factors for failure of conservative treatment. The second aim was to assess the outcome of non-antibiotic treatment in this patient group.

Methods

Study design

This study was a joint venture between the DIABOLO trial¹⁶, a multicenter randomized controlled trial comparing antibiotic with non-antibiotic treatment in 528 patients with uncomplicated acute diverticulitis¹⁷⁻¹⁹, and a retrospective cohort study in 943 patients studying risk factors for complicated diverticulitis performed in the Meander Medical Centre. The DIABOLO¹⁶ trial prospectively included all patients with Hinchey 1A and 1B diverticulitis between June 2010 and October 2012 whereas for the retrospective cohort a diagnostic specific code was used to identify all patients presenting with an episode of diverticulitis in the emergency

department between January 2005 and January 2017. The study was approved by the local Institutional Review Board of the Meander Medical Centre.

Study population

This study included all patients with an uncomplicated diverticulitis (only modified Hinchey 1A)¹⁷⁻¹⁹ with pericolic air on CT. Only patients presenting without signs of sepsis and no clinical or radiological evidence of an abscess or diffuse peritonitis at presentation were included.²⁰ Imaging was performed using spiral CT scanners (Siemens SOMATOM: Sensation 16, Definition AS, Definition Flash) with the patient in supine position. Axial slices were spaced at 3 millimetres (mm) (Definition AS / Flash) or 5 mm (Sensation 16) intervals and contained 512 x 512 pixels. Intravenous contrast (Xenetix 300/350, Guerbet, The Netherlands) was administered and bowel preparation took place with oral contrast-enhancing fluid (CEF; Telebrix Gastro, Guerbet, The Netherlands) 1 hour before start of the CT examination (unless the patient had a contraindication for intravenous or oral contrast).

All CT-reports were checked for mentioning of the following signs; “pericolic air bubbles or pockets”, “pericolic free air or gas”, “intraperitoneal free air or gas”, “extraluminal air” or “covered perforation”. Subsequently, these CTs were re-analyzed by two independent radiologists for the presence and classification of extraluminal air on CT. Both radiologists were blinded for patient characteristics, initial CT report from the participating hospital, CT report from the other expert reader, and patient outcome. In line with previous published literature¹¹⁻¹⁵, pericolic air was defined as air located less than 5 cm from the affected segment of colon, regardless of whether the air was intra- or retroperitoneal. Only patients in whom both radiologists reported extraluminal air <5cm from the affected segment were included. Patients without extraluminal air or extraluminal air >5cm from the affected segment were excluded from analysis. The volume of extraluminal air was estimated by measuring the air pocket's largest diameter in two directions in the axial plane and in the coronal plane. The presence of free fluid was scored, as well as the location of free fluid (pericolic, Douglas' pouch or diffuse).

Data collection and outcomes

Patient characteristics, clinical signs and symptoms, American Society of Anesthesiologists (ASA) Physical Status classification scores, laboratory parameters, CT-findings and initial treatment strategy (e.g. antibiotic treatment, watchful waiting), were collected from the hospital records. The primary outcome was failure of conservative management which was defined as need for emergency surgery or percutaneous abscess drainage within 30 days after presentation. The

occurrence of failure of conservative treatment was determined retrospectively in both study cohorts. Secondary outcome measures were length of hospital stay, complications (colonic obstruction, abscess, perforation) and mortality. Moreover, the primary outcome per initial treatment strategy (antibiotic or non-antibiotic treatment) was assessed. For the patients from the retrospective cohort, patients were assigned to the antibiotic treatment group if antibiotic treatment had been started within 24 hours after presentation. Antibiotic treatment was not started according to a predefined protocol but at the discretion of the attending physician.

Statistical analysis

Descriptive statistics were provided of all variables. Continuous variables are presented as means with standard deviation (SD) or medians with inter quartile range (IQR) according to their distribution. For categorical variables counts and percentages are presented. Categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate, and continuous variables were compared using the independent t test or the Mann-Whitney U test, as appropriate. Multivariable logistic regression was performed to identify risk factors for failure of conservative treatment. Variables that were univariably associated ($p < 0.20$) with failure of conservative treatment were entered into the multivariable model. Odds ratios are presented with 95 per cent confidence intervals. Two sided $P < 0.05$ was considered statistically significant. All analyses were performed using the statistical software package SPSS 24.0 (IBM Corporation, New York, USA).

Results

Patient characteristics

Figure 1 depicts the selection of patients presenting with acute Hinchey 1A diverticulitis with pericolic air on CT from the two cohorts. In total, 1471 diverticulitis patients were identified. Of these, 214 patients were excluded because of clinical or radiological signs of peritonitis or abscess (Hinchey classification $> 1A$). In 146 (12%) of the 1257 Hinchey 1A patients, extraluminal air was reported in the initial CT reports. These patients were all initially treated conservatively. The CTs of these patients were re-evaluated by two independent radiologists for the classification of extraluminal air. Thirty-five patients were excluded because at re-evaluation no extraluminal air was observed ($n=25$) or the extraluminal air was located more than 5 cm of the affected segment ($n=10$). After exclusion of two duplicate patients, a total of 109 patients were included in the FACT study; 39 patients from the DIABOLO¹⁴ trial and 70 patients from the retrospective single centre cohort. Baseline characteristics are shown in **table 1**. The mean age was 53 years (SD 11)

Figure 1 Flowchart of study participants

and 33% of the patients were female. Median amount of extraluminal air was 1.5 cc (IQR 1.0-2.5). Radiologists reported free fluid in 12 (11%) patients which was most frequently seen in Douglas' pouch (n=11). Fifty-two (48%) patients received antibiotic treatment within 24 hours after presentation. Baseline characteristics were mostly comparable between the antibiotic and non-antibiotic group. C-reactive protein (CRP) seemed to be slightly higher in the antibiotic group (median 142mg/L versus 115mg/L, and the volume of pericolic air was marginally higher in the antibiotic group (median 2.0cc versus 1.5cc) compared to the non-antibiotic group.

Primary outcome: failure of conservative management

Table 2 shows the failure of conservative management. Nine of 109 (8%) patients had failure of conservative management, two (2%) patients required percutaneous abscess drainage and seven (6%) patients required emergency surgery within 30 days after presentation. Of the patients who required emergency surgery, a second CT was made in four patients because of clinical deterioration and increasing abdominal pain. These CTs revealed an abscess in two patients and no deterioration of disease in the other two patients. Three of these patients had purulent peritonitis upon surgery, whereas in one patient no deterioration of disease was seen. Three of the patients who required emergency surgery did not undergo a second CT, but a diagnostic laparoscopy was performed in these patients where a purulent peritonitis was seen.

Table 1 Patient characteristics

	All patients (N=109)	No antibiotics (N=57)	Antibiotic treatment (N=52)*	P-value
Patient demographics				
Age, mean (SD)	53 (11)	52 (11)	55 (12)	0.137 ¹
Female gender, N (%)	36 (33%)	22 (39%)	14 (27%)	0.196 ²
ASA classification				0.403 ³
ASA I	65 (60%)	37 (65%)	28 (54%)	
ASA II	38 (35%)	18 (32%)	20 (38%)	
ASA III	6 (5%)	2 (4%)	4 (8%)	
BMI kg/m ² , mean (SD)	27.6 (4.6)	26.6 (3.6)	28.9 (5.4)	0.026 ¹
History of diverticulitis, N (%)	10 (9%)	6 (10%)	4 (9%)	0.496 ²
Clinical status				
Temperature °C, mean (SD)	37.6 (0.8)	37.5 (0.8)	37.7 (0.8)	0.118 ¹
Laboratory findings				
CRP (mg/L), median (IQR)	124 (76-199)	115 (73-179)	142 (90-218)	0.106 ⁴
WBC (10 ⁹ /L), mean (SD)	14.8 (4.1)	14.7 (3.6)	14.9 (4.6)	0.803 ¹
CT findings				
Volume of pericolic air (CC), median IQR	1.5 (1.0-2.5)	1.5 (1.0-2.0)	2.0 (1.5-3.0)	0.019 ⁴
Intraperitoneal fluid, N (%)	12 (11%)	9 (16%)	3 (6%)	0.096 ²

¹independent T-test ²Chi² test ³Fischer's exact test ⁴Mann-Whitney U test

*within 24 hours after presentation

SD = standard deviation, IQR= inter quartile range, ASA = American Society of Anesthesiologists, BMI = body mass index, CRP = C-reactive protein, WBC = white blood cell

Table 2 Treatment failure in FACT study and subgroup analysis of DIABOLO patients

FACT study	All patients (N=109)	No antibiotics (N=57)	Antibiotic treatment (N=52)*	P-value**
Percutaneous drainage N (%)	2 (2%)	0 (0%)	2 (4%)	0.23
Emergency surgery N (%)	7 (6%)	2 (4%)	5 (10%)	0.26
Total treatment failure N (%)	9 (8%)	2 (4%)	7 (13%)	0.08
DIABOLO sub analysis				
	All patients (N= 39)	No antibiotics (N=22)	Antibiotic treatment (N=17)	P-value**
Percutaneous drainage N (%)	0 (0%)	0 (0%)	0 (0%)	-
Emergency surgery N (%)	1 (3%)	0 (0%)	1 (6%)	0.44
Total treatment failure N (%)	1 (3%)	0 (0%)	1 (6%)	0.44

*within 24 hours after presentation

**Fischer's exact

One patient underwent open sigmoidectomy with diverting ileostomy, three patients underwent laparoscopic sigmoid resection with primary anastomosis, two patients underwent Hartmann procedure and one patient received laparoscopic lavage.

Outcome per initial treatment strategy

Table 2 shows the failure of conservative management per initial treatment strategy, as well as a subgroup analysis of the DIABOLO¹⁴ patients (who were randomly assigned to either antibiotic or non-antibiotic treatment). Seven of 52 (13%) patients in the antibiotic treatment group failed conservative treatment versus 2 of 57 (4%) patients in the non-antibiotic group. There was no statistically significant difference in failure of conservative treatment between patients treated with and without antibiotics ($p=0.083$). In a subgroup analysis of the 39 DIABOLO¹⁴ patients, only one patient failed conservative treatment in the antibiotic group versus nil in the non-antibiotic group ($p=0.44$).

Secondary outcome: mortality, complications, re(admittance) and hospital stay

One patient died due to persistent abdominal sepsis following a Hartmann's procedure. Eleven (10%) patients developed complications; colonic obstruction ($n=1$), perforation ($n=5$) and abscess ($n=5$). Forty (37%) patients were treated as outpatients of which two (2%) were eventually admitted to the hospital due to clinical deterioration or development of complications. Fourteen (35%) of the outpatients were treated with antibiotics. Sixty-nine (63%) patients were treated as inpatients of which seven (10%) patients were re-admitted to the hospital within 30 days after presentation due to clinical deterioration or development of complications. Thirty-eight (55%) of the inpatients were treated with antibiotics. Median length of hospital stay was 3 days (IQR 2-5).

Long term outcomes

Median follow-up was 11 months (IQR 2-24). Twenty-five of 109 (23%) patients developed recurring diverticulitis, all of whom were treated conservatively. Nineteen of 109 (17%) patients underwent elective sigmoidectomy. Indications for these resections were stenosis ($n=3$), fistula ($n=3$) and recurring diverticulitis or persistent complaints ($n=13$). One patient died due to non-diverticulitis related disease.

Risk factors for treatment failure

Table 3 shows the univariable and multivariable analyses of factors associated with failure of conservative management (need for percutaneous abscess drainage or emergency surgery). Location of free fluid was not included in the analysis as one radiologist scored these all in Douglas' pouch. The initial treatment strategy (non-antibiotic or antibiotic treatment) was included in the multivariable analysis to correct for a possible treatment effect of antibiotics. In the multivariable analysis only CRP level (OR 1.01 for each mg/L increase; 95% CI 1.001-1.02) remained statistically significant. Although not statistically significant in the multivariable analysis, leucocyte count and age seemed to be higher in the treatment failure group (mean $18.2 \times 10^9/L$ vs $14.5 \times 10^9/L$ and mean 60 years vs 52 years, respectively).

Table 3 Factors associated with failure of conservative management

	Treatment success (N=100)	Treatment failure (N=9)	P-value	Adjusted Odds ratio (95%CI)*
Patient demographics				
Age, mean (SD)	52 (10)	60 (13)	0.063 ¹	1.03 (0.96-1.10)
Female gender	34 (34%)	2 (22%)	0.715 ³	-
ASA classification			0.837 ³	-
ASA I	60 (60%)	5 (56%)		
ASA II	34 (34%)	4 (44%)		
ASA III	6 (6%)	0 (0%)		
BMI kg/m ² , mean (SD)	27.7 (4.6)	25.6 (3.9)	0.369 ¹	-
History of diverticulitis	9 (10%)	1 (11%)	1.000 ³	-
Clinical status				
Temperature °C, mean (SD)	37.6 (0.8)	37.5 (0.9)	0.723 ¹	-
Laboratory findings				
CRP (mg/L), median (IQR)	124 (75-192)	218 (97-364)	0.029 ⁴	1.01 (1.001-1.02)
Leucocytes ($10^9/L$), mean (SD)	14.5 (4.0)	18.2 (3.6)	0.008 ¹	1.20 (0.99-1.45)
CT findings				
Volume of pericolic air (CC), median IQR	1.5 (1.0-2.5)	2.0 (1.0-4.0)	0.806 ⁴	-
Intraperitoneal fluid	11 (11%)	1 (11%)	1.000 ³	-
Initial treatment				
Antibiotic treatment**	45 (45%)	7 (78%)	0.083 ²	2.48 (0.43-14.40)

¹independent T-test ²Chi² test ³Fischer's exact test ⁴Mann-Whitney U test

*Odds ratio in multivariable analysis; **within 24 hours after presentation

SD = standard deviation, IQR= inter quartile range, NS= not selected, CRP = C-reactive protein, ASA = American Society of Anesthesiologists, BMI = body mass index, CI = confidence interval

Discussion

The present study analyzed the course of diverticulitis patients presenting with isolated pericolic air on CT. The vast majority (92%) of patients recovered with conservative treatment. This indicates that diverticulitis patients with isolated pericolic air on CT can safely be treated conservatively.

The clinical relevance of pericolic air on CT in diverticulitis patients presenting without signs of generalized peritonitis or sepsis has been topic of debate. Several studies have recently been published reporting on the nonoperative management of perforated diverticulitis. Titos-Garcia et al¹⁴ and Salinnen et al¹² specifically report nonoperative treatment success rates for patients with isolated pericolic air; 90% and 99% respectively. Both studies only considered emergency surgery as treatment failure. These findings are consistent with our finding that 92% of the patients with isolated pericolic air recovered with conservative treatment.

Most studies reporting on the nonoperative management of perforated diverticulitis include patients with pericolic and distant free air. The FACT study only included patients with isolated pericolic air. We selected this patient group because literature suggests that pericolic and distant extraluminal air have a different disease course and demand different treatment strategies. In a patient with distant free air, we can no longer speak of a “covered perforation” as the perforation is no longer contained to the pericolic region. This is why free distant air is usually considered a sign of diffuse peritonitis and an indication for operative intervention whereas patients with isolated pericolic air may be treated conservatively. Recent studies report contrastingly about the risk of conservative treatment failure in patient with distant free air. Salminen et al¹², Colas et al¹⁵ and Titos-Garcia et al¹⁴ report lower success rates of conservative treatment in patients with distant free air; 62%, 59% and 62%, respectively. Contrastingly, Dharmarajan et al¹³ and Costi et al¹¹ report no difference in outcome between pericolic and distant free air. However, the number of patients presenting with distant free air was relatively small in these studies, hampering proper comparison. As patients with free distant air do show a tendency towards a more complicated course, including these patients would have led to a heterogeneous study population. We therefore chose to only include patients with isolated pericolic air to assess the outcome of (non-antibiotic) conservative treatment.

All patients in the above mentioned studies analysing the nonoperative management of diverticulitis with pericolic or free distant air, received intravenous antibiotics as part of their nonoperative management. A recently published study describes non-antibiotic treatment in diverticulitis patients with pericolic air.

Thorisson *al*²¹ analyzed predictive factors on CT imaging for progression of uncomplicated diverticulitis into complicated diverticulitis, using data from a randomized clinical trial comparing antibiotic treatment with non-antibiotic treatment in uncomplicated diverticulitis; the AVOD trial.²² They re-evaluated all CT-scans of the included patients and identified 27 (4%) patients with pericolic air and conclude that pericolic air is not a risk factor for progression into complicated diverticulitis. However, only two patients with pericolic air on CT had progression into complicated diverticulitis (one in the antibiotic group and one in the non-antibiotic group), therefore statistical power might have been insufficient to detect risk factors for progression into complicated diverticulitis.

The question remains which therapeutic approach we should adopt in diverticulitis patients with pericolic air on CT. Dharmarajan *et al*¹³ propose, based on their own observational patient data, a nonoperative management protocol in which patients with pericolic air without signs of sepsis are treated with intravenous antibiotics. Since we found a conservative treatment success rate of 92% in the present study, we feel we can safely adopt such a strategy. Fifty-seven (52%) of our patients were treated without antibiotics and of these, 55 (96%) patients were treated successfully. Moreover, we found no statistical significant difference in failure of conservative treatment between patients treated with and without antibiotics ($p=0.083$). This could indicate that antibiotic treatment might not be mandatory in patients with pericolic air. However, 64% of the study population came from a retrospective database and in these patients antibiotic treatment was started at the discretion of the attending physician. Therefore there is a high risk of confounding by indication. It is possible that patients who presented with more severe illness (who might be at higher risk of conservative treatment failure) were more likely to receive antibiotic treatment. In a subgroup analysis of the DIABOLO¹⁴ patients (who were randomly assigned to either watchful waiting or antibiotic treatment) there was also no difference in outcome found between patients treated with and without antibiotics, strengthening our conclusion that antibiotics may not be mandatory in patients with pericolic air. However, further research aimed at the non-antibiotic treatment of diverticulitis patients with isolated pericolic air should be performed before a conservative treatment strategy without antibiotics can safely be assumed.

A major strength of this study is its multicenter design and the fact that one-third of the study population came from a prospective, randomized study. Contrastingly, the other two-third of the study population came from a retrospective database

which comes with inherent limitations. The fact that two independent radiologist re-analyzed all CTs enhances the validity of our results. However, a limitation is that we did not re-analyze all CT scans in which free air was not mentioned in the CT-report, to confirm the absence of free air. It could therefore be that we missed a few patients with free air. Moreover, in the DIABOLO study diverticulitis-positive findings led to CT within 24 hours and it could be that these patients had resolution of their free air in that meantime.

The present study is limited by the small number of patients with treatment failure. In the multivariable analysis only a higher CRP level remained as a significant predictor of treatment failure. Although not statistically significant, a higher leucocyte count and higher age seemed to be associated with treatment failure. Because of the small number of treatment failures, statistical power may have been insufficient to identify risk factors for treatment failure. The primary aim of this study was however to assess the feasibility of (non-antibiotic) conservative management in patients with pericolic air and the small number reflects the low probability of treatment failure in patients with isolated pericolic air.

Although conservative management in patients with acute diverticulitis with isolated pericolic air is a suitable treatment strategy, it remains uncertain whether non-antibiotic treatment is safe in patients with isolated pericolic air due to the low event rate. A higher CRP level was significantly associated with treatment failure, and a higher leucocyte count and higher age showed a non-significant trend towards an association with treatment failure. Patients with isolated pericolic air who present with these risk factors may not be suitable for a conservative treatment strategy, and need close observation and/or treatment with antibiotics.

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Chapter 7

A multicenter retrospective cohort study
on short- and long-term outcomes of
nonsurgical treatment for complicated
diverticulitis with abscess formation

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Abstract

Background

Treatment strategies for diverticulitis with abscess formation have shifted from (emergency) surgical treatment to nonsurgical management (antibiotics with or without percutaneous drainage). The aim of this study was to assess both short- and long-term outcomes of nonsurgical treatment and to identify risk factors associated with adverse outcomes.

Methods

A multicenter, retrospective cohort study was conducted. Patients with a first episode of CT-diagnosed diverticular abscess formation (modified Hinchey Ib or II) between January 2008 and December 2015 were included, if initially treated nonsurgically. Baseline characteristics and short- and long-term data on treatment outcomes (complications, readmissions, recurrences, and (emergency) surgery) were recorded. Regression analyses were used to analyze risk factors for treatment failure, recurrences and emergency- and long-term surgery.

Results

Overall, 447 patients from ten different hospitals were included (Hinchey Ib [n=215], Hinchey II [n=232]), with a median follow-up time of 72 months (interquartile range, [55-93]). Most patients were treated without percutaneous drainage (74% [332/447]). Hinchey II patients were at higher risk of emergency surgery (13% vs 5%, $p=0.018$). Treatment strategy did not independently affect outcomes. Abscesses ≥ 3 cm and ≥ 5 cm were found to be independent risk factors for respectively short-term treatment failure and emergency surgery, (odds ratio [95% confidence interval]: 2.05 [1.09-3.86] and 2.91 [1.03-8.23]).

Conclusion

Diverticulitis with abscesses < 3 centimeter can be managed without percutaneous drainage. Abscesses ≥ 3 and ≥ 5 centimeter are at higher risk of short-term treatment failure and emergency surgery, respectively. For these Hinchey 1B and II patients, no difference in outcome between antibiotic treatment with or without percutaneous drainage was found.

Introduction

Diverticulosis is common in the Western world and is estimated to affect more than half of the population over the age of 65 years.¹ Diverticulosis might lead to diverticulitis in approximately 4.3-7% of cases^{2,3}, of which twenty-five percent present with acute complicated diverticulitis, which can consist of severe complications, such as abscess formation, perforation, stenosis or fistula formation.⁴ In approximately 15% of patients with acute complicated diverticulitis, abscess formation is present.⁵⁻⁷ This can be classified according to the modified Hinchey classification as type Ib (confined pericolic abscess <5cm) or Hinchey II (pelvic, distant intra-abdominal or retroperitoneal abscess ≥5cm).^{8,9}

Over the years, treatment strategies for diverticulitis with abscess formation have gradually shifted from (emergency) surgical treatment to nonsurgical management (antibiotics with or without percutaneous drainage (PCD)).¹⁰ Currently, guidelines advise that small pericolic abscesses can be treated with antibiotics and distant (pelvic) or larger abscesses, usually defined as ≥3-5cm, should be treated with percutaneous drainage, if possible.¹¹⁻¹³ Since patients undergoing nonsurgical treatment are at risk of adverse outcomes such as emergency surgery, disease recurrence, readmission, and even mortality (both on the short and long term),^{10,14} adequate patient selection to determine the optimal choice of treatment has come to play an important role in the management of these patients.

However, the clinical course of complicated diverticulitis with abscess formation after nonsurgical treatment, as well as the identification of risk factors for adverse outcomes, have not been adequately analyzed.^{10,12} Most of the existing studies addressing these topics are limited by a short follow-up time, small and single institutional study populations, and a lack of time-to-event analysis.¹⁵⁻²²

Therefore, the primary aim of this retrospective, multicenter, cohort study was to assess both the short- and long-term outcomes of initial nonsurgical treatment strategies for acute complicated diverticulitis with abscess formation (Hinchey Ib and II) in a large number of patients. The second aim was to identify risk factors associated with adverse outcomes, to help facilitate adequate patient selection and assess the optimal treatment strategy.

Methods

Study design

This multicenter, retrospective cohort study was conducted in two academic and eight teaching hospitals in the Netherlands, e.g. the Academic Medical Center (Amsterdam), Erasmus Medical Center (Rotterdam), Amphia Hospital (Breda),

Catharina Hospital (Eindhoven), Gelre Hospital (Apeldoorn), Havenziekenhuis (Rotterdam), IJsselland Hospital (Capelle aan den IJssel), Meander Medical Center (Amersfoort), OLVG (Amsterdam), and Reinier de Graaf Gasthuis (Delft). The study was approved by the Institutional Review Boards of all participating hospitals.

Participants

All patients of 18 years and older, who had a first episode of CT-diagnosed complicated diverticulitis with abscess formation (modified Hinchey Ib or II⁸), and who had initial nonsurgical treatment, being either antibiotic treatment (no PCD) or antibiotic treatment with percutaneous drainage (PCD), were eligible for inclusion in the cohort. Patients with perforated diverticulitis with peritonitis (Hinchey III or IV) and patients presenting with signs of sepsis or concurrent fistula formation were excluded. Potentially eligible patients that presented between January 1st 2008 and December 31st 2015 were searched for by using a diagnostic specific code (DBC or DRG), ICD-9 (International Classification of Disease), or ICD-10 codes in all hospital databases. In one of the participating hospitals, patients could only be identified between January 1st 2012 and December 31st 2015. Subsequently, patients' medical records were screened for in- and exclusion criteria, before definitive inclusion in the study cohort.

Data collection

All patients' medical records were retrospectively reviewed. Baseline patient characteristics such as age, body mass index (BMI), co-morbidities, medical and surgical history, previous episodes of uncomplicated diverticulitis, medication use, smoking, alcohol drinking habits, and American Society of Anesthesiologists (ASA) scores were collected. Radiological details on the number, location and size of abscesses were recorded, as well as clinical signs (temperature, physical examination), symptoms (nausea, vomiting, bowel complaints, rectal blood loss), and laboratory parameters (C-reactive protein [CRP] and white blood cell counts [WBC]). Details on treatment such as type and duration of antibiotic treatment, percutaneous drainage (approach, type of drain, duration of drainage), surgical procedures (e.g. elective/emergency resection or stoma reversal surgery) were recorded as well as short- and long-term treatment outcomes.

Outcomes

The short-term outcomes were: treatment failure, complications (e.g. colonic obstruction, perforation, fistula formation or clinical deterioration/progression of disease), emergency surgery (e.g. all unscheduled operations), readmissions,

persistent diverticulitis (complaints lasting >30 days) and mortality. Long-term outcomes were: episodes of recurrent (un)complicated diverticulitis, sigmoid resection and mortality. Short-term was defined as events occurring during the first 30 postoperative days, or during primary admission if a patient was still admitted after 30 days. Treatment failure was defined as the composite outcome of complications, readmissions, persistent diverticulitis, emergency surgery, mortality or need for percutaneous drainage in the no PCD group.

Statistical analyses

Multiple imputation techniques were used to impute missing data points in order to avoid selection bias. Data were assumed to be missing at random. All reported results are based on the imputed data, where the estimates of interests at the final computational step were combined across the imputed datasets using Rubin's rules.²³ Continuous variables are presented as mean with standard deviation (SD) or median with interquartile range (IQR), depending on normality of data. Continuous variables were compared using the independent T test or the Mann-Whitney U test, as appropriate. Categorical variables are presented as proportions (n) with percentages (%). Pearson's chi-squared test and Fisher's exact test were used to compare categorical data. In order to identify risk factors for treatment failure and emergency surgery, the differences in patient- and disease characteristics (e.g. signs, symptoms and additional tests (laboratory tests and CT-scan)) between patients with and without treatment failure and emergency surgery were assessed. Univariable logistic regression analyses were used to calculate the crude odds ratios (OR) with 95% confidence interval (CI) of the independent predictors. These analyses were used to quantify which (combinations of) variables were independently related to treatment failure and emergency surgery. Inclusion of the relevant diagnostic items in the multivariable model was based on clinical knowledge and p-values (p-value <0.20 or <0.05, depending on the event rate). Recurrence and sigmoid resection in the long-term follow-up were assessed with Kaplan-Meier estimates with censoring at end of study follow-up or mortality, stratified by Hinchey classification and treatment (no PCD vs PCD). The effect of Hinchey classification and treatment on the outcome were assessed with the Mantel-Cox log-rank test. Cox proportional hazards regression was used to analyze risk factors for recurrence and sigmoid resection in long-term follow-up. Hazard ratios (HR) with 95%CI will be presented as covariables associated with recurrence or sigmoid resection in long-term follow-up. Since data from different hospitals were used, differences between hospitals (e.g. local treatment protocols) could have had an effect on the outcomes. To test this bias by clustering of data,

the short-term and long-term analyses were additionally adjusted for hospital. The short-term outcomes were adjusted by fitting a generalized linear mixed model for each outcome, using a logistic regression mixed model. Hinchey classification and PCD were entered separately as fixed effect and hospital was entered as random effect. For the short-term multivariable logistic regression analyses on risk factors for treatment failure and emergency surgery, hospital was entered as covariable in each multivariable model. The long-term Cox regression analyses were adjusted by entering hospital as covariable in each multivariable model. Lastly, sensitivity analyses on the non-imputed dataset were performed to test whether the imputation technique had any influence on the outcomes at interest. The manuscript was written in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement and checklist.²⁴ All analyses were performed using the statistical software package SPSS 24.0 (IBM Corporation, New York, USA).

Results

Patient and disease characteristics

Patient and disease characteristics are shown in **Table 1**. A total of 447 patients with CT-proven Hinchey type Ib (n=215) or II (n=232) diverticulitis were included. The mean age was 61 ± 13 years and 41% of the patients were male. The mean BMI of the total cohort was 27.8 ± 5.7 kg/m². Of all patients, 270 (61%) had comorbidities and 123 (21%) patients were classified as >ASA II. Mean (SD) CRP was 168 ± 106 mg/L for the total cohort and mean WBC was $14.5 \pm 5.2 \times 10^9$ /L. Most patients were treated with amoxicillin-clavulanic acid (90/289 (31%)), cefuroxime and metronidazole (88/289 (30%)), ceftriaxone and metronidazole (41/289 (14%)) or other antibiotics (70/289 (24%)) such as clindamycin, co-trimoxazole or piperacillin tazobactam for a median of 7 days (IQR 5-12). The majority of patients (332 (74%)) were initially treated without PCD and 115 (26%) patients were treated with PCD for a median of 6 days (IQR 3-16). The PCD approach was mainly transabdominal (86/115 (75%)), guided by either ultrasound (49/115 (43%)) or CT (63/115 (55%)). Median (IQR) length of hospital stay was 7 (5-13) days. The median (IQR) follow-up duration was 72 (55-93) months.

Patients who were treated with PCD presented more often with nausea (63% vs 49%) and vomiting (37% vs 20%). Inflammatory parameters were higher in the PCD group with a higher mean C-reactive protein 222 ± 114 vs 149 ± 96 mg/L and mean WBC 16.3 ± 5.6 vs $14.3 \pm 4.9 \times 10^9$ /L. In the PCD group, more patients were classified as Hinchey II (84% vs 41%) and more patients presented with multiple

Table 1 Baseline characteristics

	Total cohort (N=447)	No PCD (N=332)	PCD (N=115)	P-value
Patient demographics				
Male gender	182 (41%)	139 (42%)	43 (37%)	0.400 ¹
Age (years)	61 (13)	60 (13)	63 (13)	0.140 ²
BMI (kg/m ²)	27.8 (5.7)	27.6 (5.5)	28.4 (6.3)	0.404 ²
Smoking	227 (51%)	167 (50%)	61 (53%)	0.603 ¹
Alcohol consumption	232 (52%)	178 (54%)	54 (47%)	0.274 ¹
Comorbidities				
ASA >II	123 (27%)	84 (25%)	39 (34%)	0.075 ¹
Patients with registered comorbidity	270 (61%)	201 (61%)	70 (61%)	0.952 ¹
Medical history				
History of diverticulitis	137 (31%)	93 (28%)	44 (38%)	0.035 ¹
History of abdominal surgery	151 (34%)	119 (36%)	32 (28%)	0.130 ¹
Medication				
NSAIDs	182 (41%)	133 (40%)	49 (43%)	0.573 ¹
Steroids	43 (10%)	35 (11%)	8 (7%)	0.239 ¹
Clinical symptoms				
Days of symptoms	7 (3-14)	7 (3-12)	8 (4-14)	0.062 ⁴
Nausea	235 (53%)	163 (49%)	73 (63%)	0.018 ¹
Vomiting	108 (24%)	65 (20%)	43 (37%)	0.001 ¹
Diffuse abdominal pain	61 (14%)	44 (13%)	16 (14%)	0.704 ³
Change in bowel habit	294 (66%)	221 (67%)	73 (63%)	0.548 ¹
Rectal blood loss	70 (16%)	44 (13%)	26 (23%)	0.044 ¹
Clinical signs				
Rebound tenderness	141 (32%)	104 (31%)	37 (32%)	0.602 ¹
Local muscular guarding/resistance	115 (26%)	81 (24%)	34 (30%)	0.259 ¹
Diffuse muscular guarding	50 (11%)	32 (10%)	18 (16%)	0.255 ³
Temperature (degrees Celsius)	37.7 (0.9)	37.7 (0.9)	37.8 (1.0)	0.319 ²
Laboratory parameters				
CRP (mg/L)	168 (106)	149 (96)	222 (114)	<0.001 ²
WBC (x10 ⁹ /L)	14.8 (5.2)	14.3 (4.9)	16.3 (5.6)	0.001 ²
Radiological parameters				
Hinchey II*	232 (52%)	135 (41%)	97 (84%)	<0.001 ¹
Largest diameter (cm)	4.2 (2.7-6.1)	3.6 (2.5-5.1)	6.4 (5.0-8.5)	<0.001 ⁴
Location abscess distant	106 (24%)	71 (21%)	35 (30%)	0.046 ¹
No. of patients with multiple abscesses	63 (14%)	40 (12%)	23 (20%)	0.035 ¹
Free air peridiverticular	143 (32%)	106 (32%)	37 (32%)	0.925 ¹
Free air abdomen	56 (13%)	36 (11%)	20 (17%)	0.252 ¹
Free fluid	90 (20%)	61 (18%)	29 (25%)	0.187 ¹
Follow-up				
Length of hospital stay (days)	7 (5-13)	7 (4-10)	10 (7-18)	<0.001 ⁴

¹Pearson's Chi-square test ²Independent T-test ³Fisher's exact test ⁴Mann Whitney U Test

*Hinchey II is defined as abscess ≥5 centimeter in diameter and/or distant abscess

Data are n (%), mean (standard deviation), or median (interquartile range).

Abbreviations: N= number, PCD= percutaneous abscess drainage, SD=standard deviation, BMI= Body Mass Index, ASA= American Society of Anesthesiologists, NSAIDs= non-steroidal anti-inflammatory drugs, IQR= inter quartile range, CRP = C-reactive protein, WBC= white blood cell count

abscesses (20% vs 12%). Median (IQR) abscess diameter was 6.4 (5.0-8.5) in the PCD group vs 3.6 (2.5-5.1) in the group treated without PCD. Median (IQR) length of hospital stay was also longer in the PCD group (10 [7-18] days vs 7 [4-10] days).

Missing data

All candidate predictors had missing data except for age, gender and ASA classification. Most variables had a missing data percentage between 1 to 20%. Three variables had a high number of missing data; BMI (45%), smoking (61%) and alcohol consumption (64%). For abscess size 31% of data were missing. In total, 2140 (15%) data items were imputed.

Short- and long-term outcomes

Short-and long-term outcomes are shown in **Table 2**. Of the total cohort, 120 (27%) patients experienced treatment failure and 40 (9%) patients required emergency surgery within 30 days after first presentation. Seventy-one (16%) patients were readmitted to the hospital within 30 days after first presentation and 63 (14%) patients had persistent diverticulitis. Five (1%) patients died due to severe sepsis caused by perforated diverticulitis. Three of these patients died after they underwent emergency surgery, whereas two patients were not treated operatively, but were abstained from further treatment due to comorbidity. One hundred and twenty-two (27%) patients experienced one or more episodes of recurrent diverticulitis. In total, 138 episodes of recurrent diverticulitis were

Table 2 Short-and long-term outcomes

	Total (N=447)	Hinchey IB (N= 215)	Hinchey II (N=232)	P-value
Short-term outcomes				
Treatment failure	120 (27%)	50 (23%)	70 (30%)	0.127 ²
Complications	99 (22%)	39 (18%)	60 (26%)	0.056 ²
Readmission	71 (16%)	32 (15%)	39 (17%)	0.618 ²
Persistent diverticulitis	63 (14%)	28 (13%)	35 (15%)	0.596 ²
Emergency surgery (sigmoid resection)	40 (9%)	11 (5%)	29 (13%)	0.018 ²
ST mortality	5 (1%)	3 (1%)	2 (1%)	0.804 ¹
Long-term outcomes				
Recurrence	122 (27%)	61 (28%)	61 (26%)	0.665 ³
Sigmoid resection	124 (28%)	63 (29%)	61 (26%)	0.675 ³
Mortality	28 (6%)	10 (5%)	18 (8%)	0.162 ³

Presented data are in N (%)

Abbreviations: PCD = percutaneous abscess drainage

**Hinchey II is defined as abscess ≥5 centimeter in diameter and/or distant abscess*

¹Fisher's exact test ²Pearson's Chi-square test ³Mantel-Cox log-rank test

recorded of which 73 (53%) episodes were uncomplicated and 49 (47%) were complicated diverticulitis episodes. Median (IQR) time to recurrence was 8 (3-24) months. One hundred and twenty-four (28%) patients required sigmoid resection in the long-term follow-up, of which 14 were in an emergency setting. Median (IQR) time to operation was 5 (3-13) months. In the long-term follow-up, 28 (6%) patients died, of which two cases were diverticulitis-related. One of these patients died due to severe sepsis caused by anastomotic leakage after Hartmann reversal surgery and one patient died due to severe sepsis caused by intestinal ischemia after sigmoid resection for diverticular stenosis.

Hinchey II patients more often required emergency surgery (13% vs 5%, $p=0.018$).

Figure 1 and **2** show the time-to-event analysis of recurrence and surgery in long-term follow-up. There were no differences between Hinchey IB and II patients in recurrence ($p=0.665$) or overall surgery ($p=0.675$). All other short- and long-term outcome parameters were comparable between Hinchey Ib and Hinchey II patients. Short- and long-term outcomes are presented separately for Hinchey Ib and II patients, as shown in **Table 3** and **4**, respectively.

Figure 1 Survival analysis Recurrence per Hinchey classification

Figure 2 Survival analysis Operation per Hinchey classification

Table 3 Short-and long-term outcomes per treatment group in Hinchey IB* patients

	Total (N=215)	No PCD (N=197)	PCD (N=18)	P-value
Short-term outcomes				
Treatment failure	50 (23%)	44 (22%)	6 (33%)	0.359 ¹
Complications	39 (18%)	32 (16%)	7 (39%)	0.048 ¹
Readmission	32 (15%)	27 (14%)	5 (28%)	0.178 ¹
Persistent diverticulitis	28 (13%)	23 (12%)	5 (28%)	0.100 ¹
Emergency surgery (sigmoid resection)	11 (5%)	10 (5%)	1 (6%)	0.693 ¹
Mortality	3 (1%)	3 (2%)	0 (0%)	1.000 ¹
Long-term outcomes				
Recurrence	69 (32%)	62 (31%)	7 (39%)	0.623 ²
Sigmoid resection	63 (29%)	57 (29%)	6 (33%)	0.474 ²
Mortality	10 (5%)	8 (4%)	2 (11%)	0.263 ²

Presented data are in N (%)

Abbreviations: PCD = percutaneous abscess drainage

*Hinchey IB is defined as abscess <5 centimeter in diameter

¹Fisher's exact test ²Mantel-Cox log-rank test

Table 4 Short-and long-term outcomes per treatment group in Hinchey II* patients

	Total (N=232)	No PCD (N= 135)	PCD (N=97)	P-value
Short-term outcomes				
Treatment failure	70 (30%)	35 (26%)	35 (36%)	0.149 ²
Complications	60 (26%)	29 (21%)	31 (32%)	0.093 ²
Readmission	39 (17%)	22 (16%)	17 (18%)	0.714 ²
Persistent diverticulitis	35 (15%)	19 (14%)	16 (16%)	0.583 ²
Emergency surgery (sigmoid resection)	29 (13%)	14 (10%)	15 (15%)	0.117 ²
Mortality	2 (1%)	0 (0%)	2 (2%)	0.332 ¹
Long-term outcomes				
Recurrence	69 (30%)	45 (33%)	24 (25%)	0.349 ³
Sigmoid resection	61 (26%)	30 (22%)	31 (32%)	0.046 ³
Mortality	18 (8%)	8 (6%)	10 (10%)	0.270 ³

Presented data are in N (%)

Abbreviations: PCD = percutaneous abscess drainage

*Hinchey II is defined as abscess ≥5 centimeter in diameter and/or distant abscess

¹Fisher's exact test ²Pearson's Chi-square test ³Mantel-Cox log-rank test

Short- and long-term outcomes in Hinchey Ib patients

Of the 215 Hinchey Ib patients, 39 (18%) experienced complications within 30 days after presentation, such as; perforation (n=4), colonic obstruction (n=2), fistula (n=3) and clinical deterioration or progression of disease (n=30). Three (1%) patients died within 30 days after presentation due to severe sepsis caused by perforated diverticulitis. In the PCD group more patients experienced complications (39% vs 16%, p=0.048). Treatment failure and need for emergency surgery did not differ between patients treated with and without PCD (**Table 3**). There were no differences in long-term outcome.

Short-and long-term outcomes in Hinchey II patients

Of the 232 Hinchey II patients, 60 (26%) patients experienced complications within 30 days after presentation, such as; perforation (n=13), colonic obstruction (n=2), clinical deterioration or progression of disease (n=40), fistula (n=3) and one patient had necrotizing fasciitis at the old drain entry point. Two (1%) patients died within 30 days after presentation due to severe sepsis caused by perforated diverticulitis. Treatment failure and need for emergency surgery did not differ between patients treated with and without PCD (**Table 4**). Patients in the PCD group had a higher risk of sigmoid resection in long-term follow-up (32% vs 22%). For the other long-term outcomes there were no differences between the two treatment groups.

Risk factors for treatment failure and emergency surgery in short-term follow-up

After univariable analysis of all possible predictors for treatment failure, the following variables were included in the multivariable analysis: age, BMI, alcohol consumption, comorbidity, NSAID prescription, nausea, CRP-level, abscess size, and initial treatment strategy (PCD yes or no). In the multivariable analysis for emergency surgery the following variables were included: history of abdominal surgery, rebound tenderness, abscess size, and initial treatment strategy (PCD yes or no) (**Supplementary Table 1**). Different cut-off sizes for abscess diameter were univariably reviewed to analyze which cut-off size could best predict the outcome. A cut-off size of 3 cm seemed to be the best predictor for treatment failure (univariable OR 2.33, 95%CI 1.32-4.11) and a cut-off size of 5 cm seemed to be the best predictor for emergency surgery (univariable OR 2.97, 95%CI 1.28-6.85). The multivariable analysis is shown in **Table 5**. A higher BMI seemed to slightly decrease the risk of treatment failure (OR 0.94, 95%CI 0.89-0.997) and an abscess ≥ 3 cm increased the risk of treatment failure (OR 2.05, 95%CI 1.09-3.86). All other variables did not seem to have an effect on the occurrence of treatment failure. For emergency surgery, history of abdominal surgery seemed

Table 5 Multivariable logistic regression analysis of risk factors for short-term treatment failure and emergency surgery

Treatment failure		
Variable	Odds ratio (95%CI)	P-value
Age (years)	1.001 (0.98-1.02)	0.955
BMI (kg/m ²)	0.94 (0.89-0.997)	0.041
Alcohol consumption	0.63 (0.36-1.10)	0.099
Comorbidity	1.40 (0.85-2.29)	0.183
NSAID prescription	0.58 (0.21-1.57)	0.242
Nausea	1.32 (0.83-2.12)	0.245
CRP (mg/L)	1.001 (0.998-1.003)	0.656
Abscess ≥ 3 cm	2.05 (1.09-3.86)	0.027
Percutaneous drainage	1.47 (0.81-2.68)	0.185
Emergency Surgery		
Variable	Odds ratio (95%CI)	P-value
History of abdominal surgery	2.05 (1.04-4.05)	0.038
Rebound tenderness	2.03 (0.98-4.21)	0.058
Abscess ≥ 5 cm	2.96 (1.08-8.13)	0.036
Percutaneous drainage	1.29 (0.56-2.99)	0.554

Abbreviations: CI= confidence interval, BMI = Body Mass Index, NSAID= non-steroidal anti-inflammatory drugs, CRP = C-reactive protein, ASA= American Society of Anesthesiologists

to increase the risk (OR 2.05, 95%CI 1.04-4.05) as well as an abscess ≥ 5 cm (OR 2.96, 95%CI 1.08-8.13). All other variables did not seem to have an effect on the risk for emergency surgery.

Two separate subgroup analyses were performed to assess the effect of PCD on the outcome in different abscess sizes (≥ 3 cm and ≥ 5 cm). The first subgroup analysis included only patients with an abscess size ≥ 3 cm (n=325). In this group there were no differences in rate of treatment failure between patients treated with (n=119) and without (n=206) PCD (36% vs 28% respectively, p=0.200). There was also no difference in rate of emergency surgery between these two groups (15% vs 18% respectively, p=0.198). The second subgroup analysis included only patients with an abscess size ≥ 5 cm (n=185). In this group there were no differences in rate of treatment failure between patients treated with (n=99) and without (n=86) PCD (35% vs 29% respectively, p=0.409). There was also no difference in rate of emergency surgery between these two groups (16% vs 12% respectively, p=0.416).

Risk factors for recurrence and sigmoid resection in long-term follow-up

After univariable analysis of all possible predictors for recurrence the following variables were included in the multivariable analysis: age, history of diverticulitis, history of abdominal surgery, rebound tenderness and sigmoid resection in short-term follow-up. In the multivariable analysis for sigmoid resection the following variables were included: age, alcohol consumption, comorbidity, history of diverticulitis, duration of symptoms, nausea, vomiting, diffuse abdominal pain, distant abscess, free peridiverticular air and initial treatment strategy (PCD yes or no) (**Supplementary Table 2**). The multivariable analysis is shown in **Table 6**. History of diverticulitis increased the risk of recurrence (HR 1.71, 95%CI 1.17-2.48). History of abdominal surgery and sigmoid resection decreased the risk of recurrence (HR 0.63, 95%CI 0.42-0.98, and HR 0.15, 95%CI 0.05-0.48, respectively). Older patients seem to be at slightly higher risk of sigmoid resection in the long-term follow-up (HR 1.01 (95%CI 1.001-1.03) and the symptoms vomiting and nausea also increased this risk (HR 1.70, 95%CI 1.02-2.82, and HR 1.85, 95%CI 1.15-2.98, respectively). All other variables did not seem to have an effect on the occurrence of sigmoid resection during long-term follow-up.

Sensitivity analyses

Hospital-adjusted analysis and sensitivity analyses on the non-imputed dataset showed similar results for all short-term outcome parameters except in Hinchey IB patients, where no significant difference in complication rate was found between treatment groups ($p=0.053$) in the hospital-adjusted analysis. In the sensitivity analysis on the non-imputed dataset, Hinchey IB patients treated with PCD did seem to be at higher risk for complications ($p=0.007$) (**Supplementary Table 3** and 4). With regards to the multivariable analyses of risk factors for treatment failure or emergency surgery, rebound tenderness seemed to be a significant predictor for emergency surgery ($p=0.038$) in the hospital-adjusted analysis, but this was not confirmed in the analysis on the non-imputed dataset. All other results remained the same (**Supplementary Table 5**). With regard to the multivariable analyses of risk factors for recurrence or sigmoid resection in long-term follow-up, history of abdominal surgery was no longer a significant predictor for recurrence ($p=0.054$) in the hospital-adjusted analysis. Additionally, from hospital-adjusted analysis, alcohol consumption (HR 0.54, 0.30-0.98, $p=0.042$) seemed to be a predictor of sigmoid resection in the long-term follow-up, whereas vomiting no longer was a significant predictor ($p=0.051$). All other results remained the same. In the sensitivity analysis on the non-imputed dataset, no significant predictors for

sigmoid resection in long-term follow-up were found, whereas history of abdominal surgery, history of sigmoid resection and history of diverticulitis remained significant predictors of recurrent diverticulitis (**Supplementary Table 6**).

Table 6 Multivariable Cox regression analysis of risk factors for recurrence and surgery in long-term follow-up

Recurrence		
Variable	Hazard ratio (95%CI)	P-value
Age in years	0.995 (0.98-1.01)	0.481
History of diverticulitis	1.71 (1.17-2.48)	0.005
History of abdominal surgery	0.63 (0.42-0.98)	0.040
Rebound tenderness	0.72 (0.46-1.13)	0.152
Sigmoid resection in short-term follow-up	0.15 (0.05-0.48)	0.001
Surgery		
Variable	Hazard ratio (95%CI)	P-value
Age in years	1.02 (1.001-1.03)	0.042
Alcohol consumption	0.64 (0.29-1.39)	0.218
Comorbidity	1.49 (0.96-2.31)	0.078
History of diverticulitis	1.30 (0.88-1.93)	0.190
Days of symptoms	1.01 (0.996-1.03)	0.136
Nausea	1.72 (1.03-2.85)	0.037
Vomiting	1.82 (1.13-2.93)	0.014
Diffuse abdominal pain	0.60 (0.29-1.25)	0.161
Distant abscess	0.72 (0.42-1.23)	0.221
Free air peridiverticular	1.39 (0.91-2.12)	0.129
Percutaneous abscess drainage	1.08 (0.69-1.69)	0.736

Abbreviations: CI= confidence interval

Discussion

The present study demonstrates that initial nonsurgical treatment of Hinchey Ib and II diverticular abscesses is comparable between patients treated with antibiotics only and those who undergo percutaneous drainage in combination with antibiotics, with regards to short- and long-term outcomes such as treatment failure, readmissions, emergency or elective surgery and mortality. Moreover, it shows that an abscess size of ≥ 3 cm is an independent risk factor for short-term treatment failure and an abscess size of ≥ 5 cm is an independent risk factor for short-term emergency surgery.

Previous studies on treatment outcomes of diverticular abscesses are often limited by factors such as small and single-institutional study populations, a lack of time-to-event analysis and short follow-up periods.^{10,12} Currently, the cohort of Hinchey stage Ib and II patients investigated by Gregersen et al.^{25,26} remains the largest cohort study reporting on both short- and long-term treatment outcomes ($n=3148$). However, an important limitation of their cohort is the absence of data on the clinical condition of the patients, as well as data on abscess size and location. This absence complicates comparison of treatment modalities, since - due to the introduction of selection bias and confounding - it may primarily reflect disease and clinical severity. Hence, with a total of 447 patients, the present study is the largest study which takes these patient and disease characteristics into account as well, and also assesses long-term outcomes. Indeed it is shown that patients undergoing PCD seem to have more advanced disease as compared to the no PCD group, considering that the majority of these patients had Hinchey stage II disease (84 vs 41%, $p<0.001$). Inherently, PCD patients had larger abscesses (6.4 [5.0-8.5] vs 3.6 [2.5-5.1] cm, $p<0.001$), as well as significantly more distant abscesses (30 vs 21%, $p=0.046$) or multiple abscesses present (20 vs 12%, $p=0.035$). Additionally, both CRP and WBC were higher amongst these patients.

The comparison of short- and long-term outcomes of Hinchey Ib and II patients in this cohort showed that Hinchey II patients more often needed emergency surgery (13% vs 5%, $p=0.018$), and, although not statistically significant, seemed to have more complications (26% vs 18%, $p=0.052$). Therefore, separate analyses on short- and long-term outcomes of both treatment groups were performed. However, except for a marginally significant difference in the number of short-term complications in Hinchey Ib patients in favor of patients treated without PCD (16 vs 39%, $p=0.048$), no further differences were found. This difference should however be interpreted with caution, particularly, because significance was not found in the additional hospital-adjusted analysis. More importantly, confounding

by indication cannot be excluded from this analysis and the difference may primarily reflect disease and clinical severity. In the long-term follow-up, Hinchey II patients treated with PCD seem to be at higher risk for sigmoid resection (32% vs 22%, $p=0.046$). In the multivariable analyses, the initial treatment strategy does not seem to be a predictor with regards to treatment failure, emergency surgery or sigmoid resection in long-term follow-up, strengthening the conclusion that treatment strategy has no effect on the outcome.

In general, short-term mortality ranged between 0-2% for both treatment groups, which compares equally to pooled average mortality rates as derived from previous studies on treatment with antibiotics (0.6%) and percutaneous drainage (1.6%).¹⁴ Furthermore, short-term emergency surgery rates ranged from 5% (Hinchey Ib) to 10% (Hinchey II) in the no PCD group and 6% (Hinchey Ib) to 15% (Hinchey II) in the PCD group, both of which are also largely in accordance with the earlier described pooled average of 12.1%.¹⁴ Reported diverticulitis recurrence rates vary from 3% to 68%, with a 28% average, and consist mostly of uncomplicated or locally complicated diverticulitis.¹⁰ Although these percentages may vary between studies because of differences in median follow-up period or use of definitions, the reported recurrence rates in the present study, seem to be in line with these earlier reports. In the light of the long-term surgery and recurrence rates found in this study, which were relatively low (and the recurrences mostly uncomplicated), it can be questioned if elective surgery is indicated in conservatively managed patients, as surgery comes with inherent complication risk and most patients seem to fare well with only conservative management.

The rates of adverse and unwanted outcomes in patients with diverticular abscess remain to be high and, self-evidently, present a major burden to the patient, as well as to associated healthcare costs. Therefore, the aim of this study was to identify potential risk factors related to these adverse outcomes in order to help improve case-by-case patient management. The results showed abscess size to be an independent predictor of adverse outcome, since an abscess size of ≥ 3 cm increased the risk of short-term treatment failure (OR 2.05, 95%CI 1.09-3.86), whereas a size of ≥ 5 cm increased the risk of emergency surgery (OR 2.91, 95%CI 1.03-8.23). These results seem to support and acknowledge that a cut-off value of 3 cm is appropriate to differentiate between small and large abscesses, and subscribe earlier reports that abscesses smaller than 3 cm can be appropriately managed without PCD.^{11,13,17,27,28} However, for abscesses larger than 3 cm, and particularly those larger than 5, it can still be debated which treatment strategy is most appropriate, as the results show no definite advantage of one strategy

over the other in short-term outcomes. An important limitation of this study is its retrospective design, which introduces the potential for selection bias and confounding by indication. However, registration of a wide range of baseline patient and disease characteristics allowed the correction for potential known confounders with multivariable logistic and Cox regression analyses. Another inevitable consequence of retrospective observational research is the potential risk of missing data, since availability of baseline and outcome data is largely dependent on the completeness of medical records. To prevent selection bias introduced by missing data, multiple imputation methods were used to handle the missing data. Sensitivity analyses on the non-imputed dataset did not significantly change the results, except for the multivariable Cox regression analysis on risk factors for sigmoid resection in the long-term follow-up, where no significant predictors were found. With regards to outcome data, it is possible that patients might have received care at the general practitioner or in other hospitals during follow-up, creating the potential for an underestimation of disease recurrences and readmissions. Lastly, the multicenter setting of this study could have introduced heterogeneity through between-hospital differences in treatment protocols. However, these differences were considered small, since all hospitals base their practice on the national guideline on the treatment of acute diverticulitis and hospital-adjusted analyses showed similar outcomes. In addition, the multicenter setting had beneficiary effects by increasing both the study's generalizability and sample size. In conclusion, this is the largest cohort of patients with Hinchey stage Ib and II abscesses reporting on abscess- and disease characteristics and assessing short- and long-term outcomes of nonsurgical treatment. It provides evidence that patients with abscesses smaller than 3 cm can be managed without PCD, whereas patients with abscesses larger than 3 and 5 cm, respectively, are at a higher risk of short-term treatment failure or emergency surgery, irrespectively of nonsurgical treatment strategy. Since no clear difference between both treatment strategies was found, it still remains debatable how to appropriately treat the latter groups of patients. Nevertheless, these data help facilitate informed and shared decision-making, as well as provide valuable information for future prospective studies regarding PCD treatment in patients with abscess formation.

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Supplementary material

Kaplan Meier curve Time To Recurrence in Hinchey IB patients

Supplementary figure 1 *Survival analysis Recurrence in Hinchey IB patients*

Kaplan Meier Curve Time To Operation in Hinchey IB patients

Supplementary figure 2 *Survival analysis Operation in Hinchey IB patients*

Kaplan Meier Curve Time To Recurrence in Hinchey II patients

Supplementary figure 3 *Survival analysis Recurrence in Hinchey II patients*

Kaplan Meier Curve Time To Operation in Hinchey II patients

Supplementary figure 4 *Survival analysis Operation in Hinchey II patients*

Supplementary Table 1 Univariable logistic regression analysis of Risk factors for ST treatment failure and emergency surgery

	Treatment failure (N=120)	Odds ratio (95%CI)	P-value	Emergency Surgery (N=40)	Odds ratio (95%CI)	P-value
Patient demographics						
Gender, N male (%)	48 (40%)	0.96 (0.63-1.47)	0.852	13 (32%)	0.62 (0.31-1.26)	0.189
Age in years, mean (SD)	62 (13)	1.01 (1.00-1.03)	0.140	63 (13)	1.01 (0.99-1.04)	0.397
BMI kg/m ² , mean (SD)	26.6 (5.5)	0.95 (0.89-1.01)	0.074	26.7 (6.1)	0.96 (0.85-1.08)	0.437
Smoking, N (%)	63 (53%)	1.10 (0.55-2.19)	0.779	23 (59%)	1.40 (0.66-2.97)	0.372
Alcohol consumption, N (%)	53 (44%)	0.64 (0.39-1.05)	0.074	12 (31%)	0.36 (0.14-0.88)	0.027
Comorbidities						
ASA >II, N (%)	37 (31%)	1.25 (0.79-1.98)	0.342	15 (38%)	1.74 (0.88-3.43)	0.113
Patients with registered comorbidity, N (%)	82 (68%)	1.54 (0.99-2.40)	0.058	27 (69%)	1.51 (0.74-3.06)	0.257
Medical history						
History of diverticulitis, N (%)	39 (33%)	1.13 (0.72-1.77)	0.600	14 (36%)	1.30 (0.65-2.59)	0.454
History of abdominal surgery, N (%)	43 (36%)	1.11 (0.71-1.73)	0.644	19 (49%)	1.99 (1.03-3.85)	0.042
Medication						
NSAIDs prescription, N (%)	39 (33%)	0.59 (0.27-1.27)	0.159	8 (21%)	0.34 (0.12-1.01)	0.052
Steroids prescription, N (%)	9 (8%)	0.67 (0.30-1.52)	0.337	3 (8%)	0.70 (0.19-2.60)	0.596
Clinical symptoms						
N days of symptoms, median (IQR)	7 (3-13)	1.00 (0.98-1.02)	0.950	10 (4-18)	1.02 (1.00-1.05)	0.058
Nausea, N (%)	71 (60%)	1.43 (0.89-2.30)	0.134	28 (72%)	2.40 (1.13-5.10)	0.023
Vomiting, N (%)	29 (24%)	0.97 (0.55-1.72)	0.916	12 (31%)	1.35 (0.57-3.23)	0.490
Diffuse abdominal pain, N (%)	15 (13%)	0.90 (0.39-2.06)	0.798	4 (10%)	0.71 (0.13-3.95)	0.680
Change in bowel habit, N (%)	78 (65%)	0.98 (0.59-1.63)	0.928	26 (67%)	1.08 (0.40-2.95)	0.869
Rectal blood loss, N (%)	20 (17%)	1.12 (0.61-2.07)	0.710	8 (21%)	1.47 (0.59-3.70)	0.408
Clinical signs						
Rebound tenderness, N(%)	38 (32%)	0.99 (0.59-1.68)	0.983	18 (46%)	2.08 (1.02-4.23)	0.043
Local muscular guarding/resistance, N (%)	35 (32%)	1.24 (0.76-2.05)	0.394	11 (28%)	1.14 (0.51-2.56)	0.745
Diffuse muscular guarding, N (%)	14 (12%)	1.08 (0.45-2.56)	0.858	4 (10%)	0.90 (0.19-4.19)	0.885
Temperature degrees Celsius, mean (SD)	37.8 (0.9)	1.11 (0.84-1.47)	0.436	37.9 (0.9)	1.31 (0.89-1.91)	0.171

Supplementary Table 1 Continued

	Treatment failure (N=120)	Odds ratio (95%CI)	P-value	Emergency Surgery (N=40)	Odds ratio (95%CI)	P-value
Laboratory parameters						
CRP mg/L, mean (SD)	179 (117)	1.001 (1.00-1.003)	0.183	204 (104)	1.003 (1.000-1.006)	0.037
WBC x10 ⁹ /L, mean (SD)	15.1 (5.2)	1.02 (0.97-1.06)	0.492	15.5 (6.3)	1.03 (0.96-1.10)	0.455
Radiological parameters						
Hinchey II, N (%)	70 (58%)	1.44 (0.88-2.37)	0.147	27 (69%)	2.40 (1.04-5.54)	0.040
Largest abscess diameter (cm), median (IQR)	4.8 (3.2-6.3)	1.08 (1.00-1.17)	0.051	5.6 (4.2-7.8)	1.20 (1.08-1.35)	0.001
Location abscess distant, N (%)	26 (22%)	0.85 (0.52-1.41)	0.530	8 (21%)	0.81 (0.36-1.83)	0.619
Multiple abscesses present, N (%)	16 (13%)	0.92 (0.50-1.69)	0.780	7 (41%)	1.38 (0.58-3.27)	0.471
Free air peridiverticular, N (%)	34 (28%)	0.88 (0.55-1.43)	0.461	10 (26%)	0.69 (0.31-1.57)	0.376
Free air abdomen, N (%)	16 (13%)	1.09 (0.47-2.53)	0.843	4 (10%)	0.74 (0.13-4.24)	0.714
Free fluid, N (%)	23 (19%)	0.92 (0.47-1.81)	0.801	9 (23%)	1.17 (0.50-2.77)	0.714
Treatment						
Antibiotics only, N (%)	79 (66%)	0.56 (0.36-0.89)	0.014	24 (60%)	0.48 (0.25-0.94)	0.033
Percutaneous abscess drainage, N (%)	41 (34%)	1.77 (1.12-2.80)	0.014	16 (40%)	2.07 (1.06-4.06)	0.033

*Hinchey 2 is defined as abscess ≥ 5 centimeter in diameter and/or distant abscess

Abbreviations: N= number, CI= confidence interval, SD = standard deviation, BMI= Body Mass Index, ASA= American Society of Anesthesiologists, NSAIDs= non-steroidal anti-inflammatory drugs, IQR= inter quartile range, CRP = C-reactive protein, WBC= white blood cell count

Supplementary Table 2 Univariable Cox regression analysis of Risk factors for recurrence and surgery in LT follow-up

	Recurrence (N=122)	Hazard ratio (95%CI)	P-value	Surgery (N=124)	Hazard ratio (95%CI)	P-value
Patient demographics						
Gender, N male (%)	54 (44%)	1.16 (0.81-1.66)	0.407	48 (39%)	0.86 (0.72-1.04)	0.860
Age in years, mean (SD)	59 (13)	0.99 (0.98-1.00)	0.084	62 (12)	1.01 (1.01-1.02)	0.053
BMI kg/m ² , mean (SD)	28.1 (5.7)	1.01 (0.96-1.05)	0.821	28.2 (5.9)	1.00 (0.97-1.04)	0.886
Smoking, N (%)	64 (52%)	1.09 (0.74-1.61)	0.664	65 (52%)	1.12 (0.65-1.94)	0.657
Alcohol consumption, N (%)	61 (50%)	0.90 (0.57-1.41)	0.632	57 (46%)	0.65 (0.36-1.17)	0.135
Comorbidities						
ASA >II, N (%)	32 (26%)	0.95 (0.64-1.43)	0.819	35 (28%)	1.17 (0.96-1.43)	0.423
Patients with registered comorbidity, N (%)	75 (61%)	1.08 (0.75-1.56)	0.665	85 (69%)	1.61 (1.10-2.36)	0.014
Medical history						
History of diverticulitis, N (%)	46 (38%)	1.51 (1.04-2.18)	0.030	41 (33%)	1.29 (0.89-1.88)	0.177
History of abdominal surgery, N (%)	30 (25%)	0.60 (0.40-0.91)	0.016	44 (35%)	1.16 (0.80-1.69)	0.429
Medication						
NSAIDs prescription, N (%)	61 (50%)	1.52 (0.71-3.24)	0.242	53 (43%)	0.97 (0.39-2.42)	0.942
Steroids prescription, N (%)	15 (12%)	1.44 (0.76-2.73)	0.263	9 (7%)	0.70 (0.32-1.50)	0.352
Clinical symptoms						
N days of symptoms, median (QR)	7 (3-13)	0.998 (0.98-1.02)	0.841	7 (4-15)	1.01 (1.00-1.03)	0.095
Nausea, N (%)	68 (56%)	1.16 (0.79-1.70)	0.454	81 (65%)	2.18 (1.41-3.37)	0.001
Vomiting, N (%)	34 (28%)	1.24 (0.83-1.85)	0.293	47 (38%)	2.42 (1.64-3.58)	<0.001
Diffuse abdominal pain, N (%)	12 (10%)	0.63 (0.25-1.56)	0.297	13 (10%)	0.63 (0.34-1.19)	0.156
Change in bowel habit, N (%)	80 (66%)	0.99 (0.62-1.57)	0.949	83 (67%)	1.04 (0.50-2.18)	0.904
Rectal blood loss, N (%)	22 (18%)	1.21 (0.72-2.03)	0.467	17 (14%)	1.02 (0.57-1.84)	0.953

Supplementary Table 2 Continued

	Recurrence (N=122)	Hazard ratio (95%CI)	P-value	Surgery (N=124)	Hazard ratio (95%CI)	P-value
Clinical signs						
Rebound tenderness, N(%)	31 (25%)	0.71 (0.46-1.12)	0.140	30 (24%)	0.72 (0.42-1.25)	0.237
Local muscular guarding/resistance, N (%)	29 (24%)	0.88 (0.55-1.41)	0.598	30 (24%)	0.94 (0.59-1.48)	0.784
Diffuse muscular guarding, N (%)	16 (13%)	1.26 (0.72-2.23)	0.418	16 (13%)	1.09 (0.39-3.08)	0.852
Temperature degrees Celsius, mean (SD)	37.8 (0.9)	1.11 (0.91-1.34)	0.309	37.7 (1.0)	0.98 (0.78-1.23)	0.845
Laboratory parameters						
CRP mg/L, mean (SD)	161 (111)	0.999 (0.997-1.001)	0.437	159 (97)	0.999 (0.998-1.001)	0.469
WBC x10 ⁹ /L, mean (SD)	14.7 (5.5)	0.99 (0.96-1.03)	0.660	14.4 (5.6)	0.98 (0.94-1.02)	0.369
Radiological parameters						
Hinchey II*, N (%)	61 (50%)	0.93 (0.64-1.35)	0.696	60 (48%)	0.95 (0.65-1.38)	0.777
Largest abscess diameter (cm), median (IQR)	4.1 (2.7-6.0)	0.97 (0.89-1.06)	0.473	4.4 (2.8-6.2)	1.04 (0.97-1.11)	0.313
Location abscess distant, N (%)	25 (20%)	0.84 (0.54-1.30)	0.438	23 (19%)	0.72 (0.45-1.13)	0.147
Multiple abscesses present, N (%)	19 (16%)	1.14 (0.70-1.87)	0.594	19 (15%)	1.17 (0.91-1.50)	0.527
Free air peridiverticular, N (%)	35 (29%)	0.82 (0.51-1.32)	0.409	47 (38%)	1.29 (0.88-1.90)	0.193
Free air abdomen, N (%)	15 (12%)	0.99 (0.57-1.73)	0.972	17 (14%)	1.05 (0.40-2.76)	0.910
Free fluid, N (%)	22 (18%)	0.85 (0.52-1.38)	0.509	24 (19%)	1.05 (0.66-1.67)	0.838
Treatment						
Antibiotics only, N (%)	93 (76%)	1.13 (0.75-1.72)	0.557	87 (70%)	0.70 (0.48-1.01)	0.065
Percutaneous abscess drainage, N (%)	29 (24%)	0.88 (0.58-1.34)	0.557	37 (30%)	1.44 (0.99-2.08)	0.065
Sigmoid resection	3 (2%)	0.16 (0.05-0.52)	0.002	0 (0%)	N/A	N/A

*Hinchey 2 is defined as abscess ≥5 centimeter in diameter and/or distant abscess

Abbreviations: N= number, CI= confidence interval, SD= standard deviation, BMI= Body Mass Index, ASA= American Society of Anesthesiologists, NSAIDs= non-steroidal anti-inflammatory drugs, IQR= inter quartile range, CRP = C-reactive protein, WBC= white blood cell count

Supplementary Table 3 Sensitivity analyses of Short- and long-term outcomes comparing Hinchey IB and II patients

	Total (N=447)	Hinchey IB (N= 215)	Hinchey II (N=232)	P-value	Hospital Adjusted P-value	P-value NI
Short-term outcomes						
Treatment failure	120 (27%)	50 (23%)	70 (30%)	0.127 ²	0.097	0.181 ²
Complications	100 (21%)	39 (18%)	61 (26%)	0.044 ²	0.059	0.114 ²
Readmission	71 (16%)	32 (15%)	39 (17%)	0.618 ²	0.603	0.778 ²
Persistent diverticulitis	63 (14%)	28 (13%)	35 (15%)	0.596 ²	0.522	0.652 ²
Emergency surgery (sigmoid resection)	40 (9%)	11 (5%)	29 (13%)	0.018 ²	0.026	0.004 ²
Mortality	5 (1%)	3 (1%)	2 (1%)	0.804 ¹	0.874	1.000 ¹
Long-term outcomes						
Recurrence	122 (27%)	61 (28%)	61 (26%)	0.665 ³	N/A	0.366 ³
Sigmoid resection	124 (28%)	63 (29%)	61 (26%)	0.675 ³	N/A	0.204 ³
Elective surgery (sigmoid resection)	110 (25%)	57 (27%)	53 (23%)	0.651 ³	N/A	0.179 ³
Mortality	28 (6%)	10 (5%)	18 (8%)	0.162 ³	N/A	0.486 ³

Presented data are in N (%)

Abbreviations: PCD = percutaneous abscess drainage, NI = non-imputed dataset, N/A=not applicable

*Hinchey II is defined as abscess ≥ 5 centimeter in diameter and/or distant abscess

¹Fisher's exact test ²Pearson's Chi-square test ³Mantel-Cox log-rank test

Supplementary Table 4 Sensitivity analyses of Short- and long-term outcomes in Hinchey IB and II patients

Hinchey IB	Total (N= 215)	No PCD (N=197)	PCD (N=18)	P-value	P-value adjusted for hospital	P-value NI
Short-term outcomes						
Treatment failure	50 (23%)	44 (22%)	6 (33%)	0.359 ²	0.356	0.112 ²
Complications	39 (18%)	32 (16%)	7 (39%)	0.049 ²	0.053	0.007 ²
Readmission	32 (15%)	27 (14%)	5 (28%)	0.178 ²	0.279	0.030 ²
Persistent diverticulitis	28 (13%)	23 (12%)	5 (28%)	0.100 ²	0.064	0.015 ²
Emergency surgery (sigmoid resection)	11 (5%)	10 (5%)	1 (6%)	0.693 ²	0.663	1.000 ²
Mortality	3 (1%)	3 (2%)	0 (0%)	1.000 ³	0.876	1.000 ²
Long-term outcomes						
Recurrence	122 (27%)	61 (28%)	61 (26%)	0.665 ³	N/A	0.207 ³
Sigmoid resection	63 (29%)	57 (29%)	6 (33%)	0.474 ²	N/A	0.642 ³
Mortality	10 (5%)	8 (4%)	2 (11%)	0.162 ³	N/A	0.071 ³
Hinchey II						
Short-term outcomes						
Treatment failure	70 (30%)	35 (26%)	35 (36%)	0.149 ¹	0.683	0.355 ¹
Complications	61 (26%)	30 (22%)	31 (32%)	0.121 ¹	0.812	0.260 ¹
Readmission	39 (17%)	22 (16%)	17 (18%)	0.714 ¹	0.442	0.547 ¹
Persistent diverticulitis	35 (15%)	19 (14%)	16 (16%)	0.583 ¹	0.792	0.581 ¹
Emergency surgery (sigmoid resection)	29 (13%)	14 (10%)	15 (15%)	0.117 ¹	0.293	0.258 ¹
Mortality	2 (1%)	0 (0%)	2 (2%)	0.332 ²	0.736	0.208 ²
Long-term outcomes						
Recurrence	69 (30%)	45 (33%)	24 (25%)	0.349 ³	N/A	0.973 ³
Sigmoid resection	61 (26%)	30 (22%)	31 (32%)	0.046 ³	N/A	0.016 ³
Mortality	18 (8%)	8 (6%)	10 (10%)	0.270 ³	N/A	0.636 ³

Presented data are in N (%)

Abbreviations: PCD = percutaneous abscess drainage, NI=non-imputed dataset, N/A=not applicable

¹Hinchey IB is defined as abscess <5 centimeter in diameter²Pearson's Chi-square test ³Fisher's exact test ³Mantel-Cox log-rank test

Supplementary Table 5 Sensitivity analysis multivariable logistic regression (short-term)

Treatment failure		Unadjusted		Adjusted for hospital		NI
Variable		Odds ratio (95%CI)	P-value	Odds ratio (95%CI)	P-value	P-value
Age (years)		1.001 (0.98-1.02)	0.955	1.000 (0.98-1.02)	0.987	N/A*
BMI (kg/m ²)		0.94 (0.89-0.997)	0.041	0.93 (0.88-0.99)	0.018	N/A*
Alcohol consumption		0.63 (0.36-1.10)	0.099	0.73 (0.38-1.42)	0.343	N/A*
Comorbidity		1.40 (0.85-2.29)	0.183	1.39 (0.83-2.33)	0.215	N/A*
NSAID prescription		0.58 (0.21-1.57)	0.242	0.62 (0.18-2.11)	0.403	N/A*
Nausea		1.32 (0.83-2.12)	0.245	1.28 (0.75-2.20)	0.365	N/A*
CRP (mg/L)		1.001 (0.998-1.003)	0.656	1.00 (0.997-1.003)	0.916	N/A*
Abscess ≥ 3cm		2.05 (1.09-3.86)	0.027	2.16 (1.11-2.30)	0.024	N/A*
Percutaneous drainage		1.47 (0.81-2.68)	0.185	1.28 (0.71-2.30)	0.416	N/A*
Emergency Surgery						
		Unadjusted		Adjusted for hospital		
Variable		Odds ratio (95%CI)	P-value	Odds ratio (95%CI)	P-value	
History of abdominal surgery		2.05 (1.04-4.05)	0.038	2.11 (1.04-4.27)	0.039	0.127
Rebound tenderness		2.03 (0.98-4.21)	0.058	2.18 (1.04-4.55)	0.038	0.093
Abscess ≥ 5cm		2.96 (1.08-8.13)	0.036	2.98 (1.06-8.43)	0.040	0.003
Percutaneous drainage		1.29 (0.56-2.99)	0.554	1.14 (0.47-2.78)	0.772	0.248

Abbreviations: CI= confidence interval, BMI = Body Mass Index, NSAIDs= non-steroidal anti-inflammatory drugs, CRP = C-reactive protein, ASA= American Society of Anesthesiologists. NI=non-imputed dataset N/A= not applicable
*too many missing variables for multiple logistic regression

Supplementary Table 6 Sensitivity analysis Cox regression (long-term)

Recurrence		Unadjusted		Adjusted for hospital		NI
Variable	Hazard ratio (95%CI)	P-value	Hazard ratio (95%CI)	P-value	Hazard ratio (95%CI)	P-value
Age in years	0.995 (0.98-1.01)	0.481	0.996 (0.98-1.01)	0.547	0.984	0.984
History of diverticulitis	1.71 (1.17-2.48)	0.005	1.77 (1.21-2.60)	0.003	0.009	0.009
History of abdominal surgery	0.63 (0.42-0.98)	0.040	0.63 (0.41-0.97)	0.052	0.024	0.024
Rebound tenderness	0.72 (0.46-1.13)	0.152	0.71 (0.44-1.15)	0.166	0.146	0.146
Sigmoid resection in short term follow-up	0.15 (0.05-0.48)	0.001	0.16 (0.05-0.51)	0.002	0.017	0.017
Surgery		Unadjusted		Adjusted for hospital		
Variable	Hazard ratio (95%CI)	P-value	Hazard ratio (95%CI)	P-value	Hazard ratio (95%CI)	P-value
Age in years	1.02 (1.001-1.03)	0.042	1.02 (1.002-1.03)	0.026	0.579	0.579
Alcohol consumption	0.64 (0.29-1.39)	0.218	0.54 (0.30-0.98)	0.043	0.593	0.593
Comorbidity	1.49 (0.96-2.31)	0.078	1.49 (0.96-2.33)	0.077	0.153	0.153
History of diverticulitis	1.30 (0.88-1.93)	0.190	1.50 (0.99-2.27)	0.058	0.803	0.803
Days symptoms	1.01 (0.996-1.03)	0.136	1.01 (0.99-1.03)	0.187	0.510	0.510
Nausea	1.72 (1.03-2.85)	0.037	1.72 (1.06-2.78)	0.028	0.190	0.190
Vomiting	1.82 (1.13-2.93)	0.014	1.67 (1.00-2.79)	0.051	0.891	0.891
Diffuse abdominal pain	0.60 (0.29-1.25)	0.161	0.52 (0.25-1.05)	0.069	0.552	0.552
Distant abscess	0.72 (0.42-1.23)	0.221	0.74 (0.41-1.35)	0.321	0.281	0.281
Free air peridiverticular	1.39 (0.91-2.12)	0.129	1.41 (0.89-2.22)	0.141	0.552	0.552
Percutaneous abscess drainage	1.08 (0.69-1.69)	0.736	0.92 (0.58-1.47)	0.731	0.890	0.890

Abbreviations: CI= confidence interval NI= non-imputed dataset

Chapter 8

Long term outcome of surgery versus conservative management for recurrent and ongoing complaints after an episode of diverticulitis; 5-year follow-up results of a multicenter randomized controlled trial (DIRECT-trial).

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Abstract

Objective

To establish whether surgical or conservative treatment leads to a higher quality of life (QoL) in patients with recurrent diverticulitis and/or ongoing complaints.

Summary background data

The six months' results of the DIRECT trial, a randomized trial comparing elective sigmoidectomy with conservative management in patients with recurrent diverticulitis (>2 episodes within 2 years) and/or ongoing complaints (>3 months) after an episode of diverticulitis, demonstrated a significantly higher QoL after elective sigmoidectomy. The aim of the present study was to evaluate QoL at 5-year follow-up.

Methods

From January 2010 to June 2014, 109 patients were randomized to either elective sigmoidectomy (N=53) or conservative management (N=56). In the present study the primary outcome was QoL measured by the Gastrointestinal Quality of Life Index (GIQLI) at five-year follow-up. Secondary outcome measures were SF-36 score, VAS pain score, EQ-5D-3L score, morbidity, mortality, perioperative complications and long-term operative outcome.

Results

At 5-year follow-up mean GIQLI score was significantly higher in the operative group (118.2 (SD 21.0)) compared to the conservative group (108.5 (SD 20.0)) with a mean difference of 9.7 (95%CI 1.7-17.7). All secondary QoL outcome measures showed significantly better results in the operative group, with a higher SF-36 physical ($p=0.030$) and mental score ($p=0.010$), higher EQ5D score ($p=0.016$) and a lower VAS pain score ($p=0.011$). Twenty-six (46%) patients in the conservative group ultimately required surgery due to severe ongoing complaints. Of the operatively treated patients, 8 (11%) patients had anastomotic leakage and re-interventions were required in 11 (15%) patients.

Conclusions

Consistent with the short term results of the DIRECT trial, elective sigmoidectomy resulted in a significantly increased QoL at 5-year follow-up compared to conservative management in patients with recurrent diverticulitis and/or ongoing complaints. Surgeons should counsel these patients for elective sigmoidectomy weighing superior quality of life, less pain and lower risk of new recurrences against the complication risk of surgery.

Introduction

Diverticulitis is currently ranked as the third most common gastrointestinal discharge diagnosis in the United States.¹ Approximately 20% of diverticulitis patients develops recurrences after a conservatively treated episode of diverticulitis and up to 33% can experience ongoing complaints.²⁻⁴ There has been major controversy on the use of elective sigmoidectomy to treat patients with recurrences and/or persistent symptoms. One of the concerns regarding this topic is the difficulty in distinguishing persistent symptoms after an episode of diverticulitis from Irritable Bowel Syndrome (IBS). As IBS is a functional disorder, operative treatment is obviously not the treatment of choice as it is unlikely to improve and might even fuel the symptoms. Moreover, operative intervention is associated with inherent complication risks, such as anastomotic leakage or abscess.⁴⁻⁷ Since (uncomplicated) diverticulitis is generally considered a mild and self-limiting disease, performing a potentially harmful procedure in these patients does not seem justified. Guidelines published by the American Society of Colon and Rectal Surgeons (ASCRS) in 2014 and the World Society of Emergency Surgery (WSES) in 2016 recommend a tailored approach for each individual patient where the impact of multiple recurrences and ongoing complaints on quality of life (QoL) should form the most decisive factor.^{8,9} It is therefore pertinent that the effect of elective sigmoidectomy on QoL in this patient group is better understood. Until recently only low quality data has been available on the operative and conservative management of recurrent diverticulitis and/or ongoing complaints, with both treatment strategies being reported as effective. The retrospective and heterogeneous nature of these studies impairs definitive conclusions. Moreover, none of these studies provide long-term follow-up data, which is of utmost importance in a disease with a chronic and recurrent nature.⁴ The DIRECT trial^{10,11} compared the effect of elective sigmoidectomy on QoL in patients with recurrent diverticulitis and/or ongoing complaints to conservative treatment in a randomized fashion. Although the study was prematurely terminated due to problems with patient accrual, the DIRECT trial¹⁰ demonstrated a significantly higher QoL at 6 months follow-up after elective sigmoidectomy compared to conservative management. The primary aim of the present study was to evaluate and compare QoL at 5-year follow-up, to determine whether the beneficial effect of surgical treatment on QoL is sustained throughout the years.

Methods

Study design and participants

The DIRECT trial^{10,11} was set up as a superiority trial, where operative intervention was expected to show higher increase of QoL compared to conservative treatment. The trial is registered with trialregister.nl, number NTR1478. The methodologic and operative details are described in the earlier published protocol and short-term results.^{10,11} Patients aged 18-75 years, who presented with either ongoing abdominal complaints (>3 months) and/or frequently recurrent left sided diverticulitis (>2 episodes within 2 years) after an objectified (CT-scan, ultrasonography or endoscopy) episode of diverticulitis were included. Ongoing abdominal complaints were defined as continuing lower left abdominal pain and/or changes in bowel habit and/or persistent blood loss. These ongoing complaints had to be accompanied by signs of persistent inflammation on either CT scan (bowel-wall thickening) or colonoscopy (hyperaemia) during outpatient visits. A minimal symptom free interval of 3 months between presentations was mandatory for it to be counted as a recurrence. Radiological examination was not mandatory to confirm recurrence. Patients were randomly assigned to receive either conservative or operative management (elective sigmoidectomy). The study was completed and approved in concordance to the declaration of Helsinki, Good Clinical Practice guidelines, and local ethical standards. Recruitment started at July 1, 2010 and the DIRECT trial^{10,11} was prematurely terminated at April 1, 2014. Main reason for this premature termination was the increasing difficulty of recruiting patients. The Consolidated Standards of Reporting Trials (CONSORT) analysis is illustrated in **figure 1**.¹² At termination, 431 patients had been screened. At this time 109 (25%) patients were included and randomly assigned to either surgical treatment (N = 53 (49%)) or conservative management (N = 56 (51%)). In the surgical group, five (9%) patients declined surgery and were treated conservatively. Of the 109 included patients, 108 were available for evaluation of subjective outcomes at five-year follow-up. All these patients were contacted by postal mail and telephone to fill out QoL questionnaires.

Elective sigmoidectomy and conservative management

Patients randomly assigned to receive elective surgery underwent an elective sigmoidectomy within three months after randomization, except for one patient who underwent surgery after one-year follow-up due to family circumstances. Laparoscopic surgery was the preferred approach in all cases. Following current guidelines, it was advised to place the distal margin of resection where the taenia coli splay out onto the upper rectum. For the proximal margin it was advised to

Figure 1 Study profile CONSORT analysis

resect in the area of pliable colon without hypertrophy or inflammation. Not all the diverticula-bearing colon had to be removed.^{10,13}

A primary anastomosis was intended in all patients who underwent surgery (i.e., both patients who were randomly assigned for resection and patients in the conservative group who underwent surgery), but if considered necessary a (temporary) loop ileostomy was created.^{10,11}

Patients randomized for conservative management were treated according to the current daily practice in the Netherlands; this treatment could consist of intensive monitoring, life style measures, supplementary dietary fibre, analgesics or laxatives when indicated to be needed by the treating physician. Antibiotics or the use of mesalazine was not routinely advised. If patients repeatedly presented themselves to the hospital with severe abdominal complaints, resection could be offered irrespective of assigned treatment. No absolute criteria for severe abdominal complaints were used to define whether a patient was allowed to undergo resection. Instead, a pragmatic approach was chosen in which it was left at the patient's and physician's discretion whether or not the symptoms were deemed too unbearable to pursue a conservative strategy.^{10,11}

Outcome parameters

The primary endpoint of the present study was QoL at 5-year follow-up measured by the Gastro-intestinal Quality of life Index (GIQLI).¹³ The minimal clinically important difference (MID) of the GIQLI score is estimated at 10 points.¹⁴⁻¹⁷ Thus, a 10 point increase on the GIQLI score corresponds with a clinically relevant positive effect on QoL. Secondary endpoints included additional QoL assessments using the EuroQol-5D-3L (EQ-5D), Visual Analogue Score for pain (VAS-pain) and the Short Form 36 health survey (SF-36).^{18,19} During the study follow-up patients were asked to fill out these questionnaires at regular time points (at inclusion and at 3, 6, 9 and 12 months and 5 years after inclusion or surgery (if randomized for surgery)). Short and long term outcomes of surgery were recorded including perioperative complications and any additional hospitalization and health care consumption of all included patients. The Clavien-Dindo classification was used in order to rank perioperative in-hospital complications in an objective and reproducible manner.²⁰

Statistical analysis

Power calculations are described in detail in previous protocol and post intervention publications.^{7,10} The original enrolment target was 214 patients, which provided 90% power to detect the MID of 10 points of the GIQLI score.¹⁴⁻¹⁷ Data were analyzed according to the intention-to-treat principle. All categorical variables were tabulated per randomization arm; continuous variables were displayed as mean with standard deviation (SD) or median with inter quartile range (IQR) according to their distribution. The paired samples T-test was used to determine significant within-group effects of the intervention (operative or conservative) on QoL (GIQLI score). The difference between the groups over time was analyzed using a mixed model with repeated measures and included all available data from patients for the five-year follow-up. The variance-covariance matrix was modeled as unstructured. The fixed effects were time (categorical), treatment group, a group*time interaction and the baseline GIQLI. The difference in GIQLI at five-year follow-up was tested using a linear contrast from this model. Differences were considered statistically significant with a p-value <0.05.

To test whether the effect of treatment on the GIQLI score was different for the recurrent and ongoing complaints group, a fully stratified model (with interactions for time, treatment group and time*treatment with stratification group) was compared to the model above. A likelihood ratio test (LRT) was used to compare the models with and without interactions for stratification group.

An additional per protocol analysis was performed to test whether protocol violations had any influence on the primary outcome. All analyses were performed using the statistical software package SPSS 24.0 (IBM Corporation, New York, USA).

Results

Baseline characteristics and completeness of follow-up

Baseline characteristics are shown in **table 1** and were comparable for both groups. There was a lower percentage of men in the operative group (28% vs 43%), but this difference was not statistically significant ($p=0.113$). The mean (SD) follow-up time was 61 (12) months for the operative group and 58 (12) months for the conservative group. One patient in the conservative group died due to non-

Table 1 Baseline characteristics

	Operative (N=53)	Conservative (N=56)
General Characteristics		
Sex (male)	15 (28%)	24 (43%)
Age (years) at inclusion	54.0 (44.5-61.5)	56.0 (47.3-63.0)
Age (years) at five year follow-up	58.0 (50.0-67.0)	60.5 (53.3-68.8)
BMI	28.7 (4.7)	27.8 (4.9)
ASA classification		
I	26 (49%)	26 (46%)
II	27 (51%)	29 (52%)
III	0 (0%)	1 (2%)
Stratification		
Recurring diverticulitis	17 (32%)	23 (41%)
Ongoing complaints	36 (68%)	33 (59%)
Quality of Life*		
VAS-pain	63.3 (21.7)	69.3 (13.6)
GIQLI	93.7 (22.6)	92.2 (21.3)
SF-36 physical	39.5 (8.4)	38.2 (8.0)
SF-36 mental	42.2 (14.0)	44.1 (9.2)
EQ-5D	0.69 (0.21)	0.74 (0.20)
Follow-up interval (months)	61 (12)	58 (11)

Data are N(%), mean (SD) or median (IQR)

* GIQLI: Gastrointestinal Quality of Life Index (score range: 0-144) VAS-pain: Visual Analogue Scale for pain (score range: 0-100) SF-36: Short Form 36 (range 0-100 EQ-5D: EuroQol-5D (score range: 0-1)

diverticulitis related disease. Of the 108 patients who were eligible for evaluation of QoL, 88 patients (82%) had complete QoL questionnaires at 5-year follow-up, as depicted in **figure 1**. Eleven (10%) patients refused to fill out the questionnaires and 9 (8%) patients were lost to follow-up. The baseline characteristics of patients with missing data did not differ from the patients with complete QoL questionnaires (data not shown).

Quality of life

The primary outcome is presented in **table 2**. At 5-year follow-up mean GIQLI score was significantly higher in the operative group (118.2 (SD 21.0)) compared to the conservative group (108.5 (SD 20.0)) with a mean difference of 9.7 (95%CI 1.7 to 17.7, $p=0.018$). The GIQLI score improved by more than ten points (indicating a clinically relevant effect) in 24 (67%) patients in the operative group. In the conservative group 26 (57%) patients had more than 10 points improvement in GIQLI score, but 14 of these patients were actually treated operatively during follow-up due to severe ongoing abdominal complaints. No clinical effect (GIQLI score deteriorating or improving by less than 10 points) was measured in 11 (31%) patients in the operative group, compared to 16 (33%) in the conservative group. One (2%) patient in the operative group had a lower GIQLI score (more than 10 points lower than the baseline score) compared to 6 (13%) patients in the conservative group. **Figure 2a** shows the course of the GIQLI score throughout the long term study follow-up. In both treatment groups the mean GIQLI score improved significantly compared to baseline ($p<0.001$). The GIQLI score at 5-year follow-up was not significantly higher compared to the 6 months results in the operative group ($p=0.248$), but it was significantly higher in the conservative group ($p=0.033$). **Figure 2b** shows the average GIQLI difference (GIQLI score minus GIQLI baseline score) throughout the study follow-up. Average GIQLI improvement over the entire study follow-up was 19.1 (95%CI 14.4 to 23.9) points in the operative group compared to 9.7 (95%CI 5.4 to 14.0) points in the conservative group ($p=0.004$). No difference was found in treatment effect between the ongoing and recurrent complaints group (LRT p -value >0.05). **Table 2** also shows the results of the SF-36 score, VAS pain score and EQ5D score. All secondary outcome measures on QoL showed significantly better results in the operative group at five-year follow-up, with a higher SF-36 physical score ($p=0.030$), a higher SF-36 mental score ($p=0.010$), a higher EQ5D score ($p=0.016$) and a lower VAS pain score ($p=0.011$).

Table 2 Quality of life during 5 year follow-up per randomization group

	Surgical treatment group (N=53)	Conservative management group (N=56)	P*
GIQLI			
0 months	93.7 (22.6)	92.2 (21.3)	0.018
3 months	106.0 (23.7)	100.5 (22.1)	
6 months	115.6 (21.8)	100.5 (22.7)	
9 months	114.2 (24.6)	101.1 (24.8)	
1 year	112.8 (23.3)	101.2 (25.3)	
5 years	118.2 (21.0)	108.5 (20.0)	
VAS-pain			
0 months	63.3 (21.7)	69.3 (13.6)	0.011
3 months	37.2 (28.1)	49.2 (25.9)	
6 months	23.9 (23.4)	49.8 (22.2)	
9 months	30.0 (28.2)	46.2 (29.4)	
1 year	30.5 (29.6)	47.5 (25.1)	
5 years	28.6 (27.9)	44.1 (27.0)	
SF-36 physical			
0 months	39.6 (8.4)	38.2 (8.0)	0.030
3 months	44.3 (9.9)	40.4 (8.4)	
6 months	47.1 (10.1)	41.4 (8.8)	
9 months	46.9 (10.5)	39.8 (7.6)	
1 year	46.7 (9.6)	42.4 (9.8)	
5 years	47.6 (9.9)	42.6 (10.5)	
SF-36 mental			
0 months	42.2 (14.0)	44.1 (9.0)	0.010
3 months	44.7 (10.9)	45.7 (9.8)	
6 months	48.4 (11.2)	46.6 (10.1)	
9 months	47.9 (11.1)	46.5 (9.1)	
1 year	48.7 (10.2)	47.8 (9.6)	
5 years	50.7 (9.4)	46.0 (9.2)	
EQ-5D			
0 months	0.69 (0.21)	0.74 (0.20)	0.016
3 months	0.75 (0.25)	0.75 (0.18)	
6 months	0.84 (0.20)	0.73 (0.19)	
9 months	0.78 (0.26)	0.73 (0.24)	
1 year	0.84 (0.15)	0.76 (0.24)	
5 years	0.85 (0.18)	0.74 (0.21)	

Data are presented as mean (SD)

GIQLI: Gastrointestinal Quality of Life Index (score range: 0-144) VAS-pain: Visual Analogue Scale for pain (score range: 0-100) SF-36 = Short Form 36 (range 0-100), EQ-5D: EuroQol-5D (score range: 0-1)

*The p-value is from the difference between the two groups, based on a contrast from a mixed model

Figure 2 a) GIQLI score throughout study follow-up b) GIQLI difference throughout study follow-up

Per protocol analysis

In the per protocol analysis mean GIQLI score was 119.8 (SD 21.3) in the operatively managed group (N=48) compared to 108.7 (SD 16.2) in the conservative management group (N=30) with a mean difference of 11.1 (95%CI 1.8 to 20.3, p=0.020). Average GIQLI improvement over the entire study follow-up was 19.9

(95%CI 15.1 to 24.6) points in the operatively managed group compared to 6.1 (95%CI 0.5 to 11.7) points in the conservative management group ($p<0.001$).

Cross-overs

At 5-year follow-up 26 (46%) patients in the conservative group ultimately required surgery due to severe ongoing abdominal complaints. The GIQLI score of these patients was significantly lower at baseline compared to patients in the conservative group who did not require surgery (83.7 (SD 20.4) versus 99.6 (SD 19.5), $p=0.004$). All other baseline characteristics were comparable between these two groups (data not shown). **Figure 3** shows the GIQLI score throughout the study follow-up of the patients in the conservative group who were successfully treated conservatively and who ultimately required surgery. In the operatively treated group ($N=26$) GIQLI score improved significantly with an average of 21.2 (95%CI 11.2 to 31.2) points compared to baseline ($p<0.001$). In the successfully conservatively treated group ($N=30$) GIQLI score did not significantly improve compared to baseline with an average of 8.0 (95%CI -0.2 to 16.3) points ($p=0.056$).

Figure 3 GIQLI score throughout study follow-up of patients randomized to conservative treatment

Elective resection and perioperative complications

Table 3 shows the perioperative data of patients randomized for surgical treatment and patients randomized for conservative management that ultimately required resection during follow-up. In total, 74 patients were operated on; 48 (91%) in the operative group and 26 (46%) in the conservative group. Of these, 60 (81%) patients were operated on within 6 months after inclusion (47 in the operative group and 13 in the conservative group). **Figure 4** illustrates the time to operation of each individual patient in both groups. In 68 patients (92%) a laparoscopic approach was used, whereas six (8%) patients underwent open resection. In four (6%) patients conversion to open procedure was needed; two due to severe adhesions, in one patient due to insufficient length and in one patient no reason was noted.

Perioperative complications are shown in **table 3** and **online supplementary table 4**. Reinterventions were needed in 10 of 48 (21%) patients in the operative group vs 1 of 26 (4%) patients in the conservative group. Seven (15%) patients in the operative group had anastomotic leakage, which all occurred within the first 6 months of follow-up. In the conservative group, one (4%) patient who was operated after the first 6 months of follow-up had anastomotic leakage. In fourteen (19%) patients a protective stoma was created, of which 8 (57%) were created during reintervention for anastomotic leakage.

Long term surgical reinterventions

Eleven of the protective stomas were resolved within six months after initial surgery (ten in the operative group and one in the conservative group). At five-year follow-up only one patient in the operative group remained with a stoma. Average time between stoma creation and stoma reversal surgery was 123 (SD 70) days. Eight (17%) patients in the operative group and two (8%) patients in the conservative group required operative repair of an incisional or trocar site hernia (eight after laparoscopic surgery and two after open surgery). (**online supplementary table 4**)

Recurrent diverticulitis

In the conservative group 17 (30%) patients had one or more episodes of recurrent diverticulitis. These were all classified as Hinchey 1A²¹. Eleven of these patients had radiological examination to confirm the diagnosis. In the operative group six (11%) patients had an episode of recurrent diverticulitis. One of these patients had an episode before surgery was performed and one patient never underwent surgery. Four patients had an episode after elective sigmoidectomy. Three of

Table 3 Perioperative data of patients randomized for surgical treatment and patients randomized for conservative management that ultimately required resection during follow-up

	Surgical treatment group (N=53)	Conservative management group (N=56)
Surgical data		
Actually operated on	48/53 (91%)	26/56 (46%)
Technique		
Laparoscopic	47/48 (98%)	21/26 (80%)
Open	1/48 (2%)	5/26 (20%)
Conversion	3/48 (6%)	1/26 (4%)
Stoma	12/48 (25%)	2/26 (8%)
Stoma at 3 months after surgery	5/48 (10%)	2/26 (8%)
Stoma at 6 months after surgery	2/48 (4%)	1/26 (4%)
Stoma at long term follow-up	1/48 (2%)	0/26 (0%)
Time inclusion to surgery	49 (33-62)	221 (71-449)
Month 1	11/48 (23%)	2/26 (8%)
Month 2	25/48 (52%)	3/26 (12%)
Month 3	9/48 (19%)	3/26 (12%)
Month 4	0/48 (0%)	2/26 (8%)
Month 5	1/48 (2%)	0/26 (0%)
Month 6	0/48 (0%)	1/26 (4%)
≥ 7 months	1/48 (2%)	13/26 (50%)
Postoperative Care		
Surgical ward	45/48 (94%)	26/26 (100%)
Duration	6.0 (4.0-7.0)	5.0 (4.0-7.0)
ICU	3/48 (6%)	0/26 (0.0)
Duration	1.0 (1.0-1.0)	0.0 (0.0-0.0)
Perioperative complications[^]		
Re-interventions ^{^^}	10/48 (21%)	1/26 (4%)
Leakage	7/48 (15%)	1/26 (4%)
Clavien Dindo*		
Grade I	6	3
Grade II	7	3
Grade IIIa	0	0
Grade IIIb	9	1
Grade IV	2	0
Grade V	0	0
Grade 'd	0	0
Pathologic evaluation		
Inflammation	27/48 (56%)	11/26 (42%)
Abscesses	3/48 (6%)	3/26 (12%)
Covered perforation	0/48 (0%)	2/26 (8%)
Fibrosis	5/48 (10%)	2/26 (8%)

Data are N (%) or median (IQR)

[^]in hospital perioperative complications^{^^}including surgical, endoscopic or radiologic intervention

*absolute number of events per group

Figure 4 Time to operation of individual patients in both treatment groups

these patients were classified as Hinchey 1A²¹ (one proven by ultrasound and two patients had no radiological examination) and were treated conservatively. The fourth patient had a CT-proven perforated diverticulitis (Hinchey 3)²¹ in the descending colon just before the anastomosis and required resection of that part of the colon. All patients had repeated labs to confirm a recurrence. (**online supplementary table 4**)

Adverse events

A total of 225 (serious) adverse events occurred during 5-year follow-up in 82 (75%) patients, of which the majority (53%) were non-diverticulitis related events. In the operative group 37 (70%) patients suffered one or more (serious) adverse events compared to 45 (80%) patients in the conservative group. One patient in the conservative group died during follow-up due to a complicated course after Endoscopic Retrograde Cholangiopancreatography (ERCP) for a pancreas divisum. (**online supplementary table 4**)

Online supplementary Table 4 (*Serious*) *Adverse Events*

	All patients (N=109)	Surgical treatment group (N=53)	Conservative management group (N=56)
Patients suffered event	82	37	45
Total (Serious) Adverse Events	225	105	120
Perioperative complications	31	24	7
Anastomotic leakage	8	7	1
Wound dehiscence	1	1	0
Wound infection	4	2	2
Abscess	4	3	1
(intraluminal) bleeding	3	1	2
Ileus	4	4	0
Respiratory insufficiency	1	1	0
CPR in OR	1	1	0
Pneumonia	0	0	0
Urinary tract infection	2	1	1
Delirium	1	1	0
Electrolyte deficiency (stoma)	2	2	0
Long term complications			
Unbearable complaints	23	0	23
Recurrent diverticulitis	23	6	17
Symptomatic stenosis	6	5	1
Fistula	1	1	0
Ileus	5	1	4
Rectal blood loss	2	1	1
Incisional/ Trocar site hernia	10	8	2
Pulmonary embolus	3	2	1
Pneumonia	1	0	1
Acute coronary syndrome	2	1	1
Urinary tract infection	2	0	2
Hospital presentation unrelated to disease	115	56	59
Mortality	1	0	1

Discussion

At 5-year follow-up elective sigmoidectomy resulted in a significantly higher QoL (GIQLI score) compared to patients treated with conservative management. This is in line with the 6 months' results published earlier. All the other QoL questionnaires (SF-36 physical score, SF-36 mental score, VAS pain and EQ5D) also showed better results after operative intervention. These results, combined with results from

previous literature^{4,10}, indicate that operative intervention is more effective in terms of increasing QoL than conservative management in patients with recurrent diverticulitis and/or ongoing complaints.

The difficulties with study accrual in the DIRECT trial^{10,11} could have led to an overestimation of the treatment (elective sigmoidectomy) effect as the study was terminated before the targeted sample size was reached. However, this problem is usually seen in trials stopped prematurely due to benefit and the DIRECT trial^{10,11} was stopped due to problems with recruitment. On the other hand, the high number of cross-overs in the conservative group (46%) could have led to an underestimation of the treatment (elective sigmoidectomy) effect. This is subscribed by the fact that the difference in QoL was larger in the per protocol analysis (mean difference 11.1 (95%CI 1.8 to 20.3)) compared to the intention to treat analysis (mean difference 9.7 (95%CI 1.7 to 17.7)). The early termination illustrates the difficulty of trials comparing surgery with non-surgical management. Patients and clinicians both have their own individual preferences, with subsequent influence on counselling and inclusion. Patient recruitment for this study was time consuming and challenging due to the elaborate patient information necessary to explain the randomization between the surgery and conservative management group. We feel that this aspect makes this study unique and difficult to repeat.

The primary outcome of the present study was disease-specific QoL measured with the GIQLI score at five-year follow-up. A difference of ten points on the GIQLI scale is considered to be clinically relevant.¹⁴⁻¹⁷ At 6 months follow-up the GIQLI score was significantly higher in the operative group compared to the conservative group with a mean difference of 14.2 points (95%CI 7.2-21.1, $p<0.001$). In the operative group, the GIQLI score remained generally the same after 6 months follow-up ($p=0.248$), whereas the GIQLI score in the conservative group increased ($p=0.033$). The increase of QoL in the conservative group, resulted in a smaller difference of the GIQLI score between the operative and conservative group at five-year follow-up. The mean difference at five-year follow-up was 9.7 points (95%CI 1.7 to 17.7, $p=0.018$), which is lower than the MID of ten points, indicating that there might not be a clinically relevant effect. However, in the per protocol analysis the mean difference was 11.1 points (95%CI 1.8 to 20.3, $p=0.020$), indicating a clinically relevant effect. In the group of patients who were randomized to conservative management but ultimately required surgery due to severe ongoing complaints, mean GIQLI scores were low from baseline up to surgery and increased on average with 21.2 (95%CI 11.2 to 31.2, $p<0.001$) points after surgery. In the group of patients who were successfully treated conservatively, the GIQLI score did not

significantly increase compared to baseline ($p=0.056$). These findings suggest that the increase in QoL in the conservative group could be the result of surgical intervention in a large part (46%) of the conservative group (cross-overs).

The question arises whether elective resection should become treatment of choice in patients with recurrent diverticulitis and/or ongoing complaints. There is a challenge in selecting the patient group that is suitable for an operative treatment strategy. Patients with ongoing complaints after an episode of diverticulitis can present with IBS-like symptoms.²² It has even been suggested that diverticulitis can induce IBS, much like post-infectious IBS.²³ The distinction between IBS and ongoing complaints after an episode of diverticulitis is very important as IBS is a functional disorder and should not be treated surgically. The etiology of persistent pain after an episode of diverticulitis is not well understood. Overlapping underlying pathophysiological mechanisms with IBS such as low-grade inflammation, altered motility, visceral hypersensitivity and altered intestinal microbiota have been suggested by previous authors.²⁴⁻²⁸ A recently published study undermined the assumption of low grade inflammation in symptomatic diverticular disease as they reported no association between colonic diverticula and mucosal inflammation. However, they included patients with symptomatic colonic diverticulosis who underwent screening colonoscopy, rather than diverticulosis patients with objectified episodes of diverticulitis.²⁹ In the DIRECT trial ongoing complaints after an objectified episode of diverticulitis had to be accompanied by signs of persistent inflammation on either CT scan (bowel-wall thickening) or colonoscopy (hyperaemia) during outpatient visits. Despite these criteria, inflammation was reported in only 58% of the pathology reports of patients with chronic complaints. This could be due to the fact that low-grade chronic inflammation is not always detectable at pathological examination. The fact that patients with ongoing complaints reported higher QoL after elective sigmoidectomy compared to conservative treatment indicates that these symptoms have, unlike IBS, a more organic cause, originating from the diseased colon segment. Therefore, these patients are suitable for resection.

Operative intervention comes with inherent complication risks. In the DIRECT trial a total of eight out of 74 (11%) operatively treated patients had anastomotic leakage (seven patients in the operative group and one patient in the conservative group). This high rate of anastomotic leakage led to a high rate of protective stomas (14 (19%)), since 57% of these stomas were created during re-operation for anastomotic leakage. These figures are rather high compared to previous literature where anastomotic leakage rates of 1-6% and protective stoma rates

of 1-4% in laparoscopic surgery for diverticular disease are reported.³⁰⁻³³ Based on our data we could not find a clear reason for this high incidence, nor could we perform a formal regression analysis to identify factors that are associated with the high anastomotic leakage and protective stoma rate, because the absolute numbers were too small. The high incidence can only be explained by the fact that the DIRECT trial has been a pragmatic trial without specific selection of surgeons or centers, thus reflecting real complication rates. In the long term follow-up a total of ten (14%) patients required operative repair of an incisional or trocar site hernia (eight (12%) after laparoscopic surgery and two (20%) after open surgery). Two recently published meta-analyses reported slightly lower hernia rates for laparoscopic colorectal surgery (7-11%), and open surgery (14%).^{34,35} Remarkably, despite the high rates of (peri)operative complications, QoL was still higher in the operative group, strengthening our conclusion that elective surgery has an important impact on improvement of QoL.

The question remains whether the benefits of surgical intervention outweigh the risk of complications. The DIRECT study and previous literature demonstrated that patients with recurrent diverticulitis and/or ongoing complaints have on average 17-24% lower QoL compared to healthy individuals.^{10,18,36} After surgical intervention these patients reported equal QoL scores compared to healthy individuals, and these results are sustained throughout the five-year follow-up. Moreover, the majority of recurrences, as seen in the conservative group in 30% of patients, were prevented in the surgery group. The recurrence rate of 30% is rather high compared to previous literature²⁻⁴. This is probably due to the fact that our study population consists of patients with recurrent diverticulitis and/or ongoing complaints rather than patients with a first episode of diverticulitis and is therefore more prone for recurrences.³⁷ Interestingly, in the operative group four patients still had a recurrence after sigmoidectomy. One of these patients even had a perforation in the descending colon right before the anastomosis and one could argue that an inadequate resection has been performed in this patient. For the other three patients we cannot say this with certainty as one patient only had ultrasonography to confirm the diagnosis and two patients only repeated labs. The fact that almost 50% of the patients who were initially randomized to conservative management ultimately required elective sigmoidectomy due to persistent severe abdominal complaints, indicates that this patient group is in need for a more aggressive therapeutic approach. We could not find any predictive factors for conservative treatment failure, except for QoL at baseline which was significantly lower in the group of patients who ultimately required surgery

compared to the patients in the conservative group who were successfully treated conservatively. This emphasizes the recommendations of the ASCRS⁸ and WSES⁹ that the impact of multiple recurrences and ongoing complaints on QoL should form the most decisive factor in selecting patients for operative intervention. Since the disease burden of recurrent diverticulitis and/or ongoing complaints is high and the beneficial effect on QoL has been established, we feel that elective resection should be offered more routinely to this patient group, naturally taking into account patients' personal risk profile. The authors acknowledge the fact that the included patients came from a selected population who were already in the secondary care circuit. Results are therefore not directly applicable to all patients with frequently recurrent diverticulitis or persistent complaints after an episode in general. Moreover, the percentage of men in our study population seems a bit low (36% of all 109 study patients), especially in the surgical group (28%). There was however no difference in sex between the surgical and conservative group ($p=0.113$) and when we looked at the cross-overs specifically, sex was not a predictor for conservative treatment failure ($p=0.983$). Previous studies report contrastingly about the sex distribution in diverticulitis. Earlier studies showed a higher incidence of diverticulitis in men³⁸, while later studies show a higher incidence of diverticulitis in women, with an average of 60% female.^{39,40} This percentage is in line with the sex distribution in the DIRECT trial. Taking all the above in account, we urge surgeons and gastroenterologists to consider and discuss operative intervention more frequently if patients present with frequent diverticulitis (> 2 episodes within 2 years) or persistent complaints (> 3 months). Physicians need to distinguish ongoing complaints from IBS, before they resort to operative intervention. An objectified preceding diverticulitis episode is therefore imperative and preferably signs of persistent inflammation on either CT scan (bowel-wall thickening) or colonoscopy (hyperaemia) are seen to accompany these persistent complaints. As the disease burden is subjective and varies between patients, physicians should weigh the disease burden and potential gain in QoL against the risks of operative intervention in collaboration with the patient to come to the decision whether or not to operate. Since this decision is complicated and requires experience and expertise, this should preferably be done in a dedicated colorectal team/center.

Consistent with the short term results of the DIRECT trial, elective sigmoidectomy resulted in a significantly increased QoL at 5-year follow-up compared to conservative management. On the one hand, surgery is accompanied by about 11% anastomotic leakage and 15% of surgically treated patients underwent

reinterventions. On the other hand, the majority of recurrences, as seen in the conservative group in 30% of patients, were prevented in the surgery group. Surgeons should therefore counsel patients for elective sigmoidectomy in case of recurrent diverticulitis and /or ongoing complaints after an episode of left sided diverticulitis weighing superior quality of life, less pain and lower risk of new recurrences against the complication risk of surgery.

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Chapter 9

Cost-effectiveness analysis of a multicenter
randomized controlled trial comparing
surgery versus conservative management
for recurrent and ongoing diverticulitis
(DIRECT-trial)

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Abstract

Background

The results of the DIRECT trial, a randomized controlled trial comparing conservative management with elective sigmoid resection in patients with recurrent diverticulitis or persistent complaints, showed that elective sigmoid resection leads to higher quality of life. The aim of this study is to determine the cost-effectiveness of surgical treatment at one and 5 year follow-up from a societal perspective.

Methods

Clinical effectiveness and resource use were derived from the DIRECT trial. The actual resource use and quality of life (EQ-5D-3L-score) were documented prospectively per individual patient and analyzed according to intention to treat principle for up to 5 year after randomization. The main outcome was the incremental cost-effectiveness ratio (ICER) expressed as costs per quality-adjusted-life-year (QALY).

Results

The study included 106 patients of whom 50 were randomized to operative treatment and 56 to conservative treatment. At one and 5 year follow-up an incremental effect (QALY difference between groups) of respectively 0.06 and 0.43 was found and an incremental cost (cost difference between groups) of respectively €6 957 and €2 674 was found, where surgery was more expensive than conservative treatment. This resulted in an ICER of €123 365 per additional QALY at one year follow-up and an ICER of €6 275 at 5-year follow-up. At a threshold of €20 000 per QALY, operative treatment has 0% probability of being cost-effective at one year follow-up, however at 5-year follow-up the probability is 95%.

Conclusion

At 5 year follow-up elective sigmoid resection in patients with recurrent diverticulitis or persistent complaints was found to be cost-effective.

Introduction

Diverticulosis is a very common disease, which poses a great financial burden on health care. It is one of the costliest gastro-intestinal diseases worldwide. In the United States the costs are estimated at 2.2 billion dollars per year.¹ Approximately 20% of patients develop recurrences after an initial episode of diverticulitis and up to 33% will continue to experience ongoing complaints such as pain and discomfort.^{2,3} Patients with recurrent diverticulitis or persistent complaints after an episode of diverticulitis can be treated either conservatively or surgically, but high-level evidence supporting either of these treatment strategies has been lacking. Traditionally elective resection was advised after a second episode of diverticulitis, since it was thought that patients with recurrent attacks were more likely to develop complications.⁴ Recent studies have proven that complications arise primarily in the first episode of diverticulitis and therefore resection for recurrent diverticulitis does not seem warranted to prevent complications.⁵ Quality of life (QoL) is therefore becoming the most important factor in the decision whether or not to perform elective sigmoid resection.^{3,6} The DIRECT trial was a multicenter randomized controlled trial comparing conservative management to elective sigmoid resection in patients with recurrent diverticulitis and/or ongoing complaints after an episode of left sided diverticulitis.⁷ The primary aim was to determine which treatment strategy leads to higher QoL. At six-months follow-up the study demonstrated a significant higher disease specific and generic QoL after elective sigmoid resection compared to conservative management⁸ and this persisted throughout the five-year follow-up.⁹ The aim of the present study was to assess the cost-effectiveness of surgical treatment versus conservative treatment alongside the DIRECT trial⁷ from a societal perspective at one and five-year follow-up.

Methods

Study design and participants

The DIRECT trial was designed as an open label, multicenter, randomized clinical trial. The trial is registered with [trialregister.nl](http://www.trialregister.nl), number NTR1478. The study design is described in detail elsewhere.⁷ Briefly, patients (18-75 years old) presenting with either recurrent or persistent abdominal complaints after an objectified (ultrasound, CT-scan or endoscopy proven) episode of left sided diverticulitis were included. Ongoing complaints were defined as ongoing left lower abdominal pain and/or persistent changes in bowel habits for a period of more than three months after an episode of diverticulitis. Frequently recurrent diverticulitis was defined

as a total of three or more presentations with clinical signs of acute diverticulitis within a period of two years. A minimal symptom free interval of 3 months between presentations was mandatory for it to be counted as a recurrence. Patients were randomly assigned to either conservative management or elective (laparoscopic) sigmoid resection. All patients signed informed consent before inclusion. When patients in the conservative group repeatedly presented themselves to the hospital with severe abdominal complaints, elective resection could be offered. It was at the patients' and physicians' discretion whether the complaints were deemed too unbearable to pursue a conservative strategy during the follow-up period.⁷

Economic evaluation

The present cost-effectiveness analysis of the DIRECT trial is performed according to guidelines for health economic analysis as issued by the Dutch Healthcare Institute.¹⁰ The primary outcome is the incremental cost-effectiveness ratio (ICER) expressed as costs per quality-adjusted-life-year (QALY) converted from The EuroQoL-5D (EQ-5D-3L) score.¹¹ The incremental effect is the difference in QALY between the two groups and the incremental costs are the difference in costs between the two groups. The ICER is then calculated by dividing the incremental costs by the incremental effect. The ICER was calculated from a societal perspective, thus including all direct and indirect costs (inside as well as outside the healthcare sector).

Quality adjusted life years

The EQ-5D-3L score was used to measure QoL at 3, 6, 9 and 12 months, and 3 and 5 years after inclusion or surgery (if randomized for surgery). The results of the EQ-5D-3L questionnaires were converted into utility values using the Dutch EQ-5D tariff. These utility values range from zero to one, where one represents optimal QoL.¹¹ QALYs were calculated by multiplying these utility values with the time spent in this health state, using interpolation between two observations. As QALY's were calculated over a 5-year time period, the maximal obtainable QALY was five (five multiplied by one (optimal EQ-5D-3L score)). Missing QoL data were handled using multiple imputation taking into account all other cost information, as well as age, gender, randomization group and treatment (e.g. whether the patient had actually received operative intervention or conservative management).¹²

Resource utilization

Resource use was prospectively documented at patient level in the DIRECT trial according to the predefined protocol.⁷ Resource use was documented within the clinical registration form or retrieved from the regular patient-reported questionnaires at inclusion and at 3, 6, 9 and 12 months and 3 and 5 years after inclusion or surgery (if randomized for surgery).

Direct medical costs included the primary surgery, primary hospital admission (ward and Intensive Care Unit stay), all additional procedures such as surgical re-interventions and percutaneous interventions, diagnostic imaging, outpatient consultation visits (with surgeon, gastroenterologist, occupational physician, general practitioner, physiotherapist), Emergency Room (ER) visits, readmissions, stoma care, stoma reversal surgery, medication, dietary costs and formal home care (nursing, personal care). Out of pockets costs (travel costs, dietary costs, other costs) and hours of informal home care were also collected with the regular patient-reported questionnaires at the aforementioned time points. Indirect non-medical costs resulting from absence from paid work or lowered productivity while at work were determined using the Health and Labour Questionnaire (HLQ)¹³, that was administered together with the cost questionnaire. The friction costs method was used to estimate the duration of lost productivity.¹⁴ The costs were estimated based on the age-adjusted average daily wages, as described in the Dutch guideline for health economic analysis.¹⁰ Missing cost data were handled using a multiple imputation model as described above.¹²

Unit costs

Table 1 shows the unit costs for different types of resource use. All cost figures reflect cost levels of 2014. Different sources were used to derive estimates of unit costs. The Dutch guideline on costing research in healthcare and the recommendations of the Dutch Health care authority (NZa) were used to estimate direct medical costs.^{10,15} The unit costs for the index operation were obtained from the hospital administration, based on bottom-up cost calculations. These bottom-up calculations were performed for each procedure (laparoscopic and open sigmoid resection, with or without protective stoma and (re)operations for adverse events). Procedure costs included costs for all reusable instruments and disposables, personnel costs per time unit and overhead costs. All healthcare consumption was valued at the level of units of consumption, not at the level of Diagnosis related groups.

Table 1 Unit cost per resource use variable

Variable	Unit cost (€)	Unit	Source
Surgery (including primary surgery and (re)operation for adverse events)			
Surgical instruments + disposables	110,85	Per operation	Meander Medical Centre
Operative time*	22	Per min	Meander Medical Centre
Specialist fee	116	Per hour	Dutch guideline ¹²
Length of hospital stay: ward	443	Per day	Dutch guideline ¹²
Length of hospital stay: ICU	2015	Per day	Dutch guideline ¹²
Stoma material	8	Per day with ileostomy	Pharmacy retail price
	13	Per day with colostomy	
Adverse events			
Treatment adverse event: percutaneous drainage	220,81	Per procedure	NZa ¹⁶
Treatment adverse event: dilatation	94,42	Per procedure	NZa ¹⁶
Diagnostic imaging/procedures			
Laboratory tests	28,80	Per test	Dutch guideline ¹²
Ultrasound	84,85	Per ultrasound	Dutch guideline ¹²
CT-scan	145	Per scan	Dutch guideline ¹²
MRI-scan	229	Per scan	Dutch guideline ¹²
Chest radiograph	55,81	Per radiograph	www.diagnostiekvoor.nl
Abdominal radiograph	84,85	Per radiograph	www.diagnostiekvoor.nl
Colonic radiograph	161,26	Per radiograph	www.diagnostiekvoor.nl
Colonoscopy	352,48	Per colonoscopy	NZa ¹⁶
Sigmoidoscopy	232,77	Per sigmoidoscopy	NZa ¹⁶
Other costs			
Emergency room	259	Per visit	Dutch guideline ¹²
General practitioner	33	Per visit	Dutch guideline ¹²
Outpatient clinic	73	Per visit	Dutch guideline ¹²
Occupational physician	136	Per visit	Arbored tariff 2015
Medication	variable	Per ATC code	Pharmacy retail price
Productivity loss	34,75	Per hour	Dutch guideline ¹²
Formal home care (nursing)	73	Per hour	Dutch guideline ¹²
Formal home care (caretaking)	50	Per hour	Dutch guideline ¹²
Formal home care (domestic help)	23	Per hour	Dutch guideline ¹²
Informal domestic help	14	Per hour	Dutch guideline ¹²

*Average costs, including personnel costs and overhead costs

Abbreviations: ICU = intensive care unit, NZa = Nederlandse Zorg Autoriteit (Dutch Healthcare Authority), ATC code = Anatomic Therapeutic Chemical code

Statistical Analysis

All patients were analyzed according to intention-to-treat principle. Continuous variables and outcomes are presented as means (with standard deviation (SD)) or medians (with inter quartile range (IQR)) according to their distribution. For the categorical variables and outcomes the counts and percentages are presented. The difference in EQ-5D score between the groups was analyzed using a mixed model with repeated measures over time and included all available data from patients for the first five years post-randomization. The variance-covariance matrix was modeled as unstructured. The fixed effects were time (categorical), treatment group, a group*time interaction and the baseline EQ-5D score. For the cost-effectiveness analysis, differences in total costs were compared with the differences in QALY's, derived from the EQ-5D score. The differences in total costs were analyzed with an independent-samples T-test. The bias-corrected and accelerated bootstrapping method (5000 replications) was used to estimate uncertainty around the cost-effectiveness ratios^{16,17} Furthermore, cost-effectiveness acceptability curves (CEACs) are presented to illustrate decision uncertainty.¹⁸ The CEAC shows the probability that elective sigmoid resection is cost-effective compared to conservative treatment for a range of threshold values for willingness to pay per additional QALY. A threshold value of €20 000 is commonly used in the Netherlands for relatively mild, non-lethal diseases.¹⁹ All analyses were performed using the statistical software package SPSS 24.0 (IBM Corporation, New York, USA).

Sensitivity analysis

Next to the societal perspective, cost-effectiveness was also calculated from a healthcare perspective, thus excluding all non-medical costs such as productivity losses, travel costs and informal home care.

Results

The Consolidated Standards of Reporting Trials (CONSORT) flowchart is illustrated in **figure 1**. Between 1 July 2010 and 1 April 2014, a total of 109 patients were enrolled in the DIRECT trial. Fifty-three patients were randomized for elective resection. In this group five (9%) patients declined surgery and were treated conservatively. Three of these patients contributed no data because they were lost to follow-up directly after they declined surgery and were therefore excluded from the analysis, leaving fifty patients for analysis. Fifty-six patients were randomized for conservative management. Twenty-six (46%) of these patients underwent surgery due to severe ongoing abdominal complaints during the

Figure 1 CONSORT flowchart

5-year follow-up period. One patient in the conservative group died due to non-diverticulitis related disease. Baseline characteristics were comparable for both groups, as shown in **table 2**.

Response rate to questionnaires

At 12 months follow-up complete data on resource use and productivity losses were available for 102 patients (96%) and 85 patients (80%) had complete QoL questionnaires. At 3-year follow-up this was the case for 27 (25%) patients and 27 (25%) patients respectively and at 5-year follow-up for 79 (75%) patients and 75 patients (71%) respectively. The baseline characteristics of responders did not differ from non-responders (data not shown).

Table 2 *Baseline characteristics*

	Operative (N=50)	Conservative (N=56)
General Characteristics		
Sex (male)	14 (28%)	24 (43%)
Age (years)	53.0 (43.8-61.3)	56.0 (47.3-63.0)
Body Mass Index	28.9 (4.7)	27.8 (4.9)
Patients with paid work	27 (54%)	31 (55%)
ASA classification		
I	24 (48%)	26 (46%)
II	26 (52%)	29 (52%)
III	0 (0%)	1 (2%)
Stratification		
Recurring diverticulitis	17 (32%)	23 (41%)
Ongoing complaints	33 (66%)	33 (59%)
Number of episodes before inclusion	2.6 (1.5)	3.1 (1.9)
Duration of symptoms (weeks)*	27.0 (13.8-53.8)	30.0 (16.3-63.0)
Hinchey Classification primary episode		
H1	34 (68%)	51 (91%)
H1B	9 (18%)	4 (7%)
H2	1 (2%)	0 (0%)
H3	1 (2%)	0 (0%)
H4	0 (0%)	0 (0%)
Undefined**	5 (10%)	1 (2%)
Medication		
Pain medication	12 (24%)	14 (25%)
Laxatives	22 (44%)	28 (50%)
Quality of Life***		
VAS-pain	60.8 (23.5)	67.8 (15.8)
GIQLI	92.6 (22.8)	92.2 (21.3)
EQ-5D	0.69 (0.21)	0.74 (0.20)

Data are N(%), mean (SD) or median (IQR)

*applies only to patients with ongoing complaints; **Five patients in the surgical group and one in the conservative group could not be classified because either an endoscopy was done or the Hinchey classification was not described in the radiological report; ***

Abbreviations: GIQLI: Gastrointestinal Quality of Life Index (score range: 0-144); VAS-pain: Visual Analogue Scale for pain (score range: 0-100); EQ-5D: EuroQol-5D (score range: 0-1)

Resource use

Table 3 lists the most commonly used healthcare resource items and productivity losses. Infrequently used healthcare resource items are not displayed but are included in the total costs. At one year follow-up, operative intervention was associated with longer hospitalisation and more diagnostic tests (laboratory tests and chest X-rays). At five year follow-up the difference in hospitalisation was less

Table 3 Mean (SD) resource utilization per treatment group

	1 year follow-up			5 year follow-up		
	Operative (N=50)	Conservative (N=56)	p-value	Operative (N =50)	Conservative (N=56)	p-value
Hospital stay (days)	9 (9)	4 (7)	0.002	12 (10)	8 (11)	0.055
Operative time (minutes)*	120 (28)	103 (32)	0.110	121 (29)	121 (56)	0.996
Diagnostic Imaging						
Abdominal ultrasound	0.4 (0.7)	0.2 (0.4)	0.072	0.6 (1.1)	0.5 (1.1)	0.354
CT abdomen	0.6 (0.9)	0.7 (1.0)	0.545	1.1 (1.9)	1.7 (2.5)	0.188
MRI abdomen	0.0 (0.0)	0.0 (0.1)	0.347	0.1 (0.3)	0.2 (0.5)	0.092
Chest X-ray	0.4 (0.1)	0.1 (0.3)	0.018	0.6 (1.7)	0.1 (0.5)	0.035
Abdominal X-ray	0.0 (0.2)	0.0 (0.1)	0.497	0.1 (0.2)	0.1 (0.4)	0.631
Colonic X-ray	0.0 (0.2)	0.0 (0.1)	0.497	0.0 (0.2)	0.0 (0.1)	0.530
Diagnostic procedures						
Colonoscopy	0.4 (0.7)	0.3 (0.6)	0.173	0.7 (1.2)	0.6 (0.8)	0.404
Laboratory tests	4.8 (3.7)	1.7 (2.9)	<0.001	6.8 (10.2)	3.9 (11.7)	0.179
ER visits	1.0 (1.1)	1.1 (1.1)	0.517	1.7 (1.6)	2.0 (1.8)	0.420
GP visits	3.3 (3.7)	4.1 (4.6)	0.304	6.8 (6.1)	11.2 (10.9)	0.012
OP visits**	0.9 (2.0)	0.6 (2.0)	0.374	1.6 (2.2)	2.2 (5.2)	0.438
Specialist visits	6.6 (5.0)	5.7 (3.8)	0.322	8.0 (7.4)	10.1 (11.0)	0.268
Productivity losses						
Absence from work (hours)**	228 (223)	187 (242)	0.519	236 (218)	229 (291)	0.919
Lost productivity while at work (hours)**	23 (44)	21 (38)	0.879	66 (107)	60 (98)	0.824

Numbers are in mean (SD)

*applies only to operated patients; **applies only to patients with paid work

Abbreviations; SD = standard deviation , ER = emergency room, GP = general practitioner, OP = occupational physician

pronounced. Operative intervention was still associated with more diagnostic tests (chest X-rays). Conservative treatment was associated with more general practitioner visits.

Costs

The mean costs (including mean differences) per patient group per resource use variable are shown in **table 4**. At one year follow-up total mean (SD) societal costs were €15 174 (12 778) for the operative group and €8 217 (10 398) for the conservative group. The mean cost difference between groups was €6 957

Table 4 Costs (€) per treatment group

	1 year follow-up			5 year follow-up		
	Operative (N=50)	Conservative (N=56)	Difference (95%CI)	Operative (N=50)	Conservative (N=56)	Difference (95% CI)
Hospitalization	4 683 (5 184)	1 867 (3 280)	2 816 (1 163 to 4 469)	5 779 (5 611)	3 778 (6 819)	2 001 (-430 to 1 981)
Operation	2 703 (1 105)	785 (1 253)	1 919 (1 461 to 2 376)	2 772 (1 038)	1 314 (1 588)	1 485 (934 to 2 025)
Stoma care	246 (518)	65 (333)	181 (-44 to 405)	443 (1 660)	106 (386)	337 (-323 to 997)
Imaging	150 (224)	133 (191)	17 (-64 to 97)	271 (444)	345 (452)	-73 (-246 to 100)
Diagnostic procedures	322 (335)	189 (305)	133 (9 to 256)	632 (746)	466 (1144)	166 (-210 to 543)
ER, GP, OP and outpatient visits	992 (848)	924 (608)	68 (-214 to 350)	1 490 (1 071)	1 914 (1603)	-424 (-966 to 108)
Productivity losses	5 150 (7 772)	3 973 (7 371)	1 177 (-1 741 to 4 094)	5 670 (7 939)	5 119 (9 104)	550 (-2 758 to 3 859)
Total healthcare costs	9 914 (7 838)	4 139 (4 844)	5 775 (3 220 to 8 329)	16 111 (10 701)	13 502 (12 442)	2 608 (-1 888 to 7 105)
Total societal costs	15 174 (12 788)	8 217 (10 398)	6 957 (2 487 to 11 428)	22 045 (14 454)	19 371 (17 721)	2 674 (-3 601 to 8 949)

Numbers are in mean (SD)

Abbreviations: CI = confidence interval, ER = emergency room, GP = general practitioner, OP = occupational physician

(95%CI 2 487 to 11 428, $p=0.003$). At five year follow-up total mean (SD) societal costs were €22 045 (14 454) for the operative group and €19 371 (17 721) for the conservative group. The mean cost difference between groups was €2 674 (95%CI -3 601 to 8 949, $p=0.400$). The cost-driving variables for both groups were operative time, length of hospital stay and productivity losses. Productivity losses throughout the study follow-up period are illustrated in **figure 2**. In the operative group, productivity losses were especially high in the first three months of follow-up, directly after elective sigmoid resection. After these first three months, productivity losses declined severely in the operative group and continued to be lower compared to the conservative group (except at one year follow-up, due to high productivity losses in one patient in the operative group who had not yet received surgery due to family circumstances). The difference in productivity losses were however not statistically significant ($p=0.095$ at one year follow-up and $p=0.215$ at 5 year follow-up).

Figure 2 Productivity losses of operative and conservative group during 5-year follow-up

High rates of anastomotic leakage strongly increased the costs in the intervention group. Seven patients (14%) had anastomotic leakage in the operative group. In the conservative group one (2%) anastomotic leakage occurred. Costs in the intervention group were also raised because of stoma care and stoma reversal

surgery. In fourteen patients a protective stoma was created (twelve in the operative group and two in the conservative group). Most protective stomata (57%) were created during re-operation for anastomotic leakage. Thirteen of these patients had stoma reversal surgery within one year follow-up (eleven in the operative group and two in the conservative group). Average time between stoma creation and stoma reversal surgery was 105 days. Nine (18%) patients in the operative group and two (4%) patients in the conservative group required operative repair of an incisional or trocar site hernia.

Quality of life

Figure 3 shows the course of the EQ-5D scores over time. At one year follow-up the mean EQ5D-scores of the operative and conservative group were 0.84 (SD 0.14) and 0.74 (SD 0.22) respectively ($p=0.003$). At five year follow-up EQ5D scores were significantly higher for operative treatment, with a mean EQ5D score of 0.82 (SD 0.18) in the operative group and 0.72 (SD 0.22) in the conservative group ($p=0.011$). The average EQ5D score over the entire study follow-up was 0.80 (95%CI 0.76-0.84) in the operative group compared to 0.71 (95%CI 0.67 to 0.74) in the conservative group ($p=0.001$).

Figure 3 EQ5D score of operative and conservative group during 5-year follow-up

Cost-effectiveness

At one year follow-up the bootstrapping method revealed an incremental effect (QALY difference between groups) of 0.06 and an incremental cost (cost difference between groups) of €6 957. This resulted in an ICER of €123 365 per additional QALY. The corresponding CEAC is shown in **figure 4** and illustrates that at the threshold of €20 000 per QALY, operative treatment has 0% probability of being cost-effective after 1 year. At five year follow-up the bootstrapping method revealed an incremental effect of 0.43 QALYs and an incremental cost of €2 674. This resulted in an ICER of €6 275 per additional QALY. The corresponding CEAC is shown in **figure 5** and illustrates that at the threshold value of €20 000 per QALY, operative treatment has 95% probability of being cost-effective after 5 years.

Figure 4 Cost-effectiveness acceptability curve at one-year follow-up

Figure 5 Cost-effectiveness acceptability curve at five-year follow-up

Sensitivity analyses

The costs and cost-effectiveness at five year follow-up were also calculated from a healthcare perspective which showed an incremental effect of 0.43 and incremental cost of €2 608. This resulted in an ICER of €6 110 per additional QALY. In this analysis operative treatment has 96% probability of being cost-effective, at the threshold of €20 000 per QALY. In the conservative group one patient had a very complicated course after Endoscopic Retrograde Cholangiopancreatography (ERCP) for a pancreas divisum which was accompanied by high costs. This patient eventually died after prolonged hospitalisation. An extra sensitivity analysis was performed to evaluate the effect of this outlier. When this patient was excluded from analysis mean cost difference between the operative and conservative group increased to €3 595 (95%CI -2 430 to 9 620, p-value = 0.239). QALY's remained higher in the operative group with a difference of 0.40 (95%CI 0.10 to 0.70, p-value = 0.010). Bootstrapping revealed an ICER of €9 072 per additional QALY. At a threshold of €20 000 per QALY, operative treatment still has 89% probability of being cost-effective.

Discussion

In this study we assessed the cost-effectiveness of elective sigmoid resection versus conservative management for patients with recurrent diverticulitis and/or ongoing complaints after an episode of left sided diverticulitis. The results add an economic perspective to the demonstrated efficacy of elective sigmoid resection in the DIRECT trial.^{8,9}

At one year follow-up the overall costs for elective sigmoid resection were, as anticipated, significantly higher than for conservative management. However, after five years the cost difference between the two groups was much less pronounced, due to rising costs in the conservative group. The effect difference between the two treatment groups was in favor of elective sigmoid resection with an increase in QoL (EQ-5D score) at one year which persisted over the following years.

After 5 years of follow-up, the costs per QALY gained were €6 275. This is far below the threshold value of €20 000 per QALY which is commonly deemed acceptable for relatively mild diseases, whereas in more severe diseases a threshold value of €80 000 per additional QALY is maintained. Although (uncomplicated) diverticulitis is deemed a relatively mild disease, the results of the QoL questionnaires indicate that the disease burden for this patient group is high, with on average a 17-24% loss of QoL compared to age matched peers.^{3,8,9} In the cost-effectiveness analysis the probability of operative intervention being cost-effective was 95% at a threshold of €20 000 per additional QALY and even 100% at the higher threshold

of €80 000 per QALY. We therefore claim that operative treatment is cost-effective and should be offered more routinely to this patient group.

The cost differences between randomization groups were as expected. At one year follow-up increased costs were found in the operative group as a result of surgical intervention and concomitant hospitalisation. However in the conservative group, 26 (46%) patients ultimately required elective sigmoid resection due to severe ongoing complaints, thus increasing the costs in this group in the long term. Productivity losses contributed strongly to increased costs in both groups. However, in the operative group productivity losses were mostly reported directly after surgery and were, although not statistically significant, lower compared to the conservative group throughout the study follow-up period.

High rate of anastomotic leakage strongly increased the costs in the intervention group. A total of eight (11%) patients had anastomotic leakage (seven patients in the operative group and one patient in the conservative group). This figure is rather high compared to current literature demonstrating rates of 6% for anastomotic leakage.²⁰⁻²³ We cannot provide a satisfying explanation for this high figure, nor could we perform a formal regression analysis to identify factors that are associated with anastomotic leakage, because the absolute numbers were too small. It can only be explained by the fact that the DIRECT trial has been a pragmatic trial without specific selection of surgeons or centers, thus reflecting real complication rates and accompanying costs. It may also indicate that elective sigmoid resection for recurrent diverticulitis or persistent complaints is accompanied by a higher chance of complications than is anticipated in literature due to procedural challenges during surgery. Remarkably, despite these high rates of anastomotic leakage and concurring reinterventions, QoL was still higher in the operative group, strengthening our conclusion that elective surgery has an important impact on improvement of QoL.

A major strength of this study is its randomized multicenter design. Furthermore this study was performed from a societal perspective and used a precise and comprehensive cost registration method. In this study all resources use was documented prospectively and all healthcare consumption was valued at the level of units of consumption, not at the level of diagnosis related groups. Therefore the results represent an accurate estimation of the actual cost per patient. Another strength of the study is the fact that we were able to collect cost-data and QoL data during five year follow-up, which provided the unique opportunity to analyze cost-effectiveness at two different moments during follow-up. The fact

that cost-effectiveness strongly improved over prolonged follow-up emphasizes the importance of long-term follow-up in cost-effectiveness studies.

This study also has a few limitations. At three year follow-up, the response rate to QoL, HLQ and health consumption questionnaires was very low (26%). This could have led to attrition bias. In order to avoid this, multiple imputation techniques were used to handle missing data.¹² At 5-year follow-up, the response rate was much higher (71-75%), strengthening the validity of our results. In the conservative group, 46% of the patients had severe ongoing abdominal complaints and were eventually operated on, which may have led to an underestimation of the incremental effect on QoL of elective sigmoid resection and makes the results of the intention-to-treat analysis somewhat uncertain. Despite this, we still found elective sigmoid resection to be cost-effective. There are several issues with regard to the generalisability of the results. Firstly, the inclusion criteria for the DIRECT trial were quite strict in a sense that only patients who had >2 episodes of diverticulitis within 2 years or had persistent complaints for >3 months were eligible for the study. Moreover, the included patients came from a selected population who were already in the secondary care circuit. Results are therefore not directly applicable to all patients with frequently recurrent diverticulitis or persistent complaints after an episode in general. Secondly, a pragmatic approach adhering to the Dutch situation was used for defining conservative management and objectifying the primary episode of diverticulitis by using both CT-scan, ultrasonography and endoscopy. There are differences across countries with regard to these topics and therefore costs for conservative management could vary between countries. Moreover, resource use and costs of laparoscopic sigmoid resection vary between countries, thus hampering the translation of our results to international contexts.^{24,25}

Elective sigmoid resection resulted in a significantly increased QoL at five year follow-up compared to conservative management. Costs were only slightly higher in the operative group and at a willingness to pay €20 000 per additional QALY, operative treatment has a probability of 95% to be cost-effective. These results add a favorable economic perspective to the demonstrated efficacy of elective sigmoid resection in the DIRECT trial.

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A stylized, light gray line drawing of a plant stem with several leaves and a flower bud at the bottom. The stem is curved, and the leaves are arranged in a spiral pattern. The flower bud is at the bottom left, with a small stem extending from it. The background is white.

Chapter 10

General discussion and future perspectives

In this new age of medicine where (almost) anything is possible, costs and effectiveness of health care are becoming more and more important. Where the sky used to be the limit, nowadays governments all over the world are struggling with ever rising health care costs. Since we keep getting older and older, this problem will only get bigger. We therefore need to analyze our resources and how we use them more critically. Cost-effectiveness is however an elusive concept and not considered very “sexy”. In this thesis we tried to lay the groundwork for more cost-effective diverticulitis treatment. As said, the incidence of diverticulosis and with it diverticulitis, is increasing worldwide and contributes majorly to healthcare costs. In the United States the costs are estimated at 2.2 billion dollars per year.¹ In order to reduce these costs we need to reassess our resource use; what is necessary and what can be left out? How can we minimise the costs of diverticulitis treatment, without giving in on quality of treatment? In order to answer these questions, we need to improve our understanding of the disease. Although the incidence is high, there is still much we don't know about diverticulosis and diverticulitis. How do diverticula arise? What is the cause of diverticulitis? Is it a bacterial or rather an inflammatory disease? Why do some patients get recurrences and others not? Should we treat uncomplicated diverticulitis with antibiotics? Can these patients be treated at home? How should we treat patients with recurrent diverticulitis or chronic complaints? What is the natural course of diverticular abscesses? How should we treat these abscesses? Is it safe to treat patients with perforated diverticulitis with primary anastomosis or should these patients receive Hartmann's procedure? And the list goes on... Naturally this thesis isn't going to answer all these questions, but we did try to answer some.

Etiology of diverticulosis

In **chapter 2** the etiology of diverticulosis is addressed. Multiple theories on the development of diverticulosis circulate. Factors that might play a role in developing diverticulosis are a low-fibre diet, thickening of the colon musculature, disordered motility and (age-related) weakening of the colon wall connective tissue (increased collagen crosslinking and progressive elastosis).²⁻⁴ A low-fibre diet increases the transit time which stimulates the colonic circular muscle.⁵ It is thought that high intracolonic pressure due to exaggerated contractions of the colonic circular muscle generates increased outward force on the colonic wall, resulting in mucosal herniation.^{6,7} While most etiology studies focussed on the colonic wall structure and motility of the colon, few examined the three-dimensional (3D) geometrical colon properties in relation to diverticulosis.⁸ In **chapter 2** we acquired

quantitative information on 3D colon geometry (length and tortuosity) with non-invasive colon examination using abdominal computed tomography (CT) data and related them to the presence of diverticulosis. Interestingly we found that diverticulosis patients have a shorter colon (which can be attributed to a shorter sigmoid and transverse colon) and that their descending and transverse colon are less tortuous compared to patients without diverticulosis. These results are in line with previous studies describing an inverse relation between diverticulosis and a redundant colon (a chronically distended, elongated, tortuous colon).⁹⁻¹¹ The pathophysiologic mechanisms behind this relation have yet to be clarified. Perhaps a shorter and less tortuous colon leads to increased intracolonic pressure causing the formation of diverticula. This mechanism can however not be derived from our data. Future studies combining our measurements with intracolonic pressure measurements could provide more information on these mechanisms. Our study was the first to use clinical CT data to analyze colon length, giving more accurate in vivo measurements. The findings of this study therefore provide important new information on colon anatomy. Moreover, these findings can provide important information for gastro-intestinal surgeons who perform colonic (left hemi- or sigmoid) resection on diverticulitis or diverticulosis patients. If diverticulosis patients indeed have a shorter and less tortuous colon, one should emphasize to mobilize the splenic flexure to gain enough colon length for a tensionless anastomosis in these patients. Also, the finding that the diverticulosis segment is on average 51 (inter quartile range 32-97) centimetre may provide background information on resection strategy and (prevention of) recurrence.

Treatment of uncomplicated diverticulitis; selecting patients at risk for complications

Most patients (80%) who present with diverticulitis have uncomplicated diverticulitis (UD) which is a mild and self-limiting disease.⁸ In the past years evidence which justifies a more conservative approach towards this costly disease has been arising. Two recent randomized clinical trials showed that the use of antibiotics in patients with UD does not provide a beneficial effect and this is now considered obsolete.^{12,13} Moreover, recent studies have indicated that UD patients can be safely treated in an outpatient setting.¹⁴⁻¹⁶ The Dutch primary care guideline 'Diverticulitis' recommends to only refer patients who are at risk of complicated diverticulitis (CD) to secondary care (emergency department) for evaluation by a surgeon or gastroenterologist.¹⁷ However, a considerable number of patients who present with UD in primary care (general/family practice) are still referred to secondary care, with the consequence of unnecessary diagnostics (ultrasound,

CT-scan), treatment and hospital admission. To reduce the health care costs of diverticulitis, these unnecessary referrals should be reduced. Such a strategy would demand a proper diagnostic tool to help distinguish UD from CD at presentation, without the use of secondary care diagnostics (ultrasound, CT-scan). In **chapter 3 and 4** we aimed to identify risk factors for CD in order to develop such a tool. UD was defined as Hinchey IA (only pericolic inflammation) and CD as >Hinchey 1A.¹⁸⁻²⁰ We found that abdominal guarding (diffuse muscular rigidity on palpation) at physical examination and inflammatory parameters (CRP and leucocytes) are predictors of CD in patients presenting at the ER with a first episode of diverticulitis. Use of a diagnostic model combining these parameters could safely rule out CD with a negative predictive value of 96% at a 7.5% probability for CD. A scoring system was provided in order to illustrate the predicted CD risk when combining the individual parameters, which can be easily used in clinical practice. The risk score illustrates that when a diverticulitis patient presents with a CRP <100 mg/L, leucocytes <15.0 x10⁹/L and no signs of abdominal guarding, the risk for CD is very low (4%). These patients can safely be withheld secondary care diagnostics and/or treatment. A major limitation of this study was that we conducted it in secondary care. When we started our quest to develop this model we aimed to conduct a prospective nationwide study including all patients with a suspicion of diverticulitis in primary care who would be referred to secondary care, since this is the population of interest. However, in the initiation of this study we encountered several practical issues which made the execution of such a study design not feasible. We therefore chose to develop the model in our own population and accepted subsequent limitations of this study. Because this study was conducted in secondary care it cannot directly be translated to primary care. Moreover, only patients with CT-proven diverticulitis were included and therefore the model is not applicable to all patients presenting with abdominal pain in the emergency department. When applying the model clinical practitioners should thus always be wary of other (serious) diagnoses. Future studies should be aimed at validating this model in primary care. Considering the large sample size that would be required for this study (at least 600 patients), at least 300 general practitioner practices would need to be involved since an average general practitioner practice sees only two diverticulitis patients per year. Hopefully such a collaboration will be possible in the future.

As said above, the majority (80%) of diverticulitis patients presents without any complications and these patients can be treated without antibiotics.¹²⁻¹⁶ However,

the implementation of a treatment strategy without antibiotics has not yet been successful worldwide as treatment failure rates of 3-24% are reported in previous literature and physicians are therefore reluctant to omit antibiotics and send patients home. Due to high risk of selection and detection bias in the available studies analyzing non-antibiotic treatment, their results are also less applicable to daily practice.¹⁵ To improve the implementation of non-antibiotic treatment we need to better identify which UD patients are eligible for non-antibiotic treatment and which UD patients are more susceptible for a complicated course (treatment failure) and should therefore receive antibiotic treatment and closer surveillance. Few studies have investigated clinical risk factors for treatment failure in patients with UD. In the few studies that are available, all patients received antibiotics.^{14,21} In **chapter 5** we assessed the clinical course of UD patients who were initially treated without antibiotics and identified risk factors for treatment failure in this patient group. The majority (565 (75%)) of patients presenting with UD were initially treated without antibiotics and treatment failure was seen in 46 (8%) of these patients. Moreover, only 12 patients (2%) had severe complications requiring invasive interventions such as percutaneous abscess drainage (n=2) or emergency surgery (n=10). This shows that the implementation of a more conservative approach without antibiotics has been successful in our hospital (Meander Medical Centre, Amersfoort, The Netherlands). As we still found a (non-antibiotic) treatment failure rate of 8%, it is pertinent to adequately select patients who are suitable for a non-antibiotic treatment strategy. Patients with a high CRP level (>170 mg/L) were at significantly higher risk for treatment failure. Clinical physicians should take these findings in consideration when selecting patients for non-antibiotic treatment. Future studies should be aimed at prospectively analyzing the implementation of these findings in a treatment protocol.

Treatment of diverticulitis patients with minor complications; are we too cautious?

The differentiation between uncomplicated and complicated diverticulitis is important as complicated diverticulitis has higher morbidity and mortality and therefore demands a more aggressive therapeutic approach. Perforated diverticulitis with purulent or fecal peritonitis requires emergency surgery (sigmoid resection with or without protective ileostomy or Hartmann's Procedure), or in some cases laparoscopic lavage. However, between uncomplicated diverticulitis (confined inflammation of the sigmoid) and perforated diverticulitis with purulent or fecal peritonitis there is a great grey area of varying degrees of disease severity. This ranges from small abscesses and small amounts of

pericolic free air to large abscesses and large amounts of distant free air. Most classification systems that categorise the severity of diverticulitis are based on CT findings, such as fluid collections, extraluminal contrast leakage or free air. The latest classification systems also include the presence of pericolic air bubbles or localized pneumoperitoneum in their classification and categorise this as “complicated diverticulitis”.²²⁻²⁵ The clinical relevance of free air on CT, however, remains unclear. Distant free air on CT is usually considered a sign of diffuse peritonitis and a strong indicator for operative intervention, whereas patients who present with isolated pericolic air may be treated conservatively.²⁶ Current guidelines on treatment of diverticulitis do not comment on uncomplicated diverticulitis patients with isolated pericolic air nor do they advise on the optimal treatment strategy. In clinical practice physicians tend to get nervous when they see free air on CT as this indicates a (however small) perforation of the colon. We hypothesised that isolated pericolic free air has no clinical significance and these patients can be considered as “uncomplicated diverticulitis”. In **chapter 6** we assessed the course of diverticulitis patients with isolated pericolic air seen on CT imaging and identified risk factors for failure of conservative treatment. Moreover, we assessed the outcome of non-antibiotic treatment as our hypothesis was that these patients do not differ from uncomplicated diverticulitis patients and should be treated accordingly. The FACT study was a joint venture between the DIABOLO trial¹², a multicentre randomized controlled trial comparing antibiotic with non-antibiotic treatment for uncomplicated acute diverticulitis and a retrospective cohort study on risk factors for complicated diverticulitis performed in the Meander Medical Centre (**chapter 4**). In the FACT study 109 uncomplicated diverticulitis patients (defined as Hinchey IA¹⁸⁻²⁰) with isolated pericolic air were included of which 9 (8%) patients experienced treatment failure. These results, combined with previous studies indicate a mild disease course with high conservative treatment success rates.²⁷⁻³¹ We therefore feel that this form should be considered “uncomplicated diverticulitis” and an initial conservative treatment strategy in this patient group is justified. The question remains whether this conservative treatment strategy should encompass antibiotics. In the FACT study 57 (52%) patients were treated without antibiotics and of these, 55 (96%) patients were treated successfully. Moreover, no statistical significant difference in failure of conservative treatment between patients treated with and without antibiotics ($p=0.083$) was found. This could indicate that antibiotic treatment might not be mandatory in patients with pericolic air. However, 64% of the study population came from a retrospective database and in these patients antibiotic treatment

was started at the discretion of the attending physician. Therefore there is a high risk of confounding by indication. As conservative treatment still failed in 8% of the patients, it is important to adequately select patients suitable for a conservative treatment strategy. In the FACT study, a higher CRP level was associated with treatment failure and, although not statistically significant, a higher leucocyte count and higher age seemed to be associated with treatment failure. Patients who present with these risk factors might not be suitable for a conservative treatment strategy and should be watched more closely. We recommend that in new diverticulitis guidelines patients with isolated pericolic air will be considered as uncomplicated diverticulitis and treated as such, taking in account risk factors for potential treatment failure.

Treatment strategies for diverticulitis with abscess formation (modified Hinchey Ib and II) have shifted from (emergency) surgical treatment to nonsurgical management (antibiotics with or without percutaneous drainage (PCD)).³² In **chapter 7** we assessed both short- and long-term outcomes of nonsurgical treatment and identified risk factors associated with adverse outcomes. Overall, 447 patients were included (Hinchey Ib [n=215], Hinchey II [n=232]), with a median follow-up time of 72 (interquartile range, [55-93]) months. All patients received antibiotics and most patients were treated without PCD (74% [332/447]). Abscesses ≥ 3 cm and ≥ 5 cm were found to be independent risk factors for short-term treatment failure and emergency surgery, respectively (odds ratio [95% confidence interval]: 2.05 [1.09-3.86] and 2.91 [1.03-8.23]). Interestingly, treatment strategy (antibiotic treatment with or without PCD) did not independently affect outcome in multivariable analyses. These findings bring a new perspective to the treatment of diverticulitis with abscess formation. Based on our findings we advise to treat abscesses <3 cm without PCD. Abscesses larger than 3 cm should be monitored more closely as these patients are at higher risk for treatment failure and emergency surgery. However, the role of PCD in these patients remains unclear. We did not find any difference in outcome between these treatment groups, regardless of abscess size. However, as this was a retrospective study, these findings need to be confirmed in prospective studies analyzing treatment of diverticular abscesses.

Treatment of recurrent diverticulitis and/or ongoing complaints

One of the major mysteries regarding diverticulitis treatment is how to treat patients with multiple recurrences or ongoing complaints. In the past years multiple studies have analyzed the effect of conservative treatment strategies on the relief of symptoms and prevention of recurrences. Different treatment strategies have been applied such as a higher fiber diet, mesalamine, rifaximine or a combination of these three. The results of these studies remain inconclusive and therefore the effect of a conservative treatment strategy is questionable.^{33,34} Logically, the best treatment strategy would be to remove the sick part of the colon (sigmoid) in order to relief symptoms and prevent recurrences. There has however been great controversy on the use of elective sigmoidectomy to treat patients with recurrences and/or persistent symptoms. One of the concerns regarding this topic is the difficulty in distinguishing persistent symptoms after an episode of diverticulitis from Irritable Bowel Syndrome (IBS). As IBS is a functional disorder, operative treatment is obviously not the treatment of choice as it is unlikely to improve and might even fuel the symptoms. Moreover, operative intervention is associated with inherent complication risks, such as anastomotic leakage or abscesses.³⁵⁻³⁸ Since (uncomplicated) diverticulitis is generally considered a mild and self-limiting disease, performing a potentially harmful procedure in these patients does not seem justified. Guidelines published by the American Society of Colon and Rectal Surgeons (ASCRS) in 2014 and the World Society of Emergency Surgery (WSES) in 2016 recommend a tailored approach for each individual patient where the impact of multiple recurrences and ongoing complaints on quality of life should form the most decisive factor.^{39,40} It is therefore pertinent that the effect of elective sigmoidectomy on quality of life in this patient group is better understood. Until recently only low quality data has been available on the operative and conservative management of recurrent diverticulitis and/or ongoing complaints, with both treatment strategies being reported as effective.³⁵ The retrospective and heterogeneous nature of these studies impairs definitive conclusions. **Chapter 8 and 9** describe the long term results of the DIRECT trial; a multicentre randomized controlled trial comparing operative with conservative treatment in patients with recurrent diverticulitis and/or ongoing complaints. The primary outcome was quality of life. In total, 109 patients were randomized to either elective sigmoidectomy (N=53) or conservative management (N=56). Elective sigmoidectomy resulted in a significantly increased quality of life at 5-year follow-up compared to conservative management, in accordance with the short-

term results at six months follow-up.⁴¹ Interestingly we had a high percentage (almost 50%) of cross-overs (patients randomized to conservative treatment who actually underwent surgery due to severe ongoing complaints). When we compared the cross-overs to the successfully conservatively treated patients, we saw that the cross-overs reported significantly lower quality of life at baseline. This emphasizes the recommendations of the ASCRS³⁹ and WSES⁴⁰ that the impact of multiple recurrences and ongoing complaints on quality of life should form the most decisive factor in selecting patients for operative intervention, as we found that quality of life at baseline predicts conservative treatment failure. Our study showed that the disease burden of recurrent diverticulitis and/or ongoing complaints is high and we established the beneficial effect of surgical intervention on quality of life. On the one hand, surgery was accompanied by 11% anastomotic leakage and 15% of surgically treated patients underwent reinterventions. On the other hand, the majority of recurrences, as seen in the conservative group in 30% of patients, were prevented in the surgery group. Moreover we looked at cost-effectiveness and found that, although the intervention was not cost-effective at one year follow-up, at five-year follow-up the probability of the intervention being cost-effective was 95%. The fact that cost-effectiveness strongly improved over prolonged follow-up emphasizes the importance of long-term follow-up in cost-effectiveness studies. This is especially the case in trials comparing operative treatment with conservative management, where it is hard to demonstrate cost-effectiveness of operative treatment within one year since costs of an operation are generally high and naturally contribute severely to overall costs in the first year. All in all we conclude that surgeons should counsel patients more frequently for elective sigmoidectomy in case of recurrent diverticulitis and /or ongoing complaints after an episode of left sided diverticulitis weighing superior quality of life, less pain and lower risk of new recurrences against the complication risk of surgery.

Conclusion

A surgeon sees on average 1-2 diverticulitis patients per week in the emergency department. Despite this high incidence, there are still many mysteries regarding this disease that remain unsolved. In order to improve the quality, as well as the cost-effectiveness of diverticulitis care, this thesis tried to solve some of these mysteries. The paradigm of diverticulitis treatment is shifting towards a more conservative approach where uncomplicated diverticulitis patients are treated at home without antibiotics. In this thesis we take it even a step further by stating that

patients with isolated pericolic air can be considered as uncomplicated diverticulitis and treated as such. Moreover, patients with small abscesses can ($<3\text{cm}$) be treated without percutaneous drainage or surgical intervention and there are indications that percutaneous abscess drainage is also not always mandatory in large abscesses ($\geq 3\text{cm}$). To safely implement a conservative outpatient treatment strategy without antibiotics, we need be able to select those patients who are at higher risk of complications and therefore not suitable for such a treatment strategy. In this thesis we developed tools which clinical physicians can use to help them in the decision whether or not to refer and/or admit a diverticulitis patient and whether or not to start antibiotic treatment. Furthermore we analyzed the optimal treatment strategy in patients with recurrent diverticulitis and/or ongoing complaints. Based on our studies we advise to offer surgery more frequently to patients presenting with recurrent diverticulitis and/or ongoing complaints as surgical intervention improves quality of life and is also proven to be cost-effective.

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A stylized, light gray line drawing of a plant stem with several leaves and a flower bud at the bottom. The stem is curved, and the leaves are arranged in a spiral pattern. Some leaves have small dark spots. The flower bud is at the bottom left, and the stem extends towards the top right.

Chapter 11

Nederlandse samenvatting

In dit nieuwe tijdperk van Geneeskunde waarin (bijna) alles mogelijk is, worden kosten en effectiviteit van gezondheidszorg steeds belangrijker. Waar vroeger de “the sky the limit” was, kampt men wereldwijd nu met steeds rijzende zorgkosten. Aangezien we steeds ouder worden (vergrijzen), zal dit probleem alleen maar groter worden. We moeten daarom kritischer kijken naar de middelen die tot onze beschikking staan en vooral ook naar hoe we deze middelen gebruiken. Kosteneffectiviteit is echter nochtans een ongrijpbaar concept en een weinig “sexy” onderwerp. In dit proefschrift hebben we geprobeerd de basis te leggen om diverticulitiszorg meer kosteneffectief te maken. De incidentie van diverticulose (uitstulpingen van de dikke darm), en daarmee diverticulitis (ontsteking van deze uitstulpingen), stijgt wereldwijd en dit draagt flink bij aan de stijgende zorgkosten. In de Verenigde Staten worden de jaarlijkse zorgkosten voor diverticulitis geschat op 2,2 miljard dollar.¹ Om deze kosten waar mogelijk te beperken, moeten we ons middelengebruik opnieuw evalueren; wat is écht nodig en wat kunnen we achterwege laten? Hoe kunnen we de kosten voor diverticulitiszorg zo laag mogelijk houden, zonder in te geven op kwaliteit? Om deze vragen te kunnen beantwoorden, moeten we onze kennis over deze ziekte verbeteren. Hoewel de incidentie hoog is, zijn er nog steeds veel onbeantwoorde vragen over diverticulose en diverticulitis. Hoe ontstaan divertikels? Hoe ontstaat diverticulitis? Is het een inflammatoire of bacteriële ziekte? Waarom krijgen sommige patiënten recidieven en andere niet? Moeten we ongecompliceerde diverticulitis met antibiotica behandelen? Moeten we deze patiënten in het ziekenhuis opnemen? Hoe moeten we patiënten met recidiverende diverticulitis of chronische klachten behandelen? Wat is het natuurlijke beloop van diverticulaire abcessen? Hoe moeten we deze abcessen behandelen? Is het veilig om patiënten met een geperforeerde diverticulitis te behandelen met een primaire anastomose (darmnaad), of moeten deze patiënten een Hartmann procedure (eindstandig colostoma) krijgen? En ga zo maar door... Dit proefschrift zal uiteraard niet al deze vragen kunnen beantwoorden. We hebben echter wel geprobeerd om er een aantal te beantwoorden.

Etiologie van diverticulose

In **hoofdstuk 2** wordt de etiologie (ontstaansleer) van diverticulose besproken. Er doen meerdere theorieën over het ontstaan van divertikels (uitstulpingen van de dikke darm) de ronde. Factoren zoals een vezelarm dieet, verdikking van de spierwand van het colon (dikke darm), verstoorde motiliteit en (leeftijd gerelateerde) verslapping van de colonwand (door een veranderde samenstelling van het bindweefsel) zouden een rol kunnen spelen bij het ontstaan van divertikels.²⁻⁴ Een vezelarm dieet verhoogt de passagetijd van feces waardoor de

circulaire spieren van de colonwand gestimuleerd worden.⁵ Er wordt gedacht dat overdadige samentrekkingen van de colonwand (door stimulatie van de circulaire spieren) leiden tot een verhoogde druk in het colon. De verhoogde druk in het colon zorgt weer voor een uitwaartse druk op de colonwand, waardoor mucosale hernaties (uitstulpingen; divertikels) ontstaan.^{6,7} Terwijl de meeste etiologische studies zich focussen op de structuur van de colonwand en de motiliteit van het colon, zijn er weinig studies die de 3-Dimensionele (3D) afmetingen van het colon hebben gerelateerd aan de aanwezigheid van divertikels.⁸ In **hoofdstuk 2** hebben we kwantitatieve metingen gedaan van de 3D afmetingen van het colon (lengte en tortuositeit (mate van draaiing)) en deze gerelateerd aan de al dan niet aanwezigheid van divertikels. Opvallend genoeg vonden we dat patiënten met divertikels een korter en minder tortueus colon hebben dan patiënten zonder divertikels. Deze resultaten komen overeen met voorgaande studies waarin een omgekeerde relatie wordt beschreven tussen diverticulose en een “overtollig” (lang en tortueus) colon.⁹⁻¹¹ De pathofysiologische mechanismes die achter deze relatie zitten, zijn nog onduidelijk. Wellicht leidt een korter en minder tortueus colon tot een verhoogde druk in het colon, wat weer divertikels kan veroorzaken. Dit kunnen wij echter niet uit onze data afleiden. Toekomstige studies zouden onze metingen kunnen combineren met drukmetingen in het colon om zo meer inzicht te krijgen in deze mechanismes. In onze studie zijn voor het eerst klinische CT data gebruikt om zo meer accurate in vivo (levende patiënten) metingen te verkrijgen van colonlengte en tortuositeit. Onze bevindingen verschaffen dan ook nieuwe inzichten in de anatomie van het colon. Daarnaast is deze informatie ook belangrijk voor chirurgen die colonresecties uitvoeren in patiënten met diverticulose (of diverticulitis). Als patiënten met diverticulose inderdaad een korter en minder tortueus colon hebben, moet men de flexuur (bocht van het colon) bij de milt goed mobiliseren om zo genoeg colonlengte te verkrijgen om een spanningsloze anastomose aan te kunnen leggen. De bevinding dat het diverticulosesegment gemiddeld 51 (32-97) centimeter lang is, kan ook belangrijk zijn bij het bepalen van de lengte van het resectiesegment. Dit gegeven kan inzicht geven hoeveel colon je moet weghalen om alle divertikels te verwijderen en zo een recidief van diverticulitis te voorkomen.

Behandeling van ongecompliceerde diverticulitis: selectie van hoog risico patiënten

De meeste (80%) patiënten presenteren zich met een milde ongecompliceerde vorm van diverticulitis die vanzelf over gaat.⁸ In de afgelopen jaren is er steeds meer bewijs gekomen dat een conservatievere benadering voor deze kostbare ziekte verantwoordt. Recent hebben twee gerandomiseerde studies aangetoond

dat het geven van antibiotica bij een ongecompliceerde diverticulitis geen effect heeft en dus achterwege gelaten kan worden.^{12,13} Daarnaast hebben meerdere studies aangetoond dat ongecompliceerde diverticulitis veilig thuis behandeld kan worden en dat deze patiënten dus niet opgenomen hoeven te worden.¹⁴⁻¹⁶ De NHG standaard (Nederlandse Huisartsenrichtlijn) "Diverticulitis" raadt dan ook aan om alléén patiënten met gecompliceerde diverticulitis door te verwijzen naar de 2^e lijn (spoedeisende hulp in het ziekenhuis) om beoordeeld te worden door een chirurg of maag-darm-lever arts.¹⁷ Er worden echter nog steeds veel ongecompliceerde diverticulitis patiënten (onterecht) doorverwezen naar de 2^e lijn met als gevolg veel onnodige diagnostiek, behandeling en ziekenhuisopnames. Om de zorgkosten voor diverticulitis te verlagen, moeten deze onnodige verwijzingen verminderd worden. Om dit te bewerkstelligen, hebben huisartsen een goed diagnostisch hulpmiddel nodig dat hen kan helpen om ongecompliceerde van gecompliceerde diverticulitis te onderscheiden, aangezien zij uiteraard geen complicaties willen missen. In **hoofdstuk 3 en 4** hebben we geprobeerd klinische risicofactoren voor het hebben van een gecompliceerde diverticulitis te identificeren om een dergelijk diagnostisch hulpmiddel te kunnen samenstellen. Ongecompliceerde diverticulitis was gedefinieerd als Hinchey IA (alleen ontsteking van het vet rondom de divertikels) en gecompliceerde diverticulitis als alles boven (dus gecompliceerder dan) Hinchey IA (abscessen, perforatie etc.).¹⁸⁻²⁰ Onze resultaten tonen dat een geprikkelde buik bij lichamelijk onderzoek en inflammatoire parameters in het lab (CRP (ontstekings eiwit) en leukocyten (witte bloedcellen)) voorspellers zijn voor het hebben van een gecompliceerde diverticulitis in patiënten die zich op de spoedeisende hulp presenteren met een eerste episode van diverticulitis. Het diagnostisch model dat deze drie parameters combineert, kan een gecompliceerde diverticulitis met 96% zekerheid uitsluiten, bij een risico van 7,5% op complicaties. Een scoringsysteem is ontwikkeld om het risico op gecompliceerde diverticulitis op basis van deze drie parameters te illustreren. De risicoscore laat zien dat als een diverticulitispatiënt zich presenteert met CRP <100mg/L, leukocyten <15,0x10⁹/L en géén geprikkelde buik, het risico op complicaties erg laag is (4%). Deze patiënten zouden dus niet doorverwezen hoeven te worden naar de 2^e lijn. Een grote beperking van deze studie is dat we de studie hebben uitgevoerd op de spoedeisende hulp in de 2^e lijn. Oorspronkelijk wilden we een prospectieve studie uitvoeren waarbij we alle patiënten met een verdenking op diverticulitis in de eerste lijn (huisartsenpopulatie) zouden includeren omdat dit daadwerkelijk de patiëntengroep is waarin we geïnteresseerd waren (en niet de al geselecteerde populatie die je in de 2^e lijn ziet). Omdat dit echter niet haalbaar bleek, hebben we besloten om de studie toch in de 2^e lijn uit te voeren, met inachtneming van

de beperkingen die dit met zich brengt. Omdat we de studie in de 2^e lijn hebben uitgevoerd, kunnen we de resultaten niet direct extrapoleren naar de eerste lijn. Tevens hebben we alleen patiënten met al bewezen diverticulitis geïnccludeerd waardoor de resultaten niet van toepassing zijn op alle patiënten die zich op de spoedeisende hulp presenteren met buikklachten. Toekomstige studies zouden zich moeten richten op het valideren van dit diagnostisch model in de eerste lijn (huisartsenpraktijk). Aangezien hiervoor minimaal zo'n 600 patiënten geïnccludeerd zouden moeten worden en een huisarts gemiddeld maar twee keer per jaar een diverticulitis patiënt ziet, zouden er minimaal 300 huisartsenpraktijken mee moeten doen aan zo'n studie. Hopelijk is zo'n samenwerkingsverband in de toekomst mogelijk.

Zoals gezegd, presenteert het grootste deel (80%) van de diverticulitis patiënten zich zonder complicaties en deze patiënten kunnen thuis behandeld worden zonder antibiotica.¹²⁻¹⁶ Ondanks dat er veel bewijs is voor een behandelstrategie zonder antibiotica, is deze strategie nog niet wereldwijd geïmplementeerd. Voorgaande literatuur beschrijft dat deze strategie in 3-24% van de gevallen onsuccesvol is (d.w.z. patiënten knappen niet op of er treden complicaties op) en artsen zijn hierdoor terughoudend met het aannemen van deze strategie. Deze studies hebben bovendien een hoog risico op selectie en detectie bias waardoor de resultaten minder goed toepasbaar zijn op de klinische praktijk.¹⁵ Om de implementatie van een behandelstrategie zonder antibiotica te verbeteren, moeten we beter kunnen bepalen welke patiënten met ongecompliceerde diverticulitis geschikt zijn voor non-antibiotische behandeling en welke patiënten een hoog risico lopen op het ontwikkelen van complicaties en daarom wel antibiotica moeten krijgen. Er zijn weinig studies die risicofactoren voor het falen van behandeling (optreden van complicaties of niet verbeteren van symptomen) hebben onderzocht. In de weinige studies die er wel zijn gedaan, kregen alle patiënten antibiotica.^{14,21} In **hoofdstuk 5** hebben we het natuurlijk ziektebeloop van patiënten met ongecompliceerde diverticulitis die initieel zonder antibiotica zijn behandeld in kaart gebracht en hebben we risicofactoren geïdentificeerd voor het falen van behandeling. Het grootste deel (565 (75%)) van de patiënten die zich op de spoedeisende hulp presenteerden met ongecompliceerde diverticulitis werd behandeld zonder antibiotica en falen van behandeling trad op bij 46 (8%) van deze patiënten. Bovendien hadden slechts 12 (2%) van deze patiënten ernstige complicaties waarvoor invasieve interventie (percutane drainage (n=2) of operatie (n=10)) nodig was. Dit toont aan dat de implementatie van een niet-antibiotische behandelstrategie in ons ziekenhuis (Meander Medisch Centrum)

succesvol is. Aangezien deze behandelstrategie nog steeds faalde bij 8% van de patiënten is het belangrijk om adequaat patiënten te selecteren die geschikt zijn voor deze behandelstrategie. Patiënten met een hoog CRP ($>170\text{mg/L}$) hadden een significant hoger risico op het falen van behandeling. Artsen zouden deze bevindingen mee moeten nemen in hun overweging om wel of niet antibiotica te starten. Toekomstige studies zouden zich moeten richten op de implementatie van deze bevindingen in een behandelprotocol.

Behandeling van diverticulitis met kleine complicaties; zijn we te voorzichtig?

Het onderscheid tussen ongecompliceerde en gecompliceerde diverticulitis is belangrijk aangezien gecompliceerde diverticulitis een hogere morbiditeit en mortaliteit heeft en daarom agressievere behandeling vergt. Geperforeerde diverticulitis met purulente of fecale peritonitis (buikvliesontsteking) vergt een spoedoperatie (sigmoïd resectie met of zonder beschermend ileostoma of een Hartmann procedure). Echter, tussen ongecompliceerde diverticulitis (lokale ontsteking van het sigmoïd) en geperforeerde diverticulitis met purulente of fecale peritonitis, zit een groot grijs gebied van verschillende ziekte stadia variërend in ernst. Dit varieert tussen kleine abcesjes en kleine hoeveelheden pericologisch vrij lucht, tot grote abcessen en grote hoeveelheden vrij lucht (luchtbelletjes rondom het colon) op afstand. De meeste classificatiesystemen scoren de ernst van diverticulitis op basis van CT bevindingen (zoals abcessen, vrij vocht, vrij lucht etc.). De meest recente classificatie systemen hebben lokaal pericologisch vrij lucht opgenomen in de classificatie en definiëren dit als “gecompliceerde diverticulitis”.²²⁻²⁵ De klinische relevantie van dit pericologisch vrij lucht is echter onduidelijk. Vrij lucht op afstand wordt meestal gezien als een teken van diffuse peritonitis en een sterke indicatie voor chirurgische interventie, terwijl patiënten met alleen pericologisch vrij lucht vaak conservatief behandeld kunnen worden.²⁶ Huidige richtlijnen over de behandeling van diverticulitis benoemen deze vorm van diverticulitis niet, noch doen ze aanbevelingen over de beste behandeling. In de praktijk neigen artsen ernaar om wat nerveus te worden van vrij lucht op CT aangezien dit een perforatie (hoe klein ook) van het colon impliceert. Onze hypothese was echter dat patiënten met lokaal pericologisch vrij lucht niet verschillen van patiënten met ongecompliceerde diverticulitis en ze dus ook als zodanig behandeld kunnen worden. In **hoofdstuk 6** hebben we het ziektebeloop van diverticulitispatiënten met geïsoleerd pericologisch lucht geanalyseerd en risicofactoren voor het falen van conservatieve (non-invasieve) behandeling geïdentificeerd. De FACT studie was een samenwerking tussen de

DIABOLO trial¹², een multicentrische gerandomiseerde studie naar het effect van antibiotische behandeling in patiënten met ongecompliceerde diverticulitis, en een retrospectieve studie naar risicofactoren voor gecompliceerde diverticulitis (**hoofdstuk 4**) uit het Meander Medisch Centrum. In totaal werden er 109 ongecompliceerde diverticulitis (Hinchey IA)¹⁸⁻²⁰ patiënten met pericologisch vrij lucht geïncubeerd waarvan de behandeling in 9 (8%) patiënten faalde. Deze resultaten, gecombineerd met resultaten uit eerdere studies, tonen een mild ziektebeloop aan met een hoog succespercentage van conservatieve behandeling.²⁷⁻³¹ Wij pleiten er dan ook voor dat deze vorm wordt gezien als “ongecompliceerde diverticulitis” en een conservatieve behandeling wordt gehandhaafd in deze patiënten. Dan resteert echter nog de vraag of deze behandeling antibiotica moet bevatten. In de FACT studie zijn 57 (52%) patiënten behandeld zonder antibiotica, waarvan 55 (96%) succesvol. Bovendien werd er geen significant verschil gevonden in uitkomst tussen patiënten die wel en niet met antibiotica behandeld werden ($p=0.083$). Dit zou kunnen betekenen dat antibiotica niet altijd noodzakelijk zijn bij deze patiënten. Echter, aangezien 64% van de studiepopulatie uit een retrospectieve database kwam waarbij antibiotica werd gestart naar goedgevoelen van de dienstdoende arts, is er een hoog risico op confounding door indicatie. Aangezien de behandeling faalde in 8% van de patiënten is het ook hier belangrijk om patiënten te selecteren die geschikt zijn voor een conservatieve behandeling (met of zonder antibiotica). In de FACT studie was een hoog CRP geassocieerd met het falen van behandeling en, alhoewel niet significant, leek een hoger leukocytenaantal en hogere leeftijd ook geassocieerd te zijn met falen van behandeling. Patiënten die zich presenteren met deze risicofactoren zijn wellicht niet geschikt voor een conservatieve behandeling en moeten goed geobserveerd worden. We bevelen aan om in nieuwe diverticulitisrichtlijnen patiënten met geïsoleerd pericologisch vrij lucht te scharen onder “ongecompliceerde diverticulitis” en ook als zodanig te behandelen, met inachtneming van de risicofactoren voor potentieel falen van behandeling.

De behandelstrategieën voor diverticulitis met abcesvorming (Hinchey IB (klein abces) en II (groot abces)) zijn verschoven van (spoed) chirurgische interventie naar niet-chirurgische behandeling (antibiotica met-of zonder percutane abces drainage).³² In **hoofdstuk 7** hebben we zowel de korte- als de lange termijnuitkomsten van niet-chirurgische behandeling in diverticulitis patiënten met abcesvorming geanalyseerd en risicofactoren voor ongewenste uitkomsten (spoedoperatie, falen van behandeling) geïdentificeerd. In totaal werden er 447 patiënten geïncubeerd (Hinchey IB ($n=215$) & Hinchey II ($n=232$)) met

een mediane follow-up tijd van 72 (inter kwartiel range [55-93]) maanden. Alle patiënten kregen antibiotica en de meeste patiënten (74% [332/447]) werden behandeld zonder percutane drainage. Een abcesgrootte van $\geq 3\text{cm}$ en $\geq 5\text{cm}$ waren onafhankelijke voorspellers van respectievelijk falen van behandeling op korte termijn en spoedoperatie (odds ratio [95% betrouwbaarheid interval]: 2.05 [1.09-3.86] en 2.91 [1.03-8.23]). Opvallend genoeg had de behandelstrategie (antibiotica mét of zonder percutane drainage) geen invloed op de uitkomst in de multivariate analyses. Deze bevindingen bieden nieuwe perspectieven op de behandeling van diverticulaire abscessen. Gebaseerd op onze resultaten, adviseren wij om abscessen $<3\text{cm}$ conservatief (antibiotisch zonder percutane drainage of chirurgische interventie) te behandelen. Patiënten met abscessen $\geq 3\text{cm}$ moeten nauwlettend in de gaten gehouden worden, aangezien deze patiënten significant hoger risico hebben op falen van behandeling en spoedoperatie. De rol van percutane drainage in deze patiëntengroep is echter nog onduidelijk. Wij vonden geen verschil in uitkomst tussen patiënten die wel en niet met percutane drainage waren behandeld, ongeacht wat de abces grootte was. Echter, aangezien dit een retrospectieve studie was, moeten deze bevindingen bevestigd worden in prospectieve studies die de behandeling van diverticulaire abscessen onderzoeken.

Behandeling van recidiverende diverticulitis en/of aanhoudende klachten

Eén van de grote mysteries omtrent diverticulitis is de behandeling van recidieven en chronische klachten. In de afgelopen jaren zijn er meerdere studies gedaan naar het effect van conservatieve behandeling op het voorkómen van recidieven en het verlichten van symptomen. Verschillende behandelstrategieën zijn hierbij ingezet zoals een vezelrijk dieet, mesalamine, rifaximine of een combinatie van deze drie. De resultaten van deze studies zijn echter inconclusief en daardoor is het effect van conservatieve behandeling twijfelachtig.^{33,34} Logischerwijs zou de beste behandelstrategie zijn het zieke deel van het colon (sigmoïd) te verwijderen om zo symptomen te verlichten en recidieven te voorkomen. Er heeft echter grote controversie geheerst over het toepassen van sigmoïd resectie als behandeling van recidiverende diverticulitis en/of aanhoudende klachten. Een van de grote bezwaren tegen deze behandeling is het feit dat aanhoudende klachten na een diverticulitis soms moeilijk te onderscheiden zijn van Irritable Bowel Syndrome (IBS). Aangezien IBS een functionele ziekte is, zou operatieve interventie de klachten niet doen verminderen en misschien zelfs wel verergeren. Daarnaast gaat operatieve interventie gepaard met het risico op complicaties

zoals naadlekkage of abcessen.³⁵⁻³⁸ Aangezien (ongecompliceerde) diverticulitis een doorgaans milde ziekte is die vanzelf overgaat, lijkt een potentieel schadelijke procedure niet gerechtvaardigd. De richtlijnen van de American Society of Colon and Rectal Surgeons (ASCRS) in 2014 en de World Society of Emergency Surgery (WSES) in 2016 bevelen zorg op maat aan waarbij het effect van de klachten op de kwaliteit van leven de doorslaggevende factor moet zijn in de beslissing wel of niet te opereren.^{39,40} Het is daarom van groot belang dat het effect van een operatie (sigmoïd resectie) op de kwaliteit van leven in deze patiëntengroep meer inzichtelijk wordt gemaakt. Tot voor kort waren er alleen studies van lage kwaliteit beschikbaar over dit onderwerp, waarin beide behandelstrategieën (conservatief en operatief) als effectief worden gerapporteerd.³⁵ De retrospectieve en heterogene aard van deze studies bemoeilijken een goeie vergelijking tussen deze behandelingen. In **hoofdstuk 8 en 9** worden de lange termijnresultaten van de DIRECT trial beschreven; een multicentrische gerandomiseerde studie die conservatieve met operatieve behandeling vergelijkt in patiënten met recidiverende diverticulitis of aanhoudende klachten. De primaire uitkomstmaat was kwaliteit van leven. In totaal werden er 109 patiënten geïncludeerd; 56 in de conservatieve groep en 53 in de operatieve (electieve sigmoïd resectie) groep. Electieve sigmoïd resectie resulteerde in een hogere kwaliteit van leven na 5 jaar follow-up vergeleken met conservatieve behandeling, conform de korte termijn resultaten op 6 maanden follow-up.⁴¹ Opvallend genoeg zijn uiteindelijk bijna 50% van de patiënten uit de conservatieve groep alsnog geopereerd i.v.m. ernstige aanhoudende klachten. Toen we deze patiënten vergeleken met patiënten die wel succesvol conservatief behandeld zijn, bleek dat de patiënten die uiteindelijk geopereerd werden een significant lagere kwaliteit van leven hadden aan het begin van de studie (baseline). Dit onderschrijft de aanbevelingen van de ASCRS³⁹ en de WSES⁴⁰ dat de impact van de aanhoudende klachten en recidieven op de kwaliteit van leven de doorslaggevende factor zou moeten zijn in de beslissing wel of niet te opereren, aangezien onze bevindingen aantonen dat kwaliteit van leven op baseline het falen van conservatieve behandeling kan voorspellen. Onze studie heeft aangetoond dat de ziektelast van recidiverende diverticulitis of aanhoudende klachten hoog is en we hebben het positieve effect van electieve sigmoïd resectie op de kwaliteit van leven vastgesteld. Aan de ene kant ging operatieve behandeling wel gepaard met 11% naadlekkage en 15% reinterventies, maar aan de andere kant werden de meeste recidieven, 30% in de conservatieve groep, voorkomen door resectie. Daarnaast hebben we ook gekeken naar de kosteneffectiviteit van operatieve behandeling en vonden dat alhoewel operatieve behandeling na

1 jaar nog niet kosteneffectief is, dit wel het geval is na 5 jaar. Het feit dat de kosteneffectiviteit verbeterde na langere follow-up, benadrukt het belang van voldoende follow-up tijd voor een kosteneffectiviteit studie. Dit is zeker het geval als operatieve met conservatieve behandeling wordt vergeleken, omdat het lastig is om binnen een jaar aan te tonen dat operatieve behandeling kosteneffectief is aangezien de kosten voor een operatie vaak hoog zijn en veel bijdragen aan de totale kosten in het eerste jaar. Dit alles in ogenschouw nemende, concluderen we dat chirurgen vaker electieve sigmoid resectie moeten aanbieden aan patiënten met recidiverende diverticulitis of aanhoudende klachten, waarbij hogere kwaliteit van leven, minder pijn en minder recidieven moeten afgewogen worden tegen de inherente complicatierisico's.

Conclusie

Een chirurg ziet gemiddeld 1 à 2 diverticulitispatiënten op de spoedeisende hulp per week. Ondanks deze hoge incidentie hangen er nog veel mysteries rondom deze ziekte. Om zowel de kwaliteit als de kosteneffectiviteit van diverticulitiszorg te verbeteren, heeft dit proefschrift geprobeerd een aantal van deze mysteries op te lossen. Het paradigma van diverticulitisbehandeling verplaatst zich richting een meer conservatieve benadering, waarbij patiënten met ongecompliceerde diverticulitis thuis behandeld worden zonder antibiotica. In dit proefschrift doen we er nog een stapje bij door te stellen dat diverticulitis patiënten met lokaal pericolisch vrijlucht beschouwd kunnen worden als ongecompliceerde diverticulitis en dus ook als zodanig behandeld kunnen worden. Voorts kunnen diverticulitis patiënten met kleine abscessen zonder percutane drainage of chirurgische interventie behandeld worden en zijn er aanwijzingen dat percutane drainage in grotere abscessen ook niet altijd noodzakelijk is. Om veilig een conservatieve behandelstrategie zonder antibiotica of ziekenhuisopname te implementeren, moeten we goed de patiënten kunnen selecteren die een hoog risico lopen op complicaties en daardoor niet geschikt zijn voor deze behandelstrategie. In dit proefschrift hebben we hulpmiddelen ontwikkeld die artsen kunnen gebruiken om hen te helpen in de beslissing wel of niet door te verwijzen naar en/of op te nemen in het ziekenhuis en wel of niet antibiotica te starten. Verder hebben we de beste behandelstrategie voor patiënten met recidiverende diverticulitis en/of aanhoudende klachten geanalyseerd. Gebaseerd op onze resultaten, adviseren wij om operatieve behandeling vaker aan te bieden aan deze patiënten aangezien operatieve behandeling leidt tot een hogere kwaliteit van leven en tevens kosteneffectief is.

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Er wordt wel eens gezegd dat promoveren hetzelfde is als trouwen met jezelf. En ik moet zeggen dat tijdens alle diepte-en hoogtepunten die een promotietraject kent, het inderdaad wel een beetje voelt als een huwelijk met jezelf. Maar trouwen met jezelf impliceert dat ik het alleen zou hebben gedaan en dat is toch echt (gelukkig) niet het geval. Zonder de hulp van alle lieve mensen om mij heen was dit proefschrift niet tot stand gekomen. Daarom volgt hieronder mijn, zeker niet volledig toereikende, dankbetuiging.

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Hendrike Bolkenstein was born on the 24th of June 1990 in Venlo (Limburg), the Netherlands. She is the daughter of Bert and Carina Bolkenstein and has an older brother (Bas) and sister (Sanne). At the age of one she moved with her family to Bilthoven (Utrecht), where she lived throughout her childhood. She attended the Utrecht Stedelijk Gymnasium College in Utrecht where she received her Gymnasium diploma Cum Laude in 2008. The same year she moved to Utrecht to study medicine.

During her last years of study she came interested in the surgical subjects and started her first studies in surgery. At first she performed a few studies in the field of trauma surgery but then switched to gastro-intestinal surgery in her last year of study. This is when she started working on her thesis on the management of (uncomplicated) diverticulitis, supervised by prof.dr. I.A.M.J. Broeders, Dr. W.A. Draaisma and Dr. E.C.J. Consten.

After receiving her medical degree in 2015, she started working as a surgical resident (not in training) in the Meander Medical Centre in Amersfoort and later (2016) at the Diaconessenhuis in Utrecht. She continued to work on her thesis during her clinical work. Nowadays she is working in St Antonius Hospital in Nieuwegein as surgical resident (not in training).

Currently she is living in Amsterdam. Besides her work she loves cooking, wine and spending time with her family and friends. Her favourite sport is horse riding, which she does frequently on her own horse named Vos.